Risk factors for the onset of musculoskeletal pain in children and adolescents

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Abstract

Background

Musculoskeletal pain is a major burden on society. Research in adults has identified risk factors associated with musculoskeletal pain onset, however at present evidence for risk factors in children and adolescents is limited.

Aims

Identify potential risk factors for musculoskeletal pain onset in children and adolescents from current literature, and generate specific hypotheses to be tested using existing cohort data.

Methods

A systematic review was conducted to summarize existing evidence of risk factors for musculoskeletal pain onset in children and adolescents. Two child and adolescent prospective cohort datasets and a local primary care consultation database were used to test hypotheses using logistic and survival regression analysis.

Results

The systematic review found evidence that sleep problems and psychological symptoms (internalizing and externalizing) were associated with musculoskeletal pain onset with added evidence of potential effect modifiers. For sleep problems, analysis within a prospective cohort showed higher odds (OR 1.35, 95%CI 0.84, 2.16) for musculoskeletal pain onset, but this association was significant only for chronic pain onset (OR 2.22, 95%CI 1.43, 3.44), with evidence of effect modification by gender (association was stronger in boys). Testing within a primary care cohort showed a 49% increased hazard of sleep consultations with musculoskeletal consultations. In a cohort of adolescents musculoskeletal pain was not significantly associated with internalizing symptoms (OR 1.43, 95%CI 0.96, 2.12), however a significant association was found for

externalizing symptoms (adjusted OR 1.99, 95% CI 1.28, 3.10), with evidence of effect modification by pubertal status and screen time use. Testing in a primary care cohort revealed a 39% increased hazard for musculoskeletal consultations.

Conclusions

Potential risk factors (sleep and psychological symptoms) and effect modifiers were identified for (chronic) musculoskeletal pain onset within child and adolescent population and primary care samples. Future work is required to explore mechanisms explaining these associations, and develop appropriate interventions.

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Chapter one. Introduction

The central aim of this thesis is to explore and describe the epidemiology of child and adolescent musculoskeletal pain, and identify risk factors for the onset of musculoskeletal pain in this population. This introduction chapter outlines current knowledge on musculoskeletal pain relevant to the aims of the thesis, including information on: the history of the understanding of pain, the conceptual definition of pain, the impact and consequences of musculoskeletal pain, the prevalence and incidence of musculoskeletal pain, and risk factors for musculoskeletal pain onset in adults. Finally, the chapter discusses areas of the literature where knowledge on the onset of musculoskeletal pain is currently lacking and where further research is needed.

1.1 History and definition of pain

1.1.1 Early theories and the biomedical model

Pain may be simply considered as an adaptive signal that is hardwired within human beings to protect from physical damage and activate the responses necessary for survival (i.e. flight or fight system, avoidance of danger) (Main, Sullivan, & Watson, 2007; Simons, Elman, & Borsook, 2014). Over the course of many years however, the understanding of pain has been interpreted in many different ways (See Figure 1.1). Early civilisation attributed pain to the effect of Gods or evil spirits, this thinking was intertwined with religious and cultural thought and beliefs, other early documented explanations were focused more on internal causes such as disequilibrium of bodily fluids and also pain was interpreted as an emotion or sensation originating in the heart (Allan & Waddell, 1989; Main et al., 2007). Coming forward in time to the last few centuries, different theories have been used to explain pain and the experience of pain. In 1664, Descartes importantly proposed a link between body and mind, and described pain as a *perception* that

exists in the brain (Moayedi & Davis, 2013). According to Descartes' theory, a sensory cue (e.g. nociception from tissue damage) would travel up the spinothalamic tract, which operates as hollow tube where "animal spirits" would flow to transmit both sensory and motor information to the brain and then the brain would act to transmit action from the nerves to the muscles in order to avoid further pain (Main et al., 2007; Moayedi & Davis, 2013). This theory assumed that there was a direct relationship between the pain sensation and the amount of tissue damage, in effect a balance between severity of damage and severity of experience (Main et al., 2007). Following Descartes' theory, Bell (1811) advanced the Specificity Theory of pain, suggesting that the brain is a heterogeneous structure and the nerves within consist of heterogeneous bundles of neurons with different specialized functions. Each dedicated fibre would therefore lead to a particular sensory region of the brain, thus suggesting a specific pain "pathway" (Moayedi & Davis, 2013). However, both Descartes' and Bell's theories had significant shortcomings, such as the evidence of variation of pain perception from individuals when a fixed measurable controlled level of nociception is applied, and also phenomenon such as phantom limb pain, which is clearly not linked to actual peripheral nociception (Main et al., 2007). Despite these shortcomings the Specificity Theory of pain became the predominant theory, and was further supported and modified by the work of von Frey (1894-1896), who proposed four somatosensory modalities, therefore distinguishing different dimensions of pain (i.e. cold, heat, pain and touch), and Sherrington (1903-1906), who described the specificity of response of the neurons to different stimuli and proposed the framework of nociception (Moayedi & Davis, 2013). These early theories of pain share the dualistic point of view that considers the body as separate from the mind (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). These theories have largely underpinned the "biomedical" point of view, much aligned to the development of medicine in the 19th and 20th century, which, in terms of the understanding of pain experience, focused only on the neurophysiological components of pain (Bendelow, 2013). The biomedical model considered pain only as a signal of the presence of damage or of an ongoing disease, and as something that could

be described within biological parameters (Engel, 1977). Within this model, only the nociceptive aspect of pain was contemplated (Bendelow, 2013). Following the tenets of this model, pain can be defined as a sensation that is provoked by the interaction of different systems that are present at the neuraxis level (Manchikanti, Singh, Datta, Cohen, & Hirsch, 2009). This definition embraces two types of pain: nociceptive pain "usually elicited by the activation of specific receptors, by 2 types of peripheral nociceptors connected with C- and A-delta fibres", and neuropathic pain, which is the consequence of "injury to sensory fibres or from damage to the central nervous system" (Manchikanti et al., 2009).

1.1.2 The biopsychosocial model of pain

In the second part of the 20th century, some authors proposed a distinction between disease, which is intended as biological damage that occurs to the body, and illness, which represents how disease is experienced (Gatchel et al., 2007). As a consequence of this line of thinking, it is possible to draw an analogy where nociception is comparable to the disease, and pain to the illness (Gatchel et al., 2007). According to this point of view, pain should be considered as an illness, where the subjective experience of pain is the result of the interconnection between body (biological), psychology (perception and experience) and culture (social influence), rather than being purely the result of organic biological damage (Bendelow, 2013; Gatchel et al., 2007). Therefore, in opposition to the biomedical model, a "biopsychosocial" model was developed, which could embrace the full experience of pain (Engel, 1977). According to the biopsychosocial model, in addition to the medical model of disease (i.e. tissue damage as an explanation for the experience of pain), other factors such as the psychological status and social interactions and context (for example the relationship of the patient with the physician within a health care system) are accounted for, and all these factors are considered in equal measure (Engel, 1977). This biopsychosocial approach was further supported by the Gate Control Theory of pain

proposed by Melzack and Wall in 1965. According to this theory, nociceptive sensory information arrives at the dorsal horn in the spinal cord from myelinated A fibres and unmyelinated C fibres. This information undergoes a modulation which may stimulate the opening or closing of the spinal "gates" located in the dorsal horn that regulate the transmission of the impulses to the nervous system and to the brain (Main et al., 2007; Waddell, 2004). This modulation depends on the balance of activity of large nerve fibres (which close the gate) and small nerve fibres (which open the gate), as well as other impulses coming from the central nervous system (i.e. top down processing), including psychological factors such as emotions and beliefs (Main et al., 2007; Waddell, 2004). Importantly according to this model, the brain (inclusive of cognitive and emotional processes) has an active role in pain processing, and this gives explanation to the persistence of pain after tissue healing, and the experience of pain in presence of non-noxious stimulus or no perceived stimulus (Gatchel et al., 2007; Melzack, 1999). A further advance of the biopsychosocial approach led to the neuromatrix theory of pain. According to this theory, pain is produced by a neurosignature of a genetically determined widespread network of neurons, called "neuromatrix", which consists of loops that involve the thalamus, cortex and limbic system that cyclically process the sensory input, again highlighting central top down processing components that direct how pain is experienced (Melzack, 1999). Within this model the brain is not only involved in the processing and modulation of the nociceptive stimulus, but it can also generate a sensory experience even in the absence of a nociceptive input, such as in the case of phantom limb pain (Melzack, 1999). The biopsychosocial theoretical paradigm is now generally accepted within the field of pain research (Gatchel et al., 2007; Roditi & Robinson, 2011), and has led to current definitions of pain inclusive of these non-biomedical factors. For example according to the International Association for the Study of Pain, pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (http://www.iasp-pain.org/Taxonomy#Pain). From this definition, which also takes into account the emotional aspect of pain, it follows that the nature of pain is subjective and

potentially unique for each individual (Gatchel et al., 2007; Main, Richards, & Fortune, 2000; Roditi & Robinson, 2011). There are many types of pain symptoms including headache, cancer pain, neuropathic pain, visceral pain and finally musculoskeletal pain (Roditi & Robinson, 2011). Among these conditions, musculoskeletal pain is the most common type of pain experienced (Dieppe, 2013), with considerable consequences on both the individual and society (see Section 1.3). The characteristics and different types of musculoskeletal pain are described in the following paragraph.

Figure 1.1 Theories of pain during history

Epoch	Theory
Early civilisations	Pain as the effect of Gods, evil spirits, the disequilibrium in the body fluids or as an emotion or sensation originated in the heart
1664	Descartes - Nerves as hollow tubes where "animal spirits" flow to transmit both sensory and motor information from the nerves to the muscles
1811	Bell, Specificity Theory of pain - Nerves are heterogeneous bundles of neurons with different specialized functions (specific pathway to pain)
1895	Goldscheider, Intensity (summation) Theory of pain - Pain occurs as a result of a stimulus of sufficient intensity
1894-1896	von Frey – Four somatosensory modalities of pain (i.e. cold, heat, pain and touch)
1903-1906	Sherrington - Specificity of response of the neurons to different stimuli and framework of nociception
1955	Sinclair - Pattern Theory of pain
1965	Melzack and Wall - Gate Control Theory of pain
1968	Melzack and Casey - Neuromatrix Theory
1977	Engel - Biopsychosocial model of pain

1.2 Musculoskeletal pain

The musculoskeletal system consists of different components (muscles, spine, joints, bones, nerves, ligaments and tendons) that work together to support body structure (Carlson & Carlson, 2011; Dieppe, 2013). Therefore musculoskeletal pain can be understood as a broad umbrella term that includes the pain experience related to these components (Dieppe, 2013). Musculoskeletal pain is common and experienced by almost everyone during their lifetime and, due to its high prevalence and impact on society (please refer to Section 1.3 and 1.4), is a major health and social concern worldwide (Dieppe, 2013). Musculoskeletal pain is experienced in many different body regions, and is often defined depending on the body region affected (e.g. spinal pain, low back pain, neck pain, knee pain, shoulder pain, foot/ankle pain, hand pain, limb pain, joint pain and widespread pain). Musculoskeletal pain is also understood in terms of its duration, with three suggested categories: acute (musculoskeletal pain that lasts up to four weeks), sub-acute (musculoskeletal pain that lasts between four and twelve weeks) or chronic musculoskeletal pain (musculoskeletal pain that lasts more than twelve weeks), these definitions have been created to assist in clinical treatment guidelines, for example to identify people who have not recovered within an expected normal recovery time (Qaseem, Wilt, McLean, & Forciea, 2017). Musculoskeletal pain may be also described and assessed in terms of pain severity, by considering pain intensity, emotional distress, activity limitations and functional limitations associated with pain (for example impact on daily activities, work, school), impact on overall health, impact on sleep, all of which conceptualise the subjective pain experience (i.e. sensory, affective and evaluative components of pain) (Dieppe, 2013; Kamaleri, Natvig, Ihlebaek, Benth, & Bruusgaard, 2008; Legault, Cantin, & Descarreaux, 2014; Melzack, 1975, 1983; Treede et al., 2015). In the next section, the impact of musculoskeletal pain is outlined.

1.3 Impact of musculoskeletal pain

There are several consequences linked to the experience of musculoskeletal pain. In accordance to the biopsychosocial model of pain that has been described previously in this chapter, the consequences of musculoskeletal pain can be classified in biopsychosocial domains. These consequences are outlined below as physical and physiological consequences, psychological affect and consequences, and social and economic consequences.

1.3.1 Physical and physiological consequences of musculoskeletal pain

Musculoskeletal pain can have several physical and physiological consequences. Potential physiological changes and symptoms associated with pain presence include dysfunction of the sympathetic nervous system (which may lead to tachycardia, hyperventilation, cold sweats, blurred vision, abdominal pain, extreme pallor, nausea, dizziness, feeling weak) (Clinch & Eccleston, 2009). In addition, individuals with musculoskeletal pain may change their posture as a coping and avoidance strategy, or damage to the musculoskeletal structure may alter posture. This may ultimately lead to a disequilibrium of the musculoskeletal system in the long-term (Clinch & Eccleston, 2009). Another potential consequence is hypersensitivity to pain. Research has shown that in the acute phase of musculoskeletal pain a change of the neuronal architecture may occur, with changes in the dorsal horn neurones that are in the pathway of transmission of pain signals to the brain. This may eventually result in central sensitization, where pain is amplified (hyperalgesia) and innocuous stimuli is experienced as painful (allodynia), thus intensifying pain perception and making individuals hypersensitive to pain (Voscopoulos & Lema, 2010). There are also specific mechanisms that can be influenced by pain, for example pain can affect the function of the hypothalamus-pituitary-adrenal (HPA) axis, which is the system involved in the survival response to stress (Gupta & Silman, 2004; Kaplow et al., 2013; McBeth et al., 2007).

In normal circumstances, the activation of the HPA axis in reaction to stress begins with the release of the corticotrophin-releasing hormone (CRH) from the hypothalamus, which stimulates the anterior pituitary to produce the adrenocorticotropic hormone (ACTH) and ultimately leads to the production of cortisol (Gupta & Silman, 2004). During a period of prolonged stress or pain, the HPA axis may become hyperactive, leading to the production of high levels of cortisol (Bergman, 2005; Generaal et al., 2014; McBeth et al., 2007). Following this hyperactive period, the HPA axis may become hypoactive with low levels of CRH, which in turn may lower the ACTH levels, consequently down-stimulating cortisol production (Generaal et al., 2014; Kaplow et al., 2013; McBeth et al., 2007). As a result of this hypo-active HPA axis status, individuals may become more sensitive to stressful life-events, and consequently more vulnerable to the impact of musculoskeletal pain (the stress diathesis hypothesis). In addition, the presence of pain can affect sleep patterns and sleep hygiene, which can result in the experience of fatigue and changes to pain sensitivity and tolerance thresholds (Clinch & Eccleston, 2009; Dueñas, Ojeda, Salazar, Mico, & Failde, 2016; Mourão, Blyth, & Branco, 2010; Tüzün, 2007). Prolonged exposure to pain (e.g. chronic pain) can also induce physical disuse of the musculoskeletal system, which may occur when an individual avoids the performance of activities for a long period of time (Leeuw et al., 2007; Waddell, 2004). This may lead to loss of function, functional limitation and disability (Waddell, 2004).

1.3.2 Psychological consequences associated with pain

There are many psychological factors associated with musculoskeletal pain. Such factors include emotional arousal, distress, and depressive and anxiety symptoms (Henschke, Kamper, & Maher, 2015; Tüzün, 2007; Waddell, 2004); for example evidence shows the prevalence of depression and anxiety is significantly higher in persons with chronic pain compared to levels in the general population (Roditi & Robinson, 2011; Tüzün, 2007) and that musculoskeletal pain is more

common in those with depression (Goesling, Clauw, & Hassett, 2013). One of the key pain related psychological concepts that has led to the explanation of the development of chronic musculoskeletal pain is pain-catastrophizing (i.e. misinterpreting pain, worrying about pain, pain anxiety, and having negative thoughts about the possibility to cope with pain). Research has demonstrated that pain catastrophizing is robustly associated with poor prognosis once someone has musculoskeletal pain, and may account for pain-associated disability more than pain itself (Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Leeuw et al., 2007; Quartana, Campbell, & Edwards, 2009; Waddell, 2004). Catastrophizing, which may develop as an adaptive response to pain, may lead to fear-avoidance behaviours (i.e. avoiding movements or limiting activities which are believed to increase pain). This may consequently contribute to the persistence or exacerbation of pain through the processes and principles of classical and operant conditioning (e.g. avoidance of pain by restricting movement, and the intrinsic rewards of avoidance such as relief leading to greater efforts to avoid pain in the future) (Keefe et al., 2004; Leeuw et al., 2007; Vlaeyen & Linton 2000; Waddell, 2004). There are other key factors directly related to the pain experience. These include illness behaviour (i.e. how the individual expresses and communicates pain and how this information is interpreted and acted upon by other individuals), hypervigilance (i.e. tendency of increased awareness of bodily symptoms misinterpreted as pain), misbeliefs about pain (e.g. that pain indicates physical damage), altered motivation (e.g. passive coping strategies to avoid pain), anhedonia (i.e. inability to feel pleasure), and the impairment of cognitive skills such as concentration, attention and memory (Clinch & Eccleston, 2009; Leeuw et al., 2007; Mourão et al., 2010; Simons et al., 2014; Tüzün, 2007; Waddell, 2004). Broader consequences involve mood disturbance (i.e. lower mood in individuals with musculoskeletal pain), coping, self-efficacy and locus of control (i.e. the individual's confidence in the ability to control pain can influence coping responses to pain), as well as general health and a lower quality of life perceived by the individuals with pain (Campbell, Bishop et al., 2013; Clinch & Eccleston, 2009; Dieppe, 2013; Dueñas et al., 2016; Henschke et al., 2015; Keefe et al., 2004; Mourão et al.,

2010). Finally, compared to people without pain, those with chronic pain show a higher vulnerability regarding neuroticism, fear of failure and social isolation (Merlijn et al., 2003).

1.3.3 Social and economic consequences of musculoskeletal pain

Musculoskeletal pain also has social consequences. For example, as society is shaped upon the needs of persons who are fully able-bodied (Waddell, 2004), and musculoskeletal pain may involve a certain degree of disability or functional limitations (Section 1.3.1), the person with musculoskeletal pain may experience a number of social disadvantages (Waddell, 2004). These include limitations on the activities (daily, leisure or strenuous activities) to which the individual is able to participate (Dieppe, 2013; Krismer & van Tulder, 2007) and fewer social contacts due to the reduction in the time available for family and friends (Dueñas et al., 2016; Tüzün, 2007). As a consequence this can lead to social isolation (Waddell, 2004) and affect the social development of the person with pain, and the level of social support they receive, which can then impact on the perception of pain and how the individual copes with pain (Campbell, Wynne-Jones, & Dunn, 2011). For example people with pain have less frequent peer relationships than their pain-free counterparts (Clinch & Eccleston, 2009), poorer capacity of carrying out normal social activities and have restrictions in engaging in daily activities or work activities (Saastamoinen, Leino-Arjas, Laaksonen, Martikainen, & Lahelma, 2006). Also, because of the uncertainty of their health status, it may be complicated for people with pain to arrange social activities (Dueñas et al., 2016). Additionally, pain has an impact on the familial structure. Families in which there is one or more persons suffering from musculoskeletal pain may modify their lifestyle in order to cope with the person in pain (Waddell, 2004) and evidence shows the impact of pain at a family and partner level, for example a change in roles (e.g. partner has to take on increased duties) leading to increased stress, anger and frustration at the family member who has pain (Strunin & Boden, 2004). In addition, persons within the family can have a more limited social life and experience

anxiety and depression as a consequence of their relative who is suffering pain (Clinch & Eccleston, 2009; Dueñas et al., 2016). Moreover, research has shown that overall relationship quality between couples can be affected when one partner has pain, with evidence that it can increase and decrease relationship quality (Vivekanantham, Campbell, Mallen, & Dunn, 2014). In addition, research also shows that pain behaviours can be influenced by partners' reactions, some reactions increasing the likelihood of future pain behaviours (e.g. solicitous responses) whilst others can increase depression and anxiety (e.g. negative responses from partners), all of which demonstrate the complexities of the reciprocal dynamics at a family level when pain is present (Campbell, Jordan, & Dunn, 2012; Leonard, Cano, & Johansen, 2006; Waddell, 2004).

Musculoskeletal pain is also linked to economic costs for both the individual and society. Overall, the economic burden of pain is significant, with both direct (direct healthcare, hospitalization, medications, outpatient visits, diagnostic tests, assistive devices, alternative therapies) and indirect (number of work days lost, productivity loss, employee retraining, administrative expenses, disability allowance and unemployment benefits in adults) costs to be considered (Breivik, Eisenberg, & O'Brien, 2013; Hoy, Brooks, Blyth, & Buchbinder, 2010; Krismer & van Tulder, 2007; Manchikanti et al., 2009). For example it has been estimated that individuals who have a back pain condition have overall healthcare expenses 60% higher than those who do not suffer of back pain (Manchikanti et al., 2009), and that back pain is one of the main reasons for sick leave and work loss (21-43% productivity loss in individuals with pain, with higher percentages with increasing severity of pain) (Dueñas et al., 2016). Overall, the mean annual cost of chronic pain has been estimated at $560-635 billion in the US (of which $11.6-12.7 billion is the cost of lost productivity, 2010 figures), being higher than the costs associated with cancer, diabetes and heart disease, and as 3-10% of gross domestic product in Europe in 2008 (Breivik, Eisenberg, & O'Brien, 2013; Gaskin & Richard, 2012; Institute of Medicine (US) Committee on Advancing Pain Research, Care, 2011). In the UK, the direct cost associated with back pain was estimated as £1632 million (1998 figures) (Maniadakis & Gray, 2000). In addition, the impact of

musculoskeletal pain can be conceptualised by means of another measure that accounts for the years an individual loses due to disability; disability-adjusted life years (DALYs). This measure is composed by the sum of the years lived with disability (YLD) and years lost due to premature mortality (YLL) (Murray et al., 2012). The proportion of the global disability-adjusted life years (DALYs) due to musculoskeletal pain was 4.7% in 1990 and has risen to 6.8% in 2010 (Murray et al., 2012). Moreover, low back pain, neck pain and other musculoskeletal disorders rank first, fourth and sixth among the leading causes of years lived with disability (YLDs) (Vos et al., 2012). Altogether this evidence clearly show the social and economic impact due to musculoskeletal pain.

1.3.4 Summary of the impact of musculoskeletal pain

In this section, the impact of musculoskeletal pain has been outlined. Physical and physiological consequences (e.g. change in posture, central sensitization, change in the HPA axis functioning, change in sleep patterns), psychological consequences (e.g. anxiety, depression, pain catastrophizing, fear-avoidance behaviours), and social (e.g. restriction in social activities, burden on the family environment) and economic consequences (e.g. direct healthcare expenses, work days lost, productivity loss) have been described. In the following section, the prevalence and incidence of musculoskeletal pain are outlined.

1.4 Prevalence and incidence of musculoskeletal pain

In this section epidemiological data representing the prevalence and incidence of musculoskeletal pain are reported. In the context of musculoskeletal pain, the term “prevalence” refers to the proportion of the population who report the experience of musculoskeletal pain in a determined time-period (e.g. lifetime, 1-year, point) while “incidence” is the proportion of new cases of musculoskeletal pain that occur over a certain period of time among all the individuals at risk (i.e. within a cohort study it would be those within the population without musculoskeletal pain at baseline who subsequently report musculoskeletal pain). Some aspects regarding the prevalence and incidence of musculoskeletal pain should be underlined. The prevalence and incidence of pain are influenced by factors such as the case-definition and the time-period considered (Cimmimo, Ferrone, & Cutolo, 2011; McBeth & Jones, 2007). For example, the prevalence or incidence would be higher if a longer interval of time was used, for example a 1-year period prevalence or incidence rate would be higher than a 1-month period prevalence or incidence rate because of the inclusion of more cases with musculoskeletal pain over the longer time period. This is shown in the text below, where estimates for the prevalence or incidence of musculoskeletal pain are higher if longer intervals are used (Table 1.1 and Table 1.2). Likewise, if less or more stringent case-definitions for musculoskeletal pain occurrence are used the prevalence or incidence can change. For example the estimate of chronic widespread pain differs depending on which criteria are used (e.g. ACR 1990 criteria, which requires bilateral pain, above and below the waist, in the axial skeleton present for at least 3 months, will always include more of the population compared to a more stringent Manchester definition, which requires pain in at least two sections of two contralateral limbs and in the axial skeleton for at least 3 months) (Henschke et al., 2015; Hunt, Silman, Benjamin, McBeth, & Macfarlane, 1999; Mourão et al., 2010). Such differences are also found based on the definition of the amount or severity of pain (e.g. to be counted one would be required to have a certain “amount” of pain or the pain would have to have a certain impact), and

on how long the period of pain would have to last (e.g. more than a day, more than a week, more than a month).

1.4.1 Prevalence of musculoskeletal pain

A scoping search of published reviews was performed and figures for the prevalence of musculoskeletal pain are shown in Table 1.1. Several of the identified reviews report on the prevalence of low back pain, neck pain and chronic widespread pain or fibromyalgia. In comparison, less information was present regarding the prevalence of pain in the shoulder, knee, ankle/foot or lower limbs (See Table 1.1). The most prevalent conditions were low back pain and neck pain. From reviews on back pain the evidence suggests that point prevalence (i.e. at the time of assessment) is estimated at approximately 20% with a large range between 4% and 60%, and 1 year period prevalence rates at 40% with a range from 36% to 85%. Reasons for the large variation in estimated prevalence rates are due to different definitions used between studies, also different populations have been studied, for example general population, workers, clinical samples. Similar estimates were reported for the 1-year prevalence of neck pain in several reviews (median 37.2%; range 12-75%). Regarding knee pain, the mean 1-year prevalence reported in a review was 25.0% (range 6.5-28%). Figures on shoulder pain reported in two reviews were similar regarding the 1-month prevalence (range 19-33%). Several authors reported on the prevalence of chronic widespread pain, with estimates ranging from 0 to 24% depending on the definition used; however, most of the estimates among the 23 studies included in a recent systematic review were between 10% and 15% (Mansfield, Sim, Jordan, & Jordan, 2016). Lower figures were reported for the prevalence of fibromyalgia (range 0.1-11%).

Table 1.1 Prevalence of musculoskeletal pain in adults			
Study	**Period**	**Site**	**Figure**
Miranda et al., 2012	-	Chronic musculoskeletal pain	14.1-85.5% [A]
McBeth & Jones, 2007	Lifetime	Back pain	51-84%
	1-year	Back pain	36-67%
	1-month	Back pain	31-42%
	Point	Back pain	13-30%
Louw et al., 2007	Lifetime	Back pain	62% (range 56-74%)
	1-year	Back pain	50% (range 40-72%)
	Point	Back pain	32% (range 16-59%)
Garcia et al., 2014	-	Low back pain	31.3% [B]
		Low back pain	16.7% (range 9.1-20.3%) [C]
		Low back pain	31.5% (range 27.7-33.6%) [D]
		Low back pain	65% (range 50.0-80.8%) [E]
Woolf & Pfleger, 2003	1-year	Low back pain	58-84%
	Point	Low back pain	4-33%
Hoy et al., 2012	Lifetime	Low back pain	38.9%
	1-year	Low back pain	38.0%
	1-month	Low back pain	30.8%
	Point	Low back pain	18.3%
Johansson et al., 2017	1-year	Mid back pain	15%
	1-year	Low back pain	43%
Manchikanti et al., 2009	1-year	Chronic low back pain	15-45%
	Point	Chronic low back pain	30%
Henschke et al., 2015	-	Chronic low back pain	5.9-11%
Miranda et al., 2012	-	Chronic Low back pain	5.1-65.2% [A]
Meucci et al., 2015	-	Chronic low back pain	4.2% (Subjects aged 24-39)
		Chronic low back pain	19.6% (Subjects aged 20-59)
		Chronic low back pain	25% (Subjects aged >60)
Miranda et al., 2012	-	Lower limb pain	50% [A]
Peat et al., 2001	1-year	Knee pain	25.0% (range 6.5-28%)
Thomas et al., 2011	Point	Foot/ ankle pain	20% (Subjects aged >45)
Manchikanti et al., 2009	1-year	Neck pain	12.1-71.5%
Fejer et al., 2006	Lifetime	Neck pain	48.5% (range 14.2-71.0%)
	1-year	Neck pain	37.2% (range 16.7-75.1%)
	6-month	Neck pain	29.8% (range 6.9-54.2%)
	1-month	Neck pain	23.3% (range 15.4-41.1%)
	1-week	Neck pain	12.5% (range 1.4%-19.5%)
	Point	Neck pain	7.6% (range 5.9-22.2%)
Hogg-Johnsons et al., 2008	1-year	Neck pain	12.1-71.5%
	1-month	Neck pain	15.4-45.3%
	1-week	Neck pain	12-14%
Johansson et al., 2017	1-year	Neck pain	32%
Reid et al., 2011	Lifetime	Chronic neck pain	5%
McBeth & Jones, 2007	1-month	Shoulder pain	20-33%
Luime et al., 2004	Point	Shoulder pain	6.9-26%
	1-month	Shoulder pain	19-31%
	1-year	Shoulder pain	5-47%
	Lifetime	Shoulder pain	7-67%

[A] Systematic review conducted on elderly Brazilian populations
[B] Overall pooled estimate
[C] Miners, oil workers and university administrative officials
[D] Nurses, senior citizens, transit bus drivers, workers enrolled in a physical rehabilitation program and university employees
[E] Truck drivers, seamstresses, sitting workers, coffee sack loaders, obese population, pregnant women, sawyers, homemakers, nurses

Table 1.1 Prevalence of musculoskeletal pain in adults			
Study	**Period**	**Site**	**Figure**
Gran, 2003	-	Chronic widespread pain	0.0-13.2%
McBeth and Jones, 2007	-	Chronic widespread pain	7-22%
Cimmino et al., 2011	-	Chronic widespread pain	11.4-24%
Mourão et al., 2010	-	Chronic widespread pain	4.2-13.3%
Shipley, 2010	-	Chronic widespread pain	10%
Mansfield et al., 2016	-	Chronic widespread pain	0-24%
McBeth and Jones, 2007	-	Fibromyalgia	1-11%
Mourão et al., 2010	-	Fibromyalgia	0.7-7.3%
Shipley, 2010	-	Fibromyalgia	2%
Reid et al., 2011	-	Fibromyalgia	2.9%
Gran, 2003	-	Fibromyalgia	0.1-3.3%

[A] Systematic review conducted on elderly Brazilian populations
[B] Overall pooled estimate
[C] Miners, oil workers and university administrative officials
[D] Nurses, senior citizens, transit bus drivers, workers enrolled in a physical rehabilitation program and university employees
[E] Truck drivers, seamstresses, sitting workers, coffee sack loaders, obese population, pregnant women, sawyers, homemakers, nurses

1.4.2 Incidence of musculoskeletal pain

In this scoping search, rates of the incidence of musculoskeletal pain were identified (Table 1.2). As with the evidence presented on prevalence, variation in estimates are wide depending on a number of factors (time frame, definition, first ever episode or new episode). For back pain, estimates for the 1-year incidence ranged from 1.5% up to 36% (Hoy et al., 2010), with a recent systematic review providing a pooled estimate (26%-27%) for community and occupational settings (Taylor, Goode, George, & Cook, 2014). Other reviews reported on the incidence for knee pain or patellofemoral pain (25%, time-frame not specified) (Callaghan & Selfe, 2007), and on the 1-year incidence estimate for neck pain (14.6-17.9%), shoulder pain (0.9-2.5%), chronic musculoskeletal pain (8.3%) and fibromyalgia (0.6%) (Cimmimo, Ferrone, & Cutolo, 2011; Gran, 2003; Hogg-Johnson et al., 2008; Luime et al., 2004).

Table 1.2 Incidence of musculoskeletal pain in adults

Study	Period	Site	Figure
Hoy et al., 2010	1-year	Low back pain	6.3-15.4% [A]
	1-year	Low back pain	1.5-36% [B]
Taylor et al., 2014	-	Low back pain	26% [A]
	-	Low back pain	27% [B]
Woolf & Pfleger, 2003	1-year	Low back pain	2.8%
Johansson et al., 2017	1-month	Mid back pain	0.4-0.7%
Meucci et al., 2015	1-year	Chronic low back pain	10.8%
Callagahan & Selfe, 2007	-	Knee pain	25% (range 3-40%)
Hogg-Johnsons et al., 2008	1-year	Neck pain	14.6 -17.9%
Luime et al., 2004	1-year	Shoulder pain	0.9-2.5%
Cimmino et al., 2011	1-year	Chronic widespread pain	8.3%
Gran, 2003	1-year	Fibromyalgia	0.6%

[A] First-ever episode of low back pain
[B] Populations pain-free at baseline in community and occupational settings

1.4.3 Summary of prevalence and incidence figures for musculoskeletal pain

An extensive body of information on the prevalence and incidence of musculoskeletal conditions has been shown in Sections 1.4.1 and 1.4.2 above. Despite the wide variability of the estimates reported, (due to variation on population, age, setting, definition, and duration), the figures reported indicate that musculoskeletal pain is common in adults, with high prevalence and incidence rates in the general population. In the next section the risk factors for the onset of musculoskeletal pain are outlined.

1.5 Risk factors for the onset of musculoskeletal pain

Evidence for factors associated with the onset of musculoskeletal pain are summarized in this section. A scoping search of recent reviews that report on risk factors for the onset of musculoskeletal pain in adults was performed to complement the full systematic review on factors in childhood and adolescence within the next chapter. A brief description of the association for potential risk factors with pain in different body sites is given below (Section 1.5.1 - 1.5.4). For ease of reading and interpretation, risk factors will be described corresponding to the biopsychosocial model of pain (i.e. biological factors, psychological factors and social factors). Only the evidence of the presence of an association is reported but not the size of effect. Most reviews report on risk factors for low back pain as most of the research has focused on this condition, although information on risk factors relative to other body sites is presented where available. Evidence is presented as a positive effect (+) if the factor is shown to increase risk, a negative sign (-) was assigned if there was no association, and a hash sign (#) if the evidence for that factor was mixed.

1.5.1 Biological factors

1.5.1.1 Age

The effect of age on musculoskeletal pain has been explored and reported in many reviews (Table 1.3). As can be seen from the evidence within Table 1.3 the majority of evidence suggest an association of greater risk of musculoskeletal pain onset with increasing age. Though there is some suggestion that this is not linear and that this relationship decreases after the 6th decade of life (Cimmimo et al., 2011; Hoy et al., 2010; McBeth & Jones, 2007).

Table 1.3 Risk factors for musculoskeletal pain in adults – Age

Risk factor	Review	Pain site	Effect
Age	Henschke et al.,2015	Musculoskeletal pain	#
	McBeth & Jones, 2007	Musculoskeletal pain	+
	Hoy et al., 2010	Musculoskeletal pain	+
	Krismer & van Tulder, 2007	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Dionne et al., 2006	Low back pain	#
	Manchikanti et al., 2009	Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	#
	Bergman, 2005	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+
	Larsson et al., 2012	Chronic widespread pain	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.1.2 Female gender

Several reviews (Table 1.4) indicate female gender to be a risk factor for musculoskeletal pain in general (Henschke et al., 2015; Hoy et al., 2010; McBeth & Jones, 2007), and chronic widespread pain and fibromyalgia more specifically (Bergman, 2005; Cimmimo et al., 2011; Gran, 2003; Larsson, Björk, Börsbo, & Gerdle, 2012; Mourão et al., 2010). However there was also evidence of mixed findings for both back pain (Louw, Morris, & Grimmer-Somers, 2007; Manchikanti et al., 2009), and neck pain (Hogg-Johnson et al., 2008; Manchikanti et al., 2009). In summary, the majority of the evidence suggests that female gender is a risk factor for the development of musculoskeletal pain. This may be partly explained by physical or physiological differences between males and females, but also by differences in pain perception and sex-role expectancies which may encourage the reporting of pain in females compared to males (Fillingim, 2000).

Table 1.4 Risk factors for musculoskeletal pain in adults – Female gender

Risk factor	Review	Pain site	Effect
Female gender	Henschke et al.,2015	Musculoskeletal pain	+
	McBeth & Jones, 2007	Musculoskeletal pain	+
	Hoy et al., 2010	Musculoskeletal pain	+
	Louw et al., 2007	Low back pain	+
	Manchikanti et al., 2009	Low back pain	#
	Manchikanti et al., 2009	Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	#
	Gran, 2003	Chronic widespread pain	+
	Bergman, 2005	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+
	Larsson et al., 2012	Chronic widespread pain	+
	Gran, 2003	Fibromyalgia	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.1.3 Physical and mechanical factors

Three reviews were identified that reported information on the association between physical factors and musculoskeletal pain (Table 1.5). Factors associated with risk of low back pain are disc degeneration (but not in neck pain, (Manchikanti et al., 2009) and behaviours such as limping or lifting heavy weights.

Table 1.5 Risk factors for musculoskeletal pain in adults – Physical and mechanical factors

Risk factor	Review	Pain site	Effect
Physical and mechanical factors	Leboeuf-Yde, 2004	Low back pain	#
	Taylor et al., 2014	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Manchikanti et al., 2009	Neck pain	-

1.5.1.4 Presence of other pain symptoms

A number of reviews have shown that previous experience of pain or pain in other body sites are risk factors for the onset of low back pain (Louw et al., 2007; Taylor et al., 2014), neck pain (Hogg-Johnson et al., 2008) and chronic widespread pain (Bergman, 2005; Mourão et al., 2010) (Table 1.6). Finally, the number of pain sites at baseline was reported as a risk factor for the transition from chronic regional pain to chronic widespread pain in another systematic review (Larsson et al., 2012). The evidence provided by these reviews suggest a link between the presence of other pain symptoms or previous experience of pain and the onset of musculoskeletal pain or the transition to widespread pain.

Table 1.6 Risk factors for musculoskeletal pain in adults – Presence of other pain symptoms

Risk factor	Review	Pain site	Effect
Presence of other Pain symptoms	Taylor et al., 2014	Low back pain	+
	Louw et al., 2007	Low back pain	+
	Hogg-Johnsons et al., 2008	Neck pain	+
	Bergman, 2005	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Larsson et al., 2012	Chronic widespread pain	+

1.5.1.5 Physical activity

There is conflicting results on the effect of physical activity on musculoskeletal pain (Table 1.7). Some evidence suggests that increases in physical activity decrease the risk for low back pain and neck pain onset, however engagement in vigorous sport activities has been shown to have a negative effect on the musculoskeletal health (Hildebrandt, Bongers, Dul, van Dijk, & Kemper, 2000). Conversely, a recent meta-analysis reported no effect of physical activity on the onset of low back pain, and a protective effect for the development of chronic low back pain (Shiri & Falah-Hassani, 2017). This is in contrast with another review that reported a significant effect for the onset of low back pain among those who regularly participated in sports (Taylor et al., 2014). Engagement in regular physical activity may be an effective preventive strategy for non-specific low back pain according to other authors (Krismer & van Tulder, 2007). Finally, another review reported low physical activity as a risk factor for chronic widespread pain (Cimmimo et al., 2011). At present the evidence is mixed, but suggestive that moderate levels of physical activity may be protective for musculoskeletal pain or chronic musculoskeletal pain.

Table 1.7 Risk factors for musculoskeletal pain in adults – Physical activity

Risk factor	Review	Pain site	Effect
Physical activity	Hildebrandt et al., 2000	Musculoskeletal pain	#
	Taylor et al., 2014	Low back pain	+
	Shiri et al., 2017	Low back pain	-
	Krismer & van Tulder, 2007	Low back pain	-
	Cimmino et al., 2011	Chronic widespread pain	+

1.5.1.6 Obesity

Seven reviews report findings on the association between BMI categories and musculoskeletal pain (Table 1.8). Four reviews reported that obesity or having a higher BMI is a risk factor for incident low back pain or chronicity of low back pain, also for chronic widespread pain and fibromyalgia (Hoy et al., 2010; Mourão et al., 2010; Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010a; Weigl, Cieza, Cantista, Reinhardt, & Stucki, 2007). However, another literature review reported that the association between obesity and low back pain did not show a dose-response pattern and was not present in monozygotic twins who were dissimilar in body weight, suggesting no evidence for causality or a potential genetic interaction effect (Leboeuf-Yde, 2004). This is supported by two reviews that reported mixed evidence for an association between BMI and low back pain (Manchikanti et al., 2009; Taylor et al., 2014). Based on the evidence of these reviews, obesity or higher BMI is likely to be associated with musculoskeletal pain, but the associations reported may be the due to other underlying factors associated to the development of musculoskeletal conditions. It may be therefore that higher BMI alone is not sufficient to cause the development of the condition, but when present together with other factors it may contribute to the development of musculoskeletal pain and to its chronicity.

Table 1.8 Risk factors for musculoskeletal pain in adults – Obesity

Risk factor	Review	Pain site	Effect
Obesity	Shiri et al., 2010	Low back pain	+
	Taylor et al., 2014	Low back pain	#
	Weigl et al., 2007	Low back pain	+
	Hoy et al., 2010	Low back pain	+
	Leboeuf-Yde, 2004	Low back pain	#
	Manchikanti et al., 2009	Low back pain	#
	Mourão et al., 2010	Chronic widespread pain	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.1.7 Smoking

Another factor suspected to be related to the onset of musculoskeletal pain is smoking (Table 1.9). Several reviews report on smoking as a risk factor for the onset of low back pain (Abate, Vanni, Pantalone, & Salini, 2013; Louw et al., 2007; Manchikanti et al., 2009; Shiri, Karppinen, Leino-Arjas, Solovieva, & Viikari-Juntura, 2010), chronic widespread pain (Bergman, 2005; Cimmimo et al., 2011; Gran, 2003) and neck pain (Hogg-Johnson et al., 2008; Manchikanti et al., 2009). The association between smoking and pain may be explained by the thousands of compounds that are present in cigarette smoke, with several of them resulting in physiological effects (Shi, Weingarten, Mantilla, Hooten, & Warner, 2010), such as changes in the neuroendocrine system that alter the perception of pain and increase the degeneration of bone (Holley et al., 2013; Shi et al., 2010). Smoking could also be responsible for an increased time of curing and the alteration of bone metabolism but is also a proxy marker for other factors such as deprivation and poor health behaviour in general (Abate et al., 2013; Holley et al., 2013; Shi et al., 2010).

Table 1.9 Risk factors for musculoskeletal pain in adults – Smoking

Risk factor	Review	Pain site	Effect
Smoking	Shiri et al. 2010	Low back pain	+
	Leboeuf-Yde, 2004	Low back pain	#
	Louw et al., 2007	Low back pain	+
	Abate et al. 2013	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Manchikanti et al., 2009	Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	+
	Gran, 2003	Chronic widespread pain	+
	Bergman, 2005	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+

1.5.1.8 Sleep problems

Sleep problems (e.g. problems falling asleep, waking up during the night, non-restorative sleep) are another factor suspected to be related to musculoskeletal pain onset, and the results of 5 reviews show a consistent link between sleep problems and musculoskeletal pain onset (Table 1.10). However, there is evidence of variation across different types of musculoskeletal conditions, for example sleep disorders were indicated as a risk factor for chronic musculoskeletal pain (Bergman, 2005; Cimmimo et al., 2011; Mourão et al., 2010), and for incident low back pain (Taylor et al., 2014). Finally, a recent review investigated the bidirectional association between sleep and pain, both in prospective and experimental research. Findings showed that sleep problems are more likely to precede pain in contrast to pain as a predictor of sleep problems (Finan, Goodin, & Smith, 2013). Possible mechanisms that may explain the association between sleep and musculoskeletal pain include an augmented production of cytokine and inflammatory mediators, moreover sleep problems may increase the muscular tension, potentially making individuals more vulnerable to muscular problems (Auvinen et al., 2010; Bonvanie, Oldehinkel, Rosmalen, & Janssens, 2016; Irwin, Olmstead, & Carroll, 2016). Other factors involved in the association between sleep and musculoskeletal pain are disturbances of the sleep architecture and genetic factors (Kelly, Blake, Power, O'keeffe, & Fullen, 2011; Moldofsky, 2001; Zhang et al., 2012). According to the above mentioned reviews, all the evidence suggests an association between sleep problems and musculoskeletal pain.

Table 1.10 Risk factors for musculoskeletal pain in adults – Sleep problems

Risk factor	Review	Pain site	Effect
Sleep problems	Taylor et al., 2004	Low back pain	+
	Finan et al., 2013	Musculoskeletal pain	+
	Bergman, 2005	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+

1.5.1.9 Familial and Genetic factors

Some reviews report on the role of familial and genetic factors on the onset and heritability of musculoskeletal pain (Table 1.11). According to a review, genetic factors explain the association between disc degeneration and low back pain, which therefore could be heritable (Manchikanti et al., 2009). In three systematic reviews on twin studies of pain, the heritability estimate of musculoskeletal pain was approximately 50% for chronic widespread pain, and approximately 35% for back pain and neck pain (Hogg-Johnson et al., 2008; Mourão et al., 2010; Nielsen, Knudsen, & Steingrímsdóttir, 2012). Another two systematic reviews report that family history of pain is a risk factor for the onset of chronic widespread pain and the transition from chronic regional pain to chronic widespread pain (Bergman, 2005; Larsson et al., 2012). Despite the reported genetic link for musculoskeletal pain, it is still difficult to identify definitive unique genetic markers for pain, for example previous research has shown that at least 358 genes are likely to be involved with pain or analgesia, and so currently research is quite a way off from identifying a specific pain genotype (Mogil, 2009, 2012).

Table 1.11 Risk factors for musculoskeletal pain in adults – Familial and genetic factors

Risk factor	Review	Pain site	Effect
Familial and Genetic factors	Manchikanti et al., 2009	Low back pain	+
	Nielsen et al., 2012	Low back pain	+
		Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	+
	Nielsen et al., 2012	Chronic widespread pain	+
	Bergman, 2005	Chronic widespread pain	+
	Larsson et al., 2012	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.2 Psychological factors

There is a large body of evidence suggesting a relationship between psychological factors (e.g. depression, anxiety, stress and somatization) and musculoskeletal pain onset (Table 1.12). Several reviews report on psychological factors such as depression, anxiety, stress, poor mental behaviours, mental distress, emotional problems, mood/emotions, cognitive functioning, pain behaviour, passive coping strategies, somatization, catastrophizing, social isolation, panic disorders and familial mood disorders as risk factors for the onset of low back pain, neck pain, musculoskeletal pain, knee pain, chronic musculoskeletal pain or fibromyalgia (Bergman, 2005; Cimmimo et al., 2011; Gran, 2003; Hogg-Johnson et al., 2008; Hoy et al., 2012; Krismer & van Tulder, 2007; Manchikanti et al., 2009; McBeth & Jones, 2007; Mourão et al., 2010; Phyomaung et al., 2014; Pinheiro et al., 2015; Taylor et al., 2014; Weigl et al., 2007).

Table 1.12 Risk factors for musculoskeletal pain in adults – Psychological factors

Risk factor	Review	Pain site	Effect
Psychological variables	McBeth & Jones, 2007	Musculoskeletal pain	+
	Taylor et al., 2004	Low back pain	+
	Krismer & van Tulder, 2007	Low back pain	+
	Pinheiro et al., 2015	Low back pain	+
	Weigl et al., 2007	Low back pain	+
	Hoy et al., 2010	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Phyomaung et al., 2014	Knee pain	#
	Manchikanti et al., 2009	Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	+
	Gran, 2003	Chronic widespread pain	+
	Bergman, 2005	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Gran, 2003	Chronic widespread pain	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.3 Social factors

1.5.3.1 Socioeconomic status

Many reviews have reported on the association between socioeconomic status and musculoskeletal pain onset (Table 1.13). Two systematic reviews reported a relationship between socioeconomic factors (including perceived inadequacy of income, lower social status, low educational status, low income, social class) and incident low back pain (Manchikanti et al., 2009; Taylor et al., 2014). With regard to neck pain, the evidence for an association with socioeconomic status is mixed (Manchikanti et al., 2009). Several indicators of low socioeconomic status (e.g. lower education, low income, being an immigrant, separated, divorced, widowed, disabled, and lower-level employee or manual worker, unemployment) were reported as risk factors for chronic widespread pain and fibromyalgia in other reviews (Bergman, 2005; Cimmimo et al., 2011; Gran, 2003; Mourão et al., 2010). Whilst there is accord on the social factors associated with musculoskeletal pain, one review suggests that rather than a direct risk factor, factors like socioeconomic status may be a risk marker, with other factors (e.g. psychosocial factors) linked to the onset of musculoskeletal pain (McBeth & Jones, 2007).

Table 1.13 Risk factors for musculoskeletal pain in adults – Socioeconomic status

Risk factor	Review	Pain site	Effect
Low socioeconomic status	McBeth & Jones, 2007	Musculoskeletal pain	+
	Taylor et al., 2004	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Manchikanti et al., 2009	Neck pain	#
	Bergman, 2005	Chronic widespread pain	+
	Gran, 2003	Chronic widespread pain	+
	Cimmino et al., 2011	Chronic widespread pain	+
	Mourão et al., 2010	Chronic widespread pain	+
	Gran, 2003	Fibromyalgia	+
	Mourão et al., 2010	Fibromyalgia	+

1.5.3.2 Ethnicity

Four reviews (Table 1.14) reported a relationship between an individuals' ethnicity and musculoskeletal pain, with non-Caucasians groups (e.g. African-American, Hispanic, South Asian, American Indians and Alaska Natives) more at risk compared to Caucasian groups (Cimmimo et al., 2011; Jimenez, Garroutte, Jundu, Morales, & Buchwald, 2012; Manchikanti et al., 2009; McBeth & Jones, 2007). Explanations involve cultural differences in the conceptualisation of pain and the measurement of pain (Jimenez, Garroutte, Jundu, Morales, & Buchwald, 2012; Manchikanti et al., 2009). However, similar to the link of socioeconomic status, ethnicity may be a risk marker rather than a risk factor (McBeth & Jones, 2007). In summary, according to this body of literature non-Caucasian individuals may be at higher risk of experiencing musculoskeletal pain, although it is not clear yet if this is a direct consequence of the ethnicity or of other underlying associated factors.

Table 1.14 Risk factors for musculoskeletal pain in adults – Ethnicity

Risk factor	Review	Pain site	Effect
Ethnicity	Jimenez et al. 2012	Musculoskeletal pain	+
	McBeth & Jones, 2007	Musculoskeletal pain	+
	Manchikanti et al., 2009	Neck pain	+
	Cimmino et al., 2011	Chronic widespread pain	+

1.5.3.3 Work and occupational factors

Table 1.15 shows 10 reviews that studied the link between various work factors and musculoskeletal pain. The evidence is mixed due to the high level of variation in the factors measured, and the differing types of employment. Key factors that appear involved in the link between employment and musculoskeletal pain onset are low levels of job satisfaction and support at work, and the physical and ergonomic aspects of the job. Based on this evidence, it appears that work does have a role on the onset of musculoskeletal pain, however there is no clear consensus yet on what the specific factors may be.

Table 1.15 Risk factors for musculoskeletal pain in adults – Work and occupational factors

Risk factor	Review	Pain site	Effect
Working	Taylor et al., 2004	Low back pain	+
	Hoy et al., 2010	Low back pain	+
	Krismer & van Tulder, 2007	Low back pain	+
	Manchikanti et al., 2009	Low back pain	+
	Campbell et al., 2013	Low back pain	#
	Leboeuf-Yde, 2004	Low back pain	-
	Kwon et al., 2011	Low back pain	#
	Ariens et al., 2001	Neck pain	+
	Manchikanti et al., 2009	Neck pain	+
	Hogg-Johnsons et al., 2008	Neck pain	+
	Cimmino et al., 2011	Chronic widespread pain	+

1.5.3.4 Alcohol consumption

Two reviews reported on the association between alcohol consumption and the onset of musculoskeletal pain (Table 1.16). The evidence from these reviews is mixed. One review reported an association between alcohol consumption and self-reported low back pain, but not in a dose-response relationship, and the association was not present when controlling for monozygotic twins who were discordant for alcohol consumption (Leboeuf-Yde, 2004). In another systematic review only one among 18 retrospective and longitudinal studies reported a clear association between alcohol consumption and low back pain (Ferreira, Pinheiro, Machado, & Ferreira, 2013). This suggests that the evidence that alcohol consumption is a factor associated with the onset of musculoskeletal pain is inconclusive. However, more research is needed to confirm that alcohol consumption does not contribute to the onset of musculoskeletal pain.

Table 1.16 Risk factors for musculoskeletal pain in adults – Alcohol consumption

Risk factor	Review	Pain site	Effect
Alcohol consumption	Leboeuf-Yde, 2004	Low back pain	#
	Ferreira et al., 2013	Low back pain	#

1.5.4 Summary of the risk factors for musculoskeletal pain in adults

In the previous sections the potential risk factors for the onset of musculoskeletal pain in adults have been described. According to the body of evidence from different reviews (whose conclusions may be partly based on findings reported from the same studies), there are some factors which seem to be predictive of the onset of musculoskeletal pain in adults. These factors are female gender, higher age, ethnicity, physical and mechanical factors, psychological factors, sleep problems and previous history of musculoskeletal pain or the presence of musculoskeletal pain in other body sites. Other factors have less conclusive support and therefore further research is needed to clarify how socioeconomic status, physical activity, smoking, obesity, familial and genetic factors, work-related factors and alcohol consumption potentially influence the onset of musculoskeletal pain. In the next section the rationale for investigating musculoskeletal pain in children and adolescents is outlined, followed by a description of prevalence and incidence figures for musculoskeletal pain in children and adolescents.

1.6 Rationale for investigating musculoskeletal pain in children and adolescents

The nature and understanding of musculoskeletal pain and how it is experienced has changed over time. In the past musculoskeletal pain has been understood as an episodic condition, the experience seen as discrete episodes of pain interceded by pain free periods, with these pain free periods reducing in frequency and length as chronicity takes hold (Axen & Leboeuf-Yde, 2013; Dunn, Hestbaek, & Cassidy, 2013). However a strong body of research that has investigated the course of musculoskeletal pain over time (using innovative statistical techniques such as latent class trajectories and latent class growth analysis) has emerged to show that, in adults, the patterns or trajectories of pain over time are relatively stable and not episodic in nature, for example people with high levels of pain severity are much more likely to have this trajectory over time compared to those with a low level of pain or no pain (Dunn, Jordan, & Croft, 2006; Dunn, Campbell, & Jordan, 2013; Lemeunier, Leboeuf-Yde, & Gagey, 2012). A recent systematic review identified eight articles that reported on the trajectories of low back pain (the most common musculoskeletal pain condition in adults), and showed that low back pain status at baseline was highly predictive of the trajectory of low back pain later in life (Lemeunier, Leboeuf-Yde, & Gagey, 2012). Specifically, individuals without low back pain at baseline were more likely to be free of low back pain at follow-up, whereas the opposite was found for those with pain at baseline. When movement to other trajectory groups occurred (e.g. movement of an individual from one pain trajectory classification to another), it was towards neighbouring groups in terms of pain intensity or frequency rather than an episodic “pain to pain free”, or vice versa, over time (Lemeunier et al., 2012). Giving more credence to the stability of pain trajectories, one recent study carried out a long term trajectory analysis over a period of 7 years in those who had consulted for back pain in primary care. The study was completed in two parts, in the first part pain trajectories were calculated using latent class analysis over a period of 6 months (using monthly measures of pain intensity), and four trajectories were identified; individuals with persistent severe pain, with fluctuating pain, with mild persistent pain, and no pain. The cohort was followed up 7 years later

and again trajectories calculated over a period of 6 months (monthly measures), and the findings show that the majority of individuals remained within their original trajectory cluster with little evidence of movement. Only 11% of individuals moved to groups of a different severity of pain (fluctuating group), thus suggesting that the pattern of episodic pain, and even increasing pain or recovering pain is not common (Dunn, Jordan, et al., 2006; Dunn, Campbell, et al., 2013). Given the growing evidence that adult pain patterns are relatively stable over time, raises the question of when might these stable patterns actually begin? One study (Dunn, Jordan, Mancl, Drangsholt, & Le Resche, 2011) considered if stability is found in a younger population. They carried out a trajectory study in adolescents (monthly measures over a period of 3 years) and the findings show some distinct differences in trajectory clusters compared to the findings in adult populations. In line with findings in adults, trajectories were identified for persistent pain, fluctuating pain, persistent mild pain and no pain, however there was also evidence of "emerging" trajectories in this age group (i.e. trajectories of increasing pain, low to high to low pain, and those of recovering pain), suggesting perhaps the starting points for trajectory development and that the origins of long term musculoskeletal pain trajectories may begin in childhood and adolescence (Dunn et al., 2011; Dunn, Hestbaek, et al., 2013). Further support for this hypothesis has come from other prospective studies, which showed that musculoskeletal pain in adolescence is predictive of musculoskeletal pain in adulthood (Brattberg, 2004; Harreby, Neergaard, Hesselsôe, & Kjer, 1995; Hestbaek, Leboeuf-Yde, Kyvik, & Manniche, 2006). As the evidence base for the emergence of "pain trajectories" within children and adolescents has grown, there is an ever increasing need to understand the beginnings of pain, and what factors are involved in these beginnings (i.e. risk factors). One drawback within research of these beginnings in adult populations is the actual identification of "first ever" musculoskeletal pain. As outlined above, musculoskeletal pain is very common, and in adults there is high likelihood that individuals have experienced periods of pain before. This prior experience of pain may shape how they respond to future pain (e.g. maladaptive coping, fear-avoidance behaviour, psychological distress), making the identification

of incident risk factors difficult. It may be that the way in which we respond to pain in early life sets the model to how we might respond as adults. Therefore, there is a need to understand the factors involved in the prediction of musculoskeletal pain onset in children and adolescents, as this potentially reduces the chance of the influence of previous experience of musculoskeletal pain. Such information on incident risk factors can then be used to give greater understanding to the forming of long term pain trajectories in adulthood. This information could then help develop appropriate interventions designed for groups of children/adolescents at high risk of long term pain, potentially averting significant individual and societal burden. Another advantage to the study of musculoskeletal pain onset in children and adolescents is the opportunity to compare differences in risk factors to those in adults, this may also reveal specific and important factors unique to children and adolescents. In the following section, estimates of the prevalence and incidence of musculoskeletal pain in children and adolescents are described.

1.7 Musculoskeletal pain in children and adolescents

In this section, estimates reported in several reviews regarding the prevalence (Section 1.7.1) and incidence (Section 1.7.2) of musculoskeletal pain in children and adolescents, are presented.

1.7.1 Prevalence of musculoskeletal pain in children and adolescents

Estimates of the prevalence of musculoskeletal pain are reported in Table 1.17. As can be seen within Table 1.17 there is a wide range of estimates dependent on pain type, body site, time-frame and in what population, which creates considerable heterogeneity. Taking the evidence together around 1-2% of children and adolescents have chronic disabling pain, with a higher level (up to 50% of those referring to primary care) for recurrent pain. In addition, Table 1.17 shows that low back (1-year prevalence 33%, range 4-51%) and neck pain (1-year prevalence range 15.8-71.5%) are the most prevalent. Lower rates were reported for limb pain (2 - 24%), chronic widespread pain (7.5%) and fibromyalgia which was estimated to have the lowest prevalence (≤ 3%). In addition, the period of sharp increase in prevalence rates of musculoskeletal pain seems to be between the age of 12 and 15 (Hill & Keating, 2009), and by the age of 18 the prevalence values are similar to those reported in adults (Jeffries, Milanese, & Grimmer-Somers, 2007).

Table 1.17 Prevalence of musculoskeletal pain in children and adolescents

Study	Period	Site	Figure
Clinch & Eccleston, 2009	-	Chronic disabling pain	1-2%
Holm et al., 2012	-	Pain >3 months	87% [A]
		Pain >12 months	48% [A]
		Recurrent pain	50% [A]
King et al., 2011	-	Musculoskeletal pain	4-40%
De Inocencio, 2004	-	Musculoskeletal pain	1.6-11.2% [A]

[A] Percentage of children among those who referred to primary care for musculoskeletal pain
[B] Rates for 100 encounters due to musculoskeletal pain

Table 1.17 Prevalence of musculoskeletal pain in children and adolescents			
Study	**Period**	**Site**	**Figure**
Hoy et al., 2012	-	Low back pain	20-30%
McBeth & Jones, 2007	-	Low back pain	8-44%
Calvo-Muñoz et al., 2013	Lifetime	Low back pain	39.9%
	1-year	Low back pain	33.6%
	1-week	Low back pain	17.7%
	Point	Low back pain	12%
Louw et al., 2007	Lifetime	Low back pain	36% (range 28-52%)
	1-year	Low back pain	33% (range 14-51%)
	Point	Low back pain	12% (range 10-14%)
Garcia et al., 2014	-	Low back pain	19.5%
Jeffries et al., 2007	Lifetime	Low back pain	7-72%
	1-year	Low back pain	7-50.8%
	1-month	Low back pain	9.8-36%
	1-week	Low back pain	9.5-35%
	Point	Low back pain	1-38.5%
Johansson et al., 2017	1-month	Mid back pain	13-35%
	1-month	Low back pain	4-36%
Hill & Keating, 2009	Lifetime	Low back pain	9-60%
	1-year	Low back pain	4-48%
	Point	Low back pain	1-49%
Henschke et al., 2015	1-month	Low back pain	9.8-36.0%
King et al., 2011	1-month	Chronic Back pain	18-24%
Fuglkjaer et al., 2017	1-year	Lower limb pain	5.8-10.9%
	1-week	Lower limb pain	4.1-19%
Smith et al., 2014		Lower limb pain	24%
Henschke et al., 2014		Lower limb pain	1.72-5.33% (boys) [B]
		Lower limb pain	1.85-4.40% (girls) [B]
Fuglkjaer et al., 2017	1-year	Upper limb pain	4.8-5.1%
	1-week	Upper limb pain	0.5-7%
Henschke et al., 2014		Upper limb pain	1.30-4.55% (boys) [B]
		Upper limb pain	1.38-3.26% (girls) [B]
Henschke et al., 2014		Spine/trunk pain	0.63-2.91% (boys) [B]
		Spine/trunk pain	0.60-2.06% (girls) [B]
Briggs et al., 2009	Lifetime	Thoracic/spine pain	15.6–19.5%
	1-year	Thoracic/spine pain	4.2–9.7%
	Point	Thoracic/spine pain	4-41%
Manchikanti et al., 2009	1-year	Neck pain	34.5-71.5%
Fejer et al., 2006	1-year	Neck pain	15.8-22.1%
	6-month	Neck pain	6-45%
	1-month	Neck pain	6.9%
Hogg-Johnsons et al., 2008	1-year	Neck pain	34.5-71.5%
	1-month	Neck pain	4.5-8.5%
	1-week	Neck pain	8%
Jeffries et al., 2007	Lifetime	Neck pain	3-21%
Johansson et al., 2017	1-month	Neck pain	5-15%
Henschke et al., 2015	1-month	Multiple pain	16% (range 12.1-35.7%)
Mourão et al., 2010	-	Chronic widespread pain	7.5%
Mourão et al., 2010	-	Fibromyalgia	0.1-3.2%
Gran, 2003	-	Fibromyalgia	1.2%
[A] Percentage of children among those who referred to primary care for musculoskeletal pain [B] Rates for 100 encounters due to musculoskeletal pain			

1.7.2 Incidence of musculoskeletal pain in children and adolescents

Compared to estimates of prevalence, less information is available in the literature about the incidence of musculoskeletal pain in children and adolescents. Eight reviews highlight evidence of 1-year incidence for general musculoskeletal pain (38%), low back pain (figures ranging from 11.8% to 33%), upper back pain (6%-35%), mid back pain (49.8%, 2-year incidence), lower limb pain (16%), upper limb pain (13.3%), neck pain (21-28%) and chronic widespread pain (7.7%) (see Table 1.18). The wide variance in the estimates reported is due to the difference in body sites considered, case definition used and number of studies included in the reviews.

Table 1.18 Incidence of musculoskeletal pain in children and adolescents

Study	Period	Site	Figure
McBeth & Jones, 2007	1-year	Musculoskeletal pain	38%
Hill & Keating, 2009	1-year	Low back pain	15-23%
Henschke et al., 2015	1-year	Low back pain	11.8-33%
McBeth & Jones, 2007	1-year	Low back pain	17.2%
Jeffries et al., 2007	1-year	Low back pain	11.8-33%
Briggs at al., 2009	1-year	Upper Back pain	6.7-35.3%
Johansson et al., 2017	2-year	Mid back pain	49.8%
	3-month	Mid back pain	3.5-3.9%
Fuglkjaer et al., 2017	1-year	Lower limb pain	16%
Fuglkjaer et al., 2017	1-year	Upper limb pain	13.3%
Jeffries et al., 2007	1-year	Neck pain	28.4%
Hogg-Johnsons et al., 2008	1-year	Neck pain	21.3%
McBeth & Jones, 2007	1-year	Chronic widespread pain	7.7%

1.7.3 Summary of musculoskeletal pain research in children and adolescents

Overall estimates of the prevalence and incidence of musculoskeletal pain in children and adolescents show how common pain is and that actually the proportion of older children and adolescents who experience musculoskeletal pain approaches the values reported for adults. This is supported by the literature that reported a sharp increase in prevalence rates of musculoskeletal pain in young populations between the age of 12 and 15 (Hill & Keating, 2009), with prevalence values reaching adult levels by the age of 18 (Dissing et al., 2017; Jeffries et al., 2007). As discussed in Section 1.6 above, there is a need for more research on musculoskeletal pain in young populations, firstly because children and adolescents should not be regarded as "small adults", but as a population with different physiology and psychosocial development, who may therefore have differences in susceptibility to the effects of risk factors compared to adults or indeed have specific and unique risk factors not generally experienced by adults (Hestbaek, Leboeuf-Yde, & Kyvik, 2006). Secondly because the identification of unique risk factors within child and adolescent populations may help to understand the nature of the onset of musculoskeletal pain that then leads to the development of high risk for adult musculoskeletal pain. However, while research carried out in adult populations on the risk factors for the onset of musculoskeletal pain is extensive, as outlined previously in this chapter (Section 1.5), currently little is known about potential risk factors for the onset of musculoskeletal pain in children and adolescents (at the time of writing this thesis). Therefore, a comprehensive systematic review on the risk factors for the onset of musculoskeletal pain in children and adolescents was performed, which is outlined in the next chapter.

Chapter two. Systematic review on the risk factors for the onset of musculoskeletal pain in children and adolescents

2.1 Introduction

As described in chapter 1 (Section 1.6), there is a need to understand factors that predict musculoskeletal pain onset in children and adolescents, and the reasons are many: children and adolescents are a distinct population different from adults, musculoskeletal pain in children and adolescents is common, there is a paucity of existing literature in this population, children and adolescents are less likely to have a history of musculoskeletal pain compared to adults (and therefore be less likely to be influenced by previous pain), patterns of pain (trajectories) over time appear different and potentially are emerging within the child and adolescent period, and that childhood and adolescent pain is linked to later adulthood pain. Whilst previous reviews on the risk factors for the onset of musculoskeletal pain in children and adolescents have been published (Jones & Macfarlane, 2005; King et al., 2011; Lardon, Leboeuf-Yde, Le Scanff, & Wedderkopp, 2014; Leboeuf-Yde, 2004; Manchikanti et al., 2009; McBeth & Jones, 2007; Paulis, Silva, Koes, & Van Middelkoop, 2014; Prins, Crous, & Louw, 2008; Shiri et al., 2010b; Sitthipornvorakul, Janwantanakul, Purepong, Pensri, & Van Der Beek, 2011), the focus of these previous reviews has been limited and restricted. For example, these reviews have not provided a broad scope of risk factors across a range of musculoskeletal conditions. They have focused only on specific risk factors such as puberty, obesity, smoking or physical activity, or they focused only on specific body sites (e.g. low back pain). Consequently, no review has been carried out on a broad range of potential risk factors for the onset of musculoskeletal pain across a range of body sites. This chapter aims to systematically review up-to-date evidence of published literature on the risk factors for musculoskeletal pain in children and adolescents. A description of the methods used to carry out the systematic review together with the results, the discussion of the results, and a

comparison with previous reviews is outlined in the following sections. As part of the development of this review chapter, it was decided to conduct a separate systematic review (using the same methodology as this chapter) with a narrowed focus on the relationship of sleep problems with musculoskeletal pain onset in children and adolescents. This review was recently published (Andreucci, Campbell, & Dunn, 2017) and a copy of the paper can be found in appendix I.

2.2 Materials and Methods

2.2.1 Inclusion criteria

Articles meeting the inclusion criteria were considered regardless of the language of publication, publication status and date of publication in order to reduce the risk of publication bias. Translations of articles were attempted whenever possible (in particular of articles published in German). The inclusion criteria regarding the study population, outcomes, setting and study design are described below.

2.2.1.1 Study population

Studies had to report on individuals aged from 6 to 19 years old. This age range was chosen because the age of six has been reported to be the starting point for children to use the word "pain" (Stanford, Chambers, & Craig, 2005; von Baeyer, 2006) and children younger than 5 years of age have a tendency to use only the extremes of the scales used to assess pain (Stinson, Kavanagh, Yamada, Gill, & Stevens, 2006; von Baeyer, 2006). The age of nineteen was chosen as this is defined as the start of adulthood by the WHO (http://www.who.int/hiv/pub/guidelines/arv2013/intro/keyterms/en/).

2.2.1.2 Outcomes

Studies had to report data on musculoskeletal pain presence as the outcome. No limitations in terms of dimensions and characteristics of musculoskeletal pain were applied (i.e. articles reporting on musculoskeletal pain in any body site and of any duration and severity were included). The use of any type of self-reported pain measure was eligible.

2.2.1.3 Setting

The studies had to be conducted in the general population, school or primary care setting as the aetiology of musculoskeletal pain from specific conditions treated in secondary care (e.g. juvenile idiopathic arthritis, cancer pain) is likely to be different.

2.2.1.4 Study design

To be included studies had to employ prospective cohort designs. These study designs are the most suitable to identify the onset of musculoskeletal pain compared to other study designs where confidence of temporal causality is reduced (i.e. cross-sectional studies).

2.2.2 Exclusion criteria

The following exclusion criteria were applied:

- Studies with a sample size ≤30. Studies with low sample sizes are less likely to provide reliable (precise) estimates, less likely to identify potentially important associations with statistical significance, and may be more likely to be subject to reporting bias (Hennekens & Buring, 1987).
- Studies conducted in populations composed of only adult individuals, since the research question focused on individuals aged 6 - 19. Studies on populations composed of both adults and children, when separate data from children could be retrieved, were included. If data on children were not shown, the study was excluded.
- Studies where the pain was not self-reported by the children but it was reported by the parents, as a difference in the reporting of musculoskeletal pain between parents and children has been observed (Haraldstad, Sørum, Eide, Natvig, & Helseth, 2011; Sundblad, Saartok, & Engström, 2006).
- Randomized controlled trials were excluded, since the primary focus is on the effectiveness of one or more interventions, and the risk of musculoskeletal pain onset in the absence of preventative intervention may not be reported. Moreover, randomized controlled trials often employ stringent selection criteria which can compromise generalizability.
- Studies of populations with specific diseases or conditions where pain was assessed and reported but was a result of the disease or underlying condition (e.g. cancer pain).
- Studies where translation was not possible.

2.2.3 Data Sources and Searches

The search was carried out by using the OVID interface. The OVID interface includes the following databases (accessed on the 20th of November 2014, further updated on the 8th of November 2016 for the published review (Andreucci et al., 2017)):

- Medline
- PsycINFO
- EMBASE
- AMED
- HMIC

For each database a combination of specific keywords relating to "children", "musculoskeletal problems" and "risk factors" was used (Please see appendix II for a full breakdown of search terms).

2.2.4 Study selection

Potentially eligible studies were those who reported data on the risk factors for the onset of new episodes of musculoskeletal pain in children and adolescents. Searches were carried out and the number of references from each database was recorded and references were imported into "Refworks" a reference management database. A number of stages were used to select studies to the review. The first stage of selection of the articles concerned only the screening of the titles. Articles were rejected for inclusion if they clearly showed no relation to the inclusion criteria based on the title (e.g. non pain study, study on adults). The second stage involved the screening of abstracts, and articles were rejected if they showed no relation to the inclusion criteria based on information provided on the abstract (e.g. study that was not prospective in design or age at follow-up was over 19 years old). Then the full-text of articles were examined for eligibility. The

number of articles remaining after each stage was recorded. Each phase was carried out by one reviewer (Alessandro Andreucci) and sub-samples (20%) were cross-checked (Paul Campbell) for consistency. Any disagreements were resolved through consensus meetings mediated by a third reviewer (Kate M Dunn). Finally, all articles that met the inclusion criteria were included for data extraction and analysis.

2.2.5 Data extraction

From each paper, data were extracted by Alessandro Andreucci and a random sub-sample (20%) of articles was cross-checked with Paul Campbell. The extraction was performed by using a data extraction form created by Alessandro Andreucci in Microsoft Excel, using the headings shown in Table 2.1.

Table 2.1 Data extraction form
Item
Article title
Authors
Date
Country
Aim of the study
Study design
Study setting
Inclusion/exclusion criteria of the study
Recruitment procedures used
N° of participants
Age range
Sex ratio
Ethnicity
Response rate
Information about non-responders
Pain definition
Pain location
Exposures analyzed
Questionnaire used
Prevalence
Incidence
Length of follow-up
Statistical analyses
Results
Conclusions
Notes

2.2.6 Quality assessment

There is no agreed gold standard quality assessment tool for observational studies, and a wide array of measures exist within the literature (Mallen, Peat, & Croft, 2006; Shamliyan, Kane, & Dickinson, 2010). A measure was chosen that encompasses the main components of study quality and the assessment of risk of bias, and is based on previous reviews with a similar focus to this current review, i.e. prospective cohort studies, focusing on musculoskeletal pain (Mallen, Peat, Thomas, Dunn, & Croft, 2007; Shraim, Mallen, & Dunn, 2013). The quality assessment tool included 15 items relative to both internal and external validity (Mallen et al., 2007; Shraim et al., 2013). The criteria that composed the quality assessment tool are shown in Table 2.2. Each item was scored positive (+) if it was found as satisfactorily presented and valid, negative (–) if absent, or (na) if it was found as not applicable. A point was given if the item was positive, while in the other two cases no one point was given. It follows that the highest possible score was 15. The quality of the articles was rated as 'high' if 11-15 items were fulfilled; 'moderate' if 6-10 items were fulfilled, and 'low' if 1-5 or no items were fulfilled, following methodology used previously (Shraim, 2013). The quality of each paper was assessed by Alessandro Andreucci and sub-samples (20%) were cross-checked with Paul Campbell for consistency.

Table 2.2 Quality assessment checklist
Item
A. Clearly defined study objective
B. Appropriate design for study question
C. Inclusion and exclusion criteria clear and appropriate
D. Representative sample (and comparison)
E. Sample size calculation presented
F. Appropriate selection of outcome
G. Appropriate measurement of outcome
H. Standardised collection of data
I. Adequate length of follow-up for research question
J. Baseline participation >70% (all groups)
K. Losses and dropouts <20%
L. Adequate description of losses and completers
M. Appropriate analysis of outcomes measured
N. Numerical description of important outcomes given
O. Adjusted and unadjusted calculations provided (with confidence interval if appropriate)

2.2.7 Evidence Synthesis

To increase confidence in the assumption of causality a number of factors (e.g. consistency of evidence, temporality, dose-response, theoretical plausibility, size of effect) were considered following previous guidance (Bhopal, 2002). For example, the choice of prospective design gives greater confidence in the temporal relationship, and another key factor is the consistency of evidence, and whether the evidence is at risk of bias. To assess the strength of evidence a "levels of evidence" approach was used following previous methodology (see Table 2.3, references of previous use (Campbell et al., 2011; Licht-Strunk, van der Windt, van Marwijk, de Haan, & Beekman, 2007)). The levels of evidence assessment considers the consistency of the reported associations for each risk factor, and also gives greater weighting to findings of higher quality and lower risk of bias. As Table 2.3 outlines, the strength of evidence was determined by the consistency of findings and the quality of the evidence. In addition, a best evidence approach was used, where only high quality studies were included. This approach allowed to assess if the consistency and direction of associations between risk factors and musculoskeletal pain onset reported in studies with a low risk of bias (based on the study quality assessment) were similar to evidence from all eligible studies. Whilst a statistical assessment of evidence for each risk factor would be additionally informative (e.g. meta-analysis), inspection of the extracted data showed high levels of heterogeneity in terms of the measurements for the risk factors and musculoskeletal pain, and therefore a meta-analysis was not performed.

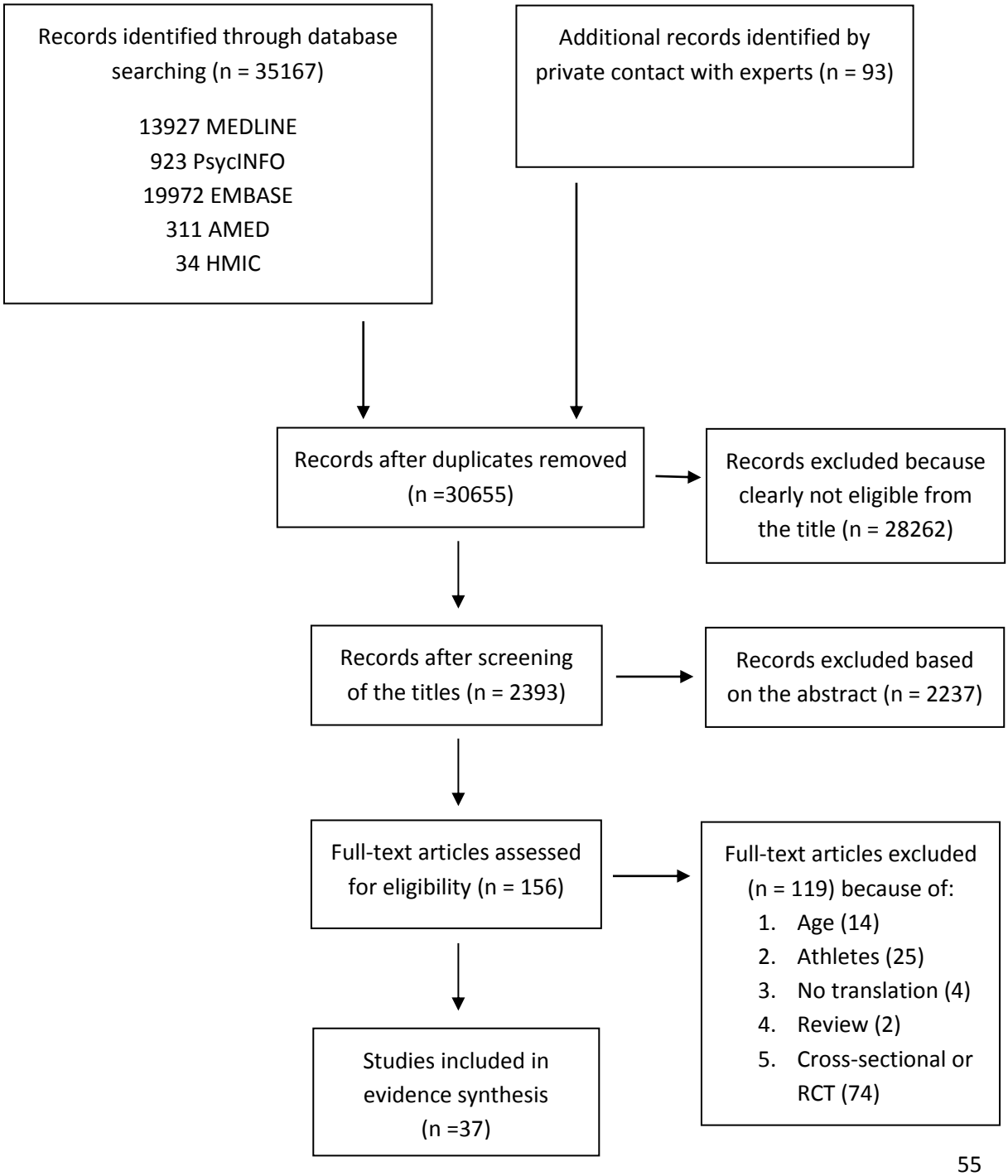
Table 2.3 Levels of evidence for association of risk factors and musculoskeletal pain	
Level of evidence	
Statistical significant associations	
Strong	Consistent associations found in at least two high quality studies
Moderate	Consistent associations found in one high quality study and at least one medium or two low quality studies
Weak	Associations found in at least two medium or three low quality studies
Inconclusive	Associations found in less than three medium/low quality studies
Inconsistent	Inconsistent findings irrespective of study quality
Associations without statistical significance	
Inconclusive	Weak, non-significant associations found in at least two studies
Insufficient	Only one study available, presenting a weak non-statistical association, irrespective of study quality

2.3 Results

2.3.1 Selection of the studies

The search strategy identified more than 35,000 publications across all 5 databases. The selection procedure finally resulted in the selection of 37 studies meeting the eligibility criteria (Figure 2.1).

Figure 2.1 Flowchart showing the process of selection of the studies



2.3.2 Study Characteristics

Included studies were from 13 different countries and the study populations ranged from 76 to 2951 individuals. The samples were recruited from schools or school settings in 22 studies and from the general population in 16 articles (one study reported information about 2 cohorts of children, of which one was recruited at school and another one from general population). Not one study was based in a primary care setting. Some cohorts were reported in more than one article. A cohort of Canadian high school students was reported in 5 studies (Feldman, Rossignol, Shrier, & Abenhaim, 1999; Feldman, Shrier, Rossignol, & Abenhaim, 2001, 2002a, 2002b; Shrier, Ehrmann-Feldman, Rossignol, & Abenhaim, 2001). Two English studies (Harrison, Wilson, & Munafo, 2014; Tobias, Deere, Palmer, Clark, & Clinch, 2013) reported data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Two other studies (Jones, Silman, & Macfarlane, 2003; Jones, Watson, Silman, Symmons, & Macfarlane, 2003) reported data from a cohort of children of Northwest England. Finally, 6 studies were drawn from the Northern Finland Birth Cohort (Auvinen et al., 2010; Jussila et al., 2014; Mikkonen et al., 2008, 2012, 2013; Paananen et al., 2010) while 4 studies were drawn from a cohort in southern Finland (El-Metwally, Salminen, Auvinen, MacFarlane, & Mikkelsson, 2007; Mikkelsson et al., 2008; Mikkelsson, Sourander, Salminen, Kautiainen, & Piha, 1999; Ståhl et al., 2008).

2.3.3 Methodological Quality

Twenty-six articles (70%) out of 37 were defined as high quality and 11 (30%) as medium quality. All the studies reported a clearly defined objective (Quality indicator A). Moreover, in all the studies the collection of data was standardized (Quality indicator H) and the outcome was selected appropriately (Quality indicator F) and the length of follow-up was adequate (e.g. Quality indicator I). However, more variability was found for other quality indicators. One of these was the study design (Quality indicator B), with 1 study using a case-control design nested within a prospective cohort study, and 4 studies in which musculoskeletal pain was assessed only at follow-up (i.e. no assessment of the presence of pain at baseline). In 7 (19%) articles the inclusion/exclusion criteria (Quality indicator C) were not clear and appropriate or were not reported at all. In 4 studies (11%) the sample was not representative (Quality indicator D), being composed of only males, being a case-control subsample or a selective subsample of the initial cohort. Only 2 studies (5%) reported a sample size calculation (Quality indicator E). In 2 studies (5%) the outcome was considered as not appropriately measured (Quality indicator G). In 18 studies (49%) the criteria "baseline participation >70%" (Quality indicator J) was not met or no information was present. In 20 studies (54%) the criteria "losses and dropouts <20%" (Quality indicator K) was not met or no information was present. In addition, in 16 (43%) articles those lost to follow-up and completers were not described adequately or no information was provided (Quality indicator L). Six (16%) studies did not meet the criteria "appropriate analysis of outcomes measured" (Quality indicator M), as information on the analysis performed was not described clearly, or only univariable analysis was carried out, or the comparison group also included children with musculoskeletal pain at baseline. In 6 (16%) articles there was no information on the effect of the risk factors on outcome (i.e. effect size of result) (Quality indicator N), only a descriptive of the level of statistical significance (yes/no) of the association was provided. Finally, 5 (14%) studies reported only unadjusted analyses. The average total score of the studies was 11.54 (score range 7 – 14).

2.4 Overall findings

The results for potential risk factors for the onset of musculoskeletal pain were grouped in eight domains based on the extracted data:

- Anthropometric measures (BMI, High growth spurt and other anthropometric features)
- Psychological domain (Conduct problems, depression and other psychological variables)
- Sleep (Quantity and quality of sleep)
- Day-time tiredness
- Physical activity (Amount of physical activity and type of physical activity)
- Sedentary activity (Watching TV, playing computer and other kind of sedentary activities)
- Smoking (Being a regular smoker and number of cigarettes smoked)
- Other risk factors (Puberty, parental pain and alcohol consumption)

A description of the results for each domain is provided below.

2.4.1 Anthropometric measures

The anthropometric measures domain includes different subdomains that are further described below:

- Body Mass Index (BMI)
- High growth spurt
- Other anthropometric measures

2.4.1.1 Body Mass Index (BMI) and musculoskeletal pain

Ten studies, of which 7 (70%) were of high quality and 3 (30%) of medium quality, reported on the association between BMI and onset of musculoskeletal pain (Table 2.4). Overall, one study reported a significant association, one reported an inconsistent association and eight no significant associations, indicating inconsistent evidence for the association of BMI with onset of musculoskeletal pain. When conducting the best evidence synthesis (i.e. including only high quality studies), one study reported an inconsistent association and six studies no significant associations. These findings suggest that current evidence indicates that it is unlikely that there is evidence for a strong or significant association between BMI and musculoskeletal pain onset.

Table 2.4 BMI and musculoskeletal pain

Study	Area of assessment	Association	Quality
Jones, Watson, et al., 2003	Back	x	High
Szpalski et al., 2002		+	Medium
Mikkonen et al., 2013		#	High
Nissinen et al., 1994		x	High
Salminen et al., 1995		x	Medium
Feldman et al., 2002a	Neck/upper limb	x	High
Brink et al., 2009		x	Medium
Feldman et al., 2002b	Musculoskeletal	x	High
Jussila et al., 2014		x	High
Paananen et al., 2010	Multisite	x	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.1.2 Height, high growth spurt and musculoskeletal pain

Overall, ten studies have described the relationship between height or high growth spurt and musculoskeletal pain (Table 2.5). Seven (70%) of these studies were of high quality while 3 (30%) were of medium quality. Three studies reported inconsistent association and 7 only reported non-significant associations with pain onset. The best evidence synthesis, which included only studies of high quality, again showed that 3 studies reported inconsistent associations and 4 reported only non-significant associations, resulting in inconsistent evidence for an association between height or high growth spurt and the onset of musculoskeletal pain. Given the direction of the evidence toward non significance, the conclusion is that an association is unlikely.

Table 2.5 Height, high growth spurt and musculoskeletal pain

Study	Area of assessment	Association	Quality
Feldman et al., 2001	Back	#	High
Janssens et al., 2011		x	High
Jones, Watson, et al., 2003		#	High
Salminen et al., 1995		x	Medium
Szpalski et al., 2002		x	Medium
Nissinen et al., 1994		#	High
Feldman et al., 2002a	Neck/upper limb	x	High
Brink et al., 2009		x	Medium
Shrier et al., 2001	Lower limb	x	High
Feldman et al., 2002b	Musculoskeletal	x	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.1.3 Other anthropometric measures and musculoskeletal pain

Overall, 17 studies explored the association between anthropometric characteristics and the onset of musculoskeletal pain (Table 2.6). Nine (53%) of these studies were of high quality and 8 (47%) of medium quality. Among the several anthropometric characteristics investigated, 9 significant findings, 10 inconsistent associations and 36 non-significant associations were reported. When using a best evidence synthesis, 2 significant associations, 3 inconsistent associations and 18 non-significant associations remain. No consistent evidence of association was found across the several anthropometric characteristics reported, and for each characteristic found as having an effect on musculoskeletal pain (i.e. low lumbar extension strength, disc degeneration, disc protrusion, Scheuermann-type changes, painful palpation of spinous processes, awkward trunk posture), the significant finding reported was from only one single study. Therefore, the strength of evidence of association found is limited. Considering where comparisons can be made across studies, the findings on joint hypermobility overall suggest inconsistent evidence of association, although some significant findings for specific body sites (i.e. shoulder, knee, ankle/foot) were reported in one study (Tobias et al., 2013).

Table 2.6 Other anthropometric measures and musculoskeletal pain				
Study	Measurement of exposure	Area of assessment	Association	Quality
Tobias et al., 2013	Joint hypermobility	Back	x	Medium
Sjolie et al., 2001	Low lumbar extension strength		+	High
	Lumbar mobility/ extension strength		#	
Burton et al., 1996	Lumbar sagittal flexibility		x	Medium
Feldman et al., 2001	Low Quadriceps flexibility		#	High
	Low Hamstrings flexibility		#	
	Low Sit-and-reach flexibility		x	
	Schober lumbar flexion		x	
	Abdominal strength		x	
Newcomer & Sinaki, 1996	Back strength		#	Medium
Salminen et al., 1995	Disc degeneration		+	Medium
	Disc protrusion		+	
	Muscular atrophy		x	
	Spinal mobility		x	
	Trunk muscle strength		x	
	Scheuermann-type changes		+	
Nissinen et al., 1994	Kyphosis		x	High
	Increase of kyphosis		x	
	Lordosis		x	
	Increase of lordosis		x	
	Hump size		#	
	Gain of hump size		x	
	Static profile of the spine		x	
Szpalski et al., 2002	Painful palpation of spine processes		+	Medium
	Awkward trunk posture		+	
Mikkonen et al., 2012	Sway Posture		#	High
Smith et al., 2008	Flat Posture		#	Medium
	Hyperlordotic Posture		#	
Ståhl et al., 2008	Joint hypermobility	Neck/upper limb	x	High
Tobias et al., 2013			x Neck x Upper arm + Shoulder	Medium
Brink et al., 2009	Head tilt angle		x	Medium
	Cervical angle		#	
	Shoulder pro- and retraction angle		x	
	Thoracic angle		x	
	Extreme cervical and thoracic angle		#	
Tobias et al., 2013	Joint hypermobility	Lower limb	x Lower leg x Hip x Thigh + Knee + Ankle foot	Medium
Shrier et al., 2001	Low flexibility		x lower limb x hip x knee x leg x ankle/foot	High
Tobias et al., 2013	Joint hypermobility	Wrist/hand Elbow	x x	Medium

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

Table 2.6 Other anthropometric measures and musculoskeletal pain				
Study	Measurement of exposure	Area of assessment	Association	Quality
El-Metwally et al., 2007	Joint hypermobility	Musculoskeletal	x	High
Tobias et al., 2013			x	Medium
Mikkelsson et al., 2008	Joint hypermobility	Multisite	x	High
Tobias et al., 2013			x	Medium
Mikkelsson et al., 1999	Tender point count		x	High
	Pain threshold		x	
+ significant association with musculoskeletal pain onset x no significant association # inconsistent association				

2.4.2 Psychological factors

2.4.2.1 Psychological factors and musculoskeletal pain

Seventeen articles concerning psychological risk factors were found and 13 (76%) were of high quality while 4 (24%) were of medium quality. Twenty significant associations, 10 inconsistent associations and 25 non-significant associations were reported for a range of psychological risk factors (Table 2.7). When only the studies of high quality were included, 10 significant associations, 10 inconsistent associations and 20 no significant associations were reported. Among the different psychological factors assessed, inconsistent evidence of association for the onset of musculoskeletal pain was found for depression (two significant associations, one inconsistent association and three non-significant associations), though the direction of effect did suggest a trend of increasing depression and musculoskeletal pain onset. Inconsistent evidence of association for the onset of musculoskeletal pain was found for anxiety (one inconsistent association and three non-significant associations). Similarly, evidence of association was inconsistent for stress or coping with stress (one inconsistent association and two non-significant associations), self-efficacy (one inconsistent association and one non-significant association), and for pain catastrophizing and somatosensory amplification (inconsistent associations from one high quality study). For child self-esteem, one high quality and one medium quality study reported three non-significant associations, indicating inconclusive evidence of association, although examination of the studies showed a trend of decreased likelihood for the onset of musculoskeletal pain with higher levels of self-esteem. For internalizing (i.e. anxiety, depressed mood) and externalizing symptoms (i.e. behavioural disorders, oppositional and conduct disorders), five high quality studies reported 4 significant associations, 2 inconsistent associations and one non-significant association across all body sites. Study results suggest that increasing levels of internalizing / externalizing symptoms are likely risk factors of the onset of musculoskeletal pain. Two studies of high quality reported on factors that can be included within the internalizing and externalizing psychological domain, such as conduct problems, hyperactivity,

emotional problems and peer problems. For conduct problems, two studies reported significant associations suggesting strong evidence of association between these potential risk factors and incident musculoskeletal pain, although both studies were drawn from the same cohort. For hyperactivity, emotional problems and peer problems the two high quality studies reported only non-significant associations (direction of association towards an increase likelihood for the onset of musculoskeletal pain), suggesting inconclusive evidence of association. A couple of studies reported on a range of psychological and behavioural factors. One medium quality study reported inconclusive evidence of association (increasing trend toward increased likelihood of musculoskeletal pain onset) for being bullied, reaction to bullying, fear of schoolmates, loneliness, difficulties to make friends, feeling of being an outsider, nervousness, difficulties verbalizing feelings and difficulties talking to mother or to father. Similarly one high quality study reported non-significant associations for satisfaction with life, critical life events, financial strain and playing time, and one inconsistent association (significant increased likelihood in girls, non-significant decreased likelihood in boys) for quarrelling in the family.

Table 2.7 Psychological factors and musculoskeletal pain				
Study	Measurement of exposure	Area of assessment	Association	Quality
Barke et al., 2014	Pain catastrophizing	Back	#	High
	Somatosensory amplification		#	
	Dysfunctional stress coping		#	
	Anxiety sensitivity		#	
Stanford et al., 2008	Anxiety/depression		x	Medium
Gill et al., 2014	Depression		#	High
	Internalizing/externalizing		#	
Larsson & Sund, 2007	Internalizing/externalizing		+	High
Jones, Watson, et al., 2003	Conduct problems		+	High
	Hyperactivity		x	
	Emotional problems		x	
	Peer problems		x	
	Prosocial behaviour		x	
Gill et al., 2014	Low perceived self-efficacy		#	High
Brattberg, 1994	Being bullied		+	Medium
	Passive reaction to bullying		+	
	Fear of schoolmates		+	
	Loneliness		+	
	Difficulties to make friends		+	
	Feeling of being an outsider		+	
	Nervousness		+	
	Difficulties verbalizing feelings		+	
	Difficulties talking to mother		+	
	Difficulties talking to father		+	
Szpalski et al., 2002	Mental health status		x	Medium
Stanford et al., 2008	Child self-esteem		x	Medium
Gill et al., 2014			x	High
Larrsson & Sund, 2007	Internalizing/externalizing	Limb	+	High
Shrier et al., 2001	Mental health status	Lower limb	+	High
Feldman et al., 2002a		Neck/upper limb	+	High
Brink et al., 2009	Depression		x	Medium
	Anxiety		x	
Gill et al., 2014	Depression		+	High
	Internalizing/externalizing		+	
	Low perceived self-efficacy		x	
	Child self-esteem		x	
El-Metwally et al., 2007	Depression	Musculoskeletal	x	High
Jussila et al., 2014	Internalizing/externalizing		+	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

Table 2.7 Psychological factors and musculoskeletal pain				
Study	Measurement of exposure	Area of assessment	Association	Quality
Kröner-Herwig et al., 2011	Satisfaction with life	Multisite	x	High
	Critical life events		x	
	School Stress		x	
	Financial strain		x	
	Playing time		x	
	Quarreling in the family		#	
	Dysfunctional stress coping		x	
	Anxiety sensitivity		x	
Mikkelsson et al., 2008	Depression		+	High
Mikkelsson et al., 1999	Depression		x	High
Kroner-Herwig et al., 2011	Internalizing/externalizing		#	High
Paananen et al., 2010	Internalizing/externalizing		x	High
Jones, Silman, et al., 2003	Conduct problems		+	High
	Hyperactivity		x	
	Emotional problems		x	
	Peer problems		x	
	Prosocial behaviour		#	
+ significant association with musculoskeletal pain onset x no significant association # inconsistent association				

2.4.3 Sleep

2.4.3.1 Sleep and musculoskeletal pain

The association between sleep patterns (both sleep quality and quantity) and the onset of musculoskeletal pain was assessed in ten studies, of which eight were of high and two of medium quality (Table 2.8). Overall two significant, five inconsistent and five non-significant associations were reported in the studies. When taking into consideration only the high quality studies, one significant, five inconsistent and four non-significant associations were reported. It should be noted that one of these studies (Auvinen et al., 2010) reported inconsistent associations in more than one body site. Seven studies reported two significant, one inconsistent and six non-significant associations for sleep quality, and direction of associations suggests that low sleep quality is associated with increased likelihood of the onset of musculoskeletal pain. Five studies reported one significant, two inconsistent and four non-significant associations for sleep quantity, and direction of association between sleep quantity and the onset of musculoskeletal pain was inconsistent. Overall the results suggest that the evidence of an association between both sleep quality or quantity and the onset of musculoskeletal pain is inconsistent. However, when pain site and sex is considered there was strong evidence of an association between low sleep quality and the onset of neck pain (in girls).

Table 2.8 Sleep and musculoskeletal pain

Study	Area of assessment	Association	Quality
Auvinen et al., 2010	Back	#	High
Szpalski et al., 2002	Back	x	Medium
Brattberg, 1994	Back	+	Medium
Auvinen et al., 2010	Neck	#	High
Ståhl et al., 2008	Neck	+	High
Auvinen et al., 2010	Shoulder	#	High
El-Metwally et al., 2007	Musculoskeletal	x	High
Jussila et al., 2014	Musculoskeletal	#	High
Mikkelson et al., 2008	Multisite	x	High
Mikkelsson et al., 1999	Multisite	x	High
Paananen et al., 2010	Multisite	x	High
Harrison et al., 2014	Multisite	#	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.4 Day-time tiredness

2.4.4.1 Day-time tiredness and musculoskeletal pain

The effect of day-time tiredness on the onset of musculoskeletal pain was assessed in 6 studies, of which 5 were of high quality (Table 2.9). Two significant associations, three inconsistent associations and three non-significant associations (two from a high quality and one from a medium quality study) were reported in the studies. Overall the evidence of association between day-time tiredness and musculoskeletal pain is inconsistent, although examination of the direction of associations reported in the studies showed an increased likelihood of the onset of musculoskeletal pain with increasing levels of day-time tiredness. In addition, strong evidence of association for the onset of neck pain in girls was reported, indicating a high likelihood of neck pain onset in girls reporting day-time tiredness.

Table 2.9 Day-time tiredness and musculoskeletal pain

Study	Area of assessment	Association	Quality
Szpalski et al., 2002	Back	x	Medium
Auvinen et al., 2010	Back	#	High
Ståhl et al., 2008	Neck	+	High
Auvinen et al., 2010	Neck	#	High
Auvinen et al., 2010	Shoulder	#	High
El-Metwally et al., 2007	Musculoskeletal	+	High
Mikkelsson et al., 2008	Multisite	x	High
Jones, Silman, et al., 2003	Multisite	x	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.5 Physical activity

2.4.5.1 Physical activity and musculoskeletal pain

The effect of physical activity on the onset of musculoskeletal pain was assessed in 20 studies, of which 14 (70%) were of high quality and 6 (30%) of medium quality (Table 2.10). Two significant associations, six inconsistent associations and 14 non-significant associations were reported in the studies. When looking at the best evidence (i.e. only the high quality studies), one significant association, four inconsistent associations and nine non-significant associations were reported. According to the levels of evidence used in this review, the evidence of association between physical activity and musculoskeletal pain is inconsistent overall. In addition, inspection of the direction of associations of studies showed inconsistent likelihood of the onset of musculoskeletal pain with increasing levels of physical activity (i.e. some studies showed an increase likelihood, while other studies showed a decrease likelihood). This, together with the high proportion of non-significant findings suggests that overall an association is unlikely.

Table 2.10 Physical activity and musculoskeletal pain

Study	Area of assessment	Association	Quality
Balagué et al., 2010	Back	+	Medium
Feldman et al., 2001		x	High
Jones, Watson et al., 2003		#	High
Salminen et al., 1995		x	Medium
Szpalski et al., 2002		x	Medium
Wedderkopp et al., 2009		#	Medium
Burton et al., 1996		#	Medium
Sjoile et al., 2001		+	High
Brattberg, 1994		x	Medium
El-Metwally et al., 2007	Musculoskeletal	#	High
Jussila et al., 2014		#	High
Feldman et al., 2002b		x	High
Sundblad et al., 2008		x	High
Kröner-Herwig et al., 2011	Multisite	x	High
Mikkelsson et al., 2008		x	High
Paananen et al., 2010		x	High
Wedderkopp et al., 2009		x	Medium
Jones, Silman, et al., 2003		#	High
Ståhl et al., 2008	Neck	x	High
Wedderkopp et al., 2009		x	Medium
Feldman et al, 2002a		x	High
Shrier et al., 2001	Lower limb	x	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.6 Sedentary activity

2.4.6.1 Sedentary activity and musculoskeletal pain

The association between sedentary activity and musculoskeletal pain was explored in 9 studies, of which 7 were of high and 2 of medium quality (Table 2.11). Nine associations were reported in the studies, of which one was significant, two were inconsistent associations and six were non-significant associations. Both the significant and the inconsistent associations were from high quality studies, while two out of six of the non-significant associations were from medium quality studies. Overall the evidence of association between sedentary activity and musculoskeletal pain in the different body sites is inconsistent, and inspection of the direction of association is also inconsistent (i.e. studies showed both an increased likelihood and a decreased likelihood for the onset of musculoskeletal pain).

Table 2.11 Sedentary activity and musculoskeletal pain

Study	Area of assessment	Association	Quality
Jones, Watson, et al., 2003	Back	x	High
Szpalski et al., 2002		x	Medium
Sjolie et al., 2001		x	High
Brink et al., 2009	Upper quadrant	x	Medium
Jussila et al., 2014	Musculoskeletal	#	High
Sundblad et al., 2008		+	High
Paananen et al., 2010	Multisite	x	High
Jones, Silman et al., 2003		x	High
Kröner-Herwig et al., 2011		#	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.4.7 Smoking

2.4.7.1 Smoking and musculoskeletal pain

The association between smoking and the onset of musculoskeletal pain was assessed in 10 studies of which nine were of high quality and one of medium quality (Table 2.12). Overall one significant association, four inconsistent associations and eight non-significant associations were reported in the studies. The best evidence synthesis (i.e. using only the high quality studies), showed four inconsistent associations and eight non-significant associations. Noteworthy, five studies were drawn from the same cohort (Feldman et al., 1999, 2001, 2002a, 2002b; Shrier et al., 2001); two of these studies reported inconsistent associations for the onset of back pain (Feldman et al., 1999, 2001), while the three other studies reported non-significant associations for neck/upper limb pain, lower limb pain and musculoskeletal pain (Feldman et al., 2002a, 2002b; Shrier et al., 2001). One of these studies (Feldman et al., 1999) reported on multiple body sites (back pain, neck/upper limb pain, lower limb pain). According to the levels of evidence used in this review, the association between smoking and the onset of musculoskeletal pain is inconsistent. Further inspection of the direction of associations of the studies showed a trend for increased likelihood of the onset of musculoskeletal pain in smokers compared to non-smokers, but with different results between genders (i.e. increased likelihood in girls, inconsistent in boys) in the only study where analysis were stratified by levels of cigarette smoking (Mikkonen et al., 2008). Overall these findings suggest that there is no evidence for an important or significant association between smoking and the onset of musculoskeletal pain.

Table 2.12 Smoking and musculoskeletal pain			
Study	Area of assessment	Association	Quality
Feldman et al., 2001	Back	#	High
Feldman et al., 1999	Back	#	High
Gill et al., 2014	Back	#	High
Mikkonen et al., 2008	Back	#	High
Brattberg, 1994	Back	+	Medium
Feldman et al., 2002a	Neck/Upper limb	x	High
Gill et al., 2014	Neck/Upper limb	x	High
Feldman et al., 1999	Neck/Upper limb	x	High
Feldman et al., 1999	Lower limb	x	High
Shrier et al., 2001	Lower limb	x	High
Feldman et al., 2002b	Musculoskeletal	x	High
Jussila et al., 2014	Musculoskeletal	x	High
Paananen et al., 2010	Multisite	x	High
+ significant association with musculoskeletal pain onset x no significant association # inconsistent association			

2.4.8 Other risk factors

2.4.8.1 Other risk factors and musculoskeletal pain

Five articles reported on the association between other risk factors such as puberty, parental pain, or alcohol consumption and the onset of musculoskeletal pain (Table 2.13). One study of high quality reported a statistically significant association between pubertal status and back pain in a cohort of American and Dutch children, resulting in inconclusive evidence according to the levels of evidence used. Three articles of medium quality reported one significant association, one inconsistent association and one non-significant association between parental pain and the onset of musculoskeletal pain, and the evidence of association is therefore inconsistent. One high quality study reported an inconsistent association between alcohol consumption and the onset of musculoskeletal pain, the evidence of association with the onset of musculoskeletal pain is therefore inconsistent.

Table 2.13 Other risk factors and musculoskeletal pain

Study	Measurement of exposure	Area of assessment	Association	Quality
Janssens et al., 2011	Pubertal status	Back	+	High
Szpalski et al., 2002	Parental pain		x	Medium
Brattberg, 1994			#	Medium
Balagué et al., 2010			+	Medium
Jussila et al., 2014	Alcohol consumption	Musculoskeletal	#	High

+ significant association with musculoskeletal pain onset
x no significant association
inconsistent association

2.5 Discussion

2.5.1 Summary of main findings

The aim of this systematic review was to identify potential risk factors for the onset of musculoskeletal pain in children and adolescents. Thirty-seven studies, of which 26 (70%) were assessed at being of high quality and 11 (30%) of medium quality were identified, reported on children and adolescents from 13 different countries (study population range 76 - 2951 individuals). In summary, none of the factors identified were supported by consistent, high quality evidence of a statistically significant association across the range of body sites according to the best evidence synthesis. However, there was evidence of statistically significant and potentially important associations when considering sub populations based on body site location and individual characteristics (e.g. sex). For example, there was a strong evidence of an association between low quality of sleep and day-time tiredness and the onset of neck pain, although this finding was only in girls. Furthermore, there was a consistent evidence for an association between conduct problems and the onset of musculoskeletal pain, although this evidence was based on two studies drawn from the same cohort. With regard to psychological factors (i.e. internalizing and externalizing symptoms), the evidence of association with the onset of musculoskeletal pain was inconsistent overall. However, inspection of the direction of associations of the studies suggest that increasing levels of internalizing and externalizing symptoms are likely risk factors for the onset of musculoskeletal pain. The evidence reported for both sleep problems and internalizing and externalizing symptoms is also supported by the proportion of significant and mixed findings found across the body sites (7/12 significant and mixed findings for sleep problems, 6/7 for internalizing and externalizing symptoms), although this did not result in an overall consistent evidence of association using the levels of evidence criteria. Regarding other potential risk factors assessed, no consistent evidence of association was found for any of the

body sites when examined singularly, and the proportion of significant and mixed findings were lower and therefore less consistent.

2.5.2 Comparison with other reviews

As mentioned in section 2.1 a number of systematic reviews have been carried out previously, however the individual focus of these previous reviews was narrower than the broad aims of this review. In addition, two other recent reviews that report information on risk factors for the onset of musculoskeletal pain in children and adolescents have since been published (Huguet et al., 2016; Kamper, Henschke, Hestbaek, Dunn, & Williams, 2016). Evidence from these reviews was integrated in the discussion for completeness.

2.5.2.1 Anthropometric measures

Findings relative to anthropometric measures were reported in three reviews. Two reviews reported an association between anthropometric factors (i.e. disc degeneration, upper lumbar pathology, muscular tightness) and back pain (Kamper, Henschke et al., 2016; Leboeuf-Yde, 2004), which is consistent with the findings for these specific anthropometric factors reported in this systematic review. Another review reported no evidence of association between joint hypermobility and the onset of musculoskeletal pain (Huguet et al., 2016) and this fits with the majority of evidence found in this review. Three reviews reported inconsistent evidence of association between taller height or high growth spurt and the onset of musculoskeletal pain (Huguet et al., 2016; Jones & Macfarlane, 2005; Kamper, Henschke et al., 2016). This is in accordance with the inconsistent evidence of association found in this systematic review, although the majority of the findings in this review were non-significant. Four reviews report that BMI is not prospectively associated with the onset of musculoskeletal pain (Huguet et al., 2016; Jones & Macfarlane, 2005; Kamper, Henschke et al., 2016; Paulis et al., 2014), and one reports

that the association between BMI and low back pain was not present in a dose-response relationship and was not observed in monozygotic twins (Leboeuf-Yde, 2004). This in accordance with results of this systematic review and seems to confirm that BMI is not a risk factor for the onset of musculoskeletal pain in children and adolescents.

2.5.2.2 Psychological factors

A number of reviews (Huguet et al., 2016; Jones & Macfarlane, 2005; Kamper, Henschke et al., 2016; King et al., 2011; McBeth & Jones, 2007; Prins et al., 2008) reported on the association between various psychological factors and the onset of musculoskeletal pain. Overall, evidence from these reviews is in line with results of this systematic review, which reported several significant findings for the association between psychological factors and the onset of musculoskeletal pain. Specifically, psychological factors such as internalizing and externalizing symptoms were found to be likely associated with the onset of musculoskeletal pain in children and adolescents.

2.5.2.3 Sleep

One recent review (Kamper, Henschke et al., 2016) reported that sleep problems are predictive of musculoskeletal pain onset, although this evidence came from only one study (Auvinen et al., 2010), which was also identified and included within this systematic review. The addition of other studies within this systematic review showed a greater level of inconsistency, although strong evidence for certain subgroups and body locations was found (i.e. neck pain in girls). This overall inconsistency may be explained by heterogeneity across studies in pain locations and measures used for both sleep and musculoskeletal pain, which makes the comparison of associations less clear, and suggests that there is a need for more research specifically focused on sleep as a risk factor for musculoskeletal pain in children. As mentioned at the beginning of this chapter a

subsequent systematic review was carried out by me and my supervisors, the findings of this review suggest that there is no general support that sleep factors are associated with musculoskeletal pain onset, however (as outlined in this chapter) some evidence exists for certain musculoskeletal body areas at higher risk and that some sub groups (e.g. gender) may be more at risk, therefore more empirical research is required (Andreucci et al., 2017).

2.5.2.4 Physical activity

Five reviews reported on the effect of physical activity on musculoskeletal pain. Three reviews did not identify any prospective evidence for an association (Jones & Macfarlane, 2005; Kamper, Henschke et al., 2016; Sitthipornvorakul et al., 2011). Differently, a review reported inconsistent evidence of association between physical activity and the onset of back pain, but included studies also on young adults and athletes (Huguet et al., 2016). Another review reported inconsistent results when physical activity was self-reported, but no association when physical activity was evaluated with an objective measurement (Leboeuf-Yde, 2004). Overall these results are in line with the results found by this systematic review, where most findings were inconsistent or non-significant and inspection of the direction of associations showed inconsistency in the likelihood of the onset of musculoskeletal pain with increasing levels of physical activity. This may be explained by the differences in measures used to assess physical activity and is in agreement with the proposed j-shaped relationship between physical activity and musculoskeletal pain (i.e. moderate levels of physical activity may be protective, but high levels of physical activity may increase the likelihood of musculoskeletal pain) (Jones & Macfarlane, 2005).

2.5.2.5 Sedentary activity

In accordance with the results of this systematic review, two reviews (Jones & Macfarlane, 2005; Kamper, Henschke et al., 2016) reported no evidence of prospective association between high levels of sedentary activity and musculoskeletal pain.

2.5.2.6 Smoking

Three reviews report an association between being a regular smoker and the onset of back pain or musculoskeletal pain (Huguet et al., 2016; Kamper, Henschke et al., 2016; Shiri et al., 2010b). This is in contrast with the results of this systematic review, which found inconsistent associations for back pain onset, but non-significant associations for other body sites. The association between smoking and musculoskeletal pain may be attributable to other factors such genetic components (Leboeuf-Yde, 2004), or smoking may be a marker of other factors such as psychological problems or unhealthy behaviours (e.g. sleep problems, lack of physical activity), which may be responsible for the onset of musculoskeletal pain (Mikkonen et al., 2008).

2.5.2.7 Pubertal status

A review reported on a link between being in a more advanced pubertal status and back pain onset, which may be due to the hormonal change that occur during puberty (Lardon, Leboeuf-Yde, Le Scanff, & Wedderkopp, 2014). However the majority of studies identified in that review were cross-sectional, and only one study was prospective (Janssens et al., 2011). This prospective study was also included in this current systematic review, and the results from that study showed that those adolescents who were in a more advanced pubertal status at baseline were at an increased likelihood for the onset of back pain (Janssens et al., 2011). In conclusion the evidence of pubertal status as a risk factor for musculoskeletal pain onset is currently inconclusive, but this finding suggests that puberty may be a risk factor for the onset of back pain and therefore more research is needed on this factor.

2.5.2.8 Alcohol consumption

A review by Leboeuf-Yde has reported evidence for an association between alcohol consumption and the onset of back pain in adolescents, which did not show a dose-relationship trend though and was not present when assessed in monozygotic twins. This suggests that the association found may explained by other unknown factors, and therefore alcohol is unlikely a risk factor for back pain (Leboeuf-Yde, 2004). In this systematic review inconsistent results were found in one study for the association between alcohol consumption and musculoskeletal pain onset, with a significant increased likelihood of musculoskeletal pain onset in girls but not in boys.

2.5.3 Strengths and weaknesses of this systematic review

2.5.3.1 Search strategy and selecting studies

There are several strengths of this systematic review. First, in order to include the widest range of literature, five databases were systematically searched without any language or time restrictions, which led to the identification of a higher number of prospective cohort studies as compared to other systematic reviews within the literature. Second, this systematic review covered a broader range of risk factors and body sites, a much broader scope compared to other systematic reviews. Third, to obtain the best evidence on the risk factors for the onset of musculoskeletal pain, only prospective cohort studies were included. This choice of study design enables a more confident estimate of incidence of the onset of musculoskeletal pain and the temporal sequence between the risk factor and musculoskeletal pain. In addition, the risk of recall bias when measuring exposure to risk factors, that is large with retrospective or case–control studies, is minimized with the use of prospective cohort studies (Delgado-Rodriguez & Llorca, 2004). However, there are also some limitations. First, despite the comprehensive search strategy used, none of the identified studies was carried out in South America, Africa, or Asia, therefore results of this systematic review may be not generalizable to these different social/cultural environments. Second, language bias is another potential limitation because papers in a language different from English are less likely to be published or be within the databases searched (grey literature). Whilst no language restrictions were applied in this systematic review, so for example three papers produced in German were translated (they did not meet the inclusion criteria), four additional papers were excluded (one paper in Swedish, one paper in Norwegian, one paper in Czech, one paper in Finnish) due to unavailability of translators. In addition, studies that do not find evidence of risk are less likely to be published and, whilst the reference lists of the included papers were searched for further published literature, alternative sources such as registers for unpublished studies and databases for PhD theses were not explored. Also, a meta-analysis of study findings was not possible, due to the high heterogeneity in definitions used in the included studies for

both the risk factors and musculoskeletal pain (e.g. presence, frequency, time period), which also limited comparability. Finally, not one of the studies identified within this systematic review was carried out in a primary care setting, which signifies the lack of knowledge on risk factors for the onset of musculoskeletal pain for children and adolescents who specifically seek healthcare.

2.5.3.2 Evidence synthesis and quality appraisal

The review made use of a previously published approach to defining levels of evidence, allowing conclusions to be systematically based both on results found and on the quality of studies. The use of numerical thresholds to define study quality helped to distinguish between studies providing low versus high quality evidence for the association between potential risk factors and the onset of musculoskeletal pain. However, an acknowledged limitation of the use of a total score for study quality is that it can obscure major flaws that are assessed by one criterion only, and key elements of bias are weighted in the same way as other aspects of study quality that do not indicate bias. For example low response rate is scored in the same way as failure to report a power calculation, clearly the latter being less impactful on the assessment of quality and bias (Shamliyan, Kane, & Dickinson, 2010). However, some important flaws were identified in the quality assessment process. For example, in the studies where musculoskeletal pain was assessed only at follow-up it was not possible to know if the subjects already had musculoskeletal pain at inception of the study. This then limits the inference of causality, and may have affected (confounded) the estimates reported, leading to an overestimation of the association found. In addition, in some studies the criteria for appropriate analysis of outcomes measured was not met or only unadjusted analyses were performed. This may have led to an overestimation of the association found compared to the estimate of the true association, because part of the effect may be due to other factors. In studies where the criteria “baseline participation >70%” and “losses and dropouts <20%” was not met, non-response bias or attrition bias may have occurred if

there was a difference in characteristics between those who participated and those who did not, or those who completed the study at follow-up and those who did not (Delgado-Rodriguez & Llorca, 2004). The use of levels of evidence to assess the strength of evidence for a risk factor had other limitations. For example, if one study reported findings relative to different levels of exposure to a risk factor, with more than one significant finding for different levels of that exposure but a non-significant finding for another level of the exposure, then the association would be regarded as mixed. In addition, if only one non-significant association from one study was present along with a number of significant findings from some studies, then the evidence of association would be regarded as inconsistent. Consequently, those factors that were investigated by fewer studies, or for which analyses were not stratified by levels of exposure, would be more likely to be assessed as having a strong evidence of association if significant findings were reported. To overcome this potential limitation, the overall proportion of significant and mixed findings vs. non-significant findings was taken into consideration, as well as the use of a best evidence synthesis that only considered high quality studies, and the inspection of the direction of associations. Another limitation is that if more than one study drawn from the same cohort report findings for the same body site, then the same result would be counted more than one time in terms of the overall count. This was the case for the evidence of association between smoking and the onset of back pain for example, as two articles reported findings drawn from the same cohort (Feldman et al., 1999, 2001), and between smoking and the onset of neck/upper limb pain (Feldman et al., 1999, 2002a). However, this limitation was taken into consideration and discussed in the evaluation of evidence (Section 2.4.7.1), and in review of the evidence and conclusions reported, the exclusion of one of the two studies would not have changed the evidence of associations. Finally, studies with a smaller sample size are more likely to have high variability in findings (i.e. low precision), and the detection of a statistically significant effect would not be possible without a sufficient sample size (Hennekens & Buring, 1987). Therefore, it may be possible that true associations were not detected because studies were underpowered, although

attempts were made to overcome this by only including studies with sample sizes above 30 participants.

2.5.4 Potential risk factors identified within the review and implications for my thesis

In the light of the findings (consistency of evidence) reported in this systematic review, two risk factors were identified that require further investigation. These two factors are: sleep (i.e. sleep problems), and psychological (i.e. internalizing and externalizing) symptoms. The rationale for investigation of these two risk factors is outlined below, including the description of further additional criteria that support the selection of these risk factors, such as consistency with research conducted in adults, theoretical plausibility, and evidence of dose-response identified in some studies included in the review, which taken together may indicate potential for causation.

2.5.4.1 Sleep problems

Sleep problems in children and adolescents are common, as between 25% and 40% experience at least one type of sleep problem during childhood and adolescence (Dosi, Figura, Ferri, & Bruni, 2015; Meltzer, Plaufcan, Thomas, & Mindell, 2014). Strong evidence of association for the onset of neck pain in children with low sleep quality (although only in girls) was found in this systematic review. Also, a larger proportion of studies reported significant or inconsistent findings rather than non-significant findings with trends showing an elevated level of risk, suggesting an element of consistency overall and specifically consistency for neck pain. In addition, in terms of coherence with the wider literature there is evidence in support of this hypothesis from studies carried out in adult populations where evidence of risk is more established (Gupta et al., 2007; McBeth, Lacey, & Wilkie, 2014; Mork & Nilsen, 2012; Onen, Alloui, Gross, Eschallier, & Dubray, 2001). There is also theoretical plausibility with evidence of potential mechanisms that may explain the association between sleep and musculoskeletal pain, as introduced in Section 1.5.1.8. For

example increased production of cytokine and inflammatory mediators has been observed in individuals with sleep problems, moreover sleep problems may increase muscular tension, potentially leading to musculoskeletal pain. In addition, studies within the systematic review that explored the effect of increasing levels of sleep problems showed a dose-response pattern of association with musculoskeletal pain (Auvinen et al., 2010; Harrison et al., 2014). This underlines that there is a need to systematically investigate the association between sleep quality and the onset of musculoskeletal pain in children.

2.5.4.2 Psychological symptoms

The 1-year prevalence of psychological symptoms in childhood and adolescence is 25% (Merikangas, Nakamura, & Kessler, 2009). Most of the studies within the review conceptualised psychological and behavioural problems within the domains of externalizing symptoms and internalizing symptoms. These domains represent a conceptualised discrimination in children and adolescents (Forns, Abad, & Kirchner, 2011) between problems that are outer-directed (e.g. behavioural actions, conduct disorders) which affect the surrounding environment (externalizing) and distress related problems (anxiety, depressed mood) which are inner directed (internalizing). Hereafter I will refer to psychological problems within these domains which have been shown to be common during childhood and more so adolescence (Corley, Beltz, Wadsworth, & Berenbaum, 2015; Downing & Bellis, 2009; Graber, 2013; Pinyerd & Zipf, 2005). A high number of significant and inconsistent findings for internalizing and externalizing symptoms (trends showing increased odds) were reported in this systematic review, together with strong evidence of an association of conduct problems (which are part of the externalizing symptoms construct) with pain. This suggests that internalizing and externalizing symptoms may potentially be linked with the onset of musculoskeletal pain. In support of this, a body of research in adults suggests that psychological factors are predictive of the onset of musculoskeletal pain (Gupta et al., 2007; McBeth & Jones,

2007; Pinheiro et al., 2015; Taylor et al., 2014). In addition, a dose-response association with musculoskeletal pain was reported in studies within the systematic review that explored the effect of increasing levels of factors pertaining to the internalizing and externalizing constructs (Jones, Silman, et al., 2003; Jones, Watson, et al., 2003). This PhD study will investigate if specific psychological and behavioural problems such as internalizing and externalizing symptoms are predictive of the onset of musculoskeletal pain in adolescents.

2.6 Summary

This chapter has outlined the design and results of a systematic review on risk factors for the onset of musculoskeletal pain in children and adolescents. In the following chapter the aim and specific objectives of this thesis will be outlined.

Chapter three. Aim and objectives of the PhD

3.1 Aim

The overall aim of this thesis is to identify potential risk factors for the onset of musculoskeletal pain in children and adolescents from the current literature (Chapter 2), and where appropriate to do so (i.e. factors identified as requiring further investigation), generate hypotheses and test those hypotheses using existing cohort data.

3.2 Specific objectives

Two potential risk factors for the onset of musculoskeletal pain in children and adolescents were identified in the systematic review performed within this thesis (Section 2.4): the presence of sleep problems and the presence of psychological symptoms. This evidence has led to the development of the objectives that are investigated within this thesis, as outlined below.

Specific objectives addressed are:

1. To investigate whether sleep problems are a risk factor for the onset of musculoskeletal pain in children.
2. To investigate whether psychological symptoms are risk factors for the onset of musculoskeletal pain in adolescents.
3. To investigate whether sleep problems and psychological symptoms are associated with consultation for musculoskeletal pain in children and adolescents within a primary care setting.

The rationale for the investigation of objectives 1 and 2 has been outlined in Section 2.5.4. In the following sections each of the research objectives are explained in more detail, including the factors selected as potential confounders and for testing for potential effect modification.

3.3 Objective number 1 - Investigation of sleep problems as a risk factor for the onset of musculoskeletal pain in children

The aim of the investigation of this objective is to investigate the association between sleep problems and the onset of musculoskeletal pain in children in more detail. Informed by the results of the systematic review (chapter 2) and additional research in adults, the selection of potential confounders to be included in the analysis (Section 3.3.1) and the variables explored for effect modification (Section 3.3.2) will be justified below.

3.3.1 Selection of potential confounders

Analysis of the association between sleep problems and the onset of musculoskeletal pain may be subject to influence from potential confounders. Previous studies have indicated that low levels of physical activity may be associated with low sleep quality (Aguilar, Vergara, Velasquez, & Garcia-Hermoso, 2015) and may also be predictive of the onset of musculoskeletal pain (Wedderkopp, Kjaer, Hestbaek, Korsholm, & Leboeuf-Yde, 2009). Psychological symptoms are associated with sleep problems (i.e. the association between sleep problems and depression is bidirectional) (Campbell, Tang, et al., 2013; Coulombe, Reid, Boyle, & Racine, 2011; Pieters et al., 2014) as well as with the onset of musculoskeletal pain in children (Jones, Silman, et al., 2003; Jones, Watson, et al., 2003; Jussila et al., 2014). Therefore analysis will be adjusted for these potential confounders.

3.3.2 Rationale for investigating effect modification

Potential effect modifiers of the association between sleep and musculoskeletal pain in children were identified. The rationale for the investigation of potential modification effect is described below.

3.3.2.1 Gender

Literature clearly shows gender differences in the rates of sleep problems and reports of pain; adult females report poorer sleep quality and more pain than males (Fillingim, 2000; Mallampalli & Carter, 2014; Zhang & Wing, 2006), boys are more likely than girls to have sleep problems or receive a diagnosis for sleep disorders (Archbold, Pituch, Panahi, & Chervin, 2002; Meltzer, Johnson, Crosette, Ramos, & Mindell, 2010), girls may become at increased risk of sleep problems compared to boys after the beginning of puberty (Bonvanie et al., 2016; Knutson, 2005). Thus, while it is clear that gender differences are present, it is still not clear which gender is potentially at higher risk for both sleep problems and musculoskeletal pain, and whether differences between genders change at different life stages (e.g. puberty). Two of the studies identified within the review explored gender differences in the association between sleep problems and musculoskeletal pain. Results suggest that low sleep quality is predictive of the onset of neck pain in girls, but not in boys (Section 2.4.3.1). However, one of these studies focused on individuals of an older age range (16-18 years old) (Auvinen et al., 2010), and the other study (Ståhl et al., 2008) included a sleep measure that was part of a broader assessment that included other psychosomatic symptoms, which may have biased their reported results. Therefore, further investigation is needed to assess potential gender effects on the association between sleep and musculoskeletal pain.

3.3.2.2 Puberty

Puberty and pubertal status may modify the association between sleep and musculoskeletal pain. During puberty a change in the secretion of hormones (i.e. melatonin) and in the circadian regulation system occurs, which affects the sleep-wake pattern, and may cause sleep problems (Carskadon & Tarokh, 2014; Dahl & Lewin, 2002). Furthermore, changes in the psychosocial context occur during pubertal development that can affect the sleep of children. This includes a change in bedtime routine and sleep duration, the increased use of technology in bed, and engagement in social activities later in the evening all of which can disrupt sleep patterns (Carskadon & Tarokh, 2014; Carskadon, 2011). In addition, as shown in the systematic review an association between advanced pubertal stage and musculoskeletal pain was reported (Section 2.5.2.7). Based on this evidence it is reasonable to hypothesize that the association between sleep problems and musculoskeletal pain may be modified by pubertal status, with a stronger association expected for later pubertal stages compared to pre-pubertal children.

3.3.2.3 Screen time

Another potential modifier of the association between sleep and musculoskeletal pain is screen time. Children are commonly exposed to high levels of artificial lights through computers, televisions and smartphones (Hale & Guan, 2015). This exposure to screen time is suspected to influence sleep patterns by decreasing the secretion of melatonin necessary for falling asleep (Aguilar et al., 2015; Hale & Guan, 2015; Higuchi, Motohashi, Liu, & Maeda, 2005), and as outlined for pubertal effects in the above section, this screen time behaviour may increase with age. Therefore, it may be postulated that the association between sleep problems and musculoskeletal pain is modified by the levels of exposure to screen time, with the association expected to be stronger in those reporting increasing levels of screen time.

3.4 Objective number 2 - Investigation of psychological symptoms as a risk factor for the onset of musculoskeletal pain in adolescents

The aim of this objective is to further investigate the association between psychological symptoms and the onset of musculoskeletal pain in adolescents, taking account of the influence of potential confounders and exploring potential effect modification by the same factors as introduced in section 3.3.2. The selection of potential confounders (Section 3.4.1) and justification of potential effect modifiers (Section 3.4.2) is outlined below.

3.4.1 Selection of potential confounders

The association between psychological symptoms and the onset of musculoskeletal pain may be confounded by several factors. Psychological symptoms are associated with cigarette use and substance use (Colder et al., 2013; King, Iacono, & McGue, 2004). In addition, several associations between smoking and back pain onset were reported in the studies identified within the review (Brattberg, 1994; Feldman et al., 1999, 2001; Gill, Davis, Smith, & Straker, 2014; Mikkonen et al., 2008). Sleep problems are also associated with psychological symptoms in adolescence (Campbell, Tang, et al., 2013; Coulombe et al., 2011; Pieters et al., 2014) and may be predictive of the onset of musculoskeletal pain (Section 2.4.3). Similarly, low levels of physical activity may be predictive of the onset of musculoskeletal pain (Wedderkopp et al., 2009). In addition, physically inactive adolescents are at higher risk of psychological symptoms compared to normally active individuals (Monshouwer, Have, van Poppel, Kemper, & Vollebergh, 2013). Therefore, potential confounders that will be considered within the analysis of the association between psychological symptoms and the onset of musculoskeletal pain will be smoking, marijuana use, drug use, physical activity, and the presence of sleep problems.

3.4.2 Rationale for investigating effect modification

Potential effect modifiers of the association between psychological symptoms and musculoskeletal pain were identified. Rationale for testing the potential effect modification is described below.

3.4.2.1 Gender

Literature reports the presence of a gender imbalance on the prevalence of psychological symptoms, with higher risk of internalizing symptoms in girls and of externalizing symptoms in boys (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004; Merikangas et al., 2009). Studies identified within the systematic review showed mixed evidence for gender in the association between psychological symptoms and the onset of musculoskeletal pain. Further analysis is therefore required to investigate the influence of gender on the association between psychological symptoms and onset of musculoskeletal pain.

3.4.2.2 Puberty

Pubertal timing is linked to the development of psychological symptoms in adolescents, as those who develop earlier or later compared to their peers are at higher risk of psychological symptoms (Graber, 2013; Kaltiala-Heino, Marttunen, Rantanen, & Rimpela, 2003; Mendle, 2014). In addition, being in a more advanced pubertal stage is suspected to be linked with musculoskeletal pain (Janssens et al., 2011; Lardon et al., 2014). It is therefore reasonable to hypothesize a difference in the association between psychological factors and the onset of musculoskeletal pain depending on the pubertal timing of adolescents. Accordingly, the potential effect modification of puberty on this association will be assessed.

3.4.2.3 Screen time

High levels of screen time are associated with psychological symptoms such as depression, anxiety, emotional and behavioural problems (Cao et al., 2011; Kremer et al., 2014; Mundy, Canterford, Olds, Allen, & Patton, 2017; Wu, Tao, Zhang, Zhang, & Tao, 2015). Thus, it may be postulated that the association between psychological symptoms and the onset of musculoskeletal pain is modified by the levels of exposure to screen time, with higher odds in those individuals with increased levels of screen time. This will be assessed by investigating the potential effect modification of screen time.

3.5 Objective number 3 - Investigation of sleep problems and psychological symptoms as risk factors for the onset of musculoskeletal pain in children and adolescents within a primary care setting

The rationale for the investigation of objective number 1 (i.e. investigation of sleep problems as a risk factor for the onset of musculoskeletal pain in children) and objective number 2 (i.e. investigation of psychological symptoms as a risk factor for the onset of musculoskeletal pain in adolescents) has been outlined in section 2.5.4. In comparison to the body of evidence of research regarding the association between sleep problems, psychological symptoms and the onset of musculoskeletal pain in children and adolescents in general population samples, currently there is no research within primary care populations as shown in the systematic review. This is a substantial omission given that health care resources are directed here. Therefore, the investigation of sleep problems and psychological symptoms as risk factors for the onset of musculoskeletal pain will be replicated in a primary care dataset. The importance of investigating the objectives of this thesis in both general population and primary care datasets is outlined below.

3.5.1 Importance of investigating the objectives in both general population and primary care datasets

The analysis of the investigation of the objectives of this thesis will take place using two distinct populations. Firstly, analysis will be carried out in two general population samples (child and adolescents) (Childhood to Adolescence Transition Study and Avon Longitudinal Study of Parents and Children). The aim is for the results to be representative of the influence of the risk factors on musculoskeletal pain onset in children and adolescents in the general population. This approach is informative from a “public health” viewpoint where potential risk factors could be identified and changed at a population level (e.g. a public media campaign to reduce sleep problems via a reduction in screen time use to lower the risk of musculoskeletal pain onset). The second

approach will study these risk factors within a population of children and adolescents who seek healthcare both for the risk factors and musculoskeletal pain. Here the argument is more strongly related to the potential for intervention within a specific target population (e.g. children/ adolescents seeking healthcare for sleep problems or psychological symptoms). This dual approach addresses the concept termed the "iceberg of disease" theory. According to this theory, a disease may metaphorically be represented as an iceberg, where the cases that are recognized by the healthcare system are those at the tip of the iceberg, whereas the bottom of the iceberg represents the majority of cases, which are not detected by the healthcare system (Bhopal, 2002). Taking only one approach, either general or healthcare populations, may miss the fact that those who generally seek healthcare are more likely to have more severe symptoms and outcomes than those who do not consult (Bhopal, 2002; Campbell & Roland, 1996). The advantages of this dual strategy is that comparisons can be made between the two samples, which can generate greater understanding of the risk factors of musculoskeletal pain onset in specific groups of children and adolescents and point to individuals and groups who are at high risk. For example, analysis within general population samples may show different results regarding the strength of risk factors and the influence of effect modifiers. This may consequently have different implications for the potential for prevention or treatment. Certainly the evidence shows that despite the high proportion of sleep, psychological and behavioural problems reported by children and adolescents in the general population (Section 2.5.4.1 and 2.5.4.2), only 4% of children are actually given a diagnosis for sleep problems (Meltzer et al., 2010), and approximately only 10% of those with a mental health disorder are seen in a specialist mental health service (Kramer & Garralda, 2000). This appears to indicate a higher level of severity within the consultation and healthcare seeking population.

3.6 Thesis outline

In this section, a brief overview of the content of the following chapters is outlined.

- **Methods chapter (Chapter 4)**

  Within this chapter the choices related to study design, methods and approach to the analysis are described, together with a brief description of the datasets used for the analyses. An analysis plan will be presented for each objective.

- **The association of sleep problems with musculoskeletal pain onset in children: description of the Childhood to Adolescence Transition Study (CATS) cohort (Chapter 5)**

  Within this chapter a description of the CATS dataset together with the descriptive analysis of the CATS dataset is provided.

- **The association of sleep problems with musculoskeletal pain onset in children: results of the Childhood to Adolescence Transition Study (CATS) cohort (Chapter 6)**

  Within this chapter the results of the analysis of the association between sleep problems and the onset of musculoskeletal pain using data from the CATS cohort is provided together with a discussion of the results (thesis objective 1).

- **The association of psychological symptoms with musculoskeletal pain onset in adolescents: description of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Chapter 7)**

  Within this chapter a description of the ALSPAC dataset together with the descriptive analysis of the ALSPAC dataset is provided.

- **The association of psychological symptoms with musculoskeletal pain onset in adolescents: results of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Chapter 8)**

  Within this chapter the results of the analysis of the association between psychological symptoms and the onset of musculoskeletal pain using data from the ALSPAC cohort is provided together with a discussion of the results (thesis objective 2).

- **The association of sleep and psychological symptoms with musculoskeletal pain onset in children and adolescents in primary care: description of the Consultations in Primary Care Archive (CiPCA) cohort (Chapter 9)**

  Within this chapter a description of the CiPCA dataset together with the descriptive analysis of the CiPCA dataset is provided.

- **The association of sleep and psychological symptoms with musculoskeletal pain onset in children and adolescents in primary care: results of the Consultations in Primary Care Archive (CiPCA) cohort (Chapter 10)**

  Within this chapter the results of the analysis of the association of both sleep and psychological symptoms with new episodes of musculoskeletal pain consultation using data from CiPCA is presented together with a discussion of the results (thesis objective 3).

- **Discussion (Chapter 11)**

  In this chapter, a discussion and reflection upon the overall results of this thesis is outlined. Potential future implications resulting from the findings of this thesis are discussed.

3.7 Summary

In this chapter, the aims and objectives of this thesis have been outlined, along with a description of the confounders included in the analysis, and the rationale for investigating potential effect modifiers. The importance of using both general population datasets and a primary care dataset to investigate the objectives has been discussed. A description of the contents of the following chapters of the thesis has been provided. In the following chapter, a description of the methods that will be used to investigate the objectives of this thesis along with a brief description of the datasets that will be used for the investigation of each objective will be outlined.

Chapter four. Methods chapter

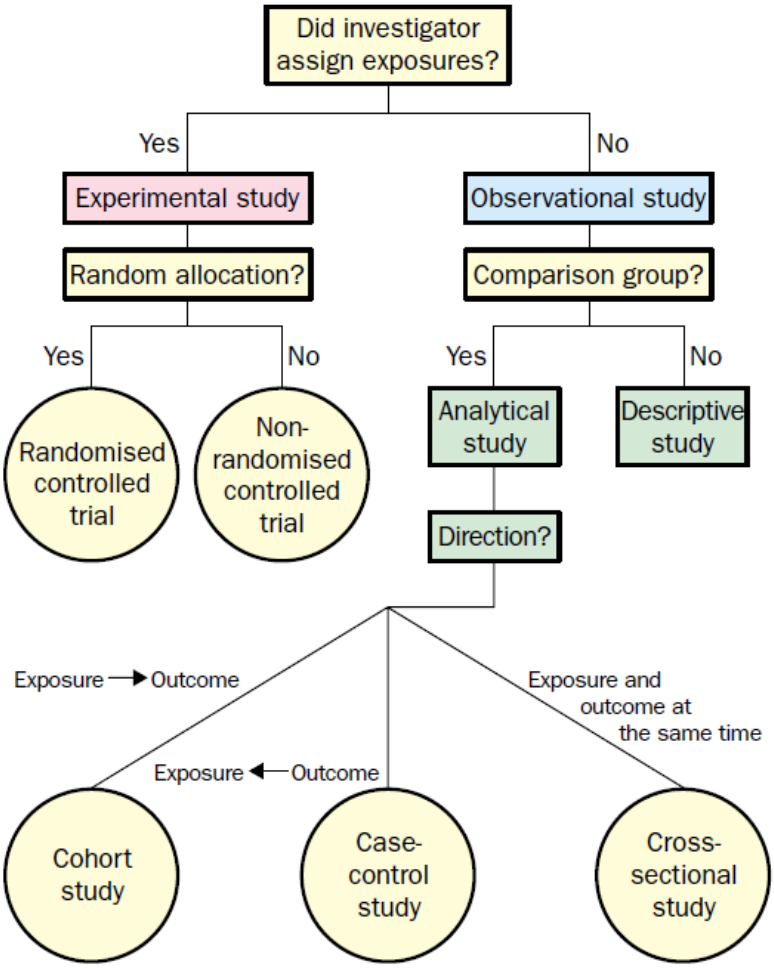
4.1 Introduction

This chapter outlines the rationale for the choice of research design and the analysis methods within this thesis. Justification will be provided for the design and analysis approaches taken in light of alternative methods. The chapter will briefly cover the range of designs used in epidemiological research (Section 4.2), reasons for the particular choice of datasets within this thesis (Section 4.3 - 4.4), as well as the analysis approach and the methods for assessment of missing data and potential risk of bias due to missing data (Section 4.5). Finally, the analysis plan for each research question is outlined (Section 4.6).

4.2 Available study designs for epidemiological studies

A range of study designs can be used within epidemiological research (please see Figure 4.1, from (Grimes & Schulz, 2002). These can be broadly classified as experimental or observational designs, depending on whether the exposure is assigned by the researcher or not, respectively (Grimes & Schulz, 2002). There are two types of experimental designs, depending on the way exposures have been allocated to participants: randomized controlled trials or non-randomised controlled trials. Observational designs can also be classified into two main categories, depending on the objective of the study: analytical and descriptive study designs. Analytical study designs are performed when the objective is to investigate an association between an exposure and outcome, while descriptive study designs are performed when the objective is to describe the exposure and the outcome. Analytical designs include case-control studies, cohort studies and cross-sectional studies (Grimes & Schulz, 2002).

Figure 4.1. Types of epidemiological studies



4.3 Suitable study design with regard to the aim of this thesis

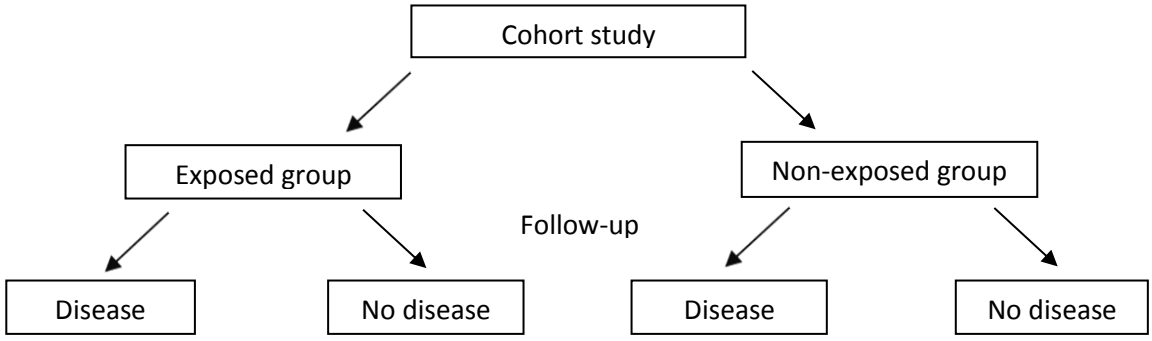
The aim of this thesis is to investigate risk factors for the onset (incidence) of musculoskeletal pain in children and adolescents identified from the general population or primary care consultation records (Section 3.1). This will be achieved by estimating both the incidence of musculoskeletal pain and the strength of association between exposure and outcome, which will be the main outcomes of the analyses included within the thesis. The incidence estimates the risk of onset of a condition (i.e. the new cases) within the population at risk in a specific period of time (Bhopal, 2002; Mourão et al., 2010). Therefore, in this thesis the incidence will be calculated as the number of new cases (i.e. those who report musculoskeletal pain at follow-up) among those at risk (i.e. those without musculoskeletal pain at baseline). Estimating incidence is important as this provides an indication of the risk of developing musculoskeletal pain within each of the samples included in this thesis. By comparing the incidence between those exposed and those unexposed to a certain risk factor, it is possible to determine which group is at higher risk of developing the disease and identify the potential causes of a disease (Bhopal, 2002). The strength of association is described through association measures (e.g. relative risk, odds ratio), which represent the ratio of the risk in those exposed compared to those unexposed to the risk factor (Bhopal, 2002). Given the aim of the thesis, which is to investigate the association between sleep problems, psychological symptoms and the onset of musculoskeletal pain, the analytical study design was considered the most suitable to address the thesis objectives. A description of analytical study designs, along with their strengths and limitations, and the reasons for selecting the cohort design are outlined in the following sections.

4.4 Description, strengths and limitations of study designs for investigating risk factors of disease onset

4.4.1 Cohort study design

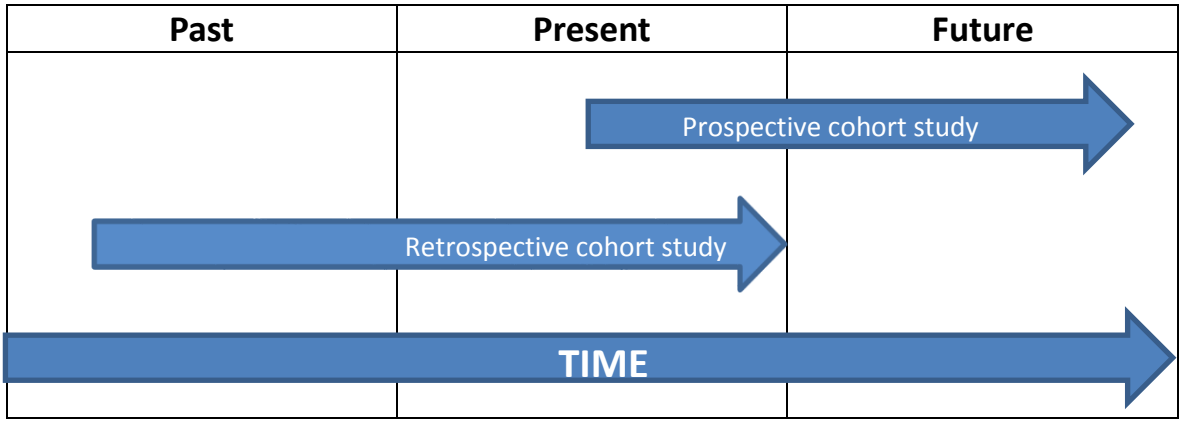
A cohort study design is where exposures to the risk factor of interest are measured in individuals still at risk of getting the disease (i.e. who are free from the disease at baseline), and individuals are classified depending on their exposure status. Subsequently, individuals are followed-up over time to observe who develops the disease, and the incidence of the disease between the exposure groups is compared (Grimes & Schulz, 2002) (see Figure 4.2). Cohort designs can be classified into two types: prospective cohort studies and retrospective cohort studies. In prospective cohort studies, the study population is defined prior to the occurrence of the outcome, exposures to risk factors are assessed and participants are prospectively followed up over time. Differently, in the retrospective cohort study both the outcome and the exposure have already occurred. The study population is defined retrospectively based on existing data, and exposures and outcome can be assessed at the same time (Hennekens & Buring, 1987) (Figure 4.3).

Figure 4.2. Cohort study[1]



[1] Exposures can be measured on categories that differ from the binary system represented in the figure such as categorical, ordinal or numerical/continuous scales

Figure 4.3. Prospective and retrospective cohort study



4.4.2 Case-control study design

The case-control study design also enables the investigation of an association between exposure and the outcome. However, differently from cohort studies, case-control studies start with the selection of the cases (i.e. those with the disease) who are matched to control individuals without the disease. When the cases and the controls are defined, then exposures to risk factors are measured retrospectively in time (Levin, 2006b).

4.4.3 Cross-sectional studies

The cross-sectional study design is a study design where both the exposure and the outcome are measured at the same point in time. This study design provides prevalence estimates and it is usually performed to give a description of the exposures and/or the outcome within a population (Levin, 2006a). However, this design can be also used to assess what factors are associated with an outcome but are not able to estimate risk (incidence of the outcome), and cannot establish whether the exposure occurred before the outcome (Hennekens & Buring, 1987).

4.4.4 Strengths and limitations of the analytical study designs

In the following section the strengths and limitations of the analytical study designs are outlined, including the different types of bias which can affect analytical study designs (described in Section 4.4.4.4). For example, studies may be affected by selection bias (i.e. the study population does not represent the source population) and information bias (i.e. bias in the measurement of the variable). In addition, the investigation of an association between a risk factor and outcome in epidemiological studies may be affected by the potential influence of confounding. A more detailed description of confounders is outlined in Section 4.5.3.

4.4.4.1 Cohort studies

Cohort studies (both prospective and retrospective studies) present several strengths. The first is that they enable estimation of the incidence of an outcome (for a definition please see Section 4.3). Another advantage is that with the cohort study design it is possible to determine the temporal sequence between the exposure and the outcome. This provides greater confidence regarding the inference of causality (i.e. the exposure is potentially causing the development of the outcome) over study designs that measure both the exposure and outcome at the same time (i.e. cross-sectional studies) (Grimes & Schulz, 2002; Hennekens & Buring, 1987). Also, with the cohort design participant enrolment can be based on the presence or absence of the exposure, which allows an accurate assessment of sample size for the analysis (i.e. enough individuals in both the exposed and non-exposed groups) (Hennekens & Buring, 1987). For this reason, cohort designs are suitable for the investigation of rare exposures. However, cohort studies also present some limitations, which can vary between prospective and retrospective cohort studies. A limitation of prospective cohort studies is cost and time, outcomes can take many years to occur, there is a need to ensure participants keep involved, and if the outcome is rare there is a need for large samples (Grimes & Schulz, 2002). Conversely, retrospective cohort designs are generally less

costly and less time-consuming than prospective cohort designs because all the information about exposures and outcome is already present. Indeed, routinely collected data (e.g. healthcare records, registers) are usually employed in retrospective studies, which allows the assessment of outcomes with a normally longer latency time compared to prospective cohort designs (Hennekens & Buring, 1987). The use of a retrospective design presents other limitations however. This design depends on available data (on past exposures as well as subsequent outcomes) from existing cohorts (for example, routinely collected healthcare data). Data are also likely to have been collected for purposes different from the one investigated, information regarding the variables of interest may be incomplete or lacking in comparison to a purposeful design cohort study (Hennekens & Buring, 1987).

4.4.4.2 Case-control studies

Case-control study designs present some strengths and limitations. Strengths of case-control designs are that they may be chosen when the outcome of interest is rare, those with the outcome can be readily identified and matched to controls, therefore in terms of time and cost they are more efficient compared to cohort designs (Levin, 2006b). However, there are some limitations linked to the use of case-control studies. For example it is impossible to estimate the incidence of the disease with this study design. This is because this study design compares cases with the outcome with a selection of controls, and it is usually not possible to reconstruct the population the cases and controls were derived from (Levin, 2006b). Another limitation is the selection of the cases, which may be incident (those who are recently diagnosed with the disease) or prevalent (existing cases who experienced the disease at any time). Incident cases are preferable because they provide more reliability on the temporal sequence between the exposure and the outcome. Conversely, with prevalent cases the exposure may have occurred after the outcome and may also have changed as a consequence of the outcome (Levin, 2006b). For example, if prevalent cases with musculoskeletal pain were selected, there would be less

confidence on the assessment of sleep problems as an exposure because sleep problems may have been influenced as a consequence of musculoskeletal pain presence, therefore the temporality of the association is less clear. Another limitation concerns the selection of controls, who should be free of the outcome, and arise from the same source population as the cases originated from (Levin, 2006b). A less accurate selection of controls may lead to bias if, for example, controls are excluded because they have a condition associated with the exposure, but cases with the same condition are included (Delgado-Rodriguez & Llorca, 2004). In case-control studies, confounding (which affects all types of design) is often dealt with by matching the cases with the controls using information regarding known confounders (Levin, 2006b). Matching for a variable that is only associated with the exposure but not with the disease can lead to overmatching, which would ultimately result in an underestimation of the association (Delgado-Rodriguez & Llorca, 2004). Finally, this study design may not be the best choice to investigate the effect of risk factors that are rare as this would require identification and selection of a large number of cases and controls (Levin, 2006b).

4.4.4.3 Cross-sectional studies

Cross-sectional designs present a strength in terms of efficiency, as exposures and outcome are assessed at the same time, which makes this design relatively inexpensive and quick to complete compared to other designs (Hennekens & Buring, 1987; Levin, 2006a). However, as only one time point is included in this study design, it is not possible to determine the temporal sequence between the exposure and the outcome, therefore inferences of causality cannot be made (Levin, 2006a). Another key limitation linked to the use of only one time point is that this does not allow to estimate the incidence, but only the prevalence (Levin, 2006a). Suppose that one wanted to investigate the association between sleep problems and musculoskeletal pain using a cross-sectional study. In this case, a higher prevalence of sleep problems might be found, but this might

be the consequence of musculoskeletal pain rather than the cause. Therefore, this might result in an overestimation of the association between sleep problems and musculoskeletal pain onset.

4.4.4.4 Bias of analytical studies

Analytical designs may be affected by bias. A common type of bias is selection bias, which may occur when the selected sample does not represent the target population, which may affect cohort, cross-sectional and case-control designs. For example in cohort (and cross sectional) designs selection bias may arise due to the effect of either selective non-participation at the start of the study (participation bias) or selective loss to follow-up (attrition bias, cohort designs only) (Delgado-Rodriguez, 2004). For example, those who decide to participate in a study may have different characteristics as compared to those who decide not to participate, as they may be healthier or have poorer health. If these characteristics are associated with the probability of the outcome, then the estimate of the association would be biased (either overestimation or underestimation). Attrition bias is a primary concern of cohort studies, especially if follow-up extends over multiple months or years. If the proportion of loss to follow-up is substantial (>30%), and individuals lost to follow-up were at a different risk to experience the outcome as compared to those that completed the study, this can produce biased estimates and can compromise the accuracy of the estimates of the study findings (Hennekens & Buring, 1987). As reported in Section 4.4.4.2, in case-control studies overmatching (which is a type of selection bias) can occur, or selection bias may arise because of an inappropriate selection of controls. In addition, hospital-based case-control studies may be affected by Berkson's bias, which is a specific type of selection bias that may occur when cases and controls have a different probability of hospitalization that is linked to the exposure (Bhopal, 2002; Delgado-Rodriguez & Llorca, 2004; Levin, 2006b).

Another major type of bias is misclassification, which result in information bias and can affect all analytical study designs. For example, in retrospective cohort studies there is risk of information

bias if knowledge of the outcome influences the classification of individuals into the exposed and non-exposed groups or vice versa, resulting in misclassification of either the exposure or the outcome (Hennekens & Buring, 1987). Similarly, the case-control study design is prone to recall bias, which is a form of information bias leading to misclassification of the exposure (Levin, 2006b). For example, individuals who experience musculoskeletal pain may be more likely to recall a certain exposure that may be suspected to be linked to pain compared to controls (Delgado-Rodriguez & Llorca, 2004). Cross-sectional designs as well are likely to be affected by misclassification (information) bias, due to the concurrent assessment of both exposures and outcomes, as the responder may report more often exposures that are related to the outcome (Levin, 2006a). Misclassification can be non-differential or differential. Non-differential misclassification, which occurs when individuals are evenly misclassified among exposure or outcome groups, will result in underestimation (i.e. weakened association) between the exposure and the outcome (Hennekens & Buring, 1987). This may happen for example when the objective is to classify those with high and low levels of physical activity. If only the number of days per week of physical activity are used as the criterion but not the type or intensity of physical activity, then those individuals that exercise strenuously but only few days a week may be wrongly allocated to the low levels of physical activity group, which may lead to an underestimation of the association with musculoskeletal pain. Differential misclassification, which occurs when individuals are unevenly misclassified among groups of the exposure or the outcome, may produce either no effect difference, an overestimation, or an underestimation of the true association. This may happen for example when the outcome is more often detected in the group of exposed individuals as compared to non-exposed because those exposed are more likely to seek medical attention and subsequently be diagnosed with the disease / outcome of interest (Hennekens & Buring, 1987). This would lead to an overestimation of the association between exposure and outcome.

4.4.5 Choice of study design

As reported in Section 4.3, in order to investigate the objectives of this thesis, two parameters need to be obtained: the incidence of the outcome and the strength of association between exposure and outcome. From the range of epidemiological (analytical) designs the prospective cohort design was considered to be best suited to obtain these parameters. Prospective cohorts allow the calculation of incidence, which is an estimate of the proportion of individuals who are free of the outcome at baseline and develop the outcome during the period of observation (follow-up) (Section 4.3). In addition, prospective cohort studies provide stronger evidence for a temporal association between risk factors and the onset of the disease, and are less susceptible to information bias (e.g. recall bias, and misclassification of the outcome) compared to the other study designs. A brief description of the three cohorts (two general population samples and a cohort identified from routinely collected electronic primary care data) used to investigate the objectives of this thesis are outlined in the following section.

4.4.6 Datasets identified for testing the objectives

The objectives of this thesis (described in Section 3.2) will be addressed using data from cohort studies conducted in general population samples and a Primary Care dataset. The cohort that will be used to investigate objective number 1 is the Childhood to Adolescence Transitions Study (CATS), the cohort that will be used to investigate objective number 2 is the Avon Longitudinal Study of Parents and Children (ALSPAC), and the cohort that will be used to investigate objective number 3 is the Consultations in Primary Care Archive (CiPCA). A brief overview of these cohorts is described below. For a fuller description of the CATS dataset, the ALSPAC dataset, and the CiPCA dataset please refer to Chapter 5, Chapter 7 and Chapter 9, respectively. The description of the cohorts will be followed by a description of the methods for the analysis that will be performed together with the analysis plan, all of which is outlined in the following sections.

Childhood to Adolescence Transitions Study (CATS)

CATS is a population-based cohort study that includes Australian schoolchildren who were 9 years old at baseline and were followed up for 4 years with assessment each year. Data collection included suitable measures for sleep problems, musculoskeletal pain (assessed as a binary variable, presence/absence of musculoskeletal pain) and the potential effect modifiers and confounders described in Section 3.3.1 and 3.3.2 for the investigation of objective number 1. In the analysis within this thesis, only data up to the first year of follow-up will be used.

Avon Longitudinal Study of Parents and Children (ALSPAC)

ALSPAC is a birth-cohort of English children and adolescents followed-up from birth up to the age of 21. Data collection for this cohort included suitable measures for psychological symptoms (in this case internalizing and externalizing symptoms), musculoskeletal pain (assessed as a binary variable, presence/absence of musculoskeletal pain) and the potential effect modifiers and confounders described in Section 3.4.1 and 3.4.2 for the investigation of objective number 2. In the analysis, only data collected when children were 13 (baseline) and 17 years old (follow-up) will be used as these correspond to the times of measurement of the exposure and outcome.

Consultations in Primary Care Archive (CiPCA)

CiPCA includes routinely collected data regarding consultations, prescriptions and referrals for patients registered with 13 general practices in North Staffordshire, England. This dataset includes coded consultations for sleep problems, psychological symptoms and musculoskeletal pain, which will be used to investigate both objectives. However, CiPCA does not include adequate information for the inclusion of the selected potential effect modifiers, and therefore effect modification will not be studied in objective 3. This analysis allows for a continued period of time for analysis and consultation data from year 2005 to year 2012 will be used.

4.5 Analysis

4.5.1 Descriptive analysis

A descriptive analysis of baseline characteristics will be performed in all datasets. Proportions (or percentages) will be presented for categorical variables and means and standard deviations for continuous data.

4.5.2 Regression methods

In epidemiological studies, the presence of a statistical association between variables is investigated, most often one or more exposures (independent variable) with an outcome (dependent variable) (Alexopoulos, 2010). For example, the statistical association between sleep problems (independent variable) and the onset of musculoskeletal pain (dependent variable) will be assessed for objective number 1. This can be investigated by means of regression analysis, which is a suitable method to predict the value of the dependent variable based on the value of the independent variable (Bland, 2015). Both univariable and multivariable regression analysis will be performed to estimate the association between risk factors (i.e. sleep problems, psychological symptoms) and the onset of musculoskeletal pain. Univariable analysis provides the crude estimate of association between only one risk factor entered in the model (e.g. sleep problems) and the outcome (e.g. musculoskeletal pain). However, the estimate provided by univariable analysis does not take into account the influence of potential confounders (for a description of confounders please refer to Section 4.5.3) (Bland, 2015). Conversely, multivariable analysis allows more than one independent variable to be entered in the model, which makes it possible to take into account the influence of potential confounders (Bland, 2015). Several multivariable regression methods are available (Bagley, White, & Golomb, 2001). The choice of the regression method to be used depends on the characteristic of the outcome data (i.e. continuous, binary, categorical, count, time-to-event data) (Bland, 2015). A description of all the regression methods is beyond

the scope of this thesis. Regression methods that were considered suitable for the analysis based on the nature of the data are outlined in the following sections.

4.5.2.1 Logistic regression

Logistic regression is the suitable method to model the relationship between one or more independent categorical or continuous exposures and a binary dependent outcome (for example the presence or absence of musculoskeletal pain) (Bland, 2015; Peng, Lee, & Ingersoll, 2002). Logistic regression is a model based on the use of the logit of the proportion as the dependent variable, which is the natural logarithm of the odds (Bland, 2015; Peng et al., 2002). This thesis addresses two main objectives within two prospective population-based cohort datasets. Within those datasets the outcome (musculoskeletal pain) is binary and there is a single time point from exposure to outcome with the need to adjust for potential confounder variables (Section 3.3.1 and 3.4.1). Therefore, logistic regression using odds ratio (OR) and 95% Confidence Interval is the most appropriate statistical method. The concept underlying the use of the odds ratio is that significantly higher odds of outcome will be observed in the exposed group as compared to the non-exposed group, if the exposure is a risk factor for the outcome (Bhopal, 2002). Conversely, significantly lower odds will be observed in the exposed group as compared to the non-exposed group, if the exposure is a protective factor for the outcome.

4.5.2.2 Survival analysis

Survival analysis is a suitable method for the analysis of time-to-event outcomes (i.e. data that take into account the time before the occurrence of an event) (Bland, 2015). Taking into consideration the nature of the data of the primary care dataset (CiPCA) with the outcome being time to consultation for a musculoskeletal pain problem, survival analysis was considered the most suitable method. There are two major methods to conducting the survival analysis: Kaplan-Meier survival curves and the Cox-regression analysis. Kaplan-Meier survival curves method comprises the creation of a "life table", which includes the probability of the event (hazard) conditional on still being at risk of the outcome (survival) for each time interval. This information is used to plot a graph (Kaplan-Meier survival curve) showing the probability of survival over time in those still at risk of the outcome (Bland, 2015). Survival curves can be plotted separately for exposed and non-exposed group with the difference between two survival curves being tested with the logrank test (Bland, 2015). Kaplan-Meier survival curves take account of individuals who are observed for only part of the study by censoring their data. The term "censored data" refers both to those individuals who are observed only for part of the study because they do not complete the study and to those individuals who do not experience the outcome before the end of follow-up (Bland, 2015). The assumption underlying censored data is that censored individuals have the same probability to experience the event after censoring as those with observed data (Bland, 2015). The magnitude of the difference between the two groups can be expressed using hazard ratio. The hazard ratio is the ratio between the hazard of the event given the presence of the exposure variable and the hazard of the event given the absence of the exposure variable (i.e. the baseline hazard, which is the hazard of the event when all exposure variables are set to zero). The association between a risk factor and a time-to-event outcome can be estimated by means of Cox-regression analysis. As with the Kaplan-Meier survival curves method, also for Cox-regression the assumption is made that the probability of censored individuals to experience the event after the censoring is the same of that of the observed individuals. In addition, another assumption that

is made is the proportional hazards assumption, which assumes that the hazard ratio for the two groups being compared is constant across the time period of follow-up. This assumption can be tested by means of the proportional hazards assumption test, either graphically (i.e. using Kaplan-Meier plots) or analytically (i.e. Schoenfeld residuals test) (Bland, 2015). This test should be run before performing the Cox regression analysis. With the Kaplan-Meier plots the assumption is met if the survival curves do not cross each other, while with the Schoenfeld residuals test the assumption is met in case of a non-significant P value ($P>0.05$).

4.5.3 Confounders

As outlined previously this study will consider the influence of potential confounders on the association between risk factors and onset of musculoskeletal pain. A confounding variable can confound the estimate of the association (either producing an overestimation or underestimation or changing the direction of the association) (Hennekens & Buring, 1987). Confounding occurs when populations being compared differ for other characteristics that are distributed differently among the populations, and these differences confound (fully or partly explain) the association (Bhopal, 2002). For example, one objective of this thesis is to assess the effect of sleep problems on the development of musculoskeletal pain. The crude association can initially be estimated by means of univariable logistic regression analysis, which will provide an estimate of the odds of developing musculoskeletal pain in those with sleep problems relative to those without sleeping problems. However, this crude estimate would not take into account the effect of other factors that may influence the association, such as psychological and behavioural problems (e.g. those with sleep problems may also be more likely to have psychological and behavioural problems, which in turn may also have a relationship with the outcome). This means that the univariable analysis does not give an indication of the true independent association. Therefore, adjusting the analysis for potential confounders gives greater accuracy to the estimation of the association. Confounding can be positive or negative. Positive confounding occurs when the estimate of the association is an overestimation or underestimation that produces a value further away from the null compared to the true association. Conversely, negative confounding occurs when the estimate of the association is a value that is closer to the null compared to the true association (Hennekens & Buring, 1987). For a justification of the confounding variables selected for the analyses in this thesis please refer to Section 3.3.1 and 3.4.1.

4.5.4 Analysis of effect modification

Analysis of effect modification will be performed within this thesis. Briefly this thesis will test whether gender, pubertal status, and screen time use modify the relationships between the exposure and outcome, for a full explanation of the rationale supporting the investigation of effect modification please refer to Section 3.3.2 and 3.4.2. An effect modifier is a variable that influences the magnitude or direction of the association between a risk factor and the outcome (Hennekens & Buring, 1987). The modification effect can be qualitative, which occurs when there is a change in the direction of the association, or quantitative, which occurs when the strength of the association depends on the levels of the effect modifier (Kamangar, 2012). The modification effect can be assessed by means of a statistical interaction test in combination with stratified analysis, which are briefly described in the following paragraphs.

4.5.4.1 Interaction test

An interaction test can be performed to assess the presence of a statistically significant modification effect. The interaction test requires that an interaction term is created and entered in the regression model in addition to the risk factor and the potential effect modifier as independent variables (Kamangar, 2012). The interaction term is a variable created from the product term of the exposure and the potential effect modifier (Kamangar, 2012). For example, when investigating if screen time is an effect modifier of the association between sleep problems and the development of musculoskeletal pain, the interaction term would be a variable that represents the product term of sleep problems multiplied by levels of screen time. A statistically significant interaction is present if the association of the interaction term with outcome is statistically significant, over and beyond the independent effects of the risk factor and the effect modifier (Bland, 2015). The interaction term indicates a difference in the magnitude of the association (between sleep problems and onset of musculoskeletal pain) in individuals with the

effect modifier versus those without the effect modifier (e.g. children with low and high levels of screen time).

4.5.4.2 Stratified analysis

Whilst interaction tests are useful, the results can be hard to interpret in terms of the actual magnitude of effect modification (as it will be a combination of the size of effect for the interaction term and the change in effect for both the risk factor and modifier). So in addition to an interaction test, stratification can be performed to observe actual differences in the magnitude or direction of the association between the exposure and the outcome across strata of the effect modifier (Hennekens & Buring, 1987). For example, it is possible to stratify the analysis of the association between sleep problems and the development of musculoskeletal pain by levels of screen time to describe the associations within these strata (i.e. separate regression models per strata of the modifier). If the observed risk differs in direction between strata (i.e. for one strata the OR is > 1 and for another strata the OR is <1), then the effect modification would be qualitative. Otherwise, if there is a difference of risk and each strata shows the same direction of association but the magnitude varies across strata (i.e. for one stratum the OR is 1.80 and for another stratum the OR is 3.20), then the effect modification would be quantitative.

4.5.5 Missing data

In epidemiological studies, the occurrence of missing data in a dataset is a common problem. Missing data can affect the validity of the findings because of limitations in the representativeness of the sample, the potential for generating biased estimates for the association, and reduction of statistical power (Kang, 2013). A reduction in statistical power will increase the probability of type-II error, which occurs when a false null hypothesis is retained instead of being rejected (i.e. true associations are missed because they are not detected with statistical significance) (Hennekens & Buring, 1987). In the following sections, the sources of missing data, patterns of missing data along with the available methods to deal with missing data in the analysis will be outlined.

4.5.5.1 Sources of missing data

The sources of missing data are many. For example, individuals may decide not to take part in the study (baseline non-response), may be lost to follow-up, may decide not to answer a particular question, or information may be missing for other reasons as in the case of data missing by design or due to data entry. In the case of baseline non-response, if individuals who respond and take part at baseline are different from the target population (i.e. responders and those who did not respond), then missing data can lead to selection bias (Delgado-Rodriguez & Llorca, 2004). In addition, selection bias may occur when data are missing due to loss to follow-up (where individuals drop out of the study over time), which is common in cohort studies (see Section 4.4.4.4). Loss to follow-up can result in a biased estimate of the association if the values for the exposure and outcome variables differ between individuals lost to follow-up and those who completed the study (Delgado-Rodriguez & Llorca, 2004). Missing data can be broadly categorized in two groups: unit non-response and item non-response. Unit non-response refers to missing information for a whole unit of analysis (a participant). For example, this may happen because it was not possible to contact an individual, or because the individual could not attend the clinic for

examination (de Leeuw, Hox, & Huisman, 2003; Pedersen et al., 2017). Differently, in case of item non-response the individuals have participated in the study but information on a particular item or measure are missing (de Leeuw et al., 2003). Missing data for an item can be categorised as: data missing by design, data missing after a point in the questionnaire (partial non-response) and data missing for some items for some respondents. Data missing by design occurs when different individuals are asked different subset of questions (e.g. an ongoing cohort recruitment where additional questions have been added to the baseline questionnaire, only those who participate after this change will have this data). Partial non-response may happen because the individual has no time to respond to the last part of the questionnaire after a time point during the interview, or where pages and sections are missing, perhaps due to printing error or a website crash (de Leeuw et al., 2003). Differently, data missing for some items for some respondents may occur purposefully, for example when questions concern sensitive topics (e.g. drug consumption, criminality, disclosure of abuse), where the individual prefers to avoid the question. Alternatively, non-response may occur because the individual was not provided with a suitable response option for a question. Finally, data may be missing for some items because of errors in data entry (de Leeuw et al., 2003).

4.5.5.2 Patterns of missing data and methods to deal with missing data

Missing data can be investigated by looking at the patterns within the dataset. Patterns of missing data can be categorized in three different groups: data missing completely at random (MCAR), missing at random (MAR) and missing not at random (NMAR) (Bland, 2015). Data are missing completely at random (MCAR) when the missingness is not related to the characteristics of the individual in the study, for example when data are missing because of flaws in the questionnaires used in the study (e.g. a printing error in a proportion of questionnaires sent to participants), or because the individual forgot to answer to some items or dropped-out from the study because

moving to another area, and this is unrelated to the research topic. When data are MCAR the estimate of the association is unbiased, although there may be a loss of power due to missing data (Kang, 2013).

Data are missing at random (MAR) when the missingness is related to the individual in the study but it is independent from the variable for which the information is missing, and can be estimated from other information available about the individual (Bland, 2015). For example information on a variable (e.g. sleep problems) may be missing because the child was ill on that day and therefore the assessment of that variable could not take place, but the level of sleep problems may be estimated based on other data collected in this child or from other children in the cohort. Data are missing not at random (NMAR) when the missingness is due to the characteristic of the variable for which the information is missing (Bland, 2015). For example, information on a sensitive item (e.g. smoking) is not reported because the child/adolescent does not want to reveal their smoking status. In case of missing data, the patterns of missingness should be explored and described, and information about the percentage of non-response for each variable at each time-point of the study should be reported. In addition, the baseline characteristics of those who completed the study should be described and compared to those who were lost to follow-up to assess the risk of selection bias due to attrition. Several approaches can be undertaken to deal with missing data, depending on the pattern of missing data:

- Complete-case analysis (i.e. omitting individuals with missing data and analysing only observations with complete data). It provides unbiased estimates if the data are MCAR, but is considered not efficient and will lead to a loss of power and lower precision of estimates (Bland, 2015; Kang, 2013; Pedersen et al., 2017).
- Using the sample mean (i.e. the mean of the variable from the observed cases in the sample is used to replace missing data). This method can be used when data are MCAR, but produces conservative estimates (Bland, 2015) and an underestimation of standard errors (Kang, 2013).

- Replacing the missing data with the last observation in time of an individual before the occurrence of missing data. This method can be used for MCAR and MAR missing data, but it is likely to produce biased estimates (Bland, 2015; Kang, 2013; Pedersen et al., 2017).
- Imputation approaches using regression in which new estimated values are entered in place of missing data (Kang, 2013) by predicting the value of the missing data through a regression method, using information available on other variables (Kang, 2013). Two imputation methods are available: single imputation and multiple imputation. With the simple imputation method the process is carried out only one time. Differently, the multiple imputation method implies the creation of more than one dataset (a rule of thumb is that the number of datasets should be equal to the percentage of missing data) with imputed data in place of missing data. Subsequently, these datasets are analysed and, by pooling the results (regression coefficients) of the single analyses of the datasets, a single overall estimate is produced together with a more realistic estimate of its variability (Bland, 2015; Kang, 2013; Pedersen et al., 2017). Multiple imputation can be used under the MCAR and MAR assumption to produce valid estimates (Bland, 2015).

4.5.5.3 Analyses to explore the patterns of missing data

In case of missing data within the thesis, the patterns of missingness will be explored and reported for both the CATS and the ALSPAC dataset (missingness cannot be measured within the CiPCA dataset because only individuals with full registration status for the whole study period were included). The percentage of individuals with missing data on any of the variables at baseline will be described, in order to understand the potential impact of missing data on sample size and precision. The effect of loss to follow-up will be assessed by describing the baseline sample characteristics of those individuals that completed the study, which will be compared to the

baseline characteristics of those who were lost to follow-up (Section 5.3 for the CATS dataset and 7.3 for the ALPSAC dataset).

4.5.5.4 Little's test of MCAR

The patterns of missing data will be explored and described (Section 4.5.5.3). In addition, Little's test of MCAR provides the opportunity to test the assumption that data are missing completely at random (MCAR). The null-hypothesis to be tested is that data are missing completely at random, which means that a significant test result ($p<0.05$) indicates that data are not missing completely at random. When performing this test, all the variables included in the model (i.e. variables with missing values and the other covariates) are to be used (Newton et al., 2010).

4.6 Analysis Plan

In this section the analysis plan for the investigation of objectives 1, 2 and 3 will be outlined. Information regarding the sample used for analysis, the measures and definitions of exposures, potential confounders, effect modifiers and musculoskeletal pain, including cut-points used, will be outlined in chapter 5, 7, and 9 respectively, as well as the imputation methods used to deal with missing data.

4.6.1 Investigation of sleep problems as a risk factor for the onset of musculoskeletal pain in children (CATS dataset)

The aim of objective 1 is to investigate whether children with sleep problems are at a greater likelihood for the onset of musculoskeletal pain compared to those without sleep problems, and whether this association is influenced by potential effect modifiers such as gender, screen time and pubertal status. Given the availability of data on musculoskeletal pain duration, a secondary aim is to assess whether sleep problems are associated with an increase in odds for the onset of chronic musculoskeletal pain (i.e. musculoskeletal pain lasting > 3 months) and if this association is influenced by the same potential effect modifiers cited above (Section 3.3.1). In order to achieve this objective the following analyses will be performed:

- Baseline descriptive analysis, to describe the sample characteristic (Section 5.4).
- Exploration and description of the patterns of missing data in order to assess the potential risk of bias due to non-response and loss to follow-up (Section 5.3).
- Calculation of the incidence of musculoskeletal pain cases at follow-up in children without musculoskeletal pain at baseline (Section 6.2.1)
- Logistic regression analysis using odds ratio (OR) and 95% Confidence Interval (95% CI) to estimate the association between sleep problems and the onset of musculoskeletal pain at follow-up (Section 6.2.2). Both unadjusted and adjusted (psychological symptoms, and

regular participation in individual and team sport) estimates will be presented.

- Potential effect modification (by gender, pubertal status and screen time) of the association between sleep problems and the onset of musculoskeletal pain will be investigated using interaction tests and examined via stratified analysis.
- The same analysis process as outlined above will be performed to assess the association between sleep problems and chronic musculoskeletal pain onset at follow-up (Section 6.2.3 and 6.2.4)

4.6.2 Investigation of psychological symptoms as risk factors for the onset of musculoskeletal pain in adolescents (ALSPAC dataset)

The aim of objective 2 is to investigate whether adolescents with psychological (internalizing and externalizing) symptoms are at a greater likelihood for the onset of musculoskeletal pain, and whether this association is influenced by potential effect modifiers including gender, screen time and pubertal status (Section 3.4.1). Given the presence of data on musculoskeletal pain duration within this dataset, a secondary aim is to assess whether children with psychological (internalizing and externalizing) symptoms are at increased odds for the onset of chronic musculoskeletal pain (i.e. musculoskeletal pain lasting > 3 months), and if this association is influenced by the same potential effect modifiers cited above. In order to achieve these objectives, the following analysis will be performed:

- Baseline descriptive analysis, in order to describe the sample characteristic (Section 7.4).
- Exploration and description of the patterns of missing data in order to assess the potential risk of bias due to non-response and loss to follow-up (Section 7.3).
- Calculation of the incidence of musculoskeletal pain cases at follow-up in adolescents without musculoskeletal pain at baseline (Section 8.2.1)
- Logistic regression analysis using odds ratio (OR) and 95% Confidence Intervals (95% CI) to estimate the association between psychological (internalizing and externalizing) symptoms and the onset of musculoskeletal pain at follow-up (Section 8.2.2 and 8.3.2). Both unadjusted and adjusted (physical activity, smoking, marijuana use, drug use) estimates will be presented.
- Potential effect modification (by gender, pubertal status and screen time) of the association between psychological (internalizing and externalizing) symptoms and the onset of musculoskeletal pain will be investigated using interaction tests and examined via stratified analysis.

- The same analysis process as outlined above will be performed to assess the association between psychological (internalizing and externalizing) symptoms and chronic musculoskeletal pain onset at follow-up (Section 8.4 and 8.5).

4.6.3 Investigation of sleep problems and psychological symptoms as risk factors for the onset of musculoskeletal pain in children and adolescents within a primary care setting

The aim of the objective 3 is to investigate whether children and adolescents who present to primary care for sleep problems and psychological symptoms are at increased likelihood for subsequent consultation for a musculoskeletal condition. This objective will be explored within the CiPCA dataset. The association between sleep problems and psychological symptoms (two separate analyses) with consultations for musculoskeletal conditions will be investigated. Analysis will be repeated for the association of these factors with persistent musculoskeletal conditions (i.e. more than one consultation for a musculoskeletal condition within a 3 month period, defined as a proxy marker of chronic musculoskeletal pain). The following analysis will be performed:

1. Baseline descriptive analysis, in order to describe the sample characteristic (Section 9.2).
2. Calculation of the frequency of consultations for musculoskeletal conditions and persistent musculoskeletal conditions during the 2-year follow-up period in individuals without a consultation for musculoskeletal pain conditions at baseline (Section 10.1.1 and 10.2.1).
3. Testing of the proportional hazard assumption (i.e. the ratio of risk for the occurrence of a consultation for musculoskeletal conditions is constant between the two groups being compared across the time period of follow-up) by means of the Schoenfeld residuals test (Section 10.1.2.1 and 10.2.2.1).
4. Graphical description of time to incident consultation for musculoskeletal pain conditions according to the exposure (i.e. sleep problems and psychological symptoms) by means of Kaplan-Meier plots (Section 10.1.2.2 and 10.2.2.2).
5. Survival analysis by means of Cox regression to estimate the association between sleep problems and psychological symptoms (two separate analyses) and time to onset of musculoskeletal pain, expressed as hazard ratio (HR) and 95% Confidence Interval of the

exposure (Section 10.1.2.3 and 10.2.2.3). Both unadjusted estimates and the estimates adjusted for potential confounders of the association (i.e. year of index date, age at index date, gender, practice and number of consultations) will be presented.

6. The same analysis process as outlined above will be performed to assess the association between sleep problems and psychological symptoms (two separate analyses) and time to persistent musculoskeletal conditions, expressed as hazard ratio (HR) and 95% Confidence Interval (Section 10.1.3 and 10.2.3).

4.7 Chapter summary

This chapter described epidemiological study designs and the analysis method that will be performed to address the objectives of this thesis. Theoretical explanations for the chosen study design (i.e. prospective cohort study) and the choice of analysis have been provided (Section 4.4 and 4.5). Descriptive analysis of all cohorts will be carried out, and results will be presented in Chapter 5, 7 and 9. Results of the regression analysis will be presented in Chapter 6, 8 and 10. For all datasets, analyses of missing data will be carried out in order to assess how the missingness of data may have influenced the estimates of the association, with results being presented in the relevant results chapters. The remainder of this thesis will now outline the description, analysis, results and discussion for each objective.

Chapter five. The association of sleep problems with musculoskeletal pain onset in children: description of the Childhood to Adolescence Transition Study (CATS) cohort

In this chapter, a description of the CATS cohort and of the measures included within the cohort are outlined, followed by a description of missing data within this cohort, and the non-responder analysis for missing data. Finally, the descriptive findings of the cohort will be reported and discussed.

5.1 Design and recruitment

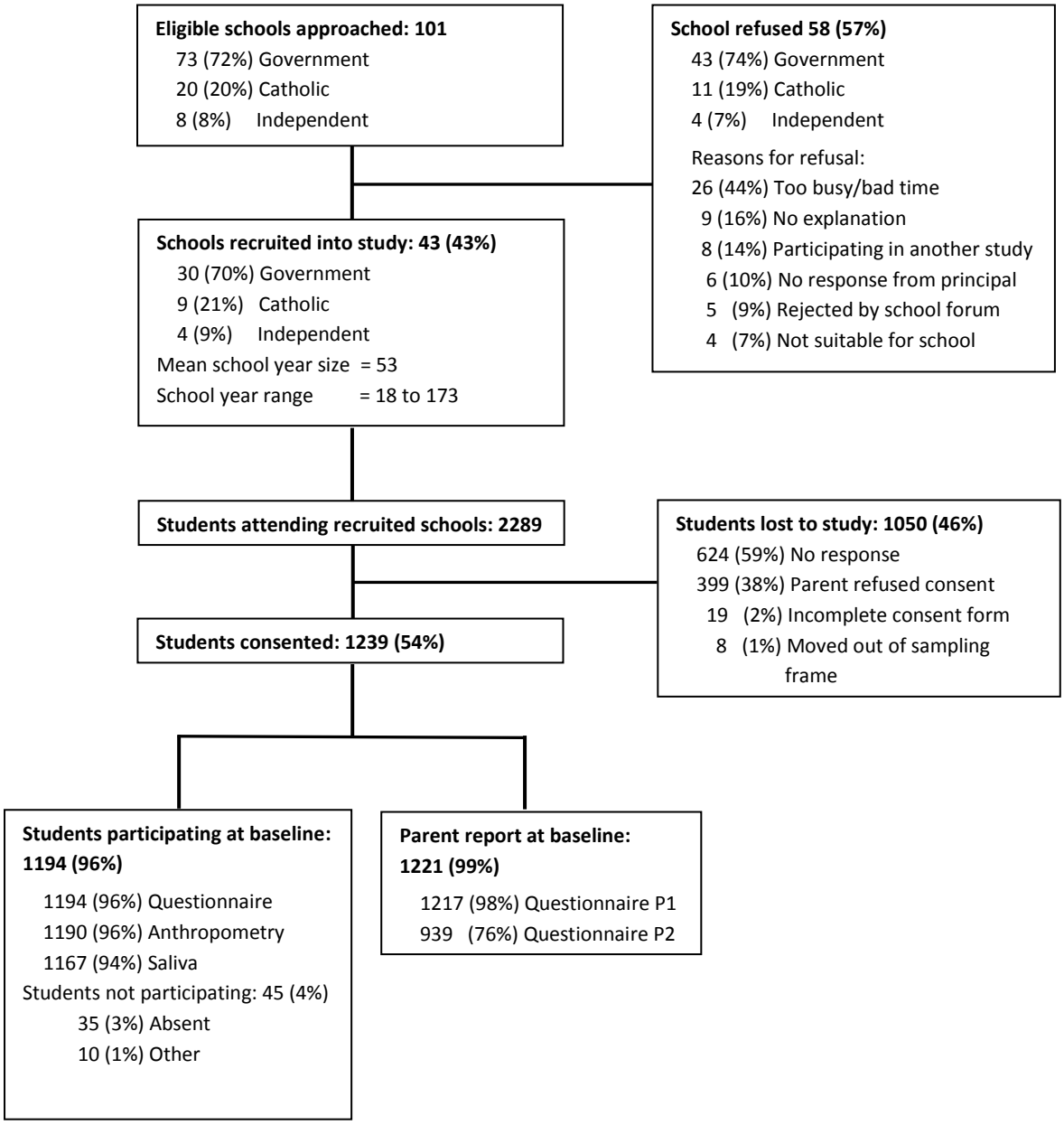
The Childhood to Adolescence Transition Study (CATS) dataset was made available via engagement of Prof. Kate Dunn with the research team who set up the cohort (Prof. George Patton, Prof. Susan Sawyer and Dr. Lisa Mundy). The CATS is a longitudinal prospective cohort study that aims to assess how the emotional, psychological, behavioural and learning development of children is affected by the hormonal changes that occur during puberty (Mundy et al., 2013). The cohort includes information from schoolchildren and their parents who reside within the metropolitan area of Melbourne, Australia. Children were 8-9 years old (grade 3) at baseline and data were collected annually for 4 years since February 2012 until year 2015. In this current study, only data from baseline to the first year of follow-up (2013) were used, and will hereafter be referred to as baseline and follow up. The recruitment consisted of a random selection of primary schools from a stratified cluster sample (strata based on Government, Catholic, Independent School type) of all the primary schools within the Metropolitan Melbourne area. The schools had to have 10 or more children enrolled in grade 3 to be selected. Both parents and children were required to give consent to take part, and a small incentive was used to encourage children participation (children were given a prize for returning the consent form). A

flow-chart (Figure 5.1) shows the process of recruitment of children and parents within CATS. A description of participants and non-participants to the study is outlined in Section 5.1.1.

5.1.1 Description of baseline participants and non-participants

Figure 5.1 (Mundy et al., 2013) shows the description of participants and non-participants to the study. Forty-three, out of 101 schools, that were approached agreed to participate in the study. Of the 58 schools who refused, the main reason for refusal was that they were too busy. Of the 43 schools who agreed to take part (2289 students), 1239 (54%) students and their parents agreed to participate. Of those who did not agree (n = 1050), the main reasons were no response or parental refusal (see Figure 5.1). Of the students and parents who agreed to participate, 1194 (96%) students and 1221 (99%) parents took part in the data collection at baseline. Among the 45 children who did not take part in data collection at baseline, 35 children were absent, and 10 children did not take part for other unspecified reasons (Mundy et al., 2013).

Figure 5.1. Flowchart of recruitment of participants to the study (Mundy et al., 2013)



5.2 Study measures

This cohort contains suitable measures to test the research hypothesis that children with sleep problems are at increased odds for the onset of musculoskeletal pain and that this relationship may be influenced by potential effect modifiers such as gender, screen time and pubertal status (Section 3.3.1). Measures self-reported by children were collected by means of an iPad APP, and from parents using self-report questionnaires (part 1 and part 2) (Kosola et al., 2017). A research assistant was present during the administration of the measures at schools, and read the questions aloud in order to help students with low literacy in using the iPad APP (Kosola et al., 2017). The variables included in the study are described below. Strengths and limitations of these measures will be discussed in Section 6.3.2.

5.2.1 Outcome measure

5.2.1.1 Musculoskeletal pain

Pain status was assessed at baseline and follow-up through the question "Thinking back over the PAST MONTH, have you had any pain or pains, which have lasted for a WHOLE DAY or LONGER?". This pain question has been used in previous child cohort studies (Jones, Silman, et al. 2003; Jones, Watson, et al. 2003). According to the answer (Yes/No), participants were classified as "having pain" or "not having pain" respectively. In the case where the response was "yes", the children were asked a further question on duration; "When did the pain start?". Possible responses were "less than three months ago" and "more of three months ago", the latter giving an indication of chronic pain status.

5.2.1.2 Pain manikin

Following the questions relative to pain status, a pain manikin was used to assess a total of 17 different pain sites in the front and the back of the body: head, neck/throat, thoracic spine, upper

back, lumbar spine, lower back, chest, abdomen, shoulder, elbow, forearm, hand, buttock, thigh, knee, shin/calf, and foot (for a graphical description of the body sites please see appendix III; the presence of pain in either one side or both sides of a body site was counted as a single site). This measure consists of a drawing of a blank body manikin and the participant has to indicate the extent and distribution of the pain. Such methods have been shown to be valid and reliable for the identification of pain sites in adult populations and in children from the age of 8 years (Hamill, Lyndon, Liley, & Hill, 2014; Kosola et al., 2017; Lacey, Lewis, Jordan, Jinks, & Sim, 2005; Margolis, Chibnall, & Tait, 1988). The different body sites (excluding those relative to the head and the abdomen), together with the answers to the questions relative to pain status and pain duration (Section 5.2.1.1), were used to create variables that represented the presence of musculoskeletal pain or chronic musculoskeletal pain. Musculoskeletal pain was entered in the analysis as a binary variable with values of 1 and 0, according to the presence or absence of self-reported musculoskeletal pain respectively. Chronic musculoskeletal pain was entered in the same format, according to the self-reported start of musculoskeletal pain “more than three months ago” or “less than three months ago” respectively.

5.2.2 Predictor measure

5.2.2.1 Sleep problems

Sleep problems in children were assessed at baseline through a single self-report question taken from the Symptom Checklist-90 (SCL-90) scale (Derogatis, Lipman, & Covi, 1973) for the child to self-report. The question was "How often you have been bothered by trouble sleeping in the last month?"

- Never
- Almost never
- Sometimes
- Often
- Almost always

Sleep problems was entered in the analysis as a binary variable with values of 1 or 0 according to the frequency of sleep problems, respectively: sleep problems (often/ almost always) and no sleep problems (Never/almost never/sometimes) following previous methodology (Schubert et al., 2002).

5.2.3 Effect modifiers measures

5.2.3.1 Gender

The child's gender was reported by the parents in the questionnaire at baseline. Gender was entered in the analysis as a binary variable with values of 1 or 0 according to gender, male or female respectively**.**

5.2.3.2 Screen time

Screen time (i.e. time that the children daily spent watching the TV, playing videogames and using the computer) was assessed at baseline through the following parent-reported questions:

- On school days, how many hours does your child spend watching TV or DVDs, on the TV or on the computer?
- On weekend days, how many hours does your child spend watching TV or DVDs, on the TV or on the computer?
- On school days, how many hours does your child spend playing videogames, either on the computer or on consoles like XBox or Playstation?
- On weekend days, how many hours does your child spend playing videogames, either on the computer or on consoles like XBox or Playstation?
- On school days, how many hours does your child spend using the computer for email, schoolwork, internet access or chat?
- On weekend days, how many hours does your child spend using the computer for email, schoolwork, internet access or chat?

These questions are adapted from questionnaires of the Longitudinal Study of Australian Children and the Lodz Electronic Aggression Prevalence Questionnaire (LEAPQ) scale (Mundy et al., 2013). Total screen time in the weekdays was calculated by multiplying by 5 each estimate (i.e. TV or DVDs, Computer or consoles, internet and e-mail use) of screen time gathered from questions relative to the weekdays. Total screen time in the weekend was calculated by multiplying by 2

each estimate (i.e. TV or DVDs, Computer or consoles, internet and e-mail use) of screen time gathered from questions relative to the weekend. The estimate of total screen time in the weekdays was added to the estimate of total screen time in the weekend in order to obtain the total weekly screen time score. Average daily screen time was calculated by dividing total screen time weekly by 7. Then percentages of children with high screen time were calculated ("high screen time" was considered as screen time >2 hours/day on average), in agreement with American Academy of Pediatrics guidelines (American Academy of Pediatrics, 2013). This approach of setting the cut-off of 2 hours/day for high and low levels of screen time has already been used before (Kremer et al., 2014). Screen time was entered in the analysis as a binary variable with values of 1 or 0 according to the amount of screen time (>2 hours/day or ≤2 hours/day, respectively).

5.2.3.3 Puberty

Information to assess pubertal development was parent-reported and was gathered through the Pubertal Development Scale (PDS) at baseline. The PDS produces a measure that can be used either continuously (score that ranges from 5 to 19) or with a categorical classification in 5 stages (pre-pubertal/ beginning pubertal/ mid-pubertal/ advanced pubertal / post-pubertal).

The PDS has been used previously (Simon, Wardle, Jarvis, Steggles, & Cartwright, 2003), and has been shown to be suitable for school-based surveys (Bond et al., 2006), with reports of validity and reliability (Petersen, Crockett, Richards, & Boxer, 1988). Within the CATS cohort the pubertal characteristics included in the PDS (growth spurt, body hair growth, skin changes, voice deepening, breast development, and finally growing hair on face in boys, and menstruation in girls) were used to calculate the pubertal score. A score was given to each of the characteristics according to whether the characteristic had already started to develop or not (1 = has not started yet; 2 = has barely started; 3 = has definitely started; 4 = seems complete; for menstruation 1 = No; 4 = Yes). The sum of these scores formed the pubertal score and allowed the 5 stages

categorization of pubertal status in children used in the analysis. Pubertal status was entered in the analysis as a binary variable with values of 1 or 0 according to pubertal stage: advanced puberty (mid-pubertal/ advanced pubertal / post-pubertal) or early puberty (pre-pubertal/ beginning pubertal) respectively. This categorization of the PDS has been used previously (Simon et al. 2003).

5.2.4 Confounders

5.2.4.1 Physical activity

Physical activity was assessed at baseline through the parent-reported question "In the last 12 months has your child regularly participated in any of the following activities (outside school hours, even if organised by the school)? (Team sport/ Individual sport)". Possible answers were "yes" or "no". This question was adapted from the Longitudinal Study of Australian Children (Vella, Cliff, Magee, & Okely, 2014). Two binary variables were created for physical activity and entered in the analysis, one for the assessment of team sports and one for individual sports. Both variables had values of 1 or 0 according to the regular participation or not in the specific sport activity assessed, respectively.

5.2.4.2 Smoking

The experience of cigarette smoking in children was assessed at baseline through the question "Have you ever smoked cigarettes?". Possible options were "Never / 1 or 2 times / 3 to 5 times / 6 to 9 times / 10 or more times". This question was adapted from Monitoring the Future and the CDC Youth Risk behaviour survey (Glaser, Van Horn, Arthur, Hawkins & Catalano, 2005; Mundy et al., 2013). Smoking status was entered in the analysis as a categorical variable with 5 categories according to the answer to the question relative to smoking.

5.2.4.3 Alcohol use

Alcohol use was assessed at baseline through the question "Have you ever had more than just a few sips of an alcoholic drink (like beer, wine, spirits or pre-mixed drinks such as Bacardi Breezers or UDL's)?". Five possible answers were present (Never / 1 or 2 times / 3 to 5 times / 6 to 9 times/ 10 or more times). This question was adapted from Monitoring the Future and the CDC Youth Risk behaviour survey (Glaser et al. 2005; Mundy et al., 2013). Alcohol consumption was entered in

the analysis as a categorical variable with 5 categories according to the answer to the question relative to alcohol consumption.

5.2.4.4 Psychological symptoms

Psychological symptoms were reported by the parents at baseline, and these symptoms were assessed using the Strengths and Difficulties Questionnaire (SDQ). The SDQ has been shown to be valid and suitable for the assessment of behavioural and emotional disorders for children aged 4 to 16 years (Goodman, Lamping, & Ploubidis, 2010; Goodman, 1997; Mundy et al., 2013). The SDQ is a 25-item questionnaire with five subscales: emotional symptoms, peer problems, conduct problems, hyperactivity and prosocial scale (Goodman, 1997). Each subscale includes 5 questions that are rated on a 3-point scale ("Not true" = 0, "Somewhat true" = 1, "Certainly true" = 2), and therefore each subscale produces a score that ranges from 0 to 10. Subscales relative to difficulties (emotional symptoms, peer problems, conduct problems, hyperactivity) can also be combined to produce a total difficulties score, which ranges from 0 to 40 (Goodman, 1997). This tool has been used in studies with similar cohorts, for example on adolescents within the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Edwards et al., 2014; Huisman et al., 2010). The items included in each subscale of the Strengths and Difficulties Questionnaire are shown in appendix IV. Psychological symptoms were entered in the analysis as a continuous variable, with values reflecting the total difficulties score.

5.3 Selection of children for analysis and missing data

The following sections outline a description of the process of selection of children used in the analysis (Section 5.3.1), and description of missing data present in the study. Investigation of missing data that originated from item non-response to the questionnaire is outlined in Section 5.3.2. Investigation of missing data that originated from loss to follow-up is outlined in Section 5.3.3.

5.3.1 Selection of children for analysis

At baseline 1194 students took part in the data collection. The self-report question on musculoskeletal pain presence at baseline was completed by 1190 children (99%), of which 718 (60%) reported musculoskeletal pain presence and 472 (40%) no musculoskeletal pain presence. Furthermore, 181 (15%) reported chronic musculoskeletal pain presence and 1,009 (85%) no chronic musculoskeletal pain presence at baseline. A description of the process of selecting subgroups used in the analysis is provided in Figure 5.2 and Figure 5.3.

Figure 5.2. Flowchart describing the selection of the children for the analysis of the onset of musculoskeletal pain

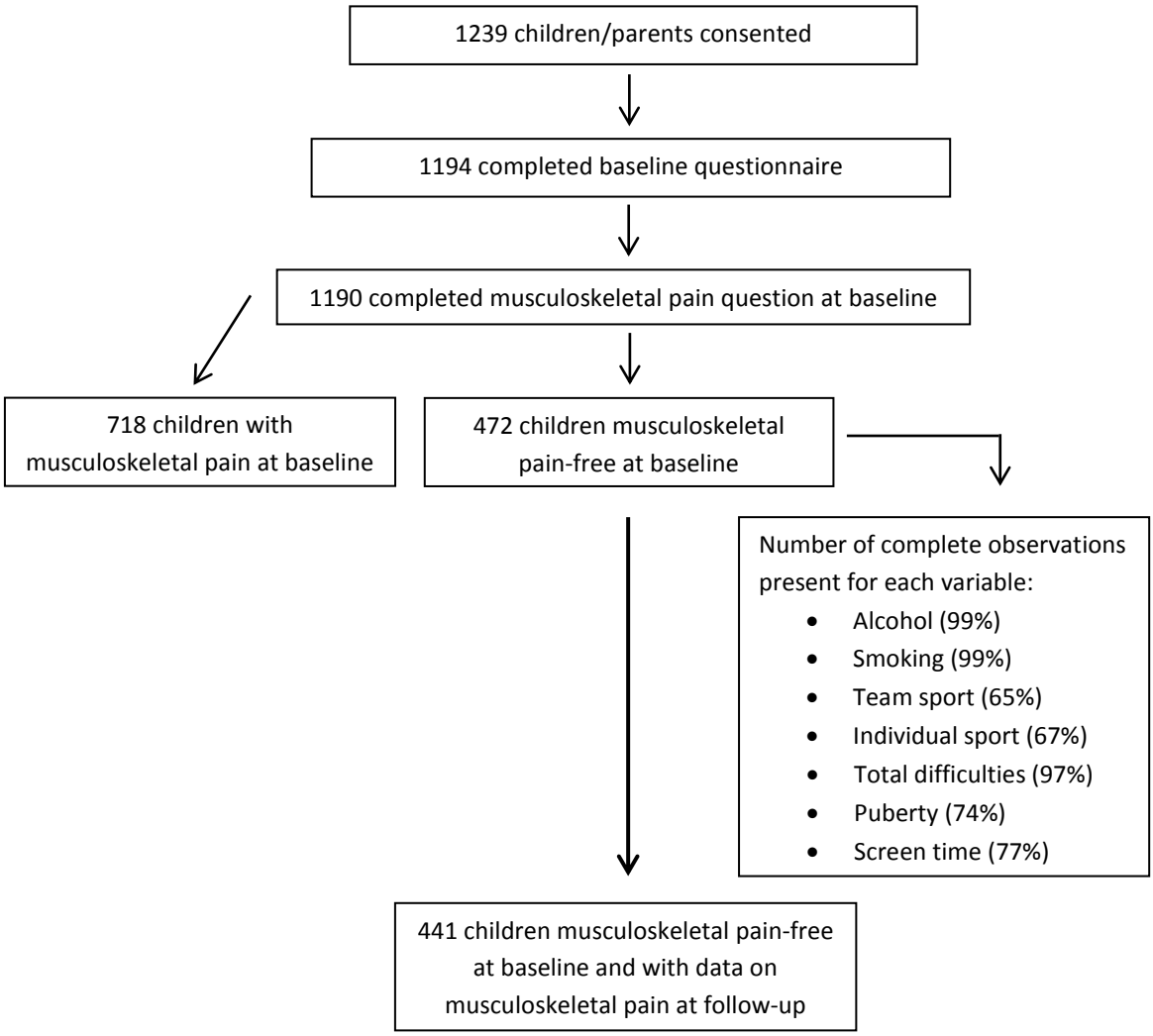
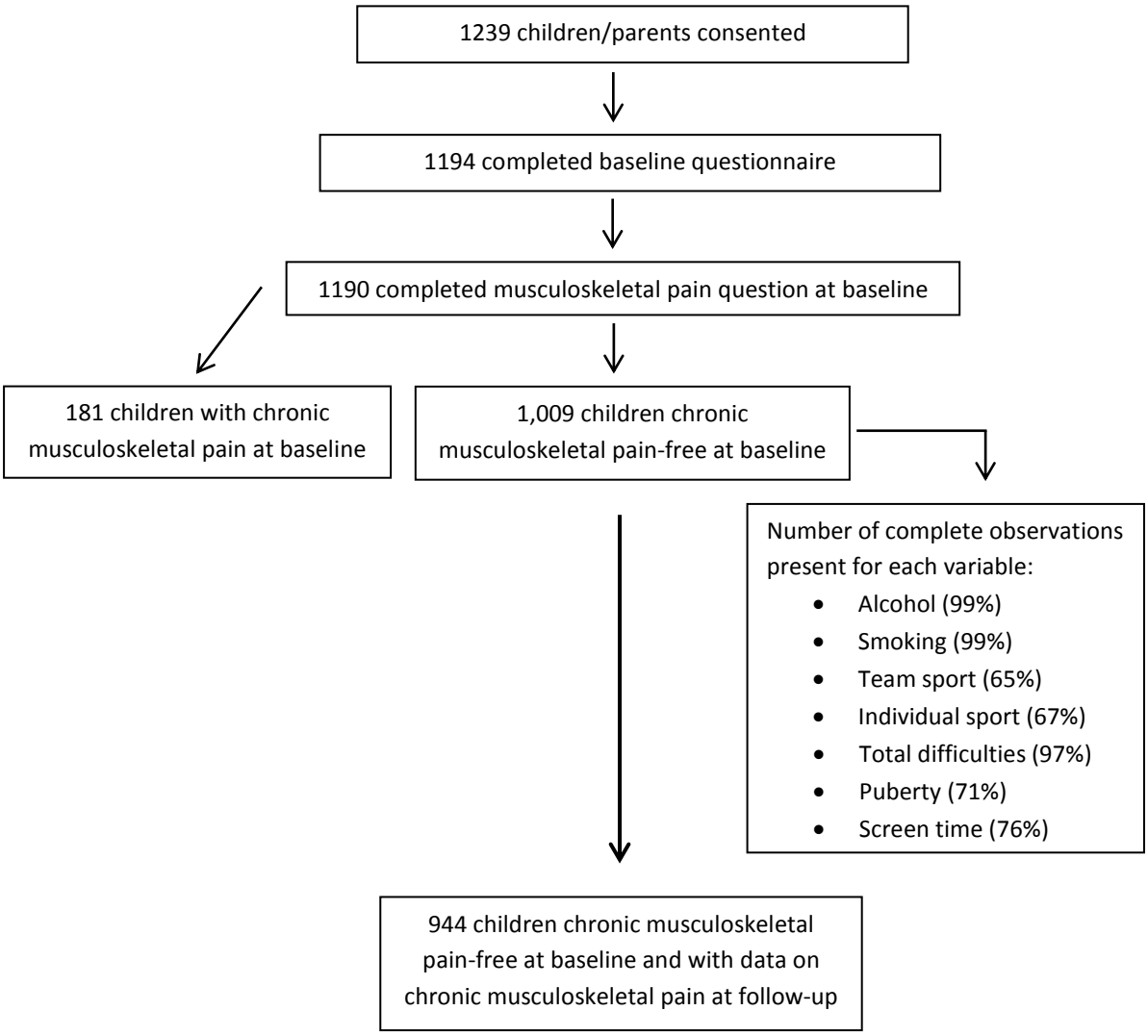


Figure 5.3. Flowchart describing the selection of the children for the analysis of the onset of chronic musculoskeletal pain



5.3.2 Missing data for baseline variables

The association between sleep problems in children at baseline and the onset of musculoskeletal pain or chronic musculoskeletal pain at follow-up was assessed in the group of children who were without musculoskeletal pain at baseline (N= 472; results shown in Section 6.2.2) and without chronic musculoskeletal pain at baseline (N=1,009; results shown in Section 6.2.4), respectively. Missing data was detected for some baseline variables. Reasons for missing data include non-completion of the questionnaire and questionnaire design, for example the parental questionnaire consisted of two parts and some parents (8.5%) were sent a shorter version. Proportions of complete data and missing data for each variable at baseline were explored and results are shown in Table 5.1. Information on missingness is important in order to understand the patterns of missing data and how this could potentially affect the analysis and results. Therefore, all variables included in the analysis were inspected for missingness. As some variables (team sport and individual sport) were not included in the short version of the questionnaire, the proportion of missing data for these variables was much higher (See Table 5.1).

Table 5.1 Percentage of Complete data Vs. Missing data at baseline		
Children without musculoskeletal pain at baseline		
	Complete data, n (%)	**Missing data, n (%)**
Physical characteristics		
Gender	472 (100%)	-
Pubertal score	349 (74%)	123 (26%)
Sleep problems		
Trouble sleeping	468 (99%)	4 (1%)
Psychological characteristics		
Total difficulties	460 (97%)	12 (3%)
Lifestyle Characteristics		
Screen time	363 (77%)	109 (23%)
Smoking	471 (99%)	1 (1%)
Alcohol	471 (99%)	1 (1%)
Team sport	308 (65%)	164 (35%)
Individual sport	317 (67%)	155 (33%)
Children without chronic musculoskeletal pain at baseline		
	Complete data, n (%)	**Missing data, n (%)**
Physical characteristics		
Gender	1,009 (100%)	-
Pubertal score	714 (71%)	295 (29%)
Sleep problems		
Trouble sleeping	1,002 (99%)	7 (1%)
Psychological characteristics		
Total difficulties	980 (97%)	29 (3%)
Lifestyle Characteristics		
Screen time	766 (76%)	243 (24%)
Smoking	1,008 (99%)	1 (1%)
Alcohol	1,007 (99%)	2 (1%)
Team sport	660 (65%)	349 (35%)
Individual sport	673 (67%)	336 (33%)

Differences in baseline characteristics between children with complete data and those with missing data (i.e. the group with missing data for team sport, individual sport, puberty and screen time) were inspected. Results show that those with complete data were slightly more likely to be boys, reported slightly more sleep problems and slightly lower scores for psychological symptoms compared to those with missing data, though the differences are generally small (e.g. < 10% difference, Table 5.2).

Table 5.2 Baseline characteristics of those with Complete data Vs. Missing data among children without musculoskeletal pain at baseline

	Complete data, n (%)	Missing data, n (%)
Physical characteristics		
Gender		
Male	127 (47.0%)	81 (40.1%)
Female	143 (53.0%)	121 (59.9%)
Sleep problems		
Trouble sleeping		
No – (Never/ Almost never/ sometimes)	204 (76.4%)	162 (80.6%)
Yes – (Often/ Almost always)	63 (23.6%)	39 (19.4%)
Psychological characteristics		
Mean score	8.1 ± 5.3	8.5 ± 5.5
Lifestyle Characteristics		
Smokers		
Never	269 (100.0%)	200 (99.0%)
1 or 2 times	-	2 (1.00%)
3 to 5 times	-	-
6 to 9 times	-	-
10 or more times	-	-
Alcohol users		
Never	192 (71.4%)	147 (72.8%)
1 or 2 times	57 (21.2%)	39 (19.3%)
3 to 5 times	13 (4.8%)	12 (5.9%)
6 to 9 times	3 (1.1%)	1 (0.5%)
10 or more times	4 (1.5%)	3 (1.5%)

In the group without chronic musculoskeletal pain at baseline, children with complete data reported slightly more sleep problems, slightly lower scores for psychological symptoms and slightly higher proportions of alcohol use, compared to those with missing data, again the differences are small (e.g. < 10% difference, Table 5.3).

Table 5.3 Baseline characteristics of those with Complete data Vs. Missing data among children without chronic musculoskeletal pain at baseline

	Complete data, n (%)	Missing data, n (%)
Physical characteristics		
Gender		
Male	275 (46.6%)	187 (44.6%)
Female	315 (53.4%)	232 (55.4%)
Sleep problems		
Trouble sleeping		
No – (Never/ Almost never/ sometimes)	380 (65.0%)	295 (70.7%)
Yes – (Often/ Almost always)	205 (35.0%)	122 (29.3%)
Psychological characteristics		
Mean score	7.9 ± 5.1	8.6 ± 5.8
Lifestyle Characteristics		
Smokers		
Never	585 (99.3%)	412 (98.3%)
1 or 2 times	3 (0.5%)	6 (1.4%)
3 to 5 times	1 (0.2%)	1 (0.3%)
6 to 9 times	-	-
10 or more times	-	-
Alcohol users		
Never	360 (61.1%)	285 (68.2%)
1 or 2 times	157 (26.7%)	93 (22.3%)
3 to 5 times	45 (7.6%)	21 (5.0%)
6 to 9 times	14 (2.4%)	7 (1.7%)
10 or more times	13 (2.2%)	12 (2.9%)

5.3.3 Missing data due to loss to follow-up at 1-year

The total number of children available at follow-up for the analysis of musculoskeletal pain onset was 441, indicating 31 children (7%) were lost to follow up (See Figure 5.2). The differences in baseline characteristics between children lost to follow-up and still present at follow-up (completers) were assessed. The proportion of girls in those lost to follow-up was higher (61.3% vs. 55.5%), and children lost to follow-up were more likely to be in the mid/advanced pubertal status (18.7% vs. 12.3%), had higher psychological symptoms scores (11.2 vs. 8.1), and were less likely to perform team sports (53.3% vs. 58.8%) and individual sports (40.0% vs. 72.2%) than completers (See Table 5.4). The total number of children available at follow-up for the analysis of chronic musculoskeletal pain onset was 944, indicating 65 children (6%) were lost to follow up (See Figure 5.3). Children lost at follow-up had higher psychological symptoms scores (10.1 vs. 8.1), were more likely to have high levels of screen time (>2 hours/day; 82.9% vs. 77.6%), and less likely to perform team sports (58.3% vs. 63.4%) and individual sports (48.0% vs. 73.5%) than completers (See Table 5.5). For a discussion of the possible effect of missing data due to loss to follow-up please refer to Section 5.5.2.

Table 5.4 Baseline values of completers vs. loss to follow-up among children without musculoskeletal pain		
Total	Completers	Lost to follow-up
	441 (93.4%)	31 (6.6%)
Sleep problems	Completers	Lost to follow-up
Yes	95 (21.7%)	7 (23.3%)
No	343 (78.3%)	23 (76.7%)
Potential effect modifier	Completers	Lost to follow-up
Gender (N %)		
Boys	196 (44.4%)	12 (38.7%)
Girls	245 (55.5%)	19 (61.3%)
Puberty		
Pre-Early puberty	292 (87.7%)	13 (81.3%)
Mid-Advanced puberty	41 (12.3%)	3 (18.7%)
Screen time		
Screen time >2 hours	279 (80.9%)	15 (83.3%)
Screen time ≤2 hours	66 (19.1%)	3 (16.7%)
Potential confounder	Completers	Lost to follow-up
Psychological symptoms score	8.1 ± 5.3	11.2 ± 6.4
Smokers		
Never	438 (99.5%)	31 (100%)
1 or 2 times	2 (0.5%)	-
3 to 5 times	-	-
6 to 9 times	-	-
10 or more times	-	-
Alcohol user		
Never	316 (71.8%)	23 (74.2%)
1 or 2 times	90 (20.5%)	6 (19.4%)
3 to 5 times	23 (5.2%)	2 (6.4%)
6 to 9 times	4 (0.9%)	-
10 or more times	7 (1.6%)	-
Physical activity		
Team sport (Yes)	170 (58.0%)	8 (53.3%)
Team sport (No)	123 (42%)	7 (46.7%)
Individual sport (Yes)	218 (72.2%)	6 (40.0%)
Individual sport (No)	84 (27.8%)	9 (60.0%)

Table 5.5 Baseline values of completers vs. loss to follow-up among children without chronic musculoskeletal pain		
Total	Completers	Lost to follow-up
	944 (93.6%)	65 (6.4%)
Sleep problems	Completers	Lost to follow-up
Yes	305 (32.5%)	22 (34.4%)
No	633 (67.5%)	42 (65.6%)
Potential effect modifier	Completers	Lost to follow-up
Gender (N %)		
Boys	434 (45.9%)	28 (43.1%)
Girls	510 (54.1%)	37 (56.9%)
Puberty		
Pre-Early puberty	620 (87.2%)	28 (87.5%)
Mid-Advanced puberty	91 (12.8%)	4 (12.5%)
Screen time		
Screen time >2 hours	567 (77.6%)	29 (82.9%)
Screen time ≤2 hours	164 (22.4%)	6 (17.1%)
Potential confounder	Completers	Lost to follow-up
Psychological symptoms score	8.1 ± 5.3	10.1 ± 6.4
Smokers		
Never	934 (99.1%)	63 (96.9%)
1 or 2 times	7 (0.7%)	2 (3.1%)
3 to 5 times	2 (0.2%)	-
6 to 9 times	-	-
10 or more times	-	-
Alcohol user		
Never	601 (63.8%)	44 (67.7%)
1 or 2 times	237 (25.2%)	13 (20.0%)
3 to 5 times	61 (6.5%)	5 (7.7%)
6 to 9 times	18 (1.9%)	3 (4.6%)
10 or more times	25 (2.6%)	-
Physical activity		
Team sport (Yes)	403 (63.4%)	14 (58.3%)
Team sport (No)	233 (36.6%)	10 (41.7%)
Individual sport (Yes)	476 (73.5%)	12 (48.0%)
Individual sport (No)	172 (26.5%)	13 (52.0%)

5.4 Results of descriptive analyses

Descriptive analyses of the baseline of the Childhood to Adolescence Transition Study (CATS) dataset were performed. The results of these analyses are shown in the following sections.

5.4.1 Baseline characteristics of the total sample

Baseline descriptive analyses of the total sample are outlined in Table 5.6. Approximately 60% of children reported having had musculoskeletal pain that lasted one day or more in the last month, with similar proportions between boys and girls, and approximately 15% of children reported chronic musculoskeletal pain (musculoskeletal pain lasting >3 months), again with similar proportions between boys and girls. Figures on sleep problems show that just over 35% of children reported sleep problems, with similar proportions between boys and girls. More girls (54%) than boys (46%) were present in the sample. Girls were on average in a more advanced pubertal development stage compared to boys (21% and 3% in the mid/advanced pubertal stage, respectively). The average number of hours of screen time per day in children was 3.3, with similar values between boys and girls (3.4 h/day vs 3.3 h/day). Accordingly, for around 78% of children the average screen time was > 2 h/day. Also, more boys had average values of screen time > 2 h/day than girls (81% vs. 75%, respectively). With regard to potential confounders, the average psychological symptoms score was 8.4 ± 5.5, and it was higher in boys compared to girls (8.9 ± 5.8 vs. 7.9 ± 5.1). Approximately 99% of children reported that they had never smoked before, and only 16 children had smoked 1 or more times. Among these children, more boys (2.4%) than girls (0.5%) reported having smoked before. Approximately 37% of children (45% boys and 31% of girls) had already had more than just one sip of alcohol, even if most of them for only 1 or 2 times. Outside school hours, 64% of children engaged in team sports, with more boys (74%) than girls (54%), while around 73% of children engaged regularly in individual sports, with no

gender differences. In the following sections, descriptive analyses of the baseline characteristics of children without musculoskeletal pain and without chronic musculoskeletal pain are outlined.

Table 5.6 Baseline characteristics of the total sample			
Age	Boys	Girls	Overall
Mean (±SD)	9.0 ± 0.4	9.0 ± 0.4	9.0 ± 0.4
Musculoskeletal pain	Boys	Girls	Overall
Yes	339 (62.0%)	379 (58.9%)	718 (60.3%)
No	208 (38.0%)	264 (41.1%)	472 (39.7%)
Chronic musculoskeletal pain	Boys	Girls	Overall
Yes	84 (15.4%)	96 (14.9%)	180 (15.1%)
No	462 (84.6%)	547 (85.1%)	1,009 (84.9%)
Sleep problems	Boys	Girls	Overall
Yes	185 (34.1%)	230 (35.8%)	415 (35.1%)
No	357 (65.9%)	412 (64.2%)	769 (64.9%)
Potential effect modifier	Boys	Girls	Overall
Gender (N %)	572 (46.2%)	667 (53.8%)	1,239
Puberty			
Pubertal score	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4
Pubertal stages			
Pre-Early puberty	403 (96.6%)	373 (78.5%)	776 (87.0%)
Mid-Advanced puberty	14 (3.4%)	102 (21.5%)	116 (13.0%)
Screen time			
Screen time (mean)	3.4 ± 1.8	3.3 ± 1.7	3.3 ± 1.8
Screen time >2 hours	345 (81.2%)	370 (74.9%)	715 (77.8%)
Screen time ≤2 hours	80 (18.8%)	124 (25.1%)	204 (22.2%)
Potential confounder	Boys	Girls	Overall
Psychological symptoms score	8.9 ± 5.8	7.9 ± 5.1	8.4 ± 5.5
Smokers			
Never	533 (97.6%)	642 (99.5%)	1,175 (98.6%)
1 or 2 times	10 (1.8%)	3 (0.5%)	13 (1.1%)
3 to 5 times	2 (0.4%)	-	2 (0.2%)
6 to 9 times	1 (0.2%)	-	1 (0.1%)
10 or more times	-	-	-
Alcohol user			
Never	299 (54.9%)	445 (68.9%)	744 (62.5%)
1 or 2 times	150 (27.5%)	159 (24.6%)	309 (25.9%)
3 to 5 times	56 (10.3%)	26 (4.0%)	82 (6.9%)
6 to 9 times	18 (3.3%)	7 (1.1%)	25 (2.1%)
10 or more times	22 (4.0%)	9 (1.4%)	31 (2.6%)
Physical activity			
Team sport (Yes)	275 (74.3%)	229 (54.3%)	504 (63.6%)
Team sport (No)	95 (25.7%)	193 (45.7%)	288 (36.4%)
Individual sport (Yes)	273 (73.4%)	319 (73.5%)	592 (73.4%)
Individual sport (No)	99 (26.6%)	115 (26.5%)	214 (26.6%)

5.4.2 Baseline characteristics of children with musculoskeletal pain

Baseline descriptive analyses of children with musculoskeletal pain are outlined in Table 5.7. Figures on sleep problems show that approximately 44% of children reported sleep problems, with similar proportions between boys and girls. There were more girls (53%) than boys (47%) with musculoskeletal pain. Approximately 22% of girls were in a mid/advanced pubertal stage (mid pubertal, late pubertal or post-pubertal stage) compared to only 3% of boys. Boys had slightly higher average number of hours of screen time per day than girls (3.3 h/day vs 3.2 h/day, respectively), and approximately 76% of children (79% of boys vs. 73% of girls) had an average of screen time of > 2 h/day. The average psychological symptoms score was 8.5 ± 5.6 and it was higher in boys compared to girls (9.1 ± 6.0 vs. 8.0 ± 5.0). Approximately 98% of children reported that they had never smoked before, and 14 children smoked 1 or more times. Approximately 44% of children (52% boys and 37% of girls) had already had more than just one sip of alcohol, even if most of them for only 1 or 2 times. Outside school hours, 68% of children engaged in team sports, with more boys (78%) than girls (59%), and 75% of children engaged regularly in individual sports, with no gender differences.

Table 5.7 Baseline characteristics of children with musculoskeletal pain			
Sleep problems	Boys	Girls	Overall
Yes	140 (41.8%)	173 (45.8%)	313 (43.9%)
No	195 (58.2%)	205 (54.2%)	400 (56.1%)
Potential effect modifier	Boys	Girls	Overall
Gender (N %)	339 (47.2%)	379 (52.8%)	718
Puberty			
Pubertal score	1.3 ± 0.3	1.5 ± 0.4	1.4 ± 0.4
Pubertal stages			
Pre-Early puberty	239 (96.8%)	215 (77.6%)	454 (86.6%)
Mid-Advanced puberty	8 (3.2%)	62 (22.4%)	70 (13.4%)
Screen time			
Screen time (mean)	3.3 ± 1.6	3.2 ± 1.7	3.3 ± 1.7
Screen time >2 hours	197 (79.1%)	211 (73.5%)	408 (76.1%)
Screen time ≤2 hours	52 (20.9%)	76 (26.5%)	128 (23.9%)
Potential confounder	Boys	Girls	Overall
Psychological symptoms score	9.1 ± 6.0	8.0 ± 5.0	8.5 ± 5.6
Smokers			
Never	326 (96.5%)	377 (99.5%)	703 (98.1%)
1 or 2 times	9 (2.6%)	2 (0.5%)	11 (1.5%)
3 to 5 times	2 (0.6%)	-	2 (0.3%)
6 to 9 times	1 (0.3%)	-	1 (0.1%)
10 or more times	-	-	-
Alcohol user			
Never	162 (47.9%)	240 (63.3%)	402 (56.1%)
1 or 2 times	105 (31.1%)	108 (28.5%)	213 (29.7%)
3 to 5 times	40 (11.8%)	17 (4.5%)	57 (7.9%)
6 to 9 times	15 (4.4%)	6 (1.6%)	21 (2.9%)
10 or more times	16 (4.7%)	8 (2.1%)	24 (3.4%)
Physical activity			
Team sport (Yes)	171 (78.1%)	147 (58.8%)	318 (67.8%)
Team sport (No)	48 (21.9%)	103 (41.2%)	171 (32.2%)
Individual sport (Yes)	163 (75.1%)	193 (75.1%)	356 (75.1%)
Individual sport (No)	54 (24.9%)	64 (24.9%)	118 (24.9%)

5.4.3 Baseline characteristics of children without musculoskeletal pain

Baseline descriptive analyses of children without musculoskeletal pain are outlined in Table 5.8. Figures on sleep problems show that approximately 22% of children reported sleep problems, with similar proportions between boys and girls. There were more girls (56%) than boys (44%) without musculoskeletal pain. Approximately 21% of girls were in a mid/advanced pubertal stage (mid pubertal, late pubertal or post-pubertal stage) compared to only 3% of boys. The average number of hours of screen time per day in children was 3.5, with similar values between boys and girls (3.5 h/day vs 3.4 h/day), and approximately 81% of children (85% of boys vs. 78% of girls) had an average of screen time of > 2 h/day. The average psychological symptoms score was 8.3 ± 5.4 and it was higher in boys compared to girls (8.8 ± 5.5 vs. 7.8 ± 5.3). Approximately 99% of children reported that they had never smoked before, and only 2 children smoked 1 or more times. Approximately 28% of children (34% boys and 23% of girls) had already had more than just one sip of alcohol, even if most of them for only 1 or 2 times. Outside school hours, 58% of children engaged in team sports, with more boys (69%) than girls (48%), while around 71% of children engaged regularly in individual sports, with no gender differences.

Table 5.8 Baseline characteristics of children without musculoskeletal pain			
Sleep problems	Boys	Girls	Overall
Yes	45 (21.7%)	57 (21.8%)	102 (21.8%)
No	162 (78.3%)	204 (78.2%)	366 (78.2%)
Potential effect modifier	Boys	Girls	Overall
Gender (N %)	208 (44.1%)	264 (55.9%)	472
Puberty			
Pubertal score	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Pubertal stages			
Pre-Early puberty	156 (96.9%)	149 (79.3%)	305 (87.4%)
Mid-Advanced puberty	5 (3.1%)	39 (20.7%)	44 (12.6%)
Screen time			
Screen time (mean)	3.5 ± 1.9	3.4 ± 1.8	3.5 ± 1.9
Screen time >2 hours	141 (84.9%)	153 (77.7%)	294 (80.9%)
Screen time ≤2 hours	25 (15.1%)	44 (22.3%)	69 (19.1%)
Potential confounder	Boys	Girls	Overall
Psychological symptoms score	8.8 ± 5.5	7.8 ± 5.3	8.3 ± 5.4
Smokers			
Never	207 (99.5%)	262 (99.6%)	469 (98.6%)
1 or 2 times	1 (0.5%)	1 (0.4%)	2 (0.4%)
3 to 5 times	-	-	-
6 to 9 times	-	-	-
10 or more times	-	-	-
Alcohol user			
Never	137 (66.2%)	202 (76.5%)	339 (71.9%)
1 or 2 times	45 (21.7%)	51 (19.3%)	96 (20.4%)
3 to 5 times	16 (7.7%)	9 (3.4%)	25 (5.3%)
6 to 9 times	3 (1.5%)	1 (0.4%)	4 (0.9%)
10 or more times	6 (2.9%)	1 (0.4%)	7 (1.5%)
Physical activity			
Team sport (Yes)	99 (68.8%)	79 (48.2%)	178 (57.8%)
Team sport (No)	45 (31.2%)	85 (51.8%)	130 (42.2%)
Individual sport (Yes)	104 (70.3%)	120 (71.0%)	224 (70.7%)
Individual sport (No)	44 (29.7%)	49 (28.9%)	93 (29.3%)

5.4.4 Baseline characteristics of children with chronic musculoskeletal pain

Table 5.9 outlines the baseline characteristics of children with chronic musculoskeletal pain. Figures on sleep problems show that approximately 49% of children reported sleep problems, with a slightly higher proportion in girls (50%) compared to boys (48%). There were more girls (53%) than boys (47%) with chronic musculoskeletal pain at baseline. Approximately 24% of girls were in a mid/advanced pubertal stage (mid pubertal, late pubertal or post-pubertal stage) compared to only 3% of boys. The average number of hours of screen time per day in children was 3.4 ± 1.7, with no gender differences in values, and approximately 80% of children (85% of boys vs. 75% of girls) had an average of screen time of > 2 h/day. The average psychological symptoms score was 9.5 ± 5.9 and it was higher in boys compared to girls (10.2 ± 6.4 vs. 8.9 ± 5.4). Approximately 97% of children reported that they had never smoked before, and only 5 children smoked 1 or more times. Approximately 47% of children (61% of boys and 35% of girls) had already had more than just one sip of alcohol, even if most of them for only 1 or 2 times. Outside school hours, 68% of children engaged in team sports, with more boys (69%) than girls (66%), while around 78% of children engaged regularly in individual sports, with no gender differences.

Table 5.9 Baseline sleep problems of children with chronic musculoskeletal pain			
Sleep problems	Boys	Girls	Overall
Yes	39 (47.6%)	48 (50.0%)	87 (48.9%)
No	43 (52.4%)	48 (50.0%)	91 (51.1%)
Potential effect modifier	Boys	Girls	Overall
Gender (N %)	84 (46.7%)	96 (53.3%)	180
Puberty			
Pubertal score	1.3 ± 0.3	1.5 ± 0.5	1.4 ± 0.4
Pubertal stages			
Pre-Early puberty	58 (96.7%)	53 (75.7%)	111 (85.4%)
Mid-Advanced puberty	2 (3.3%)	17 (24.3%)	19 (14.6%)
Screen time			
Screen time (mean)	3.4 ± 1.5	3.4 ± 2.0	3.4 ± 1.8
Screen time >2 hours	52 (85.3%)	54 (75.0%)	106 (79.7%)
Screen time ≤2 hours	9 (14.7%)	18 (25.0%)	27 (20.3%)
Potential confounder	Boys	Girls	Overall
Psychological symptoms score	10.2 ± 6.4	8.9 ± 5.4	9.5 ± 5.9
Smokers			
Never	79 (94.0%)	96 (100%)	175 (97.2%)
1 or 2 times	4 (4.8%)	-	4 (2.2%)
3 to 5 times	-	-	-
6 to 9 times	1 (1.2%)	-	1 (0.6%)
10 or more times	-	-	-
Alcohol user			
Never	33 (39.3%)	62 (64.6%)	95 (52.8%)
1 or 2 times	35 (41.7%)	24 (25.0%)	59 (32.8%)
3 to 5 times	10 (11.9%)	6 (6.2%)	16 (8.9%)
6 to 9 times	2 (2.4%)	2 (2.1%)	4 (2.2%)
10 or more times	4 (4.8%)	2 (2.1%)	6 (3.3%)
Physical activity			
Team sport (Yes)	38 (69.1%)	41 (66.1%)	79 (67.5%)
Team sport (No)	17 (30.9%)	21 (33.9%)	38 (32.5%)
Individual sport (Yes)	44 (78.6%)	48 (77.4%)	92 (77.9%)
Individual sport (No)	12 (21.4%)	14 (22.6%)	26 (22.1%)

5.4.5 Baseline characteristics of children without chronic musculoskeletal pain

Table 5.10 outlines the baseline characteristics of children without chronic musculoskeletal pain. Figures on sleep problems show that approximately 33% of children reported sleep problems, with similar proportions between boys and girls. There were more girls (54%) than boys (46%) without chronic musculoskeletal pain. Approximately 21% of girls were in a mid/advanced pubertal stage (mid pubertal, late pubertal or post-pubertal stage) compared to only 3% of boys. The average number of hours of screen time per day in children was 3.3 ± 1.7, with similar values between boys and girls (3.4 h/day vs 3.3 h/day), and approximately 78% of children (81% of boys vs. 75% of girls) had an average of screen time of > 2 h/day. The average psychological symptoms score was 8.2 ± 5.4 and it was higher in boys compared to girls (8.8 ± 5.7 vs. 7.7 ± 5.1). Approximately 99% of children reported that they had never smoked before, and only 11 children smoked 1 or more times. Approximately 36% of children (42% boys and 31% of girls) had already had more than just one sip of alcohol, even if most of them for only 1 or 2 times. Outside school hours, 63% of children engaged in team sports, with more boys (75%) than girls (53%), while around 72% of children engaged regularly in individual sports, with no gender differences.

Table 5.10 Baseline sleep problems of children without chronic musculoskeletal pain			
Sleep problems	Boys	Girls	Overall
Yes	145 (31.6%)	182 (33.5%)	327 (32.6%)
No	314 (68.4%)	361 (66.5%)	675 (67.4%)
Potential effect modifier	Boys	Girls	Overall
Gender (N %)	462 (45.8%)	547 (54.2%)	1,009
Puberty			
Pubertal score	1.3 ± 0.3	1.4 ± 0.4	1.4 ± 0.4
Pubertal stages			
Pre-Early puberty	337 (96.8%)	311 (78.7%)	648 (87.2%)
Mid-Advanced puberty	11 (3.2%)	84 (21.2%)	95 (12.8%)
Screen time			
Screen time (mean)	3.4 ± 1.8	3.3 ± 1.7	3.3 ± 1.7
Screen time >2 hours	286 (80.8%)	310 (75.2%)	596 (77.8%)
Screen time ≤2 hours	68 (19.2%)	102 (24.8%)	170 (22.2%)
Potential confounder	Boys	Girls	Overall
Psychological symptoms score	8.8 ± 5.7	7.7 ± 5.1	8.2 ± 5.4
Smokers			
Never	454 (98.3%)	543 (99.5%)	997 (98.9%)
1 or 2 times	6 (1.3%)	3 (0.5%)	9 (0.9%)
3 to 5 times	2 (0.4%)	-	2 (0.2%)
6 to 9 times	-	-	-
10 or more times	-	-	-
Alcohol user			
Never	265 (57.6%)	380 (69.4%)	645 (64.0%)
1 or 2 times	115 (25.0%)	135 (24.7%)	250 (24.8%)
3 to 5 times	46 (10.0%)	20 (3.7%)	66 (6.6%)
6 to 9 times	16 (3.5%)	5 (0.9%)	21 (2.1%)
10 or more times	18 (3.9%)	7 (1.3%)	25 (2.5%)
Physical activity			
Team sport (Yes)	232 (75.3%)	185 (52.6%)	417 (63.2%)
Team sport (No)	76 (24.7%)	167 (47.4%)	243 (36.8%)
Individual sport (Yes)	223 (72.2%)	265 (72.8%)	488 (72.5%)
Individual sport (No)	86 (27.8%)	99 (27.2%)	185 (27.5%)

5.5 Discussion

5.5.1 Descriptive analysis

5.5.1.1 Prevalence of musculoskeletal pain in the CATS cohort

Baseline descriptive analysis showed that approximately 60% (718/1190) of children reported having had musculoskeletal pain that lasted one day or more in the last month. In comparison to a range of literature carried out on children of a similar age, with reported prevalence figures between 27% - 39% (Jones, Watson, et al., 2003; Mikkelsson, Salminen, & Kautiainen, 1997; Szpalski, Gunzburg, Balague, Nordin, & Melot, 2002), the baseline prevalence of musculoskeletal pain is higher in this cohort. Although this may raise questions about the generalizability of the results of this study (Hennekens & Buring, 1987), it should be considered that a direct comparison between figures of this cohort with those of other cohorts is limited due to variability in the assessment of pain and differences in musculoskeletal pain sites. For example, other studies (as outlined above) assessed only the presence of low back pain, or the timeline on presence of musculoskeletal pain was different (e.g. at least once a month), such differences would lead to a lower reported prevalence. Furthermore differences might be explained by different methods of data collection (pain questionnaire together with pain manikin provided by means of an iPad in CATS) compared to earlier studies (paper questionnaire based), however such differences are likely to be small as electronic data collection has been shown to be comparable to paper versions (von Baeyer, Lin, Seidman, Tsao, & Zeltzer, 2011).

5.5.1.2 Sleep problems

Several studies report figures about prevalence of sleep problems in children. Figures range between 0.5% and 9.3% for having "often" sleep problems, nightmares and being too tired, in a study of Finnish adolescents 15-16 years old (Auvinen et al., 2010), and between 14% and 42% for daytime-tiredness, difficulty in falling asleep and waking up during the night in Finnish children 10-12 years old (Mikkelsson et al., 2008). In a sample of 15 years old English children, 15.2% of children considered themselves "poor sleepers" and 43.5% reported waking up during the night one or more times (Harrison et al., 2014), and a review of studies on sleep problems (ranging from difficulties in falling asleep and night waking to obstructive sleep apnea) reports a range of 25-40% for children and adolescents (Owens & Witmans, 2004). The figure from children within the CATS cohort (35% of children with sleep problems), does appear within the range of figures provided in previous studies suggesting that CATS provides a representative sample.

5.5.1.3 Differences between children with and without musculoskeletal pain or chronic musculoskeletal pain at baseline

Comparison between children with and without musculoskeletal pain or chronic musculoskeletal pain showed that the proportion of children with sleep problems was higher among those with musculoskeletal pain (44%) or chronic musculoskeletal pain (49%) compared to those without musculoskeletal pain (22%) or without chronic musculoskeletal pain (33%). These figures are consistent with the potential bi-directional relationship between musculoskeletal pain and sleep problems reported in the literature (Finan, Goodin, & Smith, 2013), where the initial presence of musculoskeletal pain may affect sleep leading to an increase of sleep problems. In addition, in accordance with the proposed reciprocal relationship between psychological symptoms and pain (Dersh, Polatin, & Gatchel, 2002; Keefe, Rumble, Scipio, Giordano, & Perri, 2004; Linton & Shaw, 2011), the average psychological symptoms score was higher among those with musculoskeletal pain (8.5 ± 5.6) or chronic musculoskeletal pain (9.5 ± 5.9) compared to those without musculoskeletal pain (8.3 ± 5.4) or without chronic musculoskeletal pain (8.2 ± 5.4). Similarly, the

proportion of those playing team sports and individuals sport was higher among those with musculoskeletal pain (68% participated in team sports, 75% in individual sports) or chronic musculoskeletal pain (68% team sports, 78% individual sports) compared to those without musculoskeletal pain (58% team sports, 71% individual sports) or without chronic musculoskeletal pain (63% team sports, 72% individual sports). It may be hypothesised that higher levels of physical activity lead to an increase in musculoskeletal pain of traumatic origin, as suggested by previous studies (El-Metwally, Salminen, Auvinen, MacFarlane, & Mikkelsson, 2007; Kamada et al., 2016).

5.5.2 Analysis of missing data due to loss to follow-up

The difference in baseline characteristics between children who completed follow-up and those lost at follow-up were described to assess the potential risk for selection bias due to attrition (Section 5.3.3). Results showed that children lost at follow-up had a higher psychological symptoms score, were more likely to be girls, reported higher levels of screen time, were in a more advanced pubertal status, and were less likely to perform individual and team sports than completers. However, the difference in these variables was small (up to a 10% difference for most variables). In addition, the proportion of children loss to follow-up was also small (7% of those without musculoskeletal pain and 6% of those without chronic musculoskeletal pain at baseline). Therefore, it is unlikely that loss to follow-up resulted in a substantive selection bias effect.

Chapter Six. The association of sleep problems with musculoskeletal pain onset in children: results of the Childhood to Adolescence Transition Study (CATS) cohort

This chapter's focus is on the analysis performed on the group of children without musculoskeletal pain and chronic musculoskeletal pain at baseline. The results of the logistic regression analysis of the association between sleep problems and the onset of both musculoskeletal pain and chronic musculoskeletal pain will be outlined, together with a discussion of the results. The following section details the process for imputation of missing data before the results of the logistic regression analysis are described. For a full description of the processes to account for missing data please see chapter 4, Section 4.5.5.

6.1 MCAR test and multiple imputation

The process of selection of children for analysis, which led to 441 children without musculoskeletal pain at baseline who reported data on musculoskeletal pain at follow-up (944 children for chronic musculoskeletal pain), was outlined in Section 5.3.1, along with a description of the baseline missing data (Section 5.3.2). A Little's test of MCAR was performed to test whether data were missing completely at random (MCAR); the test was not significant either among children without musculoskeletal pain at baseline (p = 0.14) and children without chronic musculoskeletal pain at baseline (p = 0.18), showing that data were MCAR. Following this, multiple imputation was performed to replace missing data, in order to increase statistical power and provide more accurate estimates of variability compared to complete-case analysis. A chained equation multiple imputation method was applied to impute missing baseline characteristics (the outcome musculoskeletal pain at follow-up was not imputed) taking account of all variables to be included in the analysis within the dataset. Once imputed the logistic regression analysis was

carried out (Section 6.2). A sensitivity analysis was performed with the complete-case dataset and comparisons of the main findings between the imputed and the complete-case dataset are described in appendix V.

6.2 Associations between sleep problems and musculoskeletal pain onset in children

6.2.1 Sleep problems at baseline and incidence of musculoskeletal pain in children at follow-up

The 1-year incidence of musculoskeletal pain at follow-up was 42.6% (188/441 children present at follow-up). The two sleep categories: sleep problems (often, almost always) and no sleep problems (never, almost never, sometimes) were examined in relation to the proportion of musculoskeletal pain at follow-up. The proportion of children reporting musculoskeletal pain was higher in those with sleep problems (48/96, 50.0%) compared to those with no sleep problems (140/345, 40.6%) (Table 6.1).

Table 6.1 Sleep problems at baseline and musculoskeletal pain presence at follow-up among children musculoskeletal pain-free at baseline

	Musculoskeletal pain at follow-up		
Sleep problems	**Yes**	**No**	**Total**
Yes	48 (50.0%)	48 (50.0%)	96
No	140 (40.6%)	205 (59.4%)	345
Total	188	253	441

6.2.2 Association between baseline sleep problems and musculoskeletal pain onset at follow-up (logistic regression analysis)

Logistic regression analysis was performed to investigate the association between sleep problems at baseline and the onset of musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted and then with adjustment for psychological symptoms, individual sports and team sports at baseline. Results are shown in Table 6.2. The unadjusted result shows a non-significant trend of increased odds for the onset of musculoskeletal pain in children with sleep problems (OR = 1.47; 95% CI 0.93, 2.31). This effect is attenuated after adjustment for psychological symptoms, individual sports and team sports but still shows an increased odds of musculoskeletal pain with sleep problems (Adj. OR = 1.35; 95% CI 0.84, 2.16).

Table 6.2 Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 441)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.47	0.93, 2.31
Adjusted analysis*		
Overall (N = 441)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.35	0.84, 2.16
*Analysis adjusted for psychological symptoms (total score), individual sports and team sports		

6.2.2.1 Effect modification by gender

Effect modification was assessed by performing stratified analysis by gender and an interaction test (gender # sleep problems). Results are shown in Table 6.3. Stratified analysis showed that male children with sleep problems were statistically significantly at higher odds for the onset of musculoskeletal pain (Adj. OR = 2.79; 95% CI 1.39, 5.59) compared to males without sleep problems. Conversely, a non-significant effect was found for females, though the direction of effect shows a reduction of odds (Adj. OR = 0.58; 95% CI 0.28, 1.18). The interaction test (gender # sleep problems) was significant (Adj. OR = 3.88; 95% CI 1.48, 10.16) indicating the presence of a statistically significant interaction.

Table 6.3 Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by gender

Unadjusted analysis		
Females (N = 245)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	0.87	0.46, 1.63
Males (N = 196)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.76	1.38, 5.52
Adjusted analysis*		
Females (N = 245)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	0.58	0.28, 1.18
Males (N = 196)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.79	1.39, 5.59
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Gender # Sleep problems	3.88	1.48, 10.16
*Analysis adjusted for psychological symptoms (total score), individual sports and team sports		

6.2.2.2 Effect modification by pubertal stage

Effect modification was assessed by performing stratified analysis by pubertal stages and an interaction test (puberty # sleep problems). Analysis stratified by pubertal stages showed that children with sleep problems, both in an early pubertal stage (Adj. OR = 1.38; 95% CI 0.83, 2.30) and in an advanced pubertal stage (Adj. OR = 1.31; 95% CI 0.25, 6.90) were not statistically significantly at increased odds for the onset of musculoskeletal pain (Table 6.4), with estimates of risk similar to that of the overall effect (Adj. OR = 1.35; 95% CI 0.84, 2.16, see Section 6.2.2). The interaction test (puberty # sleep problems) was not significant (Adj. OR = 1.15; 95% CI 0.22, 5.94).

Table 6.4 Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by pubertal stage

Unadjusted analysis		
Early pubertal stage (N = 377) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.45	0.89, 2.37
Advanced pubertal stage (N = 50) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.69	0.38, 7.63
Adjusted analysis*		
Early pubertal stage (N = 377) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.38	0.83, 2.30
Advanced pubertal stage (N = 50) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.31	0.25, 6.90
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Puberty # Sleep problems	1.15	0.22, 5.94

*Analysis adjusted for psychological symptoms (total score), individual sports and team sports
• Sample size vary between 377 and 391
•• Sample size vary between 50 and 64

6.2.2.3 Effect modification by screen time

Effect modification was assessed by performing stratified analysis by levels of screen time and an interaction test (screen time # sleep problems). Analysis stratified by levels of screen time showed trends of association in different directions. Children with low levels of screen time showed a non-significant trend of lessening of odds (Adj. OR = 0.79; 95% CI 0.21, 2.95). Conversely, those with high levels of screen time were at non-significant higher odds for the onset of musculoskeletal pain (Adj. OR = 1.47; 95% CI 0.88, 2.48) (Table 6.5), and the estimate was similar to that of the overall analysis (Adj. OR = 1.35; 95% CI 0.84, 2.16). The interaction test (screen time # sleep problems) was not significant (Adj. OR = 1.83; 95% CI 0.47, 7.07).

Table 6.5 Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by screen time

Unadjusted analysis		
Low screen time (≤2 hours/day) (N = 79) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	0.85	0.25, 2.90
High screen time (>2 hours/day) (N = 345) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.62	0.98, 2.68
Adjusted analysis*		
Low screen time (≤2 hours/day) (N = 79) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	0.79	0.21, 2.95
High screen time (>2 hours/day) (N = 345) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.47	0.88, 2.48
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Screen time # Sleep problems	1.83	0.47, 7.07

*Analysis adjusted for psychological symptoms (total score), individual sports and team sports
• Sample size vary between 79 and 96
•• Sample size vary between 345 and 362

6.2.3 Sleep problems at baseline and incidence of chronic musculoskeletal pain in children at follow-up

The relationship between the presence of sleep problems at baseline and the onset of chronic musculoskeletal pain in children at follow-up was tested. The sample used to carry out this analysis included those children without chronic musculoskeletal pain at baseline and who completed questionnaires at follow-up (N= 944). Ninety-nine children among these 944 developed chronic musculoskeletal pain, therefore the 1-year incidence is estimated at 10.5% (99/944). The two sleep categories: sleep problems (often, almost always) and no sleep problems (never, almost never, sometimes) were examined in relation to the proportion of chronic musculoskeletal pain at follow-up. The proportion of chronic musculoskeletal pain was approximately double in children with sleep problems (16.9%) compared to those with no sleep problems at baseline (7.4%) (Table 6.6).

Table 6.6 Sleep problems at baseline and chronic musculoskeletal pain at follow-up among children without chronic musculoskeletal pain at baseline

	Chronic musculoskeletal pain at follow-up		
Sleep problems	**Yes**	**No**	**Total**
Yes	52 (16.9%)	255 (83.1%)	307
No	47 (7.4%)	590 (92.6%)	637
Total	99	845	944

6.2.4 Association between baseline sleep problems and chronic musculoskeletal pain onset at follow-up (logistic regression analysis)

Logistic regression analysis was performed to test the association between sleep problems at baseline and the onset of chronic musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted and then with adjustment for psychological symptoms, individual sports, team sports and musculoskeletal pain at baseline. Results are shown in Table 6.7. Children with sleep problems were statistically significantly at higher odds for the onset of chronic musculoskeletal pain (Adj. OR = 2.22; 95% CI 1.43, 3.44).

Table 6.7 Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 944)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.56	1.68, 3.90
Adjusted analysis*		
Overall (N = 944)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.22	1.43, 3.44
*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain		

6.2.4.1 Effect modification by gender

Stratified analysis by gender and a test for interaction (gender # sleep problems) were carried out on the above model. Results are shown in Table 6.8. Stratification shows a very similar effect in both males (Adj. OR = 2.15; 95% CI 1.15, 4.01) and females (Adj. OR = 2.36; 95% CI 1.26, 4.43), with estimates similar to that of the overall analysis (Adj. OR = 2.22; 95% CI 1.43, 3.44, see Section 6.2.4). The interaction test was not significant (Adj. OR = 0.85; 95% CI 0.36, 1.97).

Table 6.8 Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by gender

Unadjusted analysis		
Females (N = 510)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.75	1.51, 4.99
Males (N = 434)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.40	1.32, 4.36
Adjusted analysis*		
Females (N = 510)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.36	1.26, 4.43
Males (N = 434)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.15	1.15, 4.01
Interaction term*		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Gender # Sleep problems	0.85	0.36, 1.97
*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain		

6.2.4.2 Effect modification by pubertal stage

Stratified analysis by pubertal stages and a test for interaction (puberty # sleep problems) were performed. Results are shown in Table 6.9. Stratification shows that the association is stronger in the subgroup with an advanced pubertal stage (Adj. OR = 4.15; 95% CI 0.85, 20.20), although the estimates for this subgroups shows large uncertainty (wide Confidence Intervals) and the effect is not significant. Children in an early pubertal stage (Adj. OR = 2.08; 95% CI 1.29, 3.34) showed an estimate of odds similar to that of the overall analysis (Adj. OR = 2.22; 95% CI 1.43, 3.44). The interaction test was not significant (Adj. OR = 2.02; 95% CI 0.38, 10.55).

Table 6.9 Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by pubertal stage

Unadjusted analysis		
Early pubertal stage (N = 808)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.39	1.52, 3.75
Advanced pubertal stage (N = 112)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	4.80	1.02, 22.65
Adjusted analysis*		
Early pubertal stage (N = 808)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems*	2.08	1.29, 3.34
Advanced pubertal stage (N = 112)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems*	4.15	0.85, 20.20
Interaction term*		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Puberty # Sleep problems	2.02	0.38, 10.55

*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain
•Sample size vary between 808 and 832
••Sample size vary between 112 and 136

6.2.4.3 Effect modification by screen time

Stratified analysis by levels of screen time and a test for interaction (screen time # sleep problems) were performed. Results are shown in Table 6.10. Stratified analysis showed that children with high levels of screen time were statistically significantly at increased odds for the onset of chronic musculoskeletal pain (Adj. OR = 2.22; 95% CI 1.33, 3.70), but not those with low levels of screen time (Adj. OR = 2.11; 95% CI 0.73, 6.06), and both strata showed an estimate of odds similar to that of the overall analysis (Adj. OR = 2.22; 95% CI 1.43, 3.44). The interaction test was not significant (Adj. OR = 1.20; 95% CI 0.38, 3.80).

Table 6.10 Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by screen time

Unadjusted analysis		
Low screen time (≤2 hours/day) (N = 198)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.15	0.79, 5.84
High screen time (>2 hours/day) (N = 720)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.68	1.64, 4.37
Adjusted analysis*		
Low screen time (≤2 hours/day) (N = 198)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.11	0.73, 6.06
High screen time (>2 hours/day) (N = 720)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.22	1.33, 3.70
Interaction term*		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Screen time # Sleep problems	1.20	0.38, 3.80

*Analysis adjusted for Psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain

•Sample size vary between 198 and 224

••Sample size vary between 720 and 746

6.3 Discussion

6.3.1 Interpretation of the findings and comparison with previous literature

6.3.1.1 Association between the presence of sleep problems at baseline and the onset of musculoskeletal pain or chronic musculoskeletal pain at follow-up in children

Overall the results show that the 1-year incidence for musculoskeletal pain onset was 42.6% which is similar to the 38% incidence for musculoskeletal pain reported in a relevant review of musculoskeletal pain in children (McBeth & Jones, 2007). Also, in a study that used the same pain questionnaire as used in this study, the 1-year incidence for low back pain onset was 18.6%, and given the wider range of body sites used in the CATS study (e.g. whole body) it would be expected that incidence would be higher. The incidence of chronic musculoskeletal pain onset (10.5%) was broadly in line with that reported for chronic widespread pain (7.7%) in a previously published review (McBeth & Jones, 2007).

Within the logistic regression analysis, the association between sleep problems and the onset of musculoskeletal pain was non-significant overall, however the direction of association showed a trend for increased odds (Adj. OR = 1.35; 95% CI 0.84, 2.16) (See Table 6.2), the findings on the association for chronic musculoskeletal pain onset was significant indicating an over twofold increase in odds for children reporting sleep problems compared to those without (Adj. OR = 2.22; 95% CI 1.43, 3.44) (See Table 6.7). The findings of this current study are in agreement with the results of the systematic review (Chapter 2, Section 2.4.3), which showed inconsistent evidence of association between sleep problems and the onset of musculoskeletal pain, though most studies considered in the review do report trends of non-significant increased odds for the associations as reported here. In addition, only one of the studies identified within the review investigated the association for the onset of chronic musculoskeletal pain, and reported that children with sleep problems were at significantly increased odds for chronic musculoskeletal pain (Harrison et al., 2014). This is in accordance with the results of this current study. The general direction of effects is also in line with studies conducted in adults, where individuals with sleep problems were

generally at a higher odds for incident musculoskeletal pain and chronic musculoskeletal pain (Finan, Goodin, & Smith, 2013; Gupta et al., 2007; McBeth et al., 2014; Mork & Nilsen, 2012; Nitter, Pripp, & Forseth, 2012; Taylor et al., 2014).

6.3.1.2 Potential explanations of the association between sleep problems and musculoskeletal pain onset

Results of this current study showed that children with sleep problems were at increased odds (albeit non-significant) for the onset of musculoskeletal pain, and at significant increased odds for the onset of chronic musculoskeletal pain (Section 6.3.1.1). Given that explanations of association are likely to be multifactorial, a biopsychosocial approach will be taken to explain and contextualise these results (a brief introduction to the biopsychosocial model can be found in Section 1.5.1.8). Biological factors observed in children with sleep disturbances include increased production of cytokine and inflammatory mediators (Auvinen et al., 2010; Finan et al., 2013), increased muscle tension (which may lead to pain in itself and to potential postural change and subsequent pain onset) (Auvinen et al., 2010; Bonvanie et al., 2016). Other authors have indicated specific disturbances of sleep architecture that may associate with pain, such as having a shorter duration of slow-wave-phase or a phasic alpha electroencephalogram sleep pattern within the slow-wave-sleep phase suggesting a cyclic process (Kelly, Blake, Power, O'keeffe, & Fullen, 2011; Moldofsky, 2001). Alternatively, sleep problems may affect the neurophysiology of children (possibly through a modification of the opiodergic or serotoninergic neurotransmission systems), which may result in reductions of pain thresholds (Bonvanie et al., 2016; Finan et al., 2013; Harrison et al., 2014). The association between sleep quality and pain may also be partially explained by genetic factors (e.g. susceptibility genes for both conditions), although little is known on specific genes potentially associated with both sleep and pain, and effects are most likely to be gene on gene, and gene on environment interactions (Zhang et al., 2012). There may also be psychological factors that explain the association between sleep and pain. For example, sleep

problems have been found to be more frequent in children with attention deficit hyperactivity disorder (ADHD) (Chervin, Dillon, Bassetti, Ganoczy, & Pituch, 1997; O'Brien et al., 2003), and are linked to negative affect (e.g. mood and emotions) and rumination (Finan et al., 2013), which may place children at increased odds for musculoskeletal pain. Also, sleep problems may be a marker for the development of depression (sleep problems being one of the key symptoms of depression), with evidence that both sleep and depression are linked to pain (Bonvanie et al., 2016; Campbell, Tang, et al., 2013). However, inspection of the data show that the odds for the onset of musculoskeletal pain were similar after adjustment for psychological factors (as measured by the SDQ) in this current study, therefore the proposed psychological hypothesis is less plausible. Alternatively, there may be influence from social factors that may give explanation to the association between sleep problems and musculoskeletal pain. For example child abuse and problems within the school or the family environment have been linked to sleep problems (because sleep is a state of loss of awareness of the external environment, and children need to feel safe to fall asleep (Dahl & Lewin, 2002; Noll, Trickett, Susman & Putnam, 2006), and these wider social factors are also associated with musculoskeletal pain (Brattberg, 1994; Kroner-Herwig, Gassmann, van Gessel, & Vath, 2011; Malleson, Connell, Bennett, & Eccleston, 2001; Noll et al., 2006; Smaldone, Honig, & Byrne, 2007). Similarly, another explanation may involve parental health status, as evidence shows that poor parental health (and risky health behaviour) is associated both with sleep problems and musculoskeletal pain in children (Brattberg, 1994; Smaldone et al., 2007). Overall the proposed explanations suggest potential complex interactions (a probable combination effect) for the reported association, and further work to assess these influences is required. The above factors may also play a significant role in explaining the findings for chronic musculoskeletal pain. However, the effect for chronic musculoskeletal pain was much stronger (significant finding of over double the odds). This additional effect may be explained by a bi-directional relationship between sleep and musculoskeletal pain. Here sleep problems can at first affect the onset of musculoskeletal pain, but then the presence of musculoskeletal pain

disrupts sleep and the cycle continues. This effect may have resulted in the exacerbation of the biological, psychological and social factors proposed above, making children more vulnerable to the development of chronic musculoskeletal pain. This is supported by the potential bi-directional relationship between sleep and musculoskeletal pain reported in recent reviews (Finan et al., 2013; McBeth, Wilkie, Bedson, Chew-Graham, & Lacey, 2015). In conclusion, the explanation of the association between sleep problems and musculoskeletal pain is probably complex and likely to be explained by several factors, therefore further research to unravel the proposed mechanisms is needed.

6.3.1.3 Effect modification by gender

The test for interaction between sleep and gender showed a statistically significant result. Results of analysis stratified by gender showed estimates of association that were different compared to the overall estimate for both strata. In male children with sleep problems at baseline the odds for the onset of musculoskeletal pain one year later were 179% higher compared to male children without sleep problems. Opposite, in female children the presence of sleep problems at baseline had the direction of a protective effect (42% decreased odds) on the onset of musculoskeletal pain one year later, though this estimate was not statistically significant. Overall these results suggest that the relationship between sleep problems and the onset of musculoskeletal pain may be modified by gender. There may be several explanations for these findings. Evidence shows that boys, before the period of adolescence, may be at increased likelihood of sleep problems compared to girls (Archbold, Pituch, Panahi, & Chervin, 2002; Blunden & Galland, 2014), and consequently are at increased odds of onset of musculoskeletal pain. However, girls may be at an increased odds in older adolescence (Bonvanie et al., 2016), which is consistent with the findings from the review (Chapter 2). In the review, two studies explored the relationship between sleep problems and the onset of musculoskeletal pain by gender and reported an evidence of association for neck pain onset, albeit only in girls (Auvinen et al., 2010; Ståhl et al., 2008).

However, both these studies included individuals at an older age (than this current study), the effect was only found in neck pain and the study designs (e.g. length of follow-up) and assessment of both sleep problems and musculoskeletal pain differed to this current study. In addition, findings of this current study are supported by figures on sleep problems within the data. Whilst the prevalence of sleep problems in children without musculoskeletal pain at baseline was similar in both genders (22%), further exploratory description shows that among those with sleep problems, 53% of girls reported having trouble sleeping "often" and 47% "almost always", while 33% of boys with sleep problems reported having trouble sleeping "often", with a much higher percentage at 67% reporting "almost always" indicating more frequent sleep problems in boys (and potentially an indication of greater severity) compared to girls, which may partly explain the reported modification effect. Another explanation involves psychological and behavioural factors, which may influence the sleep pattern of children. For example, a significant association between anxiety and increased need for sleep has been reported in male young adults, but not in females (Lindberg et al., 1997). Also, symptoms of inattention and hyperactivity in children may explain the findings. Attention-deficit/hyperactivity disorder (ADHD) is more common in boys compared to girls and has been associated to sleep problems (Chervin et al., 1997; O'Brien et al., 2003). However, as mentioned within the discussion of the overall effects, the potential effect of psychological symptoms was controlled for in the adjusted analysis. Regarding the onset of chronic musculoskeletal pain, results of the interaction test and of analysis stratified by gender (Section 6.2.4.1) showed no evidence of a modification effect, suggesting that the presence of sleep problems would pose a similar increase in odds for both genders. To my knowledge, no one study on the relationship between sleep and the onset of chronic musculoskeletal pain stratified by gender has been conducted in children, therefore comparison with the findings of this current study is not possible. Studies conducted in adults show inconsistent results for an effect modification of gender on the association between sleep and chronic musculoskeletal pain, but it has been proposed that gender differences on this association may begin in older

adolescence/emerging adulthood (Bonvanie et al., 2016; Mork et al., 2014; Zhang et al., 2012). Therefore, it may be possible that in children with sleep problems a modification effect by gender does not occur when pain is already present, that the proposed reciprocal relationship between sleep and pain may not be modified by gender or any such modification leads to an overall balance of the effects reported (Section 6.3.1.2). This is supported by further inspection of the data, for example children with non-chronic musculoskeletal pain at baseline reported similar frequency of sleep problems (48% of girls and 49% of boys reported having trouble sleeping "often", 52% of girls and 51% of boys "almost always") and this is quite different to those frequencies reported for the onset of musculoskeletal pain.

6.3.1.4 Effect modification by puberty

The test for interaction between sleep and puberty was not statistically significant, and results of the analysis for the onset of musculoskeletal pain stratified by pubertal stage were similar to that of the overall estimate for both strata. Overall this suggests no effect modification by pubertal stage. These results are in contrast with the hypothesis that the odds for the onset of musculoskeletal pain in children with sleep problems would change depending on pubertal status with an increase in onset aligned to a more advanced pubertal status (Section 3.3.2.2). In addition, this finding does not fully support the results of previous studies (where children were older compared to children of this sample, 11-16 years old) that have showed increased odds for musculoskeletal pain in those with a more advanced pubertal status (Janssens et al., 2011; Kløven, Hoftun, Romundstad, & Rygg, 2017; Sperotto, Brachi, Vittadello, & Zulian, 2015; Wedderkopp, Andersen, Froberg, & Leboeuf-Yde, 2005). The lack of effect modification by puberty in this current study is most likely explained by the young age of children in the sample (9 years old) leading to a lack of range of pubertal stages. Inspection of the pubertal status variable showed a right skew, with only a small minority of the cohort reporting an advanced pubertal stage (only 13% of children were in mid/advanced puberty; 3% of boys and 21% of girls). Therefore only a

small number of participants would have undergone the hypothesised effects of hormones on sleep, and the resultant change in sleep schedule (i.e. delays in bedtime, altered waking patterns) that occur during puberty (and thus potentially increase risk of musculoskeletal pain) as reported in the literature (Carskadon & Tarokh, 2014; Carskadon, 2011; Hagenauer & Lee, 2013). Conversely, a stronger yet non-significant effect for children in an advanced pubertal stage was found in the analysis for the onset of chronic musculoskeletal pain with a doubling of the effect for those in the more advanced pubertal stage. However, for both the analysis of musculoskeletal pain onset and chronic musculoskeletal pain onset, the certainty of the results was partly compromised by low sample numbers within the advanced pubertal stage groups. The wide 95% Confidence Intervals indicate a lack of precision of the estimate attributable to the small number of individuals present in the strata (only 50 and 112 children were present in the mid/advanced pubertal group in the stratified analysis for the onset of musculoskeletal pain and chronic musculoskeletal pain, respectively), and a larger sample size may have increased precision (Kamangar, 2012). Overall the results of this current study suggest a lack of evidence for effect modification by puberty on the association between sleep problems and the onset of musculoskeletal pain or chronic musculoskeletal pain in this sample of 9 years old Australian children, although this analysis was hampered by the limited range of pubertal status. Therefore, further investigation of the potential effect modification of puberty is warranted, perhaps best set within a cohort where a full range of pubertal status is present, for example a prospective cohort of children aged from 9 to 16.

6.3.1.5 Effect modification by screen time

Results of the analysis showed no significant interaction effect for the modification effect of screen time. When stratified by screen time, results showed a non-significant decrease in odds for the onset of musculoskeletal pain in children with low levels of screen time. Conversely, children with high levels of screen time were at non-significant increased odds, which was similar to the estimate found in the overall analysis prior to stratification. As with the analysis on puberty above (Section 6.3.1.4), the precision of estimates for screen time is affected by low numbers, the 95% Confidence Intervals in children with low levels of screen time widely overlap those found in children with high levels of screen time, thus lessening confidence on the conclusions that can be drawn. For the onset of chronic musculoskeletal pain results of the logistic regression analysis stratified by screen time were similar to that of the overall analysis for both strata, and the result of the interaction test was not statistically significant. This suggests no effect modification by screen time for the onset of chronic musculoskeletal pain. Overall these results do not support the hypothesis that high levels of screen time would lead to a stronger association of sleep problems with the risk of future musculoskeletal pain in children. The proposed biological mechanisms here would be a disruption on the production of melatonin, which is necessary for falling asleep (Aguilar et al., 2015; Hale & Guan, 2015; Higuchi et al., 2005), and which may have analgesic effects through the interaction with receptors placed in the central nervous systems and in the dorsal horn of the spinal cord (e.g. opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, and α1 and α2-adrenergic receptors) (Chen, Zhang, & Huang, 2016; Srinivasan et al., 2012). It was suggested that the decrease in melatonin production may consequently increase the odds for musculoskeletal pain (Section 3.3.2.3). However, it is worthy of note that there appears to be a “protective” modification effect of low screen time use on the relationship between sleep problems and musculoskeletal pain onset, although the estimate was imprecise as reported above. The protective effect found might be explained by external factors that relate to the social characteristics of the children who report low screen time use (Section 6.3.1.2), such as parental

monitoring of the children's screen time. Parents who have a discordant relationship or that spend excessive time at work, may allow their children to spend more time with electronic devices, and evidence shows that these children are more likely to have ADHD and behavioural issues (Froiland & Davison, 2016). Conversely, in families where parents have a greater monitoring on children's screen time habits, children show lower levels of both screen time and aggressive behaviour, and improved sleep (Gentile, Reimer, Nathanson, Walsh, & Eisenmann, 2014). However, the above suggested explanations for the protective effect are speculative and the results were compromised by small numbers and low precision, therefore more information is required about these potential mechanisms. There are also other potential reasons why this study did not find the hypothesised relationship of increased screen time modifying the relationship between sleep and musculoskeletal pain outcomes. One particular aspect is the amount of screen time use as defined in this current study. According to a recent systematic review that reports a consistent significant association between increased screen time use and poor sleep outcomes (reduced sleep duration and increased sleep problems), the mean estimate of screen time for children is 7 hours/day (Hale & Guan, 2015). Conversely, the mean screen time in this sample was much lower (3.3 hours a day, only 5% of children has screen time levels ≥7 hours/day). Therefore, it may be that levels of exposure to screen time were too low to show a significant effect, as confirmed by the data of this current study (proportions of children with sleep problems were similar across strata of screen time). In addition, evidence suggests that the effects of screen time, melatonin, and sleep problems are more pronounced in those already experiencing puberty (Hagenauer & Lee, 2013), however as outlined in the above section on puberty, this current study had restricted numbers within an advanced pubertal stage and therefore would be less likely to find an effect based on these components (i.e. screen time within those with advanced pubertal development). Another possible reason for the lack of effect is the definition of screen time use. The cut-off level for a high level of screen time was set following established guidelines (American Academy of Pediatrics, 2013), see Section 5.2.3.2. However, screen time use is a dynamic and

changing phenomena, with evidence of ever increasing use and therefore guidelines are often breached and moved (Bucksch et al., 2016; Hale & Guan, 2015). It may be the case that the cut-off chosen in this study was not representative of the actual amount of use, and the use of different cut-off levels for screen time (i.e. <2 hours, 2-4 hours, 4-6 hours, > 6 hours) might have produced different results. The actual measure used to assess screen time also presents some limitations, as information about key aspects of screen time was not collected in this current study. For example, the effect of screen time on sleep may vary depending on the time of the day when screen time exposure occurs (day-time vs. bedtime) (Hale & Guan, 2015). Information on media content was not present (e.g. playing violent videogames might lead to emotional problems (Mundy et al., 2017), and consequently this may affect the sleep of children and also increase odds for musculoskeletal pain onset). Also, missing from the measure and assessment of screen time was information on screen time exposure due to smartphone use, the characteristics of screen (e.g. size, closeness to face, volume of device) and the use of multiple electronic devices at the same time which may affect sleep (Hale & Guan, 2015). Finally, screen time use was parent-reported. Evidence showed that this could have led to underestimation of screen time, potentially because parents may not be fully engaged and aware of their children's screen time activities (Thorn, Delellis, Chandler, & Boyd, 2013).

6.3.2 Strengths and weaknesses

Strengths of this study include the use of a prospective cohort design, which provides incidence estimates, and allows greater confidence in the understanding of the temporal sequence between exposure and outcome (Delgado-Rodríguez & Llorca, 2004). Another is the exploration of potential effect modifiers, which were chosen based on evidence gathered from the systematic review, and enabled the examination of sub-groups of the population in whom the association between sleep problems and musculoskeletal pain may vary in strength. This approach offers to address the current inconsistencies in the evidence of an effect between sleep problems and musculoskeletal pain and has the potential to identify groups of individuals at high risk where interventions may be more relevant and impactful. To my knowledge this is the first study that explores the modifying effect of pubertal stage and screen time on the association between sleep problems and musculoskeletal pain, and adds further to the current knowledge of effect modification by gender. However, limitations are also present in this study. First, a limitation concerns the measurement and assessment of variables used within the analysis (general points of measurement and assessment are discussed in chapter 11). Information was not available about the severity, frequency and impact of musculoskeletal pain (e.g. pain interference or disability), which could have provided a better understanding of the experience of pain (Kamper, Henschke et al., 2016) and a greater scope to investigate the association with sleep problems. Furthermore, as research on the consequences and impact of pain in children has shown (see introduction, Section 1.3.3), those suffering from musculoskeletal pain or chronic musculoskeletal pain may be less likely to attend school, thus selection bias may be hypothesized (Kløven, Hoftun, Romundstad, & Rygg, 2017). However, looking at the data, if a selection bias was present in this cohort, it would be more likely to be in the opposite direction, as a high percentage of children reported baseline musculoskeletal pain (Section 5.5.1.1). Also, as with the assessment of pain, there are important components in the conceptualisation of sleep problems (i.e. sleep latency, sleep duration, sleep efficiency, use of sleep medications, sleep disruption, daytime dysfunction

due to sleep, excessive daytime sleepiness and practices of sleep hygiene, objective measures such as polysomnography and actigraphy) (Erwin & Bashore, 2017), that the current measure could not capture. Methods available for objective measures of sleep patterns such as polysomnography and actigraphy (which allows an accurate estimate of sleep quantity) are not generally suitable for use in epidemiological studies (Meltzer et al., 2013). In addition, in this study a binary sleep variable was created in order to identify children with sleep problems within the population, based on a categorization used in a previous study (Section 5.2.2.1). However, there are restrictions in the use of binary variables as they group persons from the extremes and mid points together, therefore exploratory analysis was carried out using the categorical variable with 5 frequencies of sleep problems in the analysis to examine potential differences (e.g. nonlinear relationship). Results (outlined in appendix VI) showed that increasing frequency of sleep problems were associated with increasing odds for the onset of musculoskeletal pain and chronic musculoskeletal pain (this effect was more pronounced here e.g. dose effect), and these findings are consistent with the proposed bi-directional relationship between sleep and pain (Section 6.3.1.2). Within stratified analysis carried out with the categorical variable the effects were overall in the same direction of those reported in Section 6.2, although limitations arose with the low cell count within some subgroups (children in mid/advanced puberty and with low levels of screen time) that did not allow to estimate the odds for the onset of musculoskeletal pain and chronic musculoskeletal pain (Appendix VI). There are also limitations with the conceptualisation and definition of the effect modifiers of puberty and screen time. Whilst the gold standard for the assessment of puberty is the physical examination, this method may have been perceived as too invasive by children, and was not feasible in the CATS design due to restrictions in terms of costs and time (Bond et al., 2006; Coleman & Coleman, 2002). The parent-reported pubertal development scale (PDS) has been shown to have a good agreement with physical examination of pubertal status of girls (.76), but lower agreement for boys (.54) aged 8-10 years old (Miller, Tucker, Pasch, & Eccles, 1988). This might have led to some misclassification

overall, and more so potentially in boys. For the measure of screen time, as reported in Section 6.3.1.5, a limitation is that no information is known about smartphone use, content of media, characteristics of the screen, use of multiple electronic devices and time of the day of screen time exposure. Such additional information would have led to the development of a better defined high screen user phenotype. There are also limitations with the confounder variable of physical activity, the questions used did not provide information about the intensity, duration and frequency of physical activity that can be gathered by means of validated self-reported questionnaires, therefore it was not possible to classify children adequately according to levels of physical activity (Sylvia, 2015). Another key issue is statistical power, the number of children at risk of developing musculoskeletal pain at baseline may not have been sufficiently large to estimate the association with sufficient precision (more so within the interaction and stratified analysis). There were only 472 (40%) children without musculoskeletal pain at baseline, and the resulting power to detect the effect size found (OR=1.35) was only 35.0%. A retrospective power analysis shows that the minimum sample size to detect this effect (OR = 1.35) with a power of more than 80% in a cohort where 35% of children have sleep problems (as found in this cohort) would need to be at least 1300 children (with a much larger sample size required to detect statistically significant effect modification). Finally, 6-7% of children were lost to follow-up. These children had higher psychological symptoms score, had higher levels of screen time, were in a more advanced pubertal status, and less likely to perform individual sports and team sports than completers (Section 5.5.2). If these characteristics were associated with increased odds for the onset of musculoskeletal pain or chronic musculoskeletal pain, then the results of this current study would be an underestimation of the magnitude of the association. However, given the low proportion of those lost to follow-up, this effect is unlikely to have significantly impacted on the reported results.

6.3.3 Implications

The results of this current study may be important from a clinical point of view. Indeed, although children with sleep problems at baseline were overall not significantly at higher odds of the onset of musculoskeletal pain one year later, they were twice as likely to report chronic musculoskeletal pain, that is to say musculoskeletal pain of a longer duration. This clinically would mean that having a low sleep quality, and possibly pain episodes in childhood may be a risk factor for the development of more burdensome chronic musculoskeletal pain conditions. Potential strategies for the prevention of chronic musculoskeletal conditions are outlined in the discussion chapter (Section 11.5.3.1).

6.3.4 Key messages

- The association between sleep problems and the onset of musculoskeletal pain was non-significant, however the direction of association showed a trend for increased odds, in accordance with the overall results of the systematic review conducted in this study.
- Children with high levels of sleep problems at baseline were at significantly increased odds of the onset of chronic musculoskeletal pain, and this is in line with previous studies conducted in adults.
- In male children a stronger association between sleep problems and the onset of musculoskeletal pain was found compared to girls. Effect modification by gender was not observed for the onset of chronic musculoskeletal pain.
- Effect modification of the association between sleep problems and the onset of musculoskeletal pain or chronic musculoskeletal pain by levels of screen time or pubertal stages was not observed.

Chapter seven. The association of psychological symptoms with musculoskeletal pain onset in adolescents: description of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort

In this chapter, a description of the ALPSAC cohort and the measures included within the cohort are outlined, followed by a description of the missing data, the non-response analysis for missing data, and the descriptive findings. Finally, the descriptive findings of the cohort will be discussed. Please note that the actual assessment of psychological symptoms within this analysis specifically measures the constructs of internalizing symptoms and externalizing symptoms (see Section 7.2.2 below), and these terms will be used throughout the remainder of this chapter.

7.1 Background of cohort

7.1.1 Design and recruitment

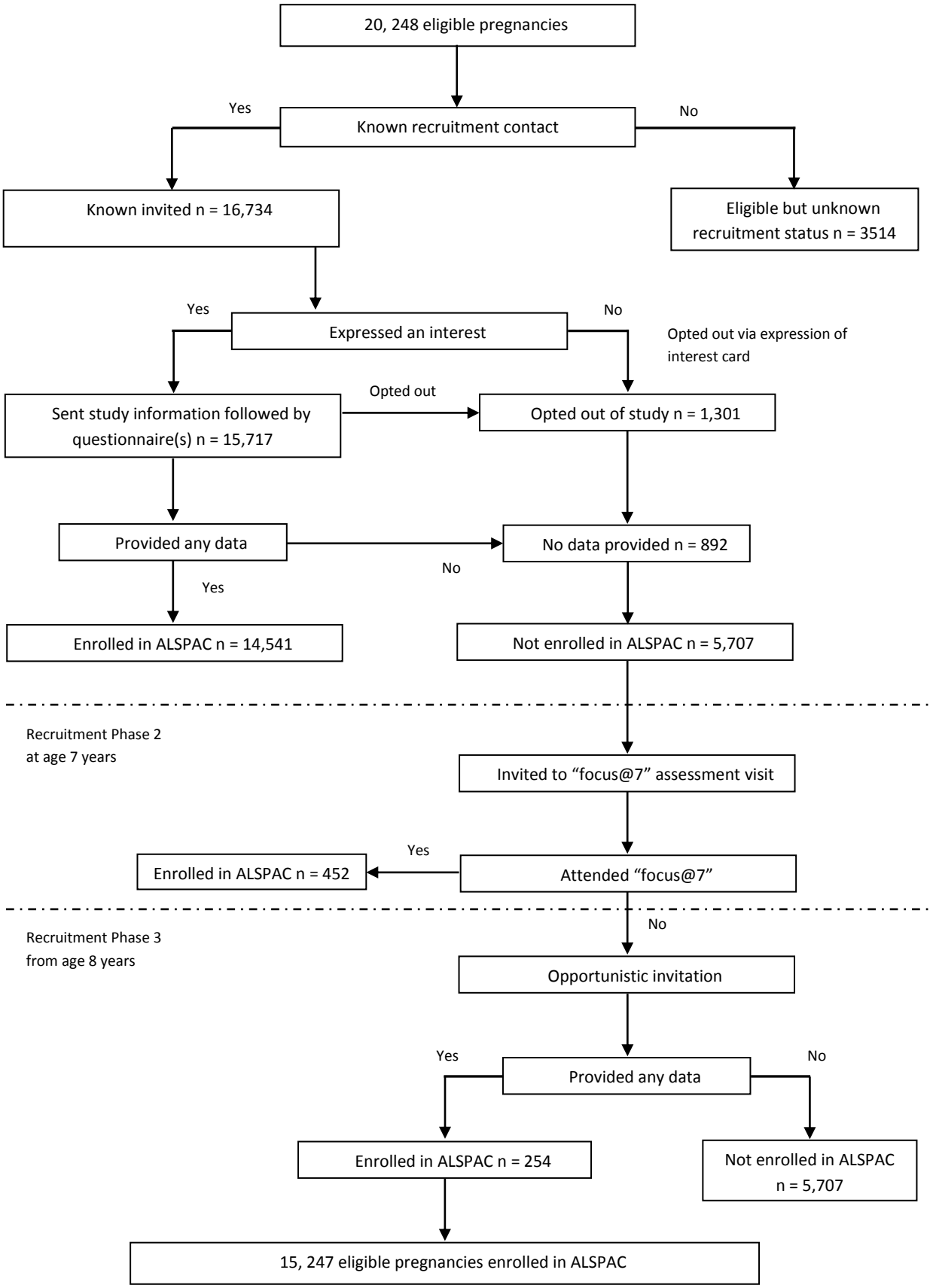
The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth-cohort that was set-up to investigate the contribution of both genetic and environmental factors on the health of both parents and children. All pregnant women resident in Avon (Southwest England) who were expected to give birth between April 1, 1991 and December 31, 1992 were invited to take part (Boyd et al., 2013; Fraser et al., 2013; Golding, Pembrey, & Jones, 2001). The recruitment was opportunistic and the strategy of enrolment included the approach of pregnant women through posters displayed in public spaces, advertisements in the local media (TV, radio and press), information sent to the mother by the hospital, and an approach by ALSPAC staff when the mother attended an ultrasound examination appointment (Boyd et al., 2013; Golding et al., 2001). It was explained to potential participants that enrolment was not compulsory, and that participants could drop out from the study at any point, also potential participants were given assurances about the confidentiality of data produced from participation (Golding et al., 2001).

Information on parents and their children were collected from pregnancy to the onward years after childbirth (Fraser et al., 2013; Golding et al., 2001).

7.1.2 Description of baseline participants and non-participants

Figure 7.1 shows the description of participants and non-participants to the study. The recruitment process included more than one stage. During the first stage 14,541 pregnancies were recruited, and that generated 14,062 live born children, 13,988 of whom were alive at 1 year of age. Further 452 and 254 children were enrolled in phase two (seven years after birth) and phase three (eight years after birth), respectively. As a result there were 15,247 eligible pregnancies enrolled in ALSPAC overall, this generated 14,701 alive children at 1 year of age (Boyd et al., 2013). In the following section, the study population included in this current study is described.

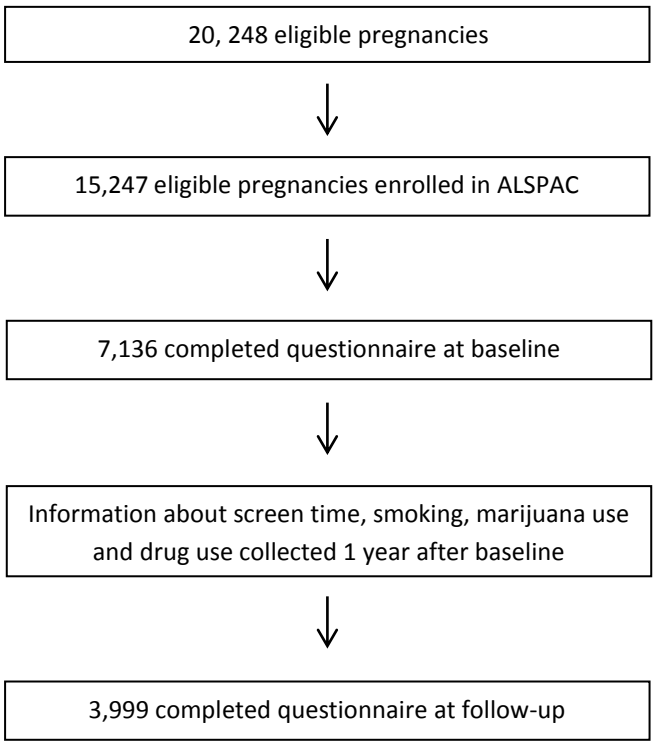
Figure 7.1. Flowchart of recruitment of participants to the ALSPAC study



7.1.3 Population eligible for this current study

In this current study, only data from the time points when adolescents were 13 years old and when they were 17 years old were used. I will hereafter refer to these two time points as baseline and follow up, respectively. Regarding the participation rate, at baseline the questionnaire with questions relative to psychological symptoms (i.e. internalizing and externalizing symptoms) was completed for 7,159 adolescents (35.4% of the initial eligible sample). The questionnaire that included the question relative to baseline pain was completed by 7,136 (35.2%) adolescents. Some variables (i.e. screen time, cigarette use, marijuana use and drug use) were collected 1 year after baseline. At follow-up (at age 17), 3,999 (19.8%) adolescents completed the questionnaire that included the question relative to musculoskeletal pain. For a description of the adolescents who represent the study population of this current study please refer to Figure 7.2. In the following section, the variables included in the study are described.

Figure 7.2. Flowchart describing the number of adolescents included in this current study



7.2 Study measures

The variables included within the analysis for this thesis are described below. Strengths and limitations of the measures will be discussed within Section 8.5.3.

7.2.1 Musculoskeletal pain

7.2.1.1 Baseline Pain

Pain presence at baseline was assessed through the question "do you often have aches and pains in your arms or legs?". Children were considered as having pain at baseline if the answer was "yes, arm(s)", "yes leg(s)", "yes both" and not having pain if the answer was "no, not often".

7.2.1.2 Musculoskeletal pain at follow-up

The question "have you had any aches or pains that have lasted for a day or longer in the past month?" was used to assess the presence of musculoskeletal pain at follow-up. In the case where the response at follow-up was "yes", the children were asked a further question on duration; "When did the pain start?". Possible responses were "less than three months ago" and "more than three months ago", the latter was chosen to indicate chronic pain status. These questions and categories have been used previously in studies on musculoskeletal pain carried out within the ALSPAC cohort (Harrison et al., 2014; Tobias et al., 2013). The follow-up question relative to pain status was also supported by a manikin (pictorial description of body areas that includes two diagrams, one for the front and one for the back of the body) as well as the sentence "Please shade in the diagrams to show where exactly you felt the pain(s)" (appendix VII). This pain manikin was used to assess a total of 26 different pain sites (e.g. back pain, neck pain, shoulder pain, etc.). This measure consists of a drawing of a blank body manikin where the subject has to indicate the extent and distribution of the pain, and these types of recording of location of bodily pain have been shown to be valid and reliable within population cohorts (Hamill et al., 2014; Lacey et al., 2005; Margolis et al., 1988). The body sites included in the manikin (excluding that

relative to the head), together with the answers to the questions relative to pain status and pain duration, were used to create outcome variables that represented the presence of musculoskeletal pain or chronic musculoskeletal pain at follow-up (i.e. adolescents who reported pain or chronic pain that related only to the head were excluded). The musculoskeletal pain measure was entered in the analysis as a binary variable with values of 1 and 0 according to the presence or absence of self-reported musculoskeletal pain, respectively. The measure of chronic musculoskeletal pain was also entered in the analysis as a binary variable with values of 1 and 0 according to the self-reported start of musculoskeletal pain “more than three months ago” or “less than three months ago” respectively.

7.2.2 Predictor

7.2.2.1 Internalizing/externalizing symptoms

Internalizing and externalizing symptoms were assessed through information given by the parents at baseline through the Strengths and Difficulties Questionnaire (SDQ). The SDQ is a 25-item questionnaire for use in children and adolescents with five subscales: emotional problems, peer problems, conduct problems, hyperactivity and prosocial behaviour (Goodman, 1997). Each subscale includes 5 questions that are rated on a 3-point scale ("Not true" = 0, "Somewhat true" = 1, "Certainly true" = 2). Therefore each subscale produced a score that ranges from 0 to 10. This scale has been used in previous studies carried out within the ALSPAC cohort (Edwards et al., 2014; Huisman et al., 2010). The specific questions for each single psychological subscale are shown in appendix IV. Two domains were created (i.e. internalizing and externalizing symptoms) by combining the "emotional symptoms" and "peer item" subscales for internalizing symptoms, and the subscales "conduct problems" and "hyperactivity" for externalizing symptoms. This approach of combining subscales into broader "internalizing" and "externalizing" constructs has been indicated in previous research using the SDQ, and this approach has been shown to be suitable for use in epidemiological studies with acceptable or good validity demonstrated specifically in adolescent populations (Goodman et al., 2010; Vella, Cliff, Magee, & Okely, 2015; Vella, Swann, Allen, Schweickle, & Magee, 2017). The range for the internalizing symptoms scale was 0-20, as was the range for externalizing symptoms scale. Binary variables were created, by using the 90th percentile cut-off as indicated in previous research (Goodman, 1997, 2001). These cut-off values obtained for the 90th percentile of each subscale matched the recommended values for abnormal levels of psychological symptoms, which can be used to identify adolescents with symptoms of clinical relevance (Goodman, 1997, 2001). Hereafter in this thesis, those adolescents with an internalizing and externalizing score >90th percentile will be referred to as having internalizing and externalizing symptoms, respectively.

7.2.3 Effect modifiers

7.2.3.1 Gender

Gender was entered in the analysis as a binary variable with values of 1 or 0 according to the gender, male or female respectively.

7.2.3.2 Screen time

Screen time was measured through self-reported information gathered with the questionnaire "Boys'/Girls' Experiences, Thoughts and Behaviour" at 14 years of age. Average daily computer use was calculated for week days and weekend days combined, and the same was done for TV watching. By using these 2 measures, the average daily screen time was calculated. In order to account for the distribution of data in terms of stratification, screen time was entered in the analysis as a categorical variable, with three categories representing low (20% lower use, approximately < 2 hours of screen time/ day), medium (60% middle use, approximately 2-4 hours of screen time/ day) and high (higher 20% use, > 4 hours of screen time/ day) levels of screen time, respectively. Screen time was entered in the analysis as a categorical variable with values of 0, 1 or 2 according to the level of screen time use (low levels of screen time, medium levels of screen time or high levels of screen time respectively).

7.2.3.3 Puberty

Pubertal stages were measured using five-point rating scales (Tanner's Sexual Maturation Scale, (Coleman & Coleman, 2002), and categorized in Tanner stages (from 1 to 5) according to the parental-responses to the questionnaire "growing and changing 5" at baseline, which included two drawings for each gender for the assessment of pubertal stages. These two drawings represented two scales for each gender (breast development and pubic hair development for girls; genital development and pubic hair development for boys), and parents indicated the stage (1 to 5) of development their child had reached in each scale. The highest between the two ratings was used to indicate pubertal stage (i.e. the highest between the breast development scale and pubic hair development scale for girls, between genital development scale or pubic hair development scale for boys), as used previously (Johnson et al., 2009). Adolescents with a Tanner stage score <3 were grouped in the pre-early puberty group, those with a Tanner stage score of 3 and 4 were grouped in the mid/advanced puberty group and those with a Tanner stage score of 5 were grouped in the post pubertal group according to categorization used previously (Bond et al., 2006). Puberty was entered in the analysis as a categorical variable with values of 0, 1 or 2 according to the pubertal stage (pre-early puberty, mid/advanced puberty or post puberty respectively).

7.2.4 Confounders

7.2.4.1 Physical activity

Parent-reported information on physical activity was gathered through the question “In the past month, what was the average number of times that your son/daughter participated in vigorous physical activity (such as running, football, swimming, athletics)?” from the questionnaire “growing and changing 5” delivered at baseline (age 13). The response options were: “none/ less than once a week/ 1-3 times a week/ 4-6 times a week/ daily”. Physical activity was entered in the analysis as a binary variable with values of 1 or 0 based on the response of frequency of physical activity (>3 times a week and ≤3 times a week, respectively) as carried out in a previous study (Ståhl et al., 2008).

7.2.4.2 Smoking

Smoking was assessed through the question “Have you ever smoked a cigarette (including roll-ups)?” taken from the questionnaire “Life of a Teenager” at age 14. Smoking was entered in the analysis as a binary variable with values of 1 or 0 based on the response “Yes” or “No” to the question relative to cigarette smoking, respectively.

7.2.4.3 Marijuana use

Marijuana use was assessed through the question “Have you ever tried cannabis (also called marijuana, hash, dope, pot, blow, skunk, puff, grass, draw, ganja, spliff, joints, smoke, weed)?” taken from the questionnaire “Life of a Teenager” at age 14. Marijuana use was entered in the analysis as a binary variable with values of 1 or 0 based on the response “Yes” or “No” to the question relative to marijuana use, respectively.

7.2.4.4 Drug use

Drug use was assessed through two questions. The first question was: “Have you ever tried inhaling or sniffing any of the following:”

- Aerosols
- Gas (butane and lighter refills)
- Glue
- Solvents (including petrol and paint thinners)
- Poppers (also called amyl nitrates, liquid gold, rush)

The second question “Have you ever tried, taken or used any of the following:”

- Amphetamines (also called speed, uppers, whizz, sulphate, billy, crystal meth)
- Ecstasy (also called 'E', pills)
- LSD (also called acid, tabs, trips, dots)
- Magic mushrooms (also called shrooms)
- Spanglers (also called spangs)
- Cocaine (also called Charlie, 'C')
- Crack (also called rock, stone)
- Heroin (also called brown, smack, gear, junk, 'H')

The questions were taken from the questionnaire “Life of a Teenager” at age 14. Drug use was entered in the analysis as a binary variable with values of 1 if the response was “Yes” to any of the drugs listed above, or 0 otherwise.

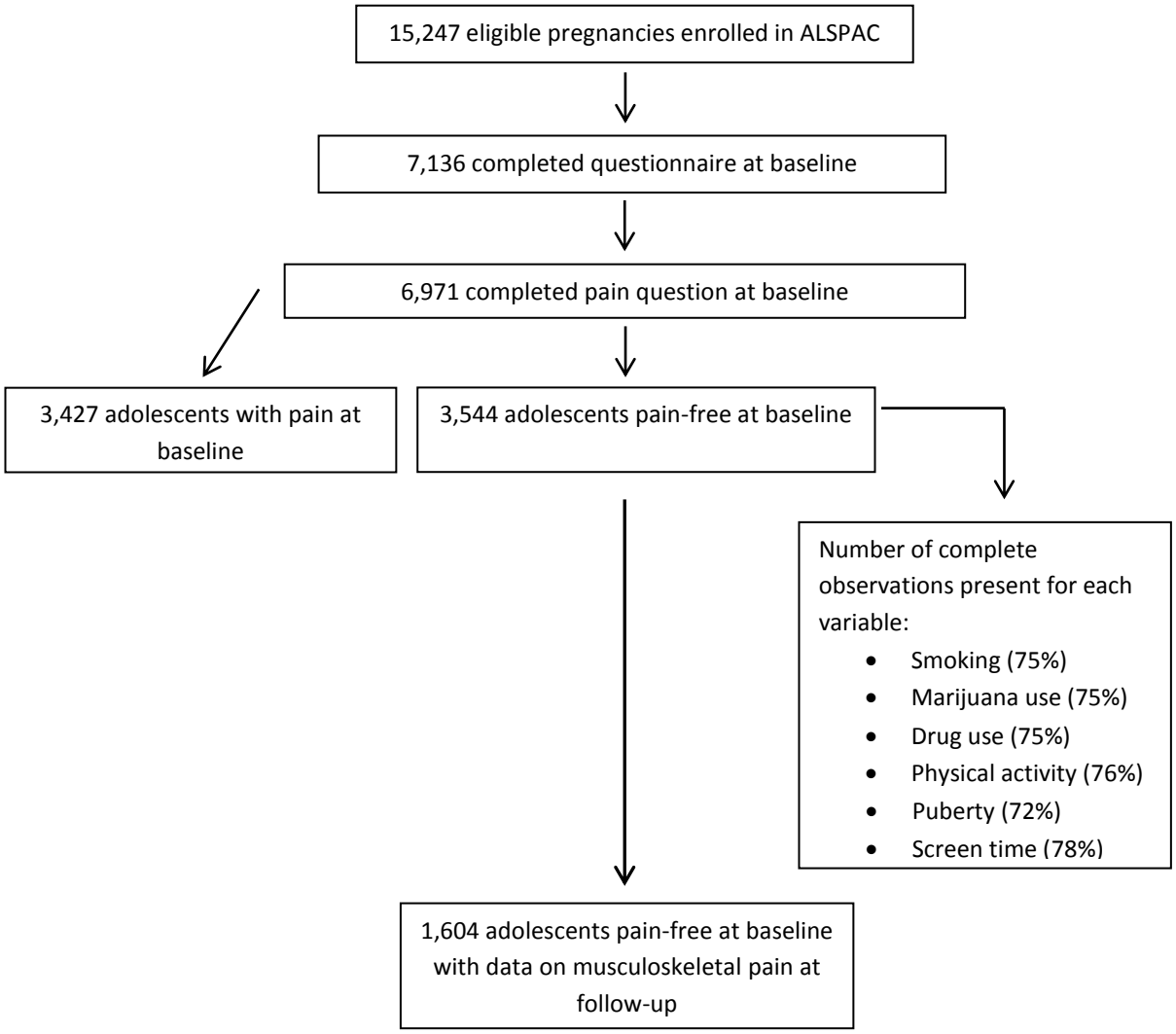
7.3 Selection of adolescents for analysis and missing data

The following sections outline a description of the process of selection of adolescents used in the analysis (Section 7.3.1) and description of missing data present in the study. Investigation of missing data that originated from item non-response to the questionnaire is outlined in Section 7.3.2. Investigation of missing data that originated from loss to follow-up is outlined in Section 7.3.3.

7.3.1 Selection of adolescents for analysis

At baseline (when children in the cohort were of age 13) 7,136 adolescents participated. The self-report question for pain presence at baseline was completed by 6,971 children (98%), of whom 3,427 (49%) reported pain in the arms or legs and 3,544 (51%) no pain in the arms or legs. Among the 3,544 children who reported no pain in the arms or legs at baseline, 1,604 (45%) reported information on the presence of musculoskeletal pain or chronic musculoskeletal pain at follow-up, and this forms the cohort for the analysis in this thesis. A description of the process of selection of individuals used in the analysis from baseline onward is provided in Figure 7.3.

Figure 7.3. Flowchart describing the selection of the adolescents for the analysis of musculoskeletal pain onset



7.3.2 Missing data for baseline variables

The association between internalizing or externalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up was assessed in the group of adolescents who were without pain at baseline and reported information on the presence of musculoskeletal pain at follow-up (N= 1,604; Figure 7.3). Missing data was found for some baseline variables because of non-completion of the questionnaire or because individual items had been missed. Therefore, all variables included in the analysis were inspected for missingness, and the proportion of complete data and missing data for each variable at baseline was estimated. Results are shown in Table 7.1.

Table 7.1 Percentage of Complete data Vs. Missing data at baseline among adolescents without pain at baseline and with data on musculoskeletal pain at follow-up

	Complete data, n (%)	Missing data, n (%)
Predictors		
Internalizing symptoms	1,467 (91.5%)	137 (8.5%)
Externalizing symptoms	1,468 (91.5%)	136 (8.5%)
Effect Modifiers		
Gender	1,604 (100%)	-
Puberty	1,260 (78.6%)	344 (21.4%)
Screen time	1,403 (87.5%)	201 (12.5%)
Confounders		
Smoking	1,378 (85.9%)	226 (14.1%)
Marijuana Use	1,383 (86.2%)	221 (13.8%)
Drug use	1,388 (86.5%)	216 (13.5%)
Physical activity	1,304 (81.3%)	300 (18.7%)

7.3.3 Missing data due to loss to follow-up

The total number of adolescents available at follow-up for the analysis of musculoskeletal pain onset is 1,604, indicating 1,940 adolescents (54.7%) were lost to follow-up (See Figure 7.3). The difference in baseline characteristics between those adolescents still present at follow-up (completers) and adolescents lost at follow-up was assessed (Table 7.2). The proportion of adolescents with internalizing (9.0% vs. 7.6%) and externalizing (8.5% vs. 6.0) symptoms was higher in the group of adolescents lost to follow-up compared to those who completed at follow-up. The proportion of males was also higher in the group of adolescents lost to follow-up compared to those who completed at follow-up (51.3% vs 41.2%, respectively). Adolescents who completed at follow-up were in a more advanced pubertal stage compared to adolescents lost to follow-up (19.5% vs. 17.4% in the post-pubertal stage, respectively). It was found that adolescents who completed at follow-up had lower levels of screen time (18.6% vs. 20.6% high screen category), lower levels of smoking experience (19.1% vs. 22.5%), lower marijuana use (6.1% vs. 7.1%), lower drugs ever (11.2% vs. 11.7%) and lower levels of physical activity (42.5% vs. 43.1%).

Table 7.2 Baseline values of completers vs. loss to follow-up		
Total	Completers	Lost to follow-up
	1,604 (45.3%)	1,940 (54.7%)
Psychological symptoms	Completers	Lost to follow-up
Internalizing (>90th percentile)	112 (7.6%)	148 (9.0%)
Internalizing (<90th percentile)	1,355 (92.4%)	1,489 (91.0%)
Externalizing (>90th percentile)	87 (6.0%)	139 (8.5%)
Externalizing (<90th percentile)	1,381 (94.0%)	1,498 (91.5%)
Potential effect modifier	Completers	Lost to follow-up
Gender (N %)		
Boys	661 (41.2%)	995 (51.3%)
Girls	942 (58.8%)	945 (48.7%)
Puberty		
Pre-Early puberty	125 (9.9%)	158 (12.3%)
Mid-Advanced puberty	889 (70.6%)	905 (70.3%)
Post puberty	246 (19.5%)	225 (17.4%)
Screen time		
Low Screen time	259 (18.5%)	205 (15.2%)
Medium Screen time	883 (62.9%)	863 (64.2%)
High Screen time	261 (18.6%)	277 (20.6%)
Potential confounder	Completers	Lost to follow-up
Smoking (No)	1,115 (80.9%)	989 (77.5%)
Smoking (Yes)	263 (19.1%)	288 (22.5%)
Marijuana use (No)	1,299 (93.9%)	1,190 (92.9%)
Marijuana use (Yes)	84 (6.1%)	91 (7.1%)
Drug use (No)	1,233 (88.8%)	1,137 (88.3%)
Drug use (Yes)	115 (11.2%)	150 (11.7%)
Physical activity >3 times a week	554 (42.5%)	601 (43.1%)
Physical activity ≤3 times a week	750 (57.5%)	793 (56.9%)

7.4 Results of descriptive analysis

Descriptive analyses of the Avon Longitudinal Study of Parents and Children (ALSPAC) dataset at baseline were performed to explore generalisability of the sample. The results of these analyses are shown in the following sections.

7.4.1 Baseline characteristics of the total sample

The baseline characteristics of the total sample are outlined in Table 7.3. In total 49% of the cohort reported the presence of pain in their arms and legs, with a higher proportion reported by girls (50.4%) compared to boys (47.7%). Girls and boys had similar mean internalizing scores (girls 2.7 ± 2.7, boys 2.6 ± 2.8), while boys had higher mean externalizing scores compared to girls (boys 4.6 ± 3.3, girls 3.7 ±2.9). These differences are shown again when applying the 90th percentile cut-off value, with 689 children with internalizing symptoms, with similar proportions between boys and girls (9.7% vs. 9.8%, respectively), and 702 children with externalizing symptoms, here more boys than girls have externalizing symptoms (12.7% vs 7.2%, respectively). More boys than girls were present in the sample (51.4% vs 48.6%, respectively). More adolescents were in the mid/advanced pubertal status (69.4%) compared to the proportion of those in pre-early puberty (11.4%) and post pubertal status (19.2%), and girls were overall in a more advanced pubertal status compared to boys (25.9% vs. 11.0% were in the post pubertal stage, respectively). Boys more often reported high levels of screen time compared to girls (20.4% vs. 18.6%, respectively). Approximately 26% of adolescents reported having ever tried smoking, with more girls (31.3%) than boys (18.9%), while 8.6% reported having ever tried marijuana, with similar proportions between genders. Approximately 15% of adolescents tried any type of drugs ever, with more girls (17.7%) than boys (12.5%). Finally, approximately 45% of adolescents performed physical activity more than 3 times a week, with more boys (53.9%) than girls (37.6%).

Table 7.3 Baseline characteristics of the sample			
Pain in arms and legs	Boys	Girls	Overall
Yes	1,510 (47.7%)	1,914 (50.4%)	3,427 (49.2%)
No	1,656 (52.3%)	1,887 (49.6%)	3,544 (50.8%)
Psychological characteristics	Boys	Girls	Overall
Internalizing score	2.6 (± 2.8)	2.7 (± 2.7)	2.6 (± 2.8)
Externalizing score	4.6 (± 3.3)	3.7 (± 2.9)	4.2(± 3.2)
Psychological symptoms >90th percentile	Boys	Girls	Overall
Internalizing	343 (9.7%)	346 (9.8%)	689 (9.8%)
Externalizing	446 (12.7%)	256 (7.2%)	702 (9.9%)
Effect modifier	Boys	Girls	Overall
Gender	7,635 (51.4%)	7,219 (48.6%)	14,854
Pubertal stage			
Pre-Early puberty	389 (15.8%)	240 (7.8%)	629 (11.4%)
Mid-Advanced puberty	1,801 (73.2%)	2,025 (66.3%)	3,830 (69.4%)
Post puberty	272 (11.0%)	791 (25.9%)	1,063 (19.2%)
Screen time			
Low	474 (17.3%)	629 (18.4%)	1,103 (17.9%)
Medium	1,708 (62.3%)	2,157 (63.0%)	3,865 (62.7%)
High	560 (20.4%)	635 (18.6%)	1,195 (19.4%)
Potential confounder	Boys	Girls	Overall
Cigarettes smoking (ever)			
Yes	489 (18.9%)	1,038 (31.3%)	1,527 (25.9%)
No	2,095 (81.1%)	2,282 (68.7%)	4,377 (74.1%)
Marijuana smoking (ever)			
Yes	216 (8.3%)	294 (8.8%)	510 (8.6%)
No	2,373 (91.7%)	3,040 (91.2%)	5,413 (91.4%)
Drug use (ever)			
Yes	328 (12.5%)	592 (17.7%)	920 (15.4%)
No	2,287 (87.5%)	2,755 (82.3%)	5,042 (84.6%)
Physical activity			
>3 times a week	1,490 (53.9%)	1,175 (37.6%)	2,665 (45.2%)
≤3 times a week	1,276 (46.1%)	1,953 (62.4%)	3,229 (54.8%)

7.4.2 Baseline characteristics of adolescents with pain at baseline

The baseline characteristics of adolescents with pain at baseline, are outlined in Table 7.4. The average internalizing score was slightly higher in girls than boys (boys 2.6 ± 2.9, girls 2.9 ± 2.8), while boys had higher average externalizing score compared to girls (boys 4.7 ± 3.2, girls 3.9 ±3.1). The use of the 90th percentile cut-off value led to 306 adolescents with internalizing symptoms, with similar proportions between boys (10.4%) and girls (10.8%). Overall 282 children had externalizing symptoms, with more boys than girls having externalizing symptoms (11.7% vs 8.1%, respectively). More girls than boys had pain at baseline (55.9% vs 44.1%, respectively). More adolescents were in the mid/advanced pubertal status (70.1%) compared to the proportion of those in pre-early puberty (10.7%) and post pubertal status (19.2%), and girls were overall in a more advanced pubertal status compared to boys (25.7% vs. 10.7% were in the post pubertal stage, respectively). Proportions of screen time levels were similar between boys and girls (18.7% vs. 18.6% had high levels of screen time, respectively). Approximately 28% of adolescents reported having ever tried smoking, with more girls (34.5%) than boys (19.9%) in proportion, while 9.6% reported having ever tried marijuana, with similar proportions between genders (9.2% in boys, 9.9% in girls). Approximately 18% of adolescents ever tried any type of drugs, with more girls (21.2%) than boys (14.4%). Finally, just below 48% of adolescents performed physical activity more than 3 times a week, with more boys (57.2%) than girls (40.8%).

Table 7.4 Baseline sample characteristics in children with pain at baseline			
Psychological characteristics	Boys	Girls	Overall
Internalizing score	2.6 (± 2.9)	2.9 (± 2.8)	2.7 (± 2.8)
Externalizing score	4.7 (± 3.2)	3.9 (± 3.1)	4.2 (± 3.2)
Psychological symptoms >90th percentile	Boys	Girls	Overall
Internalizing	140 (10.4%)	166 (10.8%)	306 (10.6%)
Externalizing	157 (11.7%)	125 (8.1%)	282 (9.8%)
Effect modifier	Boys	Girls	Overall
Gender	1,511 (44.1%)	1,916 (55.9%)	3,427
Pubertal stage	Boys	Girls	Overall
Pre-Early puberty	154 (14.9%)	102 (7.5%)	256 (10.7%)
Mid-Advanced puberty	770 (74.4%)	909 (66.8%)	1,679 (70.1%)
Post puberty	110 (10.7%)	349 (25.7%)	459 (19.2%)
Screen time			
Low	198 (17.9%)	274 (18.6%)	472 (18.3%)
Medium	704 (63.4%)	923 (62.7%)	1,627 (63.1%)
High	207 (18.7%)	274 (18.6%)	481 (18.6%)
Potential confounder	Boys	Girls	Overall
Cigarettes smoking (ever)			
Yes	208 (19.9%)	496 (34.5%)	704 (28.3%)
No	842 (80.1%)	942 (65.5%)	1,784 (71.7%)
Marijuana smoking (ever)			
Yes	97 (9.2%)	142 (9.9%)	239 (9.6%)
No	954 (90.8%)	1,302 (90.1%)	2,256 (90.4%)
Drug use (ever)			
Yes	153 (14.4%)	308 (21.2%)	461 (18.3%)
No	912 (85.6%)	1,143 (78.8%)	2,055 (81.7%)
Physical activity			
>3 times a week	654 (57.2%)	568 (40.8%)	1,222 (48.2%)
≤3 times a week	488 (42.8%)	825 (59.2%)	1,313 (51.8%)

7.4.3 Baseline characteristics of adolescents without pain at baseline

The baseline characteristics of adolescents without pain at baseline, which is the sample in which the main research question was analysed, are outlined in Table 7.5. The average internalizing score was similar for boys and girls (boys 2.4 ± 2.7, girls 2.5 ± 2.7), while boys had higher average externalizing score compared to girls (boys 4.2 ± 3.2, girls 3.3 ±2.7). The use of the 90th percentile cut-off value led to 260 adolescents with internalizing symptoms, with more boys (8.8%) than girls (8.0%) in the group. Overall 226 children had externalizing symptoms, with more boys than girls having externalizing symptoms (9.6% vs 5.1%, respectively). More girls than boys without pain at baseline were present (53.3% vs 46.7%, respectively). More adolescents were in the mid/advanced pubertal status (70.4%) compared to the proportion of those in pre-early puberty (11.1%) and post pubertal status (18.5%), and girls were overall in a more advanced pubertal status compared to boys (24.5% vs. 10.8% were in the post pubertal stage, respectively). Boys more often reported high levels of screen time compared to girls (20.8% vs. 18.6%, respectively). Approximately 21% of adolescents reported having ever tried smoking, with more girls (24.8%) than boys (15.8%) in proportion, while 6.6% reported having ever tried marijuana, with similar proportions between genders (6.2% in boys, 6.8% in girls). Approximately 11% of adolescents ever tried any type of drugs, with more girls (12.6%) than boys (9.9%). Finally, just below 43% of adolescents performed physical activity more than 3 times a week, with more boys (51.0%) than girls (35.9%).

Table 7.5 Baseline sample characteristics in children without pain at baseline			
Psychological characteristics	Boys	Girls	Overall
Internalizing score	2.4 (± 2.7)	2.5 (± 2.7)	2.5 (± 2.7)
Externalizing score	4.2 (± 3.2)	3.3 (± 2.7)	3.8 (± 3.0)
Psychological symptoms >90th percentile	Boys	Girls	Overall
Internalizing	131 (8.8%)	129 (8.0%)	260 (8.4%)
Externalizing	144 (9.6%)	82 (5.1%)	226 (7.3%)
Effect modifier	Boys	Girls	Overall
Gender	1,656 (46.7%)	1,888 (53.3%)	3,544
Pubertal stage	Boys	Girls	Overall
Pre-Early puberty	172 (15.3%)	111 (7.8%)	283 (11.1%)
Mid-Advanced puberty	831 (73.9%)	962 (67.7%)	1,794 (70.4%)
Post puberty	122 (10.8%)	349 (24.5%)	471 (18.5%)
Screen time			
Low	202 (16.3%)	262 (17.4%)	464 (16.9%)
Medium	779 (62.9%)	966 (64.0%)	1,746 (63.5%)
High	258 (20.8%)	280 (18.6%)	538 (19.6%)
Potential confounder	Boys	Girls	Overall
Cigarettes smoking (ever)			
Yes	187 (15.8%)	364 (24.8%)	551 (20.8%)
No	997 (84.2%)	1,107 (75.2%)	2,104 (79.2%)
Marijuana smoking (ever)			
Yes	74 (6.2%)	101 (6.8%)	175 (6.6%)
No	1,113 (93.8%)	1,376 (93.2%)	2,489 (93.4%)
Drug use (ever)			
Yes	118 (9.9%)	187 (12.6%)	305 (11.4%)
No	1,077 (90.1%)	1,293 (87.4%)	2,370 (88.6%)
Physical activity			
>3 times a week	634 (51.0%)	521 (35.9%)	1,155 (42.8%)
≤3 times a week	610 (49.0%)	932 (64.1%)	1,543 (57.2%)

7.5 Discussion

7.5.1 Descriptive analysis

7.5.1.1 Baseline pain

Baseline descriptive analysis showed that approximately 49% (3,427/6,971) of children reported having had pain in their arm(s) or leg(s). Figures on musculoskeletal pain provided by cohort studies conducted in adolescents of similar age to that of this study showed prevalence rates ranging from 30% to 70% (Auvinen et al., 2010; Gill et al., 2014; Mikkonen et al., 2013; Paananen et al., 2010; Sjolie & Ljunggren, 2001). Prevalence figures reported in a recent systematic review were between 15-21 % for knee and ankle foot pain and 33-63% for shoulder pain, although estimates for "often/usually" pain in the upper extremity and lower extremity were lower (9.4-11.7% and 28.9-31.9%, respectively) (Fuglkjær, Dissing, & Hestbæk, 2017). Although direct comparison with other cohorts is limited because of differences in the nature of the pain questions (i.e. body sites assessed and time-frame considered), the figures for baseline pain within this current are overall in line with those reported previously in the literature.

7.5.1.2 Predictor: psychological symptoms

In this cohort, the mean internalizing score was 2.6 (2.7 in girls; 2.6 in boys), while the mean externalizing score was 4.2 (3.7 in girls; 4.6 in boys). These values are in agreement with parent-reported normative data provided for Danish schoolchildren aged 10-12; the internalizing score is 2.7 in girls and 2.6 in boys, and the externalizing score is 2.6 in girls and 3.4 in boys (http://www.sdqinfo.com/norms/SDQ_Danish_means_and_SD_10_12_year_olds.pdf), with further evidence of comparability from a range of other countries (Japanese schoolchildren aged 13-15, http://www.sdqinfo.com/norms/JapaneseMeans.pdf, Australian children aged 11-13 http://www.sdqinfo.com/norms/AusNorm2.pdf, and American children 11-14 years old http://www.sdqinfo.com/norms/USNorm1.pdf). Taken together, the evidence from other cohorts suggests that the internalizing and externalizing scores found in this cohort are in line with normative data for this age group (adolescents) reported in the literature.

7.5.1.3 Differences between children with and without pain at baseline

Comparison between children with and without pain at baseline showed that those with pain at baseline had higher internalizing and externalizing scores (2.7 ± 2.8 and 4.2 ± 3.2, respectively) compared to those without pain at baseline (2.5 ± 2.7 and 3.8 ± 3.0, respectively). This is consistent with the reciprocal relationship between psychological symptoms and pain reported in the literature (Dersh et al., 2002; Keefe et al., 2004; Linton & Shaw, 2011). In addition, proportions of adolescents who ever tried smoking, marijuana or any type of drugs was higher among those with pain (28.3%, 9.6% and 18.3%, respectively) compared to those without pain at baseline (20.8%, 6.6%, and 11.4%, respectively). This is in accordance with the reported association between musculoskeletal pain and smoking or substance use (Brattberg, 1994; Feldman et al., 1999, 2001; Gill, Davis, Smith, & Straker, 2014; Mikkonen et al., 2008). Finally, the proportion of adolescents with high levels of physical activity was higher among those with pain

at baseline (48.2%) compared to those without pain at baseline (42.8%), in accordance with the potential increase in musculoskeletal pain of traumatic origin among adolescents with higher levels of physical activity (El-Metwally et al., 2007; Kamada et al., 2016).

7.5.2 Analysis of loss to follow-up

The results of the responder analysis showed that adolescents lost to follow-up had in proportion more internalizing and externalizing symptoms, high levels of screen time, included more males, had higher smoking levels, and were less advanced in terms of pubertal stage compared to those who completed at follow-up. Therefore if any of these factors were associated with the onset of musculoskeletal pain, then the actual observed incidence of musculoskeletal pain may be lower, compared to the expected incidence in the target population. This may potentially lead to an underestimation of the association found.

Chapter eight. The association of psychological symptoms with musculoskeletal pain onset in adolescents: results of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort

This chapter reports the results of the analysis of thesis objective number 2 (i.e. the association between psychological symptoms and the onset of musculoskeletal pain in adolescents free of pain at baseline). The results of the logistic regression analysis of the association between psychological symptoms (internalizing and externalizing symptoms in this analysis) and the onset of both musculoskeletal pain and chronic musculoskeletal pain are presented (Section 8.2 - 8.5), together with a discussion of the results (Section 8.7). The following section details the process for imputation of missing data before the results of the logistic regression tests are described.

8.1 MCAR test and multiple imputation

The process of selection of adolescents for analysis (i.e. from the initial cohort to the group of adolescents entered in the analysis) was outlined in Section 7.3.1, followed by a description of the baseline missing data (Section 7.3.2). A Little's MCAR test was performed to test whether data were missing completely at random (MCAR). Results showed the test as significant indication ($p < 0.001$) that data were not missing completely at random. The main (primary) analysis investigating the association between the presence of internalizing and externalizing symptoms and the onset of musculoskeletal pain was performed based on all adolescents with outcome data on pain presence at follow-up. Whilst the data were not MCAR simulation studies have shown that multiple imputation can reduce the risk of bias and increase the precision of estimates , and therefore multiple imputation of missing data on exposure, potential effect modifiers and confounding variables was performed under the missing at random assumption. A chained equation multiple imputation method was applied taking account of all variables to be entered in

the analysis. Once data was imputed, the logistic regression analysis was carried out (Section 8.2 - 8.5). A sensitivity analysis was performed with the complete-case dataset to assess the robustness of results of the main analysis, which are described in Section 8.6.

8.2 Association between baseline internalizing symptoms and musculoskeletal pain onset in adolescents

8.2.1 Internalizing at baseline and onset of musculoskeletal pain in adolescents at follow-up

The 4-year incidence of musculoskeletal pain at follow-up was 35.8% (575/1604 children present at follow-up). The two internalizing symptoms categories: yes (internalizing score > 90th percentile) and no (internalizing score < 90th percentile) were examined in relation to the proportion of musculoskeletal pain at follow-up. The proportion of adolescents reporting musculoskeletal pain was higher in those with internalizing symptoms (41.9%) compared to those without internalizing symptoms (35.3%) (Table 8.1).

Table 8.1 Internalizing symptoms at baseline and musculoskeletal pain presence at follow-up among adolescents pain-free at baseline

	Musculoskeletal pain at follow-up		
Internalizing symptoms	**Yes**	**No**	**Total**
Yes	52 (41.9%)	72 (58.1%)	124
No	523 (35.3%)	957 (64.7%)	1,480
Total	575	1,029	1,604

8.2.2 Results of logistic regression of the association between baseline internalizing symptoms and musculoskeletal pain onset at follow-up

Logistic regression analysis was performed to investigate the association between internalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted and then with adjustment for smoking, marijuana use, drug use and physical activity (adjustment for sleep problems was not performed due to the high percentage of missing data, > 90%) (Table 8.2). The unadjusted result showed a non-significant increased odds for the onset of musculoskeletal pain in adolescents with internalizing symptoms (OR = 1.34; 95% CI 0.90, 1.99). This effect was stronger after adjustment for smoking, marijuana use, drug use and physical activity, but still non-significant (OR = 1.43; 95% CI 0.96, 2.12).

Table 8.2 Logistic regression of the association between internalizing at baseline and musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 1,604)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.34	0.90, 1.99
Adjusted analysis*		
Overall (N = 1,604)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.43	0.96, 2.12
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.2.2.1 Effect modification by gender

Effect modification was assessed by performing an interaction test and stratification analysis by gender. Results are shown in Table 8.3. The interaction test was not significant (Female gender # Internalizing Adj. OR = 1.07; 95% CI 0.48, 2.40), indicating no presence of statistically significant effect modification. Stratified analysis showed that estimates of odds were similar between genders (Females: Adj. OR = 1.48; 95% CI 0.86, 2.52; Males: Adj. OR = 1.41; 95% CI 0.77, 2.57) and similar to the overall estimate (Adj. OR = 1.43; 95% CI 0.96, 2.12).

Table 8.3 Logistic regression of the association between internalizing at baseline and musculoskeletal pain onset at follow-up stratified by gender

Unadjusted analysis		
Females (N = 942)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.38	0.81, 2.34
Males (N = 662)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.31	0.72, 2.39
Adjusted analysis*		
Females (N = 942)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.48	0.86, 2.52
Males (N = 662)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.41	0.77, 2.57
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Female gender # Internalizing	1.07	0.48, 2.40
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.2.2.2 Effect modification by pubertal stage

A test for interaction using "Early puberty" as the reference category (Early puberty # Internalizing, Mid/Advanced puberty # Internalizing, Post puberty # Internalizing) and stratified analysis by pubertal stages were performed. Results are shown in Table 8.4. The interaction test was not significant (Mid/advanced puberty # Internalizing Adj. OR = 0.76; 95% CI 0.20, 2.96; Post puberty # Internalizing Adj. OR = 0.50; 95% CI 0.11, 2.30), indicating no presence of statistically significant effect modification, although the direction of the result does suggest a lessening of association as pubertal stage advances. Stratified analysis showed a similar decreasing odds with increasing levels of pubertal development (Early pubertal stage: Adj. OR = 2.12; 95% CI 0.59, 7.64; Mid/advanced pubertal stage: Adj. OR = 1.51; 95% CI 0.92, 2.47; Post pubertal stage: Adj. OR = 1.05; 95% CI 0.44, 2.49).

Table 8.4 Logistic regression of the association between internalizing at baseline and musculoskeletal pain onset at follow-up stratified by pubertal stage		
Unadjusted analysis		
Early pubertal stage (N = 153)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.86	0.54, 6.41
Mid/Advanced pubertal stage (N = 1,110)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.43	0.87, 2.34
Post pubertal stage (N = 297)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	0.94	0.40, 2.20
Adjusted analysis*		
Early pubertal stage (N = 153)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	2.12	0.59, 7.64
Mid/Advanced pubertal stage (N = 1,110)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.51	0.92, 2.47
Post pubertal stage (N = 297) •••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.05	0.44, 2.49
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Mid/Advanced puberty # Internalizing	0.76	0.20, 2.96
Post puberty # Internalizing	0.50	0.11, 2.30

*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity

• Sample size vary between 153 and 175

•• Sample size vary between 1,110 and 1,151

••• Sample size vary between 297 and 326

8.2.2.3 Effect modification by screen time

A test for interaction using "Low screen time" as the reference category (Low Screen time # Internalizing, Medium Screen time # Internalizing, High Screen time # Internalizing) and stratified analysis by screen time were performed. Results are shown in Table 8.5. The interaction test was not significant (Medium Screen time # Internalizing Adj. OR = 0.70; 95% CI 0.22, 2.21; High Screen time # Internalizing Adj. OR = 0.27; 95% CI 0.07, 1.11), indicating no presence of statistically significant effect modification, though a pattern of a reduction in association (odds) is seen with increasing screen time. Stratified analysis are in the direction of a decrease in odds with increasing levels of screen time, showing a non-significant increase in odds in adolescents with low levels of screen time (Adj. OR = 2.36; 95% CI 0.83, 6.74), a significant increase in odds in those with medium levels of screen time (Adj. OR = 1.67; 95% CI 1.01, 2.75) and a non-significant decrease in odds in those with high levels of screen time (Adj. OR = 0.66; 95% CI 0.25, 1.75).

Table 8.5 Logistic regression of the association between internalizing at baseline and musculoskeletal pain onset at follow-up stratified by screen time		
Unadjusted analysis		
Low screen time (N = 267)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	2.31	0.82, 6.48
Medium screen time (N = 990)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.52	0.93, 2.49
High screen time (N = 302)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	0.65	0.24, 1.73
Adjusted analysis*		
Low screen time (N = 267)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	2.36	0.83, 6.74
Medium screen time (N = 990)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.67	1.01, 2.75
High screen time (N = 302)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	0.66	0.25, 1.75
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Medium Screen time # Internalizing	0.70	0.22, 2.21
High Screen time # Internalizing	0.27	0.07, 1.11
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity • Sample size vary between 267 and 288 •• Sample size vary between 990 and 1,027 ••• Sample size vary between 302 and 334		

8.3 Association between baseline externalizing symptoms and musculoskeletal pain onset in adolescents

8.3.1 Externalizing at baseline and onset of musculoskeletal pain in adolescents at follow-up

The two externalizing symptoms categories: yes (externalizing symptoms > 90th percentile) and no (externalizing symptoms < 90th percentile) were examined in relation to the proportion of musculoskeletal pain at follow-up. The proportion of adolescents reporting musculoskeletal pain was higher in adolescents with externalizing symptoms (51.5%) compared to those without externalizing symptoms (34.8%) (Table 8.6).

Table 8.6 Externalizing symptoms at baseline and musculoskeletal pain presence at follow-up among adolescents pain-free at baseline

	Musculoskeletal pain at follow-up		
Externalizing symptoms	**Yes**	**No**	**Total**
Yes	51 (51.5%)	48 (48.5%)	99
No	524 (34.8%)	981(65.2%)	1,505
Total	575	1,029	1,604

8.3.2 Results of logistic regression of the association between baseline externalizing symptoms and musculoskeletal pain onset at follow-up

Logistic regression analysis was performed in order to test the association between externalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted and then with adjustment for smoking, marijuana use, drug use and physical activity (Table 8.7). The unadjusted result shows significant increased odds for the onset of musculoskeletal pain in adolescents with externalizing symptoms (OR = 1.99; 95% CI 1.29, 3.09). This effect is unchanged after adjustment for smoking, marijuana use, drug use and physical activity (OR = 1.99; 95% CI 1.28, 3.10).

Table 8.7 Logistic regression of the association between externalizing at baseline and musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 1,604)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.99	1.29, 3.09
Adjusted analysis*		
Overall (N = 1,604)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.99	1.28, 3.10
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.3.2.1 Effect modification by gender

Effect modification was assessed by performing an interaction test and stratification analysis by gender. Results are shown in Table 8.8. The interaction test was not significant (Female gender # Externalizing Adj. OR = 1.09; 95% CI 0.43, 2.75), indicating no presence of statistically significant effect modification. Stratified analysis showed significant associations with estimates of odds that were similar between genders (Females: Adj. OR = 2.20; 95% CI 1.10, 4.40; Males: Adj. OR = 2.03; 95% CI 1.11, 3.70), and similar to the overall estimate (Adj. OR = 1.99; 95% CI 1.28, 3.10).

Table 8.8 Logistic regression of the association between externalizing at baseline and musculoskeletal pain onset at follow-up stratified by gender

Unadjusted analysis		
Females (N = 942)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.22	1.12, 4.37
Males (N = 662)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.96	1.09, 3.53
Adjusted analysis*		
Females (N = 942)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.20	1.10, 4.40
Males (N = 662)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.03	1.11, 3.70
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Female gender # Externalizing	1.09	0.43, 2.75
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.3.2.2 Effect modification by pubertal stage

An interaction test using "Early puberty" as the reference category (Early puberty # Externalizing, Mid/Advanced puberty # Externalizing, Post puberty # Externalizing) and stratified analysis by pubertal stages were performed. Results are shown in Table 8.9. The interaction test was not significant (Mid/Advanced puberty # Externalizing Adj. OR = 4.89; 95% CI 0.60, 40.16; Post puberty # Externalizing Adj. OR = 3.49; 95% CI 0.36, 33.71), indicating no presence of statistically significant effect modification. Stratified analysis showed that those in the early pubertal stage were at non-significant decreased odds of a musculoskeletal pain outcome, those in the mid/advanced pubertal stage were at statistically significant increased odds and those at the post pubertal stage were at non-significant increased odds (Early pubertal stage: Adj. OR = 0.57; 95% CI 0.07, 4.68; Mid/advanced pubertal stage: Adj. OR = 2.49; 95% CI 1.43, 4.34; Post pubertal stage: Adj. OR = 1.81; 95% CI 0.66, 4.93).

Table 8.9 Logistic regression of the association between externalizing at baseline and musculoskeletal pain onset at follow-up stratified by pubertal stage		
Unadjusted analysis		
Early pubertal stage (N = 153)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	0.54	0.08, 3.78
Mid/Advanced pubertal stage (N = 1,110)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.50	1.44, 4.36
Post pubertal stage (N = 297)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.74	0.66, 4.57
Adjusted analysis*		
Early pubertal stage (N = 153)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	0.57	0.07, 4.68
Mid/Advanced pubertal stage (N = 1,110)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.49	1.43, 4.34
Post pubertal stage (N = 297)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.81	0.66, 4.93
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Mid/Advanced puberty # Externalizing	4.89	0.60, 40.16
Post puberty # Externalizing	3.49	0.36, 33.71
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity • Sample size vary between 153 and 175 •• Sample size vary between 1,110 and 1,151 ••• Sample size vary between 297 and 326		

8.3.2.3 Effect modification by screen time

A test for interaction using "Low screen time" as the reference category (Low Screen time # Externalizing, Medium Screen time # Externalizing, High Screen time # Externalizing) and stratified analysis by screen time were performed. Results are shown in Table 8.10. The interaction test showed no statistical effect (Medium Screen time # Externalizing Adj. OR = 0.91; 95% CI 0.22, 3.86; High Screen time # Externalizing Adj. OR = 0.54; 95% CI 0.11, 2.69), indicating no statistically significant effect modification. Stratified analysis showed a non-significant increase in odds in adolescents with low levels of screen time, a significant increase in odds for those with medium levels of screen time, and a non-significant increase in odds in those with high levels of screen time. Although stratified analysis showed an increase in odds for all strata, overall the direction of effect showed a decreasing trend of effect size of estimates with increasing levels of screen time (Low screen time: Adj. OR = 2.46; 95% CI 0.66, 9.21; Medium screen time: Adj. OR = 2.22; 95% CI 1.24, 3.99; High screen time: Adj. OR = 1.36; 95% CI 0.49, 3.77).

Table 8.10 Logistic regression of the association between externalizing at baseline and musculoskeletal pain onset at follow-up stratified by screen time		
Unadjusted analysis		
Low screen time (N = 267)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.42	0.66, 8.88
Medium screen time (N = 990)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.26	1.27, 4.02
High screen time (N = 302)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.34	0.49, 3.64
Adjusted analysis*		
Low screen time (N = 267)•		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.46	0.66, 9.21
Medium screen time (N = 990)••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.22	1.24, 3.99
High screen time (N = 302)•••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.36	0.49, 3.77
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Medium Screen time # Externalizing	0.91	0.22, 3.86
High Screen time # Externalizing	0.54	0.11, 2.69

*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity

• Sample size vary between 267 and 288

•• Sample size vary between 990 and 1,027

••• Sample size vary between 302 and 334

8.4 Association between baseline internalizing symptoms and chronic musculoskeletal pain onset in adolescents

8.4.1 Internalizing at baseline and onset of chronic musculoskeletal pain in adolescents at follow-up

The 4-year incidence of chronic musculoskeletal pain at follow-up was 17.0% (273/1604 children present at follow-up). The two internalizing symptoms categories: yes (internalizing score > 90th percentile) and no (internalizing score < 90th percentile) were examined in relation to the proportion of chronic musculoskeletal pain at follow-up. The proportion of children reporting chronic musculoskeletal pain was higher in those with internalizing symptoms compared to those without internalizing symptoms (20.5% vs. 16.7%) (Table 8.11).

Table 8.11 Internalizing symptoms at baseline and chronic musculoskeletal pain presence at follow-up among adolescents musculoskeletal pain-free at baseline

	Chronic musculoskeletal pain at follow-up		
Internalizing symptoms	**Yes**	**No**	**Total**
Yes	25 (20.5%)	97 (79.5%)	122
No	248 (16.7%)	1,234 (83.3%)	1,482
Total	273	1,331	1,604

8.4.2 Results of logistic regression of the association between baseline internalizing symptoms and chronic musculoskeletal pain onset at follow-up

Logistic regression analysis was performed to test the association between internalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted, and then with adjustment for smoking, marijuana use, drug use and physical activity (Table 8.12). The results show an increase in odds for the onset of chronic musculoskeletal pain in children with internalizing symptoms, although this effect is not significant (OR = 1.24; 95% CI 0.75, 2.05). Similarly after adjustment (smoking, marijuana use, drug use and physical activity) the increase of effect is stronger but again non-significant (OR = 1.28; 95% CI 0.77, 2.11). Due to the low number of adolescents with internalizing symptoms who report chronic musculoskeletal pain at follow-up (n = 25, Table 8.11), interaction analysis and stratified analysis to assess potential effect modification were not performed (given the low statistical power for interaction analysis, and low cell count for stratification).

Table 8.12 Logistic regression of the association between internalizing at baseline and chronic musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 1,598)		
Chronic MSK pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.24	0.75, 2.05
Adjusted analysis*		
Overall (N = 1,598)		
Chronic MSK pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.28	0.77, 2.11
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.5 Association between baseline externalizing symptoms and chronic musculoskeletal pain onset in adolescents

8.5.1 Externalizing at baseline and onset of chronic musculoskeletal pain in adolescents at follow-up

The two externalizing symptoms categories: yes (externalizing symptoms > 90th percentile) and no (externalizing symptoms < 90th percentile) were examined in relation to the proportion of musculoskeletal pain at follow-up. The proportion of children reporting chronic musculoskeletal pain was higher in adolescents with externalizing symptoms compared to those without externalizing symptoms (25.3% vs. 16.5%, respectively) (Table 8.13).

Table 8.13 Externalizing symptoms at baseline and chronic musculoskeletal pain presence at follow-up among adolescents musculoskeletal pain-free at baseline

	Chronic musculoskeletal pain at follow-up		
Externalizing symptoms	**Yes**	**No**	**Total**
Yes	25 (25.3%)	74 (74.7%)	99
No	248 (16.5%)	1,257 (83.5%)	1,505
Total	273	1,331	1,604

8.5.2 Results of logistic regression of the association between baseline externalizing symptoms and musculoskeletal pain onset at follow-up

Logistic regression analysis was performed in order to test the association between externalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up. Two stages of analysis were performed, first unadjusted and then with adjustment for smoking, marijuana use, drug use and physical activity (Table 8.14). The unadjusted result showed significant increased odds for the onset of chronic musculoskeletal pain in children with externalizing symptoms (OR = 1.69; 95% CI 1.01, 2.83). However this effect is non-significant after adjustment for smoking, marijuana use, drug use and physical activity (OR = 1.68; 95% CI 0.96, 2.73). As with the findings on internalizing, due to the low number of adolescents with externalizing symptoms who reported chronic musculoskeletal pain at follow-up (n = 25, Table 8.13), no further analysis to investigate effect modification (interaction/ stratification) was performed.

Table 8.14 Logistic regression of the association between externalizing at baseline and chronic musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 1,598)		
Chronic MSK pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.69	1.01, 2.83
Adjusted analysis*		
Overall (N = 1,598)		
Chronic MSK pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.68	0.96, 2.73
*Analysis adjusted for Smoking, Marijuana use, Drug use and Physical activity		

8.6 Sensitivity analysis: complete-case analysis

The results presented in Section 8.2 - 8.5 refer to the logistic regression analysis performed with the multiple imputed dataset. As described in Section 8.1, data was shown to be missing not completely at random. Sensitivity analysis was carried out to assess the robustness of this primary analysis and explore if different results would be obtained when using participants with complete data only. The sensitivity analysis showed that adolescents with complete data were at lower odds for the onset of musculoskeletal pain (Internalizing symptoms analysis; complete data OR = 1.17, missing data OR = 2.33; Externalizing symptoms analysis; complete data OR =1.58, missing data OR = 4.00) and chronic musculoskeletal pain (Internalizing symptoms analysis; complete data OR = 0.96, missing data OR = 2.38; Externalizing symptoms analysis; complete data OR = 1.33, missing data OR = 2.55). The lower odds found within the complete case dataset may be explained by selective loss to follow-up. For a full description of the results obtained with the complete-case analysis please refer to appendix VIII.

8.7 Discussion

This section will start with a comparison of the results in the context of the wider literature to give interpretation of the findings of this current study (Section 8.7.1), which will be followed by the strengths and weaknesses (Section 8.7.2) and finally key messages (Section 8.7.3).

8.7.1 Interpretation of the findings and comparison with previous literature

8.7.1.1 Association between the presence of internalizing and externalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up

Overall the results show that the 4-year incidence rate for musculoskeletal pain onset was 35.8%, which generally fits within the approximations from other relevant cohort studies (Feldman et al., 2002b; Jones, Watson, et al., 2003; Mikkonen et al., 2013; Paananen et al., 2010), although direct comparisons cannot be made due to differing age groups, time scales for follow-up, and measures and assessments of pain. These results indicate that a significant proportion of the adolescent population will report musculoskeletal pain onset. However, it should be noted that the baseline measure used to identify pain (i.e. to exclude those with pain presence at baseline) may have missed adolescents with musculoskeletal pain presence (i.e. this study excluded those who reported arm and leg pain only, and this may have missed proportions who may have had other bodily regional pain, such as back pain, neck pain, shoulder pain). However, literature shows many adolescents will report multisite pain (Mikkelsson et al., 1997; Rathleff, Roos, Olesen, & Rasmussen, 2013), and extremity pain (especially leg and lower limb pain) is common (Michaleff, Campbell, Protheroe, Rajani, & Dunn, 2017), nonetheless this limitation may have resulted in an overestimation of incidence. Results of the logistic regression analysis show a non-significant increasing odds effect for the association between internalizing symptoms and musculoskeletal pain onset (Table 8.2) and a significant higher odds for musculoskeletal pain onset observed in

adolescents with high levels of externalizing symptoms (Table 8.7). Several studies, identified in the systematic review within this thesis, have investigated the effect of internalizing and externalizing symptoms on musculoskeletal pain, and a range of significant and mixed findings was reported (Gill, Davis, Smith, & Straker, 2014; Jussila et al., 2014; Kroner-Herwig, Gassmann, van Gessel, & Vath, 2011; Paananen et al., 2010). Differences between the studies identified in the review and the results found in this current study may be explained by differences in how the exposure and outcome variables were measured and entered in the analysis. A comparison of findings with two studies identified within the systematic review that used the same tool (SDQ) to evaluate psychological symptoms may be attempted, although these studies investigated the separate effect for each subscale of the SDQ rather than the internalizing and externalizing constructs used here (Jones, Silman, et al., 2003; Jones, Watson, et al., 2003). These studies report a significant effect for the onset of back pain and widespread pain for medium and higher levels of conduct problems, but not for any of the other scales (hyperactivity, emotional symptoms and peer problems), where only non-significant trends for increased odds were found. This is partly consistent with our findings that externalizing symptoms (in which conduct problems form part of the externalising construct) are significantly predictive of the onset of musculoskeletal pain whereas those subscales that make up the internalizing construct (emotional symptoms, peer problems) were not, and only demonstrated a non-significant trend. This does suggest that externalizing appears a more robust marker of onset of musculoskeletal pain. On examination of the other literature there are some other important differences, for example different cut-off points were used to denote internalizing and externalizing symptoms in this study which makes comparisons difficult. Within previous studies the SDQ score was divided in three bands according to tertiles (low, medium and high) of psychological symptoms, and the "low" category was used as a reference. Conversely, in this current study the 90th percentile was used as a cut-off value, chosen to identify those with a clinical level of symptoms, and chosen based on the trends of the review which indicated increasing effects in those with greater

symptom severity. In addition, considering population norm scores (as outlined in chapter 7, Section 7.5.1.2) the internalizing score of this current study was generally in line with the norm values, however externalizing scores were slightly higher than norms, which given the evidence of a linear relationship, may have increased the likelihood of the expected effect for this construct (Section 7.5.1.2).

8.7.1.2 Association between the presence of internalizing and externalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up

The 4-year incidence rate of chronic musculoskeletal pain onset was 17.0% in this cohort. This figure is generally higher than the incidence for chronic regional pain (4.7%) and chronic widespread pain (7.7%) reported in previous cohorts (Harrison et al., 2014; McBeth & Jones, 2007), though this would be expected as this current study used less restrictive criteria to define chronic pain (all musculoskeletal pain inclusive of single site and multisite). The incident figures from this current study are within the range of incidence estimate for chronic musculoskeletal pain (11-26%) reported in studies carried out in adults (Mork et al., 2014; Nakamura, Nishiwaki, Ushida, & Toyama, 2014), however as highlighted for musculoskeletal pain onset above, the baseline exclusion of those with pain only included pain in the arms and legs and therefore the reported incidence estimate may be imprecise. As with the finding on musculoskeletal pain onset, there is a non-significant increase in odds with the presence of internalizing, and a significant increase in odds with externalizing for chronic musculoskeletal pain onset (Section 8.4.2, Table 8.12, Section 8.5.2, Table 8.14). The findings on internalizing are broadly in line with findings reported in a review that show that internalizing constructs, such as depression, are most likely not a predictor of the onset of chronic musculoskeletal pain (Dersh et al., 2002). As outlined there is a greater strength of effect for externalizing for both musculoskeletal and chronic musculoskeletal pain onset suggesting that externalizing symptoms have a more consistent role. However the relationship with externalizing to chronic musculoskeletal pain onset is perhaps

more complex (e.g. the effect was non-significant after adjustment) and may indicate that once a musculoskeletal pain episode occurs, other factors (e.g. exacerbation of substance use, or a change in the levels of physical activity), or the coping response to the initial pain episode may contribute to the development of chronic musculoskeletal pain. Potential explanations for the findings are proposed in the following section.

8.7.1.3 Potential explanation for the associations found

The overall aim of this thesis was not necessarily to investigate the mechanisms leading from internalizing or externalizing symptoms to musculoskeletal pain onset but merely to investigate the linkage and examine potential effect modification. However, in line with the biopsychosocial model of pain, in this section potential biopsychosocial explanations are briefly described. As introduced in chapter 1 (Section 1.3.1), the HPA axis may become dysfunctional in response to prolonged periods of stress. Theoretically, in response to a stressful situation, the HPA axis initially becomes hyperactive, with consequential higher production of cortisol (Generaal et al., 2014; Gupta & Silman, 2004; Hannibal & Bishop, 2014; McBeth et al., 2007). Following this hyperactive period, the HPA axis may reach an exhaustive status and become hypoactive with an increased sensitivity to stressful life-events and a decreased production of cortisol. This status may increase the vulnerability to musculoskeletal pain, as supported by evidence of association between hypocortisolism and musculoskeletal pain (Generaal et al., 2014; Hannibal & Bishop, 2014; Kaplow et al., 2013; McBeth et al., 2007). In addition, evidence shows that the HPA functioning may be modulated by psychological and behavioural factors such as rumination and attention, by early life adversities (e.g. experiences of physical, emotional, and sexual abuse), and by the experience of family problems and family discord (Frodl & O'Keane, 2013; Keiley, Howe, Dodge, Bates, & Pettit, 2001). The effect of these factors may result in either an hyperactive or hypoactive HPA status increasing the likelihood of a link to musculoskeletal pain (Alink et al., 2008; Frodl &

O'Keane, 2013; Kaplow et al., 2013; Lopez-Duran, Kovacs, & George, 2009; van voorhees & Scarpa, 2004). Another factor involved in the HPA axis activity is serotonin (serotonin levels are low in the dysfunctional HAP axis), which is a neurotransmitter also involved in the pain process (serotonin is a suppressor of substance P, a nociceptive neurotransmitter, and low levels of serotonin are associated with pain) (Gupta & Silman, 2004; Hannibal & Bishop, 2014; McBeth et al., 2007). The HPA response to stressors may work differently between individuals with externalizing and internalizing symptoms and give some explanation to the differences in effect reported. Two meta-analyses show associations between depression (which is part of the internalizing construct) in children and adolescents and HPA dysregulation (Lopez-Duran et al., 2009) and changes in cortisol (linked to both internalizing and externalizing) (Alink et al., 2008; Lopez-Duran et al., 2009) making the hypothesis of a link between psychological affect, biological changes, and increased vulnerability to musculoskeletal onset plausible, although less of an effect was noted for internalizing in this study which encompasses depression.

Whilst a biological explanation has been outlined above and some synthesis attempted between biological factors and the psychological constructs of internalizing and externalizing symptoms, there are broader psychological, behavioural, and social factors to consider that may also help to explain the reported results. For example, problems within the family environment may make adolescents more susceptible to psychological symptoms and the onset of musculoskeletal pain (Brattberg, 1994; Kroner-Herwig et al., 2011). Familial problems may originate as a result of low socioeconomic status, which may act as a stressor in the family environment and foster the development of psychological symptoms in adolescents (Alink et al., 2008; Ramchandani & Psychogiou, 2009). Other familial stressors associated with the development of internalizing and externalizing symptoms in adolescents are the presence of parental mental health and behavioural problems (e.g. depression, anxiety, substance use), with mechanisms of transmission to the offspring that may be genetic, environmental, or involve a gene–environment interaction (Ramchandani & Psychogiou, 2009). In addition, there is evidence of association between chronic

pain conditions in the parents and increased internalizing and externalizing symptoms in adolescents, which may be partly due to the anger and frustration resulting from the burden of taking care of the parents' health problems as well as behavioural influences such as children and adolescents vicariously learning how to cope (or not) with pain (Higgins et al., 2015). Evidence from the literature suggest that psychological and behavioural factors are also involved in the reciprocal relationship between psychological symptoms and pain that may lead to chronic musculoskeletal pain. In the bi-directional relationship between psychological symptoms and pain, baseline internalizing and externalizing symptoms may initially lead to pain, which in turn may act as a stressor and lead to problems in emotion regulation (e.g. anger, aggressive behaviour, nervousness, impulsivity, anxiety) increasing the influence of internalizing and externalizing factors (Vaalamo, Pulkkinen, Kinnunen, Kaprio, & Rose, 2002). In addition this stressful emotional response may result in the activation of the sympathetic nervous system, which may increase muscle tension and reduce pain tolerance (potentially because of increased catastrophizing thoughts about pain) (Keefe et al., 2004; Vaalamo et al., 2002). This bi-directional relationship may also be influenced by other pre-existing, semi-dormant factors such as pain catastrophizing, pain-related anxiety and fear of pain (often constructs related to core emotional affect such as internalizing and externalizing), which may act in a diathesis stress-model (Dersh et al., 2002; Linton & Shaw, 2011). For example, in adolescents who already suffer from anxiety and hold pain-catastrophizing or fear-avoidance beliefs about pain, the initial acute pain may start a fear-avoidance behaviour (e.g. avoiding movements or limiting activities which are believed to increase pain) that may lead to chronicity (Dersh et al., 2002; Linton & Shaw, 2011). In conclusion, the evidence presented above shows that biological (i.e. dysfunctional HPA axis), psychological, behavioural and social factors (i.e. problems in the family environment, pain catastrophizing, pain-related anxiety, fear of pain), or a combination of all these factors, are plausible explanations for the relationship between internalizing and externalizing symptoms and the onset of musculoskeletal pain or chronic musculoskeletal pain as reported within this thesis. More work is

now needed to understand the developmental aspects of these constructs and this is further discussed in chapter 11.

8.7.1.4 Effect modification by gender

The results of the interaction tests, together with results of the stratified analysis, suggest that gender is not an effect modifier of the association between musculoskeletal pain and both internalizing symptoms and externalizing symptoms. These results do not support the hypothesized difference in effect by gender proposed in Section 3.4.2.1, which was based on the known gender imbalance on the prevalence of internalizing and externalizing symptoms, with higher risk of internalizing symptoms in girls and of externalizing symptoms in boys (Maughan et al., 2004; Merikangas et al., 2009). This gender imbalance was found only for externalizing symptoms but not for internalizing symptoms in this cohort (see Section 7.4.2, Table 7.5). Considering the literature within the systematic review, the findings of this study are mostly supported, with two studies reporting no gender differences (Jussila et al., 2014; Paananen et al., 2010), which is in accordance with the results, and one study reporting a statistically significant association for the onset of multiple pain only in girls with internalizing symptoms and only in boys with externalizing symptoms (Kroner-Herwig et al., 2011). As suggested by the authors, the presence of pain at baseline may have affected the psychological vulnerability of children, potentially in a different manner between boys and girls (i.e. increasing externalizing symptoms in boys and internalizing symptoms in girls) (Kroner-Herwig et al., 2011; Vaalamo et al., 2002). This may consequently have resulted in the difference of association between genders found in that study (Kroner-Herwig et al., 2011). In conclusion, the results of this current study together with findings from the systematic review suggest that in adolescents an effect modification by gender of the association between internalizing and externalizing symptoms and the onset of musculoskeletal pain is unlikely.

8.7.1.5 Effect modification by puberty

Results of analysis for the onset of musculoskeletal pain in adolescents with internalizing symptoms stratified by levels of pubertal development showed a directional effect between strata, with decreasing odds for the onset of musculoskeletal pain with increasing levels of pubertal development (Early puberty Adj. OR = 2.12; 95% CI 0.59, 7.64; Mid/advanced puberty Adj. OR = 1.51; 95% CI 0.92, 2.47; Post puberty Adj. OR = 1.05; 95% CI 0.44, 2.49), although the interaction tests were not statistically significant. Conversely, results of the association between externalising symptoms and musculoskeletal pain showed a directional difference of effect between strata, whilst the statistical interaction tests were non-significant. Findings show a general protective effect (Adj. OR = 0.57; 95% CI 0.07, 4.68) for those in the early pubertal stage, whilst both mid/advanced pubertal status (Adj. OR = 2.49; 95% CI 1.43, 4.34) and post puberty (Adj. OR = 1.81; 95% CI 0.66, 4.93) show an increase in odds (Table 8.9). According to the potential modification effect hypothesized in Section 3.4.2.2, a difference in odds for the onset of musculoskeletal pain across strata of pubertal development was expected. The findings show the direction of effect was towards increased odds for the onset of musculoskeletal pain in those who are at an earlier or later pubertal stages compared to their peers as predicted. This effect is possibly due to the effect on psychological health of adolescents which result from hormonal interactions, social changes (e.g. the feeling of being different from peers of the same age), and brain maturation experienced during puberty (Graber, 2013; Kaltiala-Heino et al., 2003; Mendle, 2014). The levels of psychological symptoms in adolescents in this cohort are in line with these pubertal stage differences reported in the literature (Graber, 2013), such as those who develop earlier or later compared to their peers have higher levels of internalizing (Early puberty 8.6%; Mid/advanced puberty 7.0%; Post puberty 9.7%) and externalizing symptoms (Early puberty 6.9%; Mid/advanced puberty 5.7%; Post puberty 7.2%). However, the results of the stratified analysis do not fully support the potential modification effect hypothesized, as there is a “dose” effect present for internalizing (lessening odds as pubertal stage advances), and the findings on

externalizing, whilst showing differences in early and late stage, show a general increasing effect as pubertal stage advances. Potential explanations for these findings will now be discussed. One of the key elements missing from the data collection is information on the actual change and rate of development of puberty from the time at baseline (where assessed) to the time of follow up (not assessed). Taking a current "snap shot" of status does not indicate pubertal tempo (i.e. the pace of development through puberty), which varies from individual to individual (e.g. adolescents can develop at a different pace regardless of what stage they are at time of assessment) and this "rate" can affect psychological status (Mendle, 2014). This may help to explain the nonlinear effect in adolescents with externalizing and internalizing symptoms (reduced odds reported for those within the post puberty groups compared to mid/advanced in both datasets). It may be possible that a dampening effect of puberty on the association between externalizing symptoms and musculoskeletal pain occurred among adolescents who were in the post pubertal stage at baseline (i.e. the full effects of puberty were already experienced by this group as indicated by their status). However there is a clear difference between internalising and externalising within the early puberty groups (internalizing = increased effect, externalizing = decreased or protective effect). A potential explanation may be the nature of these constructs in relation to this stage of puberty. Perhaps internalising features lead to greater rumination and perhaps hypersensitivity to pain, research shows a consistent relationship with the characteristics of internalizing and pain (De Heer et al., 2014), whereas the construct of externalizing is more associated with "external" problematic behaviours such as alcohol abuse, drug abuse and antisocial behaviour (Colder et al., 2013) which is more linked to later pubertal stages (Evensen, Lyngstad, Melkevik, & Mykletun, 2016). However, any interpretation or conclusion drawn from these results is speculative and more research is required, and it must be noted that both these findings are non-significant and the confidence intervals are wide and further research is required to establish these effects.

Another potential factor which was not accounted for in the analysis is sleep problems and the interaction this may have with pubertal stage. As outlined in the findings of chapter 6 there is an effect present between sleep and pain (more so for chronic musculoskeletal pain onset), and although no modification effect was shown for puberty, there was not the range of pubertal status within the CATS cohort to investigate this fully. Certainly sleep problems are associated with psychological problems (Coulombe, Reid, Boyle, & Racine, 2011; Pieters et al., 2014), they may be predictive of the onset of musculoskeletal pain (Section 2.4.3.1 and Section 6.2), and are observed among those in a more advanced pubertal stage, due to the change in sleep patterns that occurs during puberty (Carskadon & Tarokh, 2014; Dahl & Lewin, 2002).

In conclusion, the findings of this study show some support to the hypotheses, with an expected difference in the association based on different levels of pubertal status. However explanations of this effect are most likely complex and it may be a combination of factors (pubertal status and tempo, linkage with sleep problems, external events and situations that influence expression of psychological symptoms) that explain the direction of the results reported for the modification effect of pubertal status on the relationship between internalizing and externalizing and musculoskeletal pain onset. Therefore further research which enables the tracking of variations in psychological symptoms and pubertal development during the follow-up is needed to inform more clearly the findings of this current study.

8.7.1.6 Effect modification by screen time

Results of analysis for the association between internalizing and externalizing symptoms and the onset of musculoskeletal pain stratified by levels of screen time do not support the hypothesis that an increase in odds will be found in those with higher levels of screen time use (Section 3.4.2.3). For both internalizing and externalizing symptoms, a directional effect between strata was found, with a decreasing trend of odds for the onset of musculoskeletal pain with increasing levels of screen time, although interaction tests were not significant. A variety of reasons have been considered to explain these findings. The decreasing trend found in this study may suggest that increasing levels of screen time has a lessening effect on the association between internalizing and externalizing symptoms and the onset of musculoskeletal pain. One plausible explanation may be that high levels of screen time may lessen the risk for physical trauma (and so less musculoskeletal pain) due to a decrease in physical activity (the proportion of adolescents with high levels of physical activity was 56%, 43% and 31% in those with low, medium and high screen time, respectively) and research shows higher physical activity and lower screen time use are associated with less severe mental health and psychological problems (Kremer et al., 2014). However, physical activity was adjusted for within the analysis, and the change from unadjusted and adjusted was not that marked, therefore this is unlikely to fully explain the findings. Alternatively, screen time may be a marker or indicator of other factors that may explain this relationship. For example research shows that deprivation is linked to low levels of access to electronic media (Danielsson, 2016), perhaps those with low screen time use are more susceptible to pain onset due to factors associated with deprivation such as increased disruption and problems within the family; research shows childhood abuse and other problems in the family environment are linked both to psychological problems and to the onset of musculoskeletal pain (Alink et al., 2008; Brattberg, 1994; Kroner-Herwig et al., 2011; Malleson et al., 2001; Ramchandani & Psychogiou, 2009; van voorhees & Scarpa, 2004). Low screen time users may also have less exposure to social support from online sources (social media groups), and such online

support has been shown to have beneficial effects on wellbeing (Oh, Ozkaya, & Larose, 2014). However, the explanations above to explain these weak trend effects are speculative and further research is required to understand these trends effects for screen time. In conclusion, findings from this study show an unexpected decreasing trend of odds for the onset of musculoskeletal pain in adolescents with internalizing and externalizing symptoms as screen time increases. Some explanations have been explored that may indicate more complex interactions involving other factors, however further research that includes other potential variables and confounders is required to explain these findings.

8.7.2 Strengths and weaknesses

This study includes several strengths. A key strength of this study is the use of a prospective cohort design. Such designs allow the estimation of the incidence rate, and gives greater confidence of the temporal sequence between exposure and outcome (Delgado-Rodríguez & Llorca, 2004). As with the CATS study also, another strength is that potential effect modifiers were explored based on a priori defined hypotheses (Section 3.4.2). This enabled a finer level of analysis of the role of internalizing and externalizing symptoms and pain onset within potentially important sub-groups (i.e. identification of groups of higher risk). To my knowledge this is the first study that provides information on the effect of pubertal stage and screen time on the association between internalizing and externalizing symptoms and musculoskeletal pain, and adds further to the current knowledge of the effect of gender. In addition, another strength is that internalizing and externalizing symptoms were assessed by means of the SDQ, which is a valid and suitable measure to assess behavioural and emotional disorders for children within this cohorts' age group (A. Goodman, Lamping, & Ploubidis, 2010; R. Goodman, 1997). The 90th percentile cut-off, which corresponded to the "abnormal" levels of internalizing and externalizing symptoms, was used to identify adolescents with symptoms of clinical relevance (Goodman, 1997, 2001). Advantages of this approach are that in low-risk samples (such as this general population sample) this cut-off is used to reduce the occurrence of false-positive cases and therefore reduces potential misclassification. This study also presents several limitations. First, a major drawback to this study is the assessment of pain. The questions used for the assessment of musculoskeletal pain differed between baseline and follow-up (Section 7.2.1). The baseline question (assessment of limb pain presence) may have led to an underestimation of adolescents with musculoskeletal pain at baseline. Consequently, this may have led to an overestimation of the association (i.e. adolescents who had musculoskeletal pain may have been considered as without pain at baseline and consequently part of the effect observed would be attributable to a recurrence or persistence of musculoskeletal pain rather than onset). Furthermore, with both baseline and follow up

assessments there was no information about the severity or impact of pain (e.g. pain interference or disability). Information on these factors would have enabled a greater understanding of the effects that psychological symptoms have on musculoskeletal pain. Second, there may also be limitations with regard to the assessment of effect modifiers. In this cohort puberty was assessed by means of a questionnaire that included the Tanner's Sexual Maturation scale, which was completed by the parents. Although an advantage is that parental-report is more reliable than children self-report for pubertal status assessed using this measure (Lum et al., 2015), the gold standard for the assessment of puberty is physical examination, which would have provided greater accuracy (Owen Blackmore, Berenbaum & Liben, 2008). In addition, it was not possible to assess how pubertal status changed during the follow-up period. Changes in pubertal status may have affected the psychological status of children and as a result the likelihood of experiencing musculoskeletal pain at follow-up and the potential issues about this are discussed in the sections above. The measure used for screen time use assessed the time spent using computers and watching TV, but did not provide any information on the content of screen time use (which may have an impact of the predictors and outcome), and on the use of multiple electronic devices at the same time (e.g. computer use while watching the TV). This may have provided a more accurate estimate of screen time (Hale & Guan, 2015), which may potentially have changed the percentages of adolescents within groups of exposure to screen time and perhaps changed some of the estimates found in the analysis stratified by levels of screen time. Third, some considerations are needed on the statistical power for the analysis. Post-hoc calculations showed that the resulting power to detect a statistically significant effect for the relationship between internalizing symptoms and musculoskeletal pain with an effect size of 1.43 was only 28%. The minimum sample size to detect this effect with a power of more than 80% in a cohort where 8.4% of adolescents without musculoskeletal pain have internalizing symptoms (as found in this cohort) would be at least 6000 children, with a much larger sample size required to detect effect modification (Kamangar, 2012), especially when using a high threshold for defining internalising /

externalising symptoms. In the effect modification analysis, the size of the strata was small. As a result of this, the 95% CIs of the estimates were wide, thus providing less confidence on the accuracy of the estimates found. Therefore, no conclusive statements can be made regarding the hypothesised associations tested, and in particular for the effect modification by screen time or pubertal stage (although some tentative explanations have been provided). The results of effect modification analysis of this current study are therefore informative, and future research to further test these hypotheses is needed. Finally, a limitation may concern the generalizability of the results. Only 7,136 (35.2%) adolescents among the initial 20,248 pregnancies eligible in the study completed the question relative to baseline pain (Section 7.1.2). This represented the baseline group for the analysis. If these adolescents were different from the source population (e.g. they have different levels of psychological symptoms compared to adolescents who did not participate), this would limit the generalizability of the findings, as the associations found may differ among those who did not participate to the study (Hennekens & Buring, 1987). In addition this study suffered from more than 50% of adolescents who were lost to follow-up. Examination of characteristics between those who were lost to follow up and those who remained in the study showed those lost to follow-up were significantly more likely to be males, smokers, to have increased internalizing and externalizing symptoms and high levels of screen time compared to completers. This may have affected the estimate of the incidence, and may have biased the estimates of association (i.e. towards an underestimation of effect), if those lost to follow-up were at increased odds for the onset of musculoskeletal pain and chronic musculoskeletal pain compared to those who completed to follow-up (Section 7.5.2). This is supported by the reported characteristics of the participants across waves of ALSPAC, which showed that those lost to follow-up were from families of a lower socioeconomic status (Boyd et al., 2013) which may act as a general marker for a group with increased levels of internalizing and externalizing symptoms (Alink et al., 2008; Ramchandani & Psychogiou, 2009).

8.7.3 Key messages

- No association for the onset of musculoskeletal pain and chronic musculoskeletal pain was found in adolescents with internalizing symptoms, although the direction of both the associations indicate a non-significant trend for increased odds.
- Adolescents with externalizing symptoms were at statistically significant increased odds for the onset of musculoskeletal pain and for the onset of chronic musculoskeletal pain, but this latter association was attenuated after adjustment for confounding variables.
- No gender effect modification was found in the relationship between internalizing or externalizing symptoms and musculoskeletal pain outcomes.
- Trends of decreasing odds for the onset of musculoskeletal pain in adolescents with internalizing symptoms were observed across increasing pubertal stages and levels of screen time. This suggests areas where further research is needed.
- A protective effect for the onset of musculoskeletal pain in adolescents in an early pubertal stage and increased odds in those in mid/advanced or post puberty was observed in adolescents with externalizing symptoms.
- A trend of decreasing odds for the onset of musculoskeletal pain across increasing levels of screen time were observed in adolescents with externalizing symptoms. This suggests areas where further research is needed.

Chapter nine. The association of sleep and psychological symptoms with musculoskeletal pain onset in children and adolescents in primary care: description of the Consultations in Primary Care Archive (CiPCA) cohort

This chapter will describe the Consultations in Primary Care Archive (CiPCA) cohort and the variables included (Section 9.1), followed by the descriptive findings (Section 9.2), and discussion of these descriptive findings (Section 9.3).

9.1 Background

The Consultations in Primary Care Archive (CiPCA) is a database that consists of medical consultation data (e.g. consultations, prescriptions, referrals) recorded since 1998 from a sample of general practices (up to 13) in North Staffordshire, UK (Jordan et al., 2007; Jordan et al., 2010; Porcheret et al., 2004). Comparisons have been made between CiPCA and national datasets (Royal College of General Practitioners Weekly Returns Service, General Practice Research Database [now CPRD], Fourth Morbidity Statistics from General Practice), and results show similar consultation prevalence rates of musculoskeletal conditions, providing evidence for generalisability of this regional healthcare database to the wider UK consulting population (Jordan et al., 2007), as well as evidence of European comparability (Skåne Health Care Register in Sweden) (Jordan et al., 2014). To maintain data quality, an annual cycle of training in morbidity coding, assessment and feedback is undertaken by participating CiPCA general practices and auditing is regularly performed by a dedicated Informatics team at Keele University (Jordan et al., 2010; Porcheret et al., 2004). CiPCA has ethical approval and data is pseudo anonymised (i.e. patient identifiable information is removed and only a patient ID number is used) (Jordan et al., 2010; Porcheret et al., 2004). The use of consultation data assures good representativeness of

healthcare attendance in the general population, as more than 98% of the population in the UK are registered with a general practice (Herrett et al., 2015; Jordan et al., 2010). In the following sections a description is given of the design of the study that was nested within CiPCA (Section 9.1.1) and variable development (Section 9.1.2 - 9.1.5).

9.1.1 Design and cohort definition

In this current study medical record consultation data for 11 general practices available from year 2005 to 2012 were used. This timescale was chosen based on the optimum recording quality and completeness of data (before 2005 the quality of recording was lower, after 2012 the dataset was not fully complete at time of data request) in order to maximise the largest possible sample to address the research questions.

Two studies were carried out within this part of the CiPCA dataset. Each study used a matched cohort design (individuals with exposure at baseline vs. matched individuals without exposure). Each matched cohort dataset was created by selecting the individuals with a consultation for the exposure variable (sleep problems, described in Section 9.1.4.1, and psychological diagnosis/problems, Section 9.1.4.2) between calendar years 2005 and 2010. Data were used from children and adolescents who were aged between 6 and 19 years old at baseline (i.e. date of first consultation for the exposure), and any adolescents who became older than 19 years old during the follow-up (i.e. 2 years after the first consultation for the exposure) were censored from the study. Only individuals who were continually registered at each practice for the duration of the study (i.e. between calendar years 2005 and 2010) were included to ensure capturing active consultations. To achieve this, consultation records were checked at 6 monthly intervals (July/Dec) throughout the study period. In the preparation of datasets, individuals with a recorded consultation for sleep problems (actual N = 107) and psychological diagnosis/problems (actual N = 507) were identified and considered “exposed”. These individuals were assigned an “index date”

(i.e. date of first consultation for the exposure). Each “exposed” individual identified with a consultation for the exposure variable was matched to five controls (“unexposed individuals”). Individuals were matched on age (± 2 years), gender and practice, following previous methodology for survival analysis (Green, Muller, Mallen, & Hider, 2015; Hancock et al., 2014; Jordan & Croft, 2010; Muller, Hider, Belcher, Helliwell, & Mallen, 2014). Age, gender and practice were considered as potential confounders and used as matching variables, in order to reduce risk of confounding and make the “exposed” and “unexposed” groups similar by evenly distributing potential confounders within both groups (Hennekens & Buring, 1987). Matched individuals were assigned an “index date” that was equivalent to the date of first consultation for the exposure variable. “Exposed” individuals and selected “unexposed” controls were followed-up for a period of 2-years after the “index date” (date of consultation for the exposure variable).

In addition, in order to maximise the probability that the outcome of a musculoskeletal consultation from 2005 onwards was an incident consultation, data was inspected to remove the “exposed” and matched “unexposed” individuals who had a previous musculoskeletal consultation within the time period of 2 years before the “index date” of consultation for the exposure variable. The matched “unexposed” individuals were also censored if they had a consultation for the exposure variable in the period after the index date and prior to a consultation for a musculoskeletal condition or the end of the follow-up period. A summary of the inclusion and exclusion criteria for the “exposed” and “unexposed” individuals is outlined in Table 9.1. As a result of matching two groups were within each dataset at baseline:

- Group 1: Individuals without a recorded consultation for a musculoskeletal condition who had a recorded consultation for the exposure variable (sleep problem or psychological diagnosis/problem).
- Group 2: Individuals without a recorded consultation for a musculoskeletal condition and no recorded consultation of the exposure variable.

This process resulted in the creation of two matched cohort datasets. One dataset was used to investigate the relationship between sleep problems and the onset of musculoskeletal conditions, and included 638 individuals (107 “exposed” individuals matched to 531 “unexposed” individuals). The other dataset was used to investigate the relationship between psychological diagnosis/problems and the onset of musculoskeletal conditions, and included 3,042 individuals (507 “exposed” individuals matched to 2,535 “unexposed” individuals). A statistician from the centre (Y.C.) assisted in the preparation of the datasets. A description of the identification and definition of the study variables and of the baseline characteristics of the resulting datasets is outlined in section 9.1.2 - 9.1.5 and 9.2.

Table 9.1 Criteria for inclusion and exclusion in the “Exposed” and “Unexposed” groups

Inclusion criteria	Exclusion criteria
“Exposed group”	
Consultation for the exposure variable between calendar years 2005 (start January) and 2010 (end December)	Previous musculoskeletal consultation within the time period of 2 years before the “index date” of consultation for the exposure variable
“Unexposed” group	
Five individuals matched to each of the “exposed” individuals on age (± 2 years), gender and practice	Previous musculoskeletal consultation within the time period of 2 years before the matched “index date”
	Consultation for the exposure variable after the matched “index date” and prior to a consultation for a musculoskeletal condition or the end of the 2-year follow-up period

9.1.2 Identification of variables

In order to address objective 3 (Section 3.5), it was necessary to identify appropriate recorded consultations for sleep problems, psychological symptoms, musculoskeletal pain, and potential confounders. These were identified by means of Read Codes (a full list of Read Codes for each variable is provided in appendix IX). The "Read Code" system is used within the UK to record on practice computers all consultations and patient encounters in primary care. With this system categories of symptoms and diagnoses are recorded by means of four-digit alpha-numeric codes that include the numbers from 0 to 9 and both capital and lower case letters from A to Z, with the exception of "O" and "l" for which errors can occur (Benson, 2012). The Read codes chapters A-Q follow the International Classification of Disease (ICD-10) criteria (Benson, 2012). Upon entering the medical term related to the condition, a list of Read Codes potentially relevant to the symptom/diagnosis is returned to the general practitioner, who selects and records the most appropriate Read Code for the diagnosis or symptom identified (Benson, 2012). For example if the patient had a consultation for depressive symptoms, after entering the term "depression" a list of relevant Read Codes (e.g. E11z2: Masked depression; E135: Agitated depression, E2003: Anxiety with depression) will be returned to the general practitioner, who will choose the most appropriate for the patient. A number of stages were applied to refine the list of potential Read codes used in this study. Stage 1: A review of previous relevant studies (e.g. focus on either musculoskeletal, sleep, psychological consultations) using Read-coded electronic health records was carried out to retrieve previously used code lists (Campbell et al., 2016; Carr et al., 2017; Culliford et al., 2015; Fairhurst et al., 2016; Fairhurst, Watt, Martin, Bland, & Brackenbury, 2014; Hayward, Jordan, & Croft, 2010, 2012; Hire, Ashcroft, Springate, & Steinke, 2015; John et al., 2015, 2016; Kontopantelis, Reeves, Valderas, Campbell, & Doran, 2013; Marston, Nazareth, Petersen, Walters, & Osborn, 2014; Michaleff et al., 2017; Monk, Muller, Mallen, & Hider, 2013; Olivier et al., 2010; Reeves et al., 2014; Wallander, Johansson, Ruigómez, García Rodríguez, & Jones, 2007; Windfuhr et al., 2016; Wood, Muller, & Peat, 2011). Further Read codes were added

from additional Read code lists that have been used previously within the Research Institute of Primary Care and Health Sciences. Stage 2: Further checks were carried out on all Read codes with an academic GP (E.R.) experienced in the application of Read codes during consultations. The GP checked the code lists for relevance, use and appropriateness (i.e. whether the Read code was relevant and appropriate for the condition that was to be identified, and if it was currently in use in general practices). Stage 3: All Read codes were then checked for compatibility with the CiPCA operating system (5 byte EMIS system) as many drawn from the wider literature used alternative systems (all proposed Read codes were found to be compatible within this current system). In the following sections, a description of the development and definition of variables, as used within the analysis, is outlined (Section 9.1.3 - 9.1.5).

9.1.3 Outcome variables

9.1.3.1 Musculoskeletal conditions

Survival analysis, which is the analysis method used within the CiPCA datasets, is a statistical technique that takes into account the time before the occurrence of an event and therefore is suitable where data over time are collected, as compared to a static data collection period such as baseline and follow up (for further details of this method see chapter 4, Section 4.5.2.2). In terms of the development of the variable, a recorded consultation for a musculoskeletal condition was used as the outcome. One-thousand six-hundred eleven Read codes were identified as relevant. All the individuals (aged 6-19 years) with a consultation for musculoskeletal conditions (e.g Read codes for diagnosis and symptoms for all body areas) in calendar years 2005-2012 were identified (for a list of the Read Codes pertaining to musculoskeletal conditions please see appendix IX), and the following definitions and criteria to factor time were used:

- If individuals had a recorded consultation for a musculoskeletal condition, the time passed between the index date of consultation for the exposure variable and the date of consultation for a musculoskeletal condition was calculated.
- If individuals did not have a recorded consultation for a musculoskeletal condition, the value for the variable was set as 731 days (corresponding to the 2-years of follow-up period).
- Data was censored if the date of consultation for a musculoskeletal condition exceeded the follow-up period or if matched “unexposed” individuals had a consultation for the exposure variable before the end of the follow-up period or before the consultation for a musculoskeletal condition.

9.1.3.2 Persistent musculoskeletal conditions

In order to capture individuals who appear to have chronic problems with musculoskeletal pain (i.e. in a similar vein to the chronic groups outlined in the previous cohort studies; CATS, ALSPAC) a variable was created using information on repeated musculoskeletal consultations to identify "persistent musculoskeletal pain". Whilst actual "chronicity" could not be truly established within the consultation data it was decided to create a definition based on frequency and temporal proximity of relevant musculoskeletal consultations. These persistent consulters were individuals with another consultation or consultations for a musculoskeletal condition within a 3-month period after the first consultation and before the end of follow-up. This definition was based on the finding of a study carried out in a primary care setting where individuals were asked to report when they experienced their last pain-free month. Results from that study showed that among those who reported new onset of pain within the last 3 months, only 24% had a pain-free month in the last 3 months (Dunn, de Vet, Hooper, Ong, & Croft, 2006). This suggests that individuals who consult for a musculoskeletal condition may experience a persistent condition.

9.1.4 Exposure variables

9.1.4.1 Sleep problems

A recorded consultation for sleep problems or tiredness was used as the exposure variable to test the association between sleep problems and the onset of musculoskeletal conditions. In total 88 Read codes were identified as relevant. These included Read codes for sleep problems and for daytime tiredness (e.g. persistent insomnia, nightmares, tired all the time, excessive sleep; for a list of the Read Codes pertaining to sleep problems or tiredness please see appendix IX). All the individuals (aged 6-19 years) with a consultation for sleep problems or tiredness in calendar years 2005-2010 were identified and considered as "exposed". After checking that exposed individuals did not previously consult for a musculoskeletal condition, they were included in a "Sleep problems group" and from hereafter in the text they will be referred as "individuals with sleep problems". In addition, this variable was entered as a confounder in the analysis for the association between psychological diagnosis/problems and the onset of musculoskeletal conditions. When used as a confounder, the recorded consultation for sleep problems or tiredness had to have occurred in a 2-year period prior to the exposure (i.e. recorded consultation for psychological diagnosis/problems).

9.1.4.2 Psychological diagnosis/problems

A recorded consultation for psychological diagnosis/problems was used as the exposure variable to test the association between psychological diagnosis/problems and the onset of musculoskeletal conditions. All the individuals (aged 6-19 years) with a consultation for a psychological diagnosis/problems in calendar years 2005-2010 were identified and considered as "exposed". A variety of different psychological diagnosis/problems was considered (for a total of 1020 Read codes identified), including anxiety, depression, severe mental illness, schizophrenia/psychosis, stress, neurosis, suicide/self-harm, attention deficit hyperactivity disorder (ADHD), conduct problems, hyperactivity, nervousness, anorexia, bulimia, grief and bereavement (please see appendix IX). Exposed individuals with psychological diagnosis/problems who did not previously consult for a musculoskeletal condition were included in the "psychological diagnosis/problems" group and from hereafter in the text they will be referred as "individuals with psychological diagnosis/problems". In addition, this variable was also used as a confounder in the analysis for the association between sleep problems and the onset of musculoskeletal conditions. When used as a confounder, the recorded consultation for psychological diagnosis/problems had to have occurred in a 2-year period prior to the exposure (a consultation for sleep problems or tiredness).

9.1.5 Confounders

9.1.5.1 Year of index date

The year of index date of the exposure was assessed and analysis adjusted for to check for potential age-period cohort effects, and take into account the effect of the period of study on the exposure (Bhopal, 2002). For example the exposure variable (i.e. sleep problems or psychological diagnosis/problems) may be affected by external factors that may have occurred at a different frequency during specific calendar years (e.g. increased exposure to screen time in recent years may have affected the sleep patterns and psychological health of individuals). A continuous variable was created for the year of index date and entered in the analysis.

9.1.5.2 Age at index date

The age of the individuals at the index date of the exposure was assessed and entered as a confounder in the analysis based on the knowledge that musculoskeletal pain may be associated with increasing age in children and adolescents (Henschke et al., 2015; King et al., 2011; McBeth & Jones, 2007) and such patterns have been shown in consultation data previously (Jordan et al., 2010).

9.1.5.3 Gender

The gender of the individuals was entered as a confounder in the analysis based on the knowledge that females consult more than males and may be at higher risk for musculoskeletal pain (Campbell & Roland, 1996; Henschke et al., 2015; King et al., 2011).

9.1.5.4 Practice

The analysis was adjusted for practice to check for potential effects of the practice (Campbell & Roland, 1996). For example, the decision of consulting for a health problem may be influenced by the location of the general practice (e.g. different consultation patterns between rural areas and

urban areas or because of physical distance from the practice), the decision of the doctor to initiate a consultation (e.g. follow-up for a health problem) or the presence of other type of care (e.g. patients may prefer to visit the emergency department) (Campbell & Roland, 1996). A categorical variable was created with all practices and entered in the analysis.

9.1.5.5 Number of consultations

The number of consultations was assessed by counting the number of recorded consultations of any kind in a period of 2 years prior to the index date of consultation for the exposure. Number of consultations was entered as a confounder to take into account the effect of frequent primary care attendance for other health issues, which may potentially increase the likelihood of receiving a consultation for the exposure or outcome variable (Paananen et al., 2011). A continuous variable was created for the number of consultations and entered in the analysis.

9.2 Baseline data descriptive analyses

The matching process outlined in Section 9.1.1 resulted in the creation of two matched cohort datasets. These datasets were used to investigate the association between sleep problems and consultations for musculoskeletal conditions and between psychological diagnosis/problems and consultations for musculoskeletal conditions. Descriptive analyses of the baseline variables for both datasets were carried out. The results of these analyses are shown in the following sections (Section 9.2.1 and 9.2.2, respectively).

9.2.1 Matched cohort - Sleep problems

9.2.1.1 Sleep problems

Baseline descriptive analyses of sleep problems are outlined in Table 9.2. Overall the dataset included 638 children, with 347 girls (54%) and 291 boys (46%). Figures on sleep problems show that 107 children (49 boys and 58 girls) had a recorded consultation for sleep problems in the study period ("exposed" group). Each one of these children was matched with 5 controls without a medical recorded consultation for sleep problem ("unexposed group"), resulting in 531 controls overall (242 boys and 289 girls).

Table 9.2 Baseline sleep problems

Sleep problems	Boys	Girls	Overall
Exposed (individuals with sleep problems)	49 (45.8%)	58 (54.2%)	107
Unexposed (individuals without sleep problems)	242 (45.6%)	289 (54.4%)	531
Overall	291 (45.6%)	347 (54.4%)	638

9.2.1.2 Musculoskeletal conditions

Figures regarding recorded consultations for musculoskeletal conditions showed that among the 638 individuals included in the dataset, 123 (19%) reported a recorded consultation for a musculoskeletal condition within the 2-years follow-up period (Table 9.3). The proportion of individuals with a recorded consultation for a musculoskeletal condition was higher in girls compared to boys (21.3% vs. 16.8%), respectively (Table 9.3). In addition, 32 children (5%) were persistent consulters for musculoskeletal conditions (Table 9.4). The proportion of persistent consulters was higher in girls compared to boys (6.3% vs. 3.4%, respectively) (Table 9.4).

Table 9.3 Recorded consultations for musculoskeletal conditions

Musculoskeletal conditions	Girls	Boys	Overall
No	273 (78.7%)	242 (83.2%)	515 (80.7%)
Yes	74 (21.3%)	49 (16.8%)	123 (19.3%)
Overall	347	291	638

Table 9.4 Persistent consulters for musculoskeletal conditions

Musculoskeletal conditions	Girls	Boys	Overall
No	325 (93.7%)	281 (96.6%)	606 (94.9%)
Yes	22 (6.3%)	10 (3.4%)	32 (5.1%)
Overall	347	291	638

9.2.1.3 Confounders

Table 9.5 outlines the baseline characteristics (potential confounding variables) of individuals with or without a recorded consultation, overall and stratified by exposed and non-exposed individuals.

Table 9.5 Baseline characteristics of potential confounders

Potential confounder	Exposed	Unexposed	Overall
Psychological symptoms	8 (7.5%)	19 (3.6%)	27 (4.2%)
No psychological symptoms	99 (92.5%)	512 (96.4%)	611 (95.8%)
Year of index date			
2005	25 (23.4%)	125 (23.5%)	150 (23.5%)
2006	27 (25.2%)	135 (24.2%)	162 (25.4%)
2007	17 (15.9%)	85 (16.0%)	102 (16.0%)
2008	12 (11.2%)	59 (11.1%)	71 (11.1%)
2009	19 (17.8%)	92 (17.3%)	111 (17.4%)
2010	7 (6.5%)	35 (6.6%)	42 (6.6%)
Age at index date			
6	4 (3.7%)	27 (5.1%)	31 (4.9%)
7	13 (12.2%)	54 (10.2%)	67 (10.5%)
8	7 (6.5%)	36 (6.8%)	43 (6.7%)
9	4 (3.7%)	27 (5.1%)	31 (4.9%)
10	9 (8.4%)	39 (7.3%)	48 (7.5%)
11	5 (4.7%)	24 (4.5%)	29 (4.6%)
12	7 (6.5%)	30 (5.7%)	37 (5.8%)
13	2 (1.9%)	22 (4.1%)	24 (3.8%)
14	8 (7.5%)	29 (5.5%)	37 (5.8%)
15	3 (2.8%)	31 (5.8%)	34 (5.3%)
16	8 (7.5%)	39 (7.3%)	47 (7.4%)
17	17 (15.9%)	74 (13.9%)	91 (14.3%)
18	14 (13.1%)	55 (10.4%)	69 (10.8%)
19	6 (5.6%)	44 (8.3 %)	50 (7.8%)
Mean (± SD)	13.1 (± 4.3)	13.1 (± 4.3)	13.1 (± 4.3)
Practice			
B	2 (1.9%)	10 (1.9%)	12 (1.9%)
C	6 (5.6%)	30 (5.7%)	36 (5.6%)
D	6 (5.6%)	30 (5.7%)	36 (5.6%)
E	17 (15.9%)	85 (16.0%)	102 (16.0%)
G	5 (4.7%)	25 (4.7%)	30 (4.7%)
H	9 (8.4%)	45 (8.5%)	54 (8.5%)
I	17 (15.9%)	85 (16.0%)	102 (16.0%)
L	11 (10.3%)	55 (10.4%)	66 (10.3%)
M	10 (9.4%)	50 (9.4%)	60 (9.4%)
N	9 (8.4%)	42 (7.9%)	51 (8.0%)
P	15 (14.0%)	74 (13.9%)	89 (13.9%)
Number of consultations			
1 ≤	15 (14.0%)	166 (31.3%)	181 (28.4%)
2-3	23 (21.5%)	99 (18.6%)	122 (19.1%)
4-5	17 (15.9%)	93 (17.5%)	110 (17.2%)
6-9	21 (19.6%)	81 (15.3%)	102 (16.0%)
≥10	31 (29.0%)	92 (17.3%)	123 (19.3%)
Mean (± SD)	7.2 (± 6.4)	5.2 (± 5.8)	5.5 (± 5.9)

9.2.2 Matched cohort - Psychological diagnosis/problems

9.2.2.1 Psychological diagnosis/problems

Baseline descriptive analyses of psychological diagnosis/problems are outlined in Table 9.6. Overall the dataset included 3,042 children, with 1,566 girls (51%) and 1,476 boys (49%). Figures regarding psychological diagnosis/problems show that 507 children (246 boys and 261 girls) had a recorded consultation for a psychological diagnosis/problems in the study period ("exposed group"). Each one of these children was matched with 5 controls without a recorded consultation for psychological diagnosis/problems ("unexposed group"), resulting in 2,535 controls overall (1,230 boys and 1,305 girls).

Table 9.6 Baseline Psychological diagnosis/problems

Psychological diagnosis/problems	Boys	Girls	Overall
Exposed (individuals with psy. diagnosis/problems)	246 (48.5%)	261 (51.5%)	507
Unexposed (individuals without psy. diagnosis/problems)	1,230 (48.5%)	1,305 (51.5%)	2,535
Overall	1,476 (48.5%)	1,566 (51.5%)	3,042

9.2.2.2 Musculoskeletal conditions

Figures regarding recorded consultations for musculoskeletal conditions showed that among the 3,042 individuals included in the dataset, 574 (19%) reported a recorded consultation for a musculoskeletal condition within the 2-years follow-up period (Table 9.7). Proportions of recorded consultations for musculoskeletal conditions were similar between girls and boys (Table 9.7). In addition, 124 children (4%) were persistent consulters for musculoskeletal conditions (Table 9.8). Proportions of persistent consulters for musculoskeletal conditions were similar between girls and boys (Table 9.8).

Table 9.7 Recorded consultations for musculoskeletal conditions

Musculoskeletal conditions	Girls	Boys	Overall
No	1,261 (80.5%)	1,207 (81.8%)	2,468 (81.1%)
Yes	305 (19.5%)	269 (18.2%)	574 (18.9%)
Overall	1,566	1,476	3,042

Table 9.8 Persistent consulters for musculoskeletal conditions

Musculoskeletal conditions	Girls	Boys	Overall
No	1,506 (96.2%)	1,412 (95.7%)	2,918 (95.9%)
Yes	60 (3.8%)	64 (4.3%)	124 (4.1%)
Overall	1,566	1,476	3,042

9.2.2.3 Confounders

Table 9.9 outlines the baseline characteristics (potential confounding variables) of individuals with or without a recorded consultation, overall and stratified by exposed and non-exposed individuals.

Table 9.9 Baseline characteristics of potential confounders

Potential confounder	Exposed	Unexposed	Overall
Sleep problems	26 (5.1%)	9 (0.4%)	35 (1.1%)
No sleep problems	481 (94.9%)	2,535 (99.6%)	3,007 (98.9%)
Year of index date			
2005	169 (33.3%)	845 (33.3%)	1,014 (33.3%)
2006	112 (22.1%)	560 (22.1%)	672 (22.1%)
2007	66 (13.0%)	330 (13.0%)	396 (13.0%)
2008	42 (8.3%)	210 (8.3%)	252 (8.3%)
2009	70 (13.8%)	350 (13.8%)	420 (13.8%)
2010	48 (9.5%)	240 (9.5%)	288 (9.5%)
Age at index date			
6	16 (3.2%)	107 (4.2%)	123 (4.0%)
7	19 (3.8%)	99 (3.9%)	118 (3.9%)
8	26 (5.1%)	144 (5.7%)	170 (5.6%)
9	35 (6.9%)	144 (5.7%)	179 (5.8%)
10	33 (6.5%)	156 (6.2%)	189 (6.2%)
11	21 (4.1%)	138 (5.4%)	159 (5.2%)
12	36 (7.1%)	161 (6.4%)	197 (6.5%)
13	36 (7.1%)	179 (7.1%)	215 (7.0%)
14	39 (7.7%)	187 (7.4%)	226 (7.4%)
15	42 (8.3%)	228 (8.9%)	270 (8.9%)
16	48 (9.5%)	255 (10.1%)	303 (9.9%)
17	51 (10.1%)	242 (9.5%)	293 (9.6%)
18	69 (13.6%)	225 (8.9%)	294 (9.7%)
19	36 (7.1%)	270 (10.7 %)	306 (10.1%)
Mean (± SD)	13.7 (± 3.8)	13.7 (± 4.0)	13.7 (± 4.0)
Practice			
B	49 (9.7%)	245 (9.7%)	294 (9.7%)
C	57 (11.2%)	285 (11.2%)	342 (11.2%)
D	27 (5.3%)	135 (5.3%)	162 (5.3%)
E	37 (7.3%)	185 (7.3%)	222 (7.3%)
G	23 (4.5%)	115 (4.5%)	138 (4.5%)
H	48 (9.5%)	240 (9.5%)	288 (9.5%)
I	72 (14.2%)	360 (14.2%)	432 (14.2%)
L	61 (12.0%)	305 (12.0%)	366 (12.0%)
M	44 (8.7%)	220 (8.7%)	264 (8.7%)
N	30 (5.9%)	150 (5.9%)	180 (5.9%)
P	59 (11.6%)	295 (11.6%)	354 (11.6%)
Number of consultations			
1 ≤	88 (17.4%)	851 (33.6%)	939 (30.9%)
2	54 (10.7%)	353 (13.9%)	407 (13.4%)
3-4	88 (17.4%)	453 (17.9%)	541 (17.8%)
4-8	106 (20.9%)	509 (20.1%)	615 (20.2%)
≥9	171 (33.7%)	369 (14.6%)	540 (17.8%)
Mean (± SD)	7.7 (± 8.5)	4.4 (± 5.3)	4.9 (± 6.1)

9.3 Discussion

9.3.1 Descriptive analysis

In Section 9.2 figures regarding the exposures, the outcome and potential confounders were provided. Whilst there is a lack of information within the literature specifically on primary care consultations in children and adolescents, this discussion will attempt to contextualise the findings and make comparison with figures reported in the literature.

9.3.1.1 Musculoskeletal pain

Despite the knowledge that musculoskeletal pain is common in children and adolescents, and numerous general population studies have been carried out, little is known on the prevalence of consultations for musculoskeletal conditions among children and adolescents in primary care. Six studies that were carried out in primary care settings, or that used medical health records reported annual consultation prevalence figures ranging from 2%-10% in Australian, Dutch, Spanish and English children and adolescents (De Inocencio, 1998; De Inocencio, 2004; Henschke et al., 2014; Jordan et al., 2010; Michaleff et al., 2017; van Suijlekom-Smit et al., 1997). Two of these studies were carried out within the same dataset (CiPCA) as used in this current study (Jordan et al., 2010; Michaleff et al., 2017). A direct comparison between the two studies conducted in CiPCA and this current study is complex because of differences in study period considered (from calendar year 2005 to 2012 in this current study, calendar years 2006 and 2010 in the other studies) and study design used (cross-sectional in those studies, prospective matched-cohort in the current study which did not allow to calculate the prevalence). In addition, when defining the dataset for this current study consultations for a musculoskeletal condition that occurred prior to the exposure or after the 2 years follow-up period were censored, which may have resulted in an underestimation of the prevalence of musculoskeletal conditions. However, overall the annual prevalence figures provided by the two other studies conducted in

CiPCA (5-10%) (Jordan et al., 2010; Michaleff et al., 2017) are comparable to those of studies carried out in other countries, suggesting that findings from the CiPCA cohort are generalizable.

9.3.1.2 Sleep problems

As with musculoskeletal conditions, the estimation of the prevalence of sleep problems within this current study was not possible given the method used to define the cohort at risk of the outcome (musculoskeletal conditions). Despite the knowledge that 107 children had a consultation for sleep problems between 2005 and 2010, it was not possible to calculate the total number of children at risk within this cohort due to the exclusion of children who became older than 19 years old during the study period. In addition, children with a consultation for a musculoskeletal condition prior to the consultation for sleep problems were excluded. However, data on the prevalence of sleep problems in paediatric primary care were reported in a recent systematic review, with different figures provided depending on the collection method used and the age-range considered (Honaker & Meltzer, 2016). An 11-12% prevalence of sleep problems within primary care settings, assessed with sleep questionnaires, was reported by parents in studies of children aged between 2 and 14 years old. The reported prevalence of a recorded sleep diagnosis as assessed with the International Classification of Diseases 9th Edition (ICD-9) criteria was further lower, 3.7% (Honaker & Meltzer, 2016; Meltzer et al., 2010). This suggests that sleep problems are commonly under-recognized in paediatric primary care, potentially because of an underestimation of the problem by parents of children and adolescents, or due to the lack of willingness of general practitioners to assess sleep problems if they feel not confident to manage the problem (Meltzer et al., 2014; Meltzer et al., 2010).

9.3.1.3 Psychological diagnosis/problems

As with musculoskeletal conditions and sleep problems, the estimation of the prevalence of psychological diagnosis/problems was not possible, given the definition of a cohort at risk of musculoskeletal consultations. In line with the iceberg theory of disease (Bhopal, 2002), it has been suggested that individuals consult solely if the level of psychological symptoms is severe and only approximately 10% of those with a psychological symptoms consult in primary care (Kramer & Garralda, 2000). Data on the prevalence of psychological symptoms have been reported in some studies. Figures from the "Mental health of children and young people in Great Britain, 2004" showed that approximately 10% of children aged 5-16 met the ICD-10 (International Classification of Diseases, tenth revision) criteria for a mental health problem (emotional disorder, conduct disorder, hyperkinetic disorder or any other type of psychological disorder) (Green, McGinnity, Meltzer, Ford, & Goodman, 2005). Studies in UK primary care settings that reported on the prevalence of prescriptions for psychological problems in children and adolescents were carried out. A 3.6-9.2 annual prevalence per 1000 persons (0.36-0.92%) of pharmacologically treated attention deficit hyperactivity disorder (McCarthy et al., 2012), a 63 per 100.000 person years at risk (0.063%) rate of prescription of any antipsychotic (Marston, Nazareth, Petersen, Walters, & Osborn, 2014) and 1.8% prevalence of prescription of psychotropic drugs (Schneider-Lindner, 2011) were reported. Whilst a direct comparison with figures of this current study is complex due to differences in study designs and to the use of a single outcome variable including a whole range of psychological symptoms in this current study (see Section 9.1.4.2), these figures show that the prevalence of children and adolescents that meet diagnostic criteria for psychological diagnosis/problems is approximately 10%, with much lower figures for prescription of drugs for psychological problems.

9.4 Summary

This chapter has presented the Consultations in Primary Care Archive (CiPCA) cohort, a description of the variables included within the cohort, the descriptive findings of the cohort, and a discussion of these descriptive findings. The following chapter will describe the results of analysis of the association of sleep and psychological symptoms with musculoskeletal pain onset in children and adolescents in primary care.

Chapter ten. The association of sleep and psychological symptoms with musculoskeletal pain onset in children and adolescents in primary care: results of the Consultations in Primary Care Archive (CiPCA) cohort

In this chapter the results of the survival analysis of the association between the presence of sleep problems (Section 10.1), psychological diagnosis/problems (Section 10.2) and musculoskeletal conditions, together with a discussion of the results (Section 10.3) and final key messages (Section 10.4) will be presented.

10.1 Sleep problems and onset of musculoskeletal conditions

10.1.1 Musculoskeletal pain frequency

The dataset used to investigate the association between sleep problems and musculoskeletal conditions included 638 individuals, 123 (19%) of which reported a medical recorded consultation for a musculoskeletal condition within the 2-years follow-up period (Table 10.1). The proportion of individuals with a consultation for a musculoskeletal condition was higher among individuals with sleep problems compared to those without sleep problems (28.1% vs. 17.5%, respectively) (Table 10.1). In addition, 32 (5%) individuals were persistent consulters for musculoskeletal conditions (Table 10.2). The proportion of persistent consulters for musculoskeletal conditions was similar between individuals with sleep problems and those without sleep problems (5.6% vs. 4.9%, respectively) (Table 10.2).

Table 10.1 Sleep problems and onset of musculoskeletal conditions

Consultation for musculoskeletal conditions	No	Yes	Overall
Controls without sleep problems	438 (82.5%)	93 (17.5%)	531
Individuals with sleep problems	77 (71.9%)	30 (28.1%)	107
Overall	515 (80.7%)	123 (19.3%)	638

Table 10.2 Sleep problems and persistent musculoskeletal conditions			
Persistent musculoskeletal conditions	No	Yes	Overall
Controls without sleep problems	505 (95.1%)	26 (4.9%)	531
Individuals with sleep problems	101 (94.4%)	6 (5.6%)	107
Overall	606 (95.0%)	32 (5.0%)	638

10.1.2 Survival analysis of the association between consultations for sleep problems and consultations for musculoskeletal conditions

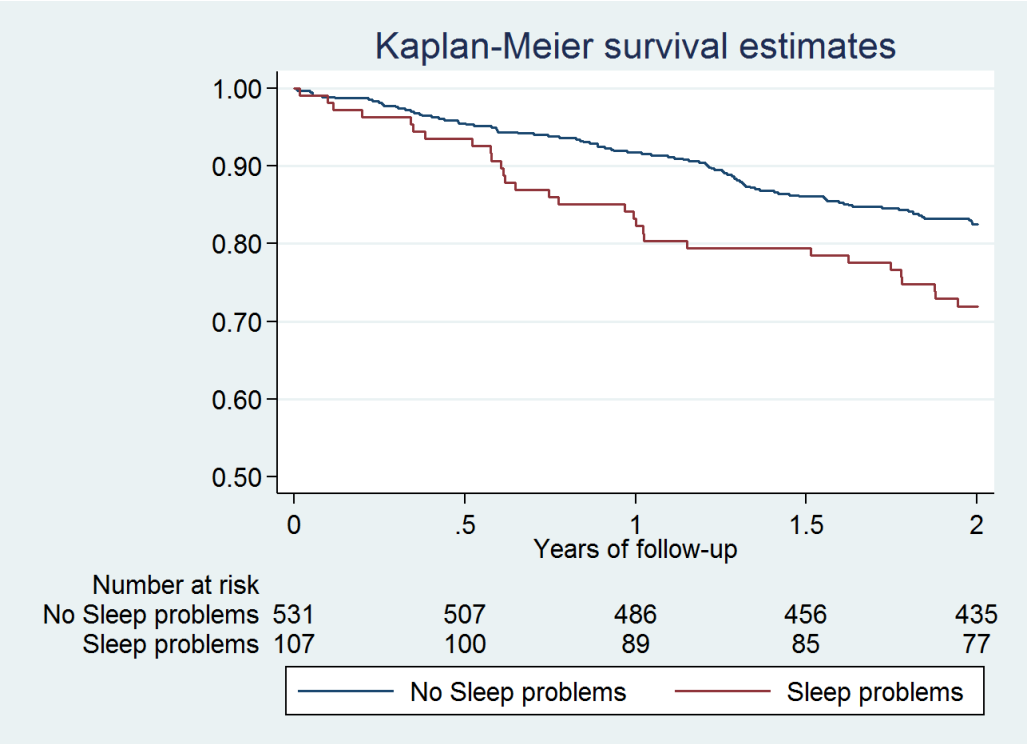
10.1.2.1 Proportional hazard assumption test

Data were tested to check the proportional hazard assumption by means of the Schoenfeld residuals test for the unadjusted and adjusted datasets and results indicated that data met the proportional hazard assumption. A Kaplan-Meier graph was used to describe the difference in survival curves in relation to the onset of a musculoskeletal condition between individuals with sleep problems compared to those without sleep problems (Section 10.1.2.2). The association between sleep problems and musculoskeletal conditions was investigated by means of Cox regression analysis (Section 10.1.2.3). Analysis were repeated to estimate the hazard for persistent musculoskeletal conditions (Section 10.1.3). Results are shown in the following sections.

10.1.2.2 Kaplan-Meier graph of the association between consultations for sleep problems and consultations for musculoskeletal conditions

Survival curves within the Kaplan-Meier graph (Figure 10.1) showed that individuals with sleep problems were at higher hazard to consult for a musculoskeletal condition during the follow-up period compared to those without sleep problems.

Figure 10.1 Association between consultation for sleep problems and musculoskeletal conditions



Further explanation of the figures shown in the graph: At 1-year follow-up, 45/531 (8.5%) individuals without sleep problems and 18/107 (16.8%) consulters with sleep problems consulted for a musculoskeletal condition or were censored from the study, respectively. At 2-year follow-up, 96/531 (18.1%) individuals without sleep problems and 30/107 (28.0%) consulters with sleep problems consulted for a musculoskeletal condition or were censored from the study, respectively.

10.1.2.3 Cox regression analysis of the association between consultation for sleep problems and consultations for musculoskeletal conditions

Cox regression analysis was performed to estimate the hazard ratio for musculoskeletal conditions in consulters with sleep problems compared to those without sleep problems. Results for both unadjusted and adjusted models are shown in Table 10.3. Results of unadjusted analysis show a statistically significant 72% increased hazard of consultation for a musculoskeletal condition in those with sleep problems compared to those without (model 1). This estimate was unchanged after adjustment for psychological diagnosis/problems, index year, gender, age at index date and practice (model 2), but was attenuated to a 49% non-significant increased hazard after further adjustment for number of consultations (model 3).

Table 10.3 Cox regression of the association between consultations for sleep problems at baseline and consultations for musculoskeletal conditions at follow-up

Unadjusted analysis (Model 1) (N = 638)		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	1.72	1.14, 2.60
Adjusted analysis* (Model 2) (N = 638)		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	1.72	1.13, 2.60
Adjusted analysis (Model 3) (N = 638)**		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	1.49	0.98, 2.27

*Analysis adjusted for Psychological diagnosis/problems, Index year, Gender, Age at index date and Practice
** Analysis adjusted for the above confounders and additionally by number of consultations

10.1.3 Survival analysis of the association between consultations for sleep problems and consultations for persistent musculoskeletal conditions

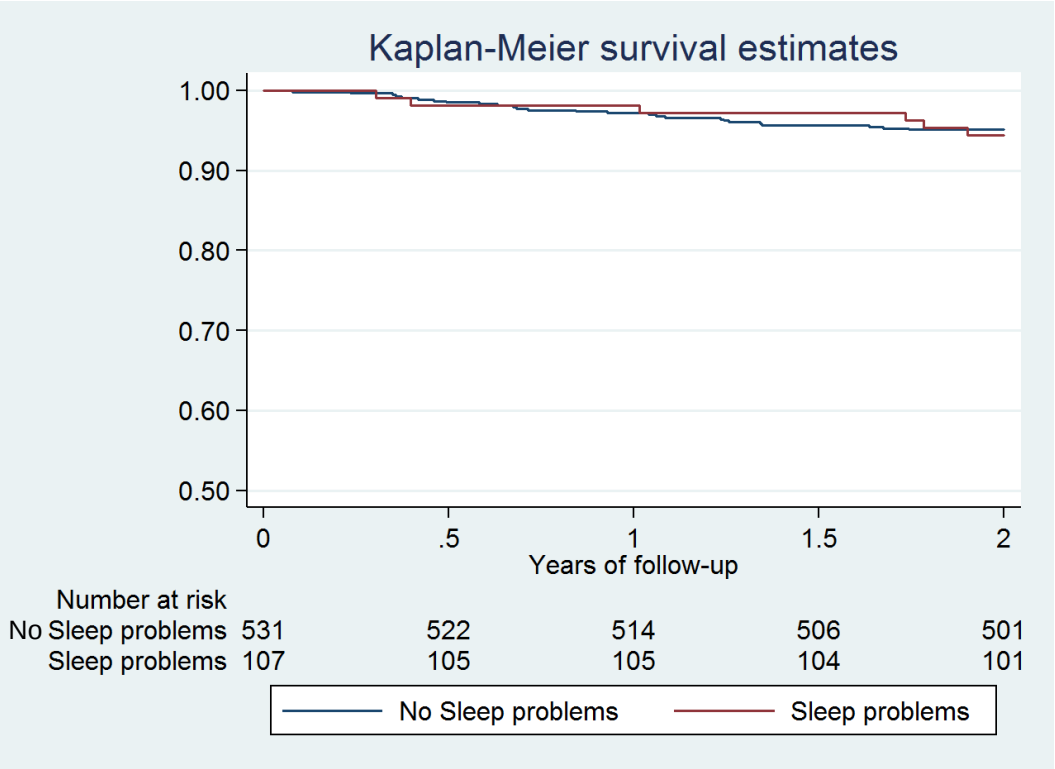
10.1.3.1 Proportional hazard assumption test

Data were tested to check the proportional hazard assumption by means of the Schoenfeld residuals test and it was found that data met the proportional hazard assumption. However, the Schoenfeld residuals test for the variable "gender" was significant ($p < 0.05$), therefore the variable "gender" was entered as a time-varying confounder (i.e. an interaction term between the confounder and a function of time t, which can take into account the variation of the effect of the confounder over time), following previous methodology (Bellera et al., 2010).

10.1.3.2 Kaplan-Meier graph of the association between consultations for sleep problems and consultations for persistent musculoskeletal conditions

The Kaplan-Meier graph (Figure 10.2) showed very little difference between survival curves for persistent musculoskeletal conditions between individuals consulting for sleep problems and those without sleep problems, suggesting a similar hazard for persistent musculoskeletal conditions between groups.

Figure 10.2 Association between consultations for sleep problems and persistent musculoskeletal conditions



Further explanation of the figures shown in the graph: At 1-year follow-up, 17/531 (3.2%) individuals without sleep problems and 2/107 (1.9%) consulters with sleep problems consulted for persistent musculoskeletal conditions or were censored from the study, respectively. At 2-year follow-up, 30/531 (5.6%) individuals without sleep problems and 6/107 (5.6%) consulters with sleep problems consulted for persistent musculoskeletal conditions or were censored from the study, respectively.

10.1.3.3 Cox regression analysis of the association between consultations for sleep problems and consultations for persistent musculoskeletal conditions

Cox regression analysis was performed to estimate the hazard ratio for consulting with persistent musculoskeletal conditions in consulters with sleep problems compared to those without sleep problems. Results for both unadjusted and adjusted models are shown in Table 10.4. Results of unadjusted analysis show that children and adolescents with a recorded consultation for sleep problems were at non-significant 14% increased hazard for persistent musculoskeletal conditions. The association was similar (6% non-significant increased hazard) after adjustment for psychological diagnosis/problems, index year, gender, age at index date and practice, but was changed to a 13% non-significant decreased hazard after further adjustment for numbers of consultations.

Table 10.4 Cox regression of the association between consultations for sleep problems at baseline and consultations for persistent musculoskeletal conditions at follow-up

Unadjusted analysis (Model 1) (N = 638)		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	1.14	0.47, 2.76
Adjusted analysis* (Model 2) (N = 638)		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	1.06	0.43, 2.59
Adjusted analysis (Model 3) (N = 638)**		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Sleep problems	0.87	0.36, 2.14

*Analysis adjusted for Psychological diagnosis/problems, Index year, Gender, Age at index date and Practice
**Analysis adjusted for the above confounders and additionally by number of consultations

10.2 Psychological diagnosis/problems and onset of musculoskeletal conditions

10.2.1 Musculoskeletal pain frequency

The dataset used to investigate the association between psychological diagnosis/problems and musculoskeletal conditions included 3,042 individuals, 19% of which reported a consultation for a musculoskeletal condition within the 2-years follow-up period (Table 10.5). The proportion of individuals with a consultation for a musculoskeletal condition was higher in individuals with psychological diagnosis/problems compared to those without psychological diagnosis/problems (26.0% vs. 17.4%, respectively) (Table 10.5). In addition, 124 individuals (4%) were persistent consulters for musculoskeletal conditions (Table 10.6). The proportion of individuals with persistent musculoskeletal conditions was higher in individuals with psychological diagnosis/problems compared to those without psychological diagnosis/problems (5.7% vs. 3.8%, respectively) (Table 10.6).

Table 10.5 Psychological diagnosis/problems and onset of musculoskeletal conditions

Consultation for musculoskeletal conditions	No	Yes	Overall
Controls without psychological diagnosis/problems	2,093 (82.6%)	442 (17.4%)	2,535
Individuals with psychological diagnosis/problems	375 (74.0%)	132 (26.0%)	507
Overall	2,468 (81.1%)	574 (18.9%)	3,042

Table 10.6 Psychological diagnosis/problems and persistent musculoskeletal conditions

Persistent musculoskeletal conditions	No	Yes	Overall
Controls without psychological diagnosis/problems	2,440 (96.2%)	95 (3.8%)	2,535
Individuals with psychological diagnosis/problems	478 (94.3%)	29 (5.7%)	507
Overall	2,918 (95.9%)	124 (4.1%)	3,042

10.2.2 Survival analysis of the association between consultations for psychological diagnosis/problems and consultations for musculoskeletal conditions

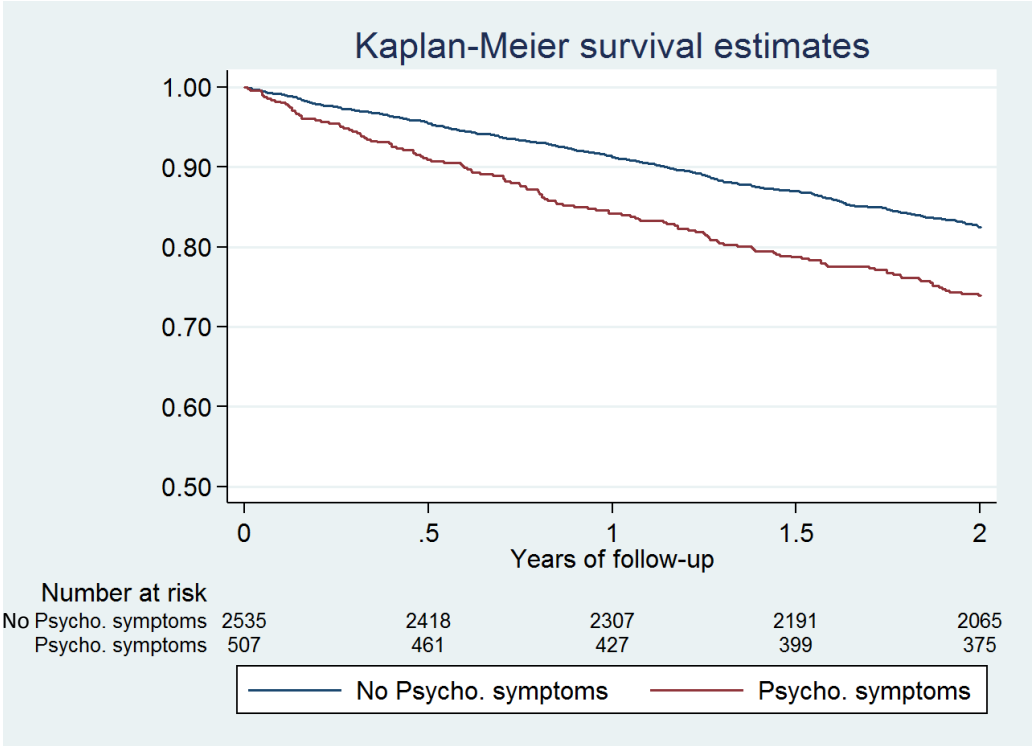
10.2.2.1 Proportional hazard assumption test

Data were tested to check the proportional hazard assumption by means of the Schoenfeld residuals test for the unadjusted and adjusted datasets and results indicated that data met the proportional hazard assumption for the unadjusted dataset but not for the adjusted dataset, where the test was significant. Therefore, the variable for which the test was significant (i.e. index year, $p = 0.002$) was entered in the analysis as a time-varying confounder following the methodology indicated in Section 10.1.3.1 (Bellera et al., 2010).

10.2.2.2 Kaplan-Meier graph of the association between consultations for psychological diagnosis/problems and consultations for musculoskeletal conditions

Survival curves within the Kaplan-Meier graph (Figure 10.3) showed that individuals with a consultation for psychological diagnosis/problems were at higher hazard for a consultation for musculoskeletal conditions during the follow-up period compared to those without psychological diagnosis/problems.

Figure 10.3 Association between consultations for psychological diagnosis/problems and musculoskeletal conditions



Further explanation of the figures shown in the graph: At 1-year follow-up, 228/2535 (9.0%) individuals without psychological diagnosis/problems and 80/507 (15.8%) consulters with psychological diagnosis/problems consulted for a musculoskeletal condition or were censored from the study, respectively. At 2-year follow-up, 470/2535 (18.5%) individuals without psychological diagnosis/problems and 132/507 (26.0%) consulters with psychological diagnosis/problems consulted for a musculoskeletal condition or were censored from the study, respectively.

10.2.2.3 Cox regression analysis of the association between consultations for psychological diagnosis/problems and consultations for musculoskeletal conditions

Cox regression analysis was performed to estimate the hazard ratio for a consultation for musculoskeletal conditions in consulters with psychological diagnosis/problems compared to those without psychological diagnosis/problems. Results for both unadjusted and adjusted models are shown in Table 10.7. Results of unadjusted analysis show that children and adolescents with a recorded consultation for psychological diagnosis/problems were at statistically significant 59% increased hazard of consultation for a musculoskeletal condition. This estimate was unchanged after adjustment for sleep problems, index year, gender, age at index date and practice, and it was attenuated to a 39% statistically significant increased hazard after further adjustment for numbers of consultations.

Table 10.7 Cox regression of the association between consultations for psychological diagnosis/problems at baseline and consultations for musculoskeletal conditions at follow-up

Unadjusted analysis (Model 1) (N = 3,042)		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.59	1.31, 1.93
Adjusted analysis* (Model 2) (N = 3,042)		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.59	1.31, 1.94
Adjusted analysis (Model 3) (N = 3,042)**		
Musculoskeletal conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.39	1.14, 1.70

*Analysis adjusted for Sleep problems, Index year, Gender, Age at index date and Practice
** Analysis adjusted for the above confounders and additionally by number of consultations

10.2.3 Survival analysis of the association between consultations for psychological diagnosis/problems and consultations for persistent musculoskeletal conditions

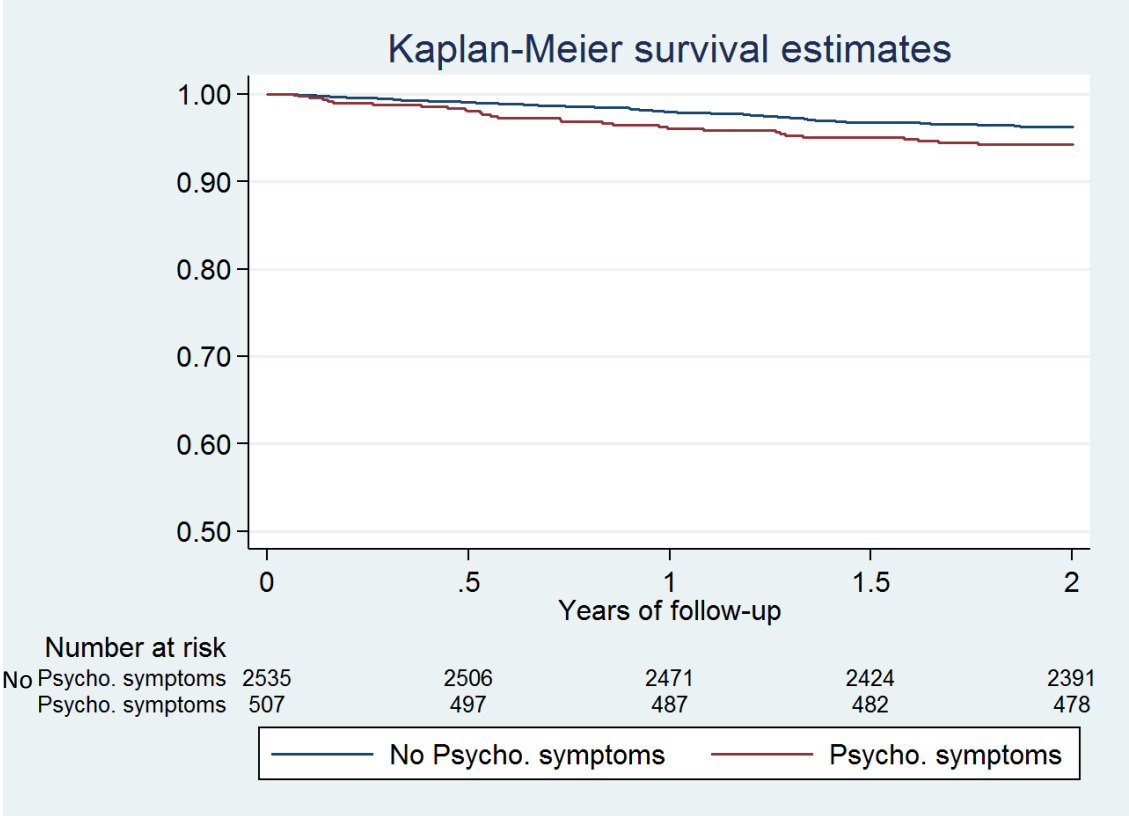
10.2.3.1 Proportional hazard assumption test

Data were tested to check the proportional hazard assumption by means of the Schoenfeld residuals test for the unadjusted and adjusted datasets and results indicated that data met the proportional hazard assumption. However, the Schoenfeld residuals test for the variable "index year" was significant, therefore this confounder was entered in the analysis as a time-varying confounder.

10.2.3.2 Kaplan-Meier graph of the association between consultations for psychological diagnosis/problems and consultations for persistent musculoskeletal conditions

Survival curves within the Kaplan-Meier graph (Figure 10.4) showed that consulters with psychological diagnosis/problems were at higher hazard for persistent musculoskeletal conditions compared to those without psychological diagnosis/problems, although the difference was small.

Figure 10.4 Association between consultations for psychological diagnosis/problems and persistent musculoskeletal conditions



Further explanation of the figures shown in the graph: At 1-year follow-up, 64/2535 (2.5%) individuals without psychological diagnosis/problems and 20/507 (3.9%) consulters with psychological diagnosis/problems consulted for persistent musculoskeletal conditions or were censored from the study, respectively. At 2-year follow-up, 144/2535 (5.7%) individuals without psychological diagnosis/problems and 29/507 (5.7%) consulters with psychological diagnosis/problems consulted for persistent musculoskeletal conditions or were censored from the study, respectively.

10.2.3.3 Cox regression analysis of the association between consultations for psychological diagnosis/problems and consultations for persistent musculoskeletal conditions

Cox regression analysis was performed to estimate the hazard ratio for consultations for persistent musculoskeletal conditions in consulters with psychological diagnosis/problems compared to those without psychological diagnosis/problems. Results for both unadjusted and adjusted models are shown in Table 10.8. Results of unadjusted analysis show that children and adolescents with a recorded consultation for psychological diagnosis/problems were at statistically significant 54% increased hazard for consultations for persistent musculoskeletal conditions. This estimate increased to a 64% significant increased hazard after adjustment for sleep problems, index year, gender, age at index date and practice, but was attenuated to a 34% non-significant increased hazard after further adjustment for numbers of consultations.

Table 10.8 Cox regression of the association between consultations for psychological diagnosis/ problems at baseline and consultations for persistent musculoskeletal conditions at follow-up

Unadjusted analysis (Model 1) (N = 3,042)		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.54	1.02, 2.33
Adjusted analysis* (Model 2) (N = 3,042)		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.64	1.08, 2.48
Adjusted analysis (Model 3) (N = 3,042)**		
Persistent MSK conditions at follow-up	**Hazard ratio**	**95% CI**
Psychological diagnosis/problems	1.34	0.88, 2.04

*Analysis adjusted for Sleep problems, Index year, Gender, Age at index date and Practice
** Analysis adjusted for the above confounders and additionally by number of consultations

10.3 Discussion

10.3.1 Interpretation of findings and comparison with previous literature

10.3.1.1 Sleep problems and onset of musculoskeletal conditions

The results of this study using primary care medical record data showed that 28% of children/adolescents with recorded sleep problems consulted in primary care with musculoskeletal pain within a 2-year follow-up period compared to 17.5% of those without recorded sleep problems. This result translated to a significant 72% increased hazard for a musculoskeletal consultation in individuals with sleep problems compared to those without sleep problems. This effect size was attenuated to a non-significant 49% increased hazard (95% CI 0.98; 2.27) after controlling for the number of consultations in the two years prior to the index (sleep) consultation (Section 10.1.2.3). Whilst the systematic review (chapter 2) showed no published studies that are directly comparable (i.e. using primary care records), attempts will be made to contextualise these results with the cohort findings within this thesis (chapter 6) and the wider literature. Whilst results from the wider literature are broadly inconsistent, they do support the general direction of effect as found in this study (i.e. increase in risk or odds for the presence of sleep problems). The effect found in CiPCA is also in accordance with the increased odds for the onset of chronic musculoskeletal pain in children and adolescents with sleep problems in the CATS dataset (Chapter 6), and in studies conducted both in children and adults (Gupta et al., 2007; Harrison et al., 2014; Mork et al., 2014). Although it is not easy to directly compare the strength of associations found in the CiPCA and CATS cohorts, slightly stronger and more precise estimates were found for the effect of sleep on pain onset in the CiPCA cohort. One potential explanation for this may be differences in severity of the condition between the cohorts. Research shows that the decision to refer to primary care (as is the case with the CiPCA cohort) occurs when the severity (or perceived severity), frequency, duration or limitations associated with the symptoms (i.e. both sleep problems and musculoskeletal pain in this current study) are more advanced

leading to an active decision to seek healthcare (Campbell & Roland, 1996; Paananen et al., 2011; Perquin et al., 2000). Therefore the reason for the more precise or stronger effects found in consultation data might have been driven by an elevated level of severity of the outcome (e.g. persistent, recurring, or more severe pain). This hypothesis is further supported by the clinical iceberg of disease theory, which suggests that there is a proportion of not recognized cases, whose severity may be milder (i.e. individuals with pre-clinical levels in this study), who do not present in primary care (Bhopal, 2002; Campbell & Roland, 1996; Last, 1963; Last & Adelaide, 2013). Such "pre-clinical" individuals, however, would respond to questions about their pain within a general population survey, but by the rationale of a linear association (as assumed in these studies), the effects overall would be weaker. The attenuation of effect size after adjustment for the number of consultations requires explanation. This reduction in effect may be explained by frequent primary care attendance, perhaps for other comorbidities (Paananen et al., 2011). In this scenario, frequent consulters would be more likely to have a consultation for both the exposure and outcome as a result of their frequent visits to general practice, compared to individuals who seldom consult (e.g. more opportunities to discuss health related problems with their doctor).

10.3.1.2 Sleep problems and persistent musculoskeletal conditions

The results of this study showed that the proportion of individuals who consulted with persistent musculoskeletal conditions within a 2-year follow-up period was similar between individuals with and without a primary care record for sleep problems (5.6% vs. 4.9%, respectively). This result translated to a small non-significant 14% increased hazard of persistent musculoskeletal conditions, which decreased to a 13% reduction in hazard after adjustment for number of consultations. Some considerations upon these results are needed. These results do not support the hypothesis posed in the previous section (10.3.1.1) that individuals consulting with new onset musculoskeletal conditions have more severe problems, where it would be expected that the effect would be stronger for those with persistent pain, as was demonstrated within the CATS cohort. A few issues need to be considered here. Firstly, only 32 individuals overall were classified as consulting with persistent musculoskeletal conditions, and therefore statistical power for this analysis was low, resulting in imprecise estimates. Secondly, and perhaps more importantly, is the way in which persistent pain was defined within this cohort. The criterion used was the presence of second or more repeat consultations for a musculoskeletal condition within a 3-month period after the first consultation for a musculoskeletal condition (see Section 9.1.3.2). Inspection of the consultation dates for musculoskeletal conditions showed that approximately half (17/32) of the repeat musculoskeletal conditions were within 10 days from the first consultation for musculoskeletal conditions. It may be possible, due to close time proximity between consultations that individuals were consulting for the same episode of pain, which may be fairly short, and not persistent or severe (perhaps a follow up appointment to check on recovery). It may be speculated that different criteria to define persistent musculoskeletal conditions could be used to capture those with genuine chronic pain (for a fuller explanation see Section 10.3.2), and such a change in definition may result in a change of the estimate (potentially in the direction of a stronger effect). In addition, the decrease in hazard after adjustment for number of consultations suggests that consultations for persistent musculoskeletal conditions was linked to primary care

attendance due to other comorbidities (Paananen et al., 2011) and may also represent partial over adjustment (i.e. a variable created based on consultation frequency adjusted for prior consultation frequency).

10.3.1.3 Psychological diagnosis/problems and musculoskeletal conditions

The results of this study using primary care records showed that 26.0% of individuals presenting with psychological diagnosis/problems subsequently consulted with musculoskeletal conditions within a 2-year follow-up period, compared to 17.4% of those without a record of psychological diagnosis/problems. This translates to a significant 59% increased hazard for musculoskeletal conditions (39% after all potential confounders were controlled for) in individuals with psychological diagnosis/problems compared to those without psychological diagnosis/problems. These findings are in line with the results for the onset of musculoskeletal pain in children with psychological problems found in the systematic review outlined in this thesis (Section 2.4.2.1) and the direction of effects found in the ALSPAC analysis reported in chapter 8, and also with the general findings of effect reported in adult populations (McBeth & Jones, 2007; Pinheiro et al., 2015; Taylor et al., 2014). Given the potentially higher severity, frequency and duration of musculoskeletal conditions in individuals who present to primary care (as outlined in the above Section 10.3.1.1), these results may support the hypothesized reciprocal relationship between psychological problems and musculoskeletal pain described in Section 8.7.1.3 of this thesis. In this scenario, latent psychological problems may set the stage for the onset of musculoskeletal conditions which initially do not require medical attention. Subsequently, musculoskeletal pain may in turn worsen the psychological status of the individual or exacerbate pre-clinical or dormant psychological problems, as suggested by the diathesis stress model (Dersh, 2002). Here the hypothesis is that individuals with elevated levels of stress (latent psychological problems) who then experience an adverse event (e.g. musculoskeletal condition) would develop greater

levels of stress, leading to difficulties in psychological coping, subsequently increasing and exacerbating both the stress (psychological problems) and experience of pain. This may result in a more severe or frequent musculoskeletal condition, or lead to chronicity, for which the individual may consequently seek care. In addition, factors related to the family environment may also partly account for the observed increased hazard for consulting healthcare for musculoskeletal conditions. Familial patterns of access to health care have been observed, with parents being the driving factor of a child or adolescents consultation. For example there is a relationship between parental catastrophizing about their child's pain and the child's own psychological reactions to pain and behaviour (Caes, Vervoort, Eccleston, Vandenhende, & Goubert, 2011), it may be that children of such parental influences may refer to primary care more frequently or present with more severe symptom (Campbell & Roland, 1996; Cardol et al., 2005, 2006, 2007). Members of the same family also share both genetic and environmental factors that may be associated with musculoskeletal pain, and an increased probability of having pain has been observed if another member of the family reports pain in both a general population setting and also within consultation populations (Campbell, Shraim, Jordan, & Dunn, 2016; Campbell, Jordan, Smith, Scotland, & Dunn, 2017; Shraim et al., 2013). Finally, as with the relationship between sleep problems and the onset of musculoskeletal conditions (Section 10.3.1.1), results of the analysis suggest that the reduction in hazard observed after adjustment for number of consultations may be explained by a behaviour of frequent primary care attendance for other comorbidities (Paananen et al., 2011) as well as potential over adjustment.

10.3.1.4 Psychological diagnosis/problems and persistent musculoskeletal conditions

Just below 6.0% of individuals with a primary care record of psychological diagnosis/problems consulted with persistent musculoskeletal conditions within a 2-year follow-up period, compared to 3.8% of those without recorded psychological diagnosis/problems. This translates to a significant 54% increased hazard of persistent musculoskeletal conditions in individuals with psychological diagnosis/problems, which was attenuated to a 34% non-significant increased hazard after that analysis was controlled for the number of consultations. As proposed in Section 10.3.1.3, factors such as maladaptive coping may explain these results. If musculoskeletal conditions persist after the first consultation, individuals with psychological diagnosis/problems may struggle to cope with the condition, leading to a subsequent new consultation for the problem. In addition, a further exacerbation of psychological problems (e.g. pain catastrophizing, pain-related anxiety, fear-avoidance behaviour) may have occurred in individuals who already have psychological problems, which may explain the non-significant higher hazard of developing persistent conditions found. However, as proposed in Section 10.3.1.2, the definition of persistent musculoskeletal conditions within this cohort should be considered when interpreting these effects. Inspection of the consultation dates showed that 43% (54/124) of persistent musculoskeletal conditions were within 10 days from the first consultation for musculoskeletal conditions, thus suggesting that the second consultation may refer to the same, potentially short episode. Therefore the use of alternative definitions of persistent pain may have been more suitable (e.g. to increase the number of consultations and to impose a longer period where those consultations take place), and could have produced different estimates of effect. In addition, as mentioned in previous sections above, the attenuation of effect after adjustment for number of consultations may suggest that the estimate of hazard for persistent musculoskeletal conditions may be partly attributable to the effect of frequent primary care attendance (Paananen et al., 2011) and may represent over adjustment.

10.3.2 Strengths and limitations of this study

There are a number of strengths with this study. First, analysis was performed using routinely collected data from a high quality primary care dataset. This brings the advantage that the entire temporal frame of data can be used compared to studies where data are collected solely at fixed points in time, and consequently allows the identification of the episodes of pain that would be missed if they occurred between the fixed time-points. Second, individuals were matched by age, gender and practice in order to reduce the risk of confounding, as these variables may be associated with increased healthcare seeking and musculoskeletal pain (Campbell & Roland, 1996; Henschke et al., 2015; Kamper et al., 2016; King et al., 2011; McBeth & Jones, 2007). Third, registration status was checked to avoid the loss of information in individuals who moved to other practices. Fourth, CiPCA includes a large sample, which is representative of the national general population: 98% of the population is registered with a GP in the UK and the prevalence of musculoskeletal consultations in CiPCA is similar to those of other national and international datasets (Herrett et al., 2015; Jordan et al., 2007, 2010, 2014). Fifth, this dataset reflects actual "real" consultation events, therefore there is no selection bias or reporting bias, and this confers an advantage over the answers given within self-report measures.

This current study also includes several limitations. First, some limitations pertain to the use of Read codes which are the codes that record the reason for consultations. For example a limitation is the inability to assess the severity, duration and impact of pain as well as the cause of the condition with Read codes (Michaleff et al., 2017; Muller, 2014). In addition, information on variables relative to lifestyle (e.g. smoking, physical activity, substance use) are generally less well recorded (Glasgow, Kaplan, Ockene, Fisher, & Emmons, 2012). As consultations for these variables were not present in this current study, it was not possible to adjust within the analysis, and so unmeasured confounders may be present. Also, as outlined previously, many individuals may have pre-clinical status for both exposure and outcome that will not be recorded (which may have included individuals in the matched controls) (Glasgow et al., 2012; Jordan et al., 2010; Muller,

2014). This is supported by the iceberg theory of disease, for which pre-clinical symptoms would go unrecognized or wrongly diagnosed, this influence is supported by the finding that psychological symptoms, sleep problems and musculoskeletal pain in children and adolescents are under-recognized in primary care settings (Bhopal, 2002; Cornish, John, Boyd, Tilling, & Macleod, 2016; Last, 1963; Last & Adelaide, 2013; Meltzer et al., 2010; Paananen et al., 2011). In addition, there are issues which may affect data quality. These include inadequate or incorrect coding of symptoms or diagnosis and missed codes in individuals who consulted for multiple health problems, as only the most prominent condition may be recorded (Jordan & Croft, 2008; Muller, 2014). Other issues include the possibility of errors when entering data because of semantic similarity of the Read code with the intended term (Benson, 2012), and that general practitioners may be limited to use certain codes which are not fully appropriate for the identified condition, such information may be better described in free text that the general practitioner can enter along with the Read code (Jordan, Porcheret, & Croft, 2004). As free-text information was not used in this study (as it was beyond the scope and timescale for the analysis), this may potentially have led to a loss of cases or important information about included consulters (e.g. additional comorbidities, outcome or exposure symptoms not coded, causes or reasons for consultation, lifestyle indicators) (Cornish, John, Boyd, Tilling, & Macleod, 2016; Muller, 2014). In addition, some overlap between the Read codes for sleep problems and psychological diagnosis/problems is present, due to the potential coexistence of certain symptoms (i.e. sleep problems as a core feature of a depression diagnosis). To overcome these influences analyses were adjusted for psychological diagnosis/problems and for sleep problems.

Second, a number of factors aside from the condition itself may influence the decision to refer to primary care. This includes the family patterns of illness behaviour, the parental economic status and job, family size, the perceived benefits of seeking care, the faith in the effectiveness of the general practitioner, the knowledge about the illness, the information seeking behaviour and the accessibility of care (Campbell & Roland, 1996; Cardol et al., 2006, 2007), all of which are not

generally measurable using electronic health records. The decision to refer to primary care may also be influenced by the parent's perceived severity of symptoms (Kamper, Dissing, & Hestbaek, 2016). However, although parents may overlook aches and pains of minor importance, good concordance between parent and child report has been shown for musculoskeletal pain of a greater severity (Kamper, Dissing, et al., 2016).

Third, the method to define a proxy for "chronic pain" or more precisely persistent pain contained some issues. The criteria (more than one consultation for musculoskeletal conditions within a 3-month period) was based on the finding of a study where individuals where asked when they had their last pain-free month. Results from that study showed that only 24% of those with new onset of pain within the last 3 months had a pain-free month in the last 3 months (Dunn, de Vet, et al., 2006). In this current study an average of 26% and 22% of those with a consultation for musculoskeletal conditions reported persistent musculoskeletal conditions, which is similar to estimates reported in previous studies carried out in children consulting for musculoskeletal pain (Michaleff et al., 2017). Despite this fits with the literature in terms of the definition chosen, most consultations for persistent musculoskeletal conditions were within 10 days from the first consultation, and it was not possible to assess if the identified persistent musculoskeletal conditions were representative of a chronic condition or not, for example this may have been a follow up appointment arranged by the general practitioner to check on progress rather than a re-consultation due to persistent pain. These issue underline the complexity in the definition of chronic musculoskeletal conditions in general, and more so within electronic health record research. It may also be the case that those with genuine chronic pain may not have consulted more than once in this period and would not have been identified as having persistent pain. Previous research on long-lasting conditions such as pain have shown that the date of consultation does not reflect the actual date of onset or the duration of the problem (Jordan et al., 2007; Michaleff et al., 2017).

Fourth, the observed attenuation of estimates after adjustment for number of consultations may be potentially attributable to the effect of over-adjustment, which occurs when the variable for which the analysis is adjusted for is in the pathway between the exposure and the outcome and tend to bias the results towards the null (Schisterman, Coleb, & Platt, 2009).

Fifth, the analysis was adjusted for practice in order to take into account potential practice effects, which include differences in consultation patterns between different areas and may be linked to the socio-economic status. For example increased consultation rates are associated with lower social class (Campbell & Roland, 1996), and children of families from a lower socio-economic status may be more exposed to problems in the family environment, which may increase the risk for musculoskeletal pain (Alink et al., 2008; Brattberg, 1994; Kroner-Herwig et al., 2011; Ramchandani & Psychogiou, 2009). However, each practice may have families from a range of different socio-economic statuses although they live in the same area. Therefore, a more detailed measure such as the familial deprivation status would have allowed a finer adjustment of the potential socio-economic influences that may have been present within the analysis, unfortunately measures on deprivation were not available.

Sixth, statistical power is a potential issue. The matched-cohort dataset used to investigate the relationship between sleep problems and musculoskeletal conditions included 638 individuals and only 123 events (medical recorded consultation for a musculoskeletal condition). Calculations showed that approximately 900 individuals would be needed to have 80% of power based on the reported effect size, indicating that the analysis was potentially underpowered to detect an association with statistical significance. Conversely, statistical power was not an issue for the matched-cohort dataset used to investigate the relationship between psychological symptoms and musculoskeletal conditions which included 3,042 and 574 events (medical recorded consultation for a musculoskeletal condition), as calculations showed a 99% power given the effect size found with this sample size. Finally, whilst these findings are of interest they are situated within the primary care system in the United Kingdom, and therefore may not be

generalizable to other healthcare systems where different models of care are practiced, for example where GPs are not the sole gatekeeper of primary care provision (Kringos et al., 2013).

10.4 Key messages

- Children and adolescents who present to primary care for sleep problems are at higher hazard for a subsequent consultation for musculoskeletal conditions.
- Children and adolescents who present to primary care with psychological symptoms are at higher hazard for a subsequent consultation for musculoskeletal conditions.
- Children and adolescents who present to primary care with sleep problems do not seem to be at higher hazard for consulting with persistent musculoskeletal conditions, while those with psychological symptoms seem to be at small non-significant increased hazard. However, the definition of persistent musculoskeletal conditions used may have influenced the estimate of hazard found.

Chapter eleven. Discussion

11.1 Thesis summary

The overall aim of this thesis was to identify potential risk factors for the onset of musculoskeletal pain in children and adolescents from the current literature, and to generate hypotheses and test those hypotheses using existing cohort data. A systematic review of the current literature was performed, and 37 studies reporting on risk factors for the onset of musculoskeletal pain were identified. From an evidence synthesis two potential risk factors for the onset of musculoskeletal pain were identified, namely the presence of sleep problems and of psychological symptoms. This led to the development of the three objectives addressed within this thesis.

1. To investigate whether sleep problems are a risk factor for the onset of musculoskeletal pain in children.
2. To investigate whether psychological symptoms are risk factors for the onset of musculoskeletal pain in adolescents.
3. To investigate whether consultations for sleep problems and psychological symptoms are associated with consultations for musculoskeletal pain in children and adolescents within a primary care setting.

In addition to the identification of risk factors from the review, a number of potential effect modifiers of the associations studied in the thesis were also identified, namely; gender, pubertal status, and screen time use. Each risk factor and effect modifiers were tested within separate general population cohort datasets, sleep problems within CATS, psychological symptoms within ALSPAC, and then both risk factors were tested within a primary care consultation population (CiPCA). A detailed description of the analyses and results undertaken in these datasets was presented in Chapters 5-10. In this chapter, a summary of the key points and findings will be

discussed, along with discussion of the strengths and limitations applicable to all datasets, as well as a discussion of the potential implications for future research and clinical practice.

11.2 Comparison between datasets

Whilst comparisons between findings from these different datasets presents difficulties, because of differences in the characteristics of the cohort, differences in the measurement of variables, different time points used, and differences in the analysis approach (logistic regression, survival analysis), some inferences may be attempted, and these are now outlined in the following paragraphs.

11.2.1 Sleep problems and musculoskeletal pain

The association between sleep problems and the onset of musculoskeletal pain was explored in a general population dataset (CATS) and a primary care dataset (CiPCA). Results of the analysis performed within the CATS dataset showed that children with sleep problems had an increased odds of reporting musculoskeletal pain onset (35% increase), albeit non-significant, and a significant increased odds (122%) for the onset of chronic musculoskeletal pain. The direction of these effects was supported within the primary care dataset, with a 72% significant higher hazard ratio (attenuated to a 49% non-significant higher hazard after adjustment for number of consultations) and a 11% non-significant higher hazard for persistent musculoskeletal conditions (13% non-significant lower hazard after adjustment for number of consultations). Whilst there is general consensus between datasets on the direction of effect (i.e. increased odds/risk), there is a difference in the strength of effect, stronger for musculoskeletal pain onset in the consultation population, and a difference for chronic/persistent musculoskeletal pain onset, with a stronger effect found in the cohort but weaker within the consultation population. One possible

explanation for the stronger effect for musculoskeletal pain onset in the consultation population may be the severity of pain of the child or adolescents who consult. As discussed in Section 10.3.1.1, it is suggested that children who refer to primary care for musculoskeletal pain, do so when the condition is more severe, frequent or of longer duration (Campbell & Roland, 1996; Paananen et al., 2011; Perquin et al., 2000). Therefore, the phenotype of those who are consulting (within the primary care dataset) may actually be more reflective of those with chronic pain within the CATS cohort, in the sense that they may have had their pain for a longer time before consulting, and given the evidence on the reasons for consultation (Campbell & Roland, 1996) they may have a greater severity of pain (unfortunately a measure of severity was not within either dataset and so could not be tested). This therefore may explain the general stronger effect for the onset of musculoskeletal pain between the two datasets. Another potential reason for this difference, specifically for the chronic findings, as discussed fully in chapter 10 (Section 10.3.1.2), is the definition of persistent pain used in CiPCA, with a high number of participants having a subsequent consultation only a short while after their index consultation, potentially indicating a short episode rather than long-term pain problem. Furthermore, such close proximity of consultations may also be routine follow up appointments and the patient may have (largely) recovered. Taking a wider perspective on the results of these specific datasets, there is some agreement with the results of the systematic review presented in this thesis, as the association between sleep problems and the onset of musculoskeletal pain was inconsistent (however the general direction was toward increased risk in the review findings), and the only study that investigated the onset of chronic musculoskeletal pain reported significantly higher odds in children with sleep problems (Harrison et al., 2014). The hypothesis that the association between sleep problems and the onset of chronic musculoskeletal pain is more evident (compared to the onset of any incident musculoskeletal pain) is also supported by studies conducted in adult populations, which report consistent associations between sleep problems and the onset of chronic musculoskeletal pain conditions (Gupta et al., 2007; McBeth et al., 2014; Mork et al.,

2014; Nitter et al., 2012). All this evidence may therefore suggest that sleep problems are a risk factor for the development of more severe or chronic musculoskeletal pain conditions. It may therefore be possible that there is a reciprocal relationship between sleep and musculoskeletal pain, where a child experiences a musculoskeletal pain event, this then disrupts sleep patterns, which could then culminate in the development of more severe or chronic musculoskeletal conditions. This hypothesis is in agreement with the potential bi-directional relationship between sleep and musculoskeletal pain reported in recent reviews (Finan et al., 2013; McBeth et al., 2015). Results of the effect modification analysis within the CATS dataset suggest a subgroup of children (i.e. boys) may be at higher risk for the onset of musculoskeletal pain. However, effect modification analysis did not show any statistically significant interaction for any of the other subgroups assessed (i.e. pubertal status, screen time). Overall, the results of the effect modification analysis should be considered exploratory and interpreted with care due to the limited sample size of subgroups in stratified analysis, which provided low power for testing the presence of an interaction effect (Bland, 2015). Further confirmatory studies with an adequate sample size are needed to test the potential effect modification of the variables assessed in this thesis.

11.2.2 Psychological symptoms and musculoskeletal pain

The relationship between psychological symptoms and the onset of musculoskeletal pain was explored in a general population dataset (ALPSAC) and a primary care dataset (CiPCA). Analysis performed within the ALSPAC dataset (where psychological symptoms were conceptualised and measured as internalizing and externalizing constructs, see chapter 7, Section 7.2.2.1) showed that children with internalizing symptoms were at 43% and 28% non-significant increased odds for the onset of musculoskeletal pain and chronic musculoskeletal pain, respectively. The results were stronger for externalizing symptoms with a 99% significant increased odds for the onset of

musculoskeletal pain, and a 68% non-significant increased odds for the onset of chronic musculoskeletal pain. Testing within the primary care consultation records (CiPCA) showed a 39% significant higher hazard for musculoskeletal pain consultation onset, and a 34% non-significant higher hazard for persistent musculoskeletal consultations. All of these results show a general increase in likelihood of a musculoskeletal event (pain or consultation) and this is in line with the findings from the systematic review, which reported both significant and inconsistent findings for internalizing and externalizing symptoms, overall in the direction of an increased likelihood of musculoskeletal pain with increasing levels of internalizing and externalizing. The results of the systematic review however did not provide clear consistent information on the individual contribution of internalizing versus externalizing factors to the onset of musculoskeletal pain. Whilst the general directions of results show an increase in likelihood of musculoskeletal pain onset, inspection of the constructs of internalizing and externalizing in the ALSPAC show that externalizing symptoms (e.g. conduct problems, behavioural problems) are more likely to be associated with musculoskeletal pain, whereas internalizing symptoms are not. The findings from primary care consultations, using a broad definition of psychological problems, show an increase in hazard, slightly more so (and significantly) for musculoskeletal consultation onset compared to persistent consultation. However, comparability between analysis for the onset of chronic musculoskeletal pain in ALSPAC and persistent musculoskeletal conditions in CiPCA is limited due to differences in the methods used to measure persistent musculoskeletal conditions (as discussed for the findings on sleep problems in Section 11.2.1 above). Overall the results of this thesis suggest that psychological symptoms in children are predictive of the development of musculoskeletal pain, either of onset (as observed in ALSPAC) or of conditions that may be more acute or severe as presented in a primary care setting. Results of the effect modification analysis for both internalizing and externalizing symptoms within the ALSPAC dataset did not show any statistically significant interaction for any of the subgroups assessed (i.e. gender, pubertal status, screen time). However some interesting trends were found, for example, a trend of decreasing

odds for the onset of musculoskeletal pain with increasing levels of screen time, a trend of increased odds of developing musculoskeletal pain with increasing pubertal stages was observed in children with externalizing symptoms, the opposite direction was found in children with internalizing symptoms (i.e. decreased odds with increasing pubertal stages). However, as with the CATS dataset discussed in the previous section, the limited sample size of subgroups in the stratified analysis provided low power for testing the presence of effect modification, and a number of variables that may potentially have confounded the analysis were not available within this dataset. Based on the general finding that psychological symptoms are a risk factor for musculoskeletal pain outcomes in children and adolescents, and that there is some evidence of particular groups at increased or decreased risk, further confirmatory studies with adequate sample size and perhaps hypothesised statistical modelling (e.g. structural models) that can account for effect modification and confounders are needed to assess the potential effect modification of the variables tested in this thesis.

11.3 Strengths and Limitations

This current thesis and studies within presents several strengths and limitations. Strengths and limitations specific to each dataset investigated were outlined in Chapter 6, 8 and 10 of this thesis. In the following paragraphs, a discussion of the general strengths and limitations are outlined.

11.3.1 Strengths of this thesis

- A comprehensive systematic review on risk factors for the onset of musculoskeletal pain was performed, which identified a larger number of studies and encompassed a broader range of body sites and risk factors as compared to previous reviews. A further focused review using the same methodology, specifically reporting on the association between sleep problems and musculoskeletal pain was performed, resulting in a peer reviewed publication (Andreucci, Campbell, & Dunn, 2017). Are Sleep Problems a Risk Factor for the Onset of Musculoskeletal Pain in Children and Adolescents? A Systematic Review. Sleep, 40(7)).
- Analyses were performed in two general population datasets (CATS and ALSPAC) and replicated within a primary care consultation dataset (CiPCA). Therefore the reported results of this thesis are informative both for the general population and also for primary care, thus providing new knowledge regarding sleep problems and psychological symptoms as potential risk factors of musculoskeletal pain in children and adolescents that is of potential public health and clinical relevance.
- Prospective designs were used for the analyses carried out within the three datasets. This design (apart from an experimental design) is the optimal to provide evidence of a temporal sequence between exposure and outcome.
- Effect modification analysis was applied based on inconsistencies of results identified by the systematic review. A priori variables (gender, screen time, pubertal status) were

identified from the systematic review and conceptually measured within the datasets. This enabled a detailed inspection of factors that potentially could increase or decrease risk between exposure and outcome.

- The large sample sizes of CiPCA and ALSPAC provided sufficient power to estimate the overall associations with sufficient precision, although this was not the case for the analysis of effect modification.
- A comprehensive search of previous studies using medical record data and an assessment of validated Read code lists available at the Research Institute for Primary Care & Health Sciences, Keele University, was carried out to define Read codes lists. These lists were reviewed by an academic GP to assess relevance, use, and appropriateness to successfully capture risk factors and outcome in the CiPCA cohort.
- A further benefit of the use of medical health records is that they are not prone to recall bias compared to the collection of data with self-report questionnaires.

11.3.2 Limitations of this thesis

- The study design presents some limitations for the CATS and ALSPAC analyses. Because both datasets included two time points (i.e. baseline and follow up) it was not possible to assess any potential changes of the variables measured at baseline during the follow-up period (e.g. were the risk factors transient or stable). This would have allowed a more detailed investigation of the temporal associations between the exposures (e.g. sleep problems and psychological symptoms from baseline to follow-up) and onset of (chronic) musculoskeletal pain (Mork et al., 2014). Also, it was not possible to capture all the musculoskeletal pain events that may have occurred between baseline and follow-up (i.e. the assessment of musculoskeletal pain at follow-up included only the events occurring within the last month, but may have missed events that occurred previously). Therefore it

is possible that estimates of incidence found are an underestimation in these datasets (Kamada et al., 2016).

- The analysis of existing data is useful but not the best option for investigating new research objectives not included within the primary aims of the original design. A bespoke cohort would have allowed a better assessment of both exposures and outcomes, and consequently of the associations investigated in this thesis. For example, on outcomes in all datasets, information on pain aetiology would be useful (e.g trauma, injury, or non-specified), also information on pain severity, frequency, and perceived impact (e.g. pain interference or disability). For the assessment of sleep problems in CATS and CiPCA, again potentially important information was not assessed such as physiological measurements, sleep length, sleep diaries, all of which may have led to greater clarity on the associations reported (Section 6.3.2 and Section 10.3.2 for discussions on these issues). Also better assessments in ALSPAC and CiPCA would have provided greater clarity on the association of psychological symptoms with musculoskeletal pain, for example measurement and assessment of psychological reactions to pain such as fear avoidance and catastrophizing may have proved insightful (see Section 8.7.2 and 10.3.2 for a discussion). These general limitations of using existing data also apply to the measurement of effect modifiers and potential confounders.
- Measures used to define sleep problems (CATS dataset) and psychological symptoms (ALSPAC dataset, internalizing/externalizing symptoms) were dichotomised based on recognised cut points, in order here to identify children with symptoms of clinical relevance. Whilst this is a commonly used approach to data analysis (especially with conditions that are widely prevalent), the dichotomisation process necessarily leads to a loss of information (e.g. two children may have nearly similar values for a variable, but after dichotomization one might be just above and the other just below the cut-off limit used, therefore will be treated differently in the analysis) (MacCallum, Zhang, Preacher, &

Rucker, 2002). This approach may have resulted in misclassification bias and a loss of precision compared to using continuous variables with linear regression (Altman, 2006; Delgado-Rodriguez & Llorca, 2004).

- In CATS and ALSPAC data were collected by means of questionnaires. Errors may occur in coding and entering the responses from the questionnaires into the datasets. In addition, when using self-report questionnaires, it is not possible to ask for clarification of items and prevent potential misunderstandings. Additionally questionnaires generally do not permit a clinical diagnosis of the pain problem (de Leeuw et al., 2003; Sperotto et al., 2015) and certainly the questions used to assess pain in these cohorts was limited.
- A limitation of using medical health records for research is that variables relative to lifestyle are generally less well recorded (Glasgow et al., 2012). As a consequence, it was not possible to adjust the analysis for certain confounders (i.e. smoking, drug use, physical activity) that may have proved informative to the reported results. Other issues for medical record approaches is the actual coding practice, there may have been potential misclassification of symptoms or diagnoses, the missing of relevant health conditions when individuals present with multiple problems and only one is coded, the possibility of errors when entering data, and the predilection of GPs for certain Read codes.
- The levels of evidence for causality include several criteria (i.e. consistency of evidence, temporality, dose-response, theoretical plausibility, magnitude of effect), some of which were not met in the analysis performed within this thesis. This study did include a prospective design which allowed the inference of causality but limitations existed in terms of the time points used for the analysis as discussed previously. Also, the evidence was not consistent, for both sleep problems and psychological symptoms, both within the systematic review and within the studies reported in this thesis. In addition, the effect for some of the associations studied in this thesis (i.e. associations between sleep problems, internalizing symptoms and the onset of musculoskeletal pain) was non-significant and of

modest size. Whilst potential biopsychosocial explanations for the findings were proposed to give theoretical plausibility (for example see Section 6.3.1.2 and 8.7.1.3), there was no opportunity to test theoretical models with appropriate scientific rigour (e.g. experimental manipulation of the exposure), and to date no conclusive evidence for mechanisms of causality have been established. Despite these limitations, the general results do suggest that increased risk of musculoskeletal pain onset is associated with both sleep problems and psychological symptoms in children and adolescents, there is also evidence of some effect modification and more research is now warranted.

- Whilst findings from the CiPCA dataset are informative they are somewhat restrictive and applicable to the primary care health system practiced in the United Kingdom and therefore may not be generalizable to different healthcare systems (Kringos et al., 2013).

11.4 Identification of incident musculoskeletal pain

In the previous section the strength and limitations of this thesis were outlined. A further drawback of this thesis is described in this paragraph, and concerns the identification of incident musculoskeletal pain in children and adolescents. As outlined in Section 3.1, the aim of this thesis was to investigate risk factors for the onset (incidence) of musculoskeletal pain in children and adolescents identified from the general population or primary care consultation records. This was achieved by estimating both the incidence of musculoskeletal pain and the strength of association between exposure and outcome. The incidence of musculoskeletal pain (Section 1.4) is the proportion of new cases of musculoskeletal pain that occur over a certain period of time among all the individuals at risk (i.e. those without musculoskeletal pain at baseline). However, 60% of children within the CATS cohort and 49% within the ALSPAC cohort reported the presence of musculoskeletal pain at baseline (Section 5.5.1.1 and 7.5.1.1). Therefore, a limitation of this thesis is that it was not possible to identify “true” incident cases of musculoskeletal pain (i.e. first ever onset of musculoskeletal pain) for all children and adolescents within the CATS and ALSPAC cohorts. In addition, figures and proportions relative to the risk factors investigated (sleep problems and psychological symptoms) as well as the potential confounders were higher/stronger among those with musculoskeletal pain at baseline compared to those without musculoskeletal pain at baseline (Section 5.5.1.3 and 7.5.1.3). It may therefore be hypothesised that children with and without musculoskeletal pain at baseline within this thesis represent different populations. In this scenario, those without musculoskeletal pain at baseline might undergo an effect similar to the healthy worker effect observed in adults (Delgado-Rodriguez & Llorca, 2004), and would therefore be healthier and consequently less likely to develop musculoskeletal pain at follow-up. Although it may be postulated that the strength of association in a cohort where it might be possible to identify the first ever onset of musculoskeletal pain in children would be different compared to the figures reported in this thesis (which may be an underestimation if children were "healthier"), it is not possible to estimate the actual difference within this thesis. Thus, future

studies tracking children from an earlier point in life (for example from the age of 6, which is the starting point for children to use the word “pain” and to form a conceptualisation of pain) with multiple time follow-up points are needed. This type of study would be more likely to identify the first ever onset of musculoskeletal pain and would allow finer investigations of any potential difference in the association between sleep problems, psychological symptoms and the onset of musculoskeletal pain between adolescents whose onset of musculoskeletal pain occurs earlier in life compared to those who experience musculoskeletal pain at a later stage.

11.5 Implications for research

11.5.1 Interpretation of the findings and relevance to public health and primary care

The results of the analyses carried out within this thesis show an increased likelihood for musculoskeletal pain (either onset or chronic) in children/adolescents with sleep problems or psychological symptoms both within general population and primary care settings (Section 11.2). However, the effect sizes reported in this current study were modest and varied depending on the outcome measured (i.e. onset of musculoskeletal pain vs. chronic/persistent musculoskeletal pain). Therefore, the key question is whether these results merit the initiation of prevention strategies (to prevent onset) or interventions (to prevent chronicity). When considering planning a prevention strategy or an intervention, epidemiological measures such as attributable risk, absolute risk reduction and numbers needed to treat or to prevent should be considered (Bhopal, 2002). The attributable risk (AR) represents the number of outcome events that would not have occurred if a particular risk factor had not been present. Therefore this measure is informative of the excess in risk produced by the risk factor compared to the baseline risk (Bhopal, 2002). This measure can be calculated by dividing the difference in the incidence between the exposed and non-exposed group over the incidence in the exposed group as in the following formula (I_e = Incidence in the exposed group; I_u = Incidence in the non-exposed group):

$$AR = (I_e - I_u) / I_e$$

The absolute risk reduction (ARR) is the difference in rates of event between the two groups and can be calculated by subtracting the incidence in the non-exposed group from the incidence in the exposed group, as in the following formula:

$$ARR = I_e - I_u$$

The numbers needed to treat (NNT) or to prevent (NNP) is a measure that indicates the number of people who need to be treated for one patient to benefit, and it is calculated as the inverse of the ARR:

NNT (or NNP): 1 / ARR

These measures have been calculated for objective number 1 (Investigation of sleep problems as a risk factor for the onset of musculoskeletal pain in children) and 2 (Investigation of internalizing and externalizing symptoms as risk factors for the onset of musculoskeletal pain in adolescents) using the unadjusted (crude) risks reported in CATS and ALSPAC. Results are shown in Table 11.1.

Table 11.1 Attributable risk, absolute risk reduction and number needed to prevent for the objectives investigated in this thesis

Objective	Exposure prevalence	I_e	I_u	AR	ARR	NNP
Sleep problems – MSK pain	21.8%	50.0%	40.6%	18.8%	9.4%	11
Sleep problems - Chronic MSK pain	32.6%	16.9%	7.4%	56.2%	9.5%	11
Internalizing – MSK pain	8.4%	41.9%	35.3%	15.8%	6,6%	15
Externalizing – MSK pain	7.3%	51.5%	34.8%	32.4%	16.7%	6
Internalizing - Chronic MSK pain	8.4%	20.5%	16.7%	18.5%	3.8%	26
Externalizing - Chronic MSK pain	7.3%	25.3%	16.5%	34.8%	8.8%	11
N.b.: Figures do not take account of adjustment for potential confounders (measured or unmeasured)						

As can be seen from the above table there is variation in all the estimates provided, with some estimates of a higher significance than others, for example sleep problems are 56.2% of the risk for the development of chronic musculoskeletal pain in CATS, whilst only 15.8% is attributable to internalizing symptoms in ALSPAC. These differences depend on many factors including the risk ratio and prevalence, and so comparisons across the board as in table 11.1 are problematic, and beyond the scope of this thesis. However one useful metric is the NNP (NNT) where it is suggested

that a threshold of single numbers (i.e. < 10 patients) has plausible clinical relevance (Citrome, 2008). Here it can be seen that an intervention targeting externalizing symptoms may be the most suitable, as 1 every 6 individuals treated would benefit from the treatment, targeting sleep problems (both onset and chronic) and externalizing for chronic musculoskeletal pain onset might be useful at 11 patients, however for other targets, an intervention may be less practical. Whilst the focus on targeting sleep problems and externalizing symptoms appears plausible, the assumptions at the basis of the interpretation should be clarified. Assumptions underlying the attributable risk for example are that: (i) the risk factor has to be a causal factor and the mechanisms of causality have to be understood; (ii) estimates of incidence have to apply to other populations (generalisability); (iii) the study is valid and accurate; (iv) there is no confounding by any other factor; and (v) and the proposed intervention would successfully reduce all of the excess risk associated with the risk factor (Bhopal, 2002). These criteria mirror some of the general limitations of the studies outlined in the above section (11.3.2) and although some mechanisms to explain the associations found have been proposed (see chapters 6 and 8, Section 6.3.1.2 and 8.7.1.3), the mechanisms most probably involve multiple factors that will vary from individual to individual, and to date conclusive evidence regarding the pathways of causality from sleep problems and psychological symptoms to the onset of musculoskeletal pain or chronic musculoskeletal pain have not been fully established. Based on these issues, and given the modest effect size of the associations found in this current study, it is recommended that more research is carried out to understand potential mechanisms of causality for these risk factors and to identify further the groups of children and adolescents who may be at increased risk via effect modification (some of which have been tentatively identified in this thesis). If causal mechanisms were more concretely identified (e.g. through better measures, repeated measures over time, experimental designs, more sophisticated modelling that allows a more in-depth analysis of causal pathway), this would lay the foundation for the design and evaluation of interventions to reduce sleep problems and psychological symptoms in order to avert the onset of musculoskeletal pain.

Considering the problem in a wider perspective, the prevention of the onset of musculoskeletal conditions may result in beneficial long-term effects for affected individuals and in terms of an overall reduction in costs for the healthcare system. (e.g. the net ingredient cost of drugs for musculoskeletal and joint conditions in England has been estimated as £224 million in 2015) (Baker, 2016). Based on the findings of this thesis and the evaluation of the results some potential approaches for future research investigating musculoskeletal pain in children and adolescents are outlined in the following section.

11.5.2 Alternative approaches to investigating musculoskeletal pain in children and recommendations for future research

The investigation of risk factors for the onset of musculoskeletal pain in children and adolescents in this thesis generated ideas regarding alternative approaches that may be used to investigate these risk factors further. These proposed approaches are described below.

11.5.2.1 The use of multiple data time points and innovative methods to collect data

Studies that collect data at multiple time points are at an advantage. For example, recent research on trajectories in individuals with musculoskeletal pain has identified different groups of people based on their experience of pain over time (Dunn et al., 2011; Dunn, Jordan, et al., 2006; Dunn, Campbell, et al., 2013). Pairing these groups up with potential risk factors can identify what factors are important in the prediction of these trajectories groups (e.g. those with persistent pain over time). There are now also newer methods, such as Latent Class Growth Modelling, where dual or even more variables can be combined within longitudinal trajectory analysis (Xie, Mchugo, He, & Drake, 2010). Here, for example, repeated data on sleep problems or on psychological symptoms can be combined with data on musculoskeletal pain through time to give clearer

indications of the proposed bi-directional longitudinal relationships (i.e. when these factors have the greatest influence), again identifying individuals at the highest risk. Furthermore, innovative strategies that are appealing to young people could be used to collect data, for example, it may be useful to develop an app for smartphones/iPads that tracks the association between exposure to risk factors and musculoskeletal pain by collecting data at regular time points. Questions may be asked daily or weekly, and a reminder system (to parents or child/young person) can be installed to ensure greater participation, something that is more difficult using paper questionnaires (Dissing et al., 2017; Fuglkjaer, Hartvigsen et al., 2017; Kamper, Dissing et al., 2016; Leboeuf-Yde, Jensen, & Axén, 2012). This allows the collection of trajectory data with a high response rate and minimal recall bias (Leboeuf-Yde et al., 2012). It may also be possible to deliver interventions aimed at managing musculoskeletal pain and preventing the transition to chronicity through the smartphone. A recent systematic review reported the presence of 61 apps for the management of low back pain, and whilst they are generally of low quality at present, this growth in the use of technology indicates the potential for e-health interventions in the future (Machado et al., 2017). In addition, data collected through smartphones/iPads may be linked to primary care data, in order to investigate whether conditions reported with electronic devices are associated with consultation for the conditions in primary care or assess additional questions not recorded within a primary care consultation (severity, impact, reactions to pain).

11.5.2.2 Additional measures to collect in future studies

Potential mechanisms to explain the pathway from sleep problems or psychological symptoms to musculoskeletal pain onset have been outlined previously within this thesis (Section 6.3.1.2 and 8.7.1.3, respectively). Therefore, if there was the possibility to set up a cohort study to investigate these presumed causal pathways, it would be important to collect additional data to gain a better understanding of the mechanisms potentially underlying associations between sleep and/or

psychological problems and onset of musculoskeletal pain. As stated previously musculoskeletal pain requires a better assessment. Information about the severity, frequency and impact of musculoskeletal pain (e.g. pain interference or disability) should be collected as this may provide a better understanding of the experience of pain (Section 11.3). As anticipated in Section 6.3.2, a validated tool for sleep problems (e.g. Sleep Disorders Inventory for Students, the Sleep Disturbance Scale for Children) would allow the assessment of the several components of sleep (Spruyt & Gozal, 2011). In addition, given the potential daily variation in pain (Tang, Goodchild, Sanborn, Howard, & Salkovskis, 2012), both sleep and pain diaries may be used to perform longitudinal studies in children and adolescents. Furthermore, the investigation of physiological/ biological pathways between sleep and musculoskeletal pain may add to the evidence for potential mechanisms of causality, and would require additional measurements. For example, levels of cytokines and inflammatory mediators may be measured in children with and without sleep problems, followed by repeated measurements of pain, including severity and impact. This may elucidate if these factors are involved in the pathway from sleep to musculoskeletal pain. In addition, the influence of social factors such as parental health status and problems within the family environment on the association between sleep problems and musculoskeletal pain in children may be elucidated, for example within a mediation analysis model in which parental health status and problems within the family environment precede sleep problems, and subsequent onset of musculoskeletal pain is investigated. Results from this type of analysis (where pathways and development through time are analysed) may potentially suggest targets for interventions.

Regarding psychological symptoms, the role of the mechanism of response to stress may be assessed. Saliva samples may be collected in children to measure the levels of cortisol and ACTH, using methodology described in previous studies (Kaplow et al., 2013; van voorhees & Scarpa, 2004). The association between the variation in levels of ACTH and cortisol and the development of musculoskeletal pain, including severity, may be subsequently assessed to elucidate the role of

HPA axis functioning and in the association between stress and musculoskeletal pain in children (Generaal et al., 2014). Another factor for which a better measure may be needed is puberty. The measurement of pubertal status at more frequent time-points may allow the assessment of pubertal tempo (i.e. the rate of change in pubertal development) among children who are experiencing puberty, and to assess the influence of such differences on the psychological development of children. Similarly to what was proposed above for sleep problems, measures to explore the effect of social factors that were not present within the datasets used in this thesis may be collected. For example, the contribution of relationship with the parents and problems in the family environment on the association between psychological symptoms and musculoskeletal pain may be assessed in a mediation model and potentially suggest future areas of intervention for the prevention of musculoskeletal pain (Section 11.5.3.1). Finally, measures regarding pain-catastrophizing (e.g. Pain Catastrophizing Scale) and fear-avoidance behaviour (e.g. Fear of Pain Questionnaire Child and Parent Proxy Report) may be included in future studies that investigate the association between sleep problems, psychological symptoms and musculoskeletal pain (Asmundson, Noel, Petter, & Parkerson, 2012). This would allow estimating the influence of these factors in the transition from the onset of musculoskeletal pain to chronicity.

11.5.2.3 Replication of the analysis within other databases and datasets

It is important that findings are replicated to inform on generalisability. The analysis carried out within this thesis using ALSPAC and CiPCA datasets were performed in populations of predominantly white ethnicity (no information of ethnicity is present within CATS). Analysis performed within this thesis may be replicated in other databases that include a different range of children of differing ethnicities, as evidence suggests differences in the experience and expression of pain (Section 1.5.3.2). Age is also an important factor, with many biological and psychological changes taking placed in a relatively short period of time (e.g. puberty) therefore replication is required in datasets of differing age, or a cohort is set up to recruit children of

different ages to assess this important factor. In addition, analysis may be replicated in other primary care databases within the UK (i.e. Clinical Practice Research Datalink, CPRD) as CiPCA is situated in general practices within a more deprived area than the national UK average (Jordan et al., 2010), and replication should take place in other countries where health care systems differ.

11.5.3 Interventions aimed at preventing the onset of musculoskeletal pain

As reported in Section 11.5.1, to date there is no established evidence regarding the causal mechanisms leading from sleep problems and psychological symptoms to musculoskeletal pain. However, if future research can provide evidence on the potential pathways proposed within this thesis or otherwise, interventions may be planned. Interventions aimed at preventing the onset or the transition to chronicity of a condition in a population require a change in the population mean of an exposure as a whole (Bhopal, 2002). Therefore, interventions aimed at decreasing the percentage of children with sleep problems or psychological symptoms may be effective in reducing the impact of musculoskeletal pain in the population.

11.5.3.1 Interventions targeting sleep problems and psychological symptoms

Several strategies directed to sleep problems or psychological symptoms may help to prevent the onset of musculoskeletal pain or the transition to chronicity. An effective strategy may be to perform routine screening in primary care settings for the detection of children and adolescents with sleep problems (for example by using a Pediatric Sleep Toolkit) and with psychological problems for early recognition of symptoms (Kramer & Garralda, 2000; Meltzer et al., 2014). This may be especially beneficial for children who present to primary care with musculoskeletal problems as they could benefit from education on sleep hygiene or on how to cope with pain to prevent the transition to chronicity and worsening of musculoskeletal problems (Incledon,

O'Connor, Giallo, Chalkiadis, & Palermo, 2016; Vriend & Corkum, 2011). However, to date there is a dearth of knowledge among general practitioners about paediatric sleep problems (Honaker & Meltzer, 2016; Vriend & Corkum, 2011). Therefore, increasing the awareness of general practitioners and the children' parents of the importance of paediatric sleep problems (which are currently under-recognized) and of the potential consequences for the musculoskeletal health of children and adolescents may be needed (Honaker & Meltzer, 2016; Meltzer et al., 2010; Vriend & Corkum, 2011). Potential interventions for sleep problems include pharmacological treatments, although this should not be the first choice of treatment due to the potential side effects and the limited long-term benefits (Honaker & Meltzer, 2016; Meltzer et al., 2014; Vriend & Corkum, 2011). In addition, other potentially effective interventions for sleep problems or psychological symptoms may be delivered in primary care settings. These interventions may have a beneficial impact on both sleep problems and psychological problems, as they are reciprocally related (Campbell, Tang, et al., 2013; Coulombe et al., 2011; Pieters et al., 2014), and may further reduce the risk for musculoskeletal conditions. Potential interventions include parental management training aimed at improving the children's psychological health and behaviour as well as interventions that are targeted directly towards children and adolescents, such as cognitive-behavioural-approaches (CBT) (Kramer & Garralda, 2000; Sukhodolsky, Smith, McCauley, Ibrahim, & Piasecka, 2016). These approaches may be directed at the resolution of sleep problems, or at improving the children' coping abilities and management of pain, and at reducing or avoiding potential adverse psychological responses to pain such as pain catastrophizing, negative thoughts about pain, pain-related anxiety and fear of pain. Potential cognitive-behavioural- approaches include anger control training, problem-solving skills training, psychological desensitization for lessening the fear of pain, psychoeducation, distraction (e.g. spending time with friends and family), deep breathing and muscle relaxation, or acceptance and commitment therapy and sleep restriction (Agoston & Sieberg, 2016; Asmundson et al., 2012; Sukhodolsky et al., 2016; Vriend & Corkum, 2011). Such treatments may also be remotely delivered, for example via Internet,

although more studies are needed to confirm their effectiveness (Agoston & Sieberg, 2016; Fisher, Law, Palermo, & Eccleston, 2015). Other types of interventions may be directed at the lifestyle of adolescents, for example interventions aimed at promoting physical activity in adolescents have been shown to be effective in decreasing the levels of internalizing and externalizing symptoms (Spruit, Assink, van Vugt, van der Put, & Stams, 2016).

11.6 Key messages

- The systematic review performed within this thesis showed that sleep problems and psychological symptoms may be associated with musculoskeletal pain in children and adolescents.
- Analysis within CATS and CiPCA datasets showed that sleep problems are a risk factor for the development of more severe or chronic musculoskeletal pain conditions in children, rather than for the onset of musculoskeletal pain.
- Analysis within ALSPAC and CiPCA datasets showed that adolescents with psychological symptoms were at significantly increased likelihood of musculoskeletal pain onset, chronic musculoskeletal pain or consultation for musculoskeletal conditions.
- Effect sizes found in this study were modest and varied depending on the outcome measured. Further analysis is required using a uniform set of optimum measures to establish greater consistency in a representative sample.
- Effect modification was examined and some interesting findings were reported, however this particular analysis suffered from a lack of statistical power and further investigation is required.
- Future research should build on the findings of this thesis and test further potential pathways from sleep problems and psychological symptoms to musculoskeletal pain (e.g. Latent Growth Modelling approaches that utilise frequent assessment stages) to identify mechanisms and groups at high risk, from which intervention studies may potentially be planned to prevent the impact of musculoskeletal pain in later life.

Reflections

During my PhD I developed a range of skills that will be helpful in my future career as a researcher. Firstly, I learnt how to conduct a systematic review of the literature to summarize existing evidence on the risk factors for the onset of musculoskeletal pain in children and adolescents. Therefore, I learnt how to develop a search strategy and to critically appraise the articles during the process of selection of the studies for inclusion and exclusion within the review. Secondly, I developed research hypotheses and planned the analysis to be tested in suitable databases, which I identified in order to carry out the research. All this process also led me to the understanding of the administration processes, which are part of the research work. Thirdly, I learnt a range of statistical techniques and methods (e.g. logistic regression analysis, survival analysis, multiple imputation for missing data) when performing the analysis during my research. Fourthly, I improved my writing skills that resulted in the production of this PhD thesis and of articles that have been submitted for publication. I also experienced the disappointment resulting from my articles initially being rejected, although I learnt that perseverance always pays off in the research field. During my PhD I also found myself in situations where new unexpected problems arose, and I learnt to quickly find a solution for them. I overall feel that during my PhD I have grown both as a person and as a student, and have learnt a range of skills (both technical and soft skills) that will be helpful in my future career as a researcher.

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Appendices

Appendix I Systematic review paper

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REVIEW

Are Sleep Problems a Risk Factor for the Onset of Musculoskeletal Pain in Children and Adolescents? A Systematic Review

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Study Objectives: Musculoskeletal pain is a major burden on the society. Adults with sleep problems are at higher risk of musculoskeletal pain onset, but there is no evidence for this relationship in children and adolescents. This study aimed to systematically review prospective studies on the risk of musculoskeletal pain onset in children and adolescents with sleep problems.

Methods: Five databases (MEDLINE, PsycINFO, AMED, EMBASE, and HMIC) were systematically searched to identify prospective studies that investigated if children and adolescents (aged 6–19 years) with sleep problems are at higher risk of musculoskeletal pain onset. Included studies were assessed for study quality and a best evidence synthesis was carried out on extracted data.

Results: Thirteen prospective studies were identified. Overall, evidence indicates that sleep problems (quality, quantity, and day time tiredness) are not risk factors for musculoskeletal pain onset. Further analysis on specific body regions shows strong evidence that sleep problems are a risk factor for neck pain onset (only in girls) and that sleep problems are not a risk factor for the onset of widespread pain.

Conclusions: Overall, sleep problems are not a risk factor for musculoskeletal pain onset in children and adolescents. Increased risk was found for some specific body regions and subgroups, but the evidence base was less strong and generally inconsistent. This review found a lack of quality in research methodology compared to research in adults, and further research with improved methodology is required.

Keywords: pain, sleep, pediatrics–adolescent, pediatrics—sleep and arousal, public health, sleep hygiene, systematic review.

Statement of Significance

Musculoskeletal pain is a major burden on the society, and there is a need to identify risk factors for the onset of musculoskeletal pain. Research carried out in adults has shown a link between sleep problems and the onset of musculoskeletal pain, but evidence is lacking about this relationship in younger populations. This is the first systematic review that has summarized prospective studies on the risk between sleep problems and the onset of musculoskeletal pain in children and adolescents. Our findings show that sleep problems are not risk factors for musculoskeletal pain onset in children and adolescents, although further analysis did reveal subgroups at some increased risk. Further research is now required to understand why particular subgroups are at increased risk.

INTRODUCTION

Musculoskeletal pain is a major concern worldwide. In developed countries, the proportion of the global disability-adjusted life years due to musculoskeletal pain is 13%,[1] and musculoskeletal conditions rank first, fourth, and sixth among the top 10 diseases in terms of global years lived with disability.[2] Musculoskeletal conditions have a significant economic burden, with the mean cost of chronic pain estimated at $560–635 billion in the United States (2010 figures)[3] and 3–10% of gross domestic product in Europe in 2008.[4] Consequences of musculoskeletal pain include psychological distress, disability, limitation of activities, limitation in social participation, and burden on the family.[5,6] Individuals who experience musculoskeletal pain during adolescence are more likely to have musculoskeletal pain in adulthood.[7–10] Studies investigating the course of pain over time report that lifelong patterns of musculoskeletal pain that can appear stable and unchanging in adulthood may begin in childhood.[11,12] However, to date, research on the epidemiology of musculoskeletal conditions has focused mainly on adult populations,[11,13–15] which are likely to identify risk factors for new episodes of musculoskeletal pain (often confounded by the experience of previous pain) rather than true risk factors for the first initial onset of musculoskeletal pain. Gaining knowledge of the factors predictive of musculoskeletal pain in childhood is important, as such knowledge could provide information on potential targets for intervention to prevent or reduce risk for child musculoskeletal pain onset and potentially avert or alter the trajectory of long-term painful musculoskeletal conditions among adults. One specific area with growing research interest and evidence from research on adults with musculoskeletal pain is the role of sleep, more specifically sleep problems (quality, quantity, resulting day time tiredness), as both a risk factor and a prognostic factor.[16] Recent reviews, both in adult and in child populations, show that sleep problems are common in those with pain[16,17] and that in adults sleep problems are more likely to precede pain (risk of new episodes of pain) in contrast to pain as a predictor of sleep problems.[16] Previous systematic reviews[18–23] on risk factors for musculoskeletal pain onset in children and adolescents have been carried out but have not yet considered the potential role of sleep problems as a risk factor for musculoskeletal pain onset in these populations. The aim of this systematic review is to evaluate evidence from prospective studies that investigated if children and adolescents with sleep problems are at higher risk for the onset of musculoskeletal pain.

METHODS

Selection of the Literature

A systematic search of the literature was carried out by one reviewer (AA) with the support of another reviewer (PC). Two approaches were used to search the literature. A broad search was carried out on risk factors for musculoskeletal pain onset in general in order to retrieve articles that may report data on sleep, where sleep was not the main focus of the study. A more specific search was also carried out using appropriate sleep terms to increase specificity. Databases were searched from inception to

the November 8, 2016. The following databases were searched through the OVID and NSH HDAS interfaces: Medline, PsycINFO, Allied and Complementary Medicine Database (AMED), Excerpta Medica dataBASE (EMBASE), and Health Management Information Consortium (HMIC). A combination of key words for each database (see Appendix 1) was used to retrieve the articles. Key words were identified by the principal investigator (AA) after consulting similar systematic reviews and discussion with other reviewers (PC and KD). An additional search was employed by consulting local experts (eg, accessing and searching personal databases of senior colleagues within the Research Institute and contacting other research experts within the field of childhood musculoskeletal pain) as well as consulting previous relevant reviews in adult populations.

Inclusion/Exclusion Criteria

Studies had to report data on musculoskeletal pain presence as the outcome and use a prospective design conducted in general population, school or primary care settings, in order to retrieve results that were generalizable to the overall population. Studies had to include individuals aged 6–19 years; this age criteria was chosen, as the age of 6 has been reported to be the starting point for children to use the word "pain," and age 19 is defined by the World Health Organization as the start of adulthood.[24–26] Articles were considered regardless of the language and date of publication in order to minimize publication bias. Studies were not included if they had a sample size ≤30, as they provide unreliable risk estimates, and studies were not included if they did not report separate data on children or adolescents. Randomized controlled trials (RCTs) were excluded as their focus is on intervention not observation, and RCTs often employ more stringent selection criteria which can compromise generalizability. Studies of populations with specific diseases or conditions where pain is assessed and reported but is a result of the disease or underlying condition (eg, cancer pain) were also excluded as well as studies where translation was not possible.

Selection Process

All the titles and abstracts of articles identified through the search process were checked to include potentially relevant studies by two authors of the review team (AA and PC). The two authors randomly checked 20% of each other's assigned titles and abstract to ensure reliability; similar checks were also carried out on the full-text articles. In the case of disagreement or inconsistency between reviewers for inclusion of an article, the third reviewer (KD) was consulted and consensus achieved.

Data Extraction

Data were extracted by the first reviewer (AA) using a standardized data extraction form (Appendix 2). Random samples of 20% of the full texts were cross-checked by the second reviewer (PC) in order to assess consistency in the extraction process, and any disagreements were resolved through discussion and consultation with the third reviewer (KD).

Quality Assessment

The assessment of study quality was carried out using a structured assessment tool. This tool was chosen based on previous systematic reviews with a similar focus to this current review (prospective studies, focus on musculoskeletal pain as outcome[27,28]). The tool reports on 15 items relative to both internal and external validity.[27,28] Each item was assessed to check if the criteria was met or not and a score was given (Table 1). This enabled the classification of articles according to methodological quality and to weigh the results of the studies (best evidence synthesis). Each item was scored positive (+) if present and a point awarded, negative (–) if absent (no point was given), or (na) if not applicable (no point was given). It follows that the highest possible score was 15. For ease of interpretation, the quality of the articles was rated in three categories: "high" (11–15 items); "moderate" (6–10 items), and "low" (1–5 or no items).

Analysis of Risk

For each finding, three possible effects were reported: significant effect (+, if significant effect reported), no effect (x, no significant effect present), mixed (#, where significant and nonsignificant effects are reported for the same body site, eg, stratified analysis on gender where an effect is reported for males but not females or different levels of exposure, eg, mixed findings from low, medium, and high levels of sleep problems). Each effect was counted within an overall assessment of risk on onset of musculoskeletal pain (ie, all findings from all body sites). Secondary analysis was carried out stratified by body pain sites reported (back pain, neck pain, shoulder pain, general musculoskeletal pain, and widespread pain). A level of evidence approach was used for the analysis (see Table 2) where the combined evidence is assessed in terms of the direction of effect and the quality of each individual study.[29,30] The levels of evidence analysis applies greater weighting to those findings of high quality. As Table 2 outlines, strength of evidence is determined by the consistency of direction of findings and study quality. Evidence of risk was explored across all body sites to

Table 1—Quality assessment checklist.

Item
A. Clearly defined study objective
B. Appropriate design for study question
C. Inclusion and exclusion criteria clear and appropriate
D. Representative sample (and comparison)
E. Sample size calculation presented
F. Appropriate selection of outcome
G. Appropriate measurement of outcome
H. Standardized collection of data
I. Adequate length of follow-up for research question
J. Baseline participation >70% (all groups)
K. Losses and dropouts <20%
L. Adequate description of losses and completers
M. Appropriate analysis of outcomes measured
N. Numerical description of important outcomes given
O. Adjusted and unadjusted calculations provided (with confidence interval if appropriate)

give an overall estimation of consistency and then for each body site in turn. The risk for the onset of musculoskeletal pain was reported using definitive categories of sleep problems retrieved from the review data (sleep quality, sleep quantity, and day time tiredness). Information on effect size (eg, odds ratio and relative risk) was reported if presented in the results of each article.

RESULTS

Study Selection

The broad electronic search (all risk factors regardless of type) yielded a total of 35 167 references. After screening of titles and abstracts, 156 full-text articles were assessed for eligibility, of which 145 were excluded because they did not meet the inclusion criteria (see Appendix 3). Finally, 11 studies met the eligibility criteria and were included. The second specific search (using specific sleep terms) yielded 3065 references. After screening of titles and abstracts, 10 full-text articles were assessed for eligibility, of which eight were excluded because they did not meet the inclusion criteria and two articles selected for inclusion. These two searches led to the inclusion of 13 articles overall (Figure 1). Seven articles were identified in both searches, four were identified from the broad search, and two within the specific sleep term search.

Quality and Characteristics of the Studies

Table 3 describes the quality and characteristics of the included studies. Overall, 8 (62%) articles of 13 were defined as high quality and 5 (38%) as medium quality; no studies were included in the low-quality criteria. Included studies were from six different countries with a total population of 18 888 (range from 191 to 4161 individuals). The samples were recruited from schools or school settings in six studies, from the general population in six articles, and from a primary care/hospital interface setting in one study. Some cohorts were reported in more

Table 2—Levels of evidence for association of risk factors for musculoskeletal pain onset in children and adolescents.

Level of evidence	
Strong	Consistent findings (≥75%) in studies of high quality, at least two studies
Moderate	Consistent findings (≥75%) in studies of high and medium/low quality with at least one study of high quality in the direction of consistent findings
Weak	Findings of only one study of high quality or consistent findings (≥75%) in studies of medium/low quality
Inconclusive	Findings in less than three studies of medium/low quality, or inconsistent findings (regardless of quality)

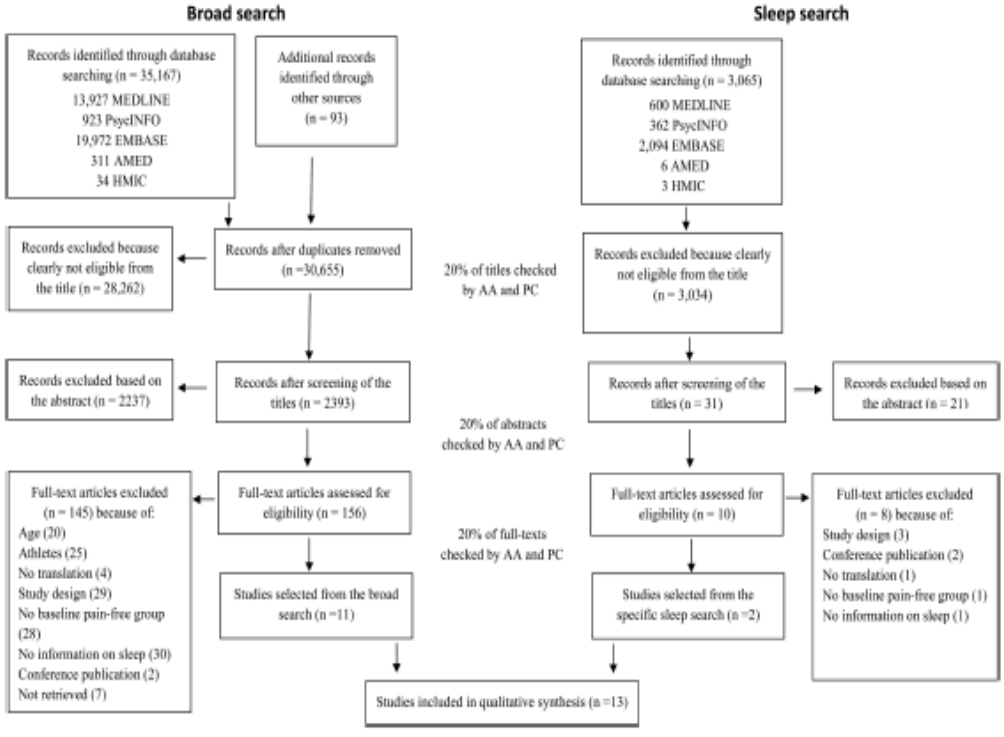

Figure 1—Flowchart showing the process of selection of the studies in the two searches.

Table 3—Articles reporting on the risk for the onset of musculoskeletal pain in children and adolescents with sleep problems.

Author (year)	Country	Setting	Sample size (baseline)	Age (baseline), years	Length of follow-up	Drop-out rate	Quality (Score)
Auvinen et al. (2010)[31]	Finland	Birth Cohort	1773	15–16	2 years	N/A	High (11)
Brattberg (1994)[7]	Sweden	School	597	8–13	2 years	21.1%	Medium (9)
El-Metwally et al. (2007)[37]	Finland	School	1192	9.8–11.8	1 year	6.6%	High (12)
Harrison et al. (2014)[38]	England	Birth Cohort	2493	15	2 years	N/A	High (11)
Incledon et al. (2016)[41]	Australia	General population	4161	10-11	2 years	8.2%	Medium (10)
Jones et al., 2003[42]	England	General population	1440	11-14	1 year	12%	High (12)
Jussila et al. (2014)[32]	Finland	Birth Cohort	1773	16	2 years	N/A	High (11)
Lewandoski Holley et al. (2016)[40]	USA	Academic medical center	191	10–17	4 months	N/A	Medium (9)
Mikkelsson et al. (2008)[36]	Finland	School	1756	9.8–11.8	4 years	3%	High (12)
Mikkelsson et al. (1999)[35]	Finland	School	363	9.8–11.8	1 year	10%	High (11)
Paananen et al. (2010)[33]	Finland	Birth Cohort	1594	16	2 years	N/A	Medium (9)
Ståhl et al. (2008)[34]	Finland	School	1268	9.8–11.8	4 years	38.5%	High (13)
Szpalski et al. (2002)[39]	Belgium	School	287	9	2 years	N/A	Medium (8)

Abbreviation: N/A, Analysis on subjects who responded to both baseline and follow-up questionnaires.

than one article. Three studies were drawn from the Northern Finland Birth Cohort,[31–33] while four studies were drawn from a cohort in southern Finland.[34–37]

Evidence

Sleep Quality

Overall, 10 findings were reported, with 2 findings[34,38] showing that children with poor sleep quality are significantly at higher risk (both findings in the direction of poor sleep quality predictive of musculoskeletal pain), one finding[31] showing mixed evidence, and seven findings[31,35–37,39,40] showing no significant higher risk (please see Table 4 for a full description of effect sizes). When considering only high-quality evidence, similar rates are found (high-quality findings; two studies[34,38] reported significant higher risk, one study[31] mixed, and five findings[31,35–37] no higher risk). Overall, this indicates a trend toward strong evidence of no effect of poor sleep quality as a risk factor for the onset of musculoskeletal pain. Further inspection at each body site was carried out. For back pain onset, there were two nonsignificant effect, one from a medium-quality study[39] and one from a high-quality study,[31] resulting in a moderate evidence of no higher risk. For neck pain onset, the findings shows one mixed[31] and one significant effect,[34] resulting in strong evidence that girls with low sleep quality are at higher risk of neck pain onset but inconsistent evidence of risk in boys. Shoulder pain shows a nonsignificant effect in one high-quality study,[31] indicating weak evidence of no higher risk. For general musculoskeletal pain onset, there are two findings (one high quality). Both report no significant effects. In the high-quality study,[37] no one of the ORs provided was significant, and the medium-quality study[40] reported no statistically significant difference in the sleep quality score between children with new-onset pain and healthy children. This resulted in a moderate evidence of no risk of musculoskeletal pain onset in children with low sleep quality. For widespread pain onset, three high-quality findings are reported. While one study[38] reported significant findings, two studies[35,36] reported no significant effects indicating inconclusive evidence.

Sleep Quantity

Overall, eight findings were reported with two of those findings[7,41] (medium quality) showing a significant effect (both findings in the direction of low sleep quantity predictive of musculoskeletal pain), two[31,32] (high quality) showing mixed evidence, and four[31,33,38] (one medium and three high quality) showing no significant effect (please see Table 5 for a full description of effect sizes). This indicates inconsistent evidence, although considering only high-quality evidence suggests a trend toward no higher risk for musculoskeletal pain onset in children with low sleep quantity. Inspection at each body site revealed that for back pain onset, two study findings, one medium quality,[7] indicating a significant effect and one high quality[31] reporting a mixed effect. Closer inspection of this mixed result showed no higher risk in girls but higher risk in boys (albeit within only one sleep quantity category). Overall, this indicates inconsistent evidence for the effect of sleep quantity on back pain onset. Both neck pain onset and shoulder pain onset show no significant higher risk from one

Table 4—Risk for the onset of musculoskeletal pain[a].

Baseline factor	Outcome				
	Back pain	Neck pain	Shoulder pain	Musculoskeletal pain	Widespread pain
Sleep quality					
+		**34** Boys: OR: 1.25, 95% CI 1.11 to 1.41 Girls: OR: 1.14, 95% CI 1.03 to 1.26			**38** Hypersomnolence problems: OR: 2.76, 95% CI 1.05 to 7.25 Waking up ≥ 2-3 times a night: OR: 2.13, 95% CI 1.22 to 3.74
#		**31** Boys: OR: 0.83, 95% CI 0.48 to 1.44 Girls: OR: 1.67, 95% CI 1.00 to 2.78			
x	39 (estimate not provided in multivariate analysis) **31** Boys: OR: 1.14, 95% CI 0.66 to 2.00 Girls: OR: 1.48, 95% CI 0.97 to 2.24		**31** Boys: OR: 1.32, 95% CI 0.77 to 2.25 Girls: OR: 1.47, 95% CI 0.91 to 2.39	**37** Non-traumatic: - Difficulty falling asleep: OR: 1.48, 95% CI 0.99 to 2.23 - Waking up during nights: OR: 1.31, 95% CI 0.82 to 2.08 Traumatic: - Difficulty falling asleep: OR: 1.47, 95% CI 0.67 to 3.24 - Waking up during nights: OR: 1.64, 95% CI 0.70 to 3.85 40 Sleep quality score - Children with new-onset pain: Mean 3.96, SD 0.58 - Healthy children: Mean 4.13, SD 0.69	**35** Higher sleep score: OR: 1.23, 95% CI 0.98 to 1.54 **36** Difficulty falling asleep: OR: 1.2, 95% CI 0.9 to 1.7 Waking up during nights: OR: 1.1, 95% CI 0.8 to 1.6

+, significant effect; x, no effect; #, mixed effect OR, Odds Ratios, All the Odds Ratios provided are for adjusted analysis; 95% CI, 95% Confidence Interval.
[a] Numbers in the table represent the study reference numbers. Numbers in bold represent the studies of high quality.

high-quality study[31] indicating weak evidence of no higher risk. Two findings are reported for general musculoskeletal pain onset, with one high-quality study[32] reporting mixed findings and one medium-quality[41] study reporting a significant effect. This indicates a moderate evidence of higher risk in boys but inconsistent evidence in girls. For widespread pain, two studies (one high quality[38] and one medium quality[33]) report no significant higher risk, indicating moderate evidence that sleep quantity is not a risk factor for onset of widespread pain.

Daytime Tiredness

Of eight findings, two[34,37] (high quality) report a significant effect (both findings in the direction of daytime tiredness predictive of musculoskeletal pain), three[31] (high quality) report mixed effects, and three[36,39,42] (two high quality) report no significant effect indicating inconsistency, with a similar conclusion if only high-quality evidence is considered (please see Table 6 for a full description of effect sizes). Examination by body site revealed one high-quality[31] study reporting mixed evidence and one medium-quality[39] study reporting no effect for back pain onset. This indicates a moderate evidence that boys with daytime tiredness are not at higher risk of back pain onset but an inconsistent evidence in girls. Similarly, for neck pain, one high-quality study[34] found a significant effect and one high-quality study[31] reported mixed effects. This indicates strong evidence that girls with daytime tiredness are at higher risk for neck pain onset but inconsistent evidence in boys. For widespread pain, two findings[36,42] (high quality) report that children with day time tiredness are not at higher risk for widespread pain onset, indicating strong evidence of no risk. Evidence is inconclusive for shoulder pain, as there is only one (high quality) mixed finding.[31] For general musculoskeletal pain onset, there is weak evidence (one high quality finding[37]) that children with day time tiredness are at higher risk of onset.

DISCUSSION

This is the first systematic review that has synthesized evidence on the risk for the onset of musculoskeletal pain in children

Table 5—Risk for the onset of musculoskeletal pain[a].

Baseline factor	Outcome				
	Back pain	Neck pain	Shoulder pain	Musculoskeletal pain	Widespread pain
Sleep quantity					
+	7 Those with trouble getting enough sleep had more pain but no estimate was reported			41 Sleep deficiency: OR: 1.86, 95% CI 1.16 to 2.97	
#	**31** Sleeping time in girls: - 7 hour or less a day: OR: 1.45, 95% CI 0.96 to 2.19 – 9/10 hours a day: OR: 0.86, 95% CI 0.58 to 1.27 - 10 hours or more a day: OR: 0.87, 95% CI 0.52 to 1.47 Sleeping time in boys: - 7 hours or less a day: OR: 1.42, 95% CI 0.86 to 2.33 - 9/10 hours a day: OR: 1.59, 95% CI 1.03 to 2.44 - 10 hours or more a day: OR: 0.93, 95% CI 0.56 to 1.54			**32** Shorter sleeping time and probability to have pain: - Boys p = .001 - Girls, p = .100	
x		**31** Sleeping time in girls: - 7 hour or less a day: OR: 1.44, 95% CI 0.90 to 2.32 - 9/10 hours a day: OR: 1.02, 95% CI 0.66 to 1.57 - 10 hours or more a day: OR: 1.55, 95% CI 0.84 to 2.87 Sleeping time in boys: - 7 hour or less a day: OR: 1.40, 95% CI 0.86 to 2.30 - 9/10 hours a day: OR: 0.98, 95% CI 0.64 to 1.50 - 10 hours or more a day: OR: 0.86, 95% CI 0.52 to 1.44	**31** Sleeping time in girls: - 7 hour or less a day: OR: 1.36, 95% CI 0.85 to 2.17 - 9/10 hours a day: OR: 1.17, 95% CI 0.76 to 1.81 - 10 hours or more a day: OR: 1.08, 95% CI 0.61 to 1.93 Sleeping time in boys: - 7 hour or less a day: OR: 1.05, 95% CI 0.66 to 1.69 - 9/10 hours a day: OR: 0.84, 95% CI 0.55 to 1.29 - 10 hours or more a day: OR: 0.85, 95% CI 0.51 to 1.39		33 Sleeping time in boys: - < 7 hours a day: OR: 1.15, 95% CI 0.66 to 1.98 - ≥ 10 hours a day: OR: 1.14, 95% CI 0.69 to 1.88 Sleeping time in girls: - < 7 hours a day: OR: 0.93, 95% CI 0.54 to 1.61 - ≥ 10 hours a day: OR: 1.12, 95% CI 0.56 to 2.27 **38** Rarely/never enough sleep: OR: 1.20, 95% CI 0.55 to 2.62

Abbreviations: +, significant effect; x, no effect; #, mixed effect; OR, Odds Ratios. All the Odds Ratios provided are for adjusted analysis; 95% CI, 95% Confidence Interval.

[a] Numbers in the table represent the study reference numbers. Numbers in bold represent the studies of high quality.

Table 6—Risk for the onset of musculoskeletal pain[a].

Baseline factor	Outcome				
	Back pain	Neck pain	Shoulder pain	Musculoskeletal pain	Widespread pain
Day-time tiredness					
+		**34** Boys: OR: 1.25, 95% CI 1.11 to 1.41 Girls: OR: 1.14, 95% CI 1.03 to 1.26		**37** Non-traumatic: OR: 1.53, 95% CI 1.03, 2.26 Traumatic: OR: 2.97, 95% CI 1.41 to 6.26	
#	**31** Boys: - often too tired: OR: 1.46, 95% CI 0.61 to 3.45 - sometimes too tired: OR: 1.16, 95% CI 0.80 to 1.68 Girls: - often too tired OR: 2.42, 95% CI 1.24 to 4.71 - sometimes too tired: OR: 1.32, 95% CI 0.93 to 1.85	**31** Boys: - often too tired: OR 1.15, 95% CI 0.48 to 2.74 - sometimes too tired OR 1.28, 95% CI 0.88 to 1.85 Girls: - often too tired: OR 3.92, 95% CI 1.55 to 9.90 - sometimes too tired: OR 1.46, 95% CI 1.00 to 2.13	**31** Boys: - often too tired: OR: 1.36, 95% CI 0.60 to 3.13 - sometimes too tired: OR: 1.57, 95% CI 1.10 to 2.25 Girls: - often too tired: OR: 1.78, 95% CI 0.83 to 3.83 - sometimes too tired: OR: 1.21, 95% CI 0.83 to 1.76		
x	39 (estimate not provided in multivariate analysis)				**36** OR: 1.1, 95% CI 0.8 to 1.6 **42** OR: 1.41, 95% CI 0.84 to 2.40

Abbreviations: +, significant effect; x, no effect; #, mixed effect; OR, Odds Ratios. All the Odds Ratios provided are for adjusted analysis; 95% CI, 95% Confidence Interval.

[a] Numbers in the table represent the study reference numbers. Numbers in bold represent the studies of high quality.

and adolescents with sleep problems (quality and quantity) or daytime tiredness. The main finding of this review is that sleep quality, sleep quantity, and daytime tiredness are not risk factors for the onset of musculoskeletal pain in children or adolescents. Further analysis at each body site revealed similar trends of no effect or inconsistent results, although some mixed findings suggest some risk for particular body regions (eg, neck pain onset) dependent on gender.

Comparison With Existing Literature

Findings from this review are in contrast with those reported in adult populations. A recent review[16] has investigated the prospective and experimental research on the relationship between sleep and pain. Within that, review findings from two prospective studies conducted in adult populations are reported, and both studies show that individuals with sleep problems were at higher risk of developing fibromyalgia[43] or chronic (both widespread and regional) musculoskeletal pain[44] at follow-up. The results from adult population studies oppose the findings within this current review, which suggest no or little risk for children and adolescents. Examination of the literature on adults does shows that most reported evidence of risk are for chronic musculoskeletal outcomes or for widespread pain, which is suggestive of a higher level of pain severity or severity threshold (ie, chronic pain samples and those with widespread pain often report higher levels of pain severity[45]), and second outcomes such as chronic pain may include populations where pain was present before the measurement of outcome and therefore potentially enable a reciprocal relationship between sleep and pain.[46,47] Taking a wider epidemiological view, there is estimations of 75–80% lifetime prevalence of musculoskeletal pain in adult populations,[48] and therefore it may be difficult to assert within those populations that this would be their first ever experience of musculoskeletal pain, as they may have experienced musculoskeletal pain before. If this is the case, the well-reported reciprocal effects between sleep and pain (once both are established) may partly explain effects within adults.[16,48] For example, evidence suggests that potential changes to dopaminergic and opiodergic signaling can occur in the presence of sleep and pain, which may then influence subsequent pain episodes.[16] This potential difference in case mix may explain the difference in the results found in children and adolescents (who generally would be less likely than adults to have already experienced musculoskeletal pain). Prospective studies carried out within adult populations have shown that individuals with sleep problems were still at higher risk for the onset of chronic

musculoskeletal pain after adjustment for baseline pain.[5,49] This may suggest that previous reciprocal relationships between sleep and pain are not factors in new onset but perhaps factors for persistence. This viewpoint on the influence of sleep on pain persistence highlights an important limitation within the current literature in this area, namely, the need to measure the relationship between pain and sleep more frequently. Findings of adult research, investigating the day-to-day relationship between sleep and pain, show that sleep is a reliable predictor of subsequent pain, but presleep pain has less of an effect and that there is variation in pain severity on a day-to-day basis.[50] At present, it is not clear whether we can understand the relationships between pain and sleep in children and adolescents in a "like for like" comparison to findings in the adult literature, until similar sophisticated measurement and study quality is obtained (eg, frequent measurement stages, objective measures such as polysomnography, actigraphy,[51] or sleep diaries[50]).

Analysis of Study Heterogeneity

The overall trend found within this review is that there is no effect of sleep problems on musculoskeletal pain onset. However, some inconsistencies and opposing results are reported when examining different pain sites, and heterogeneity may explain some of this variation. Different measures were used for both exposure and outcome between studies (See Table 7), and this made comparison between studies complex. For example, in one[34] of the two studies that reported a significant finding between low sleep quality and daytime tiredness and the onset of neck pain, sleep quality and daytime tiredness were part of a variable that also included other physical and psychological symptoms. Therefore, the effect reported may also be attributable to the other symptoms included in the variable, and this limits the strength of this finding somewhat. Also, in one[41] of the two studies that provided moderate evidence of risk for the onset of general musculoskeletal pain in children with low sleep quantity, the measure of pain also included abdominal pain, headaches and/or pains in other parts of the body occurring at least weekly. This highlights the difficulty in the ability to distinguish musculoskeletal pain from other type of pain with this measure, which may have potentially influenced the reported evidence of risk.

Strengths and Weaknesses of the Study

Five databases were systematically searched without any language or time restrictions to encompass the widest range of literature. Also, the use of a broad search (nonrestrictive search without specific sleep search terms) and a more specific search enabled the identification of additional literature (four articles were identified in the broad search, two in the specific search, and seven in both searches). Another strength is the focus solely on studies employing prospective designs. This produces the best evidence, as it provides estimates of incidence, enables the assessment of temporal sequence between exposure and the outcome, and avoids recall bias that may occur with retrospective or case–control studies.[52] The review also incorporated the use of levels of evidence, basing conclusions not only on results presented but also on the quality of studies to account for the potential effect of bias. However, it is recognized that use of total score for study quality can be overly blunt, and does not account for key elements of bias within each study (eg, response rate), and we have attempted to overcome these issues where possible. For example, two studies had a dropout rate of over 20%, which may raise the possibility of bias from loss to follow-up. However, in one of these studies, sensitivity analyses were carried out to compare the baseline characteristics of the participants who dropped out the study to those who completed the study and results commented.[34] There are some limitations. First, no one study used objective measures of sleep (eg, polysomnography and actigraphy),[51] which may have provided more accurate results, and the variation in definitions used for both the exposure and musculoskeletal pain outcome in the included studies limited the comparison and analysis. Second, some flaws were present in the design of the studies. In one study,[38] pain was only measured at follow-up, thus limiting the inference of causality. In another study,[40] the group with new-onset musculoskeletal pain consisted of children presenting to emergency medicine, and this may have represented a more severe cohort. Third, identified studies were predominantly from developed countries (ie, no studies from South America, Africa, or Asia were retrieved), so the results may be not generalizable to different social/cultural environments. Studies that do not find evidence of risk and papers in a language other than English are less likely to be published or be within the databases searched (gray literature). While we translated three papers produced in German, which did not meet the inclusion criteria, we were unable to translate six additional papers (one paper in Swedish, one paper in Norwegian, one paper in Czech, one paper in Finnish, and two papers in Chinese) and so they were excluded. Although the reference lists of the included papers were searched, other alternative sources such as registers for unpublished studies and PhD thesis were not explored. Therefore, publication bias is a possible limitation (although no language restrictions were applied). Finally, due to the heterogeneity in both exposure and outcome measure (see Table 7), it was not possible to perform a meta-analysis, which would have provided an accurate estimate of the effect of sleep problems on the onset of musculoskeletal pain.

Implications for Clinical Practice and Future Research

This systematic review provides evidence that children and adolescents with sleep problems are not at higher risk for the onset of musculoskeletal pain. These findings are opposed to the findings within the adult population literature, and this article argues that a potential reason is that in adults there may be an already established sleep–pain relationship due to prior experience of pain or that alternatively such findings are due to the measures and populations used within the studies. Therefore, while this article would not recommend routine screenings of sleep problems in children/adolescents as a way of identifying at risk individuals, it may be important to monitor children with both pain and sleep problems as once both are established may make treatment more challenging. This review does report some subgroups more at risk of developing musculoskeletal pain (eg, girls with low sleep quality and daytime tiredness more at risk of the onset of neck pain). This paper recommends more research on at risk subgroups to understand potential mechanisms and this would lay the foundation for designing interventions on the direct treatment of sleep problems to avert musculoskeletal outcomes. For example, there may be a place

Table 7—Definitions of exposure and outcome used in the studies.

Author (year)	Exposure	Outcome
Auvinen et al. (2010)[31]	Poor sleep quality: having sleeping problems "sometimes or often" (reference category was "not at all"), Daytime tiredness: being too tired "often" or "sometimes" (reference category was "never")	Any aches or pain in the last 6 months in the following areas: -Neck or occipital area -Shoulders -Low back
Brattberg (1994)[7]	Sleep quantity	Back pain often
El-Metwally et al. (2007)[37]	Sleep quality: Difficulties falling asleep and waking up during the night present at least once a week during the preceding 3 months	Pain in any musculoskeletal locations with a frequency of at least once a week during the previous 3 months
Harrison et al. (2014)[38]	Sleep quality: Frequency of problems with hypersomnolence and waking up during the night Sleep quantity (enough sleep): Always (Reference) Usually Sometimes Rarely/Never	Pain on both sides of the body, above and below the waist and in the axial skeleton that had been present for more than 3 months
Incledon et al. (2016)[41]	Sleep deficiency: "not quite" or "not nearly enough sleep" in the last month (reference categories: "plenty" or "just enough")	Abdominal pain, headaches, and/or pains in other parts of the body occurring at least weekly
Jones et al. (2003)[42]	Daytime tiredness measured with a visual analogue scale (VAS)	ACR definition of criteria for fibromyalgia to define widespread pain
Jussila et al. (2014)[32]	Sleeping time, hours a day	Any aches or pain in the last 6 months in the following areas: -Neck or occipital area -Shoulders -Low back -Elbows -Wrists -Knees -Ankle/foot area
Lewandoski Holley et al. (2016)[40]	Sleep quality: Adolescent Sleep–Wake Scale (total score was used in the analysis)	New-onset musculoskeletal pain: children presenting to an orthopedic clinic or emergency medicine
Mikkelsson et al. (2008)[36]	Daytime tiredness, difficulty falling asleep and waking up during night at least once a week for the preceding 3 months	ACR definition of criteria for fibromyalgia to define widespread pain
Mikkelsson et al. (1999)[26]	Daytime tiredness, difficulty falling asleep and waking up during night at least once a week for the preceding 3 months	Pain above and below the waist, on both sides of the body and in the axial skeleton at least once a week during the preceding 3 months
Paananen et al. (2010)[33]	Sleeping time: 7 hours a day or less 8–9 hours a day (Reference) 10 or more hours a day	Any aches or pain in the last 6 months in more than one of the following areas: -Neck or occipital area -Shoulders -Low back -Elbows -Wrists -Knees -Ankle/foot area
Ståhl et al. (2008)[34]	Physical and psychological symptoms (abdominal pain, headache, depressive mood, daytime tiredness, difficulty falling asleep, waking up during the night) at least once a week	Neck pain at least once a week
Szpalski et al. (2002)[39]	Quality of sleep, quality of falling asleep and being tired without any reason measured with a visual analogue scale (VAS)	Back pain prevalence and disability of back pain

for routine sleep screenings in some subgroups of children who could benefit from education on sleep hygiene to reduce risk of musculoskeletal pain problems.[41] Future research recommendations are a need to explore potential risk in subgroups of children and adolescents and the need for more objective measures (eg, polysomnography and actigraphy)[51] to be used in future prospective studies on sleep and musculoskeletal pain onset in children. Also, given the potential daily variation in pain,[50] there may be scope to perform longitudinal studies in children and adolescents using both sleep and pain diaries.

CONCLUSION

In conclusion, this systematic review has shown no or little risk of musculoskeletal pain onset preceded by sleep problems in children and adolescents, although some subgroups at heightened risk were identified. Given the heterogeneity of the measures used among studies, the use of more objective measures for both sleep and musculoskeletal pain is recommended. Future research exploring the daily variation in the relationship between sleep and pain may help to shed further light on the effect of sleep problems on the onset of musculoskeletal pain in children.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at SLEEP online.

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DISCLOSURE STATEMENT

None declared.

Appendix II Full search strategy used for the systematic review

Search strategy used in AMED		
	Searches	**Results**
1	exp adolescent/	3190
2	exp child/	14169
3	child$.ti,ab.	15468
4	youth.ti,ab.	683
5	schools/	633
6	pediatrics/	409
7	pediatric$.ti,ab.	1911
8	paediatric$.ti,ab.	739
9	young$.ti,ab.	6700
10	boy$.ti,ab.	1214
11	girl$.ti,ab.	1038
12	puberty/	30
13	pubert$.ti,ab.	108
14	pubescent$.ti,ab.	19
15	prepubert$.ti,ab.	62
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	26487
17	incidence.ti,ab.	3181
18	prevalence.ti,ab.	3533
19	epidemiology/	3081
20	epidemiolog$.ti,ab.	1559
21	risk factors/	1194
22	(risk adj3 factor$).ti,ab.	3206
23	(Risk adj3 assessment).ti,ab.	403
24	(Risk adj3 score).ti,ab.	67
25	(Risk adj3 reduction).ti,ab.	213
26	(Risk adj3 increase).ti,ab.	334
27	(Risk adj3 evaluation).ti,ab.	68
28	prevention/	11211
29	cohort studies/	646
30	(cohort adj3 stud$).ti,ab.	2012

31	prospective studies/	774
32	follow up studies/	1182
33	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	25032
34	pain/	10426
35	exp back/	625
36	neck/	623
37	shoulder/	1171
38	exp spine/	4898
39	low back pain/	3934
40	(chronic adj3 pain).ti,ab.	4035
41	musculoskeletal pain/	68
42	(spinal adj3 pain).ti,ab.	491
43	(widespread adj3 pain).ti,ab.	229
44	(multisite adj3 pain).ti,ab.	3
45	(regional adj3 pain).ti,ab.	218
46	(juvenile adj3 fibromyalgia).ti,ab.	15
47	35 or 36 or 37 or 38	6987
48	34 and 47	656
49	34 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 48	15961
50	**16 and 33 and 49**	**313**

Search strategy used in EMBASE		
	Searches	**Results**
1	adolescent/	1239535
2	adolescen$.ti,ab.	226385
3	child/	1310917
4	child$.ti,ab.	1255687
5	youth$.ti,ab.	50219
6	exp school/	234676
7	school$.ti,ab.	240668
8	pediatrics/	59820
9	pediatric$.ti,ab.	266869
10	paediatric$.ti,ab.	65690
11	young$.ti,ab.	580850
12	boy/	18807
13	boy$.ti,ab.	146319
14	girl/	19151
15	girl$.ti,ab.	139888
16	exp puberty/	32211
17	pubert$.ti,ab.	36310
18	pubescent$.ti,ab.	775
19	prepubert$.ti,ab.	13399
20	juvenile/	21829
21	juvenile$.ti,ab.	71151
22	teenage$.ti,ab.	20081
23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	3350694
24	incidence/	216388
25	inciden$.ti,ab.	789799
26	risk factor/	637208
27	(risk adj3 factor$).ti,ab.	499560
28	(Risk adj3 score).ti,ab.	16366
29	(cohort adj3 stud$).ti,ab.	145670
30	prospective study/	266132
31	(prospective adj3 stud$).ti,ab.	301587

32	follow up/	851350
33	(Follow up adj3 stud$).ti,ab.	66342
34	onset.ti,ab.	452094
35	predictor variable/	15145
36	predict$.ti,ab.	1211270
37	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	3820559
38	pain/	214428
39	back/	8236
40	knee/	44899
41	exp neck/	39941
42	hand/	24738
43	shoulder/	22849
44	hip/	35075
45	foot/	18239
46	elbow/	13905
47	arm/	62886
48	forearm/	18333
49	wrist/	18233
50	leg/	61490
51	ankle/	20722
52	spine/	31407
53	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	349814
54	38 and 53	22402
55	(back adj3 pain).ti,ab.	43352
56	(knee adj3 pain).ti,ab.	7979
57	(neck adj3 pain).ti,ab.	9722
58	(hand adj3 pain).ti,ab.	1437
59	(shoulder adj3 pain).ti,ab.	6709
60	(hip adj3 pain).ti,ab.	4378
61	(foot adj3 pain).ti,ab.	1719
62	(elbow adj3 pain).ti,ab.	793
63	(arm adj3 pain).ti,ab.	1893
64	(forearm adj3 pain).ti,ab.	362

65	(wrist adj3 pain).ti,ab.	1511
66	(leg adj3 pain).ti,ab.	5371
67	(ankle adj3 pain).ti,ab.	1314
68	(spinal adj3 pain).ti,ab.	4546
69	backache/	35058
70	backache.ti,ab.	2403
71	low back pain/	37028
72	(low back adj3 pain).ti,ab.	23432
73	chronic pain/	35474
74	(chronic adj3 pain).ti,ab.	54095
75	musculoskeletal pain/	5377
76	(musculoskeletal adj3 pain).ti,ab.	5348
77	(widespread adj3 pain).ti,ab.	2070
78	(multisite adj3 pain).ti,ab.	46
79	(regional adj3 pain).ti,ab.	4406
80	(juvenile adj3 fibromyalgia).ti,ab.	107
81	55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80	172807
82	38 or 54 or 81	353428
83	**23 and 37 and 82**	**19972**

Search strategy used in HMIC		
	Searches	**Results**
1	adolescen$.ti,ab.	3772
2	exp children/	18871
3	child$.ti,ab.	29219
4	youth$.ti,ab.	2005
5	exp schools/	1211
6	school$.ti,ab.	8174
7	pediatric$.ti,ab.	256
8	exp paediatrics/	584
9	paediatric$.ti,ab.	2342
10	exp young people/	10095
11	young$.ti,ab.	12284
12	boys/	231
13	boy$.ti,ab.	1146
14	girls/	345
15	girl$.ti,ab.	1255
16	exp puberty/	25
17	pubert$.ti,ab.	84
18	prepubert$.ti,ab.	5
19	juvenile$.ti,ab.	559
20	teenage$.ti,ab.	1391
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	48472
22	"incidence of disease"/	810
23	inciden$.ti,ab.	8164
24	exp risk factors/	4275
25	(risk adj3 factor$).ti,ab.	5062
26	(Risk adj3 score).ti,ab.	166
27	cohort studies/	966
28	(cohort adj3 stud$).ti,ab.	3468
29	prospective studies/	189
30	(prospective adj3 stud$).ti,ab.	2704
31	follow up studies/	191

32	(Follow up adj3 stud$).ti,ab.	828
33	onset.ti,ab.	1338
34	predict$.ti,ab.	7558
35	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34	25224
36	pain/	386
37	back pain/	314
38	knees/	42
39	neck/	89
40	exp hands/	121
41	shoulders/	20
42	exp hip joints/	143
43	exp feet/	38
44	elbows/	3
45	arms/	11
46	exp wrists/	17
47	legs/	88
48	ankles/	7
49	exp spinal column/	34
50	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	570
51	36 and 50	21
52	(back adj3 pain).ti,ab.	463
53	(knee adj3 pain).ti,ab.	23
54	(neck adj3 pain).ti,ab.	37
55	(hand adj3 pain).ti,ab.	7
56	(shoulder adj3 pain).ti,ab.	27
57	(hip adj3 pain).ti,ab.	11
58	(foot adj3 pain).ti,ab.	1
59	(elbow adj3 pain).ti,ab.	3
60	(arm adj3 pain).ti,ab.	15
61	(forearm adj3 pain).ti,ab.	1
62	(wrist adj3 pain).ti,ab.	9
63	(leg adj3 pain).ti,ab.	7
64	(ankle adj3 pain).ti,ab.	2

65	(spinal adj3 pain).ti,ab.	8
66	backache.ti,ab.	25
67	low back pain/	111
68	(low back adj3 pain).ti,ab.	209
69	(chronic adj3 pain).ti,ab.	284
70	(musculoskeletal adj3 pain).ti,ab.	39
71	(widespread adj3 pain).ti,ab.	7
72	(regional adj3 pain).ti,ab.	10
73	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	813
74	36 or 37 or 51 or 73	1157
75	**21 and 35 and 74**	**34**

Search strategy used in MEDLINE		
	Searches	**Results**
1	Incidence/	185780
2	risk factors/	600969
3	(risk adj3 factor$).ti,ab.	386758
4	(Risk adj3 score).ti,ab.	10136
5	exp Cohort Studies/	1438154
6	(cohort adj3 stud$).ti,ab.	116635
7	Prospective Studies/	390949
8	(prospective adj3 stud$).ti,ab.	236660
9	Follow-Up Studies/	520109
10	(Follow up adj3 stud$).ti,ab.	53020
11	onset.ti,ab.	362174
12	predict$.ti,ab.	1013981
13	inciden$.ti,ab.	627575
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	3500457
15	Adolescent/	1679899
16	adolescen$.ti,ab.	188599
17	exp Child/	1603455
18	child$.ti,ab.	1046293
19	youth.ti,ab.	38454
20	Schools/	22234
21	school$.ti,ab.	204181
22	Pediatrics/	41935
23	pediatric$.ti,ab.	193436
24	paediatric$.ti,ab.	44437
25	young$.ti,ab.	485527
26	boy$.ti,ab.	117801
27	girl$.ti,ab.	113007
28	exp Puberty/	15343
29	pubescent$.ti,ab.	622
30	pubert$.ti,ab.	29824
31	prepubert$.ti,ab.	11758
32	juvenile$.ti,ab.	61088
33	teenage$.ti,ab.	16425

34	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	3302779
35	Pain/	113662
36	exp Back/	16684
37	Knee/	11608
38	Neck/	23732
39	exp Hand/	73891
40	Shoulder/	10238
41	Hip/	10162
42	exp Foot/	42413
43	Elbow/	5808
44	Arm/	27933
45	Forearm/	14971
46	Wrist/	7057
47	Leg/	57437
48	Ankle/	7438
49	exp Spine/	112786
50	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49	368918
51	35 and 50	9518
52	(back adj3 pain).ti,ab.	32977
53	(knee adj3 pain).ti,ab.	6042
54	(neck adj3 pain).ti,ab.	7681
55	(hand adj3 pain).ti,ab.	1029
56	(shoulder adj3 pain).ti,ab.	5393
57	(hip adj3 pain).ti,ab.	3341
58	(foot adj3 pain).ti,ab.	1321
59	(elbow adj3 pain).ti,ab.	664
60	(arm adj3 pain).ti,ab.	1396
61	(forearm adj3 pain).ti,ab.	323
62	(wrist adj3 pain).ti,ab.	1310
63	(leg adj3 pain).ti,ab.	3898
64	(ankle adj3 pain).ti,ab.	1077
65	(spinal adj3 pain).ti,ab.	3465

66	backache.ti,ab.	2056
67	Low Back Pain/	14927
68	(low back adj3 pain).ti,ab.	18568
69	Chronic Pain/	4092
70	(chronic adj3 pain).ti,ab.	39909
71	Musculoskeletal Pain/	986
72	(musculoskeletal adj3 pain).ti,ab.	4020
73	(widespread adj3 pain).ti,ab.	1421
74	(multisite adj3 pain).ti,ab.	38
75	(regional adj3 pain).ti,ab.	2727
76	(juvenile adj3 fibromyalgia).ti,ab.	75
77	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76	103895
78	35 or 51 or 77	197923
79	**14 and 34 and 78**	**13927**

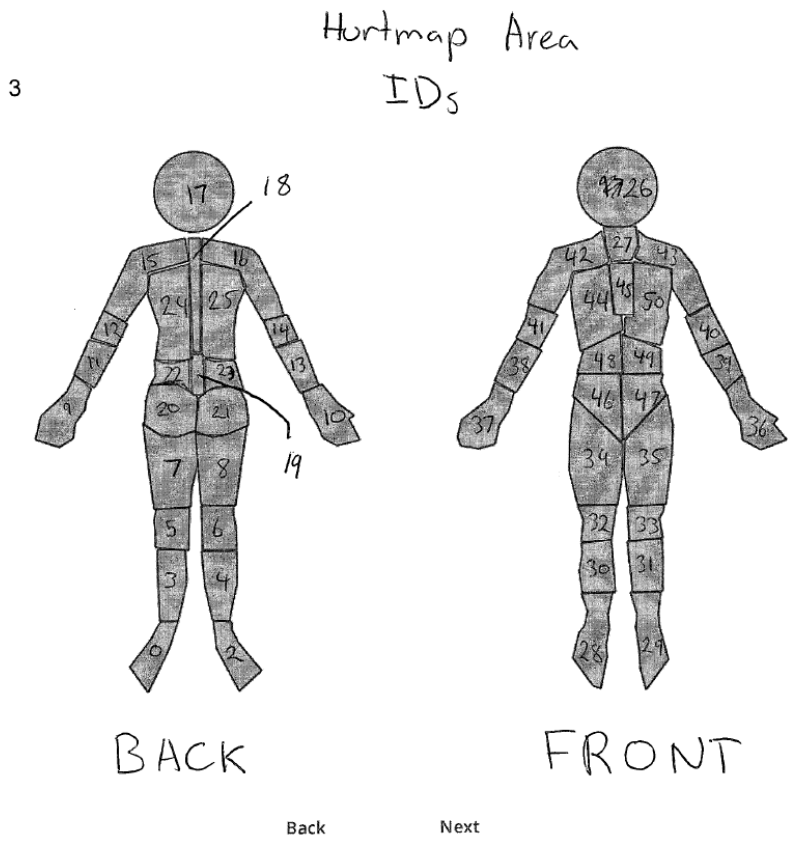
Search strategy used in PsycINFO		
	Searches	**Results**
1	adolescen$.ti,ab.	165009
2	child$.ti,ab.	490525
3	youth$.ti,ab.	61494
4	exp schools/	49630
5	school$.ti,ab.	262606
6	pediatrics/	15886
7	pediatric$.ti,ab.	21023
8	paediatric$.ti,ab.	3037
9	young$.ti,ab.	177351
10	boy$.ti,ab.	53174
11	girl$.ti,ab.	50288
12	exp puberty/	1941
13	pubert$.ti,ab.	5031
14	pubescent$.ti,ab.	224
15	prepubert$.ti,ab.	1210
16	juvenile$.ti,ab.	17828
17	teenage$.ti,ab.	10200
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	872558
19	incidence.ti,ab.	34722
20	exp risk factors/	49602
21	(risk adj3 factor$).ti,ab.	58581
22	(Risk adj3 score).ti,ab.	781
23	(cohort adj3 stud$).ti,ab.	13700
24	exp prospective studies/	436
25	(prospective adj3 stud$).ti,ab.	20976
26	exp followup studies/	12306
27	(Follow up adj3 stud$).ti,ab.	11717
28	onset.ti,ab.	68895
29	predict$.ti,ab.	302833
30	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	479711
31	pain/	18321
32	back pain/	2884

33	knee/	707
34	"neck (anatomy)"/	864
35	"hand (anatomy)"/	2682
36	"shoulder (anatomy)"/	391
37	hips/	874
38	"feet (anatomy)"/	568
39	"elbow (anatomy)"/	201
40	"arm (anatomy)"/	1501
41	wrist/	406
42	"leg (anatomy)"/	862
43	ankle/	317
44	exp spinal column/	541
45	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	8915
46	31 and 45	770
47	(back adj3 pain).ti,ab.	4057
48	(knee adj3 pain).ti,ab.	241
49	(neck adj3 pain).ti,ab.	863
50	(hand adj3 pain).ti,ab.	147
51	(shoulder adj3 pain).ti,ab.	364
52	(hip adj3 pain).ti,ab.	99
53	(foot adj3 pain).ti,ab.	72
54	(elbow adj3 pain).ti,ab.	20
55	(arm adj3 pain).ti,ab.	145
56	(forearm adj3 pain).ti,ab.	50
57	(wrist adj3 pain).ti,ab.	36
58	(leg adj3 pain).ti,ab.	210
59	(ankle adj3 pain).ti,ab.	23
60	(spinal adj3 pain).ti,ab.	583
61	backache.ti,ab.	105
62	(low back adj3 pain).ti,ab.	2451
63	chronic pain/	9741
64	(chronic adj3 pain).ti,ab.	13231
65	(musculoskeletal adj3 pain).ti,ab.	1054
66	(widespread adj3 pain).ti,ab.	403
67	(multisite adj3 pain).ti,ab.	13

68	(regional adj3 pain).ti,ab.	626
69	(juvenile adj3 fibromyalgia).ti,ab.	24
70	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69	19247
71	31 or 32 or 46 or 70	33666
72	**18 and 30 and 71**	**923**

Appendix III Pain manikin used in CATS

The pain manikin used to describe the presence of pain in the body is shown below.



The pain sites present in the manikin were grouped in 17 pain areas as follow:

- Head pain: 17 and 26
- Neck/throat pain: 27
- Shoulder pain: 15, 16, 42 and 43
- Elbow pain: 12, 14, 40 and 41
- Hand pain: 9, 10, 36 and 37
- Forearm pain: 11, 13, 38 and 39
- Upper back pain: 24 and 25
- Lower back pain: 22 and 23
- Thoracic spine pain: 18
- Lumbar spine pain: 19
- Knee pain: 5, 6, 32 and 33
- Foot pain: 0, 2, 28 and 29
- Abdominal pain: 46, 47, 48 and 49
- Chest pain: 44, 45 and 50
- Buttock pain: 20 and 21
- Thigh pain: 34 and 35
- Shin/calf pain: 3, 4, 30 and 31

Appendix IV Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire includes the following items, which are listed below:

Hyperactivity Scale:

- Restless, overactive, cannot stay still for long
- Constantly fidgeting or squirming
- Easily distracted, concentration wanders
- Thinks things out before acting
- Sees tasks through to the end, good attention span

Emotional Symptoms Scale:

- Often complains of headaches, stomach-aches or sickness
- Many worries, often seems worried
- Often unhappy, down-hearted or tearful
- Nervous or clingy in new situations, easily loses confidence
- Many fears, easily scared

Conduct Problems Scale:

- Often has temper tantrums or hot tempers
- Generally obedient, usually does what adults request
- Often fights with other children or bullies them
- Often lies or cheats
- Steals from home, school or elsewhere

Peer Problems Scale:

- Rather solitary, tends to play alone
- Has at least one good friend
- Generally liked by other children
- Picked on or bullied by other children
- Gets on better with adults than with other children

Prosocial Scale:

- Considerate of other people's feelings
- Shares readily with other children (treats, toys, pencils etc)
- Helpful if someone is hurt, upset or feeling ill
- Kind to younger children
- Often volunteers to help others (parents, teachers, other children)

Appendix V Association between baseline sleep problems and the onset of musculoskeletal pain between the imputed and the complete-case dataset

Comparison of the odds for the onset of musculoskeletal pain in analysis performed with the multiple imputed dataset and the complete-case dataset

The estimates for the onset of musculoskeletal pain obtained with the multiple imputed dataset and the complete-case dataset were compared. Results for the association between sleep problems and the onset of musculoskeletal pain (Table I) and the onset of chronic musculoskeletal pain (Table II) are shown. Results showed that the estimates of odds for the onset of musculoskeletal pain or chronic musculoskeletal pain reported in the adjusted analysis performed within the multiple imputed dataset were slightly lower than those reported with the complete-case dataset. This may be explained by the fact that the inclusion of the group of children with missing data for the confounding variables has lowered the odds for the onset of musculoskeletal pain. This is consistent with the results of the sensitivity analysis performed to explore the difference in odds for the onset of musculoskeletal pain between the group of children with complete data and those with missing data for the confounding variables (Please see below section “Sensitivity analysis between the group of adolescents with complete data and those with missing data for the confounding variables”).

Table II Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up	
Complete-case dataset	
Unadjusted (n=438)	**Odds ratio (95%CI)**
Sleep problems	1.48 (0.94, 2.34)
Adjusted (n=279)	**Odds ratio (95%CI)**
Sleep problems	1.53 (0.87, 2.70)
Multiple imputed dataset	
Imputed Unadjusted analysis (n=441)	**Odds ratio (95%CI)**
Sleep problems	1.47 (0.93, 2.31)
Imputed Adjusted analysis (n=441)	**Odds ratio (95%CI)**
Sleep problems	1.35 (0.84, 2.16)

Table II Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up	
Complete-case dataset	
Unadjusted (n=938)	**Odds ratio (95%CI)**
Sleep problems	2.56 (1.68, 3.90)
Adjusted (n=609)	**Odds ratio (95%CI)**
Sleep problems	2.32 (1.37, 3.90)
Multiple imputed dataset	
Imputed Unadjusted analysis (n=944)	**Odds ratio (95%CI)**
Sleep problems	2.56 (1.68, 3.90)
Imputed Adjusted analysis (n=944)	**Odds ratio (95%CI)**
Sleep problems	2.22 (1.43, 3.44)

Sensitivity analysis between the group of adolescents with complete data and those with missing data for the confounding variables

Sensitivity analysis were performed to explore the difference in odds for the onset of musculoskeletal pain between the group of children with complete data (N = 279) and those with missing data (N = 159) for the confounding variables. Results from the unadjusted logistic regression analysis showed that children with missing data for the confounding variables were at lower odds for the onset of musculoskeletal pain compared to those with complete data (Table III). Similarly, children with missing data (N = 329) for the confounding variables were at lower odds for the onset of chronic musculoskeletal pain compared to with complete data (N = 609) (Table IV).

Table III Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up		
Group with missing data (N = 159)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.06	0.46, 2.46
Group with complete data (N = 279)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.67	0.96, 2.89

Table IV Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up		
Group with missing data (N = 329)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	1.68	1.02, 2.77
Group with complete data (N = 609)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Sleep problems	2.08	1.47, 2.96

Appendix VI Sensitivity analysis with sleep problems as a categorical variable

Analysis of the association between sleep problems and the onset of musculoskeletal pain and chronic musculoskeletal pain with sleep problems entered as a categorical variable with 5 frequencies of sleep problems (never sleep problems as the reference group) were carried out. Results showed that increasing frequency of sleep problems were associated with overall increasing odds for the onset of musculoskeletal pain and chronic musculoskeletal pain. The effect was more pronounced and linear for the association between sleep problems and the onset of chronic musculoskeletal pain compared to analysis for the onset of musculoskeletal pain. The low cell count within some subgroups (children in advanced puberty, Table VII and Table XI, and with low levels of screen time, Table VIII) did not permit to estimate the odds for the onset of musculoskeletal pain and chronic musculoskeletal pain. Results are outlined below (Table V – Table XII).

Table V Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up

Unadjusted analysis		
Overall (N = 441)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.20	0.70, 2.06
Sometimes	1.48	0.88, 2.47
Often	2.13	1.03, 4.38
Almost always	1.55	0.82, 2.95
Adjusted analysis*		
Overall (N = 441)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.23	0.71, 2.13
Sometimes	1.49	0.88, 2.52
Often	1.99	0.95, 4.18
Almost always	1.45	0.75, 2.79
*Analysis adjusted for psychological symptoms (total score), individual sports and team sports		

Table VI Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by gender		
Unadjusted analysis		
Females (N = 245)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.12	0.54, 2.32
Sometimes	1.08	0.54, 2.13
Often	1.44	0.57, 3.66
Almost always	0.59	0.22, 1.55
Males (N = 196)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.20	0.53, 2.74
Sometimes	2.13	0.96, 4.73
Often	3.48	1.09, 11.15
Almost always	3.78	1.50, 9.52
Adjusted analysis*		
Females (N = 245)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.15	0.53. 2.46
Sometimes	0.97	0.47, 1.99
Often	0.90	0.32, 2.53
Almost always	0.39	0.14, 1.12
Males (N = 196)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.19	0.52, 2.74
Sometimes	2.19	0.97, 4.96
Often	3.52	1.08, 11.47
Almost always	3.88	1.52, 9.91
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Gender # Sleep problems	4.03	1.51, 10.78
*Analysis adjusted for psychological symptoms (total score), individual sports and team sports		

Table VII Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by pubertal stage		
Unadjusted analysis		
Early pubertal stage (N = 377) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.13	0.62, 2.06
Sometimes	1.60	0.90, 2.82
Often	1.81	0.82, 3.99
Almost always	1.75	0.87, 3.51
Advanced pubertal stage (N = 50) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
Adjusted analysis*		
Early pubertal stage (N = 377) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.15	0.63, 2.12
Sometimes	1.62	0.91, 2.88
Often	1.76	0.78, 3.95
Almost always	1.70	0.83, 3.49
Advanced pubertal stage (N = 50) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Puberty # Sleep problems	1.10	0.21, 5.79
*Analysis adjusted for psychological symptoms (total score), individual sports and team sports • Sample size vary between 377 and 391 •• Sample size vary between 50 and 64		

Table VIII Logistic regression of the association between sleep problems at baseline and musculoskeletal pain onset at follow-up stratified by screen time

Unadjusted analysis		
Low screen time (≤2 hours/day) (N = 79) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
High screen time (>2 hours/day) (N = 345) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.26	0.67, 2.37
Sometimes	1.74	0.96, 3.14
Often	2.79	1.26, 6.21
Almost always	1.68	0.82, 3.46
Adjusted analysis*		
Low screen time (≤2 hours/day) (N = 79) •		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
High screen time (>2 hours/day) (N = 345) ••		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	1.25	0.66, 2.37
Sometimes	1.73	0.94, 3.16
Often	2.59	1.14, 5.88
Almost always	1.52	0.72, 3.20
Interaction term*		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Screen time # Sleep problems	1.74	0.45, 6.80

*Analysis adjusted for psychological symptoms (total score), individual sports and team sports

• Sample size vary between 79 and 96

•• Sample size vary between 345 and 362

Table IX Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up

Unadjusted analysis

Overall (N = 944)

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.91	0.42, 1.98
Sometimes	1.39	0.68, 2.84
Often	2.65	1.31, 5.35
Almost always	2.96	1.51, 5.81

Adjusted analysis*

Overall (N = 944)

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.90	0.41, 1.98
Sometimes	1.41	0.69, 2.88
Often	2.53	1.24, 5.13
Almost always	2.89	1.45, 5.73

*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain

Table X Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by gender

Unadjusted analysis		
Females (N = 510)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.99	0.32, 3.07
Sometimes	1.22	0.42, 3.54
Often	2.96	1.07, 8.19
Almost always	2.95	1.08, 8.06
Males (N = 434)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.84	0.28, 2.53
Sometimes	1.66	0.64, 4.33
Often	2.43	0.90, 6.52
Almost always	3.05	1.22, 7.62
Adjusted analysis*		
Females (N = 510)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.93	0.30, 2.90
Sometimes	1.15	0.39, 3.37
Often	2.71	0.97, 7.61
Almost always	2.92	1.05, 8.14
Males (N = 434)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.88	0.29, 2.64
Sometimes	1.69	0.65, 4.44
Often	2.40	0.88, 6.50
Almost always	2.96	1.17, 7.51
Interaction term*		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Gender # Sleep problems	0.82	0.35, 1.93

*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain

Table XI Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by pubertal stage

Unadjusted analysis		
Early pubertal stage (N = 808)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.92	0.40, 2.12
Sometimes	1.47	0.68, 3.15
Often	2.56	1.19, 5.52
Almost always	2.82	1.34, 5.89
Advanced pubertal stage (N = 112)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
Adjusted analysis*		
Early pubertal stage (N = 808)•		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	0.92	0.40, 2.14
Sometimes	1.48	0.69, 3.21
Often	2.47	1.13, 5.38
Almost always	2.75	1.29, 5.87
Advanced pubertal stage (N = 112)••		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Almost never	/	/
Sometimes	/	/
Often	/	/
Almost always	/	/
Interaction term*		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Puberty # Sleep problems	1.99	0.38, 10.50

*Analysis adjusted for psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain

•Sample size vary between 808 and 832

••Sample size vary between 112 and 136

Table XII Logistic regression of the association between sleep problems at baseline and chronic musculoskeletal pain onset at follow-up stratified by screen time

Unadjusted analysis

Low screen time (≤2 hours/day) (N = 198)•

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.95	0.20, 4.46
Sometimes	0.83	0.15, 4.58
Often	1.79	0.35, 9.20
Almost always	2.19	0.49, 9.79

High screen time (>2 hours/day) (N = 720)••

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.88	0.35, 2.23
Sometimes	1.59	0.69, 3.64
Often	2.95	1.30, 6.72
Almost always	3.23	1.48, 7.04

Adjusted analysis*

Low screen time (≤2 hours/day) (N = 198)•

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.89	0.19, 4.30
Sometimes	0.82	0.15, 4.59
Often	1.92	0.36, 10.07
Almost always	2.15	0.47, 9.93

High screen time (>2 hours/day) (N = 720)••

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Almost never	0.85	0.33, 2.17
Sometimes	1.60	0.69, 3.69
Often	2.73	1.19, 6.29
Almost always	2.98	1.34, 6.63

Interaction term*

Chronic musculoskeletal pain at follow-up	Odds ratio	95% CI
Screen time # Sleep problems	1.19	0.37, 3.77

*Analysis adjusted for Psychological symptoms (total score), individual sports, team sports and baseline musculoskeletal pain

•Sample size vary between 198 and 224

••Sample size vary between 720 and 746

Appendix VII Pain manikin used in ALSPAC

The pain manikin used to describe the presence of pain in the body, together with the questions used to assess the pain presence, is shown below.

Focus 17 | Pain Questionnaire | Form F17PQ | v1 | 11.11.08

Visit Number

Visit Date / / 20

In this study, we are interested in whether or not you have experienced pain over the past three to six months.

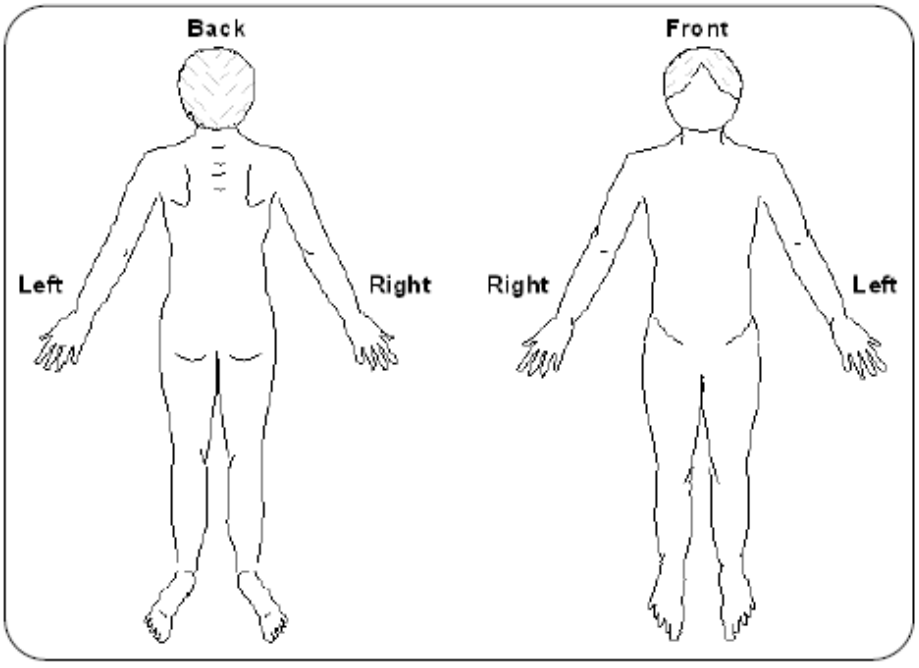
PQ1 Have you had any aches or pains that have lasted for a day or longer in the past month?

Yes 1☐ No 2☐ → **If no, please go straight to question PQ14 on page 4**

PQ2 When did the pain start?

Less than 3 months ago 1☐ More than 3 months ago 2☐

PQ3 Please shade in the diagrams to show **where exactly** you felt the pain(s)



Please turn over and continue with question PQ4

The pain sites marked in the manikin were grouped in the following 26 pain areas:

- Head pain
- Neck/throat pain
- Right shoulder pain
- Right elbow pain
- Right hand pain
- Right lower arm pain
- Left shoulder pain
- Left elbow pain
- Left hand pain
- Left lower arm pain
- Right knee pain
- Right hip pain
- Right foot/ankle pain
- Right shin/calf pain
- Left knee pain
- Left hip pain
- Left foot/ankle pain
- Left shin/calf pain
- Upper right back pain
- Lower right back pain
- Upper left back pain
- Lower left back pain
- Right buttock pain
- Left buttock pain
- Upper back/neck pain
- Lower back pain

Appendix VIII Association between baseline internalizing and externalizing symptoms and the onset of musculoskeletal pain in those with missing data and those with complete data for the confounding variables

Comparison of the odds for the onset of musculoskeletal pain in analysis performed with the multiple imputed dataset and the complete-case dataset

The estimates for the onset of musculoskeletal pain obtained with the multiple imputed dataset and the complete-case dataset were compared. Results for the association between internalizing symptoms, externalizing symptoms and the onset of musculoskeletal pain (Table XIII and Table XIV) and the onset of chronic musculoskeletal pain (Table XV and Table XVI) are shown. Results showed that the estimates of odds for the onset of musculoskeletal pain or chronic musculoskeletal pain reported in the adjusted analysis performed within the multiple imputed dataset were consistently stronger in comparison to the complete-case. The pattern of adjustment showed a general reduction of effect in the complete case analysis, whereas there is a similar or increased effect within the multiple imputation dataset. This suggests the imputation of data leads to an increase in effect because the group with missing data includes individuals with a greater propensity to report musculoskeletal pain outcomes, as shown below in Section "Sensitivity analysis between the group of adolescents with complete data and those with missing data for the confounding variables".

Table XIII Logistic regression of the association between internalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up	
Complete-case dataset	
Unadjusted (n=1,467)	**Odds ratio (95%CI)**
Internalizing >90th	1.35 (0.91, 1.99)
Adjusted (n=1,148)	**Odds ratio (95%CI)**
Internalizing >90th	1.23 (0.78, 1.93)
Multiple-imputed dataset	
Imputed Unadjusted analysis (n=1,604)	**Odds ratio (95%CI)**
Internalizing >90th	1.34 (0.90, 1.99)
Imputed Adjusted analysis (n=1,604)	**Odds ratio (95%CI)**
Internalizing >90th	1.43 (0.96, 2.12)

Table XIV Logistic regression of the association between externalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up	
Complete-case dataset	
Unadjusted (n=1,468)	**Odds ratio (95%CI)**
Externalizing >90th	2.04 (1.32, 3.16)
Adjusted (n=1,149)	**Odds ratio (95%CI)**
Externalizing >90th	1.59 (0.95, 2.67)
Multiple-imputed dataset	
Imputed Unadjusted analysis (n=1,604)	**Odds ratio (95%CI)**
Externalizing >90th	1.99 (1.29, 3.09)
Imputed Adjusted analysis (n=1,604)	**Odds ratio (95%CI)**
Externalizing >90th	1.99 (1.28, 3.10)

Table XV Logistic regression of the association between internalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up	
Complete-case dataset	
Unadjusted (n=1,461)	**Odds ratio (95%CI)**
Internalizing >90th	1.23 (0.75, 2.02)
Adjusted (n=1,143)	**Odds ratio (95%CI)**
Internalizing >90th	0.96 (0.52, 1.78)
Multiple-imputed dataset	
Imputed Unadjusted analysis (n=1,598)	**Odds ratio (95%CI)**
Internalizing >90th	1.24 (0.75, 2.05)
Imputed Adjusted analysis (n=1,598)	**Odds ratio (95%CI)**
Internalizing >90th	1.28 (0.77, 2.11)

Table XVI Logistic regression of the association between externalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up	
Complete-case dataset	
Unadjusted (n=1,462)	**Odds ratio (95%CI)**
Externalizing >90th	1.69 (1.01, 2.82)
Adjusted (n=1,144)	**Odds ratio (95%CI)**
Externalizing >90th	1.29 (0.67, 2.49)
Multiple-imputed dataset	
Imputed Unadjusted analysis (n=1,598)	**Odds ratio (95%CI)**
Externalizing >90th	1.69 (1.01, 2.83)
Imputed Adjusted analysis (n=1,598)	**Odds ratio (95%CI)**
Externalizing >90th	1.68 (0.96, 2.73)

Sensitivity analysis between the group of adolescents with complete data and those with missing data for the confounding variables

Sensitivity analysis were performed to explore the difference in odds for the onset of musculoskeletal pain between the group of adolescents with complete data (N = 1,149) and those with missing data (N = 319) for the confounding variables. Results showed that adolescents with missing data for the confounding variables were at higher odds for the onset of musculoskeletal pain compared to those with complete data (Table XVII and Table XVIII). Similarly, adolescents with missing data for the confounding variables were at higher odds for the onset of chronic musculoskeletal pain compared to those with complete data (Table XIX and Table XX).

Table XVII Logistic regression of the association between internalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up

Group with missing data (N = 319)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	2.33	0.99, 5.50
Group with complete data (N = 1,149)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	1.17	0.75, 1.82

Table XVIII Logistic regression of the association between externalizing symptoms at baseline and the onset of musculoskeletal pain at follow-up

Group with missing data (N = 319)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	4.00	1.67, 9.59
Group with complete data (N = 1,149)		
Musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.58	0.94, 2.64

Table XIX Logistic regression of the association between internalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up		
Group with missing data (N = 318)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	2.38	0.96, 5.90
Group with complete data (N = 1,144)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Internalizing symptoms	0.96	0.52, 1.76

Table XX Logistic regression of the association between externalizing symptoms at baseline and the onset of chronic musculoskeletal pain at follow-up		
Group with missing data (N = 318)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	2.55	1.07, 6.07
Group with complete data (N = 1,144)		
Chronic musculoskeletal pain at follow-up	**Odds ratio**	**95% CI**
Externalizing symptoms	1.33	0.70, 2.56

Appendix IX Read Codes for the variables used within CiPCA

Musculoskeletal pain

Musculoskeletal pain		
Read Code	**Description**	
14V50	H/0: arthrodesis toe	foot
16	Baker's cyst	knee
16...	Back sprain NOS	back
16...	Baker's cyst	knee
16A	Stiff neck symptom	neck
16A2	Stiff neck	neck
16A3	Torticollis - symptom	neck
16A3	Wry neck symptom	neck
16A3	Wry neck/torticollis	neck
16AZ	Stiff neck symptom NOS	neck
16C	Backache symptom	back
16C2	Backache	back
16C3	Backache with radiation	back
16C4	Back pain worse on sneezing	back
16C5	C/O - low back pain	lower back
16C6	Back pain without radiat NOS	back
16C6	Back pain without radiation NOS	back
16C7	C/O - upper back ache	upper back
16C8	Exacerbation of backache	back
16C9	Chronic low back pain	lower back
16CA	Mechanical low back pain	lower back
16CZ	Backache symptom NOS	back
16J0	Swollen calf	lower leg
16J1	Swollen toe	foot
16J2	Swollen thumb	hand
16J3	Swollen joint	unspecified
16J4	Swollen knee	knee
16J5	Facial swelling	head
16J6	Swollen hand	hand
16J7	Swollen foot	foot
16Z2	Growing pains	unspecified
182	Chest pain	chest
1822	Central chest pain	chest
1823	Precordial pain	chest
1824	Anterior chest wall pain	chest
1826	Parasternal pain	chest
1828	Atypical chest pain	chest

182B	Rib pain	chest
182B0	Costal margin chest pain	chest
182C	Chest wall pain	chest
182Z	Chest pain NOS	chest
1832	Ankle swelling	ankle
1832	Ankle swelling symptom	ankle
1833	Leg swelling	lower limb
1833	Leg swelling symptom	lower limb
1834	Finger swelling	hand
1834	Swollen finger	hand
19690	Abdominal wall pain	abdomen
1973	Left subcostal pain	chest
1974	Right subcostal pain	chest
1A53	C/O - loin pain	pelvis
1A53	C/O - lumbar pain	lower back
1A53	C/O - renal pain	lower back
1A53	Lumbar ache - renal	lower back
1A59	C/O pelvic pain	pelvis
1D12	C/O: stiffness	unspecified
1D130	C/O - pain in toes	foot
1D131	C/O - pain in big toe	foot
1D17	Morning stiffness - joint	unspecified
1D22	C/O - a chest wall symptom	chest
1D22	Symptom: chest wall	chest
1D24	Symptom: trunk posterior	back
1D26	C/O - upper limb symptom	upper limb
1D26	Symptom: upper limb	upper limb
1D27	Symptom: lower limb	lower limb
1D28	C/O - ankle symptom	ankle
1D28	C/O - foot symptom	foot
1D28	Symptom: ankle/foot	ankle/foot
1DCC	Aching muscles	unspecified
1M0	Pain in upper limb	upper limb
1M00	Elbow pain	elbow
1M00	Pain in elbow	elbow
1M01	Pain in wrist	wrist
1M1	Pain in lower limb	lower limb
1M10	Knee pain	knee
1M11	Foot pain	foot
1M12	Anterior knee pain	knee
1M13	Ankle pain	ankle
ASDFGHI3	Hip Pain?	hip
ASDFGHI4	Hip Pain	hip
ASDFGJO2	Joint Symptoms	unspecified

ASDFGJO3	Joint Pain	unspecified
ASDFGKN2	Knee Pain?	knee
ASDFGKN3	Knee Pain	knee
ASDFGKN4	Knee Pain Affects Sleep?	knee
ASDFGKN5	Knee Pain Affects Sleep	knee
ASDFGKN6	Knee Pain Does Not Affect Sleep	knee
ASDFGMU2	Muscle Symptoms	unspecified
ASDFGTE2	Tendon Symptoms	unspecified
DEGRADE_EVENT_1730_49	[DEGRADE Muscle Injury]	unspecified
DEGRADE_EVENT_2469_340	[DEGRADE Knee Pain]	knee
DEGRADE_EVENT_3154_40	[DEGRADE Knee Pain]	knee
EGTON1	Arthralgia	unspecified
EGTON107	Deformity of Feet	foot
EGTON110	Muscle Injury	unspecified
EGTON211	Sore Thumb	hand
EGTON224	Painful Shoulder	shoulder
EGTON264	Low Back Pain	lower back
EGTON267	Injury To Left Hand	hand
EGTON273	Left Loin Pain	pelvis
EGTON279	Painful Right Knee	knee
EGTON303	Groin Pain	pelvis
EGTON304	Painful Left Arm	upper limb
EGTON307	Myalgia	unspecified
EGTON309	Sore Neck	neck
EGTON312	Painful Elbow	elbow
EGTON436	Radiculopathy	unspecified
EGTON444	Gluteal Muscle Injury	unspecified
EGTON56	Calcaneal Spur	foot
EGTON57	Plantar Fasciitis	foot
EGTONBO1	Both Hips Unstable	hip
EGTONBO3	Both Hips Click	hip
EGTONHI2	Hip Unstable	hip
EGTONHI3	Hip Clicks	hip
EGTONHY1	Hyper-Extension Injury Of Finger	hand
EGTONLE3	Left Hip Unstable	hip
EGTONLE5	Left Hip Clicks	hip
EGTONRI3	Right Hip Unstable	hip
EGTONRI5	Right Hip Clicks	hip
EMISNQAN8	Ankle injury NOS	ankle
EMISNQFO5	Forced plantar flexion injury of ankle	ankle
EMISNQIN18	Inversion injury of ankle	ankle
EMISNQMU15	Musculoskeletal symptom	unspecified

EMISNQMU2	Musculoskeletal pain present	unspecified
EMISNQMU4	Musculoskeletal pain moderate	unspecified
EMISNQMU5	Musculoskeletal pain severe	unspecified
EMISNQNE5	Nerve root pain present	unspecified
EMISNQSC20	Scoliosis of thoracic spine	upper back
EMISNQTE2	Tenderness of head of fibula	lower leg
EMISNQTH14	Thoracic back pain	upper back
EMISREQ|M2I5(9)	Hand joint pain -Req.	hand
HNG0157	(hn) Spinal Injury	back
HNG0160	(hn) Sports Injury	unspecified
HNG0162	(hn) Soft tissue injuries	unspecified
HNG0162	[RFC] Soft tissue injuries	unspecified
M4A8	Muscle Injury	unspecified
MAWBYHI1	Hip Pain	hip
MAWBYKN1	Knee Pain	knee
MAWBYMU1	Musculoskeletal Symptoms	unspecified
MHTBAGO1	Golfers Elbow-Epicondylitis	elbow
MUNNUKN1	Knee Pain	knee
N	Musculoskelet/connectiv tissue	unspecified
N064	Transient arthropathy	unspecified
N0640	Transient arthr.-site unspecif	unspecified
N0641	Transient arthr.-shoulder	shoulder
N0642	Transient arthr.-upper arm	upper arm
N0643	Transient arthr.-forearm	forearm
N0644	Transient arthr.-hand	hand
N0645	Transient arthr.-pelvic/thigh	pelvis/thigh
N0646	Transient arthr.-lower leg	lower leg
N0647	Transient arthr.-ankle/foot	ankle/foot
N0648	Transient arthr.-other specif.	unspecified
N0649	Transient arthr.-multiple site	unspecified
N064A	Transient arthropathy-shoulder	shoulder
N064B	Transient arthrop-sternoclav j	shoulder girdle
N064C	Transient arthr-acromioclav jt	shoulder girdle
N064D	Transient arthropathy-elbow	elbow
N064E	Transient arthropathy-dist RUJ	forearm
N064F	Transient arthropathy-wrist	wrist
N064G	Transient arthropathy-MCPJ	hand
N064H	Transient arthrop-PIPJ-fing	hand
N064J	Transient arthrop-DIPJ-fing	hand
N064K	Irritable hip	hip
N064K	Transient arthropathy-hip	hip
N064L	Transient arthropathy-SIJ	pelvis
N064M	Transient arthropathy-knee	knee
N064N	Transient arthrop, tib-fib jnt	lower leg

N064P	Transient arthropathy-ankle	ankle
N064Q	Transient arthrop-subtalar jnt	foot
N064R	Transient arthrop-talonav jnt	foot
N064S	Transient arthrop-oth tars jnt	foot
N064T	Transient arthropathy-1st MTPJ	foot
N064U	Transient arthrop-less MTPJ	foot
N064V	Transient arthropathy-IPJ-toe	foot
N064z	Transient arthropathy NOS	unspecified
N06z8	Arthropathy NOS-other specif.	unspecified
N06zz	Arthropathy NOS	unspecified
N07	Internal derangement of knee	knee
N070	Medial meniscus derangement	knee
N0700	Medial menisc.derang.unspecif	knee
N0701	Old bucket handle tear-medial	knee
N0702	Medial menisc.ant.horn derang.	knee
N0703	Medial menisc.post.horn derang	knee
N0704	Parr beak tear-post/med menisc	knee
N0705	Periph detach-medial meniscus	knee
N0706	Radial tear of medial meniscus	knee
N0707	Horiz cleavage tear-med menisc	knee
N0708	Multiple tears of medial meniscus	knee
N0708	Multiple tears-medial meniscus	knee
N0709	Cyst of medial meniscus	knee
N070A	Old tear of medial meniscus	knee
N070B	Old tear post horn med menis	knee
N070z	Medial meniscus derange.NOS	knee
N070z	Medial meniscus derangement NOS	knee
N071	Lateral meniscus derangement	knee
N0710	Lateral menisc.derang.unspecif	knee
N0711	Old bucket handle tear-lat men	knee
N0712	Lateral menisc.ant.horn derang	knee
N0713	Lateral menisc.post.horn deran	knee
N0714	Lateral meniscus derangem.NOS	knee
N0715	Parr beak tear-post/lat menisc	knee
N0716	Periph detach-lateral meniscus	knee
N0717	Radial tear of lateral meniscus	knee
N0717	Radial tear-lateral meniscus	knee
N0718	Horiz cleavage tear-lat menisc	knee
N0719	Multiple tears-lat meniscus	knee
N071A	Cyst of lateral meniscus	knee
N071B	Discoid lateral meniscus	knee
N071C	Old tear of lateral meniscus	knee
N072	Meniscus derangement NEC	knee
N072	Torn medial meniscus	knee

N0720	Old torn meniscus of knee	knee
N0721	Degen lesion artic cart knee	knee
N0721	Degenerative lesion of articular cartilage of knee	knee
N0722	Cyst of semilunar cartilage	knee
N073	Loose body in knee	knee
N073	Rice bodies in knee	knee
N074	Chondromalacia patellae	knee
N07y	Oth. internal knee derangement	knee
N07y0	Old lat.collat.lig.disruption	knee
N07y1	Old med.collat.lig.disruption	knee
N07y2	Old ant.cruciate lig.disrupt.	knee
N07y3	Old post.cruciate lig.disrupt.	knee
N07y4	Old capsular knee lig.disrupt.	knee
N07y5	Locked knee	knee
N07y6	Patellofemoral maltracking	knee
N07y7	Old part tear lat collat lig	knee
N07y8	Old compl tear lat collat lig	knee
N07y9	Old post/lat caps complex tear	knee
N07yA	Old part tear med collat lig	knee
N07yB	Old compl tear med collat lig	knee
N07yC	Old med capsular complex tear	knee
N07yD	Old part tear ant cruciate lig	knee
N07yE	Old comp tear ant cruciate lig	knee
N07yF	Old part tear post cruciat lig	knee
N07yG	Old comp tear post cruciat lig	knee
N07yH	Locking knee	knee
N07yy	Other knee lig. old disruption	knee
N07yz	Other intern.knee derang.NOS	knee
N07yz	Other internal knee derangement NOS	knee
N07z	Internal knee derangement NOS	knee
N08	Other derangement of joint	unspecified
N080	Articular cart.disor.excl.knee	unspecified
N0800	Artic.cart.dis.-site unspecif.	unspecified
N0801	Artic.cart.dis.-shoulder	shoulder
N0802	Artic.cart.dis.-upper arm	upper arm
N0803	Artic.cart.dis.-forearm	forearm
N0804	Artic.cart.dis.-hand	hand
N0805	Artic.cart.dis.-pelvic/thigh	pelvis/thigh
N0806	Artic.cart.dis.-ankle/foot	ankle/foot
N0807	Artic.cart.dis.-other specif.	unspecified
N0808	Artic.cart.dis.-multiple sites	unspecified
N0809	Hill-Sachs lesion	shoulder
N080B	Artic cart disord oth j-should	shoulder
N080C	Chondrolysis-femoral head	hip

N080z	Articular cartilage disord.NOS	unspecified
N081	Loose body in joint-excl.knee	unspecified
N0810	Loose body in joint	unspecified
N0810	Loose body in joint - unspec.	unspecified
N0811	Loose body joint-shoulder	shoulder
N0812	Loose body in joint upper arm	upper arm
N0813	Wrist joint loose body	wrist
N0814	Loose body joint-hand	hand
N0815	Loose body joint-pelvic/thigh	pelvis/thigh
N0816	Loose body in ankle joint	ankle
N0816	Loose body joint-ankle/foot	ankle/foot
N0817	Loose body in joint, joint OS	unspecified
N0818	Loose joint body-multip joints	unspecified
N0819	Loose body in shoulder joint	shoulder
N081A	Loose body, oth joint-shoulder	shoulder
N081B	Loose body in elbow joint	elbow
N081C	Loose body in wrist joint	wrist
N081D	Loose body in hip joint	hip
N081E	Loose body, oth joint-pelvis	pelvis
N081F	Loose body in ankle joint	ankle
N081G	Loose body in foot joint	foot
N081z	Loose joint body (ex.knee)NOS	unspecified
N082Z	Non-trau subl acromiocl joint	shoulder girdle
N083a	Carpal instability, V.I.S.I.	hand
N083b	Carpal instab, ulnar transloc	hand
N083c	Carpal instab, dorsal sublux	hand
N083C	Recurrent sublux shoulder-ant	shoulder
N083d	Carpal instability, other	hand
N083D	Recurrent sublux shoulder-post	shoulder
N083f	Recurrent sublux - CMC joint	hand
N083F	Recurrent sublux shoulder-inf	shoulder
N083h	Recurrent sublux - MCP joint	hand
N083h	Recurrent subluxation of MCP joint	hand
N083H	Recurrent sublux shoulder-ant	shoulder
N083k	Recurrent sublux - IP joint	hand
N083K	Recur sublux shoulder-multidir	shoulder
N083M	Habitual sublux shoulder	shoulder
N083P	Recurrent subluxation of elbow	elbow
N083q	Recurrent sublux - patella	knee
N083R	Recurr sublux, sup rad-uln jt	forearm
N083t	Recurrent sublux - ankle	ankle
N083T	Recurrent sublux-radial head	elbow
N083v	Recurrent sublux-subtal joint	foot
N083V	Recurr sublux, inf rad-uln jt	forearm

N083w	Recurrent sublux-oth foot jt	foot
N083x	Recurrent subluxation hip	hip
N083X	Carpal instability	hand
N083Y	Recurrent subluxation of wrist	wrist
N083Z	Carpal instability, D.I.S.I.	hand
N084	Contracture of joint	unspecified
N0840	Joint contracture-site unspec	unspecified
N0841	Joint contracture-shoulder	shoulder
N0842	Elbow joint contracture	elbow
N0842	Joint contracture-upper arm	upper arm
N0843	Wrist joint contracture	wrist
N0844	Joint contracture of the hand	hand
N0844	Joint contracture-hand	hand
N0845	Joint contracture-pelvic/thigh	pelvis/thigh
N0846	Knee joint contracture	knee
N0847	Joint contracture-ankle/foot	ankle/foot
N0848	Joint contracture-other specif	unspecified
N0849	Contracture of multiple joints	unspecified
N084a	Flexion contracture-knee	knee
N084A	Flexion contracture-shoulder	shoulder
N084b	Equinus contracture of the ankle	ankle
N084b	Equinus contracture-ankle	ankle
N084B	Extension contracture-shoulder	shoulder
N084c	Calcaneus contracture-ankle	ankle
N084C	Abduction contracture-shoulder	shoulder
N084d	Flexion contracture of MTPJ	foot
N084D	Adduction contracture-shoulder	shoulder
N084e	Extension contracture of MTPJ	foot
N084E	Int rotat contracture-shoulder	shoulder
N084f	Flexion contracture of toe IPJ	foot
N084F	Ext rotat contracture-shoulder	shoulder
N084g	Exten contracture of toe IPJ	foot
N084G	Flexion contracture - elbow	elbow
N084H	Extension contracture - elbow	elbow
N084J	Pronation contracture - forearm	forearm
N084J	Pronation contracture-forearm	forearm
N084K	Supination contracture-forearm	forearm
N084L	Flexion contracture - wrist	wrist
N084M	Extension contracture- wrist	wrist
N084N	Uln deviat contracture-wrist	wrist
N084P	Rad deviat contracture-wrist	wrist
N084Q	Flexion contracture of MCPJ	hand
N084R	Extension contracture of MCPJ	hand
N084S	Flexion contracture of PIP joint	hand

N084S	Flexion contracture of PIPJ	hand
N084T	Flexion contracture of DIP joint	hand
N084T	Flexion contracture of DIPJ	hand
N084U	Flexion contracture of hip	hip
N084V	Extension contracture of hip	hip
N084W	Abduction contracture of hip	hip
N084X	Adduction contracture of hip	hip
N084Y	Int rotation contracture-hip	hip
N084z	Contracture of joint NOS	unspecified
N084Z	Ext rotation contracture-hip	hip
N086	Unsp.intrapelv.protr.acetabul.	pelvis
N0860	Protrusio acetabuli	pelvis
N0861	Protrus.acetabuli-pelvic/thigh	pelvis/thigh
N086z	Protrusio acetabuli NOS	pelvis
N087	Fibrocartilage lesion of joint	unspecified
N0872	Glenoid labrum detachment	shoulder
N0873	Glenoid labrum tear	shoulder
N0874	Triangular fibrocartilage tear	shoulder
N0875	Triangular fibrocartil detach	shoulder
N0876	Acetabular labrum detachment	hip
N0877	Acetabular labrum tear	hip
N0878	Snapping shoulder	shoulder
N08y	Instability of joint	unspecified
N08y	Other joint derangement NEC	unspecified
N08y0	Oth.joint deran.NEC-site unsp.	unspecified
N08y1	Oth.joint deran.NEC-shoulder	shoulder
N08y2	Oth.joint deran.NEC-upper arm	upper arm
N08y3	Oth.joint deran.NEC-forearm	forearm
N08y4	Oth.joint deran.NEC-hand	hand
N08y5	Oth.joint deran.NEC-pelv/thigh	pelvis/thigh
N08y6	Oth.joint deran.NEC-lower leg	lower leg
N08y7	Oth.joint deran.NEC-ankle/foot	ankle/foot
N08y8	Oth.joint deran.NEC-other spec	unspecified
N08y9	Oth.joint deran.NEC-mult.sites	unspecified
N08yz	Other joint derange.NEC NOS	unspecified
N08z	Joint derangement NOS	unspecified
N08z0	Joint derange.NOS-site unspec.	unspecified
N08z1	Joint derange.NOS-shoulder	shoulder
N08z2	Joint derange.NOS-upper arm	upper arm
N08z3	Joint derange.NOS-forearm	forearm
N08z4	Joint derange.NOS-hand	hand
N08z5	Joint derange.NOS-pelvic/thigh	pelvis/thigh
N08z6	Joint derange.NOS-ankle/foot	ankle/foot
N08z7	Joint derange.NOS-other spec.	unspecified

N08z8	Joint derange.NOS-multipl.site	unspecified
N08zz	Joint derangement NOS	unspecified
N09	Other/unspecif.joint disorders	unspecified
N090	Effusion of joint	unspecified
N090	Swelling of joint - effusion	unspecified
N0900	Joint effusion-site unspecif.	unspecified
N0901	Joint effusion-shoulder region	shoulder
N0902	Joint effusion-upper arm	upper arm
N0903	Joint effusion of the forearm	forearm
N0903	Wrist joint effusion	wrist
N0904	Joint effusion of the hand	hand
N0904	Joint effusion-hand	hand
N0905	Joint effusion-pelvic/thigh	pelvis/thigh
N0906	Effusion - knee joint	knee
N0906	Joint effusion of the lower leg	lower leg
N0906	Joint effusion-lower leg	lower leg
N0906	Knee joint effusion	knee
N0907	Joint effusion-ankle/foot	ankle/foot
N0908	Joint effusion-other specif.	unspecified
N0909	Effusion of multiple joints	unspecified
N090A	Effusion of shoulder	shoulder
N090B	Effusion of sternoclav joint	shoulder girdle
N090B	Effusion of sternoclavicular joint	shoulder girdle
N090C	Effusion of acromioclav joint	shoulder girdle
N090D	Effusion of elbow	elbow
N090E	Effusion of distal RUJ	forearm
N090F	Effusion of wrist	wrist
N090G	Effusion of MCP joint	hand
N090H	Effusion of PIP joint - finger	hand
N090H	Effusion of PIP joint of finger	hand
N090J	Effusion of DIP joint - finger	hand
N090K	Effusion of hip	hip
N090L	Effusion of sacro-iliac joint	pelvis
N090M	Effusion of knee	knee
N090N	Effusion, tibio-fibular joint	lower leg
N090P	Effusion of ankle	ankle
N090Q	Effusion of subtalar joint	foot
N090R	Effusion of talonavicular joint	foot
N090R	Effusion, talonavicular joint	foot
N090S	Effusion of other tarsal joint	foot
N090T	Effusion of 1st MTP joint	foot
N090U	Effusion of lesser MTP joint	foot
N090V	Effusion of IP joint of toe	foot
N090W	Intermittent hydrarthrosis	unspecified

N090X	Chronic joint effusion	unspecified
N090Y	Acute joint effusion	unspecified
N090z	Effusion of joint NOS	unspecified
N094	Ache in joint	unspecified
N094	Pain in joint - arthralgia	unspecified
N0940	Arthralgia - site unspecified	unspecified
N0940	Arthralgia of unspecified site	unspecified
N0941	Arthralgia - shoulder	shoulder
N0941	Arthralgia of the shoulder region	shoulder
N0941	Painful Shoulder	shoulder
N0941	Shoulder joint pain	shoulder
N0942	Arthralgia - upper arm	upper arm
N0942	Arthralgia of the upper arm	upper arm
N0942	Elbow joint pain	elbow
N0943	Arthralgia - forearm	forearm
N0943	Arthralgia of the forearm	forearm
N0943	Wrist joint pain	wrist
N0944	Arthralgia - hand	hand
N0944	Arthralgia of the hand	hand
N0944	Hand joint pain	hand
N0945	Arthralgia - pelvic/thigh	pelvis/thigh
N0945	Arthralgia of the pelvic region and thigh	pelvis/thigh
N0945	Coxalgia	hip
N0945	Hip joint pain	hip
N0945	Irritable hip	hip
N0945	Pain in joint - coxalgia	hip
N0946	Arthralgia - lower leg	lower leg
N0946	Arthralgia of the lower leg	lower leg
N0946	Knee joint pain	knee
N0947	Ankle joint pain	ankle
N0947	Ankle/foot joint pain	ankle/foot
N0947	Arthralgia - ankle/foot	ankle/foot
N0947	Arthralgia of the ankle and foot	ankle/foot
N0948	Arthralgia - other specified	unspecified
N0948	Arthralgia of other specified site	unspecified
N0949	Arthralgia of multiple joints	unspecified
N0949	Multiple joint pain	unspecified
N094A	Arthralgia of shoulder	shoulder
N094B	Arthralgia - sternoclav joint	shoulder girdle
N094C	Arthralgia - acromioclav joint	shoulder girdle
N094D	Arthralgia of elbow	elbow
N094E	Arthralgia of distal RUJ	forearm
N094F	Arthralgia of wrist	wrist
N094F	Wrist pain	wrist

N094G	Arthralgia of MCP joint	hand
N094H	Arthralgia of PIP joint of finger	hand
N094H	Arthralgia of PIPJ of finger	hand
N094J	Arthralgia of DIP joint of finger	hand
N094J	Arthralgia of DIPJ of finger	hand
N094K	Arthralgia of hip	hip
N094K	Coxalgia	hip
N094K	Hip pain	hip
N094K	Osteoarthritis	unspecified
N094L	Arthralgia of sacro-iliac joint	pelvis
N094L	Arthralgia of SIJ	pelvis
N094M	Arthralgia of knee	knee
N094N	Arthralgia of tib-fib joint	lower leg
N094P	Arthralgia of ankle	ankle
N094Q	Arthralgia of subtalar joint	foot
N094R	Arthralgia of talonavic joint	foot
N094R	Arthralgia of talonavicular joint	foot
N094S	Arthralgia of oth tarsal joint	foot
N094S	Arthralgia of other tarsal joint	foot
N094T	Arthralgia of 1st MTP joint	foot
N094U	Arthralgia of lesser MTP joint	foot
N094V	Arthralgia of IP joint of toe	foot
N094W	Anterior knee pain	knee
N094z	Arthralgia NOS	unspecified
N094z	Joint pain NOS	unspecified
N095	Joint stiffness NEC	unspecified
N0950	Stiff joint NEC-site unspecif.	unspecified
N0951	Shoulder joint stiffness	shoulder
N0951	Shoulder stiff	shoulder
N0951	Stiff joint NEC-shoulder	shoulder
N0952	Elbow stiff	elbow
N0952	Stiff joint NEC-upper arm	upper arm
N0953	Stiff joint NEC of the forearm	forearm
N0953	Wrist stiff	wrist
N0954	Hand joint stiff	hand
N0954	Hand joint stiffness	hand
N0954	Stiff joint NEC of the hand	hand
N0954	Stiff joint NEC-hand	hand
N0954	Stiff joint NEC, of the hand	hand
N0955	Stiff joint NEC-pelvic/thigh	pelvis/thigh
N0956	Knee stiff	knee
N0956	Stiff joint NEC-lower leg	lower leg
N0957	Stiff joint NEC-ankle/foot	ankle/foot
N0958	Stiff joint NEC-other specif.	unspecified

N0959	Multiple joint stiffness	unspecified
N0959	Multiple stiff joints	unspecified
N095A	Stiff shoulder NEC	shoulder
N095B	Stiff sternoclavic joint NEC	shoulder girdle
N095C	Stiff acromioclavicular joint NEC	shoulder girdle
N095D	Stiff elbow NEC	elbow
N095E	Stiff distal rad-uln joint NEC	forearm
N095F	Stiff wrist NEC	wrist
N095G	Stiff MCP joint NEC	hand
N095H	Stiff PIP joint of finger NEC	hand
N095J	Stiff DIP joint of finger NEC	hand
N095K	Stiff hip NEC	hip
N095L	Stiff sacro-iliac joint NEC	pelvis
N095M	Stiff knee NEC	knee
N095N	Stiff tibio-fibular joint NEC	lower leg
N095P	Stiff ankle NEC	ankle
N095Q	Stiff subtalar joint NEC	foot
N095R	Stiff talonavicular joint NEC	foot
N095S	Stiff other tarsal joint NEC	foot
N095T	Stiff 1st MTP joint NEC	foot
N095U	Stiff lesser MTP joint NEC	foot
N095V	Stiff IP joint of toe NEC	foot
N095W	Stiff finger	hand
N095z	Joint stiffness NEC NOS	unspecified
N096	Joint crepitus	unspecified
N096	Musculoskeletal pain - joints	unspecified
N096	Other joint symptoms	unspecified
N0960	Other joint sympt.-site unspec	unspecified
N0960	Weakness of joint	unspecified
N0961	Other joint sympt.-shoulder	shoulder
N0961	Other joint symptoms of the shoulder region	shoulder
N0962	Other joint sympt.-upper arm	upper arm
N0963	Other joint sympt.-forearm	forearm
N0963	Other joint symptoms of the forearm	forearm
N0964	Other joint sympt.-hand	hand
N0964	Other joint symptoms of the hand	hand
N0965	Hip snapping	hip
N0965	Other joint sympt.-pelv./thigh	pelvis/thigh
N0966	Knee gives way	knee
N0966	Other joint sympt.-lower leg	lower leg
N0966	Unstable knee	knee
N0967	Other joint symptoms of the ankle and foot	ankle/foot
N0967	Unstable ankle	ankle
N0968	Other joint sympt.-other spec.	unspecified

N0969	Other joint sympt.-multip.site	unspecified
N096A	Other symptoms - shoulder	shoulder
N096B	Other symptoms - sternoclav jt	shoulder girdle
N096C	Other symptoms - acromioclav j	shoulder girdle
N096D	Other symptoms - elbow	elbow
N096E	Other symptoms - distal RUJ	forearm
N096F	Other symptoms - wrist	wrist
N096G	Other symptoms - MCPJ	hand
N096H	Other symptoms - PIPJ finger	hand
N096H	Other symptoms - PIPJ, finger	hand
N096J	Other symptoms - DIPJ, finger	hand
N096K	Other symptoms - hip	hip
N096L	Other symptoms - SIJ	pelvis
N096M	Other symptoms - knee	knee
N096N	Other symptoms - tib-fib joint	lower leg
N096P	Other symptoms - ankle	ankle
N096Q	Other symptoms - subtal joint	foot
N096R	Other symptoms - talonav joint	foot
N096S	Other symptoms - oth tarsal jt	foot
N096T	Other symptoms - 1st MTPJ	foot
N096T	Other symptoms in 1st MTP joint	foot
N096U	Other symptoms - lesser MTPJ	foot
N096V	Other symptoms - IPJ of toe	foot
N096V	Other symptoms in IP joint of toe	foot
N096z	Other joint symptoms NOS	unspecified
N097	Difficulty in walking	unspecified
N0970	Walking difficulty due to unspecified site	unspecified
N0970	Walking difficulty-site unspec	unspecified
N0971	Walking diffic.-pelvic/thigh	pelvis/thigh
N0972	Walking difficulty-lower leg	lower leg
N0973	Walking difficulty-ankle/foot	ankle/foot
N0974	Walking difficulty-other spec.	unspecified
N0975	Walking difficulty-multip.site	unspecified
N097z	Difficulty in walking NOS	unspecified
N098	Synovial osteochondromatosis	unspecified
N0980	Synov osteochondromat-shoulder	shoulder
N0981	Synov osteochondromat st-cla j	shoulder girdle
N0982	Synov osteochondromat ac-cla j	shoulder girdle
N0983	Synov osteochondromat-elbow	elbow
N0984	Synov osteochondromat-dist RUJ	forearm
N0985	Synov osteochondromat-wrist	wrist
N0986	Synov osteochondromat-MCPJ	hand
N0987	Synov osteochondromat PIPJ-fin	hand
N0988	Synov osteochondromat DIPJ-fin	hand

N0989	Synov osteochondromat-hip	hip
N098A	Synov osteochondromat-SIJ	pelvis
N098B	Synov osteochondromat-knee	knee
N098C	Synov osteochondromat-tibfib j	lower leg
N098D	Synov osteochondromat-ankle	ankle
N098E	Synov osteochondromat-subtal j	foot
N098F	Synov osteochondromat-talnav j	foot
N098G	Synov osteochondromat-oth ta j	foot
N098H	Synov osteochondromat-1st MTPJ	foot
N098J	Synov osteochondromat-les MTPJ	foot
N098K	Synov osteochondromat-IPJ-toe	foot
N099	Clicking joint	unspecified
N0990	Clicking shoulder	shoulder
N0991	Clicking sternoclavic joint	shoulder girdle
N0991	Clicking sternoclavicular joint	shoulder girdle
N0992	Clicking acromioclavicular joint	shoulder girdle
N0993	Clicking elbow	elbow
N0994	Clicking distal rad-uln joint	forearm
N0995	Clicking wrist	wrist
N0996	Clicking MCP joint	hand
N0997	Clicking PIP joint of finger	hand
N0998	Clicking DIP joint of finger	hand
N0999	Clicking hip	hip
N099A	Multiple clicking joints	unspecified
N099B	Clicking sacro-iliac joint	pelvis
N099C	Clicking knee	knee
N099D	Clicking tibio-fibular joint	lower leg
N099E	Clicking ankle	ankle
N099F	Clicking subtalar joint	foot
N099G	Clicking talonavicular joint	foot
N099H	Clicking other tarsal joint	foot
N099J	Clicking 1st MTP joint	foot
N099K	Clicking lesser MTP joint	foot
N099L	Clicking IP joint of toe	foot
N09A	Patellofemoral disorder	knee
N09AX	Disorder of patella unspecified	knee
N09AX	Disorder of patella, unspec	knee
N09B	Osteophyte	unspecified
N09y	Other spec. joint disorders	unspecified
N09y0	Other joint dis.-site unspec.	unspecified
N09y1	Other joint dis.-shoulder	shoulder
N09y2	Other joint dis.-upper arm	upper arm
N09y3	Other joint dis.-forearm	forearm
N09y4	Other joint dis.-hand	hand

N09y5	Other joint dis.-pelvic/thigh	pelvis/thigh
N09y6	Other joint dis.-lower leg	lower leg
N09y7	Other joint dis.-ankle/foot	ankle/foot
N09y8	Other joint dis.-other specif.	unspecified
N09y9	Other joint dis.-multiple site	unspecified
N09yz	Other joint disorders NOS	unspecified
N09z	Joint disorder NOS	unspecified
N09z	Joint disorders NOS	unspecified
N09z0	Joint disord.NOS-site unspecif	unspecified
N09z1	Joint disord.NOS-shoulder	shoulder
N09z2	Joint disord.NOS-upper arm	upper arm
N09z3	Joint disord.NOS-forearm	forearm
N09z4	Joint disord.NOS-hand	hand
N09z5	Joint disord.NOS-pelvic/thigh	pelvis/thigh
N09z6	Joint disord.NOS-lower leg	lower leg
N09z7	Joint disord.NOS-ankle/foot	ankle/foot
N09z8	Joint disord.NOS-other specif.	unspecified
N09z9	Joint disord.NOS-multiple site	unspecified
N09zz	Joint disorders NOS	unspecified
N0y	Arthropathies OS	unspecified
N0z	Arthropathies NOS	unspecified
N1	Vertebral column syndromes	back
N12	Acute back pain - disc	back
N12	Intervertebral disc disorders	back
N12	Slipped intervertebral disc	back
N120	Cervical disc displ.-no myelop	neck
N120	Cervical disc displacement	neck
N120	PID - prol cerv disc,no myelop	neck
N120	PID - prol cerv discno myelop	neck
N121	Thoracic disc displ.-no myelop	upper back
N122	Lumbar disc displacement	lower back
N122	Lumbar disc lesion - displaced	lower back
N122	PID - prolapsed lumbar disc	lower back
N123	Disc unsp.displ.-no myelopathy	back
N123	Intervertebral disc prol. NOS	back
N123	PID - prol i/v disc, no myelop	back
N123	Prolapsed intervertebral disc without myelopathy	back
N129	PID - prol i/v disc + myelop	back
N1290	Unspec.disc disorder+myelop.	back
N1291	Cervical disc disord.+myelop.	neck
N1292	Thoracic disc disord.+myelop.	upper back
N1293	Lumbar disc disord.+myelopathy	lower back
N129z	Disc disorder+myelopathy NOS	back
N12B	Disc prolapse with myelopathy	back

N12B0	Cx disc prolapse + myelopathy	neck
N12B1	Th disc prolapse + myelopathy	upper back
N12B2	Lu disc prolapse + myelopathy	lower back
N12C	Disc prolapse + radiculopathy	back
N12C	Disc prolapse with radiculopathy	back
N12C0	Cx disc prolapse+radiculopathy	neck
N12C1	Th disc prolapse+radiculopathy	upper back
N12C2	Lu disc prolapse+radiculopathy	lower back
N12C3	Lu disc prol+caud eq compress	lower back
N12C4	Prol lumb interv disc sciatic	lower back
N12D	Narrowing disc space	back
N12z	Intervertebral disc lesion NOS	back
N12z	Other/unspec.disc disorders	back
N12z0	Other disc disorders unspecif.	back
N12z1	Other cervical disc disorders	neck
N12z2	Other thoracic disc disorders	upper back
N12z3	Other lumbar disc disorders	lower back
N12z5	Annular tear of cervical disc	neck
N12z6	Resorption of cervical disc	neck
N12z9	Annular tear of thoracic disc	upper back
N12zA	Resorption of thoracic disc	upper back
N12zD	Annular tear of lumbar disc	lower back
N12zE	Resorption of lumbar disc	lower back
N12zH	Cerv disc disord + radiculopth	neck
N12zH	Cervical disc disorder with radiculopathy	neck
N12zz	Disc disorders NOS	back
N13	Cervical disorder NOS	neck
N13	Other cervical disorders	neck
N131	Cervicalgia	neck
N131	Cervicalgia - pain in neck	neck
N131	Pain in cervical spine	neck
N132	Cervicocranial syndrome	head/neck
N133	Cervicobrachial syndrome	neck & upper limb
N134	Brachial (cervical) neuritis	upper limb
N134	Brachial radiculitis	upper limb
N134	Cervical radiculitis	upper limb
N134	Cervical root pain	upper limb
N134	Ulnar neuritis	upper limb
N135	Torticollis unspecified	neck
N1350	Intermittent torticollis	neck
N1351	Rheumatic torticollis	neck
N135z	Stiff neck NOS	neck
N135z	Torticollis NOS	neck
N135z	Wry neck	neck

N138	Cervicalgia	neck
N13y	Other cervical syndromes	neck
N13y0	Cervical syndrome NEC	neck
N13y2	Crick in neck	neck
N13y3	Cervical root syndrome	neck
N13yz	Other cervical syndromes NOS	neck
N13z	Cervical and neck disorders NOS	neck
N13z	Cervical/neck disorder NOS	neck
N14	Back disorders - other	back
N14	Other/unspecif.back disorder	back
N141	Acute back pain - thoracic	upper back
N141	Pain in thoracic spine	upper back
N142	Acute back pain - lumbar	lower back
N142	Low back pain	lower back
N142	Lumbago	lower back
N142	Pain in lumbar spine	lower back
N1420	Lumbago with sciatica	lower back & lower limb
N143	Acute back pain + sciatica	lower back & lower limb
N143	Acute back pain with sciatica	lower back & lower limb
N143	Back pain - lower	lower back
N143	Low Back Pain	lower back
N143	Sciatica	lower back & lower limb
N144	Thoracic/lumbosacral neuritis	back
N1440	Thoracic nerve root pain	upper back
N1440	Thoracic neuritis unspecified	upper back
N1440	Thoracic neuritis, unspecified	upper back
N1441	Lumbosacral neuritis unspecif.	lower back
N144z	Thoracic/lumbosac.neuritis NOS	back
N145	Acute back pain - unspecified	back
N145	Back pain unspecified	back
N145	Back pain, unspecified	back
N145	Backache NOS	back
N145	Backache unspecified	back
N145	Backache, unspecified	back
N146	Disorders of the sacrum	pelvis
N1463	Lumbosacral instability	lower back
N1463	Lumbosacral strain	lower back
N1464	Sacroiliac instability	pelvis
N1465	Sacral instability NOS	pelvis
N1466	Sacroiliac disorder	pelvis
N146z	Disorders of the sacrum NOS	pelvis

N146z	Sacral disorder NOS	pelvis
N146z	Sacroiliac strain	pelvis
N147	Disorders of the coccyx	pelvis
N1470	Unspecified disorder of coccy	pelvis
N1470	Unspecified disorder of coccyx	pelvis
N1470	Unspecified disorder of the coccyx	pelvis
N1471	Hypermobility of the coccyx	pelvis
N1472	Coccygodynia	pelvis
N1472	Pain in coccyx	pelvis
N147z	Coccygeal disorder NOS	pelvis
N147z	Coccyx disorder NOS	pelvis
N1487	Atlanto-occipital instability	neck
N1488	Atlanto-axial instability	neck
N1489	Cervical spine instability	neck
N148A	Cervico-thoracic instability	neck & upper back
N148B	Thoracic spine instability	upper back
N148C	Lumbar spine instability	lower back
N149	Back stiffness	back
N14X	Sacrococygeal disorders,NEC	pelvis
N14y	Facet joint syndrome	back
N14y	Other back symptoms	back
N14z	Back disorder/symptom NOS	back
N14z	Back disorders NOS	back
N14z	Spinal disorder NOS	back
N1y	Vertebral column disorders OS	back
N1y0	Rec atlantoax subl + myelopath	neck
N1z	Vertebral column disorder NOS	back
N21	Peripheral enthesopathies	unspecified
N210	Bursitis - shoulder	shoulder
N211	Rotator cuff shoulder syndrome	shoulder
N211	Rotator cuff shoulder syndrome and allied disorders	shoulder
N211	Shoulder syndrome	shoulder
N2110	Rotator cuff syndrome unspecif	shoulder girdle
N2110	Rotator cuff syndrome unspecified	shoulder girdle
N2110	Supraspinatus syndrome	shoulder girdle
N2111	Calcifying tendinitis shoulder	shoulder
N2112	Bicipital tenosynovitis	upper arm
N2113	Supraspinatus tendinitis	shoulder girdle
N2114	Part thickn rotator cuff tear	shoulder
N2115	Full thickn rotator cuff tear	shoulder
N2115	Full thickness rotator cuff tear	shoulder
N2116	Subacromial bursitis	shoulder
N2117	Subdeltoid bursitis	upper arm
N2118	Bursitis of shoulder	shoulder

N211z	Painful arc syndrome	shoulder
N211z	Rotator cuff syndrome NOS	shoulder
N211z	Subacromial bursitis	shoulder
N212	Other shoulder affections NEC	shoulder
N2121	Scapulohumeral fibrositis	shoulder girdle
N2122	Subacromial impingement	shoulder
N2123	Coracoid impingement	shoulder
N2124	Impingement syndr of shoulder	shoulder
N2124	Impingement syndrome of shoul	shoulder
N2124	Impingement syndrome of shoulder	shoulder
N2125	Shoulder tendonitis	shoulder
N212z	Other shoulder affect.NEC NOS	shoulder
N213	Enthesopathy of elbow region	elbow
N213	Enthesopathy of the elbow region	elbow
N2130	Elbow enthesopathy unspecified	elbow
N2131	Golfer's elbow	elbow
N2131	Golfers elbow	elbow
N2131	Medial epicondylitis - elbow	elbow
N2131	Medial epicondylitis of the elbow	elbow
N2132	Lateral epicondylitis - elbow	elbow
N2132	Lateral epicondylitis of the elbow	elbow
N2132	Tennis elbow	elbow
N2132	Tennis elbow - epicondylitis	elbow
N2133	Bursitis - elbow	elbow
N2133	Olecranon bursitis	elbow
N2134	Biceps tendinitis	upper arm
N2135	Triceps tendinitis	upper arm
N213z	Elbow enthesopathy NOS	elbow
N214	Enthesopathy of wrist/carpus	wrist/hand
N2140	Bursitis of wrist	wrist
N2141	Bursitis of hand	hand
N214z	Wrist/carpus enthesopathy NOS	wrist/hand
N215	Enthesopathy of hip region	hip
N2150	Hip enthesopathy, unspecified	hip
N2151	Bursitis - hip	hip
N2151	Bursitis of hip	hip
N2152	Gluteal tendinitis	buttock
N2153	Iliac crest spur	pelvis
N2154	Psoas tendinitis	thigh
N2155	Trochanteric tendinitis	thigh
N2156	Adductor tendinitis	thigh
N2157	Trochanteric bursitis	thigh
N2158	Snapping hip	hip
N2159	Iliotibial band syndrome	knee

N215A	Ischial bursitis	pelvis
N215z	Hip enthesopathy NOS	hip
N216	Enthesopathy of knee	knee
N216	Enthesopathy of the knee	knee
N2160	Bursitis - knee	knee
N2160	Bursitis of knee NOS	knee
N2160	Bursitis of the knee NOS	knee
N2160	Popliteal bursitis	knee
N2160	Semi-membranosus bursitis	unspecified
N2161	Pes anserinus tendin./bursitis	unspecified
N2162	Tibial collateral lig.bursitis	knee
N2163	Fibular collat.lig.bursitis	knee
N2164	Patellar tendinitis	knee
N2165	Prepatellar bursitis	knee
N2166	Infrapatellar bursitis	knee
N2167	Subpatellar bursitis	knee
N2168	Biceps femoris tendinitis	thigh
N2169	Semimembranosus tendinitis	unspecified
N216z	Knee enthesopathy NOS	knee
N216z	Suprapatellar bursitis	knee
N217	Enthesopathy of ankle/tarsus	ankle/foot
N217	Tarsus enthesopathy	ankle/foot
N217	Tendinitis of ankle/tarsus	ankle/foot
N2170	Enthesopathy of ankle unspec.	ankle
N2171	Enthesopathy of tarsus unspec.	foot
N2172	Metatarsalgia NOS	foot
N2173	Achilles bursitis	ankle
N2173	Haglunds deformity	foot
N2174	Achilles tendinitis	ankle
N2175	Tibialis anterior tendinitis	lower leg
N2176	Tibialis posterior tendinitis	lower leg
N2177	Calcaneal spur	foot
N2178	Peroneal tendinitis	lower leg
N2179	Plantar fasciitis	foot
N217A	Posterior calcaneal exostosis	foot
N217B	Anterior ankle impingement	ankle
N217C	Fibular impingement	lower leg
N217z	Ankle/tarsus enthesopathy NOS	ankle/foot
N21y	Other periph. enthesopathies	unspecified
N21y0	Anterior shin splints	lower leg
N21y1	Posterior shin splints	lower leg
N21z	Enthesopathy NOS	unspecified
N21z0	Capsulitis NOS	unspecified
N21z2	Adductor tendonitis	unspecified

N21z2	Bicepital tendonitis	unspecified
N21z2	Supraspinatus tendonitis	shoulder
N21z2	Tendinitis NOS	unspecified
N21z2	Tendonitis adductor	unspecified
N21z2	Tendonitis bicepital	unspecified
N21z2	Tendonitis NOS	unspecified
N21z3	Bone spur NOS	unspecified
N21z3	Exostosis of unspecified site	unspecified
N21z3	Osteophyte of unspecified site	unspecified
N21z4	Subungual exostosis	hand & foot
N21z5	Subungual exostosis great toe	foot
N21z5	Subungual exostosis of great toe	foot
N21z6	Subungual exostosis lesser toe	foot
N21z6	Subungual exostosis of lesser toe	foot
N21z7	Exostosis	unspecified
N21zz	Peripheral enthesopathy NOS	unspecified
N22	Other synovium/tendon/bursa	unspecified
N220	Synovitis and tenosynovitis	unspecified
N220	Synovitis/tenosynovitis	unspecified
N2200	Synovitis or tenosynovitis NOS	unspecified
N2200	Synovitis/tenosynovitis NOS	unspecified
N2201	Synovit./tenosynovitis+dis EC	unspecified
N2202	Tendon sheath giant cell tumor	unspecified
N2204	De Quervain's disease	wrist/hand
N2204	De Quervains disease	wrist/hand
N2204	Radial styloid tenosynovitis	wrist/hand
N2204	Thumb trigger	hand
N2204	Trigger thumb - acquired	hand
N2205	Other hand/wrist tenosynovitis	wrist/hand
N2205	Other tenosynovitis of hand	hand
N2205	Other tenosynovitis of the hand	hand
N2205	Other tenosynovitis of the wrist	wrist
N2205	Other tenosynovitis of wrist	wrist
N2205	Synovitis/tenosyn.- hand	hand
N2205	Synovitis/tenosyn.- wrist	wrist
N2205	Tendonitis of thumb	hand
N2205	Tensynovitis of fingers	wrist/hand
N2206	Tenosynovitis of ankle	ankle
N2207	Tenosynovitis of foot	foot
N220A	Flexor tenosynovitis of wrist	wrist
N220B	Flexor tenosynovitis of finger	hand
N220C	Flexor tenosynovitis of thumb	hand
N220D	Extensor tenosynovitis of wrist	wrist
N220D	Extensor tenosynovitis-wrist	wrist

N220E	Extensor tenosynovitis of finger	hand
N220E	Extensor tenosynovitis-finger	hand
N220F	Extensor tenosynovitis of thumb	hand
N220F	Extensor tenosynovitis-thumb	hand
N220G	Acquired trigger thumb	hand
N220H	Achilles tenosynovitis	ankle
N220J	Tibialis ant tenosynovitis	lower leg
N220J	Tibialis anterior tenosynovitis	lower leg
N220K	Tibialis post tenosynovitis	lower leg
N220K	Tibialis posterior tenosynovitis	lower leg
N220L	Exten hal longus tenosynovitis	lower leg
N220M	Exten dig longus tenosynovitis	foot
N220N	Peroneus longus tenosynovitis	lower leg
N220P	Peroneus brevis tenosynovitis	foot
N220Q	Transient synovitis	unspecified
N220R	Chron crep synovit hand/wrist	wrist/hand
N220S	Synovitis of hip	hip
N220T	Synovitis NOS	unspecified
N220V	Synovitis of knee	knee
N220z	Other synovitis and tenosynovitis	unspecified
N220z	Other synovitis/tenosynovitis	unspecified
N220z	Shoulder synovitis	shoulder
N220z	Synovitis of knee	knee
N221	Bunion	foot
N222	Specific bursitides	unspecified
N2220	Beat elbow	elbow
N2221	Beat hand	hand
N2222	Beat knee	knee
N2223	Miners' elbow	elbow
N2224	Miners' knee	knee
N2225	Housemaids knee	knee
N2225	Housemaids' knee	knee
N2226	Calcium deposit in bursa	unspecified
N222z	Specific bursitides NOS	unspecified
N223	Bursitis NOS	unspecified
N223	Postcalcaneal bursitis	unspecified
N22y4	Synovial plica	knee
N22y4	Synovial plica of knee	knee
N22yN	Achilles degeneration	ankle
N22yz	Other synovial disorder NOS	unspecified
N22yz	Other tendon disorder NOS	unspecified
N22z	Synovial/tendon problem NOS	unspecified
N22z	Synovium/tendon/bursa dis.NOS	unspecified
N23	Fascia disorders	unspecified

N23	Ligament disorders	unspecified
N23	Muscle, ligament and fascia disorders	unspecified
N23	Muscle/ligament disorder NOS	unspecified
N23	Muscle/ligament/fascia disord.	unspecified
N232	Muscle wasting and disuse atrophy NEC	unspecified
N232	Muscle wasting/atrophy NEC	unspecified
N2322	Muscle wasting NEC	unspecified
N232z	Muscle wasting/atrophy NEC NOS	unspecified
N232z	Muscle wasting/disuse atrophy NEC NOS	unspecified
N233z	Other specif.musc.disorder NOS	unspecified
N234	Laxity of ligament	unspecified
N235	Double-jointed (hypermobility)	unspecified
N235	Hypermobility syndrome	unspecified
N239	Myofascial pain syndrome	unspecified
N23y	Other muscle/ligament/fascia	unspecified
N23y1	Calcification of ligament	unspecified
N23y4	Spasm of muscle	unspecified
N23y9	Calcific tendinitis	unspecified
N23yA	Diastasis of muscle	unspecified
N23yD	Muscle strain	unspecified
N23yE	Spasm of back muscles	back
N23yz	Other musc./lig./fasc.dis.NOS	unspecified
N23z	Muscle/ligament disorder NOS	unspecified
N23z	Muscle/ligament/fascia dis.NOS	unspecified
N24	Other soft tissue disorders	unspecified
N2401	Fibrositis unspecified	unspecified
N2402	Muscular rheumatism	unspecified
N2403	Rheumatic pain	unspecified
N2405	Fibrositis of neck	neck
N2406	Fibrositis arm	upper limb
N241	Myalgia and myositis unspecified	unspecified
N241	Myalgia/Myositis - Lower Leg	lower leg
N241	Myalgia/myositis - multiple	unspecified
N241	Myalgia/Myositis - Shoulder	shoulder
N241	Myalgia/Myositis - Upper Arm	upper arm
N241	Myalgia/Myositis -Pelvis/Thigh	pelvis/thigh
N241	Myalgia/myositis NOS	unspecified
N241	Myalgia/myositis unspecified	unspecified
N241-97	Myalgia/myositis - shoulder	shoulder
N2410	Intercostal myalgia	chest
N2410	Muscle pain	unspecified
N2410	Myalgia unspecified	unspecified
N2411	Myositis unspecified	unspecified
N241z	Myalgia or myositis NOS	unspecified

N241z	Myalgia/myositis - NOS	unspecified
N241z	Myalgia/myositis NOS	unspecified
N242	Neuralg./neurit./radicul.unsp.	unspecified
N242	Neuralgia/neuritis - fore arm	forearm
N242	Neuralgia/Neuritis - Hand	hand
N242	Neuralgia/Neuritis - Lower Leg	lower leg
N242	Neuralgia/neuritis NOS	unspecified
N242-92	Neuralgia/neuritis - lower leg	lower leg
N242-93	Neuralgia/Neurit.-Pelvis/Thigh	pelvis/thigh
N2420	Neuralgia unspecified	unspecified
N2421	Neuritis unspecified	unspecified
N2422	Radiculitis unspecified	unspecified
N2423	Neuropathic pain	unspecified
N242z	Neuralg./neurit./radiculit.NOS	unspecified
N242z	Neuralgia/neuritis - NOS	unspecified
N242z	Policeman's disease	unspecified
N2431	Hypertrophy of knee fat pad	knee
N244	Fasciitis unspecified	unspecified
N245	Ankle pain	ankle
N245	Arm pain	upper limb
N245	Foot pain	foot
N245	Hand pain	hand
N245	Heel pain	foot
N245	Leg pain	lower limb
N245	Pain in buttock	buttock
N245	Pain in left arm	upper limb
N245	Pain in left leg	lower limb
N245	Pain In Left Leg	lower limb
N245	Pain in limb	limb
N245	Pain in limb - multiple	limb
N245	Pain In Limb NOS	limb
N245	Pain in right arm	upper limb
N245	Pain In Right Arm	upper limb
N245	Pain in right leg	lower limb
N245	Pain In Right Leg	lower limb
N245	Shoulder pain	shoulder
N245	Thigh pain	thigh
N245-94	Pain in limb NOS	limb
N2450	Finger pain	hand
N2450	Hand pain	hand
N2450	Thumb pain	hand
N2451	Foot pain	foot
N2451	Toe pain	foot
N2452	Aching leg syndrome	lower limb

N2452	neuropathic pain	unspecified
N2452	Pain in leg	lower limb
N2453	Pain in arm	upper limb
N2454	Calf pain	lower leg
N2455	Axillary pain	upper arm
N2455	Pain In Right Leg	lower limb
N2456	Pain In Left Leg	lower limb
N2456	Tender heel pad	foot
N2457	Pain In Right Arm	upper limb
N2457	Shoulder pain	shoulder
N2459	Pain in buttock	buttock
N247	Other musculoskel.limb sympts.	unspecified
N2470	Swelling of calf	lower leg
N2470	Swelling of limb	limb
N2470	Swollen legs	lower limb
N2470	Swollen lower leg	lower leg
N2471	Leg cramps	lower limb
N2471	Night cramps	unspecified
N2472	Cramp	unspecified
N247z	Hand cramps	hand
N247z	Musculoskel.limb symptoms NOS	limb
N247z	Musculoskeletal limb symptoms NOS	limb
N2480	Myofascial pain syndrome	unspecified
N24z	Polyalgia	unspecified
N24z	Soft tissue disorders NOS	unspecified
N3	Musculosk.inflam/deform.+other	unspecified
N30z8	Costochondritis NOS	chest
N32	Osteochondropathies	unspecified
N320	Vertebral epiphysitis	back
N3200	Juvenile spine osteochond.unsp	back
N3201	Scheuermann's disease	back
N3201	Scheuermanns disease	back
N3202	Calve's vertebral osteochondr.	back
N320z	Juvenile spine osteochondr.NOS	back
N321	Pelvis juvenile osteochondrop.	pelvis/hip
N3210	Juv.osteochond.hip/pelvis unsp	pelvis/hip
N3211	Pseudocoxalgia	pelvis/hip
N3212	Ischiopubic synchondrosis	pelvis
N3213	Juvenile osteochond.-acetabul.	pelvis
N3214	Juven.osteochond.-iliac crest	pelvis
N3215	Symphysis pubis osteochond.	pelvis
N3216	Coxa plana	unspecified
N3217	Pseudocoxalgia	pelvis/hip
N321z	Juv.osteochond.-hip/pelvis NOS	pelvis/hip

N322	Non tr.slipped upper fem.epiph	hip
N3221	Non traum acute-on-chron SUFE	hip
N3222	Non traumatic chronic SUFE	hip
N323	Juvenile osteochondritis -hand	hand
N3230	Juven.osteochond.arm unspecif.	upper limb
N3231	Juven.osteochond.hand unspecif	hand
N3234	Humerus head juv. osteochondr.	upper arm
N3235	Metacarpal head juv. osteoch.	hand
N3237	Radial head juven. osteochond.	forearm
N323z	Juven.osteochond.-arm/hand NOS	upper limb
N324	Juvenile osteochond.- leg/foot	lower limb
N324	Juvenile osteochondrosis - leg	lower limb
N3240	Juvenile osteochondr.-leg unsp	lower limb
N3243	Juv.osteoch.secondary.pat.ctre	knee
N3244	Osgood-Schlatter's dis.(tibia)	lower leg
N3244	Osgood-Schlatters dis - osteochondrosis of tibial	lower leg
N3244	Osgood-Schlatters dis.(tibia)	lower leg
N3244	Tibial tubercle juv. osteoch.	lower leg
N324z	Juvenile osteochondr.-leg,NOS	lower limb
N325	Juvenile osteochondrosis-foot	foot
N3250	Juvenile osteochond.-foot unsp	foot
N325z	Juvenile osteochond.-foot NOS	foot
N326	Other juven.osteochondroses	unspecified
N3260	Juvenile apophysitis NOS	unspecified
N3261	Juvenile epiphysitis NOS	unspecified
N3262	Juvenile osteochondritis NOS	unspecified
N3263	Juvenile osteochondrosis NOS	unspecified
N326z	Juvenile osteochondroses NOS	unspecified
N327	Osteochond dissecans	unspecified
N327	Osteochondritis dissecans	unspecified
N3270	Osteochondritis dissec-patella	knee
N3271	Osteochondr diss-lat fem cond	thigh
N3272	Other osteochondr dissec-knee	knee
N3273	Osteochondr dissec-hum head	upper arm
N3274	Osteochondr dissec-capitellum	unspecified
N3275	Osteochondr dissec-radial head	forearm
N3276	Other osteochondr diss-elbow	elbow
N3277	Osteochondritis dissec-wrist	wrist
N3278	Osteochondr dissec-fem head	thigh
N3279	Osteochondritis dissec-talus	foot
N327y	Osteochondr dissec-other site	unspecified
N328	Juv osteochondrosis of spine	back
N32y	Slipped radial epiphysis	unspecified
N32yz	Other spec.osteochondrop.NOS	unspecified

N32z	Osteochondropathy NOS	unspecified
N32z0	Apophysitis NOS	unspecified
N32z1	Epiphysitis NOS	unspecified
N32z2	Osteochondritis NOS	unspecified
N32z2	Osteochondritis of knee	knee
N32z3	Osteochondrosis NOS	unspecified
N32zz	Osteochondropathy NOS	unspecified
N33	Other bone/cartilage disorders	unspecified
N3370	Disuse atrophy of bone	unspecified
N3372	Algodystrophy of hand	hand
N3373	Algodystrophy of knee	knee
N3374	Algodystrophy of foot	foot
N337z	Algoneurodystrophy NOS	unspecified
N33A	Bone pain	unspecified
N33A0	Bony pelvic pain	pelvis
N33A1	Clavicle pain	shoulder girdle
N33C	Complex regionl pain syndrom I	unspecified
N33z	Bone/cartilage disorder NOS	unspecified
N33z1	Epiphyseal arrest	unspecified
N33z2	Chondromalacia NOS	unspecified
N33z8	Complete epiphyseal arrest	unspecified
N33z9	Partial epiphyseal arrest	unspecified
N33zE	Costochondritis	chest
N33zF	Disorder of bone unspecified	unspecified
N33zF	Disorder of bone, unspecified	unspecified
N33zG	Disorder of cartilage, unspec	unspecified
N33zJ	Chondritis	unspecified
N33zL	Osteitis of symphysis pubis	pelvis
N33zz	Bone or cartilage disorders NOS	unspecified
N33zz	Bone/cartilage disorders NOS	unspecified
N33zz	Costochondritis NOS	chest
N34	Fallen arches	foot
N34	Flat foot	foot
N34	Flat foot - pes planus	foot
N340	Pes planus - acquired	foot
N3400	Hypermobile flat foot	foot
N3401	Rigid flat foot	foot
N341	Talipes planus - acquired	foot
N34z	Arches fallen	foot
N34z	Flat foot NOS	foot
N35	Acquired deformities of toe	foot
N350	Hallux valgus - acquired	foot
N351	Hallux varus - acquired	foot
N352	Hallux rigidus - acquired	foot

N353	Acq hammer deformity-great toe	foot
N353	Hallux malleus	foot
N354	Hammer toe - acquired	foot
N354	Other hammer toe - acquired	foot
N355	Claw toe - acquired	foot
N356	Clawing of great toe	foot
N357	Crossover toe	foot
N358	Mallet toe	foot
N359	Bunionette	foot
N35A	Over-riding 5th toe	foot
N35y	Other acquired toe deformity	foot
N3631	Coxa valga - acquired	hip
N3632	Coxa vara - acquired	hip
N3633	Acq internal femoral torsion	hip
N3634	Persistent femoral anteversion	hip
N3635	Acq external femoral torsion	hip
N363z	Acquired hip deformity NOS	hip
N364	Acquired genu valgum/varum	knee
N3640	Acquired genu valgum	knee
N3640	Knock knee	knee
N3641	Acquired genu varum	knee
N3641	Bow legged	lower limb
N364z	Acquired genu valgum/varum NOS	knee
N365	Genu recurvatum - acquired	knee
N366	Acquired knee deformity NOS	knee
N3660	Flexion deformity of knee	knee
N367	Acquired ankle/foot deformity	ankle/foot
N367	Other acquir.ankle/foot deform	ankle/foot
N3670	Acquir.ankle/foot deform.unsp.	ankle/foot
N3671	Acquired equinovarus-clubfoot	ankle/foot
N3672	Acquired equinus foot deform.	ankle/foot
N3672	Acquired equinus foot deformity	foot
N3673	Aquired cavus foot deformity	foot
N3674	Acquired claw foot	foot
N3675	Acquired cavovarus foot deform	foot
N3675	Acquired cavovarus foot deformity	foot
N3676	Other acquir.calcaneus deform.	foot
N3677	Acquired talipes NEC	foot
N3678	Acquired varus heel	foot
N3679	Acquired valgus heel	foot
N367A	Plantar flexion-midtarsal jnt	foot
N367F	Acq plantar-flexed forefoot	foot
N367G	Acq plantar-flexed first ray	foot
N367H	Acq plantar-flexed fifth ray	foot

N367J	Acquired dorsiflexed forefoot	foot
N367K	Acquired dorsiflexed first ray	foot
N367L	Acquired supinated forefoot	foot
N367M	Acquired pronated forefoot	foot
N367N	Acquired forefoot adductus	foot
N367P	Acquired forefoot abductus	foot
N367Q	Serpentine foot	foot
N367z	Acquired ankle or foot deformity NOS	ankle/foot
N367z	Acquired ankle/foot deform.NOS	ankle/foot
N368	Other knee deformity	knee
N3680	Acq internal tibial torsion	lower leg
N3681	Acq external tibial torsion	lower leg
N3681	Acquired external tibial torsion	lower leg
N3682	Chronic instability of knee	knee
N369	Flexion deformity	unspecified
N36y	Other deformity of bone	unspecified
N36y	Torsion tibia	lower leg
N36y0	Acquired unequal leg length	lower limb
N36y1	Acquired unequal arm length	upper limb
N37	Curvature of spine	back
N37	Curvature of spine - acquired	back
N370	Adolescent postural kyphosis	back
N371	Acquired kyphosis	back
N3710	Acquired postural kyphosis	back
N3711	Radiation kyphosis	back
N3712	Post-laminectomy kyphosis	back
N3713	Kyphosis due to oth treatment	back
N371z	Acquired kyphosis NOS	back
N372	Acquired lordosis	lower back
N3720	Acquired postural lordosis	lower back
N3721	Post-laminectomy lordosis	lower back
N3722	Other post-surgical lordosis	lower back
N372z	Acquired lordosis NOS	lower back
N373	Kyphoscoliosis and scoliosis	back
N373	Kyphoscoliosis/scoliosis	back
N373	Kyphoscoliosis/scoliosis-acqu.	back
N3730	Idiopathic scoliosis	back
N3731	Idiopathic kyphoscoliosis	back
N3732	Resolving infant.idiopath.scol	back
N3733	Progressive infant.idiop.scol.	back
N3734	Radiation scoliosis	back
N3735	Thoracogenic scoliosis	upper back
N3736	Postural scoliosis	back
N3737	Adolescent idiopath scoliosis	back

N3737	Adolescent idiopathic scoliosis	back
N3738	Post-surgical scoliosis	back
N3739	Scoliosis due to oth treatment	back
N373z	Kyphoscoliosis or scoliosis NOS	back
N373z	Kyphoscoliosis/scoliosis NOS	back
N374	Spine curvature+other condits.	back
N3740	Curvature of spine unspecified	back
N3741	Kyphosis + other condition	back
N3742	Lordosis + other condition	lower back
N3743	Scoliosis + other condition	back
N3744	Kyphosis in skeletal dysplasia	back
N3745	Neuromuscular kyphosis	back
N3747	Lordosis in skeletal dysplasia	lower back
N3748	Lordosis in hip disease	lower back
N3749	Neuromuscular lordosis	lower back
N374A	Scoliosis in skelet dysplasia	back
N374B	Neuromuscular scoliosis	back
N374C	Scoliosis in neurofibromatosis	back
N374D	Scoliosis in conn tiss anomal	back
N374E	Flatback syndrome	back
N374W	Lordosis unspecified	lower back
N374W	Lordosis, unspecified	lower back
N374X	Other and unspecified kyphosis	back
N374X	Other+unspecified kyphosis	back
N374z	Spine curvature+other cond.NOS	back
N37y	Other curvatures of spine	back
N37z	Curvature of spine NOS	back
N37z0	Acquired hunchback	back
N37zz	Curvature of spine NOS	back
N38	Other acquired deformity	unspecified
N383	Acquired chest and rib deformity	chest
N383	Acquired chest/rib deformity	chest
N3830	Acquired chest deformity unsp.	chest
N3831	Acquired rib deformity unsp.	chest
N3831	Acquired rib deformity, unspecified	chest
N3832	Acquired pectus carinatum	chest
N3833	Acquired pectus excavatum	chest
N383z	Acquired chest/rib deform.NOS	chest
N385	Acquired deformity spine NOS	back
N386	Pelvic obliquity	pelvis
N38y	Other acquired deformity	unspecified
N38yz	Other acquired deformity NOS	unspecified
N38z	Acquired deformity NOS	unspecified
N39	Nonallopathic lesions, NEC	unspecified

N390	Nonallopathic lesion-head reg	head
N391	Nonallopathic lesion-cervical	neck
N392	Nonallopathic lesion-thoracic	upper back
N393	Nonallopathic lesion-lumbar	lower back
N394	Nonallopathic lesion-sacral	pelvis
N395	Nonallopathic lesion-pelvic	pelvis
N396	Nonallopathic lesion-legs	lower limb
N397	Nonallopathic lesion-arms	upper limb
N398	Nonallopathic lesion-rib cage	chest
N399	Nonallopathic lesion-abd.+oth.	abdomen
N39z	Nonallopathic lesion NEC NOS	unspecified
N3y	Musculoskeletal disorders OS	unspecified
N3y0	Biomec lesn,not elsewh clas	unspecified
N3y00	Segmental & somatic dysfunctn	unspecified
N3y01	Subluxatn complex (vertebral)	back
N3z	Musculoskeletal problems NOS	unspecified
N3z	Other musculoskeletal dis. NOS	unspecified
N3z	Other musculoskeletal disorder NOS	unspecified
Ny	Musculoskeletal diseases OS	unspecified
Ny2	Repetitive strain injury	unspecified
Nyu	[X]Ad muscskl+con t dis cls tm	unspecified
Nyu35	[X]Other derangements/patella	knee
Nyu36	[X]Other disorders of patella	knee
Nyu37	[X]Other meniscus derangements	knee
Nyu38	[X]O spontn disrptn/lig(s)knee	knee
Nyu39	[X]Oth intrnl derangemnts/knee	knee
Nyu3A	[X]Oth articulr cartilag disor	unspecified
Nyu3B	[X]O spcf joint derangmnts,NEC	unspecified
Nyu3C	[X]Other instability of joint	unspecified
Nyu3D	[X]Other spcfd joint disorders	unspecified
Nyu3E	[X]Disorder of patella, unspec	knee
Nyu5	[X]Deforming dorsopathies	back
Nyu50	[X]Other secondary kyphosis	back
Nyu51	[X]Other+unspecified kyphosis	back
Nyu52	[X]Other lordosis	lower back
Nyu53	[X]Other idiopathic scoliosis	back
Nyu54	[X]Other secondary scoliosis	back
Nyu55	[X]Other forms of scoliosis	back
Nyu57	[X]O recur atlantoaxl subluxtn	neck
Nyu58	[X]Oth recur vertebrl subluxtn	back
Nyu59	[X]Oth spcf deform dorsopaths	back
Nyu5A	[X]Lordosis, unspecified	lower back
Nyu5B	[X]Spin osteochondrosis, unsp	back
Nyu73	[X]Lumb+o intrvrt disc d+mylop	back

Nyu74	[X]Lumb+o intvt disc d+radiclp	back
Nyu75	[X]O spc intervert disc displm	back
Nyu78	[X]Sacrococygeal disorders,NEC	pelvis
Nyu7A	[X]Other dorsalgia	back
Nyu7B	[X]Cervical disc disord, unsp	neck
Nyu8	[X]Disorders of muscles	unspecified
Nyu83	[X]Oth ruptr/muscl(nontraumtc)	unspecified
Nyu84	[X]Muscle wasting and atrophy NEC	unspecified
Nyu84	[X]Muscle wasting+trophy,NEC	unspecified
Nyu8B	[X]Disorder of muscle unspecified	unspecified
Nyu8B	[X]Disorder of muscle, unspec	unspecified
Nyu9	[X]Disorders/synovium+tendon	unspecified
Nyu91	[X]Oth synovitis+tenosynovitis	unspecified
Nyu92	[X]Spontans ruptr/oth tendons	unspecified
Nyu94	[X]O spcf diso/synovium+tendon	unspecified
Nyu95	[X]Synovitis+tenosyn/bact d CE	unspecified
Nyu96	[X]O diso/synovm+tendon/dis CE	unspecified
Nyu97	[X]Synovial hypertrophy, NEC	unspecified
NyuA	[X]Other soft tissue disorders	unspecified
NyuA0	[X]Other bursitis of elbow	elbow
NyuA1	[X]Other bursitis of knee	knee
NyuA2	[X]Other bursitis of hip	hip
NyuA3	[X]O sft t d rl/use,overu+prss	unspecified
NyuA6	[X]Other bursitis NEC	unspecified
NyuA6	[X]Other bursitis,NEC	unspecified
NyuA7	[X]Other bursa disorder	unspecified
NyuA8	[X]Fasciitis,NEC	unspecified
NyuAA	[X]Oth sft tis diso/oth dis CE	unspecified
NyuAC	[X]O enthespath/lw limb,exc ft	lower limb
NyuAC	[X]O enthespath/lw limbexc ft	lower limb
NyuAD	[X]Other enthesopathy of foot	foot
NyuAE	[X]Other enthesopathies,NEC	unspecified
NyuAF	[X]Oth spcf soft tissu disords	unspecified
NyuAG	[X]Uns sof tis d,use/overu/prs	unspecified
NyuAJ	[X]Enthesopathy lowr limb,unsp	lower limb
NyuD	[X]Chondropathies	unspecified
NyuD0	[X]O juv osteochndrsis/hp+pelv	pelvis/hip
NyuD1	[X]O juv osteochndrsis/up limb	upper limb
NyuD2	[X]O spf juvnl osteochondrosis	unspecified
NyuD3	[X]Oth spc osteochondropathies	unspecified
NyuD4	[X]Oth spcf disordrs/cartilage	unspecified
NyuDE	[X]Disorder cartilage, unspec	unspecified
NyuE	[X]Oth dis musculosk+connect	unspecified
NyuE0	[X]O spc acq defrm/muscskl sys	unspecified

NyuE2	[X]O postproced muscskel disor	unspecified
NyuE3	[X]Other biomechanical lesions	unspecified
NyuE4	[X]Postproc muscsk disord,unsp	unspecified
NyX	Postproc muscsk disord,unsp	unspecified
Nz	Musculoskeletal and connective tissue diseases NOS	unspecified
Nz	Musculoskeletal diseases NOS	unspecified
OX353C	Sciatica Chronic /ox	lower back & lower limb
OX709MF	Sore Feet /ox	foot
OX7259AP	Intervertebral Disc Prolapsed /ox	back
OX7259AP	Prolapsed Disc /ox	back
OX7280AD	Pain Neck /ox	neck
OX7289A	Back Pain With Sciatica /ox	lower back & lower limb
OX7289CB	Chronic Backache /ox	back
OX7289CH	back pain /ox	back
OX735AA	Scoliosis Acquired /ox	back
OX738DB	Deformity Foot /ox	foot
OX738VC	In-Toeing /ox	foot
OX7873E	Pain Knee /ox	knee
OX8479	Back Strain/Sprain /ox	back
OX848ML	Pulled Muscle /ox	unspecified
OX8830L	Laceration Finger /ox	hand
OX9963B	Injury Wrist /ox	wrist
OX9965F	Injury Finger /ox	hand
OX9967B	Injury Foot /ox	foot
OX9967C	Injury Knee /ox	knee
OXT741	Leg Problem /ox	lower limb
R00z2	[D]General aches and pains	unspecified
R00z2	[D]Pain generalized	unspecified
R01	[D]Musculoskeletal symptoms	unspecified
R01	[D]Nerv/musculoskeletal sympt.	unspecified
R01z	[D]Nerv/musculoskel.symp.other	unspecified
R01z1	[D]Growing pains - limbs	limb
R01z2	[D]Musculoskeletal pain	unspecified
R01zz	[D]Nerv/musculoskel.sympt.NOS	unspecified
R022K	[D]Buttock swelling	buttock
R04	[D]Head and neck symptoms	head/neck
R0400	[D]Face ache	head
R0400	[D]Facial pain	head
R040z	[D]Jaw pain	head
R040z	[D]Pain in head NOS	head
R042	[D]Head swelling/mass/lump	head
R042	[D]Neck swelling/mass/lump	neck
R042	[D]Swell.masslump head/neck	head/neck

R0420	[D]Swelling face	head
R0420	[D]Swelling in head or neck	head/neck
R04z	[D]Head and neck other sympt.	head/neck
R04zz	[D]Head and neck symptoms NOS	head/neck
R065	[D]Chest pain	chest
R0650	[D] Retrosternal chest pain	chest
R0650	[D]Chest pain unspecified	chest
R0652	[D]Anterior chest wall pain	chest
R0659	[D]Parasternal chest pain	chest
R065A	[D]Musculoskeletal chest pain	chest
R065B	[D]Non cardiac chest pain	chest
R065B	[D]Non-cardiac chest pain	chest
R065C	[D]Retrosternal chest pain	chest
R065D	[D]Central chest pain	chest
R065z	[D]Chest pain NOS	chest
R090B	[D]Groin pain	pelvis
R090C	[D]Loin pain	pelvis
R090G	[D] Pelvic pain	pelvis
R090G	[D] Perineal pain	pelvis
R090G	[D]Pelvic and perineal pain	pelvis
R090J	[D]Right upper quadrant pain	trunk
R090K	[D]Left upper quadrant pain	trunk
R90C	Left Loin Pain	pelvis
Ryu04	[X]Other chest pain	chest
Ryu3	[X]Sym/sign inv nv/muscskel sy	unspecified
Ryu70	[X]Other chronic pain	unspecified
S4	Subluxations	unspecified
S402	Closed subluxation jaw	head
S460	Acute meniscal tear medial	knee
S460	Bucket handle tear - current injury	knee
S460	Bucket handle tear-current inj	knee
S4600	Ac meniscal tear,med,ant horn	knee
S4600	Ac meniscal tearmedant horn	knee
S4601	Ac meniscal tear,med,post horn	knee
S4601	Ac meniscal tearmedpost horn	knee
S4602	Ac menscl tear,med,bckt hndle	knee
S4602	Ac menscl tearmedbckt hndle	knee
S4603	Ac meniscal tear,med,radial	knee
S4604	Ac mnscl tr,med,periph,dtchmt	knee
S4605	Ac mnscl tear,med,horiz clvge	knee
S461	Acute meniscal tear lateral	knee
S461	Acute meniscal tear, lateral	knee
S4610	Ac meniscal tear,lat,ant horn	knee
S4611	Ac meniscal tear,lat,post horn	knee

S4611	Ac meniscal tearlatpost horn	knee
S4612	Ac menscl tear,lat,bckt hndle	knee
S4612	Ac menscl tearlatbckt hndle	knee
S4613	Ac meniscal tear,lat,radial	knee
S4613	Ac meniscal tearlatradial	knee
S4614	Ac mnscl tr,lat,periph,dtchmt	knee
S4615	Ac mnscl tear,lat,horiz clvge	knee
S462	Other acute meniscus tear	knee
S46B	Tear/articulr cart/knee,currnt	knee
S46D	Recurrent subluxation of patella	knee
S46D	Recurrent subluxation, patella	knee
S498	Cls sublux cervical spine	neck
S4980	Cls sublux cervical spine,unsp	neck
S4981	Cls sublux atlanto-occiptl jt	neck
S4982	Cls sublux atlanto-axial jt	neck
S4983	Closed subluxation C2/C3	neck
S4984	Closed subluxation C3/C4	neck
S4985	Closed subluxation C4/C5	neck
S4986	Closed subluxation C5/C6	neck
S4987	Closed subluxation C6/C7	neck
S4988	Closed subluxation C7/T1	neck
S4989	Cl spn sublx+cerv crd lsn,unsp	neck
S498A	Cl spn sublx+comp cerv crd lsn	neck
S498B	Cl spn sublux+ant cerv crd lsn	neck
S498C	Cl spn sublx+cntrl crv crd lsn	neck
S498D	Cl spn sublux+post crv crd lsn	neck
S498x	Cls sublux mlti cerv vertebrae	neck
S498z	Cls sublux cerv vertebra NOS	neck
S49A	Cls sublux thrcic+lumbar spine	back
S49A0	Closed subluxation lumbar spine	lower back
S49A0	Cls sublux lumbar spine	lower back
S49A1	Cls sublux thrcic spine	upper back
S49A2	Cl spn sublx+thrc crd lsn,unsp	upper back
S49A3	Cl spn sublx+comp thrc crd lsn	upper back
S49A4	Cl spn sublx+ant thrc crd lsn	upper back
S49A5	Cl spn sublx+cent thrc crd lsn	upper back
S49A6	Cl spn sublx+post thrc crd lsn	upper back
S49A7	Cl spn sublx+lmbr crd lsn,unsp	lower back
S49A8	Cl spn sublx+comp lmbr crd lsn	lower back
S49A9	Cl spn sublx+ant lmbar crd lsn	lower back
S49AA	Cl spn sublx+cent lmbr crd lsn	lower back
S49AB	Cl spn sublx+post lmbr crd lsn	lower back
S49AC	Cl spn sublx+cauda equina lsn	lower back
S49Az	Cls sublux thrc+lmbr spine NOS	back

S49B2	Op spn sublx+thrc crd lsn,unsp	upper back
S49B3	Op spn sublx+comp thrc crd lsn	upper back
S49B4	Op spn sublx+ant thrc crd lsn	upper back
S49B5	Op spn sublx+cent thrc crd lsn	upper back
S49B6	Op spn sublx+post thrc crd lsn	upper back
S49B7	Op spn sublx+lmbr crd lsn,unsp	lower back
S49B8	Op spn sublx+comp lmbr crd lsn	lower back
S49B9	Op spn sublux+ant lmbr crd lsn	lower back
S49BA	Op spn sublx+cent lmbr crd lsn	lower back
S49BB	Op spn sublx+post lmbr crd lsn	lower back
S49BC	Op spn sublx+cauda equina lsn	lower back
S49Bz	Op sublx thrc+lmbr vertbra NOS	back
S49C	Closed sublux other vertebra	back
S49C0	Closed sublux spine, unsp	back
S49C1	Closed subluxation of coccyx	pelvis
S49C2	Closed subluxation of sacrum	pelvis
S49Cz	Closed subluxation spine NOS	back
S49Ez	Oth closed subluxation NOS	unspecified
S5	Sprains and strains	unspecified
S5	Sprains and strains of joints and adjacent muscles	unspecified
S50	Sprain of shoulder and upper arm	shoulder/upper arm
S50	Sprain shoulder/upper arm	shoulder/upper arm
S50	Sprained shoulder	shoulder
S500	Sprain acromio-clav ligament	shoulder
S500	Sprain, acromio-clav ligament	shoulder
S500	Sprain, acromio-clavicular ligament	shoulder
S501	Sprain, coraco-clav ligament	shoulder
S502	Coracohumeral sprain	shoulder
S503	Sprain infraspinatus tendon	shoulder
S503	Sprain, infraspinatus tendon	shoulder
S504	Rotator cuff sprain	shoulder
S505	Sprain subscapularis tendon	shoulder
S505	Sprain, subscapularis tendon	shoulder
S506	Sprain supraspinatus tendon	shoulder
S506	Sprain, supraspinatus tendon	shoulder
S507	Sprain shoulder joint	shoulder
S507	Sprain, shoulder joint	shoulder
S5070	Sprain shoulder joint anterior	shoulder
S5070	Sprain,shoulder joint,anterior	shoulder
S5071	Sprain shoulder joint posterior	shoulder
S5071	Sprain,shoulder jnt,posterior	shoulder
S508	Sprain biceps tendon	upper arm
S508	Sprain, biceps tendon	upper arm

S509	Sprain long head of biceps tendon	upper arm
S509	Sprain,long head biceps tendon	upper arm
S50A	Sprain triceps tendon	upper arm
S50A	Sprain, triceps tendon	upper arm
S50w	Other shoulder sprain	shoulder
S50w	Shoulder strain	shoulder
S50x	Other upper arm sprain	upper limb
S50x	Otherupperarmsprain	upper arm
S50X	Spr/str oth/un part shl gir	upper arm
S50y	Shoulder sprain NOS	shoulder
S50z	Upper arm sprain NOS	upper arm
S51	Forearm sprain	forearm
S51	Sprain - fore arm	forearm
S51	Sprain elbow/forearm	upper limb
S51	Sprain of elbow and forearm	upper limb
S51	Sprained elbow	elbow
S510	Sprn,elbw jt,rdl clltrl lgmnt	elbow
S511	Sprn,elbw jt,uln clltrl lgmnt	elbow
S512	Radiohumeral sprain	elbow
S513	Ulnohumeral sprain	elbow
S51w	Other elbow sprain	elbow
S51x	Other forearm sprain	forearm
S51y	Elbow sprain NOS	elbow
S51z	Forearm sprain NOS	forearm
S52	Sprain - wrist	wrist
S52	Sprain of wrist and hand	wrist/hand
S52	Sprain wrist/hand	wrist/hand
S520	Sprain wrist ligament	wrist
S5200	Wrist sprain unspecified	wrist
S5201	Carpal joint sprain	hand
S5202	Sprn prox radcrp lgmnt non-sp	forearm
S5203	Distal radioulnar joint sprain	forearm
S5204	Sprain radial collateral ligament	forearm
S5204	Sprn radial collateral lgmnt	forearm
S5205	Sprn volar rad-carp lig non-sp	wrist
S5206	Sprn volar rad-carp lig sprfcl	wrist
S5207	Sprn radio-scapho-cptate lgmnt	wrist
S5208	Sprain radio-lunate ligament	wrist
S5209	Sprn radio-scapho-lunate lgmnt	wrist
S520A	Sprn dorsal radio-carpal lgmnt	wrist
S520B	Sprn ulnr carpal complx non-sp	wrist
S520C	Sprain ulnar-carpal meniscus	wrist
S520D	Sprn triangular fibrocartilage	unspecified
S520E	Sprain ulno-lunate ligament	wrist

S520F	Sprain ulnar collateral ligament	forearm
S520F	Sprn ulnar collateral lgmnt	forearm
S520G	Sprn shrt intrnsc lgmnt non-sp	unspecified
S520H	Sprain scapho-trapezium ligament	hand
S520H	Sprn scapho-trapezium lgmnt	hand
S520J	Sprn luno-triquetral lgmnt	hand
S520K	Sprain scapho-lunate ligament	hand
S520L	Sprn volar intrcrp/V lgmnt	hand
S520M	Sprn dorsal intercarpal lgmnt	hand
S520z	Wrist sprain NOS	wrist
S521	Hand sprain	hand
S521	Tendon injury - hand	hand
S5210	Finger sprain	hand
S5210	Hand sprain unspecified	hand
S5210	Thumb sprain	hand
S5211	Carpometacarpal sprain	hand
S5212	Metacarpophalangeal sprain	hand
S5213	Interphalangeal sprain	hand
S5213	Sprained finger/thumb	hand
S5214	Midcarpal joint sprain	hand
S521z	Hand sprain NOS	hand
S521z	Sprain - hand NOS	hand
S522	Sprain thumb	hand
S5220	Sprain thumb C.M.C.J	hand
S5221	Sprn thumb MCPJ non specific	hand
S5222	Sprn thmb MCPJ rdl collat lgmt	hand
S5223	Sprn thmb MCPJ uln collat lgmt	hand
S5224	Sprn thumb IPJ non specific	hand
S5225	Sprn thmb IPJ rdl collat lgmt	hand
S5226	Sprn thmb IPJ uln collat lgmnt	hand
S5227	Hyperextension injury of thumb	hand
S523	Sprain finger	hand
S5230	Sprain finger C.M.C.J.	hand
S5231	Sprn finger MCPJ non specific	hand
S5232	Sprn fngr MCPJ rdl collat lgmt	hand
S5233	Sprn fngr MCPJ uln collat lgmt	hand
S5234	Sprn finger PIPJ non specific	hand
S5235	Sprn fngr PIPJ rdl collat lgmt	hand
S5236	Sprn fngr PIPJ uln collat lgmt	hand
S5237	Sprn finger DIPJ non specific	hand
S5238	Sprn fngr DIPJ rdl collat lgmt	hand
S5239	Sprn fngr DIPJ uln collat lgmt	hand
S523F	Hyperextension injury of finger	hand
S524	Sprain tendon wrist or hand	wrist/hand

S5240	Sprain wrist extensors	wrist
S5241	Sprain wrist flexors	wrist
S525	Sprain tendon of thumb	hand
S5250	Sprn,flxr pollicis longus tndn	hand
S5251	Sprn,extnsr pollicis long tndn	hand
S5251	Sprnextnsr pollicis long tndn	hand
S526	Sprain tendon of finger	hand
S5260	Sprn,flxr digit superfic tndn	hand
S5261	Sprn,flxr digit profundus tndn	hand
S5262	Sprn,extnsr digitorum tendon	hand
S52z	Wrist and hand sprain NOS	wrist/hand
S52z	Wrist/hand sprain NOS	wrist/hand
S53	Groin sprain	pelvis
S53	Hamstring sprain	thigh
S53	Hip sprain	hip
S53	Sprain hip/thigh	hip/thigh
S53	Sprain of hip and thigh	hip/thigh
S53	Sprained hip	hip
S53	Sprained thigh - upper leg	thigh
S53	Thigh sprain	thigh
S530	Iliofemoral sprain	thigh
S531	Ischiocapsular sprain	unspecified
S532	Sprain hip joint	hip
S532	Sprain, hip joint	hip
S533	Sprain quadriceps tendon	thigh
S533	Sprain, quadriceps tendon	thigh
S534	Sprain patellar tendon	knee
S534	Sprain, patellar tendon	knee
S535	Sprain hamstring tendon	thigh
S535	Sprain, hamstring tendon	thigh
S53w	Other hip sprain	hip
S53x	Other thigh sprain	thigh
S53y	Hip sprain NOS	hip
S53z	Thigh sprain NOS	thigh
S54	Knee sprain	knee
S54	Leg sprain	lower limb
S54	Sprain - lower leg	lower leg
S54	Sprain knee/leg	knee
S54	Sprain of knee and leg	knee
S54	Sprained knee	knee
S540	Sprain - lateral knee ligament	knee
S540	Sprn/prt tr,knee,lat coll lgmt	knee
S540	Sprn/prt trkneelat coll lgmt	knee
S5400	Sprn,knee jt,lat collat lgmt	knee

S5400	Sprnknee jtlat collat lgmt	knee
S5401	Part tear,knee,lat collat lgmt	knee
S541	Sprain - medial knee ligament	knee
S541	Sprain med.collateral lig.knee	knee
S5410	Sprn,knee jt,medial collat	knee
S5410	Sprnknee jtmedial collat	knee
S5411	Part tear,knee,mdl collat lgmt	knee
S5411	Part tearkneemdl collat lgmt	knee
S542	Sprain -cruciate knee ligament	knee
S542	Sprain cruciate ligament knee	knee
S5421	Part tr,knee,ant cruciate lgmt	knee
S5421	Part trkneeant cruciate lgmt	knee
S5422	Prt tr,knee,post cruciate lgmt	knee
S5422	Prt trkneepost cruciate lgmt	knee
S543	Sprain superior tibiofibular	lower leg
S544	Sprain plantaris tendon	foot
S544	Sprain, plantaris tendon	foot
S545	Tear of ligament of knee joint	knee
S54w	Other specified knee sprain	knee
S54x	Other specified leg sprain	lower limb
S54x1	Sprain gastrocnemius	lower leg
S54y	Knee sprain NOS	knee
S54y	Sprained knee NOS	knee
S54z	Leg sprain NOS	lower limb
S55	Sprain ankle/foot	ankle/foot
S55	Sprain of ankle and foot	ankle/foot
S550	Ankle sprain	ankle
S550	Sprained ankle	ankle
S5500	Ankle sprain unspecified	ankle
S5500	Ankle sprain, unspecified	ankle
S5501	Deltoid ligament ankle sprain	ankle
S5501	Sprain ankle joint medial	ankle
S5501	Sprain, ankle joint, medial	ankle
S5502	Sprain ankle joint lateral	ankle
S5502	Sprain, ankle joint, lateral	ankle
S5503	Distal tibiofibular sprain	ankle
S5504	Sprain - Achilles tendon	ankle
S5504	Sprain, tendocalcaneus (Achilles tendon)	ankle
S5504	Sprntndocalcan(Achilles tndn)	ankle
S5505	Part tear,ankle,medial lgmt	ankle
S5505	Part tearanklemedial lgmt	ankle
S5506	Part tear,ankle,lat lgmt	ankle
S5506	Part tearanklelat lgmt	ankle
S550z	Ankle sprain NOS	ankle

S550z	Sprain - ankle NOS	ankle
S551	Foot sprain	foot
S5510	Foot sprain unspecified	foot
S5510	Foot sprain, unspecified	foot
S5511	Sprain, tarso-metatarsal joint	foot
S5512	Sprn,metatarso-phalangeal jt	foot
S5513	Sprained toe	foot
S5513	Sprninter-phalangeal jttoe	foot
S5513	Toe sprain	foot
S5514	Sprain mid tarsal joint	foot
S5514	Sprain, mid tarsal joint	foot
S5515	Sprain, flexor tendon, foot	foot
S5516	Sprain extensor tendon foot	foot
S5516	Sprain, extensor tendon, foot	foot
S551z	Foot sprain NOS	foot
S551z	Sprain - foot NOS	foot
S55z	Ankle and foot sprain NOS	ankle/foot
S55z	Ankle/foot sprain NOS	ankle/foot
S56	Sprain pelvic ligament	pelvis
S560	Sprain, lumbosacral ligament	lower back
S561	Sacroiliac ligament sprain	pelvis
S5610	Sprn,ant sacro-iliac lgmt	pelvis
S5611	Sprn,post sacro-iliac lgmt	pelvis
S562	Sprain, sacrospinous ligament	pelvis
S563	Sprain, sacrotuberous ligament	pelvis
S564	Sprain, iliolumbar ligament	lower back
S56y	Other spec sacroiliac sprains	pelvis
S56z	Sacroiliac sprain NOS	pelvis
S57	Back sprain excl. lumbosacral	back
S57	Sprain of other parts of back	back
S57	Sprain other parts of back	back
S570	Neck sprain	neck
S570	Sprained neck	neck
S5700	Neck sprain unspecified	neck
S5700	Torticollis - traumatic	neck
S5700	Whiplash injury	neck
S5701	Cervical ant.longit.lig.sprain	neck
S5702	Atlanto-axial joint sprain	neck
S5703	Atlanto-occipital joint sprain	neck
S5704	Whiplash injury	neck
S570z	Neck sprain NOS	neck
S571	Thoracic back sprain	upper back
S571	Thoracic sprain	upper back
S572	Lumbar back sprain	lower back

S572	Lumbar sprain	lower back
S573	Sacrum sprain	pelvis
S5730	Sacral sprain unspecified	pelvis
S5730	Sacral sprain, unspecified	pelvis
S5731	Sacral/coccyx sprain	lower back
S5731	Sacrococcygeal sprain	pelvis
S573z	Sacrum sprain NOS	pelvis
S574	Coccyx sprain	pelvis
S57X	Spr/str ot/un pt lum sp/pel	lower back
S57z	Back sprain NOS	back
S57z	Sprain - back	back
S57z0	Pulled back muscle	back
S5Q6	Inj tendon rotator cuff should	shoulder
S5y	Other sprains and strains	unspecified
S5y1	Jaw sprain	head
S5y1	Sprained jaw	head
S5y10	Jaw sprain unspecified	head
S5y10	Jaw sprain, unspecified	head
S5y11	Temporomandibular sprain	head
S5y1z	Jaw sprain NOS	head
S5y3	Rib sprain	chest
S5y3	Sprained ribs	chest
S5y30	Rib sprain unspecified	chest
S5y31	Chondrocostal joint sprain	chest
S5y32	Costal cartilage sprain	chest
S5y3z	Rib sprain NOS	chest
S5y4	Sternum sprain	chest
S5y40	Sternum sprain unspecified	chest
S5y41	Sternoclavicular sprain	shoulder girdle
S5y42	Chondrosternal sprain	chest
S5y43	Xiphoid cartilage sprain	chest
S5y4z	Sternum sprain NOS	chest
S5y5	Pelvis sprain or complete tear	pelvis
S5y50	Sprain of pelvis unspecified	pelvis
S5y50	Sprain of pelvis, unspecified	pelvis
S5y51	Sprain symphysis pubis	pelvis
S5y51	Sprain, symphysis pubis	pelvis
S5y51	Sprained symphisis pubis	trunk & pelvis
S5y5z	Sprain of pelvis NOS	pelvis
S5yX	Spr/str oth/unsp parts thor	chest
S5yy	Other spec sprains and strains	unspecified
S5yy	Other specified sprains and strains	unspecified
S5yz	Other sprains NOS	unspecified
S5yz	Other sprains/strains NOS	unspecified

S5yz1	Muscle injury / strain	unspecified
S5z	Ligament sprain NOS	unspecified
S5z	Muscle sprain NOS	unspecified
S5z	Rectus muscle sprain	unspecified
S5z	Sprains and strains NOS	unspecified
S5z	Tendon injury - lower limb	lower limb
S5z	Tendon sprain NOS	unspecified
S902	Tendon injury - upper limb	upper limb
SC07	Sprain - late effect	unspecified
SC08	Late effect-tendon injury	unspecified
SJ30	Cervical nerve root injury	neck
SJ30	Cervicalnerverootinjury	neck
SJ303	Cervical nerve root injury - C4	neck
SJ304	Cervical nerve root injury - C5	neck
SJ305	Cervical nerve root injury - C6	neck
SJ306	Cervical nerve root injury - C7	neck
SJ321	Lumbar nerve root injury - L2	lower back
SJ34	Brachial plexus injury	limb
SJ34	Brachialplexusinjury	limb
SJ35	Lumbosacral plexus injury	lower back & pelvis/lower limb
SJ43	Latrl cutaneous branch T12 inj	back
SJ50	Axillary nerve injury	upper arm
SJ51	Median nerve injury	upper limb
SJ511	Cls injmed nrveplm sns brnch	upper limb
SJ52	Ulnar nerve injury	forearm
SJ52	Ulnarnerveinjury	forearm
SJ520	Closed injury ulnar nerve	forearm
SJ520	Closedinjuryulnarnerve	limb
SJ528	Inj/ulnar nerve/wrist+hand lev	wrist/hand
SJ53	Radial nerve injury	wrist/hand
SJ534	Inj/radial nerv/wrist+hand lev	wrist/hand
SJ56	Digital nerve injury	hand
SJ566	Injury of digital nerve of thumb	hand
SJ6	Leg peripheral nerve injury	lower limb
SJ60	Sciatic nerve injury	lower limb
SJ60	Sciaticnerveinjury	lower limb
SJ61	Femoral nerve injury	thigh
SJ62	Posterior tibial nerve injury	thigh
SJ63	Peroneal nerve injury	lower limb
SJ642	Cls inj lat cutan nerve thigh	thigh
SJ7z	Injury to other nerve NOS	unspecified
SJ7z	InjurytoothernerveNOS	unspecified
SJ9	Injur/nerv+spinl crd/thorx lev	back

SJB	Inj/nerves/should+upp arm levl	shoulder/upper arm
SJB0	Injury/ulnar nerve/upp arm lev	upper arm
SJB0	Injury/ulnarnerve/upparmlev	upper arm
SJz	Peripheral nerve injury NOS	unspecified
SJz-98	Peripheral nerve injury NOS	unspecified
SK0y	Compartmentsyndrome	unspecified
SK0y1	Compartment syndrome forearm	forearm
SK0y5	Compartment syndrome leg	lower limb
SK0y5	Compartmentsyndromeleg	lower limb
SK1	Other specified injury	unspecified
SK112	Other interscapular injuries	shoulder
SK113	Other buttock injuries	buttock
SK114	Other back injuries	back
SK114	Otherbackinjuries	back
SK115	Other abdominal wall injuries	abdomen
SK116	Other flank injuries	trunk
SK117	Other groin injuries	pelvis
SK117	Othergroininjuries	pelvis
SK122	Other shoulder injuries	shoulder
SK122	Othershoulderinjuries	shoulder
SK123	Other upper arm injuries	upper arm
SK12z	Other should/upper arm inj.NOS	shoulder/upper arm
SK12z	Othershould/upperarminj.NOS	shoulder girdle/upper arm
SK13	Injury arm NOS	upper limb
SK13	Other elbow/forearm/wrist inj.	upper limb
SK130	Other elbow injuries	elbow
SK130	Otherelbowinjuries	elbow
SK131	Injury arm	upper limb
SK131	Other forearm injuries	forearm
SK131	Otherforearminjuries	forearm
SK132	Other wrist injuries	wrist
SK132	Otherwristinjuries	wrist
SK133	Unspecified injury of wrist	wrist
SK133	Unspecifiedinjuryofwrist	wrist
SK13z	Elbow/wrist/forearm inj.NOS	upper limb
SK14	Other hand injury (exc.finger)	hand
SK14	Other hand injury, excluding finger	hand
SK14	Otherhandinjury(exc.finger)	hand
SK14	Tendon injury to hand NOS	hand
SK140	Unspecified injury of hand	hand
SK140	Unspecifiedinjuryofhand	hand

SK15	Other finger injuries	hand
SK15	Otherfingerinjuries	hand
SK150	Other finger injuries unsp.	hand
SK150	Other finger injuries unspecified	hand
SK150	Other finger injuries, unspecified	hand
SK150	Otherfingerinjuriesunsp.	hand
SK151	Other fingernail injuries	hand
SK151	Otherfingernailinjuries	hand
SK152	Other thumb injuries unsp.	hand
SK152	Other thumb injuries unspecified	hand
SK152	Other thumb injuries, unspecified	hand
SK152	Otherthumbinjuriesunsp.	hand
SK154	Finger injury	hand
SK15z	Other finger injuries NOS	hand
SK15z	OtherfingerinjuriesNOS	hand
SK16	Other hip and thigh injuries	hip/thigh
SK16	Other hip/thigh injuries	hip/thigh
SK160	Other hip injuries	hip
SK160	Otherhipinjuries	hip
SK161	Other thigh injuries	thigh
SK161	Otherthighinjuries	thigh
SK17	Injury toe	foot
SK17	Injurytoe	foot
SK17	Other knee/leg/ankle/foot inj.	lower limb
SK170	Other knee injury	knee
SK170	Otherkneeinjury	knee
SK171	Injury leg NOS	lower limb
SK171	Other leg injury	lower limb
SK171	Otherleginjury	lower limb
SK172	Other ankle injury	ankle
SK172	Otherankleinjury	ankle
SK173	Foot injury	foot
SK173	Other foot injury	foot
SK173	Otherfootinjury	foot
SK174	Calf injury	lower leg
SK174	Calfinjury	lower leg
SK175	Injury of lower leg	lower leg
SK175	Injuryoflowerleg	lower limb
SK17z	Knee/leg/ankle/foot injury NOS	lower limb
SK1D0	Inj/adductor musc+tendon/thigh	thigh
SK1E	Inj/musc+tendon/lower leg levl	lower leg
SK1F	Injury of muscle and tendon at ankle and foot level	ankle/foot
SK1z	Other injury NOS	unspecified
SK1z	OtherinjuryNOS	unspecified

SKz	Injury NOS	unspecified
SKz	InjuryNOS	unspecified
Syu18	[X]Spr/str jt/lg ot/un pt neck	neck
Syu3	[X]Injabd/low back/lum sp/pel	lower back
Syu31	[X]Sup inj ab/low back/peluns	trunk & pelvis
Syu36	[X]Spr/str ot/un pt lum sp/pel	lower back & pelvis/lower limb
Syu3K	[X]Oth sp inj abd/low back/pel	lower back & pelvis/lower limb
Syu3L	[X]Unsp inj abd/low back/pelv	trunk & pelvis
Syu4	[X]Inj to shoulder/upper arm	shoulder/upper arm
Syu46	[X]Spr/str oth/un part shl gir	shoulder girdle
Syu4E	[X]Unspecif inj should/up arm	shoulder/upper arm
Syu5	[X]Inj to elbow & forearm	forearm
Syu5F	[X]Oth spec inj elbow/forearm	forearm
Syu5G	[X]Unspecif inj elbow/forearm	forearm
Syu6	[X]Injuries to the wrist and hand	wrist/hand
Syu66	[X]Spr/str ot/uns prt wris/hnd	wrist/hand
Syu6C	[X]Inj int mus/tn ot finwt/hd	wrist/hand
Syu6M	[X]Unsp injury wrist and hand	wrist/hand
Syu6M	[X]Unspecified injury of wrist and hand	wrist/hand
Syu7	[X]Injuries to the hip and thigh	hip/thigh
Syu8	[X]Inj to knee and lower leg	knee
Syu84	[X]Sprn/str oth unsp part knee	knee
Syu9	[X]Injuries to the ankle and foot	ankle/foot
Syu96	[X]Sprn/str oth/unsp part foot	foot
Syu9B	[X]Inj oth mus/ten,ank/foot lv	ankle/foot
Syu9C	[X]Inj uns mus/ten of ank/foot	ankle/foot
Syu9G	[X]Oth specif inj ankle/foot	ankle/foot
SyuB8	[X]Unspecif inj leg lev unsp	lower limb
SyuBJ	[X]Inj unsp muscle+tendon trnk	trunk
UNMAPM4AB	Muscle strain	unspecified
UNMAPP2R	Hamstring injury	thigh
UNMAPPC0	Shoulder injury	shoulder
UNMAPPC4	Wrist injury	wrist
UNMAPPC5	Ankle injury	ankle
UNMAPPC6	Back injury	back

Sleep problems and tiredness

Sleep problems and tiredness	
Read code	**Description**
1662	Night sweats
1736.	Paroxysmal nocturnal dyspnoea
173B.	Nocturnal cough / wheeze
173D.	Nocturnal dyspnoea
1B1B.	C/O - insomnia
1B1B0	Initial insomnia
1B1B1	Middle insomnia
1B1B2	Late insomnia
1B1D.	Nightmares – symptom
1B6C.	Excessive somnolence
1BX..	Sleep observations
1BX0.	Delayed onset of sleep
1BX1.	Excessive sleep
1BX2.	Sleeping pattern
1BX3.	Early morning waking
1BX4.	C/O - dreams
1BX5.	C/O - sweet/pleasant dreams
1BX6.	C/O - unpleasant dreams
1BX7.	C/O - bizarre dreams
1BX8.	C/O - vivid dreams
1BX9.	Light sleep
38D0.	Pittsburgh sleep quality index
663N.	Asthma disturbing sleep
663N0	Asthma causing night waking
663N1	Asthma disturbs sleep weekly
663N2	Asthma disturbs sleep frequently
66Yq.	Asthma causes night time symptoms 1 to 2 times per week
66Yr.	Asthma causes symptoms most nights
7065A	Sleep studies NEC
7P1B0	Polysomnography
8G9B.	Sleep hygiene behaviour education
8Q0..	Sleep management
9Ngt.	On melatonin for sleep disorder
c88G.	Vantage Pharmacy Sleep Aid 50mg tablet
c88H.	Care Night Time Sleep Aid 25mg tablet
E205.	Tired all the time
E274.	Non-organic sleep disorders
E2740	Unspecified non-organic sleep disorder

E2741	Insomnia NOS
E2742	Persistent insomnia
E2743	Hypersomnia NOS
E2744	Persistent hypersomnia
E2745	Jet lag – disorder
E2746	Shifting sleep-work schedule
E2747	Sleepwalking
E2748	Night terrors
E2749	Nightmares
E274A	Sleep drunkenness
E274B	Repeated rapid eye movement sleep interruptions
E274C	Other sleep stage or arousal dysfunction
E274D	Restless sleep
E274E	"Short-sleeper"
E274F	Sleep rhythm inversion
E274y	Other non-organic sleep disorder
E274z	Non-organic sleep disorder NOS
Eu460	[X]Fatigue syndrome
Eu51.	[X]Nonorganic sleep disorders
Eu510	Nonorganic insomnia
Eu511	Nonorganic hypersomnia
Eu512	Nonorganic disorders of the sleep/wake schedule
Eu513	[X]Sleepwalking
Eu514	Sleep terrors
Eu515	[X]Nightmares
Eu51y	[X]Other nonorganic sleep disorders
Eu51z	[X]Nonorganic sleep disorder, unspecified
F13z2	Restless legs syndrome
F270.	Cataplexy
F271.	Narcolepsy
Fy0..	Sleep disorders
Fy00.	Disorders of initiating and maintaining sleep
Fy01.	Disorders of excessive somnolence
Fy02.	Disorders of the sleep-wake schedule
Fy03.	Sleep apnea
Fy04.	Sleep-related respiratory failure
G3300	Nocturnal angina
G331.	Prinzmetal's angina
R005.	[D]Insomnia - symptom
R0050	Sleep disturbance, unspecified
R0051	[D]Insomnia with sleep apnoea
R0052	Insomnia NOS

R0053	Hypersomnia sleep apnoea
R0054	[D]Hypersomnia NOS
R0055	[D]Sleep rhythm inversion
R0056	Sleep rhythm irregular
R0057	Sleep-wake rhythm non-24-hour cycle
R0058	Sleep dysfunction with sleep stage disturbance
R0059	[D]Sleep dysfunction with arousal disturbance
R005z	[D]Sleep dysfunction NOS
R0084	[D]Night sweats
ZV1B1	[V]Personal history of unhealthy sleep-wake schedule

Psychological diagnosis/problems

Severe mental illness	
Read code	**Description**
1464	H/O: schizophrenia
146D.	H/O: manic depressive disorder
146H.	H/O: psychosis
212T.	Psychosis, schizophrenia and bipolar affective disorder resolved
9H6..	On national service framework mental health
9H8..	On severe mental illness register
E02..	Drug psychoses
E03y3	Unspecified puerperal psychosis
E1…	Non-organic psychoses
E10..	Schizophrenic disorders
E100.	Simple schizophrenia
E1000	Unspecified schizophrenia
E1001	Subchronic schizophrenia
E1002	Chronic schizophrenic
E1003	Acute exacerbation of subchronic schizophrenia
E1004	Acute exacerbation of chronic schizophrenia
E1005	Schizophrenia in remission
E100z	Simple schizophrenia NOS
E101.	Hebephrenic schizophrenia
E1010	Unspecified hebephrenic schizophrenia
E1011	Subchronic hebephrenic schizophrenia
E1012	Chronic hebephrenic schizophrenia
E1013	Acute exacerbation of subchronic hebephrenic schizophrenia
E1014	Acute exacerbation of chronic hebephrenic schizophrenia
E1015	Hebephrenic schizophrenia in remission
E101z	Hebephrenic schizophrenia NOS
E102.	Catatonic schizophrenia
E1020	Unspecified catatonic schizophrenia
E1021	Subchronic catatonic schizophrenia
E1022	Chronic catatonic schizophrenia
E1023	Acute exacerbation of subchronic catatonic schizophrenia
E1024	Acute exacerbation of chronic catatonic schizophrenia
E1025	Catatonic schizophrenia in remission
E102z	Catatonic schizophrenia NOS
E103.	Paranoid schizophrenia
E1030	Unspecified paranoid schizophrenia
E1031	Subchronic paranoid schizophrenia
E1032	Chronic paranoid schizophrenia
E1033	Acute exacerbation of subchronic paranoid schizophrenia
E1034	Acute exacerbation of chronic paranoid schizophrenia

E1035	Paranoid schizophrenia in remission
E103z	Paranoid schizophrenia NOS
E104.	Acute schizophrenic episode
E105.	Latent schizophrenia
E1050	Unspecified latent schizophrenia
E1051	Subchronic latent schizophrenia
E1052	Chronic latent schizophrenia
E1053	Acute exacerbation of subchronic latent schizophrenia
E1054	Acute exacerbation of chronic latent schizophrenia
E1055	Latent schizophrenia in remission
E105z	Latent schizophrenia NOS
E106.	Residual schizophrenia
E107.	Schizo-affective schizophrenia
E1070	Unspecified schizo-affective schizophrenia
E1071	Subchronic schizo-affective schizophrenia
E1072	Chronic schizo-affective schizophrenia
E1073	Acute exacerbation subchronic schizo-affective schizophrenia
E1074	Acute exacerbation of chronic schizo-affective schizophrenia
E1075	Schizo-affective schizophrenia in remission
E107z	Schizo-affective schizophrenia NOS
E10y.	Other schizophrenia
E10y0	Atypical schizophrenia
E10y1	Coenesthopathic schizophrenia
E10yz	Other schizophrenia NOS
E10z.	Schizophrenia NOS
E11..	Affective psychoses
E110.	Manic disorder, single episode
E1100	Single manic episode, unspecified
E1101	Single manic episode, mild
E1102	Single manic episode, moderate
E1103	Single manic episode, severe without mention of psychosis
E1104	Single manic episode, severe, with psychosis
E1105	Single manic episode in partial or unspecified remission
E1106	Single manic episode in full remission
E110z	Manic disorder, single episode NOS
E111.	Recurrent manic episodes
E1110	Recurrent manic episodes, unspecified
E1111	Recurrent manic episodes, mild
E1112	Recurrent manic episodes, moderate
E1113	Recurrent manic episodes, severe without mention psychosis
E1114	Recurrent manic episodes, severe, with psychosis
E1115	Recurrent manic episodes, partial or unspecified remission
E1116	Recurrent manic episodes, in full remission
E111z	Recurrent manic episode NOS

E112.	Single major depressive episode
E1120	Single major depressive episode, unspecified
E1121	Single major depressive episode, mild
E1122	Single major depressive episode, moderate
E1123	Single major depressive episode, severe, without mention of psychosis
E1124	Single major depressive episode, severe, with psychosis
E1125	Single major depressive episode, in partial or unspecified remission
E1126	Single major depressive episode, in full remission
E112z	Single major depressive episode NOS
E113.	Recurrent major depressive episode
E1130	Recurrent major depressive episodes, unspecified
E1131	Recurrent major depressive episodes, mild
E1132	Recurrent major depressive episodes, moderate
E1133	Recurrent major depressive episodes, severe, without mention of psychosis
E1134	Recurrent major depressive episodes, severe, with psychosis
E1135	Recurrent major depressive episodes, in partial or unspecified remission
E1136	Recurrent major depressive episodes, in full remission
E1137	Recurrent depression
E113z	Recurrent major depressive episode NOS
E114.	Bipolar affective disorder, currently manic
E1140	Bipolar affective disorder, currently manic, unspecified
E1141	Bipolar affective disorder, currently manic, mild
E1142	Bipolar affective disorder, currently manic, moderate
E1143	Bipolar affect disord, currently manic, severe, no psychosis
E1144	Bipolar affect disord, currently manic,severe with psychosis
E1145	Bipolar affect disord,currently manic, part/unspec remission
E1146	Bipolar affective disorder, currently manic, full remission
E114z	Bipolar affective disorder, currently manic, NOS
E115.	Bipolar affective disorder, currently depressed
E1150	Bipolar affective disorder, currently depressed, unspecified
E1151	Bipolar affective disorder, currently depressed, mild
E1152	Bipolar affective disorder, currently depressed, moderate
E1153	Bipolar affect disord, now depressed, severe, no psychosis
E1154	Bipolar affect disord, now depressed, severe with psychosis
E1155	Bipolar affect disord, now depressed, part/unspec remission
E1156	Bipolar affective disorder, now depressed, in full remission
E115z	Bipolar affective disorder, currently depressed, NOS
E116.	Mixed bipolar affective disorder
E1160	Mixed bipolar affective disorder, unspecified
E1161	Mixed bipolar affective disorder, mild
E1162	Mixed bipolar affective disorder, moderate
E1163	Mixed bipolar affective disorder, severe, without psychosis
E1164	Mixed bipolar affective disorder, severe, with psychosis
E1165	Mixed bipolar affective disorder, partial/unspec remission

E1166	Mixed bipolar affective disorder, in full remission
E116z	Mixed bipolar affective disorder, NOS
E117.	Unspecified bipolar affective disorder
E1170	Unspecified bipolar affective disorder, unspecified
E1171	Unspecified bipolar affective disorder, mild
E1172	Unspecified bipolar affective disorder, moderate
E1173	Unspecified bipolar affective disorder, severe, no psychosis
E1174	Unspecified bipolar affective disorder,severe with psychosis
E1175	Unspecified bipolar affect disord, partial/unspec remission
E1176	Unspecified bipolar affective disorder, in full remission
E117z	Unspecified bipolar affective disorder, NOS
E11y.	Other and unspecified manic-depressive psychoses
E11y0	Unspecified manic-depressive psychoses
E11y1	Atypical manic disorder
E11y2	Atypical depressive disorder
E11y3	Other mixed manic-depressive psychoses
E11yz	Other and unspecified manic-depressive psychoses NOS
E11z.	Other and unspecified affective psychoses
E11z0	Unspecified affective psychoses NOS
E11z1	Rebound mood swings
E11z2	Masked depression
E11zz	Other affective psychosis NOS
E12..	Paranoid states
E120.	Simple paranoid state
E121.	Chronic paranoid psychosis
E122.	Paraphrenia
E123.	Shared paranoid disorder
E12y.	Other paranoid states
E12y0	Paranoia querulans
E12yz	Other paranoid states NOS
E12z.	Paranoid psychosis NOS
E13..	Other nonorganic psychoses
E130.	Psychotic reactive depression
E131.	Acute hysterical psychosis
E132.	Reactive confusion
E133.	Acute paranoid reaction
E134.	Psychogenic paranoid psychosis
E135.	Agitated depression
E13y.	Other reactive psychoses
E13y0	Psychogenic stupor
E13y1	Brief reactive psychosis
E13yz	Other reactive psychoses NOS
E13z.	Nonorganic psychosis NOS
E14z.	Childhood schizophrenia NOS

E1y..	Other specified non-organic psychoses
E1z..	Non-organic psychosis NOS
Eu02z	[X] Senile psychosis NOS
Eu052	[X]Organic delusional [schizophrenia-like] disorder
Eu0z.	unspecified organic psychosis
Eu2..	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.	[X]Schizophrenia
Eu200	[X]Paranoid schizophrenia
Eu201	[X]Disorganised schizophrenia
Eu202	[X]Catatonic schizophrenia
Eu203	[X]Atypical schizophrenia
Eu204	[X]Post-schizophrenic depression
Eu205	[X]Residual schizophrenia
Eu206	[X]Simple schizophrenia
Eu20y	[X]Other schizophrenia
Eu20z	[X]Schizophrenia, unspecified
Eu21.	[X]Schizotypal disorder
Eu22.	[X]Persistent delusional disorders
Eu220	[X]Delusional disorder
Eu221	[X]Delusional misidentification syndrome
Eu222	[X]Cotard syndrome
Eu22y	[X]Other persistent delusional disorders
Eu22z	[X]Persistent delusional disorder, unspecified
Eu23.	[X]Acute and transient psychotic disorders
Eu230	[X]Acute polymorphic psychot disord without symp of schizoph
Eu231	[X]Acute polymorphic psychot disord with symp of schizophren
Eu232	[X]Brief schizophreniform disorder
Eu233	[X]Other acute predominantly delusional psychotic disorders
Eu23y	[X]Other acute and transient psychotic disorders
Eu23z	[X]Acute and transient psychotic disorder, unspecified
Eu24.	[X]Induced psychotic disorder
Eu25.	[X]Schizoaffective disorders
Eu250	[X]Schizoaffective disorder, manic type
Eu251	[X]Schizophreniform psychosis, depressive type
Eu252	[X]Schizoaffective disorder, mixed type
Eu25y	[X]Other schizoaffective disorders
Eu25z	[X]Schizoaffective psychosis NOS
Eu2y.	[X]Other nonorganic psychotic disorders
Eu2z.	[X]Unspecified nonorganic psychosis
Eu30.	[X]Bipolar disorder, single manic episode
Eu300	[X]Hypomania
Eu301	[X]Mania without psychotic symptoms
Eu302	[X]Mania with psychotic symptoms
Eu30y	[X]Other manic episodes

Eu30z	[X]Manic episode, unspecified
Eu31.	[X]Bipolar affective disorder
Eu310	[X]Bipolar affective disorder, current episode hypomanic
Eu311	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu312	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu313	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu314	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu315	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu316	[X]Bipolar affective disorder, current episode mixed
Eu317	[X]Bipolar affective disorder, currently in remission
Eu318	[X]Bipolar affective disorder type I
Eu319	[X]Bipolar affective disorder type II
Eu31y	[X]Other bipolar affective disorders
Eu31z	[X]Bipolar affective disorder, unspecified
Eu323	[X]Single episode of psychogenic depressive psychosis
Eu328	[X]Major depression, severe with psychotic symptoms
Eu329	[X]Single major depressive episode, severe, with psychosis, psychosis in remission
Eu32A	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
Eu332	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu3z.	[X]Affective psychosis NOS
Eu44.	[X]Hysterical psychosis
Eu531	[X]Puerperal psychosis NOS
Eu843	[X]Symbiotic psychosis
ZV110	[V]Personal history of schizophrenia
ZV111	[V]Personal history of manic-depressive psy

Dementia		
28E..	Cognitive decline	(+ daughter codes)
66h..	Dementia monitoring	(+ daughter codes)
6AB..	Dementia annual review	(+ daughter codes)
8CMZ.	Dementia care plan	(+ daughter codes)
E00	Senile/presenile dementia	NOT E00 "Senile and presenile organic psychotic conditions"
E000.	Uncomplicated senile dementia	(+ daughter codes)
E001.	Presenile dementia	(+ daughter codes)
E002.	Senile dementia with depressive or paranoid features	(+ daughter codes)
E003.	Senile dementia with delirium	(+ daughter codes)
E004.	Arteriosclerotic dementia	(+ daughter codes)
E041.	Dementia in conditions EC	(+ daughter codes)
Eu00.	[X]Dementia in Alzheimer's disease	(+ daughter codes)
Eu01.	[X]Vascular dementia	(+ daughter codes)
Eu02.	[X]Dementia in other diseases classified elsewhere	(+ daughter codes)
Eu041	[X]Delirium superimposed on dementia	
F110.	Alzheimer's disease	(+ daughter codes)
F111.	Picks disease	(+ daughter codes)
F112.	Senile degeneration of brain	(+ daughter codes)
F116.	Lewy body disease	(+ daughter codes)
F21y2	Binswanger's disease	
Fyu30	[X]Other Alzheimer's disease	

Schizophrenia/psychosis		
E00y.	Other senile psychoses	(+ daughter codes)
E00z.	Senile or presenile psychoses NOS	(+ daughter codes)
E01	Alcoholic psychoses	
E010.	Alcohol withdrawal delirium	(+ daughter codes)
E013.	Alcohol withdrawal hallucinosis	(+ daughter codes)
E015.	Alcoholic paranoia	(+ daughter codes)
E01y.	Other alcoholic psychosis	(+ daughter codes)
E01z.	Alcoholic psychosis NOS	(+ daughter codes)
E02	Drug psychoses	
E020.	Drug withdrawal syndrome	(+ daughter codes)
E021.	Drug-induced paranoia or hallucinatory states	(+ daughter codes)
E022.	Pathological drug intoxication	(+ daughter codes)
E02yz	Other drug psychoses NOS	
E02z.	Drug psychosis NOS	(+ daughter codes)
E03y3	Unspecified puerperal psychosis	
E1	Non-organic psychoses	
E10..	Schizophrenic disorders	(+ daughter codes)
E11	Affective psychoses	
E110..	Manic disorder single episode	(+ daughter codes EXCEPT E1105 "Single manic episode in partial or unspecified remission" and E1106 "Single manic episode in full remission")
E111.	Recurrent manic episodes	(+ daughter codes EXCEPT E1115 "Recurrent manic episodes, partial or unspecified remission" and E1116 "Recurrent manic episodes, in full remission")
E1124	Single major depressive episode, severe, with psychosis	
E1134	Recurrent major depressive episodes, severe, with psychosis	
E114.	Bipolar affective disorder, currently manic	(+ daughter codes EXCEPT E1145 "Bipolar affective disorder, currently manic, in partial or unspecified remission" and E1146 "Bipolar affective disorder, currently manic, in full remission")
E115.	Bipolar affective disorder, currently depressed	(+ daughter codes EXCEPT E1155 "Bipolar affective disorder, currently depressed, in partial or unspecified remission" and E1156 "Bipolar affective disorder, currently depressed, in full remission")
E116.	Mixed bipolar affective disorder	(+ daughter codes EXCEPT E1165 "Mixed bipolar affective disorder, in partial or unspecified remission" and E1166 "Mixed

		bipolar affective disorder, in full remission")
E117.	Unspecified bipolar affective disorder	(+ daughter codes EXCEPT E1175 "Unspecified bipolar affective disorder, in partial or unspecified remission" and E1176 "Unspecified bipolar affective disorder, in full remission")
E11y	Other and unspecified manic-depressive psychoses	
E11y0	Unspecified manic-depressive psychoses	
E11y1	Atypical manic disorder	
E11y3	Other mixed manic-depressive psychoses	
E11yz	Other and unspecified manic-depressive psychoses NOS	
E11z.	Other and unspecified affective psychoses	
E12..	Paranoid states	
E13..	Other nonorganic psychoses	
E1y..	Other specified non-organic psychoses	
E1z..	Non-organic psychosis NOS	
Eu02z	[X] Presenile psychosis NOS	
Eu02z	[X] Senile psychosis NOS	
Eu20.	[X]Schizophrenia	
Eu22.	[X]Persistent delusional disorders	
Eu23.	[X]Acute and transient psychotic disorders	
Eu25.	[X]Schizoaffective disorders	
Eu2y.	[X]Other nonorganic psychotic disorders	
Eu2z.	[X]Unspecified nonorganic psychosis	
Eu30.	[X]Manic episode	
Eu31.	[X]Bipolar affective disorder	
Eu323	[X]Severe depressive episode with psychotic symptoms	
Eu328	[X]Major depression, severe with psychotic symptoms	
Eu329	[X]Single major depressive episode, severe, with psychosis, psychosis in remission	
Eu32A	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission	
Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp	
Eu3z	[X]Affective psychosis NOS	
Eu531	[X]Puerperal psychosis NOS	

Stress		
13H4	Marital problems	
13H41	Marital breakdown	
13H42	Marital conflict	
13HT1	Stress at home	
13JM.	Problems at work	(+ daughter codes)
1B1L.	Stress related problem	(+ daughter codes)
1B1T.	Feeling stressed	(+ daughter codes)
9ON..	Stress monitoring admin.	(+ daughter codes)
E28..	Acute reaction to stress	(+ daughter codes EXCEPT E28z "Examination fear", E28z "Flying phobia, and E28z "Stage fright" but include E28z "Acute stress reaction NOS")
E29y1	Other post-traumatic stress disorder	
Eu43	[X]Reaction to severe stress, and adjustment disorders	
Eu430	[X]Acute reaction to stress	
Eu431	[X]Post - traumatic stress disorder	
Eu433	[X]Acute post-traumatic stress disorder following military combat	
Eu434	[X]Chronic post-traumatic stress disorder following military combat	
Eu435	[X]Delayed post-traumatic stress disorder following military combat	
Eu43y	[X]Other reactions to severe stress	
Eu43z	[X]Reaction to severe stress, unspecified	
R007z	[D]Work stress	No other synonyms for R007z
R00zW	[D]State of emotional shock and stress, unspecified	
ZV4B2	[V]Stressful work schedule	
ZVu4E	[X]Other stressful life events affecting family & household	
13HT1	Stress at home	
1B1L.	Stress-related problem	
1B1T.	Feeling stressed	
388Z.	Depression anxiety stress scales depression score	
9ON..	Stress monitoring admin.	
9ON1.	Attends stress monitoring	
9ON4.	Stress monitoring 1st letter	
9ON5.	Stress monitoring 2nd letter	
9ON6.	Stress monitoring 3rd letter	
9ON7.	Stress monitoring verbal inv.	
9ON8.	Stress monitoring phone invite	

9ONA.	Stress monitoring check done	
9ONZ.	Stress monitoring admin.NOS	
E28..	Acute reaction to stress	
E280.	Acute panic state due to acute stress reaction	
E281.	Acute fugue state due to acute stress reaction	
E282.	Acute stupor state due to acute stress reaction	
E283.	Other acute stress reactions	
E2830	Acute situational disturbance	
E2831	Acute post-trauma stress state	
E283z	Other acute stress reaction NOS	
E284.	Stress reaction causing mixed disturbance of emotion and conduct	
E28z.	Acute stress reaction NOS	
E29..	Adjustment disorder	
E291.	Prolonged depressive adjustment reaction	
E292.	Adjustment reaction with predominant disturbance of other emotions	
E2921	Adolescent emancipation disorder	
E2924	Adjustment reaction with anxious mood	
E292y	Adjustment reaction with mixed disturbance of emotion	
E292z	Adjustment reaction with disturbance of other emotion NOS	
E293.	Adjustment reaction with predominant disturbance of conduct	
E2930	Adjustment reaction with aggression	
E2931	Adjustment reaction with antisocial behaviour	
E2932	Adjustment reaction with destructiveness	
E293z	Adjustment reaction with predominant disturbance of conduct NOS	
E294.	Adjustment reaction with mixed disturbance of emotion and conduct	
E29y.	Other adjustment reactions	
E29y1	Other post-traumatic stress disorder	

E29y2	Adjustment reaction with physical symptoms	
E29yz	Other adjustment reactions NOS	
Eu4..	[X]Neurotic, stress-related and somatoform disorders	
Eu430	[X]Acute stress reaction	
Eu43y	[X]Other reactions to severe stress	
Eu43z	[X]Reaction to severe stress, unspecified	
R00zW	[D]State of emotional shock and stress, unspecified	

Neurosis		
E20	Neurotic disorders	
E201.	Hysteria	(+ daughter codes EXCEPT E2019 "Multiple personality")
E203.	Obsessive-compulsive disorders	(+ daughter codes)
E204	Neurotic depression reactive type	(NOT E204 "Postnatal depression")
E205	Neurasthenia - nervous debility	(NOT E205 "Tired all the time")
E206.	Depersonalisation syndrome	(+ daughter codes)
E207.	Hypochondriasis	(+ daughter codes)
E20y.	Other neurotic disorders	(+ daughter codes)
E20z.	Neurotic disorder NOS	(+ daughter codes)
E2C40	Neurotic delinquency	
Eu341	[X]Dysthymia	(NOT Eu341 "[X]Depressive personality disorder" OR Eu341 "[X]Persistent anxiety depression")
Eu4	[X]Neurotic, stress - related and somoform disorders	
Eu401	[X]Social neurosis	(NOT Eu401 "[X]Social phobias" OR Eu401 "Anthropopobia")
Eu411	[X]Anxiety neurosis	(No other Eu411)
Eu42.	[X]Obsessive - compulsive disorder	(+ daughter codes)
Eu44.	[X]Dissociative [conversion] disorders	(+ daughter codes)
Eu45.	[X]Somatoform disorders	(+ daughter codes)
Eu460	[X]Neurasthenia	(NOT Eu460 "[X]Fatigue syndrome")
Eu46y	[X]Other specified neurotic disorders	
Eu46z	[X]Neurotic disorder, unspecified	
M184.	Dermatitis artefacta	(+ daughter codes)
M240E	Alopecia neurotica	
E20..	Neurotic disorders	
E20z.	Neurotic disorder NOS	
E21y7	Neurotic personality	
E2C40	Neurotic delinquency	
Eu341	[X]Depressive neurosis	
Eu411	[X]Anxiety neurosis	
Eu42.	[X]Obsessive-compulsive neurosis	
Eu420	[X]Predominantly obsessional thoughts or ruminations	

Eu421	[X]Predominantly compulsive acts [obsessional rituals]	
Eu422	[X]Mixed obsessional thoughts and acts	
Eu42y	[X]Other obsessive-compulsive disorders	
Eu42z	[X]Obsessive-compulsive disorder, unspecified	
Eu452	[X]Hypochondriacal neurosis	
Eu453	[X]Somatoform autonomic dysfunction	
Eu46.	[X]Other neurotic disorders	
Eu460	[X]Neurasthenia	
Eu461	[X]Depersonalization - derealization syndrome	
Eu46y	[X]Other specified neurotic disorders	
Eu46z	[X]Neurosis NOS	
M184.	Neurotic excoriation	
M240E	Alopecia neurotica	
ZV112	[V]Personal history of neurosis	

Perinatal mental health		
62T1.	Puerperal depression	(+ daughter codes)
6G00.	Postnatal depression counselling	(+ daughter codes)
E204	Postnatal depression	(NOT E204 "Neurotic depression reactive type")
Eu530	[X]Postnatal depression NOS	(NOT Eu530 "[X]Mild mental and behavioural disorders associated with the puerperium, not elsewhere classified")
Eu530	[X]Postpartum depression NOS	(NOT Eu530 "[X]Mild mental and behavioural disorders associated with the puerperium, not elsewhere classified")
Eu531	[X]Severe mental and behavioural disorders associated with the puerperium, not elsewhere classified	

Anxiety with depression		
E2003	Anxiety with depression	
Eu341	[X]Persistant anxiety depression	(NO other terms for Eu341)
Eu412	[X]Mixed anxiety and depressive disorder	

Anxiety		
1B13.	Anxiousness	(+ daughter codes)
1B14.	Tenseness	(+ daughter codes)
1B16.	Agitated	(+ daughter codes)
1B1V.	C/O - panic attack	(+ daughter codes)
2258.	O/E - anxious	(+ daughter codes)
225J.	O/E - panic attack	(+ daughter codes)
E200.	Anxiety states	(+ daughter codes)
E202.	Phobic disorders	(+ daughter codes)
E280.	Acute panic state due to acute stress reaction	(+ daughter codes)
E28z	Flying phobia	(No other terms for E28z)
E2920	Separation anxiety disorder	
E2923	Specific academic or work inhibition	
E2924	Adjustment reaction with anxious mood	
E2D0	Disturbance of anxiety and fearfulness in childhood and adolescence	
E2D00	Childhood and adolescent overanxiousness disturbance	
E2D0z	Disturbance of anxiety and fearfulness in childhood and adolescence NOS	
Eu341	[X]Persistant anxiety depression	(NO other terms for Eu341)
Eu40.	[X]Phobic anxiety disorders	(+ daughter codes)
Eu41.	[X]Other anxiety disorders	(+ daughter codes)
Eu606	[X]Anxious [avoidant] personality disorder	
Eu930	[X]Separation anxiety disorder of childhood	
Eu931	[X]Phobic anxiety disorder of childhood	
Eu932	[X]Social anxiety disorder of childhood	
1288	FH: Anxiety state	
1466	H/O: anxiety state	
2258	O/E - anxious	
2259	O/E nervous	
173f.	Anxiety about breathlessness	
1B12.	Nerves, nervousness	
1B13.	ANXIOUSNESS	
1B14.	Tenseness	`
1B16.	Agitated	
1B1V.	C/O - panic attack	
1BK..	WORRIED	
2256	O/E - agitated	
225J.	O/E - panic attack	
2J4..	Worried well	
6897	Anxiety screening	
8G52.	Antiphobic therapy	

8G94.	Anxiety management training	
E2…	Neurotic; personality and other nonpsychotic disorders	
E20..	Neurotic disorders	
E200.	Anxiety disorder	
E2000	Anxiety state unspecified	
E2001	Panic disorder	
E2002	Generalised anxiety disorder	
E2003	Anxiety with depression	
E2004	Chronic anxiety	
E2005	Recurrent anxiety	
E200z	Anxiety state NOS	
E201.	Hysteria	
E2011	Hysterical blindness	
E2012	Hysterical deafness	
E2013	Hysterical tremor	
E2014	Hysterical paralysis	
E2015	Hysterical seizures	
E2016	Other conversion disorder	
E2017	Hysterical amnesia	
E2018	Hysterical fugue	
E2019	Multiple personality	
E201A	Dissociative reaction unspecified	
E201B	Compensation neurosis	
E201C	Phantom pregnancy	
E201z	Hysteria NOS	
E202.	Phobic disorders (& [social] or [phobic anxiety])	
E2020	Phobia unspecified	
E2021	Agoraphobia with panic attacks	
E2022	Agoraphobia without mention of panic attacks	
E2023	Social phobia; fear of eating in public	
E2024	Social phobia; fear of public speaking	
E2025	Social phobia; fear of public washing	
E2026	Acrophobia	
E2027	Animal phobia	
E2028	Claustrophobia	
E2029	Fear of crowds	
E202A	Fear of flying	
E202B	Cancer phobia	
E202C	Dental phobia	
E202D	Fear of death	
E202E	Fear of pregnancy	
E202z	Phobic disorder NOS	
E203.	Obsessive-compulsive disorder	
E2030	Compulsive neurosis	

E2031	Obsessional neurosis	
E203z	Obsessive-compulsive disorder NOS	
E205.	Neurasthenia - nervous debility	
E206.	Depersonalisation syndrome	
E207.	Hypochondriasis	
E20y.	Other neurotic disorders	
E20y0	Somatization disorder	
E20y1	Writer's cramp neurosis	
E20y2	Other occupational neurosis	
E20y3	Psychasthenic neurosis	
E20yz	Other neurotic disorder NOS	
E20z.	Neurotic disorder NOS	
E28..	Acute reaction to stress	
E280.	Acute panic state due to acute stress reaction	
E281.	Acute fugue state due to acute stress reaction	
E282.	Acute stupor state due to acute stress reaction	
E283.	Other acute stress reactions	
E2830	Acute situational disturbance	
E2831	Acute posttrauma stress state	
E283z	Other acute stress reaction NOS	
E284.	Stress reaction causing mixed disturbance of emotion/conduct	
E28z.	Acute stress reaction NOS	
E29..	Adjustment reaction	
E2900	Grief reaction	
E291.	Prolonged depressive reaction	
E292.	Adjustment reaction; predominant disturbance other emotions	
E2920	Separation anxiety disorder	
E2921	Adolescent emancipation disorder	
E2922	Early adult emancipation disorder	
E2923	Specific academic or work inhibition	
E2924	Adjustment reaction with anxious mood	
E2925	Culture shock	
E292y	Adjustment reaction with mixed disturbance of emotion	
E292z	Adjustment reaction with disturbance of other emotion NOS	
E293.	Adjustment reaction with predominant disturbance of conduct	
E2930	Adjustment reaction with aggression	
E2931	Adjustment reaction with antisocial behaviour	
E2932	Adjustment reaction with destructiveness	
E294.	Adjustment reaction with disturbance emotion and conduct	
E29y.	Other adjustment reactions	

E29y1	Other post-traumatic stress disorder	
E29y2	Adjustment reaction with physical symptoms	
E29y3	Elective mutism due to an adjustment reaction	
E29y4	Adjustment reaction due to hospitalisation	
E29y5	Other adjustment reaction with withdrawal	
E29yz	Other adjustment reactions NOS	
E29z.	Adjustment reaction NOS	
E2D0.	Disturbance of anxiety and fearfulness in childhood and adolescence	
E2D00	childhood and adolescent overanxiousness disturbance	
E2D0z	disturbance of anxiety and fearfulness in childhood and adolescence NOS	
E2y..	Other specified neuroses or other mental disorders	
E2z..	Neuroses or other mental disorder NOS	
Eu054	[X]Organic anxiety disorder	
Eu341	[X]Dysthymia	
Eu4..	[X]Neurotic; stress - related and somoform disorders	
Eu40.	[X]Phobic anxiety disorders	
Eu400	[X] Agoraphobia (& [without history of panic disorder] or [with panic disorder])	
Eu401	[X]Social phobias	
Eu402	[X]Specific (isolated) phobias	
Eu403	[X]Needle phobia	
Eu40y	[X]Other phobic anxiety disorders	
Eu40z	[X]Phobic anxiety disorder, unspecified	
Eu41.	[X]Other anxiety disorders	
Eu410	[X]Panic disorder [episodic paroxysmal anxiety]	
Eu411	[X]Generalized anxiety disorder	
Eu412	[X]Mixed anxiety and depressive disorder (& mild anxiety depression)	
Eu413	[X]Other mixed anxiety disorders	
Eu41y	[X] Anxiety disorders: [other specified] or [anxiety hysteria]	
Eu41z	[X]Anxiety disorder, unspecified	
Eu42.	[X]Obsessive - compulsive disorder	
Eu420	[X]Predominantly obsessional thoughts or ruminations	
Eu421	[X]Predominantly compulsive acts [obsessional rituals]	
Eu422	[X]Mixed obsessional thoughts and acts	
Eu42y	[X]Other obsessive-compulsive disorders	
Eu42z	[X]Obsessive-compulsive disorder; unspecified	
Eu43.	[X]Reaction to severe stress; and adjustment disorders	

Eu430	[X]Acute stress reaction	
Eu431	[X]Post - traumatic stress disorder	
Eu432	[X]Adjustment disorders	
Eu43y	[X]Other reactions to severe stress	
Eu43z	[X]Reaction to severe stress; unspecified	
Eu44.	[X]Dissociative [conversion] disorders	
Eu440	[X]Dissociative amnesia	
Eu441	[X]Dissociative fugue	
Eu442	[X]Dissociative stupor	
Eu443	[X]Trance and possession disorders	
Eu444	[X]Dissociative motor disorders	
Eu445	[X]Dissociative convulsions	
Eu446	[X]Dissociative anaesthesia and sensory loss	
Eu447	[X]Mixed dissociative [conversion] disorders	
Eu44y	[X]Other dissociative [conversion] disorders	
Eu44z	[X]Dissociative [conversion] disorder; unspecified	
Eu45.	[X]Somatoform disorders	
Eu450	[X]Somatization disorder	
Eu451	[X]Undifferentiated somatoform disorder	
Eu452	[X]Hypochondriacal disorder	
Eu453	[X]Somatoform autonomic dysfunction	
Eu454	[X]Persistent somatoform pain disorder	
Eu455	[X]Globus pharyngeus	
Eu45y	[X]Other somatoform disorders	
Eu45z	[X]Somatoform disorder; unspecified	
Eu46.	[X]Other neurotic disorders	
Eu460	[X]Neurasthenia	
Eu461	[X]Depersonalization - derealization syndrome	
Eu46y	[X]Other specified neurotic disorders	
Eu46z	[X]Neurotic disorder; unspecified	
Eu515	Dream anxiety disorder (nightmrs)	
Eu605	[X]Obsessive-compulsive personality disorder	
Eu606	[X]Anxious [avoidant] personality disorder	
Eu930	[X]Separation anxiety disorder of childhood	
Eu931	[X]Phobic anxiety disorder of childhood	
Eu932	[X]Social anxiety disorder of childhood	
Eu93y	[X]Childhood overanxious disorder	
R2y2.	(D) nervousness	
ZV655	[V]Worried well	

Depression		
1B17.	Depressed	(+ daughter codes)
1B1U.	Symptoms of depression	(+ daughter codes)
1BT..	Depressed mood	(+ daughter codes)
2257.	O/E - depressed	(+ daughter codes)
62T1.	Puerperal depression	(+ daughter codes)
6G00.	Postnatal depression counselling	(+ daughter codes)
9H90.	Depression annual review	(+ daughter codes)
E11	Depressive psychoses	(No other terms for E11)
E112.	Single major depressive episode	(+ daughter codes EXCEPT E1126 "Single major depressive episode, in full remission")
E113.	Recurrent major depressive episode	(+ daughter codes EXCEPT E1136 "Recurrent major depressive episodes, in full remission")
E115.	Bipolar affective disorder, currently depressed	(+ daughter codes)
E118.	Seasonal affective disorder	(+ daughter codes)
E11y	Other and unspecified manic-depressive psychoses	
E11y0	Unspecified manic-depressive psychoses	
E11y2	Atypical depressive disorder	
E11y3	Other mixed manic-depressive psychoses	
E11yz	Other and unspecified manic-depressive psychoses NOS	
E11z2	Masked depression	
E135.	Agitated depression	(+ daughter codes)
E2003	Anxiety with depression	
E204.	Neurotic depression reactive type	(+ daughter codes)
E290	Brief depressive reaction	
E290z	Brief depressive reaction NOS	
E291.	Prolonged depressive reaction	(+ daughter codes)
E2B..	Depressive disorder NEC	(+ daughter codes)
Eu3	[X]Mood - affective disorders	
Eu31	[X]Manic-depressive illness	(PLUS all other terms for Eu31 EXCEPT "[X]Bipolar affective disorder")
Eu313	[X]Bipolar affect disorder cur epi mild or moderate depressn	
Eu314	[X]Bipolar affective disorder, current episode severe depression without psychotic symptoms	
Eu315	[X]Bipolar affective disorder, current episode severe depression with psychotic symptoms	
Eu32.	[X]Depressive episode	(+ daughter codes)

Eu33.	[X]Recurrent depressive disorder	(+ daughter codes EXCEPT Eu334 "[X]Recurrent depressive disorder, currently in remission")
Eu34	[X]Persistent mood affective disorders	
Eu341	[X]Dysthymia	
Eu34y	[X]Other persistent mood affective disorders	
Eu34z	[X]Persistent mood affective disorder, unspecified	
Eu3y.	[X]Other mood affective disorders	(+ daughter codes)
Eu3z	[X]Unspecified mood affective disorder	(NOT Eu3z "Affective psychosis NOS")
Eu412	[X]Mixed anxiety and depressive disorder	
Eu530	[X]Postnatal depression NOS	(NOT Eu530 "[X]Mild mental and behavioural disorders associated with the puerperium, not elsewhere classified"
Eu530	[X]Postpartum depression NOS	(NOT Eu530 "[X]Mild mental and behavioural disorders associated with the puerperium, not elsewhere classified"
Eu920	[X]Depressive conduct disorder	
1285	FH: Depression	
1287	FH: Manic depressive state	
1465	H/O: depression	
2257	O/E – depressed	
2258	O/E - anxious	
2259	O/E nervous	
6891	Depression screen	
6896	Depression screening using questions	
12G3.	FH: Puerperal depression	
1B12.	'Nerves' - nervousness	
1B13.	Anxiousness	
1B17.	Depressed	
1B1U.	Symptoms of depression	
1BK..	Worried	
1BP0.	Loss of interest in previously enjoyable activity	
1BT..	Depressed mood	
1BU..	Loss of hope for the future	
2J4..	Worried well	
388b.	Depression anxiety stress scales anxiety score	
388g.	Beck depression inventory second edition score	
62T1.	Puerperal depression	
6G00.	Postnatal depression counselling	

8BK0.	Depression management programme	
8CAa.	Patient given advice about management of depression	
9H90.	Depression annual review	
9H91.	Depression medication review	
9H92.	Depression interim review	
9HA0.	On depression register	
9k40.	Depression - enhanced service completed	
9kQ..	On full dose long term treatment depression - enh serv admin	
E11..	Depressive psychoses	
E112.	Single major depressive episode	
E1120	Single major depressive episode, unspecified	
E1121	Single major depressive episode, mild	
E1122	Single major depressive episode, moderate	
E1123	Single major depressive episode, severe, without psychosis	
E1124	Single major depressive episode; severe; with psychosis	
E1125	Single major depressive episode, partial or unspec remission	
E1126	Single major depressive episode; in full remission	
E112z	Single major depressive episode NOS	
E113.	Recurrent depression: [major episode] or [endogenous]	
E1130	Recurrent major depressive episodes, unspecified	
E1131	Recurrent major depressive episodes, mild	
E1132	Recurrent major depressive episodes, moderate	
E1133	Recurrent major depressive episodes, severe, no psychosis	
E1134	Recurrent major depressive episodes; severe; with psychosis	
E1135	Recurrent major depressive episodes,partial/unspec remission	
E1136	Recurrent major depressive episodes; in full remission	
E1137	Recurrent depression	
E113z	Recurrent major depressive episode NOS	
E115.	Manic-depressive - now depressed	
E1150	Bipolar affective disorder, currently depressed, unspecified	

E1151	Bipolar affective disorder, currently depressed, mild	
E1152	Bipolar affective disorder, currently depressed, moderate	
E1153	Bipolar affect disord, now depressed, severe, no psychosis	
E1154	Bipolar affect disord, now depressed, severe with psychosis	
E1155	Bipolar affect disord, now depressed, part/unspec remission	
E1156	Bipolar affective disorder, now depressed, in full remission	
E115z	Bipolar affective disorder, currently depressed, NOS	
E118.	Seasonal affective disorder	
E11y.	Other and unspecified manic-depressive psychoses	
E11y0	Unspecified manic-depressive psychoses	
E11y1	Atypical manic disorder	
E11y2	Atypical depressive disorder	
E11y3	Other mixed manic-depressive psychoses	
E11yz	Other and unspecified manic-depressive psychoses NOS	
E11z2	Masked depression	
E130.	Reactive depressive psychosis	
E135.	Agitated depression	
E2003	Anxiety with depression	
E201.	Hysteria	
E2010	Hysteria unspecified	
E201z	Hysteria NOS	
E204.	Neurotic depression reactive type	
E2112	Depressive personality disorder	
E290.	Brief depressive reaction	
E290z	Brief depressive reaction NOS	
E291.	Prolonged depressive reaction	
E2B..	Depressive disorder NEC	
E2B0.	Postviral depression	
E2B1.	Chronic depression	
Eu204	[X]Post-schizophrenic depression	
Eu251	[X]Schizoaffective disorder, depressive type	
Eu3..	[X]Mood - affective disorders	
Eu31.	[X]Manic-depressive illness	
Eu313	bipolar affective disorder, current epi, mild or mod depression	

Eu314	[X]Bipol aff disord, curr epis sev depress, no psychot symp	
Eu315	[X]Bipolar affect dis cur epi severe depres with psyc symp	
Eu32.	[X]Depressive episode	
Eu320	[X]Mild depressive episode	
Eu321	[X]Moderate depressive episode	
Eu322	[X] Severe depressive episode without psychotic symptoms: (& [single episode agitated depression] or [single episode major depression] or [single episode vital depression])	
Eu323	[X] Severe depressive episode with psychotic symptoms: (& single episode of [major depression] or [psychogenic depressive psychosis] or [psychotic depression] or [reactive depressive psychosis])	
Eu324	[X]Mild depression	
Eu325	[X]Major depression, mild	
Eu326	[X]Major depression, moderately severe	
Eu327	[X]Major depression, severe without psychotic symptoms	
Eu328	[X]Major depression; severe with psychotic symptoms	
Eu329	[X]Single major depr ep; severe with psych; psych in remiss	
Eu32A	[X]Recurr major depr ep; severe with psych; psych in remiss	
Eu32y	[X] Depression: [other episodes] or [atypical] or [single episode masked NOS]	
Eu32z	[X] (Depression: [episode, unspecified] or [NOS (& reactive)] or [depressive disorder NOS]	
Eu33.	[X]Recurrent depressive disorder	
Eu330	[X]Recurrent depressive disorder, current episode mild	
Eu331	[X]Recurrent depressive disorder, current episode moderate	
Eu332	[X]Depression without psychotic symptoms: [recurrent: [major] or [manic-depressive psychosis, depressed type] or [vital] or [current severe episode]] or [endogenous]	
Eu333	[X]Recurrent depress disorder cur epi severe with psyc symp	

Eu334	[X]Recurrent depressive disorder; currently in remission	
Eu33y	[X]Other recurrent depressive disorders	
Eu33z	[X]Recurrent depressive disorder, unspecified	
Eu34.	[X]Persistent mood affective disorders	
Eu341	[X]Persistant anxiety depression	
Eu34y	[X]Other persistent mood affective disorders	
Eu34z	[X]Persistent mood affective disorder, unspecified	
Eu3y1	[X]Recurrent brief depressive episodes	
Eu3z.	[X]Unspecified mood affective disorder	
Eu412	[X]Mixed anxiety and depressive disorder	
Eu43.	[X]Reaction to severe stress, and adjustment disorders	
Eu430	[X]Acute stress reaction	
Eu431	[X]Post - traumatic stress disorder	
Eu432	[X]Adjustment disorders	
Eu43y	[X]Other reactions to severe stress	
Eu43z	[X]Reaction to severe stress, unspecified	
Eu530	[X]Postnatal depression NOS	
Eu53z	[X]Puerperal mental disorder, unspecified	
Eu920	[X]Depressive conduct disorder	
R007z	[D]Postoperative depression	
R2y2.	[D]Nervousness	
ZV655	[V]Worried well	
ZV790	[V]Screening for depression	

Suicide/self-harm	
TK...	Suicide and selfinflicted injury
TK0..	Suicide + selfinflicted poisoning by solid/liquid substances
TK00.	Suicide + selfinflicted poisoning by analgesic/antipyretic
TK01.	Suicide + selfinflicted poisoning by barbiturates
TK010	Suicide and self inflicted injury by Amylobarbitone
TK011	Suicide and self inflicted injury by Barbitone
TK014	Suicide and self inflicted injury by Phenobarbitone
TK01z	Suicide and self inflicted injury by barbiturates

TK02.	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
TK03.	Suicide + selfinflicted poisoning tranquilliser/psychotropic
TK04.	Suicide + selfinflicted poisoning by other drugs/medicines
TK05.	Suicide + selfinflicted poisoning by drug or medicine NOS
TK06.	Suicide + selfinflicted poisoning by agricultural chemical
TK07.	Suicide + selfinflicted poisoning by corrosive/caustic subst
TK08.	Suicide and selfinflicted poisoning by arsenic and its compounds
TK0z.	Suicide + selfinflicted poisoning by solid/liquid subst NOS
TK1..	Suicide + selfinflicted poisoning by gases in domestic use
TK10.	Suicide + selfinflicted poisoning by gas via pipeline
TK11.	Suicide + selfinflicted poisoning by liquified petrol gas
TK1y.	Suicide and selfinflicted poisoning by other utility gas
TK1z.	Suicide + selfinflicted poisoning by domestic gases NOS
TK2..	Suicide + selfinflicted poisoning by other gases and vapours
TK20.	Suicide + selfinflicted poisoning by motor veh exhaust gas
TK21.	Suicide and selfinflicted poisoning by other carbon monoxide
TK2y.	Suicide + selfinflicted poisoning by other gases and vapours
TK2z.	Suicide + selfinflicted poisoning by gases and vapours NOS
TK3..	Suicide + selfinflicted injury by hang/strangulate/suffocate
TK30.	Suicide and selfinflicted injury by hanging
TK31.	Suicide + selfinflicted injury by suffocation by plastic bag
TK3y.	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
TK3z.	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
TK4..	Suicide and selfinflicted injury by drowning
TK5..	Suicide and selfinflicted injury by firearms and explosives
TK50.	Suicide and selfinflicted injury by handgun
TK51.	Suicide and selfinflicted injury by shotgun
TK52.	Suicide and selfinflicted injury by hunting rifle
TK54.	Suicide and selfinflicted injury by other firearm
TK5z.	Suicide and selfinflicted injury by firearms/explosives NOS
TK6..	Suicide and selfinflicted injury by cutting and stabbing
TK60.	Suicide and selfinflicted injury by cutting
TK61.	Suicide and selfinflicted injury by stabbing
TK6z.	Suicide and selfinflicted injury by cutting and stabbing NOS
TK7..	Suicide and selfinflicted injury by jumping from high place
TK70.	Suicide+selfinflicted injury-jump from residential premises
TK71.	Suicide+selfinflicted injury-jump from oth manmade structure
TK72.	Suicide+selfinflicted injury-jump from natural sites
TK7z.	Suicide+selfinflicted injury-jump from high place NOS
TKx..	Suicide and selfinflicted injury by other means
TKx0.	Suicide + selfinflicted injury-jump/lie before moving object
TKx00	Suicide + selfinflicted injury-jumping before moving object

TKx0z	Suicide + selfinflicted inj-jump/lie before moving obj NOS
TKx1.	Suicide and selfinflicted injury by burns or fire
TKx2.	Suicide and selfinflicted injury by scald
TKx3.	Suicide and selfinflicted injury by extremes of cold
TKx4.	Suicide and selfinflicted injury by electrocution
TKx5.	Suicide and selfinflicted injury by crashing motor vehicle
TKx6.	Suicide and selfinflicted injury by crashing of aircraft
TKx7.	Suicide and selfinflicted injury caustic subst, excl poison
TKxy.	Suicide and selfinflicted injury by other specified means
TKxz.	Suicide and selfinflicted injury by other means NOS
TKz..	Suicide and selfinflicted injury NOS
U2…	[X]Suicide

ADHD	
1P00.	Hyperactive behaviour
6A61.	Attention deficit hyperactivity disorder annual review
8BPT.	Drug therapy for ADHD (attention deficit hyperactivity disorder)
8BPT0	Stimulant drug therapy for ADHD (attention deficit hyperactivity disorder)
8BPT1	Non-stimulant drug therapy for ADHD (attention deficit hyperactivity disorder)
9Ol8.	Attention deficit hyperactivity disorder monitoring invitation first letter
9Ol9.	Attention deficit hyperactivity disorder monitoring invitation second letter
9OlA.	Attention deficit hyperactivity disorder monitoring invitation third letter
dc1..	DEXAMFETAMINE SULFATE
dc11.	*DEXEDRINE 5mg tablets
dc12.	*DUROPHET 7.5mg m/r capsules
dc13.	*DUROPHET 12.5mg m/r capsules
dc14.	*DUROPHET 20mg m/r capsules
dc1v.	DEXAMFETAMINE SULFATE 1mg/mL oral solution
dc1w.	DEXAMFETAMINE SULFATE 5mg tablets
dc1x.	DEXAMPHETAMINE SULPHATE 7.5mg m/r capsules
dc1y.	DEXAMPHETAMINE SULPHATE 12.5mg m/r capsules
dc1z.	DEXAMPHETAMINE SULPHATE 20mg m/r capsules
dw11.	METHYLPHENIDATE HYDROCHLORIDE 10mg tablets
dw12.	RITALIN 10mg tablets
dw16.	EQUASYM XL 20mg m/r capsules
dw17.	CONCERTA XL 18mg m/r tablets
dw18.	CONCERTA XL 36mg m/r tablets
dw1C.	EQUASYM XL 10mg m/r capsules
dw1D.	EQUASYM XL 30mg m/r capsules
dw1E.	MEDIKINET XL 10mg m/r capsules

dw1F.	MEDIKINET XL 20mg m/r capsules
dw1G.	MEDIKINET XL 30mg m/r capsules
dw1H.	MEDIKINET XL 40mg m/r capsules
dw1I.	CONCERTA XL 27mg m/r tablets
dw1J.	MEDIKINET 5mg tablets
dw1K.	MEDIKINET 10mg tablets
dw1L.	MEDIKINET 20mg tablets
dw1M.	MEDIKINET XL 5mg m/r capsules
dw1n.	METHYLPHENIDATE HYDROCHLORIDE 54mg m/r tablets
dw1q.	METHYLPHENIDATE HYDROCHLORIDE 5mg m/r capsules
dw1r.	METHYLPHENIDATE HYDROCHLORIDE 27mg m/r tablets
dw1s.	METHYLPHENIDATE HYDROCHLORIDE 40mg m/r capsules
dw1t.	METHYLPHENIDATE HYDROCHLORIDE 10mg m/r capsules
dw1u.	METHYLPHENIDATE HYDROCHLORIDE 30mg m/r capsules
dw1v.	METHYLPHENIDATE HYDROCHLORIDE 36mg m/r tablets
dw1w.	METHYLPHENIDATE HYDROCHLORIDE 18mg m/r tablets
dw1x.	METHYLPHENIDATE HYDROCHLORIDE 20mg m/r capsules
dw1y.	METHYLPHENIDATE HYDROCHLORIDE 5mg tablets
dw1z.	METHYLPHENIDATE HYDROCHLORIDE 20mg tablets
dw21.	STRATTERA 10mg capsules
dw22.	STRATTERA 18mg capsules
dw23.	STRATTERA 25mg capsules
dw24.	STRATTERA 40mg capsules
dw25.	STRATTERA 60mg capsules
dw26.	STRATTERA 80mg capsules
dw27.	STRATTERA 100mg capsules
dw2t.	ATOMOXETINE 100mg capsules
dw2u.	ATOMOXETINE 80mg capsules
dw2v.	ATOMOXETINE 60mg capsules
dw2w.	ATOMOXETINE 40mg capsules
dw2x.	ATOMOXETINE 25mg capsules
dw2y.	ATOMOXETINE 18mg capsules
dw2z.	ATOMOXETINE 10mg capsules
dw31.	ELVANSE 30mg capsules
dw32.	ELVANSE 50mg capsules
dw33.	ELVANSE 70mg capsules
dw3x.	LISDEXAMFETAMINE DIMESYLATE 70mg capsules
dw3y.	LISDEXAMFETAMINE DIMESYLATE 50mg capsules
dw3z.	LISDEXAMFETAMINE DIMESYLATE 30mg capsules
E2E..	Overactive child syndrome
E2E0.	Child attention deficit disorder
E2E00	Attention deficit without hyperactivity

E2E01	Attention deficit with hyperactivity
E2E0z	Child attention deficit disorder NOS
E2E1.	Hyperkinesis with developmental delay
E2E2.	Hyperkinetic conduct disorder
E2Ey.	Other hyperkinetic manifestation
E2Ez.	Hyperkinetic syndrome NOS
Eu90.	[X]Hyperkinetic disorders
Eu900	[X]Attention deficit hyperactivity disorder
Eu901	[X]Hyperkinetic conduct disorder
Eu902	[X]Deficits in attention, motor control and perception
Eu90y	[X]Other hyperkinetic disorders
Eu90z	[X]Hyperkinetic disorder, unspecified
Eu9y7	[X]Attention deficit disorder

Conduct problems	
13HN.	Vandalism record
13HN0	Theft
13HN1	Shoplifting
13HN2	Forged/altered prescription
13Z4C	Behavioural problems at school
13Zb.	Bullies children
13Zc.	Bullies adults
1B1X.	Behavioural problem
1P5..	Aggressive behaviour
1P50.	Violent acts towards others
1P51.	Physically abusive behaviour
1P52.	Verbally abusive behaviour
1P53.	Argumentative behaviour
38G01	Strengths and Difficulties Questionnaire - conduct problems score
38G03	Strengths and Difficulties Questionnaire - peer problems score
E213.	Aggressive personality
E2C..	Behaviour disorder
E2C0.	Aggressive unsocial conduct disorder
E2C00	Aggressive outburst
E2C01	Anger reaction
E2C0z	Aggressive unsocial conduct disorder NOS
E2C1.	Nonaggressive unsocial conduct disorder
E2C10	Unsocial childhood truancy
E2C11	Solitary stealing
E2C12	Tantrums
E2C1z	Nonaggressive unsocial conduct disorder NOS

E2C2.	Socialised conduct disorder
E2C20	Socialised childhood truancy
E2C23	Group delinquency
E2C2z	Socialised conduct disorder NOS
E2C4.	Mixed disturbance of conduct and emotion
E2C40	Neurotic delinquency
E2C4z	Mixed disturbance of conduct and emotion NOS
E2Cy.	Other conduct disturbances
E2Cy0	Breath holder
E2Cyz	Other conduct disturbances NOS
E2Cz.	Unspecified disturbance of conduct
E2Cz0	Juvenile delinquency unspecified
E2Czz	Disturbance of conduct NOS
E2930	Adjustment reaction with aggression
E2931	Adjustment reaction with antisocial behaviour
Eu603	[X]Aggressive personality disorder
Eu911	[X]Unsocialised aggressive disorder
Eu912	[X]Group delinquency
Eu92.	[X]Emotional behavioural problems
R06z0	[D]Breath-holding spell
U3E..	[X]Stabbing
ZV4G7	[V] Bullying of child

Hyperactivity	
1P00.	Hyperactive behaviour
38G02	Strengths and Difficulties Questionnaire - hyperactivity score
6A61.	Attention deficit hyperactivity disorder annual review
8BPT.	Drug therapy for ADHD (attention deficit hyperactivity disorder)
8BPT0	Stimulant drug therapy for ADHD (attention deficit hyperactivity disorder)
8BPT1	Non-stimulant drug therapy for ADHD (attention deficit hyperactivity disorder)
9Ol8.	Attention deficit hyperactivity disorder monitoring invitation first letter
9Ol9.	Attention deficit hyperactivity disorder monitoring invitation second letter
9OlA.	Attention deficit hyperactivity disorder monitoring invitation third letter
dw...	Drugs used to treat hyperactivity disorders
dw3..	LISDEXAMFETAMINE
dw31.	ELVANSE 30mg capsules
dw32.	ELVANSE 50mg capsules
dw33.	ELVANSE 70mg capsules
dw3x.	LISDEXAMFETAMINE DIMESYLATE 70mg capsules
dw3y.	LISDEXAMFETAMINE DIMESYLATE 50mg capsules

dw3z.	LISDEXAMFETAMINE DIMESYLATE 30mg capsules
E2E0.	Child attention deficit disorder
E2E0z	Child attention deficit disorder NOS
Eu900	[X]Disturbance of activity and attention

Nervous	
1B12.	Nerves - nervousness
E205.	Nervous exhaustion
E20z.	Nervous breakdown

Grief and bereavement	
675..	Grieving counselling
6751	Bereavement counselling
675Z.	Grieving counselling NOS
13M..	Family bereavement
13MZ.	Family bereavement NOS
E2900	Grief reaction
Eu432	adjustment disorders
ZV628	[V]Uncomplicated bereavement

Anorexia	
1612	Anorexia symptom
1467	H/O: anorexia nervosa
E271.	AN - Anorexia nervosa
E2756	Non-organic loss of appetite
Eu500	[X]Anorexia nervosa
Eu501	[X]Atypical anorexia nervosa
Eu50y	[X]Psychogenic loss of appetite
R030.	[D]Anorexia
R0300	[D]Appetite loss
R030z	[D]Anorexia NOS

Bulimia	
E2751	Bulimia (non-organic overeating)
Eu502	[X]Bulimia NOS
Eu503	[X]Atypical bulimia nervosa