Keele University

Attitudes, beliefs and physical activity in older adults with knee pain

Jonathan Quicke

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Declaration Part 1. To be bound in the thesis

SUBMISSION OF THESIS FOR A RESEARCH DEGREE

Part I. DECLARATION by the candidate for a research degree.

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This thesis contains confidential information and is subject to the protocol set down for the submission and examination of such a thesis. N/A

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Name of candidate: Jonathan Quicke

Research Institute: Primary Care Sciences Lead Supervisor: Dr Melanie Holden

I certify that:

(a) The thesis being submitted for examination is my own account of my own research
(b) My research has been conducted ethically. Where relevant a letter from the approving body confirming that ethical approval has been given has been bound in the thesis as an Annex
(c) The data and results presented are the genuine data and results actually obtained by me during the conduct of the research
(d) Where I have drawn on the work, ideas and results of others this has been appropriately acknowledged in the thesis
(e) Where any collaboration has taken place with one or more other researchers, I have included within an 'Acknowledgments' section in the thesis a clear statement of their contributions, in line with the relevant statement in the Code of Practice (see Note overleaf).
(f) The greater portion of the work described in the thesis has been undertaken subsequent to my registration for the higher degree for which I am submitting for examination
(g) Where part of the work described in the thesis has previously been incorporated in another thesis submitted by me for a higher degree (if any), this has been identified and acknowledged in the thesis
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Declaration

This PhD project was advertised as an “ACORN studentship” part funded by Keele University and part funded by Arthritis Research UK. The funding for the studentship was obtained by Dr Melanie Holden and Professor Nadine Foster at the Arthritis Research UK Primary Care Centre. The initial PhD idea and research questions formed part of the studentship project and are credited to the above.

Throughout the course of the PhD project I developed the questions and ideas for this thesis with ongoing guidance from my supervisors Dr Melanie Holden and Professor Nadine Foster. During the course of the project I received additional statistical methodological and Stata coding support for data analysis thesis Parts 2 to 4 from Dr Reuben Ogollah and epidemiological advice from Professor Peter Croft.

I received systematic review search guidance from Jo Jordan who also reviewed the systematic review protocol. Dr Mel Holden, Professor Nadine Foster and Dr Martin Thomas supported the systematic review and provided advice, *“second reviewer”* screening, risk of bias and result data extraction double checking.

The data analyses within Parts 2 to 4 of this thesis were secondary. The datasets used were compiled by others prior and during my time on the PhD project. Professor Nadine Foster was the primary investigator for the BEEP trial while Dr Melanie Holden was the primary investigator for the ABC-Knee study. Since these datasets were used for primary projects the data was already cleaned by Elaine Nichols (the statistician responsible for these datasets).

Abstract

Knee pain in older adults is common and often disabling, with the majority of knee pain in adults over the age of 45 being attributed to osteoarthritis (OA). Regular physical activity and exercise are recommended for all older adults with knee pain and are associated with reduced pain and improved function. However, physical activity levels are low in this population and there is uncertainty regarding its long-term safety, whether change in physical activity level is associated with future pain and function, and the relationship between attitudes and beliefs about physical activity and physical activity level. This thesis addressed these research questions.

A systematic review of safety outcomes from 49 published studies found exercise was safe for the majority of older adults with knee pain, although most evidence related to low impact, moderate cardiovascular intensity exercise.

Secondary data analysis of an exercise randomised controlled trial for older adults with knee pain (n=514) did not find an association between change in physical activity level between baseline and three months and clinical outcome at either three or six months.

Secondary cross-sectional data analysis, using baseline data from the same trial and a community survey of older adults with knee pain (n=611), found that a number of scales measuring attitudes and beliefs about physical activity were associated with physical activity level in multivariable models. Positive outcome expectations, self-efficacy for exercise, kinesiophobia and a composite scale measuring physical activity attitude themes were associated with physical activity level.

Further longitudinal analysis from the trial showed that positive outcome expectations and self-efficacy for exercise remained associated with future physical activity level at three and six months within multivariable models whilst negative outcome expectations were not.

The original thesis findings have contributed to a better understanding of attitudes, beliefs and physical activity in older adults with knee pain.

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Acknowledgements

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I would like to acknowledge my fantastic supervisors Dr Melanie Holden and Professor Nadine Foster. As my lead supervisor, I am hugely grateful to Mel for her faith, support, encouragement and advice which, beyond the call of duty, even continued during her maternity leave. Nadine has also been wise, measured and inspirational from the first day I contacted her expressing my interest in researching at Keele. Thank you both.

I would also like to thank my wider advisory team- Dr Reuben Ogollah for statistical support and Professor Peter Croft for epidemiological advice. It has been a pleasure working with them. Dr Martin Thomas and Jo Jordan also provided additional support with the systematic review- Martin as an enthusiastic study reviewer and Jo as an advisor with the search filters and protocol reviewer.

Thanks to everyone at Keele who has shared knowledge with me over the three years. It is not possible to list everyone here but I would like to mention, Professor Kate Dunn and Professor George Peat's epidemiology enthusiasm, Professor Kelvin Jordan, Elaine Nichols and Rebecca Whittle's statistical conversations, all my peers, and everyone involved in the BEEP trial and ABC-Knee study.

Last but not least thanks to Angie, my family and friends for sharing me with the PhD and all the musicians who helped provide my thesis soundtrack!

Context of the thesis

I undertook a BSc in Physiotherapy at Nottingham University, graduating in 2003 and, having worked in musculoskeletal outpatients, I specialised in interdisciplinary pain management and functional restoration programmes. I completed a Physiotherapy MSc in 2012 at Nottingham University. Enthused by these experiences and keen to contribute to the science underpinning psychologically informed physiotherapy I applied for this PhD studentship. This PhD research was undertaken full time. The initial outline title and research questions of the PhD were defined prior to my involvement.

List of abbreviations

α	Alpha significance value
ABC-Knee	Keele Attitudes and Behaviours Concerning Knee pain
ACT	Acceptance and Commitment Therapy
AMED	The Allied and complementary MEdical Database
ARUK	Arthritis Research United Kingdom
ASES	Arthritis Self-Efficacy Scale
β	Beta regression coefficient
BEEP	Benefits of Effective Exercise for knee Pain
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CHAMPS	Community Healthy Activities Program for Seniors
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health
CPG	Chronic Pain Grade
DOH	Department of Health
EN	Elaine Nichols
GAD7	General Anxiety Disorder 7
GP	General Practitioner
ICC	Intra Class Correlation
ICH	International Conference on Harmonisation
ITE	Individually Tailored Exercise
JJ	Jo Jordan
JQ	Jonathan Quicke
KL	Kellgren and Lawrence score
MDC	Minimum Detectable Change
MET	Metabolic equivalent score
MH	Dr Melanie Holden
MRI	Magnetic Resonance Imaging

MT	Dr Martin Thomas
n	Number
NHS	National Health Service
NICE	National Institute for health and Care Excellence
NIOSHTIC	United States National Institute for Occupational Safety and Health
NSAID	Non-Steroidal Anti Inflammatory
NF	Professor Nadine Foster
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OEE	Outcome Expectations for Exercise
OR	Odds Ratio
OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International
OPAPAEQ	Older Person's Attitudes towards Physical Activity and Exercise Questionnaire
PA	Physical Activity
PASE	Physical Activity Scale for the Elderly
PEDro	Physiotherapy Evidence Database
PhD	Doctor of Philosophy
PHQ8	Patient Health Questionnaire
POM	Proportional Odds Model
PPOM	Partial Proportional Odds Model
PROSPERO	International prospective register of systematic reviews
QUIPS	QUality in Prognostic Studies tool
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
Ref	Reference category
RO	Dr Reuben Ogollah
SEE	Self-Efficacy for Exercise
SMD	Standard Mean Difference

STAR	Short Telephone Activity Recall questionnaire
TEA	Targeted Exercise Adherence
TKR	Total Knee Replacement
TSK	Tampa Scale for Kinesiophobia
UC	Usual Care
UK	United Kingdom
UK RiME	United Kingdom Research into Musculoskeletal Epidemiology
US	United States
VIF	Variance Inflation Factor
WCPT	World Confederation for Physical Therapy
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WSP	Manchester Widespread Pain

Chapter 1

Thesis introduction and overview

1.1 Introduction

This chapter provides an initial overview of the thesis. It gives a brief background rationale for the research (which is developed in further detail in chapter 2), states the overall thesis aim and associated research questions before providing a layout of the thesis structure and a synopsis of each chapter. Publication and dissemination outputs arising from this body of work are also highlighted.

1.2 Concise thesis rationale

Knee pain in older adults is common, with the majority of pain in adults over the age of 45 being attributable to osteoarthritis (OA) (National Institute for Health Care and Excellence, NICE, 2014). It is a major cause of disability (Guccione et al, 1994; Vos et al, 2012) and is associated with comorbidities (Jinks et al, 2002; Fransen et al, 2014) and increased all-cause mortality (Nüesch et al, 2011; Liu et al, 2015). Physical activity and exercise play an important role in the core management of older adults with knee pain (Bennell & Hinman, 2011; Fernandes et al, 2013; McAlindon et al, 2014; NICE, 2014) and are associated with improvements in pain, physical functioning and wider health benefits (Warburton et al, 2010; Autenrieth et al, 2013; Fransen et al, 2015). However, despite the numerous health benefits associated with regular physical activity and exercise, physical activity levels in this population are low, with less than half meeting guideline recommended levels (Wallis et al, 2013; NICE, 2014; Holden et al, 2015). Hence, the benefits of physical activity are not being achieved in the majority of older adults with knee pain.

In order to optimise the benefits of physical activity in older adults with knee pain, it is important to understand both the factors that are linked to physical activity level and also the mechanisms of action for physical activity and exercise interventions in improving important clinical outcomes such as pain and physical function (Veenhof et al, 2012; Nicolson et al, 2015; Runhaar et al, 2015). Although physical activity behaviour is complex, attitudes and beliefs about physical activity have been identified as potentially key physical activity behaviour determinants yet have not been empirically investigated in older adults with knee pain (Hendry et al, 2006; Biddle & Mutrie, 2008; Holden et al, 2012).

Many older adults with knee pain and the health care practitioners whom they consult are uncertain regarding the safety of long-term physical activity, in part due to their attitudes and beliefs about the condition and the role that physical activity and exercise can play in its' management (Hendry et al, 2006; Holden et al, 2009; Cottrell et al, 2010; Holden et al, 2012). Systematically reviewing the published evidence relating to the safety of long-term physical activity may help address this uncertainty.

Mechanisms of action for the clinical benefits associated with physical activity and exercise are incompletely understood (Runhaar et al, 2015). Although higher levels of physical activity and physical activity interventions have been associated with lower levels of pain and higher physical functioning (Dunlop et al, 2011; Fransen et al, 2015; Stubbs et al, 2015) it is unknown if change in physical activity levels per se are associated with future clinical outcome in terms of pain and physical function.

Key attitudes and beliefs about physical activity in older adults with knee pain include those regarding the safety of physical activity, kinesiophobic attitudes and beliefs (fear of movement, pain and harm), self-efficacy and outcome expectations about physical activity (Heuts et al, 2004; Hendry et al, 2006; Biddle & Mutrie, 2008; Holden et al, 2012). The cross-sectional and longitudinal relationships between these salient attitudes and beliefs and physical activity level have not previously been quantitatively modelled in older adult with knee pain populations. A deeper understanding of these relationships together with increased knowledge surrounding the safety of long-term physical activity and changes in physical activity level may contribute to the design of interventions aimed at increasing physical activity levels and improving clinical outcomes in older adults with knee pain.

1.3 Thesis aims and research questions

The overall thesis aim was to investigate the attitudes and beliefs about physical activity and physical activity levels of older adults with knee pain, with a view to providing new knowledge that can inform future physical activity interventions in this population. The thesis investigated the following research questions in older adults with knee pain:

1) Is long-term physical activity safe?
2) Are changes in physical activity level associated with future clinical outcomes in terms of pain and function?
3) Are attitudes and beliefs about physical activity associated with physical activity level?
4) Can attitudes and beliefs about physical activity predict future physical activity level?

In order to answer these questions, the thesis is presented in four parts, each including different data analyses (see figure 1.1 below).

Figure 1.1 Thesis research parts

Part 1:

Is long-term physical activity safe for older adults with knee pain?

Investigated using a systematic review collating evidence from randomised controlled trials, prospective cohort studies and case control studies.

Part 2:

Are changes in physical activity level associated with future clinical outcomes in terms of pain and function in older adults with knee pain?

Investigated using quantitative secondary data analyses using longitudinal trial data.

Part 3:

Are attitudes and beliefs about physical activity associated with physical activity level in older adults with knee pain?

Investigated using quantitative secondary data analyses using baseline trial and cross-sectional survey data.

Part 4:

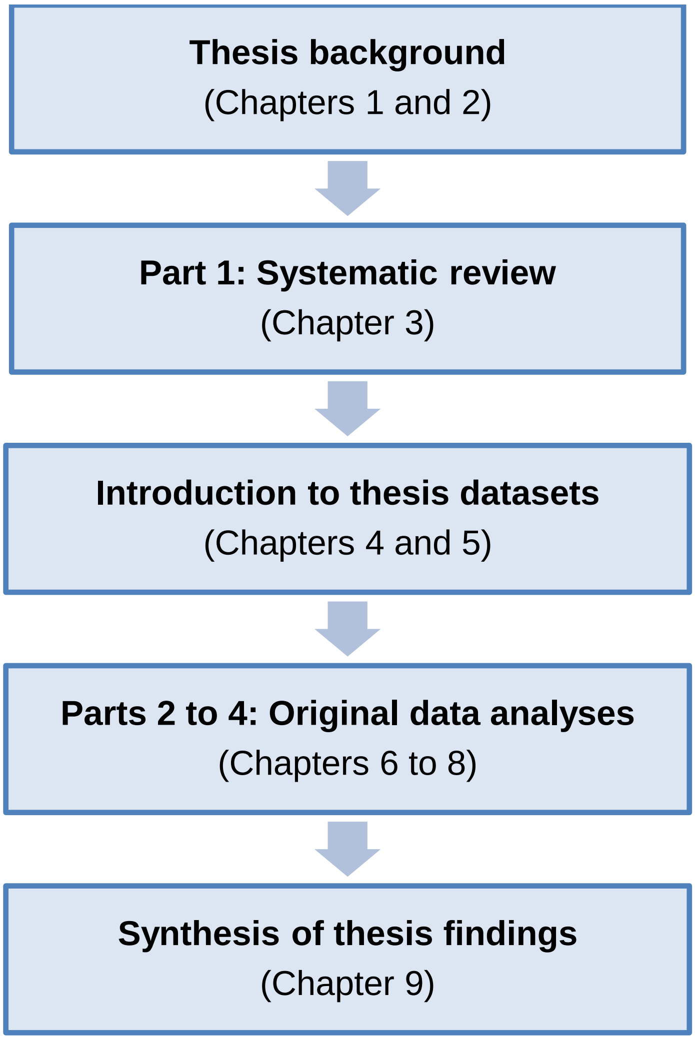
Can attitudes and beliefs about physical activity predict future physical activity level in older adults with knee pain?

Investigated using quantitative secondary data analyses using longitudinal trial data.

1.4 Thesis overview

An overview of the thesis structure is provided in figure 1.2 overleaf whilst a brief synopsis of the thesis chapters is provided in the following section.

Figure 1.2 Thesis overview



1.5 Thesis chapter synopsis

Chapter 2: Attitudes, beliefs and physical activity in older adults with knee pain.

This chapter provides a more detailed rationale for the thesis. It introduces the problem of knee pain in older adults, its link to OA and the role of physical activity and exercise for this population. Salient theories relating to physical activity behaviour are discussed, before focussing on the existing literature exploring attitudes and beliefs about physical activity in older adults with knee pain. The chapter concludes with the thesis aim and research questions.

Chapter 3: **The safety of long-term physical activity in older adults with knee pain**

Thesis Part 1. Many older adults with knee pain and healthcare practitioners who manage them are uncertain regarding the safety of physical activity for older adults with knee pain. This chapter uses systematic review methodology to investigate the safety of long-term physical activity for older adults with knee pain. Evidence from randomised controlled trials (RCTs), prospective cohort studies and case-control studies are synthesised prior to narrative synthesis and discussion of findings.

Chapter 4: **The Benefits of Effective Exercise for older adults with knee Pain trial (BEEP) dataset**

This chapter introduces the BEEP trial dataset used within Parts 2, 3 and 4 of this thesis. The rationale for the trial is briefly explained prior to the justification for selecting this dataset as appropriate for addressing the thesis research questions. Variables and outcome measures included in the trial and used within this thesis are described and discussed alongside longitudinal descriptive statistics for clinical outcome, self-report physical activity, self-efficacy and outcome expectations for exercise.

Chapter 5: **The Attitudes and Behaviour Concerning Knee pain Study (ABC-Knee Study) dataset**

This chapter introduces the community survey of older adults with knee pain (the ABC-Knee study) used within Part 3 of this thesis. The rationale for this study and the justification for utilising this dataset to answer thesis research questions are discussed. Dataset variables are described and discussed including clinical outcome, self-report physical activity, attitudes about physical activity, fear of movement and injury, and self-efficacy for physical activity with arthritis.

Chapter 6: Change in physical activity and future clinical outcome in older adults with knee pain

Thesis Part 2. This chapter uses regression analyses of longitudinal BEEP trial data to investigate the association between change in physical activity level and future clinical outcome (in terms of pain and function at three and six months follow-up).

Chapter 7: **The relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain**

Thesis Part 3. This chapter uses regression analyses of cross-sectional BEEP trial baseline data and the ABC-Knee study data to investigate the associations between attitudes and beliefs about physical activity and physical activity level, in older adults with knee pain.

Chapter 8: **Attitudes and beliefs about physical activity and future physical activity level in older adults with knee pain**

Thesis Part 4. This chapter uses regression analyses of longitudinal BEEP trial data to investigate if attitudes and beliefs about physical activity are associated with future physical activity level in older adults with knee pain at three and six months follow-up.

Chapter 9: **Synthesis of thesis findings**

This chapter summarises, evaluates and synthesises the key findings from the thesis. It highlights clinical and research recommendations for increasing physical activity level in older adults with knee pain.

1.6 Research output arising from this thesis

Several results from the research within this thesis have been disseminated to date, including a paper publication and oral presentations at scientific conferences. Further publications and conference abstracts are also planned.

1.6.1 Research publication

Quicke, J. G., Foster, N. E., Thomas, M.J., & Holden, M. A. Is long-term physical activity safe for older adults with knee pain? A systematic review. Osteoarthritis and Cartilage 2015; 23(19): 1445-1456.

1.6.2 Systematic review registration

Quicke, J., Foster, N., Thomas, M., & Holden, M. Is long-term physical activity safe for older adults with knee pain? A systematic review. PROSPERO 2014:CRD42014006913 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014006913

1.6.3 Oral conference presentations

I) Scientific conference presentations

Quicke, J., Foster, N., Thomas M., & Holden, M. (2014). Is long-term physical activity safe for older adults with knee pain? A systematic review. Osteoarthritis Research Society International (OARSI) 2014 World Congress (Paris).

Quicke, J., Foster, N., Ogollah, R., & Holden, M. (2014). The association between physical activity attitudes, beliefs and behaviour in older adults with knee pain. UK Research into Musculoskeletal Epidemiology (UK RiME) Annual Showcase 2014 (Manchester).

Quicke, J., Foster, N., Ogollah, R., & Holden, M. (2015). The relationship between attitudes, beliefs and physical activity in older adults with knee pain. World Confederation of Physical Therapy (WCPT) 2015 World Congress (Singapore).

Quicke, J., Foster, N., Croft, P., Ogollah, R., & Holden, M. (2015). Is change in physical activity level associated with clinically important improvement in pain and function in older adults with knee pain? Arthritis Research UK Physical activity and osteoarthritis conference 2015 (Loughborough).

II) Conference presentations within Keele University

Quicke, J., Foster, N., Thomas, M., Holden, M. (2013). Is long-term physical activity safe for older adults with knee pain? Systematic review methods. Arthritis Research UK and Primary Care Keele Postgraduate Symposium (Keele).

Quicke, J., Foster, N., Thomas, M., Holden, M. (2014). Is long-term physical activity safe for older adults with knee pain? Systematic review results. Arthritis Research UK and Primary Care Keele Postgraduate Symposium (Keele).

1.6.4 Awards for research dissemination

Best oral presentation at the Keele Postgraduate Symposium 2013

Best session oral presentation at the Keele Postgraduate Symposium 2014

OARSI Young Investigator Award 2014

Chartered Society of Physiotherapy Robert Williams Travel Award for the World Confederation of Physical Therapy 2015

1.7 PhD funding

This research was supported by an ACORN doctoral studentship which was part funded by Keele University and part funded by the Arthritis Research UK Centre for Primary Care Research at Keele University.

1.8 Chapter Summary

This chapter introduced the thesis, its’ research aim, objectives and structure together with a chapter synopsis.   The next chapter provides a more in depth background introduction to the thesis and work up to the research questions it addresses.

Chapter 2

Background

2.1 Chapter introduction

This chapter presents salient literature on attitudes, beliefs and physical activity in older adults (over the age of 45 years) with knee pain relevant to this thesis. It begins by describing the substantial problem of knee pain in older adults, highlighting the associated individual and societal burden. Key definitions of knee pain in older adults and related nomenclature are provided before briefly explaining what is known about aetiology and prognosis. Best practice management of knee pain in older adults is introduced focussing specifically on physical activity. Current techniques of physical activity measurement are critiqued, followed by interpretation of current physical activity levels in older adults with knee pain. The potential benefits of regular activity are juxtaposed against the current levels of physical activity in older adults with knee pain. Increasing long-term physical activity is highlighted as an important challenge in improving clinical outcome in this population. Attitudes and beliefs about physical activity are highlighted as likely important determinants of the observed sub optimal levels of physical activity behaviour based on theoretical, qualitative and epidemiological literature. Uncertainty over the safety of physical activity for older adults with knee pain is identified as a key factor. The chapter concludes with a summary of the pertinent gaps in the literature that this thesis seeks to address.

2.2 The problem of knee pain in older adults

2.2.1 Individual burden

Knee pain in older adults is common (Jinks et al, 2004). Its prevalence and impact are likely to rise in the future due to an ageing population and increasing levels of obesity (Zhang & Jordan, 2010; Hunter et al, 2014). Precise incidence and prevalence rates vary depending on differing knee pain definitions and population sources (Pereira et al, 2011). In the UK, the one year period prevalence of knee pain in adults over the age of 50 years old is estimated at around 50% (Jinks et al, 2004). Approximately a quarter of all older adults experience chronic knee pain lasting three months or more (Jinks et al, 2004). In terms of pain severity, approximately half of all the adults who report pain also experience severe knee pain (Jinks et al, 2002, 2004). Furthermore, about half of older adults who report knee pain also experience bilateral knee symptoms (Jinks et al, 2002).

Knee pain in older adults is a major cause of disability (McAlindon et al, 1992; Guccione, 1994; Guccione et al, 1994; Vos et al, 2012). Globally, knee pain in older adults accounts for 10% of all years lived with disability due to musculoskeletal conditions (Vos et al, 2012) and is associated with reduced walking speed (Osaki et al, 2012; Marcum et al, 2014; Morone et al, 2014), difficulty with stairs (Fransen et al, 2014; Morone et al, 2014), and falls (Scott et al, 2012; Fransen et al, 2014). Likely linked to reduced mobility, knee pain in older adults has also been associated with reductions in social participation (Wilkie et al, 2007) and the presence of four or more comorbidities (Fransen et al, 2014). Comorbidities interact together further compounding disability (Reeuwijk et al, 2010). In addition, influenced by pain, associated disabilities and reduced social participation, older adults with knee pain experience lower quality of life (Losina et al, 2012; Hoogeboom et al, 2013; Hunter et al, 2014) and higher levels of depression (Jinks et al, 2002). Importantly, knee pain in older adults and the severity of its related disability are associated with increased all-cause mortality (Nüesch et al, 2011; Hawker et al, 2014; Liu et al, 2015).

2.2.2 Socioeconomic burden

Quantifying the economic burden to the UK from older adults with knee pain is challenging. This is due to the lack of knee joint pain specific economic literature together with heterogeneity in the definitions of knee pain and economic modelling approaches used in available studies (Oxford Economics, 2010; Chen et al, 2012; Hunter et al, 2014). Knee pain incurs costs that can be split into direct costs (hospital and other healthcare costs) and indirect costs (occupational costs, disability benefit costs and informal carer costs) (Hunter et al, 2014). A significant number of older adults seek healthcare support as a result of their knee pain problem with around 4% of all adults over the age of 55 consulting their general practitioner (GP) at least once a year (Peat et al, 2001). Each primary care consultation is estimated to cost £45 (Royal College of General Practitioners, 2015) whilst other healthcare costs include treatments offered in services such as physiotherapy, rheumatology and orthopaedics. Medication costs, including topical and oral non-steroidal anti-inflammatory drugs (NSAIDs) and the additional management of NSAID-related iatrogenic events, are estimated to be tens of millions of pounds (Moore, 2002; Chen et al, 2012). However, the largest direct cost incurred from older adults with knee pain is due to total knee replacement surgery (TKR) (Hunter et al, 2014). In 2010 it was estimated that around £526 million was spent on TKR within the National Health Service (NHS) (Chen et al, 2012).

Indirect costs are likely to contribute the largest economic burden to society (Hunter et al, 2014). Indirect occupational costs are due to absenteeism (time lost from work such as sick days), presenteeism (losses in productivity that occur due to knee pain whilst at work), early retirement, and premature death (causing both income loss and reduced taxation) (Hunter et al, 2014). Although knee pain specific indirect cost figures are lacking in the literature, some idea of the potential scale of these costs can be crudely estimated from more general joint pain literature (Oxford Economics, 2010; Chen et al, 2012). For example, costs incurred due to loss of production from work absenteeism due to joint pain in older adults were estimated at £3.3 billion in 2008 in the UK, with the combined cost of disability living allowance and informal carer costs estimated at a similar amount (Oxford Economics, 2010). A significant proportion of these costs are likely due to knee pain in older adults.

2.3 Knee pain in older adults and osteoarthritis

Having excluded serious pathologies and other specific conditions (for example, fracture and inflammatory arthropathies, such as rheumatoid arthritis) the majority of knee pain in older adults is attributed to OA (NICE, 2014). OA refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life (Dieppe & Lohmander, 2005; Dekker et al 2009; NICE, 2014). Clinical symptoms include pain, stiffness, and reduced function whilst signs of crepitus, reduced joint range and bony enlargement are also common (Dieppe & Lohmander, 2005). OA can affect multiple joints and it is common for older adults with knee pain to experience pain in more than one joint (NICE, 2014). Knee OA is also associated with multiple interacting impairments, including pain, knee and hip extensor muscle weakness, reduction in knee joint range of movement, loss of proprioception and balance as well as reduced cardiovascular fitness (Bennell et al, 2011). Clinical outcome in terms of pain and physical function are variable between individuals and can fluctuate over time (NICE, 2014).

Knee pain severity in older adults is complex and comprises multiple elements including nociception and inflammation from tissues (such as subchondral bone changes and synovitis), central and peripheral neural sensitisation resulting in hyperalgesia (increased sensitivity to pain), together with higher centre modulation from psychosocial factors (such as low mood, distress, anxiety, catastrophizing socioeconomic status and occupation) (Dieppe & Lohmander, 2005; Arendt-Nielsen et al, 2010; Bennell et al, 2011; Linton & Shaw, 2011; Cleveland et al, 2013; Cruz-Almeida et al, 2013; Neogi, 2013; Sinikallio et al, 2014). Similar psychosocial factors (with the addition of fear of movement and harm) also have important influences on physical activity behaviour and functional outcome (Dieppe & Lohmander, 2005; Main et al, 2008; Cleveland et al, 2013; Cruz-Almeida et al, 2013; Holla et al, 2014; Sinikallio et al, 2014).

Traditionally OA was considered a progressive degenerative condition, however, this is no longer the case with the OA process now considered to be one of ongoing repair and remodelling (NICE, 2014). From a pathoanatomical viewpoint, OA involves the whole of synovial joints including the articular cartilage, menisci, sub chondral bone, synovium, capsule, and surrounding muscles and tendons (Dieppe & Lohmander, 2005; Bennell et al, 2011). It is characterised by focal areas of cartilage loss, subchondral bone changes, associated osteophytes and synovitis (Neogi & Zhang, 2013; NICE, 2014).

OA has been defined within the literature in a number of ways, based on the anatomical joint(s) affected (for example, tibiofemoral, patellofemoral and multi-joint OA (Peat et al, 2004)) as well as clinical symptoms, radiographic findings or both (for example, as either symptomatic OA, radiographic OA or combined symptomatic and radiographic OA) (Altman et al, 1986; Peat et al, 2006b). There is an association between clinical symptoms of increased pain severity, stiffness and poorer physical function with radiographic OA in older adults with knee pain (Duncan et al, 2007). However, not all older adults with radiographic OA experience OA symptoms and similarly OA symptoms may be present in the absence of radiographic findings (Dieppe & Lohmander, 2005; Bedson & Croft, 2008; Finan et al, 2013). This imperfect concordance could in part be due to limitations in radiographic imaging (as oppose to more sensitive Magnetic Resonance Imaging (MRI)) and, in part, due to the complex interacting determinants of pain discussed above (Neogi & Zhang, 2013).

The National Institute for Health Care and Excellence recommend that routine treatment decisions for the management of patients with OA are based on an individual's signs, symptoms and holistic context rather than their knee structural imaging (NICE, 2014). In line with NICE guidelines, the term *"knee pain in older adults"* is used primarily within this thesis with the assumption that most older adults with knee pain will have a clinical syndrome of OA and some will have radiographic changes in either the tibiofemoral and/or patellofemoral joints (NICE, 2014). It is accepted that the literature referenced within this thesis is taken from authors using heterogeneous definitions of knee pain and OA.

2.4 Risk and prognostic factors for knee pain in older adults

2.4.1 Risk factors

Knee pain in older adults has multiple risk factors and can be considered as the result of a complex interplay of systemic factors (including age, obesity, female gender and genetics), local factors (including previous knee injury, knee varus and valgus malalignment), and psychosocial factors (including depression) (Dieppe &

Lohmander, 2005; Blagojevic et al, 2010; Baker-LePain & Lane, 2012; Heijink et al, 2012; Neogi & Zhang, 2013; Silverwood et al, 2015). The potential contribution of physical activity as a risk or protective factor is equivocal in the literature (Vignon et al, 2006; Bennell et al, 2011; Neogi & Zhang, 2013; Richmond et al, 2013). This is due in part to differing risks for differing physical activities, and methodological limitations within studies, such as bias due to residual confounding and incomplete adjustment (Richmond et al, 2013; Szklo & Nieto, 2014). These epidemiological concepts are discussed later in the thesis (see chapter 3, section 3.3.2; chapter 6, section 6.6.3; chapter 7, sections 7.3.5 & 7.5.3). Occupational activity risk factors include heavy lifting and kneeling (Richmond et al, 2013; Silverwood et al, 2015). Sport and physical activity level per se have yielded conflicting results with the majority of studies showing no association between sports participation or levels of physical activity and knee pain onset (Richmond et al, 2013; Silverwood et al, 2015). It is likely that any association between participation in sports and knee pain onset are linked to joint injury such as meniscal and anterior cruciate ligament tears (Bennell et al, 2011; Neogi & Zhang, 2013; Richmond et al, 2013). For example, participation in football, tennis and hockey were not associated with knee OA onset in one large case-control study that adjusted for knee injury, however, if knee injury was not adjusted for they were associated with OA onset (Thelin et al, 2006).

2.4.2 Prognostic factors

There is some uncertainty within the literature about the most important prognostic factors in older adults with knee pain, primarily due to the methodological challenges in identifying them (Neogi & Zhang, 2013; Zhang et al, 2010). These challenges include heterogeneous definitions of condition onset and progression, ceiling effects in some measures of radiographic OA progression and bias due to conditioning on a collider, which have been discussed in detail outside of this thesis (Cole et al, 2010; Zhang et al, 2010; Neogi & Zhang, 2013). Key prognostic factors can also be classified into systemic factors (age, obesity, multiple comorbidities and pain in multiple joints) and local factors (varus and valgus malalignment, infrapatellar synovitis and joint effusion) with a dearth of evidence exploring psychosocial factors (Tanamas et al, 2009; Chapple et al, 2011; Felson et al, 2013; Bastick et al, 2015a, 2015b).

Physical activity and sports participation have been suggested not to be associated with progression of knee pain in systematic reviews of observational studies (Chapple et al, 2011; Bastick et al, 2015a). However, these conclusions are based on limited evidence from observational studies (Schouten et al, 1992; Lane et al, 1998; Cooper et al, 2000; Sharma et al, 2003). Confidence in the findings from these studies is reduced because of unadjusted confounding, limitations in the measurement of physical activity and self-selection for physical activity (Lane et al, 1998; Chapple et al, 2011; Neogi & Zhang, 2013).

2.5 Best practise management of knee pain in older adults

Currently, there is no available cure for knee pain in older adults; hence treatment aims focus around patient education on the nature and self-management of knee pain, pain reduction, and improvement in physical function (Hunter & Felson, 2006; NICE, 2014). Many guidelines exist for the management of knee pain in older adults; recommendations overlap and are generally split into non-pharmacological, pharmacological and surgical management (Hochberg et al, 2012; Fernandes et al, 2013; McAlindon et al, 2014; NICE, 2014).

Physical activity and exercise have been consistently recommended as a core part of condition management for all older adults with knee pain. Regardless of knee pain severity or comorbidity, contemporary clinical guidelines all recommend a range of exercise types, including strengthening and aerobic exercise (Hochberg et al, 2012; Fernandes et al, 2013; McAlindon et al, 2014; NICE, 2014). Specific advice on exercise type, delivery and dose is often lacking, although some guidelines have recommended the individualisation of exercises in either one-to-one or class settings based on personal preference and local service availability, initiated at a dose within the individual's current capacity and gradually increased over time (Fernandes et al, 2013; NICE, 2014). Recent systematic reviews have attempted to provide specific detail on the optimal exercise prescription type and dose by synthesising findings from multiple RCTs investigating different exercise interventions (Uthman et al, 2013; Juhl et al, 2014). However, different authors have reached conflicting conclusions. Based on their meta-analysis of 60 lower limb OA RCTs, Uthman and colleagues (2013) recommend a combination of strengthening, flexibility and aerobic exercise, whilst Juhl et al (2014) recommend interventions containing either strengthening or aerobic exercise or functional performance exercise carried out three times a week based on evidence from meta-analysis of 48 knee OA RCTs.

2.6 Defining physical activity and exercise

Physical activity comprises *"a range of behaviours involving movement and expenditure of calories"* (Department of Health, 2009) (DOH). Exercise is considered as a subset of physical activity and is defined as "*planned, structured and repetitive body movement, with the intent of improving or maintaining one or more facets of physical fitness or function*" (Caspersen et al, 1985; Biddle &

Mutrie, 2008). Therapeutic exercise is any type of exercise specifically aimed at reducing the symptoms of knee pain (Fransen & McConnell, 2008). Other types of physical activity include; occupational activity, domestic activity, active travel, recreational activity and sport (DOH, 2009).

Physical activity can also be subcategorised based on compressive load (into high and low impact) as well as cardiovascular intensity (into vigorous, moderate, low and sedentary activity). High impact activities have high compressive load on joints and involve both feet being intermittently off the ground (for example running and jumping) whilst low impact exercises have low compressive loads (for example walking, cycling and swimming) (Hunter & Eckstein, 2009). Vigorous intensity physical activity causes sweating together with heart and breathing rate increase to the point where only a few words can be spoken without pausing for breath (for example, running or intensive weight training) (DOH, 2011). Moderate intensity physical activity is commonly defined as activity that will raise the heart and breathing rate whilst allowing conversation (for example fast walking, cycling), whilst low intensity physical activity does not cause increased breathing rate (DOH, 2011). Sedentary activities are those that occur whilst lying down or sitting, that require low energy expenditure (Pate et al, 2008).

Within this thesis, the term *"physical activity"* is primarily used for consistency, since both therapeutic exercise and physical activity more generally are of clinical interest and health benefit (see sections 2.9 & 2.10.1). Sedentary behaviour is considered as a distinct concept from physical activity and is outside the scope of this thesis since its effects are independent to physical activity level per se (Owen et al, 2010).

2.7 Measuring physical activity level

Accurate physical activity measurement is required to identify current physical activity levels and changes in physical activity level (Prince et al, 2008). Physical activity can be measured in several different ways which can be dichotomised into "*direct*" and "*self-report*" measures (Prince et al, 2008). The most commonly used methods for measuring physical activity in older adults are concisely summarised in table 2.1, whilst further detail on self-report questionnaires and accelerometry are subsequently provided since these were the two types of measures within the datasets utilised for this thesis (the thesis datasets are described in full within chapters 4 and 5).

Self-report questionnaires are the most common approach for measuring physical activity level in older adults with knee pain (Prince et al, 2008; Terwee et al, 2011) and validated tools for older adults include the International Physical Activity Questionnaire (Craig et al, 2003), the Short Telephone Activity Recall questionnaire (STAR) (Matthews et al, 2005) and the Physical Activity Scale for the Elderly (PASE) (Washburn et al, 1993). In general, these measures benefit from being relatively cheap, practical to use with large samples, and capable of assessing frequency and duration of a broad range of physical activities (Prince et al, 2008). However, they are prone to a range of potential biases: recall bias due to inaccurate memory (Prince et al, 2008); the Hawthorne effect, whereby the very act of being monitored can alter physical activity behaviour (Van Sluijs et al, 2006) and; social desirability biases, whereby some individuals, in order to portray themselves in keeping with perceived cultural norms, may report physical activity that differs from their actual levels (Adams et al, 2005). Furthermore, they may be associated with significant individual errors due to misclassification of physical activity intensity and duration by participants (Washburn et al, 1993; Craig et al, 2003; Matthews et al, 2005) and may therefore both over and under estimate actual physical activity level (Prince et al, 2008).

Accelerometry is considered an important direct physical activity measure and has also been used in older adults with knee pain literature (Wallis et al, 2013). Accelerometers are electric or electromechanical portable devices that capture movement in up to three planes as a voltage signal proportional to acceleration. This signal can then be converted to total or average daily activity or time spent in different activity intensities (Bassett & John, 2010). It is believed to provide the most accurate measurement of duration, frequency and intensity of activity (Murphy, 2009; Bassett & John, 2010). Although still prone to the Hawthorne effect, accelerometry is not at risk of many of the key sources of bias associated with the self-report measures described above (Prince et al, 2008; Bassett & John, 2010). However, it is relatively expensive, requires specialist data cleaning and analysis and tends to underestimate physical activity (due to an inability to register some types of physical activity such as cycling, swimming and walking at very slow speeds as well as sub optimal wearing positions) (Murphy, 2009). A further concern for researchers is that some users may forget to wear or do not tolerate wearing accelerometer devices which may lead to missing data (Murphy, 2009).

Table 2.1 Common physical activity measurement approaches

Physical activity measurement approach	Strengths	Limitations
Self-report measures		
Self-report questionnaire: These often contain questions on activity type, duration, intensity and frequency, from which physical activity levels are subsequently calculated.	✓ Can measure frequency, duration and intensity ✓ Cheap ✓ Practical for large samples ✓ Relatively low participant burden	× Recall bias × Questions may be misinterpreted × Errors in activity classification and estimation × Social desirability bias × May under and overestimate physical activity
Regular exercise diary: Participants regularly report their activity levels in diaries. Detail of reported activity varies.	✓ Can measure frequency, duration and intensity ✓ Cheap ✓ Practical for large samples ✓ Reduced recall bias	× Participant burden due to repeated recording × High risk of missing data × Some recall bias × Social desirability bias
Direct measures		
Accelerometry: Electric or electromechanical portable device that captures movement in up to three planes as a voltage signal proportional to acceleration. Can convert this signal into total or average daily activity or time spent in different activity intensity.	✓ Accurate measure of frequency, duration and intensity ✓ Can be worn for extended periods	× Expensive × Requires specialist data cleaning and analysis × Tends to underestimate physical activity × Cannot capture swimming/ cycling × Compliance issues in regularly wearing the device × Suboptimal positioning/ slow walking may affect output
Pedometery: Electric or electromechanical portable devices worn on the hip that count the number of steps by detecting motion.	✓ Relatively cheap ✓ Practical for large samples ✓ Can be worn for extended periods ✓ Easy to interpret ✓ Can be a motivational tool	× Feedback effect × Errors in calibration × May register false movement when in cars/trains × Slow walking/ obesity may result in undercounting × Compliance issues in regularly wearing the device

References: (Sallis & Saelens, 2000; Welk et al, 2000; Shephard, 2003; Westerterp & Plasqui, 2004; Adams et al, 2005; Prince et al, 2008; Murphy, 2009; Bassett & John, 2010; Terwee et al, 2011; Scholes et al, 2014)

There is no single *"gold standard"* for measuring physical activity level (Prince et al, 2008; Sun et al, 2013) with the optimum choice of measure dependent on the specific context (Prince et al, 2008; Terwee et al, 2011). Heterogeneous approaches to the measurement of physical activity can lead to different estimates of physical activity level in older adults with knee pain, making the direct comparison of the results between different studies and comparison of results to physical activity guidelines challenging (Sun et al, 2013). The following section describes adult physical activity guidelines in detail.

2.8 Physical activity guidelines

Current physical activity guidelines recommend adults and older adults should engage in 150 minutes of moderate intensity exercise per week in bouts of ten or more minutes (Chodzko-Zajko et al, 2009; DOH, 2011; Garber et al, 2011). Alternatively, they recommend engaging in 75 minutes of vigorous intensity activity over a week to gain similar health benefits or a mixture of both vigorous and moderate intensity (Chodzko-Zajko et al, 2009; DOH, 2011; Garber et al, 2011) or 7,000 to 10,000 steps a day (Garber et al, 2011; Wallis et al, 2013). In addition, they advise carrying out muscle strengthening exercises for major muscle groups, such as those in the legs, on at least two days a week (Chodzko-Zajko et al, 2009; DOH, 2011; Garber et al, 2011). Adults aged 65 and over at risk of falls, are also advised to engage in exercise to improve balance on at least two days a week (Chodzko-Zajko et al, 2009; DOH, 2011). Older adults with chronic health conditions, who are highly deconditioned preventing them from achieving 150 minutes of weekly moderate exercise, should be as physically active as their condition and abilities allow (Chodzko-Zajko et al, 2009). When commencing exercise, this group should engage in individually tailored low intensity and shorter duration exercise initially, that is subsequently progressed gradually as tolerated (Chodzko-Zajko et al, 2009). In general, the choice of physical activity should also be tailored to individual's preferences, enjoyment and the available facilities (Chodzko-Zajko et al, 2009; Garber et al, 2011).

2.9 The general benefits of physical activity

Being physically active over the long-term has a wide range of health benefits for all adults (Warburton et al, 2006; Haskell et al, 2007; Chodzko-Zajko et al, 2009; DOH, 2009, 2011) including being positively associated with both life expectancy and quality of life (Rejeski & Mihalko, 2001; Franco et al, 2005; Penedo & Dahn, 2005; Warburton et al, 2006) and inversely associated with multimorbidity (Autenrieth et al, 2013). Adults who carry out some physical activity gain some health benefits, whilst higher levels of physical activity are associated with greater health benefits (DOH, 2011). In older adults, there is strong evidence that regular physical activity can assist in reversing age-related decline in physical functioning and also assist in maintaining both mobility and independent living (Taylor, 2014).

Regular physical activity has been associated with lower prevalence of many health conditions including hypertension, diabetes, obesity and heart disease and it is also recommended in the secondary management of the aforementioned conditions (Warburton et al, 2006, 2010; Haskell et al, 2007; Nelson et al, 2007). Physical activity is protective against certain common cancers, such as breast cancer and colon cancer, as well as stroke and falls (Warburton et al, 2010; NICE, 2013b). With regards to mental health, physical activity has been recommended in the prevention and management of depression and age related cognitive decline (Chodzko-Zajko et al, 2009; NICE, 2009; Denkinger et al 2012).

2.10 Physical activity in older adults with knee pain

This section covers the benefits of physical activity interventions for older adults with knee pain, the challenge of maintaining physical activity benefits long-term, the potential mechanisms of action explaining physical activity benefits and the current levels of physical activity in this population.

2.10.1 The clinical benefits

Physical activity in various forms, including strengthening, aerobic exercise (such as walking and cycling), exercising in water and Tai Chi has been shown to have a range of beneficial effects for older adults with knee pain (Bennell & Hinman, 2011). Multiple large systematic reviews of RCTs have shown physical activity interventions have small to medium effect sizes in terms of pain reduction and improvement in physical function (Tanaka et al, 2013; Uthman et al, 2013; Juhl et al, 2014; Fransen et al, 2015), which is comparable to the effect sizes achieved by treatment with NSAIDs (Bjordal et al, 2004; Bjordal, 2006; Fransen et al, 2015). Effect sizes, such as the *"standardised mean difference"* (SMD), are measures for quantifying the magnitude of difference between two groups and are explained in detail outside of this thesis (Higgins & Green, 2009; Sullivan & Feinn, 2012). The latest comprehensive Cochrane review and meta-analysis of 44 RCTs by Fransen et al (2015) found a pain reduction SMD of -0.49 with a 95% confidence interval (95%CI) of -0.39 to -0.59 and a SMD physical function improvement of -0.52 (95%CI -0.39, -0.64) immediately post physical activity intervention. Additional clinical benefits found from physical activity interventions include improvements in physiological impairments associated with knee pain in older adults (such as improved strength and balance) and small improvements in quality of life (Bennell & Hinman, 2011; Fransen et al, 2015). Combined physical activity and diet interventions have also been shown to have significant weight reduction effects in obese older adults with knee pain (Messier et al, 2004; Miller et al, 2006).

Fewer studies have investigated the long-term follow up of physical activity interventions and there is greater uncertainty regarding the long-term benefits (Fransen et al, 2015). The effects of physical activity interventions decline over time as highlighted by long-term follow up studies (Pisters et al, 2007; Fransen et al, 2015). Fransen and colleagues (2015) meta-analysed 12 RCTs that measured pain outcome two to six months after physical activity intervention and reported a SMD of -0.24 (95%CI -0.35, -0.14). From meta-analysis of 10 RCTs that measured physical function at this long-term follow up they reported a SMD of -0.15 (95%CI 0.26, -0.04) (Fransen et al, 2015). These treatment effects are notably smaller than those immediately post intervention as described above.

Given that current best evidence shows physical activity interventions to be effective in the short-term but effects on pain and function decline over time, a key challenge is the maintenance of physical activity benefits over time. Non-adherence is considered to be the primary reason for the reduction in effectiveness over time (Marks & Allegrante, 2005; Holden, 2010; Jordan et al, 2010), hence, both understanding and improving adherence to long-term physical activity is of great research and clinical interest (Holden, 2010; Rankin et al, 2012).

2.10.2 Physical activity mechanisms of action

Although the evidence is unequivocal that physical activity can improve pain and function in older adults with knee pain, the mechanisms of action for these positive effects are not fully understood and have been considered a *"black box"* phenomenon (Runhaar et al, 2015). Mechanisms of action theories for pain reduction from physical activity are ordered below into changes in neurotransmission theories, mechanical theories and psychosocial theories. Neurotransmission explanations include reduction in temporal summation and pressure pain thresholds, which are linked to hyperalgesia and central sensitization (Henriksen et al, 2014). Physical activity may also cause pain gating by providing competing sensations with pain transmission (Melzack & Wall, 1965) or endorphin release which may cause a diminished sensitivity to pain (Schwarz & Kindermann, 1992; Koltyn, 2002). Considering mechanical theories, physical activity may reduce pain through joint loading leading to improved cartilage quality (Beckwée et al, 2013) or through strengthening of the muscles surrounding the knee increasing joint stability and shock absorbency (Fitzgerald et al, 2012; Beckwée et al, 2013; Knoop et al, 2014). Regular physical activity may also improve knee pain in overweight and obese older adults by contributing to weight loss that in turn reduces biomechanical joint load and inflammation (Christensen et al, 2005; Messier, 2010). Psychosocial explanations for pain reduction include improvement in mood, reduced distress and reduced fear of physical activity that may modulate and reduce the pain experience in higher centres (Hoffman & Hoffman, 2007; Villemure & Schweinhardt, 2010; Fitzgerald et al, 2012). Furthermore therapeutic relationships with health practitioners leading physical activity programmes that include rapport, collaboration, empathy and affective bond (Hall et al, 2010) may influence positive treatment outcome expectations, self-efficacy for physical activity and mood which may also modulate the pain experience (Gifford, 1998; Abhishek & Doherty, 2013; Bennell et al, 2014).

Physical function may be improved by physical activity via the reduction of physical impairments, for example, by strengthening quadriceps muscles and stabilising the knee joint, improving joint range of movement or facilitating weight loss (Bennell et al, 2011; Knoop et al, 2014). In addition, physical activity may alter cognitive factors linked to physical function such as improving self-efficacy for physical activity and reducing fear (Sharma et al, 2003; Focht et al, 2005; Fitzgerald et al, 2012), by providing positive mastery experiences from successfully carrying out activity. In conclusion, it is likely that exercise and physical activity effect pain and physical function through multiple interacting mechanisms that are unique within individuals.

All of the above theories relate to specific mechanism of action theories, however, it is unknown if change in physical activity level per se is sufficient to change pain and physical function. This is important to understand as it could potentially act as a treatment mediator of exercise interventions. Mediators are factors that change in response to treatment that help explain the relationship between treatment and outcome (Mansell et al 2014). Change in physical activity level may influence a range of the above mechanisms for action (for example, increasing physical activity level may contribute to muscle strengthening and improved mood and in turn reduce pain). It is also of clinical relevance and specific interest to this thesis, since some older adults with knee pain believe that increasing physical activity level may be unsafe, which may influence their physical activity behaviour (Hendry et al, 2006; Holden et al, 2012). The links between attitudes and beliefs and physical activity behaviour are explored in sections 2.12, 2.13 and 2.14. The subsequent section acts as a precursor to this by describing actual levels of physical activity in older adults with knee pain.

2.10.3 Physical activity levels in older adults with knee pain

Older adults with knee pain have low levels of physical activity (Wallis et al, 2013; Holden et al, 2015). There is large variation in physical activity levels reported within the literature, and similarly to older adults without knee pain, levels appear higher in studies using self-report measures than in studies using direct assessment of physical activity level, such as accelerometry (Sun et al, 2013; Wallis et al, 2013; Holden et al, 2015). Estimates of physical activity level may also vary depending on the sample characteristics (including varying sociodemographics).

Recently, Holden et al (2015) measured physical activity level in a community sample of 611 older adults (aged 50 and above) with knee pain in the UK using the self-report STAR questionnaire (this survey data are also utilised in chapters 5 and 7 of this thesis). They found only 44% were sufficiently active to meet current physical activity guidelines. A systematic review of directly measured physical activity level in older adults with knee pain also found that low to moderate proportions of older adults with knee pain meet recommended guideline levels (Wallis et al, 2013). In the studies that only included physical activity in bouts of 10 minutes or more, 13% (95%CI 7, 20) met guideline recommended levels of 150 minutes per week of moderate or vigorous physical activity. However, if the length of bouts was not considered, the figure rose to 41% (95%CI 23, 61). The proportion of participants meeting the recommended 10,000 steps a day was only 19% (95%CI 8, 33). Levels of physical activity were found to be lower in studies judged to be of higher quality (Wallis et al, 2013). The average level of physical activity, across 21 studies involving 3266 older adults with knee pain, was 50 minutes (95%CI, 46, 55) of moderate or vigorous physical activity per week, when measured in bouts of 10 minutes or more, or 7753 daily steps (95%CI 7582, 7294).

There is some evidence that those with knee pain have lower levels of physical activity than their pain-free counterparts (Shih et al, 2006; de Groot et al, 2008; Farr et al, 2008; Herbolshsheimer et al, 2016) yet, there is also conflicting literature which has suggested no statistically significant difference between those with and without knee pain (Neogi et al, 2010; Holden et al, 2015). However, it is of note that Holden and colleagues did identify trends towards lower proportions of older adults with knee pain meeting guideline levels than their pain-free counterparts (44% vs 50%, p=0.06).

Since overall levels of physical activity in older adults with knee pain are low, many older adults with knee pain are not gaining the health and clinical benefits associated with regular physical activity (Peeters et al, 2015). Numerous factors have been associated with physical activity level in older adults with knee pain. Key factors that have been consistently negatively associated with physical activity level include: older age, female gender, non-white ethnicity, increased severity of knee pain, worse physical function and slower walking speed (Veenhof et al, 2012; Stubbs et al, 2015). Factors that have some evidence for positive association with higher physical activity level from single studies include partner support and higher work function whilst there is conflicting evidence for BMI and depression being associated with physical activity level (Stubbs et al, 2015). It is also of note that previous physical activity level has consistently been associated with current physical activity level in adult populations without knee pain (Bauman et al, 2012) although this has not been empirically investigated in older adults with knee pain to the author's knowledge. Whilst it is acknowledged that physical activity behaviour is complex with multiple interacting determinants some of which act as facilitators and some as barriers (Biddle & Mutrie, 2008; Gyurcsik et al, 2009; Brittain et al, 2011; Stevenson & Roach, 2012; Nicolson et al, 2015) arguably the factors of the greatest clinical importance are common, strong and potentially modifiable factors (Gyurcsik et al, 2009; Nicolson et al, 2015).

Attitudes and beliefs about physical activity are potentially modifiable factors that may determine physical activity level (Biddle & Mutrie, 2008). They have been strongly linked to physical activity in behaviour theories such as physical activity, pain behaviour, social cognition and behaviour change theories (Abraham & Michie, 2008; Biddle & Mutrie, 2008; Main et al, 2008) as well as qualitative research exploring narratives about the barriers and facilitators to physical activity (Hendry et al, 2006; Brittain et al, 2011; Holden et al, 2012; Nicolson et al, 2015). However, there is a relative dearth of epidemiological literature investigating associations between attitudes and beliefs about physical activity and physical activity levels in older adults with knee pain (Veenhof et al, 2012; Stubbs et al, 2015). Empirically investigating the relationship between attitudes and beliefs about physical activity and physical activity level is a focal part of this thesis since this knowledge may help inform targets for optimising future interventions in older adults with knee pain.

The following sections begin by defining attitudes and beliefs about physical activity, before identifying salient theoretical and qualitative literature that links attitudes and beliefs about physical activity to physical activity behaviour. The few previous epidemiological studies that have investigated the relationship between attitudes and beliefs about physical activity and physical activity level in older adults with joint pain are introduced and important gaps in the literature that informed the research questions addressed within this thesis are highlighted.

2.11 Defining attitudes and beliefs about physical activity

Most individuals hold a tacit understanding of attitudes and beliefs, yet these phenomena have been debated and defined in a number of ways within the literature (Tesser & Shaffer, 1990; Eagly & Chaiken, 2007; Pratkanis et al, 2014). Adding to the confusion, the two concepts are often defined with some degree of overlap (Rosenberg & Hovland, 1960; Campbell et al, 2013). It is acknowledged that the definitions of attitudes and beliefs are open to debate beyond the scope of this thesis, however, it is deemed important to define the choice of terminology used within it for clarity and consistency. Attitudes are defined in this thesis as *"affect and feelings about physical activity"* (Biddle & Mutrie, 2008) whilst beliefs are defined in this thesis as *"cognitions or thoughts about physical activity"* (Biddle & Mutrie, 2008). They are best understood as *"pre-existing views, shaped by our social and cultural history"* (Main et al, 2008) and *"perceptual reactions to physical activity"* (Biddle & Mutrie, 2008), with *"expectations"* being beliefs about the future (Main et al, 2008).

This thesis is primarily focussed on attitudes and beliefs about physical activity since these attitudes and beliefs have a clear behavioural target (physical activity) hence are theoretically more likely to be associated with the behaviour of interest then other more general attitudes and beliefs (Biddle and Mutrie 2008). However, it is accepted that individuals also hold illness perceptions and beliefs about knee pain itself (including its nature, meaning, consequences and what to do about it)

(Ogden 2007, Petursdottir et al 2010, Linton and Shaw 2011, Holden et al 2012), which may influence attitudes and beliefs about physical activity.

2.12 Physical activity behaviour theories comprising attitudes and beliefs

Numerous theories of behaviour identify attitudes and beliefs about physical activity as pertinent in determining physical activity level (Biddle & Mutrie, 2008). Comprehensive accounts of theories of physical activity (Biddle & Mutrie, 2008), social cognition (Ogden, 2007; Biddle & Mutrie, 2008) and pain behaviour (Main et al, 2008) can be found elsewhere whilst this section will briefly focus on a few key theories in the context of this thesis.

2.12.1 Physical activity theories

An important overarching general framework of physical activity level is the ecological framework (Biddle & Mutrie, 2008). This identifies physical activity level as complex and determined by multiple factors both internal and external to the individual. Attitudes and beliefs about physical activity are an important example of an internal factor whilst external factors include governmental policy, physical environmental and social factors (Biddle & Mutrie, 2008). In the context of this thesis, the framework is useful in a number of ways. It highlights attitudes and beliefs about physical activity as important in explaining physical activity level and also offers additional factors that could be included within multivariable physical activity models that investigate the relationship between attitudes and beliefs about physical activity and physical activity level. In addition, it is useful in considering a broad range of factors that may affect physical activity level that cannot be measured directly yet may explain additional variance in physical activity level.

2.12.2 Social cognition theories

Social cognition theories suggests that behaviour is governed by expectations, incentives and social cognitions (Bandura, 1977; Ogden, 2007). They can help highlight the potential antecedent roles of attitudes and beliefs about physical activity in understanding physical activity level within this thesis. *"Cognition"* is defined as *"the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses"* (Waite, 2007). There are a plethora of social cognitive models within the literature that can be applied to physical activity in older adults with knee pain, for example the theory of planned behaviour, protection motivation theory and the health action process approach (described in detail outside of this thesis) (Ogden, 2007; Biddle & Mutrie, 2008).

Key attitude and belief concepts of interest to this thesis that feature in multiple models, include physical activity outcome expectation beliefs, perceived risk of harm, self-efficacy and subjective norm beliefs (Conner & Norman, 2005; Ogden, 2007; Biddle & Mutrie, 2008). Outcome expectation beliefs and perceived risks are judgements regarding the consequences of behaviour (Bandura, 1977; Feather & Newton, 1982; Albery & Munafo, 2008). Theoretically, if an individual believes the benefits of physical activity outweigh the risks he will be more likely to engage in higher levels of physical activity. Self-efficacy is a key construct in predicting behaviour (Bandura, 2004; Sperber et al, 2014) and is related to the confidence an individual has in their ability and resources to carry out a behaviour successfully (Armitage & Conner, 2000). An individual's belief that they can produce the desired effect by their actions is important in incentivising them to act and persevere in the face of difficulties (Bandura, 2004). Hence, an individual who has confidence and positive past experience of successfully carrying out regular physical activity, despite knee pain, may be more likely to continue with regular physical activity behaviour. Subjective norms or social normative beliefs relate to an individual's perception of social normative pressures, or important others' beliefs regarding behaviour, and the value held about behaving in line with the important other's wishes (Ogden, 2007; Albery & Munafo, 2008). For example, if important others such as valued family members, friends or healthcare practitioners believe regular physical activity is beneficial and recommend it for knee pain, then an individual is more likely to carry it out, however, if important others hold sceptical or pain avoidant views towards physical activity, this may contribute to reductions in physical activity level.

2.12.3 Pain behaviour models

Pain behaviour models adopt a biopsychosocial approach, often overlapping with elements of social cognitive theory, to aid understanding of pain and pain related behaviour, including physical activity (Main et al, 2008). Three important pain behaviour models applicable to this thesis are; the mature organism model (Gifford, 1998), the fear-avoidance model (Vlaeyen et al, 1995; Vlaeyen & Linton, 2012) and the biopsychomotor model (Sullivan, 2008). Core components of these three models are that attitudes and beliefs about pain are modulated by higher centres to alter patterns of pain perception and pain related behaviour. The fear avoidance model is arguably the most directly relevant to physical activity and proposes that in some individuals there is a fear and catastrophic belief that activities will cause pain and further damage which can lead to activity avoidance and a vicious cycle of deconditioning, disability and pain (Vlaeyen et al, 1995;

Vlaeyen & Linton, 2012, Holla et al, 2014). The following sections move on from theory to summarise the existing research investigating the relationships between attitudes and beliefs about physical activity behaviours in older adults with knee pain.

2.13 Qualitative and mixed methods research of attitudes and beliefs about physical activity behaviour

Qualitative and mixed methods research has explored the attitudes and beliefs about physical activity of older adults with knee pain which may contribute to physical activity engagement or avoidance (Campbell et al, 2001; Hendry et al, 2006; Thorstensson et al 2006; Petursdottir et al, 2010; Holden et al, 2012; Smith et al, 2014). A consistent and key finding throughout the qualitative literature was the concern many older adults with knee pain have about the safety of physical activity (Campbell et al, 2001; Hendry et al, 2006; Thorstensson et al, 2006; Petursdottir et al, 2010; Holden et al, 2012; Smith et al, 2014). For example, there was no consensus from 611 older adults with knee pain regarding the safety of exercise (Holden et al, 2012). When interviewed, some individuals hold negative outcome expectations regarding the safety of exercise that are expressed as fear of pain, harm and further *"wear and tear"* with exercise (Campbell et al, 2001; Hendry et al, 2006; Holden et al, 2012). These negative outcome expectations have been thematically linked to long-term physical activity habits and those *"retired from exercise"* and *"long-term sedentary"* (Hendry et al, 2006).

Many studies found no consensus regarding the perceived benefits of exercise (Campbell et al, 2001; Hendry et al, 2006; Holden et al, 2012). Positive and negative outcome expectations of physical activity have been commonly identified and linked to physical activity behaviour (Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012; Smith et al, 2014). For example, those who believed that exercise was beneficial, that their condition would deteriorate without regular physical activity, and that it helped reduce pain were more likely to belong to *"long-term active"* and *"converted to exercise"* groups (Hendry et al, 2006). However, a number of negative outcome expectations were also identified (in addition to the aforementioned concerns regarding safety) that were associated with reduced physical activity participation. For example, some older adults with knee pain believed exercise to be inappropriate due to age, pain, comorbidity or exercise setting, which may act as a barrier in the long-term to this type of behaviour (Holden et al, 2012; Smith et al, 2014) whilst others were resigned that their condition was progressive and could not be improved by exercise (Campbell et al, 2001; Hendry et al, 2006).

Narratives of both high and low self-efficacy have been repeatedly identified and thematically linked to physical activity behaviour within semi-structured interviews of older adults with knee pain (Campbell et al, 2001; Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012). For example, low physical activity self-efficacy beliefs relating to pain, comorbidities, poor physical capacity, older age and lack of facilities have been identified (Hendry et al, 2006; Holden et al, 2012) and linked to groups of participants who were both *"long-term sedentary"* and those *"retired from exercise"* (Hendry et al, 2006). Conversely, positive physical activity self-efficacy beliefs relating to previous successful experiences of exercise have also been identified as a facilitator of physical activity (Hendry et al, 2006; Holden et al, 2012) and linked to *"long-term active"* behaviour (Hendry et al, 2006).

Attitudes and beliefs about physical activity linked to social factors may also be important. The perceived support that older adults with knee pain feel regarding keeping active and the recommendations of important others may be important themes relating to physical activity (Biddle & Mutrie, 2008; Petursdottir et al, 2010). Older adults with knee pain who believe that they have had good physical activity related support and advice from healthcare practitioners, family members and also gym staff are more likely to be active and belong to *"converted to exercise"* and *"long-term active"* groups (Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012; Smith et al, 2014). However, those who believe they have nobody to exercise with may be deterred from the behaviour (Holden et al, 2012).

Attitudes and beliefs surrounding the effort required to carry out physical activity, its' perceived importance and relative priority of physical activity compared to other life commitments may also be linked to physical activity (Sechrist et al, 1987; Biddle & Mutrie, 2008; Holden et al, 2012; Smith et al, 2014). Life events such as divorce or caring responsibilities may be prioritised above regular physical activity, whilst reports of insufficient time as a barrier may also be linked to the perceived importance of regular physical activity in comparison to other life commitments (Hendry et al, 2006; Holden et al, 2012; Smith et al, 2014).

Affect during exercise may also be a potent factor in predicting future physical activity (Biddle & Mutrie, 2008; Ogden, 2007). Individuals who have the attitude that exercise is enjoyable and makes them feel better may be more likely to carry it out whilst the opposite affect with exercise is likely to act as a barrier to future exercise (Hendry et al, 2006; Biddle & Mutrie, 2008; Holden et al, 2012).

It is possible to map many of the above attitude and belief themes to theoretical models of physical activity behaviour discussed previously, thus highlighting their potential importance. In the absence of knee pain specific empirical research investigating the relationship between attitudes, beliefs and physical activity, the section below focusses on these relationships in older adults with joint pain more generally (containing mostly OA participants but often defined non-specifically in the literature as *"arthritis"*).

2.14 Epidemiological research into attitudes, beliefs and physical activity

Self-efficacy for exercise has been consistently associated with self-report physical activity in cross-sectional studies. A survey of 141 adults with arthritis found high self-efficacy for exercise was positively associated with regular exercise (Der Ananian et al, 2008), whilst a large survey of 1051 adults with arthritis found higher self-efficacy beliefs and positive outcome expectations of physical activity to be associated with meeting recommended guideline levels of physical activity (Hutton et al, 2010). Most recently, Sperber et al (2014) carried out secondary data analysis of a lifestyle physical activity intervention trial in 339 older adults with arthritis (of mean age 69 years old) in the United States (US). They investigated the relationship between self-efficacy for exercise and self-report physical activity level and found a significant and positive cross-sectional association at baseline.

Few studies have investigated the longitudinal relationships between attitudes and beliefs and future physical activity levels. Sperber and colleagues (2014) found an association between change in self-efficacy for exercise and change in physical activity over time. Peeters et al (2015) investigated factors associated with increase in self-report physical activity level in 692 insufficiently active older adults with arthritis over two years. They found an association between both increased self-efficacy for exercise and increased encouragement to exercise with increase in physical activity level. However, they did not find an association between a number of other baseline attitudes and beliefs about physical activity and future increase in physical activity level, including physical activity past experiences, physical activity behavioural intention, perceived need and required demand to exercise or motivation to exercise for social and health wellbeing.

To summarise the above, there is a paucity of studies that have empirically investigated the relationships between attitudes and beliefs about physical activity and physical activity level in older adults with joint pain, and an absence of literature focussing specifically on those with knee pain attributable to OA. Inferring from general arthritis populations, outcome expectations and self-efficacy for physical activity appear to warrant further quantitative investigation in knee pain populations. Theoretically important attitude and belief concepts such as fear of movement and harm, and enjoyment of physical activity also warrant research in older adults with knee pain. It is unclear if attitudes and beliefs about physical activity can predict future physical activity levels in older adults, hence, this also warrants investigation in older adults with knee pain.

2.15 Summary and research questions

In summary, this chapter introduced the common problem of knee pain in older adults and discussed physical activity as a core treatment highlighting its many associated clinical and general health benefits. Although physical activity interventions have been shown to reduce pain and improve function in this population, the long-term safety of physical activity is unclear for many older adults with knee pain. Clarifying the safety of long-term physical activity for older adults with knee pain is of clinical interest and may help inform these populations. Furthermore, although exercise interventions have been shown unequivocally to reduce pain and improve function in older adults with knee pain, the mechanisms of action remain incompletely understood and it is uncertain if changing physical activity level per se explains the observed clinical improvements. Actual levels of physical activity in older adults with knee pain are low and adherence to exercise programmes reduces over the long-term. Although determinants of physical activity level are complex, attitudes and beliefs about physical activity are theoretically important in explaining physical activity level, yet have not been fully investigated in older adults with knee pain. Self-efficacy beliefs, outcome expectations, enjoyment, fears and safety beliefs about physical activity are potentially important in explaining physical activity level and warrant further empirical investigation. Understanding the cross-sectional and longitudinal relationships between attitudes and beliefs about physical activity and physical activity level is potentially important in explaining the sub-optimal levels of physical activity in older adults with knee pain and may yield clues to future modifiable targets for novel interventions aimed at increasing physical activity. Thus, the above gaps in knowledge informed the specific research questions which this programme of research addresses- in older adults with knee pain:

1. Is long-term physical activity safe?

2. Are changes in physical activity level associated with future clinical outcomes in terms of pain and function?

3. Are attitudes and beliefs about physical activity associated with physical activity level?
4. Can attitudes and beliefs about physical activity predict future physical activity level?

The following chapter addresses the first of these four questions using systematic review methodology. Box 2.1 below summarises the key background messages.

Box 2.1 Background key messages

- Knee pain in older adults is common and likely to increase in the future with rising levels of obesity and an ageing population
- Most older adults with knee pain have a clinical syndrome problem of OA and some will have radiographic changes in their tibiofemoral and/or patellofemoral joints
- Regular physical activity is recommended in clinical guidelines for all older adults with knee pain regardless of pain severity or comorbidity
- Regular physical activity is associated with reduced pain, improved function and general health benefits in older adults with knee pain
- Most older adults with knee pain have low levels of physical activity
- Uncertainty exists in both older adults with knee pain and the health care practitioners, whom they consult, over the safety of physical activity for older adults with knee pain which may act as a barrier to the behaviour
- It is unknown if increasing physical activity level per se explains the benefits in pain and function
- Attitudes and beliefs about physical activity are theoretically important in predicting physical activity level however, there is a dearth of studies investigating this relationship in older adults with knee pain

Chapter 3

The safety of long-term physical activity for older adults with knee pain

3.1 Chapter introduction

This chapter addresses the first thesis research question using systematic review methodology, to determine the safety of long-term physical activity for older adults with knee pain (thesis Part 1). The chapter begins by stating the aims of the review, followed by the rationale for the methods chosen and full description of the review methods. Results from the systematic review are subsequently presented before being discussed, considering strengths and weaknesses, together with the clinical and research implications of the findings.

Before describing the systematic review, it is important to first define what is meant by *"safety"*. The word *"safe"* pertains to a phenomena that is "*not likely to cause or lead to harm or injury; not involving danger or risk*" (Waite, 2007). Hence, the outcome domains for this review were selected to reflect this definition in the context of older adults with knee pain. A physical activity safety premise was defined a priori based on multiple factors associated with knee pain or OA progression and harm.

Box 3.1 Systematic review safety premise

The premise was made that for long-term physical activity to be considered safe, it would not lead to severe adverse events, increasing pain, reducing physical function, progression of structural OA as evidenced by radiographs or MRI, or surrogate measures of condition progression such as progression to TKR or increased analgesia use.

3.2 Aim and objectives

This systematic review aimed to determine the safety of long-term physical activity in older adults with knee pain. Specific objectives were to:

1. Identify existing RCTs, longitudinal cohort studies and case-control studies that investigate the safety of long-term physical activity in older adults with knee pain.
2. Summarise, assess risk of bias, and critically appraise the included studies.
3. Investigate if long-term physical activity is associated with the following safety related outcome domains: adverse events, worsening pain or function and structural progression of OA as evidenced by radiographs or MRI.
4. Investigate if long-term physical activity is associated with TKR and analgesic use as secondary safety related outcome domains.

3.3 Methods

Systematic reviews involve the collation of available evidence fitting pre-specified study eligibility criteria in order to answer specific research questions (Mulrow, 1994; Cook, 1997; Higgins & Green, 2009). They provide a synthesis of multiple study results and can establish if the results of individual studies are consistent and 49eneralizable (Mulrow, 1994). They are designed using systematic, transparent and reproducible methods that are chosen to minimise bias, theoretically leading to reliable conclusions (Antman et al, 1992; Higgins & Green, 2009). Unlike narrative reviews, which rely on the author's selection and critical appraisal of evidence, systematic reviews aim to reduce author selection bias and subjective evidence synthesis by having explicit inclusion/ exclusion criteria, systematic search processes and explicit risk of bias assessment procedures (Higgins & Green, 2009). Systematic reviews therefore require more time and effort than narrative reviews (Higgins & Green, 2009) and the strength of their conclusions is limited by the quality and quantity of available primary studies that can be included (Akobeng, 2005).

3.3.1 Overview of systematic review stages

The stages of the thesis systematic review are described below and summarised in figure 3.1.

Figure 3.1 The systematic review process

Development of the inclusion criteria for eligible studies:

- Participants with knee pain aged 45 yrs or over/ OA diagnosis
- RCTs, prospective longitudinal cohorts and case-control studies
- Physical activity intervention or exposure over at least 3 months
- At least one safety outcome domain measured

↓

Search strategy:

- Multiple databases of peer reviewed published studies
- Double reviewer screened titles, abstracts, and full texts
- Search of included studies reference lists

↓

Data extraction:

- Study method, participant number, OA definition, physical activity type, intensity and duration, safety results
- Double reviewer safety outcome data checking

↓

Risk of bias assessment:

- Separate risk of bias assessment for RCTs and observational studies (Higgins et al, 2011; Hayden et al, 2013)
- Double reviewer quality assessment and consensus

↓

Data synthesis:

- Narrative synthesis of physical activity safety outcome patterns
- Safety conclusion

3.3.2 Eligibility criteria for included studies

The inclusion and exclusion criteria have been ordered into type of study designs, publication types, study populations, study interventions or exposures and safety outcome domains. They are summarised in table 3.1 and described in detail below.

I) Type of study designs

Three different study designs were included in the review: RCTs, prospective longitudinal cohort studies and case-control studies. These methods were included as each can provide unique and mutually exclusive information regarding the question of whether long-term physical activity is safe for older adults with knee pain. Together their evidence can be triangulated to counter individual method limitations. There are, however, some challenges associated with including all three study designs, including maintaining consistent inclusion criteria across different study designs, synthesising varying safety outcomes (for example, mean treatment effects seen in RCTs and odds ratios seen in prospective cohorts) and consistently assessing study risk of bias across different designs.

Randomised controlled trials (RCTs)

RCTs can give safety outcome information, including adverse events, from specific physical activity interventions in controlled experimental conditions. RCTs are thought of as the *"gold standard"* design for testing the comparable effectiveness of interventions as they are considered to have the least risk of bias (Sackett et al, 2000; Akobeng, 2005; Zhang et al, 2010; Jewell, 2011). For example, randomisation of participants aims to equalise both known and unknown confounding variables between groups which helps eliminate selection bias (Sackett et al, 2000; Kunz et al, 2007; Jewell, 2011). A confounder is a third variable (not the outcome or exposure variable of interest) that distorts the relationship between the exposure and the outcome (Fletcher et al, 2012) (see chapter 7, section 7.3.5 for a causal diagram explanation of confounding). In the case of RCTs the exposure of interest is the physical activity intervention and the outcome a safety domain related measure. Selection bias can occur if there are systematic differences between baseline characteristics of the groups that are being compared which are associated with outcome (Higgins & Green, 2009). Non-randomised trials were hence excluded as they are at increased risk of such bias.

However, there are limitations associated with RCTs. RCT participants with knee pain who meet the inclusion criteria and provide consent to participate in a RCT testing physical activity interventions may be systematically different from the general population of older adults with knee pain. This may therefore limit the generalisability of findings from RCTs. In addition, few RCTs are conducted over a period of several years due to cost implications and the challenge of loss to follow-up at the longer-term time-points. This has implications for long-term safety outcomes such as progression of structural OA detected using imaging such as radiographs, which have a greater responsiveness in periods over two years (Reichmann et al, 2011). Finally, it could be considered unethical to carry out a long-term trial that was showing physical activity to be unsafe (Fletcher et al, 2012). Hence, for the purposes of the current systematic review of long-term physical activity safety other study designs were also included to help overcome the limitations of the RCT design.

Prospective longitudinal cohort studies

Prospective longitudinal cohort studies were included in the review as they give longitudinal safety information from observed samples, thus overcoming the potential limited generalisability of RCTs and are well suited to questions of prognosis (Mallen et al, 2006). They involve a baseline sample of older adults with knee pain, exposed to varying physical activity types and intensities, being observed over a long period of time for safety related outcomes whilst also adjusting for other known confounders. They hence allow the calculation of odds ratios of safety outcomes based on physical activity exposures. They permit large numbers of individuals to be observed, often over a period of years, in a pragmatic manner (Fletcher et al, 2012). Hence, they may have a better chance than RCTs of recording rare or long-term safety outcomes such as TKR (Higgins & Green, 2009). However, the disadvantage of these observational studies is the extraneous differences between groups exposed and not exposed to physical activity (Fletcher et al, 2012), since it is only possible to adjust for known or hypothesised confounding factors on safety outcomes. Confounding is particularly problematic in older adults with knee pain attributable to OA, since there are uncertainties and methodological challenges regarding prognostic factors for OA radiographic and clinical symptom progression (Zhang et al, 2010; Chapple et al, 2011; Neogi & Zhang, 2013; Bastick et al, 2015a, 2015b) and there may be unknown unadjusted extraneous prognostic variables that bias results (Zhang et al, 2010; Szklo & Nieto, 2014).

Retrospective cohort studies involve analysing observational data or medical records after both exposure and outcome have already occurred to calculate post-hoc risk ratios (Hennekens & Buring, 1987; Szklo & Nieto, 2014). This type of study design was not included in this review as it is less likely to gather sufficient baseline information, relevant confounders or detailed physical activity exposure (Fletcher et al, 2012; Szklo & Nieto, 2014). It is hence at increased risk of unknown and unadjusted confounding. In addition, retrospective cohort studies are usually taken from *"survival"* populations with available data to look back at, rather than the *"true"* cohort of all older adults with knee pain which may limit their generalisability (Fletcher et al, 2012). For example, individuals who are deceased or who did not access healthcare are all likely to be underrepresented in such analyses. Cross-sectional studies involve data collection at a single point of time (Sim & Wright, 2000) and were also excluded from this review as they are unable to give a temporal relationship between physical activity exposure and safety outcomes. Cross-sectional studies are hence at risk of temporal bias, where inference about cause and effect may be erroneous, as it is not possible to tell whether the exposure (physical activity level) or safety outcome came first and in which order they influence each other (Szklo & Nieto, 2014).

Case-control studies

Case-control studies were included in the review. These studies usually select participants on the basis of whether or not they have a particular disease event under study (Fletcher et al, 2012). For example, subjects are either *"cases"* having undergone a TKR (due to knee pain or OA progression) or *"controls"* who are otherwise similar people who have not undergone TKR. Cases and controls can then be compared to estimate the odds of individuals becoming cases based on certain risk factor exposures (e.g. type or dose of physical activity undertaken). The advantages of case-control studies are that they allow the study of specific outcomes without the need for a very large cohort or a long follow-up period

(Hennekens & Buring, 1987). Confounding can be reduced by matching the cases and controls for other key prognostic variables (e.g. age and gender), stratification or post-hoc statistical adjustment controlling for the effect of the confounders within multivariable mathematical models (Szklo & Nieto, 2014). The disadvantages of these studies are that they are relatively hard to set up in terms of finding appropriate matched controls and they are prone to recall bias issues (Fletcher et al, 2012). Recall bias is a systematic error that is caused by differences in the accuracy or completeness of the recollections by study participants regarding events or experiences from the past (Last, 2000; Fletcher et al, 2012). For example, some participants may have difficulty remembering the exact levels and types of physical activity carried out in the past or may tend to report higher levels of physical activity for social desirability (Motl et al, 2005).

II) Type of publication

Only full text, peer reviewed, published empirical studies were included. Studies were excluded if they were reviews, patient guides, books, abstracts only or conference presentations without full text publications. The rationales for these exclusions were to try to ensure at least some level of both quality (thus removing the potential bias from studies that had not undergone some peer review quality control) and detail (thus removing those studies with insufficient detail of their methods and results to draw clear safety inferences). PhD theses were also excluded, but peer reviewed published papers from PhD research were included. The concern in excluding studies that were abstracts only, PhD theses and other unpublished work is publication bias. Publication bias may occur if the publication of research findings is dependent on the nature and direction of the results (Higgins & Green, 2009). For example, it is possible that studies suggesting a beneficial effect or safe outcome of physical activity are more likely to be published than studies showing no effect or harm. This phenomenon has been named the *"file drawer problem"* (Rosenthal, 1979). Studies in all languages were included to reduce language bias. Language bias occurs where studies that are not published in English are excluded from a review solely on their language of publication rather than any quality or method criteria potentially influencing the review conclusions in a systematic way (Higgins & Green, 2009).

III) Type of participants

The included participants were adults, over the age of 45 (older adults), with knee pain, or adults of any age with knee OA. The cut-off age of 45 years old was chosen as the majority of knee pain in older adults over this age is likely to be attributable to OA (NICE, 2014). Original definitions of knee pain and OA, used by individual study authors, were accepted. Adults who had been diagnosed with patellofemoral or tibiofemoral OA using clinical or radiographic definitions or a combination of both were included. Any clinical diagnosis of OA was accepted including self-reported knee pain attributed to OA, NICE (2014) clinical criteria (adults 45 years and over with knee pain, and, either no morning joint-related stiffness, or morning stiffness that lasts no longer than 30 minutes) and the American College of Rheumatologists' criteria (three of six from: knee pain, aged over 50 years, morning stiffness less than 30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth) (Altman et al, 1986). Radiographic OA diagnosis involves joint space narrowing, osteophytes and sclerotic bone (Neogi and Zhang, 2013). A common scale for assessing radiographic OA is the Kellgren Lawrence (KL) score (Kellgren & Lawrence, 1957). This scale ranges from 0 to 4, with 0 being *"no radiographic features of arthritis"* and 4 being *"severe OA"*.

Scores of 2 to 4 are usually considered indicative of radiographic OA, although scores of 1 to 4 have also been used in the literature and were accepted as part of this review (Kellgren & Lawrence, 1957; Emrani et al, 2008).

This systematic review excluded studies describing OA or knee pain incidence since it was specifically aimed to address the question of physical activity safety in older adults with existing knee pain or OA. Studies with mixed populations such as knee and hip OA, or OA and rheumatoid arthritis participants were excluded unless they carried out and reported independent subgroup outcome analysis for older adults with knee pain or OA. This was because these groups were considered heterogeneous in terms of aetiology. For example, unlike OA, rheumatoid arthritis is considered an auto immune, systemic condition (NICE, 2013c) whilst hip OA has differing biomechanical and prognostic factors to knee OA (Wright et al, 2009; Bennell & Hinman, 2011; Bastick et al, 2015b).

IV) Type of intervention/ exposure

Any intervention or exposure that investigated physical activity carried out explicitly over at least three months was included. All types of physical activity as defined in chapter 2 were included (e.g. occupational activity, therapeutic exercise and sport as well as domestic, travel and recreational activity) since different types of physical activity may have differing safety profiles. Three months was chosen as "*long-term*" for this review as for many older adults knee pain is chronic (Jinks et al, 2004; Fransen et al, 2015), hence, in the absence of a cure, interventions of health behaviour used in symptom management should ideally be well tolerated and sustainable over an extended time period (Pisters et al, 2007). Three months also provides sufficient time to observe changes in pain and function, as well as to detect adverse events. In addition, three months may be a pragmatic exercise intervention length in most settings. Studies that did not explicitly carry out or report physical activity over three months or more were excluded, as it was unclear if physical activity was maintained over a long-term period which would jeopardise the validity of any long-term physical activity safety inferences. For example, a prospective cohort study that defined physical activity exposure crudely by *"being a jogger or member of a sports club"* (Schouten et al, 1992) was excluded since the physical activity variable was considered insufficient evidence of engagement in physical activity for at least three months.

V) Type of outcomes

As discussed in section 3.1, the choice of safety domains was derived from the definition of *"safe"* in the context of older adults with knee pain. To be included in the systematic review, a study must have included an outcome measure from at least one of the following safety related domains: adverse events (e.g. falls, secondary injuries), self-reported pain (e.g. Western Ontario and McMaster Universities OA Index (WOMAC) pain subscale, visual analogue pain scale), physical functioning (e.g. WOMAC function, 6 minute timed walk) or progression of structural OA as evidenced by radiographs or MRI (e.g. radiographic reduced joint space/ KL advancement, MRI cartilage volume, MRI joint space narrowing).

Secondary safety outcome domains of interest were pain relief medication (analgesic) usage and progression to TKR surgery (number of incident TKRs). Analgesic use can be considered a crude surrogate measure of pain severity, whilst TKR is associated with late stage OA, and both are of significant healthcare and economic cost interest (Altman et al, 2005; Losina et al, 2009; Chen et al, 2012). Both analgesic use and TKR were not considered as primary outcomes because analgesics are often used irregularly by people with OA including some who report severe pain (Blamey et al, 2009), whilst the decision to proceed to TKR is highly variable between clinicians and services (Altman et al, 2005; Wright et al, 2011).

Table 3.1 Summary of study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Study designs	
• RCTs/ prospective cohort studies/ case-control studies	• Cross-sectional observational studies/ retrospective cohort studies/ non-randomised controlled trials
Publications	
• Full text, published studies • All languages • All countries and settings	• Abstracts only, posters, non-peer reviewed, theses, books, unpublished studies
Participants	
• Adults with mean age 45 years old and over with knee pain, or adults with knee OA	• Serious pathology not attributable to OA (inflammatory arthropathies/ fracture/ cancer/ metabolic disorder) • Heterogeneous knee and other OA joint participants without separate knee sample data analysis • Mean participant age under 45 • OA/ knee pain incidence studies
Intervention	
• Three months or more of physical activity intervention or exposure	• Physical activity not explicitly carried out or measured for three months or more
Outcome domains	
• Contains at least one primary safety related outcome measure from the following domains: self-report pain, function, adverse events, radiographic/ MRI biomarkers of OA progression or progression to TKR.	

Abbreviations: MRI=Magnetic Resonance Imaging; OA=Osteoarthritis; RCT=Randomised Controlled Trial; TKR=Total Knee Replacement.

3.3.3 Search strategy

A comprehensive search strategy was carried out within this systematic review. This section describes the databases searched, the creation of the MEDLINE search filter and its translation to additional databases. It goes on to describe the procedures for carrying out each stage of the search.

I) Electronic databases

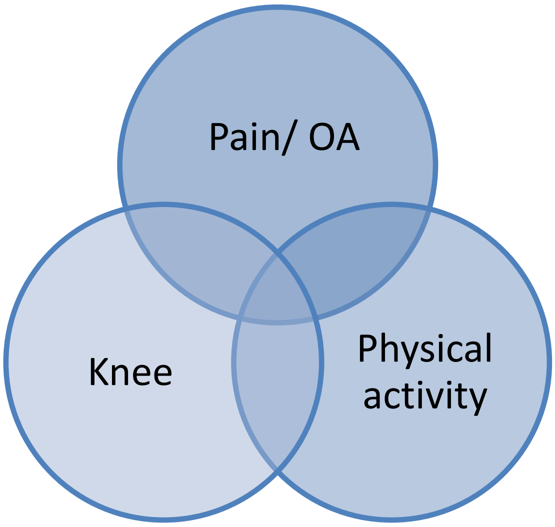
Studies were identified by searching electronic bibliographic databases from inception until 16th May 2013. In order to capture relevant literature pertaining to different types of physical activity, a broad range of medical, allied health and occupational health databases were searched. MEDLINE, EMBASE, AMED (The Allied and complementary Medical Database) and PEDro (Physiotherapy Evidence Database) were accessed via the OVID interface. MEDLINE and EMBASE are the largest two electronic medical databases and, although much of their content overlaps, they also contain many mutually exclusive journal records (Higgins & Green, 2009). PEDro and AMED both contain some mutually exclusive content and may include relevant physical activity studies not indexed by other biomedical databases. Using the EBSCO interface, CINAHL (the Cumulative Index to Nursing and Allied Health) and SPORTDiscus were searched. CINAHL is the largest full text collection of nursing and allied health literature whilst SPORTDiscus is the largest sports medicine and sports full text database (CINAHL. From: www.ebscohost.com/biomedical-libraries/the-cinahl-database, accessed November 2013; SPORTDiscus. From: www.ebscohost.com/academic/sportdiscus, accessed: November 2013). The Cochrane Collaboration trials database CENTRAL was also searched as it includes Cochrane review groups' hand searched trials, as well as selected

EMBASE and MEDLINE trials. In addition, occupational databases individually searched were the Health and Safety Information Centre of the International Labour Office (CISDOC), UK Health and Safety Executive Information Services (HSELINE) and the US National Institute for Occupational Safety and Health (NIOSHTIC-2). CISDOC and HSELINE and NIOSHTIC-2 are large, regularly updated, international databases covering all aspects of occupational health and safety (Cochrane Work. From: http://osh.cochrane.org/other-osh-databases, accessed: November 2013).

II) Search filters

A comprehensive search filter strategy was first designed for MEDLINE and then adapted to the other databases. The search filters comprised three main topic areas; the knee, pain/ OA, and physical activity (figure 3.2).

Figure 3.2 Venn diagram of search filter topics



The filters were created by adapting existing Cochrane systematic reviews and Keele University ARUK Centre for Primary Care Research OA and pain filters and then combining them using the Boolean operator “AND” (Fransen & Mcconnell, 2008; Blagojevic et al, 2010; Jordan et al, 2010). Both subject headings and free text search words were combined in carrying out the search. The initial MEDLINE search filter was piloted during its development to ensure it captured known primary studies expected to be included. It also underwent peer review by an Information Specialist within the research centre (JJ) before being finalised. A copy of the final MEDLINE search filter is provided in box 3.2. The adaptation process to additional databases involved searching for MEDLINE subject heading terms and mapping them to the closest matching heading term in the new database. For databases where a complex compound search filter was not possible (e.g. PEDro, CISDOC) a simplified adaptation was searched without multiple subheadings and synonyms.

By including a comprehensive search filter and applying it to multiple medical, allied health professional and occupational health databases, each including mutually exclusive content, there is increased likelihood of a highly sensitive search. "*Sensitivity*", in this context, is defined as the number of relevant studies identified divided by the total number of relevant studies in existence (Higgins & Green, 2009). The disadvantages of the comprehensive search strategy is the time taken to complete it, whilst including multiple databases with overlapping content reduces precision. "*Precision*", in this context, is defined as the number of relevant studies identified divided by the total number of studies identified (Higgins & Green, 2009).

Box 3.2 MEDLINE search filter

1	exp osteoarthritis/
2	osteoathr$.tw.
3	OA.ti
4	arthrosis.mp.
5	exp pain/
6	1 OR 2 OR 3 OR 4 OR 5
7	knee/
8	exp knee joint/
9	6 AND (7 OR 8)
10	(knee adj3 pain).mp.
11	6 OR 9 OR 10
12	exp exercise/
13	exp sports/
14	exp rehabilitation/
15	exp physical exertion/
16	exp physical endurance/
17	exp physical fitness/
18	exp exercise tolerance/
19	exp occupational exposure/
20	exp occupational medicine/
21	exp physical therapy modalities/
22	exp exercise test/
23	exp recreation/
24	exp leisure activities/
25	exp activities of daily living/
26	exertion$.tw.
27	exercis$.tw.
28	sport$.tw.
29	((physical OR motion) adj5 (fitness OR therp$)).tw.
30	(physical$ adj2 endu$).tw.
31	((strength$ OR isometric$ OR isotonic$ OR isokinetic$ OR aerobic$ OR endurance or weight$) adj5 (aerobic$ OR endurance or weight$) adj5 (train$)).tw.
32	physiotherap$.tw.
33	kinesiotherap$.tw.
34	rehab$.tw.
35	(skate$ OR skating).tw.
36	run$.tw.
37	jog$.tw.
38	treadmill$.tw.
39	swim$.tw.
40	bicycle$.tw.
41	(cycle$ OR cycling).tw.
42	walk$.tw.
43	(row OR rows OR rowing).tw.
44	muscle strength$.tw.
45	activit$ of daily living.tw.
46	((leisure OR travel OR work OR physical or occupation$ or recreation$) adj5 (activit$ OR exercise$ or train$)).tw.
47	(activit$) adj5 (daily living).tw.
48	OR/12-47
49	11 AND 48

III) Running and screening the searches

Once the database searches had been completed, the total number of reference hits from each database was recorded and all hits from databases that were compatible with importing into the *"Refworks"* database program were combined (all except the occupational databases and PEDro). Imported references were screened for duplicates that were subsequently removed. The next stages involved systematically screening titles, abstracts and full text against the inclusion and exclusion criteria using a pre-piloted study eligibility prompt sheet (Appendix I). Irrelevant articles were excluded at each stage. At all stages screening was carried out independently by the author and a second reviewer (one of MH, NF or MT). Where there was disagreement between the two reviewers or uncertainty regarding whether studies met the criteria, the studies were discussed with a third reviewer to aid consensus prior to a final decision. Reference lists of included studies were checked to look for additional relevant studies that may have been missed from the electronic search. These studies were combined with hand searched studies identified from the remaining databases (that were non-compatible with Refworks) and screened for eligibility criteria, before adding them to the final included study list. One additional paper (Mikesky et al, 2006) was added during the peer review process of the published paper of this review (Quicke et al, 2015).

3.3.4 Systematic review registration

The systematic review was registered with an international database for prospective registering of systematic reviews (PROSPERO) during the search stage and prior to data extraction. This allows transparency in the planned methods and reduces the chance of the work being replicated (PROSPERO 2014:CRD42014006913)

3.3.5 Data extraction

Data on study author, year, participants, study design, physical activity type and intensity, safety outcome domains and safety outcome measure results (as pre-specified in table 3.1) were extracted. Extraction of basic study descriptive detail, cardiovascular intensity and physical activity impact categorisation were carried out by the author. Where target heart rates were stipulated within RCT interventions, less than 50% of maximum heart rate was defined as low intensity, 50 to 70% as moderate intensity, and more than 70% as vigorous intensity (CDC Measuring physical activity intensity. From: http://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm, accessed: November 2012). In the absence of target heart rate information, physical activities were classified based on metabolic equivalents score (MET). MET scores relate to the ratio of a specific physical activity metabolic work rate to that of a standard resting metabolic rate (Ainsworth et al, 2011), with higher MET scores indicating greater physical activity intensity. A MET score of less than 3 was defined as low intensity, 3 to 6 as moderate intensity, whilst a score greater than 6 was considered vigorous (Ainsworth et al, 2011). Physical activity impact was categorised into high and low impact on a case by case judgement based on the likely amount of compressive load and whether both feet were intermittently off the ground (Hunter & Eckstein, 2009). Safety outcome results were extracted by the author, and double checked independently by one of three reviewers (MH, NF, and MT). If more than one paper provided data from the same study, data were included only once and treated as part of the original study. Within RCTs, baseline and also primary post-intervention time point follow-up data (over three months) were utilised, whilst in observational studies baseline characteristics and primary study endpoint data (over three months) were extracted.

Adverse events reported in included studies were extracted and were also standardised, where possible, into three ordered categories (mild, moderate and severe) to allow comparison across studies. Adverse event severity descriptors were: a) *"mild"* defined as bothersome but requiring no change in therapy, b) *"moderate"* defined as requiring change in therapy, additional treatment, or hospitalisation, and c) *"severe"* defined as disabling or life-threatening (Calis & Young, 2004). This classification was chosen over the more common *"non-serious"* and *"serious"* adverse event dichotomy (ICH Harmonised Tripartite Guideline, 1996; Ioannidis et al, 2004) as it is more information rich and allows greater category discrimination. Within RCTs, pain and physical function data were extracted if a study either: a) carried out statistical comparison testing between physical activity and non-physical activity intervention groups at post-intervention follow-up, or; b) carried out statistical comparison testing within the physical activity intervention group over time from baseline to post-intervention. Where 95% confidence intervals (95% CI) were available without p values for treatment effect or within group change over time, these were extracted and interpreted. Outcome measure data were not extracted if they spanned multiple safety outcome domains without individual domain scoring, for example, data from a paper that only reported on combined pain and function using the Lequesne index, which is a composite pain and function index (Lequesne et al, 1987), would not be extracted. When multiple outcome measures were used in a study for an individual safety outcome domain, only one was utilised. Priority was first given to the study's primary outcome measure and then to OA specific, previously published and validated outcome measures. If the results of primary outcome measures were in different directions this was noted as *"inconsistent"* in the results. Numbers and proportions of TKRs occurring in participants within exercise and non-exercise groups within RCTs were extracted along with adjusted odds ratios and confidence intervals for progression to TKR amongst case-control studies for varying levels of physical activity exposure.

3.3.6 Risk of bias of included studies

Bias is "*a systematic error or deviation from the truth in results or inferences*" and can lead to underestimation or overestimation of the true intervention or exposure effect (Higgins & Green, 2009). A key source of potential bias in systematic reviews is bias related to the limitations of the original studies contained within it (Sanderson et al, 2007; Higgins & Green, 2009). Hence, assessing risk of bias within primary studies is an essential part of conducting systematic reviews (Sanderson et al, 2007; Higgins & Green, 2009). It allows the author to make informed judgements about the potential limitations of individual study results and draw inferences regarding their internal validity which is then used to inform the overall review critical analysis discussion, evidence synthesis and strength of conclusions (Egger et al, 2001; Higgins & Green, 2009).

Including several different study designs in a systematic review poses challenges for consistently assessing risk of bias, since risk of bias tools designed specifically for one study design are often inappropriate for other designs. There is no current gold standard or clear consensus for choice of risk of bias tool for either RCTs or for observational studies (Moher et al, 1995; Katrak et al, 2004; Mallen et al, 2006; Sanderson et al, 2007; Shamliyan et al, 2012). Therefore, two commonly used risk of bias tools specifically designed for each study design were piloted by the author, and one other reviewer (NF), on three studies before making a decision on the final tool selection for each study type (Jadad et al, 1996; Higgins et al, 2011; Hayden et al, 2013; Wells et al. From: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed December 2013). The pilot and rationale for the selection of risk of bias assessment tools is described in more detail in Appendix II.

I) Selected risk of bias tools

The Cochrane risk of bias tool was selected for RCTs (Higgins et al, 2011) and the modified Quality In Prognostic Studies tool (QUIPS) (Hayden et al, 2013) was selected for observational studies. Concise summary information on these tools is provided in boxes 3.3 and 3.4 below whilst full detail is given in Appendix III.

II) Carrying out risk of bias assessments

Two independent reviewers carried out risk of bias assessment on the included studies (JQ and one of MH, NF or MT). Where there was disagreement between two reviewers, consensus was reached either through discussion or after involvement of a third reviewer where needed. Risk of bias results are explained and discussed later in sections 3.4.5 and 3.5.6.

Box 3.3 Cochrane risk of bias tool

Cochrane RCT risk of bias tool summary (Higgins et al, 2011)

This tool contains six risk of bias domains, with each domain judged as "low", "unclear" or "high" risk of bias based on specific guidance.

Domain	Source of bias	Risk of bias judgement
Selection bias:	Random sequence generation	low/ unclear/ high
	Allocation concealment	low/ unclear/ high
Performance bias:	Blinding of participants and personnel	low/ unclear/ high
Detection bias:	Blinding of outcome assessment	low/ unclear/ high
Attrition bias:	Incomplete outcome data	low/ unclear/ high
Reporting bias:	Selective outcome reporting	low/ unclear/ high
Other bias:	Anything else ideally pre-specified	low/ unclear/ high

Abbreviation: RCT=Randomised Controlled Trial.

Box 3.4 Modified quality in prognostic studies tool

Modified quality in prognostic studies tool (Hayden et al, 2013)

This tool contains six risk of bias domains, comprising several questions within each domain. Domains are judged to be at "low" "moderate" or "high" risk of bias.

Domain	Source of bias questions	Risk of bias judgement
Study participation:	Sample matches population of interest?	low/ moderate/ high
Study attrition:	Incomplete outcome data?	low/ moderate/ high
Prognostic factor:	Adequately measured?	low/ moderate/ high
Outcome:	Adequately measured?	low/ moderate/ high
Study confounding:	Important confounders accounted for?	low/ moderate/ high
Analysis/ reporting:	Appropriate analysis and reporting?	low/ moderate/ high

3.3.7 Data synthesis

Systematic review data synthesis approaches include meta-analysis and narrative synthesis (Higgins & Green, 2009). Meta-analysis involves the quantitative pooling of results from individual studies in order to summarise individual study findings and increase the overall sample size, hence increasing the statistical power of the analysis and effect estimate precision (Akobeng, 2005; Higgins & Green, 2009). It requires homogeneity of included studies in terms of methodological homogeneity and outcome result statistical homogeneity (i.e. are the results sufficiently similar in direction and magnitude to justify pooling them quantitatively) (Egger et al, 2001; Higgins & Green, 2009). Narrative synthesis involves the use of words and text to summarise and explain the findings of the synthesis. Despite the term narrative it can also involve the use of statistical data (Popay et al, 2006. *Narrative synthesis*. from: http://www.lancaster.ac.uk/shm/research/nssr/research/dissemination/publications/NS_Synthesis_Guidance_v1.pdf Accessed; Nov 2013). It is well suited to answering a wide range of questions, not only those relating to intervention effectiveness, and is useful when the heterogeneity of the included studies is so great that meta-analysis is inappropriate (Higgins & Green, 2009).

For the current systematic review, meta-analysis was considered inappropriate for two reasons. Firstly, the systematic review was primarily interested in the overall question of long-term physical activity safety rather than treatment effect per se; hence a pooled measure of treatment effect magnitude was not of primary concern. Secondly, the included studies were considered to be very heterogeneous in terms of: a) participant diagnosis of knee pain/OA, severity and comorbidity; b) long-term physical activity type, intensity and duration; c) control or comparison groups; and d) safety outcome domains. Narrative synthesis was chosen as it permits the triangulation and summary of the descriptive statistics from multiple heterogeneous studies, and a narrative conclusion from a range of safety data in order to address the question of safety of long-term physical activity.

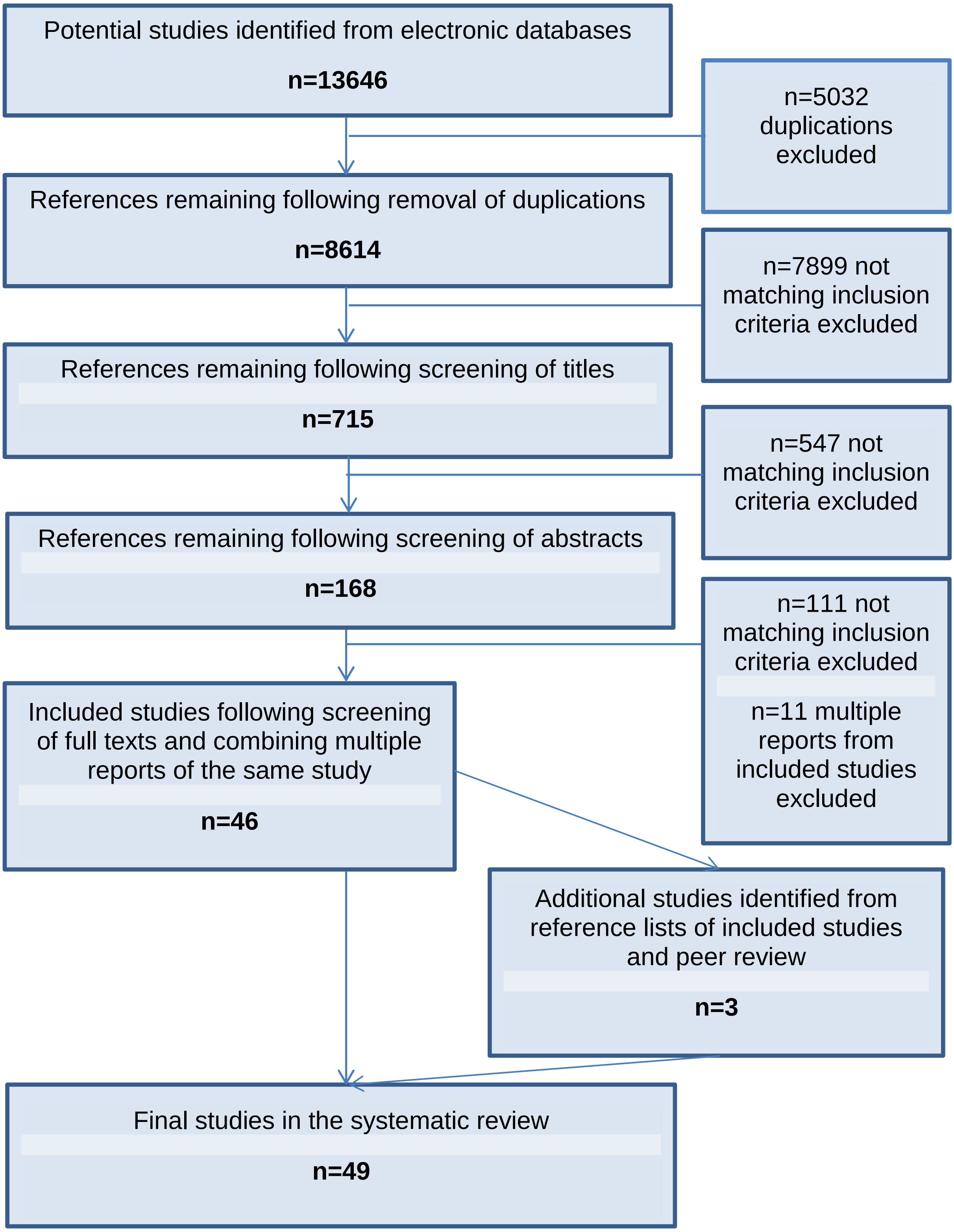
3.4 Results

This section begins by illustrating the study selection process and flow of study numbers through each search stage. Description of included studies' design, participants, physical activity interventions/ exposures, safety outcome domains and findings are provided. Further description and synthesis of safety findings is subsequently given by individual safety outcome domains. The section concludes with risk of bias assessment of the included studies.

3.4.1 Study search and inclusion

As summarised in figure 3.3, there were 8,614 unique references identified from the electronic databases which reduced to 715, 168 and 46 after screening titles, abstracts and full texts respectively using the study eligibility criteria (previously described in section 3.3.2 and summarised in table 3.1). Two further studies were added from the reference list searching and one from the peer review feedback during submission of the study for publication, leaving a total of 49 included studies.

Figure 3.3 Study search flow chart



3.4.2 Description of included studies

The 49 primary studies included in the systematic review comprised 8,920 participants from 48 RCTs and one case-control study undertaken in 16 different countries. All were published in English except one that was published in Czechoslovakian and translated into English (Olejarova et al, 2008). Full details of the included studies are given in table 3.2.

I) Randomised controlled trials

Included RCTs varied widely in size, ranging from 17 to 2,203 participants (median=87). Participants included older adults with knee pain and/ or a diagnosis of OA, with severity of radiographic OA ranging from Kellgren Lawrence grade I-IV in studies utilising radiographic OA (n=32). Four studies' participants were specifically selected to be overweight or obese and one additional study investigated overweight participants who also had Type II Diabetes. Levels of individual comorbidities varied within the remaining studies although many excluded participants with a history of cardiovascular disease or those deemed "unfit to exercise" for other health reasons.

Over half of the RCTs (n=27) had more than one physical activity treatment arm giving a total of 78 physical activity interventions tested. All of the RCTs investigated physical activity in the form of therapeutic exercise. Therapeutic exercise type, intensity and duration varied widely. "Mixed" exercise interventions combining strengthening, stretching and aerobic exercise were most common (n=46 of the 78 interventions tested), followed by interventions that specifically focussed on strengthening (n=17), aerobic exercise (including walking and cycling) (n=5), balance and agility (n=5), Tai Chi (n=4) and range of movement exercises (n=1). The majority of interventions were classified as moderate cardiovascular intensity (n=71) with fewer being high intensity (n=5) and low intensity (n=2). All of the exercise interventions were considered low impact since none involved running, jumping or other high impact weight bearing movements. Interventions included both one-to-one and group exercise interventions carried out in a variety of supervised settings, including community settings, hospital outpatient departments and participant's homes, as well as unsupervised home exercise with supervised reviews. The duration of exercise interventions ranged from 3 to 30 months whilst frequency varied from one to three sessions per week. Categorising the number of RCTs into groups of ascending exercise intervention duration; 24 studies had exercise interventions lasting from 3 up to 6 months, 14 studies from 6 up to 12 months, two studies were from 12 up to 18 months and eight studies were between 18 and 30 months. Follow-up length ranged from 3 to 60 months. There was considerable heterogeneity in the type of non-physical activity comparison and control groups including; non-specific "control" or waiting list (n=17), condition/ condition management education (n=12), non-physical activity comparisons (surgery, diet, manual therapy and glucosamine sulphate) (n=9), and placebo interventions (e.g. calcium and magnesium tablet) (n=2).

II) Case-control study

The case-control study (Manninen et al, 2001), carried out in Finland, investigated 281 participants who had undergone TKR and 524 randomly selected age matched controls. They investigated exposure to cumulative hours of recreational physical activity adjusting for age, body mass index, physical work stress, knee injury and smoking. They used logistic regression models to calculate TKR odds ratios for different levels of physical activity exposure. They analysed those who had undertaken low and high levels of regular lifetime recreational physical activity and compared them to the reference category of adults who had not undertaken regular recreational physical activity.

III) Excluded studies

The main reasons for excluding RCTs from the systematic review were that the interventions did not comprise exercise for periods of at least three months or they included mixed patient groups for example, those with both knee and hip OA that did not present individual data for the subgroup with knee OA. The main reasons for excluding observational studies were: a) they included samples investigating knee pain/OA incidence, b) they were published as abstracts only and c) they failed to explicitly measure physical activity over at least three months.

Table 3.2 Table of included studies

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Abbott et al, 2013	206	Clinical OA	I1: exercise therapy I2: manual therapy I3: exercise and manual therapy C: usual care	I1 and I3: 9 sessions of mixed exercise + HEP/ moderate intensity/ 12 months	12	Adverse events Pain TKR
Ağlamış et al, 2008, 2009	34	Clinical and radiographic OA (KL II-IV)	I1: multicomponent exercise C: no treatment	I1: 3 x weekly mixed exercise/ moderate intensity/ 3 months	3	Pain Function
Avelar et al, 2011	23	Clinical and radiographic	I1: squat + body vibration I2: squat	I1: 3 x weekly squatting exercise with whole body vibration plate/ moderate intensity/ 3 months I2: As above without vibration	3	Pain Function
Baker et al, 2001	46	Clinical and radiographic OA	I1: strength training C: nutrition education	I1: 12 sessions of lower limb strengthening + HEP/ moderate intensity/ 4 months	4	Adverse events Pain Function
Bautch et al, 1997	34	Clinical and radiographic OA	I1: exercise C: minimal treatment	I1: 3 x weekly walking / low intensity/ 3months	3	Pain Structural OA
Bennell et al, 2005	140	Clinical and radiographic OA	I1: physiotherapy C: sham US	I1: 8 sessions of individual physiotherapy including global strengthening, taping and massage +HEP/ moderate intensity 6 months	3, 6	Adverse events Pain Function TKR Analgesic use
Bennell et al, 2010	89	Clinical and radiographic OA	I1: hip strengthening C: no treatment	I1: 7 sessions of hip strengthening exercises + HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function
Brismée et al, 2007	41	Clinical OA	I: Tai Chi C: health and ageing related education	I1: 3 x weekly Yang style Tai Chi in a class for 6 weeks + further 6 weeks HEP/ moderate intensity/ 3 months	3, 4	Adverse events Pain Function Analgesic use

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Dias et al, 2003	50	Clinical and radiographic OA	I1: exercise and walking C: educational session	I1: 2 x weekly mixed exercise and walking for 6 weeks + 6weeks HEP/ moderate intensity/ 3 months	3, 6	Function
Durmus et al, 2012	39	Clinical and radiographic OA	I1: exercise I2: exercise + glucosamine sulphate	I1 and I2: 3 x weekly strengthening and flexibility/ moderate intensity/ 3 months	3	Pain Function Structural OA
Ettinger et al, 1997	439	Clinical and radiographic tibiofemoral OA.	I1: aerobic exercise I2: resistance exercise C: health education	I1: 3 x weekly walking sessions in the first 3 months + further HEP with ongoing support/ moderate intensity/ 18 months I2: 3 x weekly general body strengthening sessions + further HEP with ongoing support/ moderate intensity/ 18 months	3, 9,18	Adverse events Pain Function Structural OA
Farr et al, 2010	171	Clinical and radiographic OA (KL II)	I1: resistance training I2: self-management I3: resistance training + self-management	I1 and I3: 3 x weekly sessions of aerobic warm up, stretching and global strengthening/ moderate intensity/ 9 months	3, 9	Pain
Fitzgerald et al, 2011	183	Clinical and radiographic OA (KL II-IV)	I1: standard exercise I2: agility and perturbation	I1: 12 supervised sessions of lower limb stretching and strengthening + HEP with phone contact and review/ moderate intensity/ 6 months I2: as I1 + agility training with stepping directional changes and balance exercises/ moderate intensity/ 6 months	6,12	Adverse events Pain Function TKR
Foroughi et al, 2011	54	Clinical OA	I1: progressive resistance training I2: sham exercise	I1: 3 x weekly knee extension and hip abduction and adduction Keiser machine strengthening/ high intensity/ 6 months I2: as I1 without hip adduction or single knee extension	6	Adverse events Pain Function

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Foy et al, 2011	2203	Knee pain, mean age >45yrs, type II DM, BMI >25	I1: intensive lifestyle intervention I2: Diabetes support and education	I1: 3 x weekly sessions including graded walking HEP, diet planning +/- supervised exercise in the first 6 months + 3 sessions a month and further HEP for 6 months/ moderate intensity/ 12 months	12	Pain Function
Hasegawa et al, 2010	28	Knee pain, mean age >45yrs	I1: strength and balance exercise	I1: weekly lower limb strength and balance exercises + 2 x weekly HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function
Jenkinson et al, 2009 Plus Barton et al, 2009;	389	Knee pain, mean age >45yrs, BMI ≥28	I1: diet advice + knee strengthening exercise I2: diet advice I3: knee strengthening exercise I4: advice leaflet	I1 and I3: contact every 4 months, phone support, staged flexibility, strengthening and aerobics HEP/ moderate intensity/ 24 months	24	Pain Function TKR
Kawasaki et al, 2008	142	Clinical and radiographic OA (KL II-III)	I1: exercise + glucosamine I2: exercise + risedronate I3: exercise	I1-3: twice daily lower limb strength, flexibility HEP with reviews at home every 3mths/ moderate intensity/ 18 months	18	Pain Function Structural OA Analgesic use
Kawasaki et al, 2009	102	Clinical and radiographic OA	I1: therapeutic HEP I2: hyaluronate injection	I1: twice daily lower limb strength and flexibility HEP with check-ups every month/ moderate intensity/ 6 months	6	Adverse events Pain Function Analgesic use
Keefe et al, 2004	72	Knee pain and OA diagnosis	I1:spouse assisted coping skills I2:spouse assisted coping skills and exercise I3:exercise alone C:standard care control	I2 and I3: weekly mixed exercise/ high intensity/ 3 months	3	Pain
Kirkley et al, 2008	188	Clinical and radiographic OA (KL II-IV)	I1: arthroscopy followed by exercise I2: individualised exercise	I1 and 2: weekly physiotherapy individualised exercise/ moderate intensity/ 3 months	3,6,12,18, 24	Pain Function

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Lim et al, 2008	107	Clinical and radiographic OA	I1: varus alignment and quadriceps strengthening I2: neutral alignment and quadriceps strengthening C1: varus alignment without new exercise C2 neutral alignment without new exercise	I1 and I2: 7 sessions of physiotherapy quadriceps strengthening with theraband + HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function
Manninen et al, 2001 ##	750	Cases: total knee replacement due to OA control: age matched older adults	Different categories of cumulative life hours of physical exercise	Retrospective cumulative lifetime hours of physical ex since leaving school divided into low/ medium/ high for different periods of life compared to no regular exercise.	Lifetime	TKR incidence Odds ratios for exposure to different cumulative life hours of physical exercise
McCarthy et al, 2004	214	Clinical and radiographic OA	I1: class based exercise program I2: home exercise	I1 2 x weekly mixed exercise class for 2 months + strengthening and balance individual tailored HEP/ moderate intensity/ 12 months I2: strengthening and balance individual tailored HEP/ moderate intensity/ 12 months	2,6,12	Pain Function
McKnight et al, 2010	273	Clinical and radiographic OA (KL II)	I1: strength training I2: self-management education I3: combined strength training and self-management	I1 and I3: 3 x weekly mixed exercise for 9months + 15 months of developing self-directed long term exercising habits with booster sessions/ moderate intensity/ 24 months	3,9,18, 24	Adverse events Pain Function TKR
Messier et al, 2000	24	Clinical and radiographic OA	I1: exercise + diet therapy I2: exercise	I1 and I2: 3 x weekly sessions of walking and global strength training/ moderate intensity/ 6 months	3, 6	Pain Function

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Messier et al, 2007	89	Radiographic OA	I1: Glucosamine and Chondroitin + exercise. I2: supplement placebo + exercise	I1: phase one: 6 months of Glucosamine and chondroitin then phase two: 6 months of 2 x weekly exercise aerobic exercise and lower limb strengthening + HEP/ moderate intensity I2: as I1 but placebo in phase 1	6, 12	Pain Function Analgesic use
Mikesky et al, 2006	221	Radiographic OA sub group within older adult sample	I1: lower extremity strength training I2: range of motion exercises	I1: 3 x weekly sessions of global strength training for first 12 months with reducing supervision, followed by HEP and 6 monthly follow ups/ moderate intensity/ 30 months I2: 3 x weekly global range of motion exercise sessions with supervision and follow up as above	12, 18, 24, 30	Adverse events Pain Function Structural OA
Miller et al, 2006	87	Clinical OA BMI ≥30	I1: intensive weight loss C: weight stable education	I1: 3 x weekly sessions of aerobic walking and lower limb strength exercises/ high intensity/ 6 months	6	Adverse events Pain Function
Ni et al, 2010	35	Clinical OA	I1: Tai Chi C: wellness education and stretching	I1: average 3 x weekly Yang style Tai Chi sessions/ moderate intensity/ 6 months C: weekly stretching sessions/ low intensity/ 6 months	6	Adverse events Pain Function
Olejarova et al, 2008	157	Clinical and radiographic OA	I1: combination of Glucosamine sulphate + exercise I2: Glucosamine sulphate I3: exercise C: no intervention	I1 and I3: 2 x weekly lower limb isometric strengthening and flexibility/ moderate intensity/ 6 months	3, 6 (all groups) 9, 12 (only I1 and I2)	Pain Function Analgesic use
O'Reilly et al, 1999	191	Knee pain, mean age >45yrs	I1: exercise C: no treatment control	I1: daily HEP including quadriceps and hamstring exercises with 4 home visits/ moderate intensity/ 6 months	6	Pain Function Analgesic use

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Osteras et al, 2012	17	Knee pain, MRI degenerative meniscus, mean age >45yrs	I1: medical exercise therapy I2: arthroscopic partial meniscectomy	I1: 3 x weekly aerobic cycling and lower limb strengthening exercises/ moderate intensity/ 3 months	3	Pain Function
Péloquin et al, 1999	137	Clinical and radiographic OA (KL I-III)	I1: cross training exercise C: OA education	I1: 3 x weekly mixed exercise sessions/ moderate intensity/ 3 months	3	Adverse events Pain Function
Pisters et al, 2010	150	Clinical OA	I1: behavioural graded activity I2: usual exercise therapy	I1: ≤18 sessions of graded activity (time contingent increase in problem activities) + individually tailored exercise therapy + further HEP and up to 7 booster sessions up to a year/ moderate intensity/ 12 months. I2: ≤18 sessions of exercise therapy + further HEP	3, 15, 60	Pain Function
Rejeski et al 2002 plus Messier et al, 2004	316	Clinical and radiographic OA, BMI ≥28	I1: diet I2: exercise I3: diet + exercise C: healthy lifestyle education	I2 and I3: 3 x weekly aerobic walking and lower limb strength exercises for 4 months with the choice to do supported HEP or continued facility group exercise/ moderate intensity/ 18 months	6 ,18	Adverse events Pain Function Structural OA
Rogind et al, 1998	25	Clinical and radiographic OA (KL III+)	I1: physical training C: unclear control	I1: 2 x weekly global strength, flexibility and balance exercise/ moderate intensity/ 3 months	3, 12	Adverse events Pain Function
Salacinski et al, 2012	37	Clinical and radiographic OA (KL I-III)	I1: cycling C: control	I1: 2 x weekly cycling/ moderate intensity/ 3 months	3	Pain Function

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Sayers et al, 2012	33	Clinical OA	I1: high speed power training I2: slow speed strength training C: stretching and cycling control	I1:3 x weekly high speed resisted concentric knee extension, cycling and stretching/ moderate intensity/ 3 months I2: as I1 but slow speed knee extension. I3: 3 x weekly cycling and stretching sessions/ moderate intensity/ 3 months	3	Pain Function
Schlenk et al, 2011	26	Clinical OA	I1: self-efficacy based lower extremity exercise and walking C: usual care	I1: 15 mixed exercise + self-efficacy intervention + exercise videotape + telephone counselling and monitoring sessions + HEP/ moderate intensity/ 6 months	6	Function
Silva et al, 2008	64	Clinical and radiographic OA	I1: water based exercise I2: land based exercise	I1: 3 x weekly heated pool lower limb stretching and strengthening exercises/ moderate intensity/ 4 months I2: 3 x weekly stretching and strengthening exercise/ moderate intensity/ 4 months	4	Pain Function Analgesic use
Simão et al, 2012	35	Clinical and radiographic OA	I1: squat group I2: platform group C: normal activities control	I1: 3 x weekly squat exercises/ moderate intensity/ 3 months I2: 3 x weekly squat exercise on a vibrating platform/ moderate intensity/ 3 months	3	Pain Function
Somers et al, 2012	232	Clinical and radiographic OA, BMI 25-42	I1: pain coping skills training I2: behavioural weight management I3: pain coping skills and behavioural weight management C: standard care control	I2 and I3: 3 months supervised flexibility and aerobic cycling exercise + 3 months unsupervised flexibility and aerobic exercise/ moderate intensity/ 6 months	6, 12, 18	Pain Function
Song et al, 2003	72	Clinical and radiographic OA	I1: Tai Chi C: control	I1: 3 x weekly supervised and HEP Sun style Tai chi sessions/ moderate intensity/ 3 months	3	Pain Function

Study author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up (months)	Safety domains
	No.	Knee pain/ OA diagnosis				
Talbot et al, 2003	34	Clinical and radiographic OA	I1: arthritis self-management program I2: walking + self-management program	I2: 12 OA self-management sessions + monthly reviewed walking program with pedometers and diaries/ moderate/ 3 months	3,6	Pain Function
Thomas et al, 2002	786	Knee pain, mean age >45yrs	I1: exercise + telephone I2: exercise +telephone + placebo I3: exercise I4: telephone I5: placebo C: no intervention	I1-3: 4 sessions in the first 2 months then visits every 6 months + HEP of local knee strengthening exercise/ moderate intensity/ 24 months	6,12,18, 24	Pain Function
Topp et al, 2002	102	Clinical OA	I1: dynamic resistance training I2: isometric resistance training C: control	I1: weekly theraband resisted lower limb strengthening + HEP/ moderate intensity/ 4 months I2: weekly lower limb isometric exercise + HEP/ moderate intensity/ 4 months	4	Pain Function Analgesic use
Wang et al, 2009	40	Clinical and radiographic OA (KL II+)	I1: Tai Chi C: wellness education and stretching	I1: 2 x weekly supervised Tai Chi sessions for 3 months + 3 months further home Tai Chi/ moderate intensity/ 6 months	3, 6, 11	Adverse events Pain Function Analgesic use
Wang et al, 2011	84	Clinical and radiographic OA	I1: aquatic exercise I2: land based exercise C: control	I1: 3 x weekly global flexibility and aerobic aquatic exercise/ moderate intensity/ 3 months I2: 3 x weekly mixed exercise/ moderate intensity/ 3 months	3	Adverse events Pain Function

Key: All studies were RCTs except when labelled with ## for case control study; mixed exercise indicates strengthening, flexibility and aerobic exercise

Abbreviations: BMI=Body Mass Index; HEP=Home Exercise Program; KL=Kellgren and Lawrence osteoarthritis grade; I1=Intervention group 1, I2=Intervention group 2 etc., C=Control; OA=Osteoarthritis; TKR=Total Knee Replacement

3.4.3 Summary of safety results

This section describes and summarises the included study results by each individual safety outcome domain: adverse events, pain, physical function, progression of OA as evidenced by imaging, TKRs and analgesic use.

I) Adverse events

Adverse events were only explicitly reported in 21 of the 48 included RCTs (see table 3.3). Some authors reported adverse events generally without attributing severity whilst others split adverse events into "*minor*" or "*mild*" and "*serious*", however, definitions of these terms were often lacking. According to the standardised adverse event categorisation (Calis & Young, 2004), no studies reported severe adverse events related to physical activity. Moderate adverse events were rare being reported in between 0 to 6% of physical activity intervention participants in any included study. These included five falls with one resulting in a fractured wrist and one a head laceration, one foot fracture caused by a participant dropping a weight on their foot, three drop-outs related to increased knee or other joint pain and one inguinal hernia attributed to physical activity. Mild adverse events were reported in between 0 to 22% of physical activity participants within individual studies and usually involved muscle soreness and temporary or mild increase in joint pain.

Table 3.3 Summary of adverse events

Study author	Adverse event outcomes from physical activity groups: Description	Frequency/ Severity
Abbott et al, 2013	1 inguinal hernia related to physical activity.	Very rare/ moderate
Baker et al, 2001	0 adverse events due to physical activity.	N/A
Bennell et al, 2005	Minor pain with physical activity reported in 22% of the physical activity group.	Minority/ mild
Bennell et al, 2010	3 participants reported back pain, one back and hip pain, and one reported aggravated varicose veins and knee pain.	Minority/ mild
Brismee et al, 2007	Minor muscle soreness, foot and knee pain reported.	Minority/ mild
Ettinger et al, 1997	2 falls in I1 and I2, 1 participant dropped weight on foot causing foot fracture in I2.	Very rare/ moderate
Foroughi et al, 2011	2 minor adverse events.	Very rare/ mild
Fitzgerald et al, 2011	0 adverse events reported.	N/A
Hasegawa et al, 2010	0 adverse events reported.	N/A
Kawasaki et al, 2009	0 participants needed to halt treatment due to severe adverse events.	Unclear
Lim et al, 2008	4 reported increased knee pain and 2 reported hip and groin pain attributed to the intervention in I1 3 had increased knee pain and 1 withdrew with neck pain in I2 2 participants (1 from each alignment group) stopped the treatment due to increased knee pain	minority/ mild-moderate
McKnight et al, 2010	15 adverse events were definitely related to the study, 13 were probably related 30 were possibly related. These consisted of: increased knee pain, accident/ injury related to strength training and pain/ soreness from strength training. 1 participant withdrew due to exacerbating pre-existing back pain.	Minority/ mild very rare/ moderate
Mikesky et al, 2006	1 participant dropped out due to increased knee pain with strength training	very rare/ moderate
Miller et al, 2006	No serious adverse events	unclear
Ni et al, 2010	5 participants complained of minor muscle soreness, foot and knee pain	very rare/ mild
Peloquin et al, 1999	1 participant dropped out due to knee inflammation from physical activity	very rare/ moderate
Rejeski et al, 2002	1 adverse event during physical activity- a participant tripped and sustained a laceration to his head	very rare/ moderate
Rogind et al, 1998	0 adverse events were reported	N/A
Song et al, 2003	Temporary mild pain in I1. Dropouts were mainly due to personal reasons not activity related factors.	Unclear/ mild
Thomas et al, 2002	52 (11%) of those in the physical activity group reported minor side effects.	Very rare/ mild
Wang et al, 2009	1 participant in I1 reported an increase in knee pain. #	very rare/ mild
Wang et al, 2011	1 participant in I1 reported dizziness during physical activity. 2 participants in I2 reported increased pain after physical activity.	Very rare/ mild

Key: +=findings from primary paper and follow-up papers ; I1=physical activity intervention group 1, I2=physical activity intervention group 2, **N/A**=none reported, **very rare**=0-15%, **minority**=16-25% (modified from Hubal & Day, 2006), **mild**=bothersome but requiring no change in therapy, **moderate**=requiring change in therapy, additional treatment, or hospitalisation, **severe**=disabling or life-threatening (Calis & Young, 2004), **unclear**=Insufficient adverse event reporting detail; #=one participant reported a newly diagnosed cancer that was not attributed to physical activity.

II) Pain

In total, 46 studies provided data on knee pain. The WOMAC pain scale (Bellamy et al, 1988) and numerical pain rating scale were the two most common outcome measures. No studies found significantly higher pain with physical activity (see table 3.4). Only 29 studies carried out between group statistical testing comparing physical activity to non-physical activity interventions. Of these, 19 showed pain to be significantly lower in the physical activity groups, whilst seven found no statistically significant difference between groups, and two showed inconsistent effects of pain using multiple physical activity intervention groups.

Of the studies that statistically analysed change in pain over time within a physical activity group (n=28), most showed statistically significant improvement in pain (n=20) with only five studies showing no significant change and three showing inconsistent results within multiple physical activity interventions.

III) Physical function

In total, 43 studies measured physical function. The WOMAC function subscale (Bellamy et al, 1988) and various objective lower limb function tests (e.g. 6 minute timed walk test) were the most common outcome measures. No studies found physical function to be lower with physical activity (see table 3.4). Only 28 studies carried out between group statistical testing comparing physical activity to non-physical activity interventions. The majority showed physical function was significantly better in physical activity groups (n=15), whilst a minority found no statistical difference between groups (n=11), and two studies showed inconsistent results within multiple physical activity intervention groups.

Of the studies that explored change in function over time within a physical activity group (n=28), most showed statistically significant improvement (n=19), with only two studies showing no significant change, and seven showing inconsistent results across multiple physical activity interventions.

IV) Progression of OA as evidenced by imaging

Six studies reported heterogeneous measures of OA progression from imaging of the tibiofemoral joint, including KL score, joint space width, OA severity and cartilage volume (see table 3.5). Five of the six used radiographs and a single study used MRI. Duration of time period for measuring progression of OA ranged from 3 to 30 months (median 18 months). Of the five RCTs that measured changes in radiographic OA using imaging, none provided any evidence of greater structural progression of OA in those engaged in long-term physical activity versus non-physical activity groups or those within physical activity group over time. A single small RCT found statistically significant improvements in the majority of MRI measured cartilage thickness and volume measures over time within physical activity groups. Contrastingly, a single RCT found non-significant trends towards radiographically measured joint space narrowing within physical activity groups over time.

Table 3.4 Summary of RCT pain and physical function outcomes

Study author	Pain		Physical function	
	Between group N=29	Within group N=28	Between group N=28	Within group N=28
Aglamis et al, 2008	✓	✓	✓	✓
Avelar et al, 2011		✓		#
Baker et al, 2001	✓	✓	↔	✓
Bautch et al, 1997		✓		
Bennell et al, 2005	↔	✓	↔	✓
Bennell et al, 2010	✓		✓	
Brismee et al, 2007	✓	✓	✓	✓
Dias et al, 2003			✓	✓
Durmus et al, 2012		✓		✓
Ettinger et al, 1997	✓		✓	
Farr et al, 2010		✓		
Fitzgerald et al, 2011		↔		✓
Foroughi et al, 2011		✓		✓
Foy et al, 2011	✓		✓	
Hasegawa et al, 2010	✓	✓	✓	✓
Jenkinson et al, 2009	✓	↔	✓	✓
Kawasaki et al, 2008		✓		✓
Kawasaki et al, 2009	↔		↔	
Keefe et al, 2004	↔			
Lim et al, 2008	✓		↔	
McKnight et al, 2010		✓		✓
Messier et al, 2000		#		✓
Messier et al, 2007		↔		#
Mikesky et al, 2006		↔		
Miller et al, 2006	✓		✓	
Ni et al, 2010	✓		✓	
O'Reilly et al, 1999	✓	✓	✓	✓
Osteras et al, 2012	↔			
Peloquin et al, 1999	✓	✓	#	#
Pisters et al, 2010		✓		✓
Rejeski et al, 2002	#	✓	#	#
Rogind et al, 1998	↔	#	↔	#
Salancinski et al, 2012	✓	✓	↔	↔
Sayers et al, 2012	↔	↔	↔	↔
Schlenk et al, 2011			↔	✓
Silva et al, 2008		✓		✓
Simao et al, 2012	#		↔	
Somers et al, 2012	✓	#	✓	#
Song et al, 2003	✓		✓	
Talbot et al, 2003	↔		↔	✓
Thomas et al, 2002	✓		✓	
Topp et al, 2002	↔	✓	↔	#
Wang et al, 2009	✓	✓	✓	✓
Wang et al, 2011	✓			

Key: ✓=significantly lower pain in physical activity group over time or compared to non-physical activity group/ significantly better physical function in physical activity group over time or compared to non-physical activity group; ↔ =no significant difference over time or between groups; #=mixed significant improvements and non-significant results across multiple physical activity interventions. All significance tests set at $\alpha = 0.05$; N=number of studies providing extracted evidence.

Footnote: Unable to extract data from: Abbott et al, 2013; Kirkley et al, 2008; McCarthy et al, 2004; Olejarova et al, 2008 due to no data/ no non-physical activity control/ no within group stats.

Table 3.5 Summary of OA structural progression on imaging outcomes

Study author	Radiographic or MRI biomarker outcomes	
	Outcome measure	Result
Bautch et al, 1997	Radiographic/ tibiofemoral/ antero-posterior/ KL severity	No within physical activity group change over time
Durmus et al, 2012	MRI /tibiofemoral/ cartilage volume	Some MRI parameter improvements within physical activity group over time
Ettinger et al, 1997+	Radiographic/ tibiofemoral/ antero-posterior and lateral/ OA severity	No between group difference post intervention
Mikesky et al, 2006	Radiographic/ tibiofemoral/ antero-posterior/ joint space width, joint space narrowing and ostophytosis severity	Both physical activity groups showed non-significant trends towards joint space width narrowing over time
Kawasaki et al, 2008	Radiographic/ tibiofemoral/ anteroposterior/ joint space width	No between group difference post intervention
Rejeski et al, 2002+	Radiographic/ tibiofemoral and patellofemoral/ anteroposterior and sunrise/ joint space width and KL	No between group difference post intervention No within physical activity group change over time

Key: +=results were taken from the primary trial paper and additional follow-up papers pertaining to the same trial.

Abbreviations: KL=Kellgren Lawrence Osteoarthritis grading; MRI=Magnetic Resonance Imaging.

3.4.4 Secondary safety outcomes

I) Total knee replacement

Four RCTs reported TKRs within the study intervention period in enough detail to permit data extraction, as did the single case-control study. Two additional RCTs were not included in the analysis as they only reported joint replacement generically without specifying knee or hip (Pisters et al, 2010; Abbott et al, 2013). Table 3.6 provides a summary of the TKR findings. Duration of follow-up period for monitoring TKR ranged from 6 to 24 months (median 18 months). Summing all TKR results across RCTs, there was no evidence of a higher proportion of participants proceeding to TKRs within those engaged in long-term physical activity compared to those who were not (n=10/633 participants or 1.6%, and 10/352 participants or 2.8% respectively). There was also no clear pattern with regards to exercise intervention type and those studies that included participants who went on to have TKR surgery.

The case-control study (Manninen et al, 2001) investigated cases of Finnish adults who underwent TKR versus age matched controls. They concluded that TKR risk decreased with increasing recreational physical activity. Using adults with a history of no regular physical activity as a reference, after adjustment for age, body mass index, physical work stress, knee injury and smoking, the odds ratios (and 95% CI) of TKR were 0.91 (0.31, 2.63) in men with low cumulative hours of physical activity and 0.35 (0.12, 0.95) in those with a high number of accumulative hours. In women the respective results for low and high cumulative hours of physical activity were 0.56 (0.30, 0.93) and 0.56 (0.32, 0.98).

Table 3.6 Summary of total knee replacement outcomes

Study Author	Participant number	Physical activity interventions/ exposure	Monitoring duration (months)	Total number of TKRs at post-intervention time-point per group (% of treatment group) in RCTs/ adjusted OR (95%CI) for case-control study
Bennell et al, 2005	140	I1: physiotherapy (including exercise, taping and soft tissue mobilisations) C: sham ultrasound therapy	6	I1: 2 (3) C: 1 (2)
Fitzgerald et al, 2011	183	I1: strength and flexibility exercise I2: agility, balance, strength and flexibility exercise	12	I1: 3 (3) + 5 UKR I2: none + 1 UKR
Jenkinson et al, 2009	389	I1: diet advice + flexibility and strengthening exercise I2: diet advice I3: flexibility and strengthening exercise I4: advice leaflet control	24	I1: 2 (2) I2: 6 (5) I3: 2 (2) I4: 3 (4)
Manninen et al, 2001##	750	Low cumulative hours physical activity High cumulative hours physical activity	N/A	Male *(ref category is no regular physical activity)* Low cumulative hours 0.91 (0.31, 2.63) High cumulative hours physical activity 0.35 (0.12, 0.95) Female Low cumulative hours 0.56 (0.30, 0.93) High cumulative hours physical activity 0.56 (0.32, 0.98)[r]
McKnight et al, 2010	214	I1: strength exercise I2: self-management education I3: combined strength exercise and self-management	24	I1: 1 (1) I2: none I3: none

Key: All studies were RCTs except when labelled with ## for case-control study; odds ratios adjusted for age, body mass index, physical work stress, knee injury and smoking.

Abbreviations: OR=Odds Ratio; TKR=Total Knee Replacement; UKR=Uni-compartmental Knee Replacement.

II) Analgesic use

Ten RCTs measured analgesic pain medication use (table 3.7). Analgesic use was generally treated within studies as a secondary outcome measure or as a reported co-intervention. The method of monitoring analgesic use also varied between studies. Categorisation varied from study to study and included; *“non-steroidal anti-inflammatory medication”* (N=6), “analgesics” (N=5), *“medication”* used as a general term (N=2) whilst one study monitored *“acetaminophen, aspirin, other analgesics, or corticosteroids”* (Messier et al, 2007). Statistical analysis of analgesic use was not carried out in most studies and the general level of reporting detail was low.

There was a general pattern of studies reporting no difference between the analgesic medication use between physical activity groups versus controls at post-intervention follow-up time points. Nine studies stated that levels of analgesia either reduced over time or were stable in physical activity groups. The study by Bennell et al (2010) was the only study to report increased medication use with physical activity during the intervention period and reported that 18 of 45 physical activity participants increased their medication use at some point during the intervention whilst 15 of 45 decreased their use.

Table 3.7 Summary of analgesic use outcomes

Study author	No.	Physical activity interventions/ exposure	Time period (months)	Analgesic outcomes (n=10 studies)	
				Type/ method	Analgesia use results
Bennell et al, 2005	140	I1: physiotherapy C: sham ultrasound	0-6	Analgesics, NSAID use/ method not reported	Similar I1 and C group use over the treatment period (analgesics, 23% vs 21%; NSAIDs, 22% vs 24%).
Bennell et al, 2010	89	I1: hip strengthening C: no treatment	0-3	Medication use/ patient logbook	18 in I1 and 14 in C increased use, 15 and 9 respectively decreased use.
Kawasaki et al, 2008	142	I1: ex + glucosamine I2: ex. + risedronate I3: exercise	0, 18	NSAID use/ monitored at check-ups every three months	No significant difference between the scores at baseline and 18 months f/u within or between groups.
Kawasaki et al, 2009	102	I1: therapeutic HEP I2: hyaluronate injection	0, 6	NSAID use/ monitored at check-ups every month	No significant difference between the scores at baseline and 6 months f/u or between the groups.
Messier et al, 2007	89	I1: Glucosamine and Chondroitin + aerobic walking and strength ex. I2: placebo + aerobic walking and strength ex.	0, 12	Acetaminophen, Aspirin, other analgesics at bl and 12 months	N of participants using acetaminophen reduced from baseline to 12 month follow-up by 37% in I1 and 11% in I2. No change in use of other analgesia.
Olejarova et al, 2008	157	I1: Glucosamine sulphate + ex. I2: Glucosamine sulphate I3: ex. C: no intervention	0, 6	Analgesics, NSAID use/ monitored at bl and six months	All groups showed trends of decreased use over time.
O'Reilly et al, 1999	191	I1: strength exercise C: no treatment control	0-6	Analgesics/ self-report everyday no further method detail	Decreased slightly in the exercise group and was unchanged in the control group
Silva et al, 2008	64	I1: water based ex I2: land based ex.	0-4	NSAID use/ daily record of diclofenac use	Decreased significantly over time in both groups. No difference between groups.
Topp et al, 2002	102	I1: dynamic resistance training I2: isometric resistance training C: control	0, 4	OA Medication/ list of medications at bl and four months	No statistically significant change in medication use within the groups over time or between the treatment groups at 4 month f/u.
Wang et al, 2009	40	I1: Tai Chi C: wellness education and stretching	0, 3	NSAID use/ % reported NSAID use at bl and three months	55% and 30% of I1 took NSAIDS at bl and three months respectively vs 70 % and 50% in C.

Key:
Green text=evidence of no increase in analgesic use with physical activity (PA);
Orange text=inconsistent evidence of increasing and decreasing analgesic use with PA;
Red text=evidence of increase in analgesia use with PA.

Footnote: All significance tests set at $\alpha = 0.05$; "Time period" indicates whether analgesic use was measured at specific time points e.g. 0, 3, or continuously: 0-3

Abbreviations: bl=baseline; ex=exercise; f/u=follow-up; HEP=Home Exercise Programme; I1=Intervention group 1, I2=Intervention group 2, I3=Intervention group 3, C=Control group; N=Number; NSAIDS=Non-Steroidal Anti-Inflammatory Drugs.

3.4.5 Risk of bias of included studies

The risk of bias of included RCTs varied widely. Figure 3.4 shows an overall summary of risk of bias whilst individual study assessments are shown in table 3.8. Although explicitly high risk of bias assessments were relatively uncommon (7% of all judgements), many studies were frequently at unclear risk of bias due to inadequate reporting detail (61% of all judgements) whilst only a minority of assessments concluded low risk of bias (32% of all judgements). Risk of selection bias due to systematic differences between baseline characteristics of the compared groups (Higgins and Green, 2009) was mixed. Although the majority of studies were explicit in their use of appropriate randomisation, such as computer generated random numbers (n=31, 65%), many provided unclear information about their allocation concealment methods (n=31, 65%). Risk of performance bias due to systematic exposure to factors other than the interventions of interest (Higgins & Green, 2009) was scored as unclear throughout as it is not possible to blind participants involved in an physical activity intervention to the fact that they are carrying out exercise. Risk of detection bias, due to knowledge of the intervention group by researchers measuring outcome (Higgins & Green, 2009), was judged as low in the majority of studies (n=26, 54%) as a result of blinded outcome assessors or participant self-report outcome measures. However, it was also often judged to be unclear (n=18, 38%), for example, when authors reported blinding with ambiguous terms such as “single” or “double blind” without further explicit information as to whom exactly was blinded. Risk of attrition bias due to systematic differences in loss to follow-up between groups (Higgins & Green, 2009) was low in over a third of studies (n=19, 40%) but was unclear in a similar number of studies (n=20, 42%) and seven studies (15%) were judged to be at high risk of bias due to different numbers of drop-outs between intervention groups and the reasons for drop-outs being potentially related to safety outcomes. Reporting bias was unclear in the vast majority of studies (n=44, 92%) due to a lack of a published protocol with which to check that all planned outcomes were analysed and reported. The "other sources of bias" category judgements were mixed. This category allowed the reviewers to consider factors that are not necessarily directly related to risk of bias including participant generalisability, imprecision, potential conflicts of interest and contamination. Risk of bias assessment for the case-control study by Manninen et al (2001), was considered moderate in four domains (attrition, prognostic factor measurement, confounding and statistical analysis and reporting) and low in two (selection, and statistical analysis and reporting).

Figure 3.4 Summary of risk of bias from RCTs

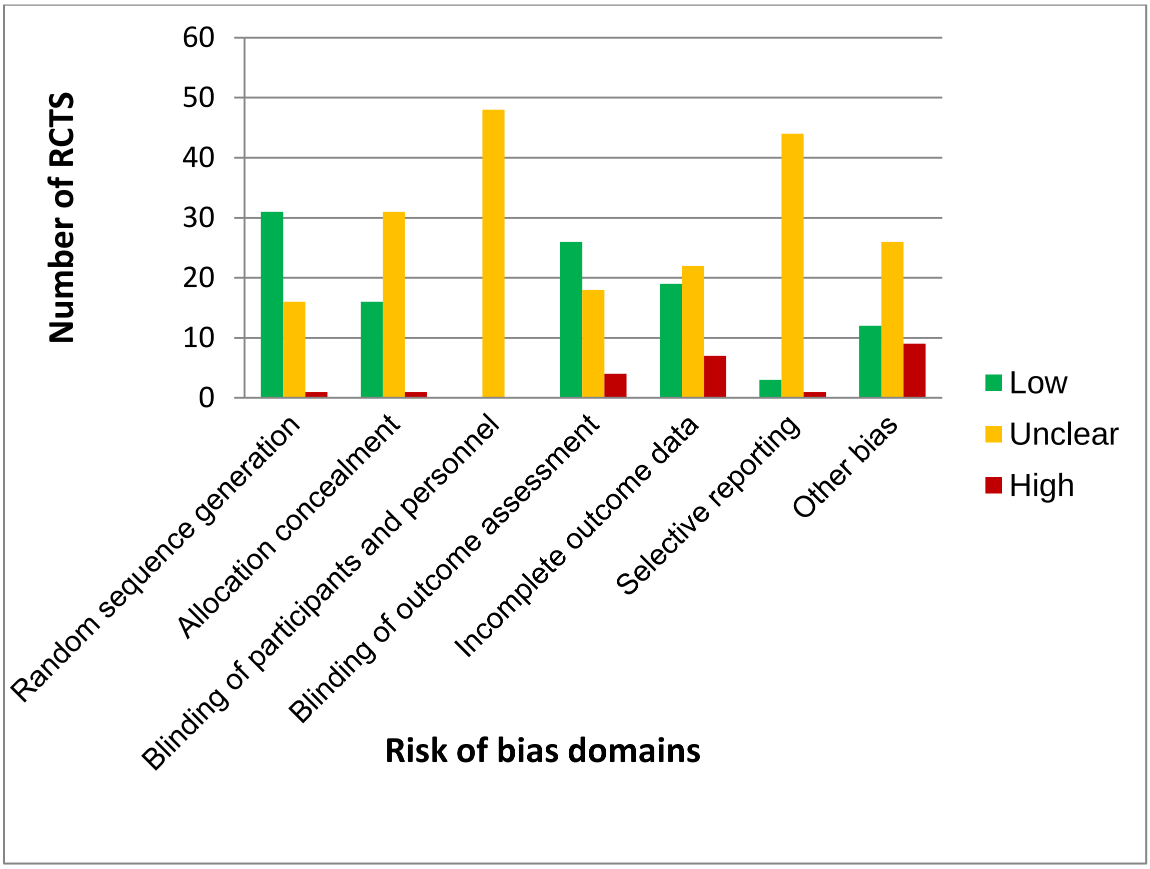


Table 3.8 RCT risk of bias judgements

Study author	Risk of bias domains						
	1	2	3	4	5	6	7
Abbott et al, 2013	l	l	u	l	u	l	l
Aglamis et al, 2008+	l	l	u	l	h	u	h
Avelar et al, 2011	u	u	u	u	u	u	h
Baker et al, 2001	u	u	u	h	l	u	l
Bautch et al, 1997	u	u	u	u	u	u	u
Bennell et al, 2005	l	l	u	l	h	u	u
Bennell et al, 2010	l	l	u	l	l	l	l
Brismee et al, 2007	l	u	u	l	u	u	u
Dias et al, 2003	l	l	u	l	u	u	u
Durmus et al, 2012	u	u	u	u	l	u	u
Ettinger et al, 1997+	l	l	u	u	u	u	l
Farr et al, 2010	l	u	u	u	u	u	l
Fitzgerald et al, 2011	l	u	u	l	l	u	l
Foroughi et al, 2011	u	u	u	u	l	h	u
Foy et al, 2011	l	l	u	u	l	u	u
Hasegawa et al, 2010	u	u	u	u	l	u	h
Jenkinson et al, 2009+	l	h	u	u	l	u	u
Kawasaki et al, 2008	u	u	u	u	h	u	u
Kawasaki et al, 2009	l	u	u	l	h	u	u
Keefe et al, 2004	u	u	u	u	u	u	u
Kirkley et al, 2008	l	u	u	l	u	u	u
Lim et al, 2008	l	l	u	l	l	u	l
McCarthy et al, 2004	l	l	u	l	u	u	l
McKnight et al, 2010	l	l	u	h	l	u	l
Messier et al, 2000	u	u	u	l	u	u	u
Messier et al, 2007	u	u	u	u	u	u	h
Mikesky et al, 2006	u	u	u	l	h	u	u
Miller et al, 2006	u	u	u	u	l	u	u
Ni et al, 2010	l	u	u	l	u	u	u
Olejarova et al, 2008	h	u	u	u	u	u	h
O'Reilly et al, 1999	l	l	u	u	l	u	l
Osteras et al, 2012	u	u	u	h	l	u	h
Peloquin et al, 1999	l	u	u	l	u	u	u
Pisters et al, 2010	l	u	u	l	u	u	u
Rejeski et al, 2002+	l	l	u	l	u	u	u
Rogind et al, 1998	l	u	u	l	l	u	u
Salancinski et al, 2012	l	u	u	u	h	u	u
Sayers et al, 2012	l	u	u	l	u	u	h
Schlenk et al, 2011	u	u	u	u	u	u	u
Silva et al, 2008	l	u	u	l	l	u	l
Simao et al, 2012	u	l	u	l	u	u	u
Somers et al, 2012	l	u	u	l	u	u	u
Song et al, 2003	l	l	u	l	h	u	h
Talbot et al, 2003	l	u	u	h	u	u	h
Thomas et al, 2002	l	u	u	l	l	u	l
Topp et al, 2002	u	u	u	u	l	u	u
Wang et al, 2009	l	l	u	l	l	l	u
Wang et al, 2011	l	l	u	l	l	u	u

Key: Risk of bias domains: 1) Random sequence generation; 2) Allocation concealment; 3) Blinding of participants and personnel; 4) Blinding of outcome assessment; 5) Incomplete outcome data; 6) Selective reporting; 7) Other bias.

Green l=low risk of bias; Orange u=unclear risk of bias; Red h=high risk of bias

3.4.6 Summary of results

In summary, 49 studies were included in this review comprising 48 RCTs and a single case-control study. All RCT physical activity interventions were classified as therapeutic exercise and were mostly moderate intensity, low impact, mixed exercise comprising strengthening, aerobic and stretching exercises over periods of 3 to 30 months. **Synthesising the consistent evidence from the 49 included studies, the main finding was that long-term therapeutic exercise is safe for most older adults with knee pain.** Summarising key findings from individual safety outcome domains:

- There was no reported evidence of severe adverse events, moderate adverse events were very rare (ranging from 0 to 6% of participants within RCTs), whilst mild adverse events occurred in a minority (0 to 22% of participants) undertaking long-term exercise interventions.
- There was no evidence of exercise being associated with increased pain at a group level although a small minority of participants reported mild or temporary increases in pain during therapeutic exercise interventions.
- There was no evidence of exercise being associated with lower physical function at a group level.
- There was no evidence of OA imaging progression associated with long-term exercise intervention.
- There was no evidence of increased TKR incidence in exercise groups within trials or increased risk of TKR with increasing lifetime hours of recreational physical exercise in a case-control study.
- Most trials monitoring use of analgesics found no evidence of a difference over time within exercise groups or between groups post-intervention.

3.5 Discussion

This section synthesises, critiques and evaluates the findings from the systematic review. It begins by recapping the aim and main finding before discussing the included studies providing critique and risk of bias evaluation. The discussion is then split into separate sections covering each safety outcome domain before comparing the review findings to existing research, reflecting on the overall strengths and limitations of the review and highlighting clinical and research implications from the findings. The chapter closes with a summary and bridge to the subsequent thesis chapter.

This systematic review aimed to determine the safety of long-term physical activity in older adults with knee pain. It included multiple safety outcome domains and different types of study designs in order to reach a robust a conclusion. No previous systematic reviews have specifically focussed on safety in this population by combining evidence form multiple safety outcome domains and study types. Since the vast majority of studies meeting the inclusion criteria related specifically to therapeutic exercise, firm conclusions can only be made about this specific physical activity domain. The main finding was that long-term therapeutic exercise was safe for most participants across all outcome domains.

3.5.1 Included studies

In total 49 studies were included in this systematic review comprising 48 RCTs and a single case-control study. The RCTs were heterogeneous in terms of participants, exercise interventions, comparison/control groups, safety outcome domains and outcome measures. As a result, a narrative synthesis was carried out rather than a meta-analysis.

I) Risk of bias of the included studies

Risk of bias varied widely within included studies. Potentially of most concern was the unclear and, at times, high risk of attrition bias due to loss to follow-up in just over half of the RCTs (n= 22 and 6 respectively), whilst the case-control was considered at moderate risk of bias due to losses to follow up. It is likely that those participants who drop out of RCTs may be different in important ways than those who are retained through to longer-term follow-ups. If those who drop-out are those who are more likely to have experienced problems with exercise, such as an increase in pain or an adverse event than participants who are retained, then the safety of exercise may be overestimated. However, safety findings were consistent regardless of the risk of attrition bias within individual studies. For example, three large RCTs with low risk of attrition bias still concluded exercise to be safe and reported no severe adverse events after two years of moderate intensity strengthening and mixed exercise (Thomas et al, 2002; Jenkinson et al, 2009; McKnight et al, 2010).

Risk of reporting bias within included studies was often a concern within included RCTs. Reporting bias can occur when there is selective or inadequate outcome reporting within a study (Higgins et al, 2011). Although 21 studies explicitly reported adverse events, the majority did not (n=26). Only four studies had an available protocol to cross check if authors initially intended to monitor adverse events. Hence, it is not clear whether the studies that did not report adverse events either monitored adverse events but did not experience any, monitored adverse events but did not report any, or did not monitor adverse events and hence did not report any regardless of whether they occurred or not.

A number of studies included within the systematic review were at high risk of imprecision due to small sample sizes (n=5). Although not strictly a risk of bias issue, imprecision refers to random error meaning *"that multiple replications of the same study will produce different effect estimates because of sampling variation even if they would give the right answer on average"* (Higgins & Green, 2009). However, imprecision and random sampling variation were unlikely to lead to spurious safety conclusions from this systematic review, since safety findings were consistent amongst multiple studies with the majority being adequately powered.

3.5.2 Included participants

Included RCT participants were wide ranging in terms of age, severity of knee pain and comorbidities. However, it is possible that some specific sub-groups were underrepresented due to strict study exclusion criteria and the lack of observational studies, which may reduce the generalisability of the findings. Participants with specific risk factors, such as cardiovascular disease, history of cardiac events or those who were deemed *"unfit for physical activity"* were often excluded from RCTs. These individuals are more likely to have serious adverse events during and immediately following exercise (Schmied & Borjesson, 2014). Had these individuals been included this may have altered the consistency of the safety findings. In addition, participants who consent to participate in RCTs testing physical activity interventions may differ systematically from those who do not (Bartlett et al, 2005) and this may introduce an important selection bias. For example, the oldest and most frail tend to be under represented within trials (Bartlett et al, 2005). In addition, applying self-efficacy theory (Bandura, 1977), an individual participating in a physical activity trial may have higher outcome expectancy or self-efficacy for physical activity than the typical older adult with knee pain (which could be partly based on previous positive experiences of that activity). Equally, inferring from qualitative research (Hendry et al, 2006; Holden et al, 2012), it is possible that older adults with knee pain with negative physical activity experiences and negative attitudes about physical activity or fear of harm may be less likely to consent to participate in a physical activity RCT. This may therefore limit the ability to generalise the findings to all older adults with knee pain.

3.5.3 Included types of physical activity intervention

Only one category of physical activity (as described in section 3.3.2, IV), namely therapeutic exercise was included within RCTs in this review. Physical activity associated with domestic activities such as gardening and heavy housework, occupational activity and travel were not represented. In addition, only the case-control study (Manninen et al, 2001) contained any information on physical activity more broadly. Whilst various types and intensities of therapeutic exercise within this systematic review may be similar to activities within other physical activity categories (e.g. walking), caution is required in making inferences from the review findings since safety may still differ between categories. For example, a walking therapeutic exercise program and walking on a pavement as a travel activity may have similar safety results, but cycling on an exercise bike compared to cycling on roads may not (due to the additional risk of road traffic accidents). Equally, competitive sport may also contain additional elements that might increase the risk of injury. Looking at the types of exercise interventions included within the systematic review, most were moderate intensity and all were low impact. Hence, it is not possible to confidently draw conclusions about the safety of high impact exercises, such as running, from the included studies. Exercise interventions varied in duration from 3 to 30 months hence care must be taken in inferring safety findings to periods longer than this.

3.5.4 Discussion of safety domains

I) Adverse events

There were no severe adverse events reported within the studies included in this review, moderate adverse events were rare and only a minority of participants experienced mild adverse events indicating therapeutic exercise is safe for most older adults with knee pain. Falls were the most common moderate severity adverse event, experienced by five participants out of a total of 8920. High quality systematic review evidence has shown exercise actually reduces the number of falls in community dwelling older adults (Gillespie et al, 2012). However, in view of the high prevalence of falls in older adult populations- 30% of adults over the age of 65 falling at least once a year (Gillespie et al, 2012; NICE, 2013b), and the large numbers of participants carrying out long-term exercise in this systematic review, this figure appears relatively low and suggests that falls might have been under reported.

Mild adverse events were reported in a minority of participants within RCTs and were mostly temporary and or mild increases in knee pain. However, regardless of being categorised as *“mild”* these adverse events may still hold clinical importance. This is because even temporary or mild pain attributed to physical activity may still contribute to physical activity avoidance behaviour, deconditioning and disability through fear of pain or harm (Hendry et al, 2006; Vlaeyen & Linton, 2012; Holla et al, 2014).

II) Pain and physical function

Consistently, there was no evidence from RCTs (n=46) that long-term therapeutic exercise was associated with increased pain at a group level. However, a minority of individuals did experience mild or temporary increases in pain described as a mild adverse event. Similarly, there was no evidence of worsening physical function with long-term exercise from included RCTs (n=43). A potential issue regarding these group level statistics is that these may also hide some individuals who have negative safety outcomes if the majority improve. However, with the inclusion of adverse events as a safety outcome domain these individuals are likely to be accounted for within the review.

III) Progression of structural OA

There was no evidence of progression of structural OA on imaging with long-term therapeutic exercise, although there are unique limitations with regards to this safety domain. Firstly, only five studies measured progression of structural OA on imaging over time so there was a dearth of evidence to synthesise. Secondly, four studies monitored radiographs over less than two years and there is evidence that radiographs may lack the sensitivity or responsiveness to detect change within this time-frame (Reichmann et al, 2011). In addition, two studies used the KL scale for categorising OA severity and two used joint space width. Both of these scores are subject to ceiling effects especially with groups that are selected based on pre-existing radiographic OA (Zhang et al, 2010; Neogi & Zhang, 2013) and therefore they have limitations as structural OA progression tools. It was notable that no studies measured structural knee OA using imaging of the patellofemoral joint which should be considered when drawing inferences about this phenotype of knee OA.

IV) TKR

There was no evidence that long-term physical activity was associated with higher incidence of TKR. The case-control study by Manninen et al (2001) found that higher levels of physical activity were actually protective of progressing to TKR. Only very crude statistics were available from the five RCTs that monitored TKR since TKRs were not primary outcomes within any of the trials, hence a degree of caution is required in interpreting the findings. Undergoing a TKR is a proxy outcome measure for late stage knee pain in older adults attributable to OA (Altman et al, 2005; Wang et al, 2011b), it is undertaken by some older adults with moderate to severe knee pain and individuals often have symptoms for many years prior to undergoing the surgery (Wang et al, 2011b; Wright et al, 2011). However, the RCTs recording TKR only monitored the number of TKRs in intervention groups over periods of 6 to 24 months. This may be an insufficient time period to capture a difference in TKR numbers between exercise and non-exercise groups if one indeed exists. Furthermore, indications for TKR vary between clinicians and are also influenced by individual, socioeconomic and healthcare provision factors (Altman et al, 2005; Wright et al, 2011) which can be considered as unadjusted confounding in any inferences that are made from the available RCT evidence.

V) Analgesia use

There was a general pattern of studies reporting no difference in analgesic medication use between therapeutic exercise groups compared to controls within the ten RCTs that reported this. This suggests that long-term therapeutic exercise is safe in that it does not lead to additional use of analgesics. Furthermore, it can be inferred that analgesia use is unlikely to have been a co-intervention that confounded the safety outcome domain findings of pain and physical function discussed previously.

3.5.5 Comparisons to existing research

This systematic review builds on previous expert consensus (Roddy et al, 2005; Bennell & Hinman, 2011) in concluding that long-term therapeutic exercise is likely safe for the majority of older adults with knee pain. The findings also support recent clinical guidelines recommending physical activity (including strengthening and aerobic exercise) as a core treatment for all older adults with knee pain regardless of age, pain or disability levels or co-morbidities (Fernandes et al, 2013; McAlindon et al, 2014; NICE, 2014).

Comparing the safety domain findings to existing literature, the adverse event results of this systematic review were consistent with a recent comprehensive Cochrane systematic review of RCTs of land-based exercise in older adults with OA (Fransen et al, 2015) which also found no evidence of severe adverse events. Furthermore, they summarised the rate of drop-out from exercise interventions and found it comparable to control groups (event rate 14% compared to 15%). Whilst drop-out can occur for many reasons other than adverse events this finding does support the hypothesis that therapeutic exercise is well tolerated by the vast majority of participants engaging in exercise interventions.

The safety findings regarding pain and physical function are well supported by recent systematic review evidence which show a consistent pattern of reductions in pain and improvements in physical function associated with therapeutic exercise (Uthman et al, 2013; Juhl et al, 2014; Fransen et al, 2015). Although these systematic reviews did not limit their inclusion of RCTs to those with interventions of three months or more, they concluded that, at a group level, exercise interventions reduce pain and improve physical function and that further trials are unlikely to change this conclusion (Uthman et al, 2013; Fransen et al, 2015).

The safety findings regarding structural OA progression from this review can be compared to other systematic reviews (Belo et al, 2007; Bastick et al, 2015a) and contemporary physical activity studies investigating additional types of physical activity (Multanen et al, 2014; Lo et al, 2015). Although there is a relative dearth of evidence within the aforementioned comparative systematic reviews, both sets of authors concluded from three observational studies (that did not meet the inclusion criteria for this review) (Schouten et al, 1992; Lane et al, 1998; Cooper et al, 2000), that there was strong evidence that running and regular sports activity were not associated with structural progression. This conclusion is further supported by a recent prospective cohort study by Lo and colleagues (2015) that found running in older adults with knee pain, with a past history of running, was not associated with increased risk of OA progression. Adding to the novel literature on high impact physical activity, a RCT by Multanen et al (2014) provided initial evidence for the safety of gradually progressed high-impact physical activity carried out over 12 months (in the form of step aerobic jumping exercises) in postmenopausal female older adults with knee pain (Multanen et al, 2014). These findings support and add to the safety findings from therapeutic exercise RCTs within this systematic review.

There is a dearth of existing papers to compare the TKR findings of this systematic review to. Wang et al (2011b) completed a prospective cohort study investigating the relationship between physical activity and TKR in older adults with and without knee pain. They found that high levels of physical activity (high frequency and high intensity) were associated with an increased hazard risk of TKR compared to no regular physical activity (adjusted Hazard ratio 1.46, 95%CI: 1.13 to 1.87), but other levels of physical activity such as walking and moderate physical activity were not associated with TKR. Although their finding regarding high frequency and high intensity physical activity runs contrary to the findings from this systematic review, the heterogeneous sample including individuals with and without knee pain makes robust comparison difficult. To the author's knowledge, no other systematic reviews have compared analgesia use within exercise interventions to non-exercise controls.

Important clinical sub-groups at increased risk of harm, including those with cardiovascular disease, the frail elderly and those at highest risk of falling were likely to be underrepresented within the included studies of the systematic review (discussed in section 3.5.2). Although it was not possible to make confident inferences about the safety of long-term physical activity for these sub-groups from the systematic review findings, some inferences can be made from existing physical activity literature for these sub-groups regardless of knee pain. Specifically tailored therapeutic exercise interventions have been shown to be relatively safe and recommended for the frail elderly (Gillespie et al, 2012; NICE, 2013b; Silva et al, 2013) and to be considered appropriate for adults with cardiovascular disease (Thompson et al, 2007; NICE, 2013a).

3.5.6 Strengths and limitations of this systematic review

The strengths of this systematic review include having a clear review protocol and prospective registration with PROSPERO, a comprehensive search strategy alongside double reviewer screening, quality assessment and data extraction checking. The systematic review also included different study designs alongside original synthesis of data from several safety construct domains.

Despite the comprehensive search strategy, using a broad range of electronic databases, reference list searching of included studies yielded two additional studies that were also added to the review, whilst peer review during publication identified a further study for inclusion. Hence, although these extra opportunities to identify relevant studies is a strength, finding three studies that were not included within the initial electronic search indicates that the search strategy was not completely exhaustive. Therefore, although it is highly likely that the vast majority of relevant studies were included in this review, it is possible others may remain undetected. However, it is unlikely that the overall conclusions about therapeutic exercise safety would be altered by the finding of small numbers of additional studies due to the consistency of the safety findings from the large number of studies included.

A potential strength and limitation of this review was the strict criteria for only including observational studies that had explicitly monitored physical activity over three months or more. This was a strength because physical activity can fluctuate over time and studies that measured physical activity using a surrogate measure or as a snap-shot over a short period of time (for example days or a week) may not be a valid measure of long-term physical activity. However, the limitation of this was that most observational studies were excluded from the review. This meant that despite efforts to combine safety evidence from both RCTs and observational studies, most of the evidence about safety was from RCTs. As discussed previously (section 3.5.2), this has implications for the generalisability of the findings.

Publication bias due to the inclusion/ exclusion criteria, as discussed in section 3.3.2, is also a potential limitation (Higgins & Green, 2009). Studies with positive findings have been shown to be more likely to be published within journals (Rosenthal, 1979). If unpublished studies exist that show physical activity to be unsafe then this could alter the conclusions of the review. However, given the large number of trials, investigating a range of physical activities all having similar safety findings, this situation appears unlikely.

Some safety domain finding conclusions were also limited by the dearth of available evidence and the sub-optimal study follow-up time periods, in particular those related to physical activity other than therapeutic exercise and safety domains of progression of structural OA and progression to TKR (section 3.5.4). A dearth of evidence limits safety domain conclusion strength whilst suboptimal follow up time periods for progression of structural OA and progression to TKR would also tend to bias these safety domain findings towards an interpretation of therapeutic exercise being safe.

3.5.7 Clinical implications

The findings from the systematic review offer reassurance to some clinicians and older adults with knee pain who perceive that knee pain attributed to OA is a *"wear and tear"* condition that deteriorates with time and is made worse by regular physical activity (Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012). In terms of education, it is appropriate to educate older adults with knee pain about the general benefits of regular physical activity and therapeutic exercise and reassure them that although a minority of individuals may experience mild or temporary increases in pain with long-term therapeutic exercise, pain does not equal harm (Main et al, 2008) or structural progression of OA and most will experience a reduction in pain and improvement in function if they persist with long-term exercise. Many types of long-term therapeutic exercise have been shown to be safe for most older adults with knee pain regardless of pain severity. This allows choice in therapeutic exercise selection based on baseline functioning, individual health goals, personal preferences and factors likely to facilitate adherence such as enjoyment and “fit” with lifestyle (Hendry et al, 2006; Chodzko-Zajko et al, 2009; Jordan et al, 2010; Dekker, 2012). However, given the relative dearth of current evidence about the long-term safety of high impact, high intensity physical activity, such as running, tennis or football for older adults with knee pain, it is perhaps wise to advise on low impact, moderate intensity strengthening and aerobic exercise at present, which has a larger body of evidence behind it.

3.5.8 Research implications

The findings from this systematic review have highlighted a number of gaps in the literature and contributed to the generation of future research recommendations, including investigating the safety of additional categories of physical activity, investigating the safety of long-term physical activity for clinically important comorbid subgroups, and optimising the measurement and reporting of safety domain outcomes and long-term physical activity. Considering these in turn, although recent research is starting to address the safety of high impact physical activities including running (Multanen et al, 2014; Lo et al, 2015), there is still a lack of available quality evidence regarding the safety of sport, occupational, domestic and travel activities. Hence, there is a need for high quality, observational studies to provide insight into these types of lifestyle choices and occupational physical activities, which by their nature, are not easy to research using RCTs.

Although physical activity is recommended for sub-groups of older adults with knee pain at increased risk of harm and adverse events, such as those with cardiovascular disease (in the absence of unstable angina and chronic heart failure), frailty and those who are at increased risk of falls (section 3.5.5) (Chodzko-Zajko et al, 2009; NICE, 2013a, 2013b), to the author's knowledge, studies have not specifically investigated the safety and benefits of specially tailored long-term physical activity in older adults with knee pain and these comorbidities. Since these sub-groups represent a significant number of older adults with knee pain (Kadam et al, 2004; Stubbs et al, 2014), who often partake in reduced levels of physical activity (Yardley & Smith, 2002; Shiroma & Lee, 2010; Smith et al, 2015) yet may benefit from regular physical activity, this research is of clinical importance.

Optimising the measurement and reporting of safety domain outcomes will help improve the quality and confidence in the findings from future physical activity safety research. Future RCTs investigating physical activity in older adults with knee pain should ensure that adverse events are considered during protocol writing, during the trial itself and then explicitly reported within publications regardless of whether or not they occurred. Ideally, reporting detail should include how adverse events were monitored, graded, how frequent they were, as well as any attributions regarding cause (Ioannidis et al, 2004; Schulz et al, 2010). In order to give further clarity to the unclear risk of reporting bias (discussed in 3.5.1) RCTs should publish their protocols making it transparent a priori which safety outcomes they had investigated. In addition, where possible, reasons for trial drop-out should be clearly reported to allow judgements to be made regarding attrition bias (Higgins & Green, 2009; Schulz et al, 2010).

Future trials seeking to monitor progression of structural OA on imaging should consider also imaging the patellofemoral joint since this joint may also be affected by long-term physical activity and be clinically symptomatic (Duncan et al 2006; Peat et al, 2012), yet was not assessed in any of the studies within this systematic review. Following on from the discussion in 3.5.4 regarding the optimal length of time to detect radiographic OA structural changes, future studies investigating the progression of structural OA should either include radiographs with sufficiently long follow up for adequate responsiveness (two years or more) (Reichmann et al, 2011) or MRI which, although more expensive, has been considered a more reliable and responsive longitudinal measure of structural OA change (Guermazi et al, 2011; Hunter et al, 2011).

Since there is a dearth of evidence of sufficient follow-up length relating to the safety of long-term physical activity and progression to TKR (see section 3.5.4), the evidence base could be strengthened by carrying out UK case-control studies using joint registry data or long-term follow-up and survival analysis of inception cohorts such as the Osteoarthritis Initiative (OAI) (Nevitt et al, 2006), whilst adjusting for potential confounders such as socioeconomic status.

Measuring physical activity over the long-term is challenging. The majority of measures included in observational studies considered for inclusion within this review were either cross-sectional snapshots of physical activity level, not validated for measuring extended periods of physical activity, or at risk of recall bias. Future research using practical non-invasive wearable technology linked via applications to central databases that can capture physical activity level data over extended periods may help in this regard (Sun et al, 2015).

3.6 Chapter summary

This chapter used systematic review methodology to investigate the safety of long-term physical activity for older adults with knee pain. The premise was made that for long-term physical activity to be considered safe, it would not be associated with severe adverse events, increasing pain, decreasing physical function, progression of structural OA (as viewed on radiographs or MRI scans), increased incidence of TKR or increased use of analgesics. In order to capture the best evidence regarding each of these domains, a comprehensive search of multiple electronic databases was carried out looking for RCTs, case-control studies and prospective longitudinal cohort studies. To be included in the systematic review these studies had to have investigated some form of physical activity explicitly carried out for three months or more, in older adults with knee pain, that included a measure of at least one of these safety domains.

In summary, drawing on the narrative synthesis of evidence from 48 included RCTs and one case-control study, therapeutic exercise was found to be safe for most older adults with knee pain; however, a minority of participants experienced increased pain and a few individuals experienced moderate adverse events such as falls. There was insufficient evidence relating to other categories of physical activity and this limits the generalisability of the findings to all types of physical activity. More research is required investigating the safety of other categories of physical activity and specific comorbid sub-groups.

The safety findings from this systematic review provide the foundations for this PhD thesis. With the premise that long-term therapeutic exercise is safe for most older adults with knee pain (and an absence of evidence suggesting that other categories of physical activity to be unsafe), Part 2 of the investigates whether changes in physical activity level per se is associated with future clinical outcomes of pain and function (chapter 6). In order to further understand physical activity behaviour in this population this thesis is also interested in whether attitudes and beliefs about physical activity are associated with and can predict future physical activity level. Thesis Parts 3 and 4 investigate the cross-sectional and longitudinal associations between attitudes and beliefs about physical activity and physical activity level. The subsequent chapters 4 and 5 introduce the datasets utilised in addressing the remaining research questions.

Chapter 4

The Benefits of Effective Exercise for knee Pain (BEEP) trial dataset

4.1 Chapter introduction

This chapter introduces the Benefits of Effective Exercise for knee Pain (BEEP) randomised trial and dataset utilised within Parts 2, 3 and 4 of this thesis. It aims to familiarise the reader with the BEEP trial patient sample and variables measured in order to aid future interpretation of the thesis findings. The chapter begins by highlighting why the BEEP dataset was selected as an appropriate one with which to answer the research questions summarised previously (chapter 1, section 1.3). The BEEP trial rationale and methods are then summarised before describing the sample baseline characteristics, followed by a summary of results pertinent to this thesis, including clinical variables, physical activity level, and attitudes and beliefs about physical activity at baseline, three and six months follow-up. The chapter ends with a concise discussion of some key considerations in using the BEEP dataset within this thesis.

4.2 Reasons for selecting the BEEP trial dataset

The BEEP trial dataset was selected for quantitative secondary data analysis within this thesis because it included older adults with knee pain, validated clinical outcomes of pain and function (Bellamy et al, 1988; Pham et al, 2003), measures of physical activity level (Washburn et al, 1993) and measures of attitudes and beliefs about physical activity (Resnick & Jenkins, 2000; Resnick, 2005) which have been both theorised and shown in joint pain populations to be associated with physical activity level (Biddle & Mutrie, 2008; Der Ananian et al, 2008; Hutton et al, 2010). Furthermore, the trial data was suitable for use as a longitudinal cohort allowing both the cross-sectional and longitudinal research questions posed within this thesis to be addressed. Data at multiple time-points were utilised including baseline, three and six months. These time points were selected because the trial interventions lasted up to six months (hence change in physical activity level from baseline was most likely to occur in this time-period), six months was the primary trial follow-up time-point and additional reminders were sent to optimise questionnaire response and minimise missing data at his point. Furthermore, these time points were pragmatically available for analysis at the time of carrying out this thesis.

4.3 BEEP trial rationale and method overview

The BEEP trial was a pragmatic, multicentre, three arm parallel RCT primarily designed to test the clinical and cost-effectiveness of two physiotherapy-led physical activity interventions *("individually tailored exercise"* and *"targeted exercise adherence"*) compared to usual physiotherapy care (see Foster et al 2014 for the detailed trial protocol). In the subsequent methods section only elements relevant to the secondary data analysis carried out for this thesis will be reported and discussed. These include participant recruitment, treatment interventions, available variables and the handling of missing data.

4.3.1 Participants

The BEEP trial included 514 adults aged 45 years and older with current pain and/or stiffness in one or both knees. Participants were recruited from 65 general practices in the midlands and northwest regions of England and were identified by one of three methods: 1) records of those consulting at their general practice in the last year with knee pain, 2) a population survey that identified those with knee pain who had a chronic pain grade of between two and four (Von Korff et al, 1992) and, 3) referrals to physiotherapy from general practice for knee pain (Foster et al, 2014).

Exclusion criteria comprised those who had received an exercise programme from a physiotherapist or a knee joint injection in the last three months, those residing in nursing home accommodation or those unable to get to physiotherapy treatment centres. In addition, those with serious pathology (for example inflammatory arthritis or malignancy) or those with knee pain caused by a recent trauma (sports injury, fall or accident) were also excluded, as were those who had undergone joint replacement surgery on the affected limb or were on the waiting list for such surgery. Finally, those for whom physical activity interventions were contra-indicated (such as those with unstable cardiovascular disorders, severe hypertension, unstable angina or congestive heart failure) were also excluded (Foster et al, 2014).

4.3.2 Intervention arms

All three intervention arms were delivered in one of five NHS physiotherapy services, by a team of 47 physiotherapists (15 delivered usual care (UC), 17 delivered individually tailored exercise (ITE) and 15 delivered targeted exercise adherence (TEA)). All participants received an advice and information booklet in addition to the physical activity programme. They could also receive other physiotherapy interventions if deemed appropriate (e.g. manual therapy and electrotherapy) but the emphasis of the treatment was exercise. All participants were allowed to access other care settings and this was recorded (though very few received treatments other than exercise within the trial) (Foster et al, 2014, Hay et al 2015 under review)

I) Usual Care

The UC protocol was matched to usual UK physiotherapy practice (Holden et al, 2008) and comprised lower limb exercise selected from a template of commonly prescribed exercises (printed from PhysioTools computer software), including both weight-bearing and non-weight-bearing lower limb muscle strengthening and range of movement or stretching exercises. These participants received up to four one-to-one treatment sessions over a 12 week period with limited scope for individualisation and progression (Foster et al, 2014).

II) Individually tailored exercise

The ITE intervention arm consisted of a supervised individually tailored and progressed lower limb exercise programme. It comprised individualised strengthening (both weight-bearing and non-weight bearing), stretching and balance exercises together with functional task training which was progressed in intensity during 6 to 8 treatment sessions over a period of 12 weeks. Physiotherapists facilitated patient goal setting, provided written, individualised and changing over time exercise sheets (printed from PhysioTools computer software) and encouraged the participants to maintain an exercise diary in order to self-monitor their progress and aid in the further progression and individualisation of the exercise programme over the treatment sessions (Foster et al, 2014).

III) Targeted exercise adherence

The TEA intervention group initially consisted of individually tailored and progressed lower limb exercises, as above, but then shifted emphasis to general physical activity adherence over time. In addition to the individualised lower limb programme, physiotherapists assessed patients' current general physical activity levels, their attitudes and beliefs towards physical activity, and their behavioural intentions to increase general physical activity. Participants in the TEA group received 4 treatment sessions in the first 12 weeks and a further 4 to 6 contacts from week 12 through to 6 months (totalling between 8 to 10 contacts over a 6 month period). Sessions from week 12 to 6 months could be via telephone or face-to-face with an emphasis on encouraging long-term physical activity engagement and adherence. Physiotherapists had an adherence enhancing "toolkit" of optional tools and techniques to use with BEEP trial participants based on their individual assessment and feedback. The toolkit included patient educational aids, behavioural aids, cognitive behavioural aids and local physical activity opportunities (full details are available in the published protocol of the BEEP trial, Foster et al 2014 with a summary provided in Appendix IV).

4.3.3 Outcome measures

I) Clinical outcome measures

The BEEP trial primary outcome measures were lower limb pain and physical function measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al, 1988). The WOMAC pain subscale ranges from 0 to 20 (with 0 being no pain and 20 maximum pain on activity) and the function subscale ranges from 0 to 68 (with 0 being no disability and 68 being maximum disability). The WOMAC captures self-reported pain during activities and the degree of difficulty with everyday physical activities (Bellamy et al, 1988), is commonly used in OA research studies (allowing comparisons to other studies) and has been shown to have adequate face, content and construct validity as well as responsiveness and test-retest reliability (Bellamy et al, 1988; McConnell et al, 2001). "*Validity*" in general relates to the degree to which an instrument measures the construct it appears to measure (Polit & Yang, 2015). "*Reliability*" in general relates to the extent that a measurement is free from measurement error and the extent to which scores for people who have not changed are the same for repeated measures, whilst responsiveness relates to the ability of a measure to detect change in a construct when it has occurred (Mokkink et al, 2010; Polit & Yang, 2015).

Also of interest to this thesis was the proportion of participants classified as *"treatment responders"* measured by the internationally agreed Outcome Measures in Rheumatology Clinical Trials (OMERACT-OARSI) clinical responder criteria (Pham et al, 2003, 2004). This criteria dichotomises individuals into those deemed to have responded or not to treatment. The OMERACT-OARSI responder criteria was developed as a single universal measure of clinically important symptom change post intervention within RCTs of adults with OA that would allow comparison across studies (Pham et al, 2004). It includes consideration of both relative and absolute change of multiple clinically important outcome domains of pain, function and patient global assessment of change. Participants met the OMERACT-OARSI response criteria if a) relative change in WOMAC pain or function was ≥50% and absolute change was ≥20% or b) at least two of the following were satisfied: relative change in pain ≥20% and absolute change ≥10% or participants reported they were "better", "much better" or "completely recovered" on a 6 item global rating of change question (van der Windt et al 1998, Pham et al 2004). Absolute change was measured from baseline to follow-up and relative change calculated by dividing absolute change by the baseline score. Both of these scores were calculated after re scaling the WOMAC pain scores from 1 to 101 to avoid dividing by 0 during the calculation of relative change (EN personal communication). Box 4.1 below provides the algorithm for participant categorisation:

Box 4.1 OMERACT-OARSI responder criteria (Pham et al, 2003)

High improvement in pain or function ≥ 50% and absolute change ≥ 20

YES= RESPONSE

NO

Improvement in at least 2 of 3 from:

- Pain ≥ 20% and absolute change ≥ 10
- Function ≥ 20% and absolute change ≥ 10
- Patient's global assessment ≥ 20% and absolute change ≥ 10

YES= RESPONSE

NO= NO RESPONSE

Footnote: Relative change = $\%\ of\ change = (\frac{final\ score\ minus\ baseline\ score}{baseline\ score}) \times 100$

Absolute change = $final\ score - baseline\ score\ (on\ a\ 1 - 101\ interval\ scale)$

Limitations of the scale are that in dichotomising any continuous outcome measure some information is lost (Szklo & Nieto, 2014), in particular the measure is unable to pick up if clinical outcome actually deteriorates, and furthermore since it measures change in an individual from baseline within RCTs it is likely to include both regression to the mean and placebo effect due to treatment (Barnett et al, 2005). An additional consideration is that, by including both a relative and absolute change in pain, participants with lower baseline pain and function scores may be less able to meet absolute change requirements.

II) Physical activity level measures

Physical activity level was measured within the BEEP trial by the Physical Activity Scale for the Elderly (PASE) (Washburn et al, 1993) and through accelerometry on a sub-sample of participants. The PASE, as briefly introduced in chapter 2, section 2.7, is a self-report measure of physical activity level which has been validated in a community sample of healthy adults over the age of 65 years old (Washburn et al, 1993). The scale is scored from 12 questions regarding the frequency and duration of household, leisure time, and work-related physical activity over the last week and is summed with weighting specific to the intensity of those activities (see Appendix V for additional detail on these questions and how the score is calculated). This general physical activity scale gives a continuous score from 0 to around 400 with higher scores indicating higher levels of physical activity (Washburn et al, 1993). The PASE has been shown to have adequate construct validity in terms of correlation with 6 minute walk test (r=0.35) and knee strength (r=0.41) in older adults with knee pain (Martin et al 1999) and good reliability in older adults generally as indicated by a test-retest intra class correlation coefficient of 0.75 over 3-7 weeks (Washburn et al, 1993). It has been used regularly in other RCTs and prospective cohorts of older adults with knee pain (Petrella & Bartha, 2000; Sharma et al, 2003; Dunlop et al, 2011; Bossen et al 2013; Felson et al, 2013; Fransen et al, 2014; Bindawas & Vennu, 2015). However, responsiveness has not been evaluated in older adults with knee pain and since the commencement of this thesis, the measure has also been associated with substantial individual measurement errors within older adults with hip pain and those following TKR as evidenced by minimal detectable change scores of 87 points and 93% respectively (Svege et al, 2012; Bolszak et al, 2014). Further critique of the measurement of self-reported physical activity level generally was provided in Chapter 2, section 2.7.

The BEEP trial also included a direct measure of physical activity level in the form of accelerometry. However, this was not used in the analyses of this thesis because it was only measured in a small sub-sample of participants (originally intended to be 90) and was prone to substantial missing data (likely *"missing not at random"*) (Sterne et al, 2009) (see section 4.3.4 for further explanation of categories of missing data). Only 28 participants provided complete baseline, three and six month data on key measures such as average counts per minute. The data was likely *"not missing at random"* since some factors that were unobserved were likely to be systematically associated with physical activity such as refusal to wear an accelerometer and forgetfulness with wearing the accelerometer which are potentially linked to adherence to the physical activity protocol per se. Hence, the accelerometer data was deemed neither appropriate for multiple imputation nor the complete case data large or valid enough for precise multivariable modelling and drawing robust inferences from (Babyak, 2004; Sterne et al, 2009; Olsen et al, 2012).

III) Attitude and belief measures

The BEEP trial dataset included measures of participants' attitudes and beliefs about exercise and physical activity. Both the Self-Efficacy for Exercise scale (SEE) (Resnick & Jenkins, 2000) and the Outcome Expectations from Exercise scale 2 (OEE) (Resnick, 2005) were included in the BEEP trial. These address important components of social cognition theories that are hypothesised to predict behaviour (introduced previously in chapter 2, section 2.12.2). The SEE scale is a nine item scale scored between 0 and 10 with higher scores indicating greater exercise self-efficacy (Resnick & Jenkins, 2000). It contains items relating to confidence in the ability to exercise three times a week for twenty minutes given potential barriers such as pain, being busy, feeling down and not having an exercise partner or enjoying exercise (a full list of items and precise phrasing is provided in Appendix VI) (Resnick & Jenkins, 2000). The OEE scale is split into two separate subscales with one focussing on positive outcome expectations (positive OEE) and the other focussing on negative outcome expectations of exercise (negative OEE) (Resnick, 2005). Both subscales are aggregated to be scored between 1 and 5 with higher scores indicating more positive outcome expectations for exercise (Resnick, 2005). The positive OEE subscale contains 9 items containing positive exercise outcome statements and a Likert scale of agreement. The statements relate to both physical and mental factors, for example, *"exercise improves my endurance for carrying out my daily activities"* and *"exercise makes my mood better in general"* (Resnick, 2005). The negative OEE subscale contains 4 items containing negative exercise outcome statements, for example, *"exercise is something I avoid because it may cause me to have pain"* and *"exercise makes me fearful that I will fall or get hurt"* (Resnick, 2005) (a full copy of the positive OEE and negative OEE subscale items are provided in Appendix VI). Both subscales were analysed individually to allow separate understanding of both positive and negative outcome expectations.

Both the SEE and OEE have been investigated for clinimetric properties in older adult populations (mean age 85) (Resnick & Jenkins, 2000; Resnick, 2005). The SEE is considered to have adequate construct and criterion validity being significantly associated with mental and physical health measured by the 12 item short form health survey and exercise activity in the previous three months measured by participation in aerobic activity (Resnick & Jenkins, 2000). It has some evidence for reliability in the form of internal consistency as indicated by a Cronbach's α of 0.92 (Resnick and Jenkins, 2000). Similarly, there is some evidence for the validity and reliability of the OEE in an older adult sample (Resnick, 2005). The positive and negative OEE have been shown to be significantly correlated with self-report physical activity measured by the Yale Physical activity Scale (Pearson's correlations of 0.32 and 0.34 respectively) and SEE (0.69 and 0.61 respectively). In terms of internal consistency, the positive OEE has a Cronbach's α of 0.93 and the negative OEE a score of 0.80. Despite being validated in general older adult populations, both scales also contain items relating to pain and hence are likely to be suitable for a knee pain population.

IV) Additional important variables for this thesis

The BEEP trial dataset included several other baseline variables of particular interest to this thesis including baseline characteristics of participants' sociodemographics (age, BMI and individual socioeconomic classification (ISC)) (Office for National Statistics, 2010), number of comorbidities, presence of widespread pain measured by the Manchester widespread pain criteria (pain reported in at least two sections of two contralateral limbs and in the axial skeleton plus pain duration of at least three months) (MacFarlane et al, 1996), depression measured by the Patient Health Questionnaire-8 (PHQ8) (Kroenke et al, 2001), and anxiety measured by the Generalized Anxiety Disorder-7 (GAD7) (Spitzer et al, 2006). These variables were of interest as they have previously been shown to be associated with either physical activity level, physical function or pain intensity in older adults with knee pain and hence may influence associations between other variables central to this thesis (Sale et al, 2008; Veenhof et al, 2012; Cleveland et al, 2013; Cruz-Almeida et al, 2013; Sinikallio et al, 2014; Stubbs et al, 2015).

4.3.4 Data analysis

The primary data analysis and results of the BEEP trial focused on between-group clinical effectiveness of the interventions (Foster et al 2014), but this is not the focus of this thesis, and is not reported here. Instead this section focusses on general analysis methods pertinent to this thesis, including the handling of missing data, recoding of variables and statistical adjustment of the intervention arms. The specific data analysis methods for each thesis research question are subsequently provided in chapters 6 to 8.

I) Handling of missing data

Complete case analysis was selected for the cross-sectional data analysis of baseline BEEP trial data (thesis Part 3) as there were very few missing data at this time-point (see table 4.1) and the assumption was made that complete case data analysis results would be very similar to the intended sample results (Taris, 2000). This analysis involved only using participants with complete data available. However, multiple imputation was utilised for the longitudinal analyses within this thesis, because there were greater levels of missing data over time as participants either dropped out of the trial follow-up (unit non-response) or did not complete all measures within the follow-up questionnaires (item non response) (see figure 4.1 and table 4.1 respectively) (Sterne et al, 2009). For this dataset 25 imputations were created. This process was carried out by the statistician responsible for the initial BEEP trial analysis (EN).

Multiple imputation involves replacing missing variable values with a set of plausible values that represent the uncertainty about the true value (estimated from other available data) and then subsequently combining the plausible values to get an estimation of the missing value (Sterne et al, 2009). It has the effect of producing a dataset with all the participants preserved, hence maximising the sample size for data analysis and improving precision of results (Sterne et al, 2009). It also seeks to reduce the bias associated with loss to follow-up and missing data (Sterne et al, 2009). Bias due to differential losses to follow-up is considered a type of selection bias and occurs when participants who are lost to follow-up over the course of a study are different from those remaining under observation throughout the study (Szklo & Nieto, 2014). Risk of bias due to missing data depends both on the reasons for missingness and the amount of missing data (Szklo & Nieto, 2014). Three categories of missingness have been defined in the literature. Data missing completely at random (MCAR), for example accidental loss of ten completely random cases, data missing at random (MAR), which is due to systematic differences between missing values and observed values that can be explained by differences in observed values, or data missing not at random (MNAR) in which there are systematic differences between missing and observed values even after observed data are taken into account (Sterne et al, 2009). MCAR data are likely to represent the least risk of bias. Although it is not possible to be certain using observed data (Sterne et al, 2009), an assumption of data missing at random was made since it is likely that missing values can be estimated from observed values.

II) Variable recoding and intervention arm adjustment

A number of variables from the original BEEP trial dataset were recoded for use in this thesis for various reasons, such as category number reduction for simplified clinical interpretation and creation of variables commensurate to existing literature. For example, individual participant comorbidities were recoded into three simplified categories: no comorbidities, one comorbidity and two or more comorbidities, whilst the BMI continuous value was calculated from height and weight and then also categorised into underweight/ normal, overweight and obese so baseline data could be compared to other samples. Finally, in order to model the potentially confounding effect of each BEEP trial intervention on the longitudinal associations investigated within this thesis, intervention arm was adjusted for as a covariate using multivariable modelling.

4.4 BEEP trial results

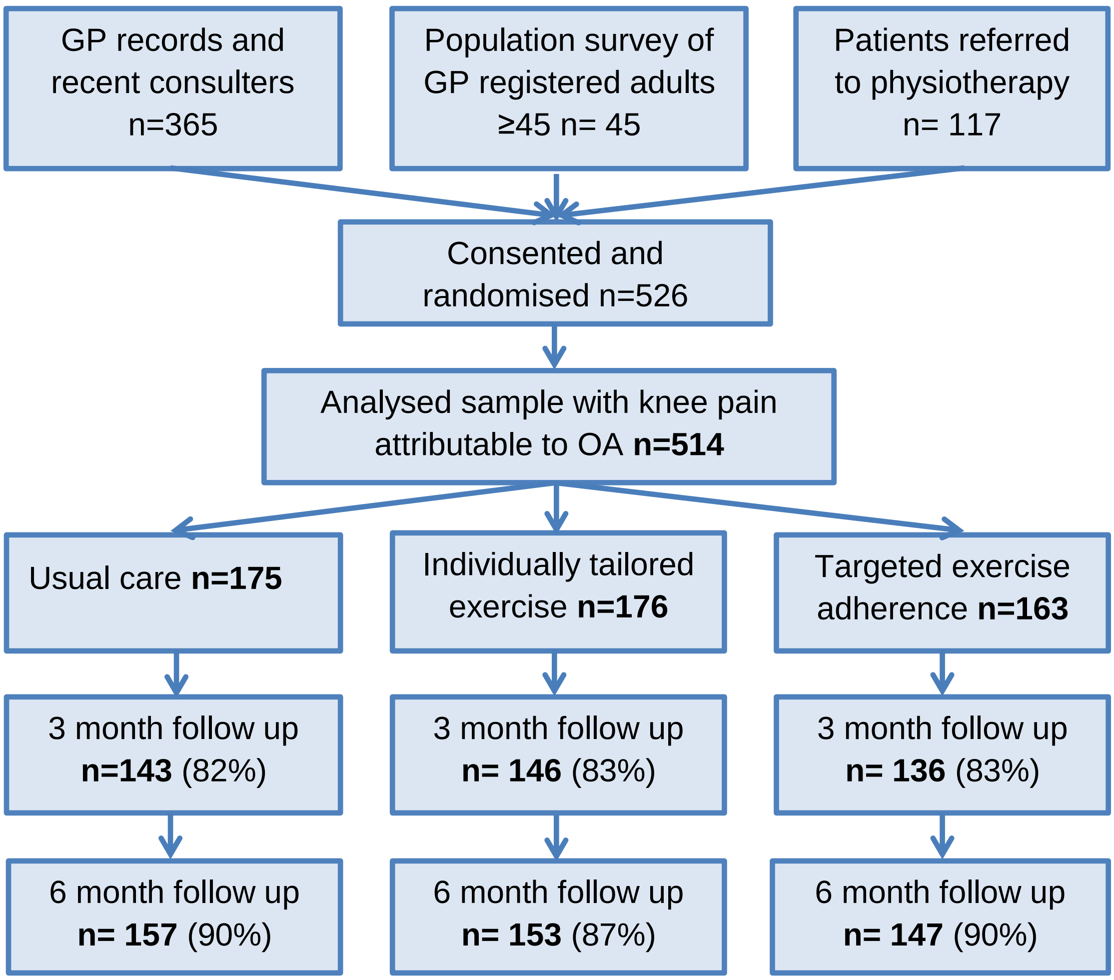
This section uses the BEEP trial dataset as a longitudinal cohort and presents the results that are of direct relevance to the thesis research questions. It serves as a precursor to more complex data analyses reported in Parts 2 to 4 of this thesis (chapters 6, 7 and 8). The results described include participant flow, participant baseline characteristics and outcome measures of WOMAC pain, function, OMERACT-OARSI responders, PASE, SEE scale, positive OEE and negative OEE scales at baseline, three and six months follow-up.

4.4.1 Participant flow

From the 526 older adults with knee pain who were randomised in the trial, 514 had knee pain attributable to OA and formed the dataset for analysis. Twelve were excluded as ineligible following physical assessment due to having other explanations of knee pain (such as referred back and hip pain). Of the 514 baseline participants analysed within the thesis, 425 (83%) provided outcome data at three months and 457 (89%) provided data at six months (figure 4.1). Those lost to follow-up had slightly worse knee pain and function at baseline, higher levels of anxiety and depression at baseline and were less likely to have used facilities for physical activity in the last 7 days (Hay et al, 2015 under review).

The specific numbers who provided data on clinical outcome measures, physical activity and attitude and beliefs towards physical activity pertinent to this thesis are also given in table 4.1. Looking at the trends for missing data, the levels of baseline missing data were very low (as would be expected in a RCT) rising to approximately 15-20% at three and six months for most measures. However, there were higher levels of missing data for physical activity level measured by the PASE which reached 30% missing data at three months.

Figure 4.1 Flow chart of the BEEP trial participant flow



Footnote: Percentages given refer to the participant proportion at follow up from each intervention arm.

Table 4.1 Participant missing data at each time-point for key BEEP variables

Variables	Number of participants providing data (% of 514))		
	Baseline	**3 months**	**6 months**
WOMAC pain	505 (98)	417 (81)	453 (88)
WOMAC function	504 (98)	414 (81)	452 (88)
WOMAC stiffness	509 (99)	422 (82)	456 (89)
OMERACT-OARSI response	N/A	403 (78)	445 (87)
PASE	463 (90)	358 (70)	386 (75)
SEE	501 (97)	421 (82)	405 (79)
Positive OEE	508 (99)	420 (82)	410 (80)
Negative OEE	508 (99)	419 (82)	411 (80)

Footnote: All percentages are proportions of complete data in relation to the baseline sample of 514

Abbreviations: OEE=Outcome Expectations for Exercise; OMERACT-OARSI=Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International; PASE=Physical Activity Scale for the Elderly; SEE=Self-Efficacy for Exercise; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

4.4.2 Baseline characteristics

The baseline characteristics of the 514 trial participants are summarised in table 4.2. The sample contained similar proportions of men and women with a mean age of 63 years (range 45 to 90 years old). The majority of participants were categorised as being either overweight (42%) or obese (39%) with a mean BMI of 29.6 (standard deviation +/-5.6). In terms of clinical severity, participants had a mean WOMAC pain score of 8.4 (s.d. +/-3.5), and physical disability a mean WOMAC function score 28.1 (s.d. +/- 12.2). The majority of the sample (76%) reported knee pain that had been present for more than one year. Just over two-thirds of participants reported at least one comorbidity (68%), and one-third reported more than two comorbidities.

Table 4.2 Summary of BEEP trial participant baseline characteristics

Characteristic	Total (n=514)
Age, *n* (%), years	
45-50	52 (10)
50-59	153 (30)
60-69	183 (36)
70-79	99 (19)
≥80	27 (5)
Gender, *n* (%)	
Female	262 (51)
BMI, *n* (%), *	
Underweight/ normal	97 (20)
Overweight	208 (42)
Obese	192 (39)
Employment status, *n* (%) *	
Currently employed	214 (42)
Socioeconomic category, *n* (%) *	
Professional	166 (43)
Intermediate	94 (25)
Routine and manual work	124 (32)
Comorbidities, *n* (%)	
Yes	350 (68)
1 comorbidity	180 (35)
2 or more comorbidities	170 (33)
High blood pressure	240 (47)
Angina/ heart failure/ heart attack	24/ 9/ 19 (5/ 2/ 4)
Asthma	67 (13)
Diabetes	66 (13)
PHQ 8, 0-24, mean (s.d.) *	4.0 (+/-4.7)
GAD 7, 0-21, mean (s.d.) *	3.3 (+/-4.5)
WOMAC, mean (s.d.)	
Pain, 0-20, *	8.4 (+/-3.5)
Function, 0-68, *	28.1 (+/-12.3)
Stiffness, 0-8, *	3.7 (+/-1.7)
Knee pain duration, *n* (%), years *	
< 1	125 (25)
1-5	198 (39)
5-10	94 (19)
10+	91 (18)
Widespread pain *n* (%) *	
Yes	79 (15)

Footnote: Baseline complete case analysis; *=subject to missing data (hence individual item frequencies may not add to total sample).

Abbreviations: GAD 7=Generalised Anxiety Disorder Questionnaire; PHQ 8=Personal Health Depression Questionnaire (higher scores indicate lower mood); s.d.=standard deviation; Widespread pain=Manchester Widespread Pain (MacFarlane et al, 1996); WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

4.4.3 Key BEEP trial results

Table 4.3 provides a summary of the relevant clinical, physical activity level and attitude and belief results over time from the BEEP trial multiple imputed dataset.

Table 4.3 Summary statistics from BEEP variables over time

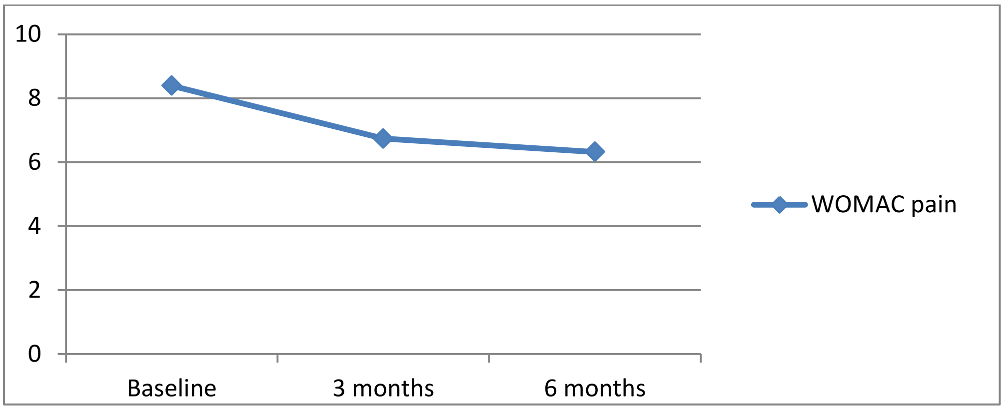
Variables (range)	Baseline	3 months	6 months
WOMAC pain (0-20)	8.4 (3.5)	6.7 (3.6)	6.3 (3.9)
WOMAC function (0-68)	28.1 (12.2)	23.6 (12.5)	21.7 (13.7)
OMERACT-OARSI responders (%)	NA	45	52
PASE (0-400+)	177.0 (83.3)	192.1 (87.9)	190.5 (89.3)
SEE (0-10)	5.4 (2.3)	5.7 (2.3)	5.6 (2.2)
Positive OEE (1-5)	3.9 (0.6)	4.0 (0.6)	4.0 (0.6)
Negative OEE (1-5)	3.5 (0.8)	3.8 (0.8)	3.8 (0.8)

Footnote: Multiple imputed data. All values are mean scores (standard deviation) except OMERACT-OARSI response which are given in percentages. All scores indicate higher levels of the variable except WOMAC function with higher scores indicating lower functioning.

Abbreviations: OEE=Outcome Expectations for Exercise; OMERACT-OARSI=Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International; PASE=Physical Activity Scale for the Elderly; SEE=Self-Efficacy for Exercise; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

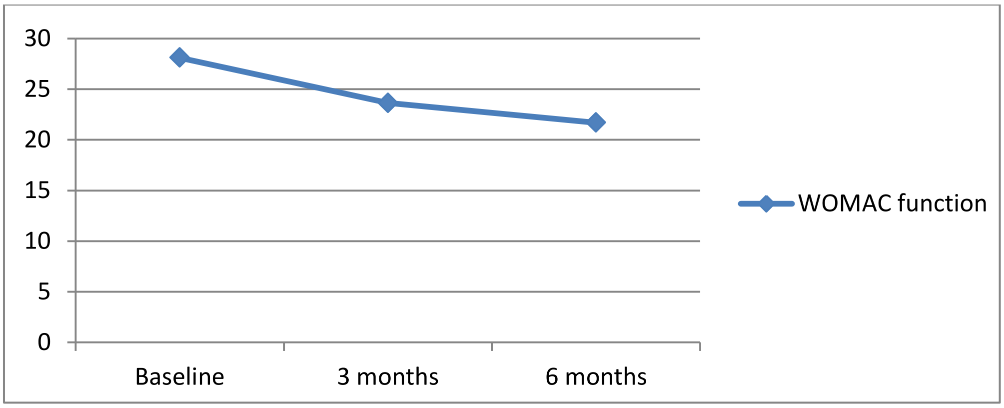
Both WOMAC pain and WOMAC physical function scores improved from baseline to three months with additional smaller improvements between three and six months (highlighted by figure 4.2 and 4.3). The baseline mean PASE physical activity level score was 177 and mean physical activity level showed modest increases at three months, rising to 192.1 (absolute increase of 15.1 from baseline) before it plateaued at six months at 190.5 (see figure 4.4). All three attitudes and beliefs about physical activity variables remained relatively stable over time with very small improvements from baseline to three and six months.

Figure 4.2 WOMAC pain over time



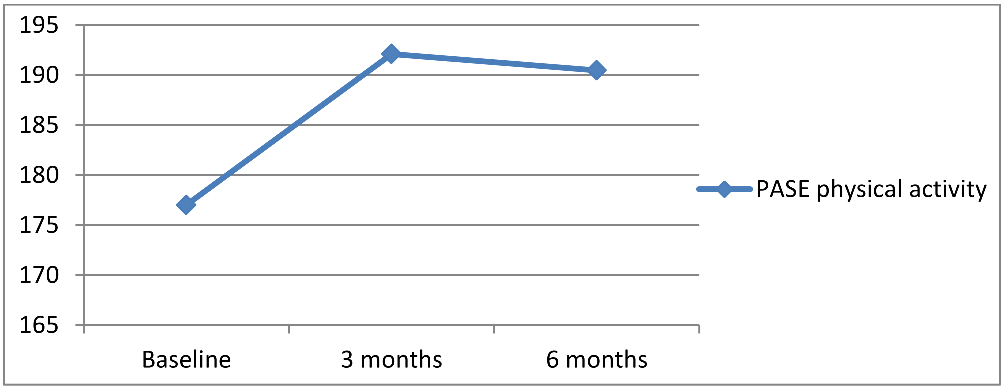
Footnote: Multiple imputed data; points plotted are mean scores.
Abbreviations: WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index (scale ranges from 0-20 with higher scores indicating higher levels of pain).

Figure 4.3 WOMAC function over time



Footnote: Multiple imputed data; points plotted are mean scores.
Abbreviations: WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index (scale ranges from 0-68 with higher scores indicating worse function).

Figure 4.4 PASE physical activity level over time



Footnote: Multiple imputed data, mean scores; N.B. Y axis starts at 165 not 0.
Abbreviations: PASE=Physical Activity Scale in the Elderly, multiple imputed data (scores range from 0-400+ with higher scores indicating higher levels of physical activity).

4.5 Key considerations in using the BEEP dataset for this thesis

This section discusses the BEEP sample in the context of other samples of older adults with knee pain within the literature. It considers the dataset results in terms of the thesis research questions considering sample size, missing data and outcome measures as well as the strengths and limitations of using a RCT as a longitudinal cohort for secondary data analyses.

4.5.1 Baseline characteristics in context

Comparing the BEEP trial sample to other samples of older adults with knee pain is helpful in drawing inferences about the generalisability of the findings within later chapters of this thesis. Considering the sociodemographics and clinical characteristics of the BEEP sample; participants were of similar age, BMI, knee pain severity and disability to other UK RCT samples of older adults with knee pain who consult in primary care (Hay et al, 2006; Foster et al, 2007) which allows confidence in generalising the sample to similar trial populations. However, BEEP trial participants had more severe knee pain and functional problems than general community samples of older adults with knee pain who may or may not be consulting a healthcare professional (O'Reilly et al, 1999; Jinks et al, 2002; Thomas et al, 2002; Peat et al, 2006b; Holden et al 2014). This finding is expected considering most of the BEEP trial sample came from health care consulters who often haver higher levels of pain and disability than the general community population with knee pain (Bedson et al, 2007). One difference from comparable UK samples was the roughly equal proportion of males and females within the BEEP trial sample, as many other research studies of knee pain in older adults include a higher proportion of female participants (Hay et al, 2006; Foster et al, 2007; Holden et al, 2015). Furthermore, previous research suggests that participants with certain sociodemographic characteristics such as the oldest adults may be underrepresented generally within trials (Bartlett et al, 2005). Comparing to existing surveys of older adults with knee pain in the community, who themselves may underrepresent the most elderly (Peat et al, 2006b, Holden et al, 2015), confirms this since only 5% of the BEEP trial sample were 80 years or older (compared to 6% and 10% in the referenced comparison studies).

Interpreting and comparing baseline physical activity level as measured by the PASE within the BEEP trial dataset is not straightforward as the scale does not equate simply to either minutes spent in different intensities of activity or benchmarks of physical activity required to meet physical activity guidelines (Washburn et al, 1993). To the author's knowledge, there are no previous UK RCTs including samples comprised exclusively of older adults with knee pain who completed the PASE. However, it is possible to compare the PASE scores to other similar international populations of older adults with knee pain who used the measure. The BEEP trial sample had roughly comparable PASE scores to similar samples from the US (Sharma et al, 2003; Neogi et al, 2010; Dunlop et al, 2011; Bindawas & Vennu, 2015) and a cohort of Australian male older adults with knee pain (Fransen et al, 2014). This suggests the physical activity levels within the BEEP trial sample are roughly generalizable to other populations of older adults with knee pain. These samples had mean PASE scores ranging from 120 to 182. Two comparison samples with slightly lower PASE scores either had higher BMI (Bindawas & Vennu, 2015) or older mean age (Fransen et al, 2014) which may account for this (Stubbs et al, 2015).

Comparing the attitude and belief about physical activity scales (SEE and OEE) to other populations of older adults with knee pain is challenging due to the dearth of available literature. Self-efficacy for exercise at baseline within the BEEP trial sample (mean score 5.4) was slightly lower than a comparable US sample of older adults with knee pain (mean score 6.3) from a lifestyle physical activity RCT (Sperber et al, 2014). Outcome expectations for exercise has not, to the authors knowledge, been measured in older adults with knee pain using the OEE scale (Resnick, 2005), however, the BEEP trial findings were comparable to an older US population without knee pain (Resnick, 2005) and other populations of older adults with arthritis generally report similar positive health outcome expectations with regular physical activity (Hutton et al, 2010). In conclusion, the clinical outcomes, physical activity measure and attitude and beliefs about physical activity data from the BEEP trial are roughly comparable to similar populations of older adults with knee pain.

4.5.2 Considerations for future thesis research questions

To be suitable for answering the research questions in this thesis, the dataset needed to be sufficiently large, without high loss to follow-up and demonstrate a sufficient change in mean physical activity level over time. Considering these in turn, the dataset of 514 appears sufficiently large for multivariable model building (Szklo & Nieto, 2014) and this was also further investigated with post-hoc power analyses following model building within Parts 2, 3 and 4 of the thesis. Missing data levels were generally very low at baseline, allowing complete-case analysis to be considered appropriate for thesis Part 3 (and the assumption to be made that the associations of interest between attitudes and beliefs about physical activity and physical activity level in the complete cases is likely to be very similar to that of the whole sample). Missing data over time at three and six months appears acceptable for the majority of salient variables (less than 20%) although the level of missingness in the physical activity level data at three months was of more concern at 30%. Missing data at three and six month follow-ups for longitudinal data analyses were hence managed with multiple imputation. Although multiple imputation preserves sample size, risk of bias due to missing data leading to selection bias remains higher for the longitudinal data analyses especially if any of the data were not missing at random (Sterne et al, 2009). This is a limitation and particular threat to the internal validity of Part 4 of the thesis when physical activity at three and six months is the outcome variable of interest.

In addition, the analyses used to address the research questions investigating the associations between change in physical activity level and future clinical outcome (thesis Part 2) require sufficient change in PASE over time. There was modest mean change in physical activity level between baseline and three months (absolute change 15.1) but not between three months and six months (absolute change -1.6). Hence the analysis included the change in PASE measured between baseline and three months. It was originally planned to model change in physical activity level and change in pain between three and six months in order to reduce the effects of regression to the mean immediately following trial inclusion from the analyses (this phenomenon is discussed in section 4.5.3 below). However, in the absence of meaningful change in physical activity level in this later time period this was not possible (chapter 6 describes the selected analyses in further detail).

The BEEP trial dataset captures important variables for research questions within this thesis, however, despite the PASE, SEE and OEE being validated in older adults and the rationale previously stated for using them in an older adults with knee pain sample (see section 4.3.3), some uncertainty remains regarding whether these measures have adequate content validity and are sufficiently responsive in such a sample. These points are discussed further in future chapters in relation to specific thesis analyses.

4.5.3 Using a trial as a longitudinal cohort for secondary analyses

The benefits of using the BEEP trial as a longitudinal cohort for secondary data analyses within this thesis were that the sample size was sufficiently large to consider multivariable analyses; data were readily available and included relevant variables to address the thesis research questions. Study attrition was relatively low in most variables and the sample relatively homogeneous (in terms of knee pain attributed to OA) due to the inclusion and exclusion criteria. Although it had higher levels of pain and worse function than community samples of older adults with knee pain, it was roughly similar in terms of physical activity level and attitudes and beliefs about physical activity to other samples of older adults with knee pain which allows some wider generalisability of the findings relating to these variables.

The limitations of using a trial as a longitudinal cohort are also noteworthy. The methodological design of RCTs that usually allow causation to be inferred (see chapter 3, section 3.3.2 for a full explanation) are no longer applicable when the trial data are utilised as a single longitudinal cohort. Any relationships between attitudes, beliefs, physical activity and clinical outcomes may be confounded by treatment effects or other variables. As a result statistical adjustment is required to manage confounding when interpreting associations between variables of interest to the thesis questions (Szklo & Nieto, 2014). Furthermore, since the trial was already underway with all participants recruited and in follow-up stages at the time of writing this thesis, there was no option for investigating additional attitudes and beliefs about physical activity or physical activity level measures. One of the major concerns in the use of trial data as a longitudinal cohort is the risk of regression to the mean. This statistical phenomenon occurs when unusually large or small measurements tend to be followed by measurements that are closer to the mean (Davis, 1976; Barnett et al, 2005). In the case of older adults with knee pain entering the BEEP trial, it is likely that participants consult healthcare professionals (in two of the three methods of identification of BEEP trial participants) and enter the trial when their symptoms are relatively severe. This may mean that their symptoms are likely to improve in the following months due to the natural fluctuation of knee pain (Neogi, 2013). Whilst this effect would tend to be evenly spread amongst intervention arms and hence not alter treatment effect size in the original trial analysis, it is more of a threat to the internal validity of the secondary data analyses within this thesis as it may impact on secondary associations between physical activity level and clinical measures over time.

4.6 Chapter summary

This chapter summarised the BEEP trial and the key clinical, physical activity level, and attitudes and beliefs about physical activity variables from 514 older adults with knee pain within the dataset that is used in Parts 2, 3 and 4 of this thesis. Longitudinal data at baseline, three and six month follow-ups were described. Increases in mean self-reported physical activity level and improvements in pain and function were shown between baseline and three months, whilst attitudes and beliefs about physical activity remained relatively static over time. The next chapter describes a second dataset of older adults with knee pain from a cross-sectional community survey that is also used for secondary data analysis within this thesis.

Chapter 5

The Attitudes and Behaviours Concerning Knee pain study (ABC-Knee) dataset

5.1 Chapter introduction

This chapter introduces the Attitudes and Behaviours Concerning Knee Pain (ABC-Knee) study and dataset that is utilised within Part 3 of this thesis. It aims to orientate the reader to the ABC-Knee sample and the variables measured within the dataset in order to aid future interpretation of the findings from Part 3. The chapter begins by highlighting why the ABC-Knee data set was selected for analysis within this thesis. Background to the study rationale and methods are then summarised before providing the cross-sectional sample characteristics and results focussing on attitudes and beliefs about physical activity, physical activity level and clinical variables. The chapter ends with a discussion about key considerations for using this dataset within the thesis, including its strengths and limitations for this purpose.

5.2 Reasons for selecting the ABC-Knee study

Many of the reasons for selecting the ABC-Knee dataset for secondary quantitative data analysis within this thesis were similar to the reasons for selecting the BEEP dataset (chapter 4, section 4.2). The ABC-Knee data included a sub-group of older adults with knee pain, a self-report measure of physical activity level (Matthews et al, 2005) and measures of attitude and belief constructs about physical activity (Lorig et al, 1989; Vlaeyen et al, 1995; Terry et al, 1997) which have been theorised or shown in pain populations to be associated with physical activity (Biddle & Mutrie, 2008; Brady, 2011; Koho et al, 2011). Whilst there was some theoretical conceptual overlap between the attitude and belief constructs measured within the ABC-Knee dataset and the BEEP dataset, such as self-efficacy for exercise (Lorig et al, 1989; Resnick, 2005), the ABC-Knee data also included other theoretically distinct measures. For example, it contained a measure of fear of movement and harm (Vlaeyen et al, 1995) and a composite scale that comprised physical activity attitudes about vigorous activity, health outcomes, social benefits and tension release (Terry et al, 1997). Importantly, it also included a community sampling frame that is different from the sampling frame used for the BEEP trial (which comprised mostly healthcare consulters). Using these two different sampling frames within Part 3 of the thesis allowed more confidence in generalising inferences about the relationships between attitudes and beliefs about physical activity and physical activity level than from using the BEEP data alone.

5.3 The ABC-Knee study rationale and method overview

The ABC-Knee study explored attitudes and beliefs about physical activity and physical activity behaviour in adults aged 50 years and older (Holden et al, 2012, 2015). It involved both a cross-sectional community sample questionnaire mailed to 2234 older adults and also a purposeful sub-sample of 22 participants who underwent semi-structured interviews (Holden et al, 2015). Only the 611 older adults who responded to the survey and reported knee pain were used for quantitative secondary data analysis within this thesis and will be discussed here. The sections below describe the participant sample frame, variables and the handling of missing data.

5.3.1 Participant sample frame and recruitment

Participants were drawn from a simple random sample of 2234 older adults (aged 50 years and over) in the community registered at a single large general practice in Cheshire (total practice population of adults aged 50 years and older, n=8158). All individuals were sent a cross-sectional questionnaire including a screening question regarding whether or not they had had knee pain in the previous 12 months (Jinks et al, 2004). Reminder postcards were sent out at two weeks and a second questionnaire was sent out to all non-responders at four weeks in order to optimise the response rate (Holden et al, 2012). Of the 1276 questionnaire responders (59% of the total sampled), there were 611 with knee pain who were included in the data analysis for this thesis. Unlike the BEEP trial, there were no exclusion criteria such as previous history of TKR or inflammatory arthropathy (which is likely to result in a more heterogeneous knee pain sample) and, due to the community sampling frame, the sample was not representative of those consulting healthcare practitioners for their knee problem.

5.3.2 Measures within the ABC-Knee dataset

I) Physical activity

Self-report physical activity level was measured using the Short Telephone Activity Recall Questionnaire (STAR) (Matthews et al, 2005) modified for use in survey form. This measure categorises individuals into three discrete physical activity levels: those who are *"inactive"*, those who are *"insufficiently active"*, and those *"meeting current guidelines"* (as defined by carrying out 30 minutes of moderate intensity physical activity at least five times a week in bouts of at least 10 minutes). The STAR measures frequency and duration of moderate and vigorous general physical activity carried out in a usual week based on three questions (a copy can be found in Appendix V). Its' clinimetric properties have been investigated in an adult population (mean age 46 years old) (Matthews et al 2005). The STAR has been validated against Actigraph accelerometry and physical activity recall in the previous 24 hours. The STAR showed adequate Pearson's correlations of 0.3-0.4 for its' three outcome categories with physical activity recall in the previous 24 hours but low correlations of 0.1-0.3 when compared to Actigraph accelerometry. In terms of 3 day test-retest reliability for meeting moderate, vigorous and overall recommended guideline levels of physical activity, the Kappa scores were inconsistent ranging from 0.46 to 0.81 (Matthews et al, 2005). In summary, the STAR benefits from being brief to administer and easy to interpret, although its clinimetric properties in older adults with knee pain are unknown.

II) Attitude and belief measures

Attitude and belief variables about physical activity within the ABC-Knee dataset included the Tampa Scale for Kinesiophobia (TSK) (Vlaeyen et al, 1995), the Arthritis Self Efficacy Scale (ASES) (Lorig et al, 1989) and the Older Persons Attitudes towards Physical Activity and Exercise Questionnaire (OPAPAEQ) (Terry et al, 1997). These measures are discussed below whilst additional scale details and item phrasing is provided in Appendix VI).

The TSK measures movement related fear of pain and (re)injury including catastrophic beliefs about pain with activity and harm (Vlaeyen et al, 1995). The original 17 item version of the TSK was used which produces a scale score from 17 to 68 with higher scores indicating greater fear of movement and re/injury (Vlaeyen et al, 1995). It was created based on the fear avoidance model (previously discussed in chapter 2, section 2.12.3). TSK scores have been shown to be associated with functional limitations in joint pain populations and have good construct validity as evidenced by significant correlations with a range of related measures including the Pain Catastrophising Scale, the Fear Avoidance Beliefs Questionnaire, the Beck depression inventory and pain intensity (Pearson's correlations ranging from r= 0.23 to 0.53) (Heuts et al, 2004; French et al, 2007).

In addition, the measure has acceptable internal consistency, Cronbach α= 0.84 (French et al, 2007).

The ASES measures perceived self-efficacy to cope with the consequences of chronic arthritis (Lorig et al, 1989). The original ASES scale contains three self-efficacy subscales that capture personal judgements of capability relating to domains of activity including pain management, physical functioning and a composite scale that captures physical activity, fatigue and mood (these subscales are named *"pain" "function"* and *"other"*). It has been frequently used in the older adult with knee pain literature as one scale and also as separate subscales (psychometric testing has been carried out on both the combined scale and individual subscales) (Lorig et al 1989, Brady, 2011; Brand et al, 2013). The ASES data within the ABC-Knee dataset was the self-efficacy for *"pain"* and *"other"* subscales (Lorig et al, 1989). Only the ASES *"other"* scale was included in the analysis within this thesis since half of its items relate directly to physical activity and its other three items may be indirectly related to physical activity (Lorig et al, 1989) (see Appendix VI for further detail). The ASES pain subscale was not considered an attitude and belief about physical activity scale since it only contains a single item directly related to physical activity. The ASES *"other"* subscale was scored from 10 to 100 with higher scores considered to indicate greater levels of self-efficacy for physical activity. The ASES *"other"* subscale has demonstrated construct validity in a sample of older adults with arthritis with significant Pearson's correlations between change scores with pain, disability and depression. It has good reliability in arthritis populations as evidenced by internal consistency (Cronbach's α= 0.87) and test-retest reliability (2-29 days between retesting intra class correlation coefficient= 0.90) (Lorig et al 1989). It is of note that the TSK and

ASES *"other"* also contain some items that measure illness perceptions that are related to attitudes and beliefs about physical activity (such as beliefs about the nature of pain, see Appendix VI for detail).

The OPAPAEQ is a composite scale of attitudes and beliefs about physical activity and exercise covering themes of *"tension release"*, *"health promotion"*, *"vigorous activity"* and *"social benefits"* (Terry et al, 1997). It was designed for older adults generally (Terry et al, 1997) but contains some items that relate to pain hence was deemed appropriate for older adults with knee pain. It produces a score between 14 and 70 with higher scores indicating more positive attitudes about physical activity and exercise (Terry et al, 1997). The OPAPAEQ is considered to have acceptable reliability in adults aged 50 years or over in the form of internal consistency of its theme components with Cronbach's alphas varying from 0.68-0.89 (Terry et al, 1997).

The dataset also included 23 individual attitude and belief statements about exercise modified from previous published exercise consensus (Roddy et al, 2005). However, after initial exploration, it was decided against using these individual statements since they had neither been developed into a cohesive scale nor validated, and much of their content overlapped with theoretical constructs that had been covered in the other included attitude and belief scales. For example, individual statements addressing attitudes about safety and enjoyment of physical activity overlap with items within the TSK and OPAPAEQ respectively. Furthermore, the use of such a large number of ordinal variables within multivariable model building would be both challenging to interpret and require a much larger sample size to avoid overfitting (Hosmer & Lemeshow, 2000).

III) Clinical measures and sociodemographics

The ABC-Knee dataset included the WOMAC subscales of pain, physical function and stiffness (Bellamy et al, 1988) (described in detail within chapter 4, section 4.3.3) and the Chronic Pain Grade (CPG) (Von Korff et al, 1992) which measures severity of pain and disability in the previous six months. The CPG categorises participants into 5 categories: category 0 is pain free, category I is low pain severity and low disability, category II-IV represent categories of high pain and increasing disability (Von Korff et al, 1992). It has been shown to be a valid and reliable measure of chronic pain severity in postal questionnaires (in terms of construct validity, convergent validity and internal consistency) (Smith et al, 1997) and has been used previously to categorise populations of older adults with knee pain (Peat et al, 2006a). In addition, the dataset included measures of comorbidities (recoded for multivariable analyses as a single categorical variable of “no comorbidities”, “one comorbidity” and “two or more comorbidities” from individual comorbidity data), depression (as screened by two questions about the frequency of feeling down depressed or hopeless and having little pleasure or interest in doing things) (Haggman et al, 2004), and previous use of exercise to treat knee pain in the last month. It also captured a range of sociodemographics including age, height and weight (which were recoded into BMI), work status, individual socioeconomic classification (Office for National Statistics, 2010) (collapsed and recoded into a three category variable of professional, intermediate and routine or manual occupations), and marital status.

5.3.3 Data analysis

The previous primary data analysis of the ABC-Knee study, external to this PhD thesis, involved descriptive statistics of attitudes and beliefs about physical activity and physical activity level and is presented elsewhere (Holden et al, 2012, 2015). Data analyses within this thesis began with the recoding and collapsing of some ABC-Knee variables (BMI, depression, socioeconomic classification, marital status, comorbidities and CPG) into a smaller number of categories to simplify their interpretability, improve comparison to other studies and reduce the likelihood of model overfitting in future multivariable modelling (Menard, 2010). Complete case analysis was selected for the cross-sectional data analyses of the ABC-Knee since the amount of missing data for key ABC-Knee measures was considered very low (see table 5.1). The specific ABC-Knee data analysis methods used within this thesis are described in detail in chapter 7.

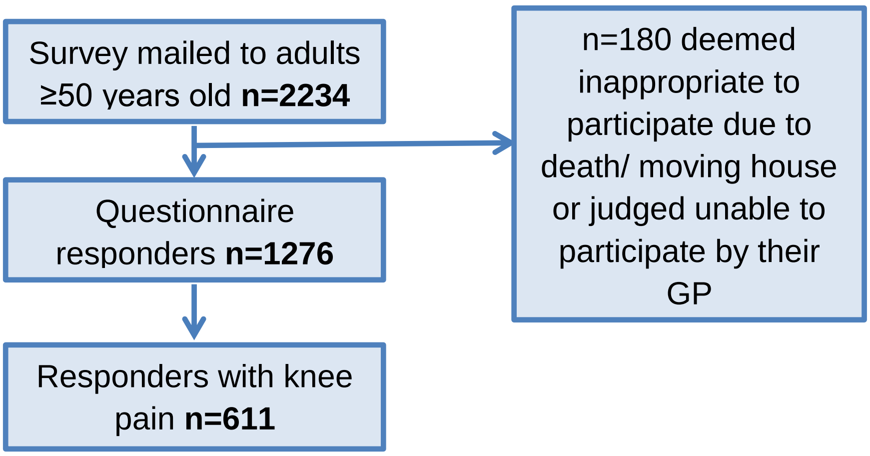
5.4 ABC-Knee results

This section describes the survey response, missing data and characteristics of the 611 older adults with knee pain from the ABC-Knee dataset utilised within this thesis.

5.4.1 Survey response

Of the 2234 GP registered older adults, there were 180 exclusions during the mailing process (e.g. due to death, moving house). There were 1276 survey responders (59%), of whom 611 reported knee pain (figure 5.1) (Holden et al, 2015).

Figure 5.1 Flow chart of the ABC-Knee study participant flow



5.4.2 Missing data

Proportions of missing data within the 611 older adults with knee pain were very low. A median of 95% and a range of 92-97% provided data for the key clinical, physical activity and attitudes and beliefs about physical activity measures used within this thesis (table 5.1).

Table 5.1 Participant missing data for key ABC-Knee measures

Variables	Number of participants providing data (% of total sample of 611 older adults with knee pain)
WOMAC pain (%)	591 (97)
WOMAC function (%)	585 (96)
STAR (physical activity) (%)	578 (95)
TSK (%)	563 (92)
OPAPAEQ (%)	585 (96)
ASES other (%)	580 (95)

Abbreviations: ASES other=Arthritis Self Efficacy Scale other domain; OPAPAEQ=Older Person's Attitudes towards Physical Activity and Exercise Questionnaire; STAR=Short Telephone Activity Recall Questionnaire; TSK=Tampa Scale for Kinesiophobia; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

5.4.3 Participant characteristics

The characteristics of the 611 responders with knee pain are summarised in table 5.2 overleaf. Fifty seven percent of the responders were female, the mean age was 65.5 years (ranging from 50 to 95 years old) and 60% of the sample were overweight or obese. In terms of clinical severity, the mean WOMAC score was 4.6 (s.d. +/- 4.2) for pain and 15.6 (s.d. +/- 15.1) for physical function. Knee pain had been present for less than three months in 58% of the sample. Of those with knee pain, 60% also reported one or more comorbidity whilst 26% reported two or more comorbidities.

Table 5.2 Characteristics of survey responders with knee pain

Characteristic	Total (n=611)
Age, *n* (%), years	
50-59	213 (35)
60-69	190 (31)
70-79	147 (24)
≥80	61 (10)
Gender, *n* (%)	
Female	349 (57)
BMI, *n* (%), KG/m^2 *	
Underweight	10 (2)
Normal	213 (38)
Overweight	228 (40)
Obese	115 (20)
Employment status, *n* (%) *	
Currently employed	185 (32)
Socioeconomic category, *n* (%) *	
Professional	212 (41)
Intermediate	121 (23)
Manual/ routine	189 (36)
With a partner, *n* (%)	442 (74)
Comorbidities, *n* (%)	
Yes	366 (60)
1 comorbidity	209 (34)
2 or more comorbidities	158 (26)
High blood pressure	283 (46)
Heart disease	79 (13)
Asthma	64 (11)
Diabetes	54 (9)
Other[a]	96 (16)
WOMAC, mean (s.d.) *	
Pain, 0-20,	4.6 (4.16)
Function, 0-68,	15.6 (15.10)
Stiffness, 0-8,	2.3 (1.98)
Chronic Pain Grade *	
Grade I	386 (67)
Grade II-IV	194 (33)
Knee pain chronicity, *n* (%) *	
≥ 3 months	241 (42)
GP consultation in the last year for knee problem, *n* (%)	152 (25)
Feeling down or depressed, n (%) *	
Often/ always	73 (12)
Little interest or pleasure in doing things, n (%) *	
Often/ always	54 (9)
Advised to exercise for knee pain, n (%) *	217 (37)
Used exercise for knee pain in last month, *n* (%) *	233 (40)

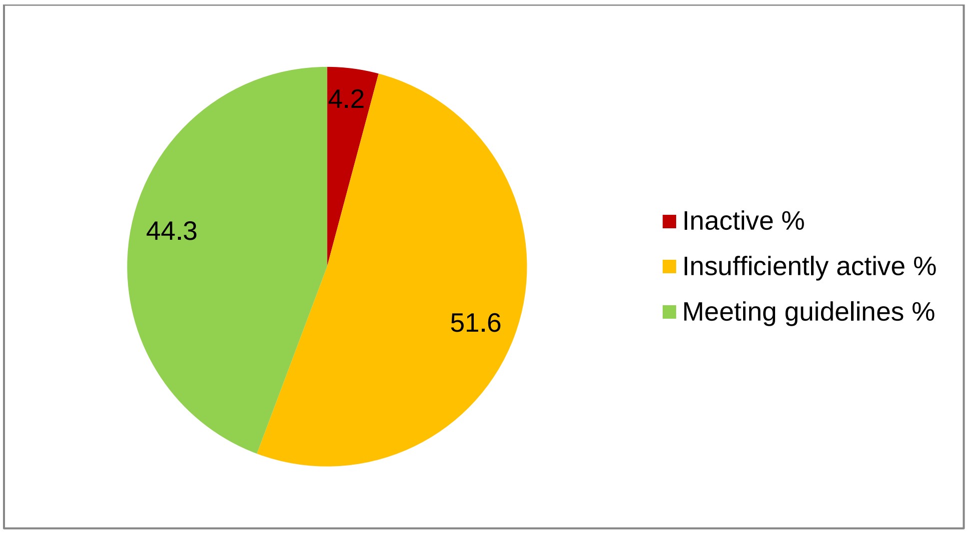
Key: *=subject to missing data (hence individual item frequencies may not add to total sample); [a]Includes stroke, cancer, Parkinson's disease and chronic bronchitis/emphysema.

Abbreviations: BMI=Body Mass Index; Chronic pain grade I=low disability low pain intensity, grade II=low disability and high pain intensity, III=high disability and moderate limitation of activities, IV=high disability and severe limitation of activities; GP=General Practitioner; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

5.4.4 Key ABC-Knee results

Less than half of older adults with knee pain in the community sample of the ABC-Knee study reported meeting recommended physical activity guidelines (44.3%), the majority were insufficiently active (51.6%) with a small group being inactive (4.2%) (figure 5.2). The mean scores and standard deviations of the attitude and belief scales are displayed in table 5.3 below (Holden et al, 2015). Key thesis variable mean scores are then displayed by STAR physical activity category in table 5.4. These data are displayed as a precursor to multivariable analyses later in the thesis and allow the observation of crude trends between physical activity level category and clinical severity/ attitudes and beliefs about physical activity to be viewed. The figures in table 5.4 appear to show trends of higher pain, lower function, increased fear of movement and harm, less positive attitudes about physical activity and less self-efficacy for physical activity associated with lower levels of physical activity. The *"inactive"* category appears to be particularly heterogeneous from the other two categories with a notably more severe clinical presentation and negative attitude and belief variable profile.

Figure 5.2 Physical activity level measured by the STAR



Footnote: previously published in (Holden et al, 2015)

Table 5.3 ABC-Knee attitude and beliefs towards physical activity

Attitude and belief variable (possible range)	Mean score (+/-standard deviation)
TSK (17-68)	35.5 (7.9)
OPAPAEQ (14-70)	52.8 (6.6)
ASES *"other"* (10-100)	64.6 (22.3)

Abbreviations and footnotes: ASES other=Arthritis Self Efficacy Scale other domain (higher scores interpreted to represent higher physical activity self-efficacy); OPAPAEQ=Older Person's Attitudes towards Physical Activity and Exercise Questionnaire (higher scores indicate more positive attitudes towards exercise and physical activity); TSK=Tampa Scale for Kinesiophobia (higher scores indicate greater movement related fear).

Table 5.4 Key variable mean scores by STAR physical activity categories

STAR category	Key clinical and attitude and belief variable mean scores				
	WOMAC pain	WOMAC function	TSK	OPAPAEQ	ASES "other"
Inactive	9.4	34.3	42.1	47.4	48.5
Insufficiently active	4.5	15.7	35.9	52.1	64.3
Meeting guidelines	4.3	14.0	34.4	54.3	67.3

Abbreviations and footnotes: ASES other=Arthritis Self Efficacy Scale other domain (scored from 10 to100, higher scores interpreted to represent higher physical activity self-efficacy); OPAPAEQ= Older Person's Attitudes towards Physical Activity and Exercise Questionnaire (scored from 14 to 70, higher scores indicate more positive attitudes towards exercise and physical activity); STAR=Short Telephone Activity Recall Questionnaire; TSK=Tampa Scale for Kinesiophobia (scored from 17-68, higher scores indicate greater movement related fear).

5.5 Key considerations in using the ABC-Knee dataset for this thesis

This section discusses the ABC-Knee dataset in comparison to the BEEP trial dataset and in the context of other samples of older adults with knee pain. It also considers the dataset in relation to future research questions within this thesis, including its inherent strengths and weaknesses for this purpose.

5.5.1 Participant characteristics in context

The participants within the ABC-Knee study represent a community sample of older adults with knee pain, many of whom had not consulted in the last year for their knee pain. They represent a different sample to the BEEP trial participants (described in chapter 4, sections 4.4.2 and 4.5.1), most of whom were recent knee pain consulters. Considering the sociodemographic characteristics of the 611

ABC-Knee participants with knee pain in comparison to the BEEP trial participants, those in the ABC-Knee sample were slightly older (mean age 65.5 compared to 63 years old) and more likely to be female (57% compared to 51%). The differences in mean age are expected given that RCTs tend to underrepresent the oldest adults often due to inclusion and exclusion criteria (for example the exclusion of those who have undergone TKR who tend to be older) (Peat et al, 2011). Fewer participants in the ABC-Knee sample were obese (20% compared to 39%) perhaps due to the associations between obesity and pain severity (Garver et al, 2014), and pain severity and consultation behaviour (Bedson et al, 2007) whilst fewer were currently employed (32% compared to 42%), potentially due to their older age. Overall, the knee problems of the ABC-Knee participants were also less clinically severe than the BEEP trial participants, with lower mean WOMAC pain (4.6 compared to 8.4), and function scores (15.6 compared to 28.1), indicating less pain and higher physical functioning. This finding is expected given that the ABC-Knee sample contained less healthcare consulters who are associated with greater clinical severity (Bedson et al, 2007). In terms of duration of knee pain, ABC-Knee participants had pain of a shorter duration overall, with the majority reporting pain for less than three months (58%), in comparison to the BEEP trial participants, who mostly reported pain for greater than a year (75%).

Overall levels of physical activity were low with 44% being sufficiently active to meet current guideline recommendations according to the self-report STAR. However, this is a higher proportion compared to most other existing studies measuring physical activity level in older adults with knee pain using accelerometry or pedometry (Wallis et al, 2013) (see chapter 2, section 2.10.3) and also higher than a study that measured self-report physical activity level (Shih et al 2006). Whilst there may be some fluctuation in physical activity across different samples, this may also suggest the STAR questionnaire has a tendency to over-estimate physical activity level when compared to other methods of measuring physical activity such as accelerometry and pedometry. This phenomenon has also been suggested in non-knee pain populations (Matthews et al, 2005). Comparing the ABC-Knee STAR physical activity levels to the self-report PASE physical activity levels within the BEEP trial is not currently possible since they are incommensurable.

Comparing the attitudes and beliefs about physical activity scale scores to other similar samples, the TSK scores in the BEEP trial sample (mean 35.5) were higher than a younger sample (mean age 51) of older adults with pain generally attributed to OA (mean TSK 28.3) (Heuts et al, 2004) and similar to a large sample of older adults with knee or hip pain (mean age 71.5, mean TSK 38.7) (Shelby et al, 2012). It is not possible to compare the ABC-Knee OPAPAEQ findings to other samples of older adults with knee pain, due to the lack of studies measuring this to the author's knowledge. The ASES *"other"* scale score was also similar to a number of samples of older adults with knee pain (Brand et al, 2013). In summary, the attitudes and beliefs about physical activity appear roughly generalizable to other populations of older adults with knee pain though different sample characteristics such as age may influence attitudes and beliefs between samples.

5.5.2 Considerations for future thesis research questions

The proportions of missing data in the ABC-Knee dataset for key thesis variables were generally very low, and ranged from 3 to 8%. Hence, complete-case analysis was considered appropriate for the ABC-Knee analysis in Part 3 of the thesis, since the risk of bias from such low levels of missing data is likely to be very low. The sample sizes of 611 was initially considered sufficient to carry out multivariable analyses, although post-hoc power calculations further investigated this and are discussed in chapter 7.

Strengths of the ABC-Knee dataset include its' easily interpretable physical activity level measure (Matthews et al, 2005), whilst it also includes theoretically important, and mutually exclusive measures of attitude and beliefs about physical activity that were not included within the BEEP trial dataset. The community sampling frame may represent a broader range of the total population of older adults with knee pain in the community in comparison to that of the BEEP trial dataset, and may also include older adults with less positive attitudes and beliefs towards physical activity who were less likely to enter an exercise trial (Bartlett et al, 2005). Using the findings from both the BEEP and ABC-Knee datasets will increase the generalisability of inferences about the relationship between attitudes, beliefs and physical activity in older adults with knee pain.

There a number of limitations to the ABC-Knee dataset including its cross-sectional nature, non-response bias, the broad screening method for knee pain, the sampling frame, and the clinimetric properties of the STAR and OPAPAEQ. Firstly, since the ABC-Knee pain dataset is cross-sectional in nature it is not possible to infer causation from its' data analysis since the temporal relationship between variables is not known (Hill, 1965; Szklo & Nieto, 2014).

Secondly, non-response to the ABC questionnaire may affect the generalisability of the findings. Although the response rate was considered reasonable (59%), because 41% of individuals who were sent questionnaires did not reply, the data is at risk of non-response bias (Armstrong & Overton, 1997). Non-response bias occurs when those who respond to questionnaires and provide data are systematically different to those who do not (Armstrong & Overton, 1997; Holden et al, 2015). Other observational studies of community samples of older adults with knee pain have suggested those who do not respond may fall into two categories, those who are younger, still in employment with minor episodes of knee pain and the most elderly with severe knee pain and comorbidities (Herzog & Rodgers, 1988; Peat, 2006b). Although these groups may be somewhat underrepresented in the ABC-Knee dataset, the descriptive statistics (see table 5.2) reveal a broad range of age, pain and comorbidities were still captured within the dataset so the effect of any non-response bias from the aforementioned groups may not be of critical concern to the generalisability of findings from future analyses. However, since it was clear the questionnaire was about attitudes, beliefs and physical activity it is possible that the least active older adults would be least interested, more likely not to respond and hence under-represented (Holden et al, 2015). Any non-response bias resulting from this is difficult to confirm or disprove but may have contributed to the relatively high levels of physical activity compared to other studies of older adults with knee pain (discussed in 5.5.1).

Thirdly, due to the broad method of screening for individuals with knee pain (any knee pain in the previous 12 months), some knee pain within the ABC-Knee dataset will likely be from causes other than OA, for example, pain associated with a recent injurious fall or pain associated with a recent joint replacement. This needs to be considered when drawing inferences about the generalisability of the findings. A further point regarding generalisability is that the participants were sampled from a single GP practice register in one area of the UK (Holden et al, 2015). This should be considered when applying the findings to other UK older adults with knee pain as the socio-demographics of registered patients vary between GP practices. For example, the Cheshire sample has a lower ethnic mix than the entire UK (Holden et al, 2015).

Although the majority of ABC-Knee dataset variables key to the analyses within this thesis have been validated in older adults with joint pain, the OPAPAEQ and STAR and have only been validated in general older adult populations (Terry et al, 1997; Matthews et al, 2005). The OPAPAEQ measures a broad range of attitude and beliefs about physical activity including perceived health benefits and one item regarding pain. Although, it is likely that the OPAPAEQ will remain reasonably valid for use in older adults with knee pain, given its general physical activity theoretical underpinnings and the inclusion of an item relating to pain (Matthews et al, 2005) its' clinimetric properties in this population are unknown. The STAR measure is easily interpretable and considered suitable for measuring physical activity at a population level, yet it is also associated with substantial individual classification errors (Matthews et al, 2005), and can only crudely differentiate individuals into three broad categories of physical activity level. As a result of its low number of discriminatory categories and since the vast majority (96%) of ABC-Knee participants were classified into just two categories (*"insufficiently active"* and *"meeting current recommended levels of physical activity"*), it may not ideally suited to detect associations with attitude and belief variables.

5.6 Chapter summary

This chapter summarised the cross-sectional ABC-Knee dataset of older adults with knee pain (n=611) containing sociodemographic, clinical, physical activity level and attitudes and beliefs about physical activity variables that will be used in Part 3 of this thesis. Descriptive statistics showed that less than half of the sample were meeting guideline recommended levels of physical activity. The relationship between attitudes and beliefs about physical activity and those who are *"inactive"*, *"insufficiently active"* and those *"meeting current recommended levels of physical activity"* will be investigated in chapter 7, adjusting for potential confounders. The subsequent chapter uses longitudinal BEEP data to explore if change in physical activity is associated with future clinical outcome.

Chapter 6

Change in physical activity level and future clinical outcome in older adults with knee pain

6.1 Introduction

This chapter investigates the association between change in physical activity level over time and future clinical outcome in terms of pain and function in older adults with knee pain and forms Part 2 of this thesis. This research question is important in understanding how exercise interventions work in improving pain and physical function (see chapter 2.10.2). In order to address this research question, it describes longitudinal data analysis of the BEEP dataset (introduced in chapter 4). Following a statement of the aim and objectives, the rationale for and description of the data analysis methods are provided. Descriptive statistics of change in physical activity level, pain and physical function statistics between baseline and three months are briefly highlighted before presenting the main results and discussing the findings.

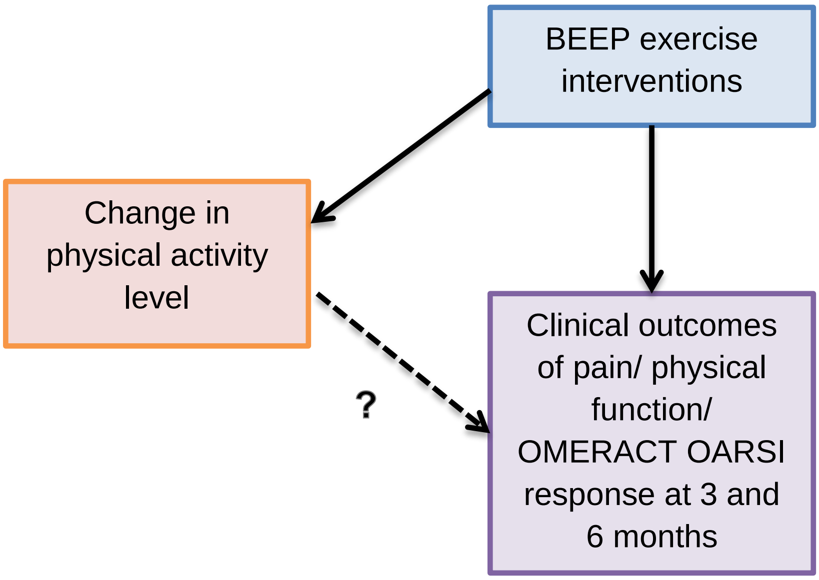
6.2 Chapter aim and objectives

The overall aim of this chapter was to investigate if change in physical activity level over time is associated with future clinical outcomes in terms of pain and physical function in older adults with knee pain. Using the BEEP dataset the specific objectives were to investigate if change in physical activity level between baseline and three months:

1. Is associated with pain and physical function at three months.
2. Is associated with pain and physical function at six months.
3. Can predict clinically important treatment response at three months.

A generic causal diagram for the relationships under investigation (the dashed line with a question mark) for this chapter is highlighted in figure 6.1 below.

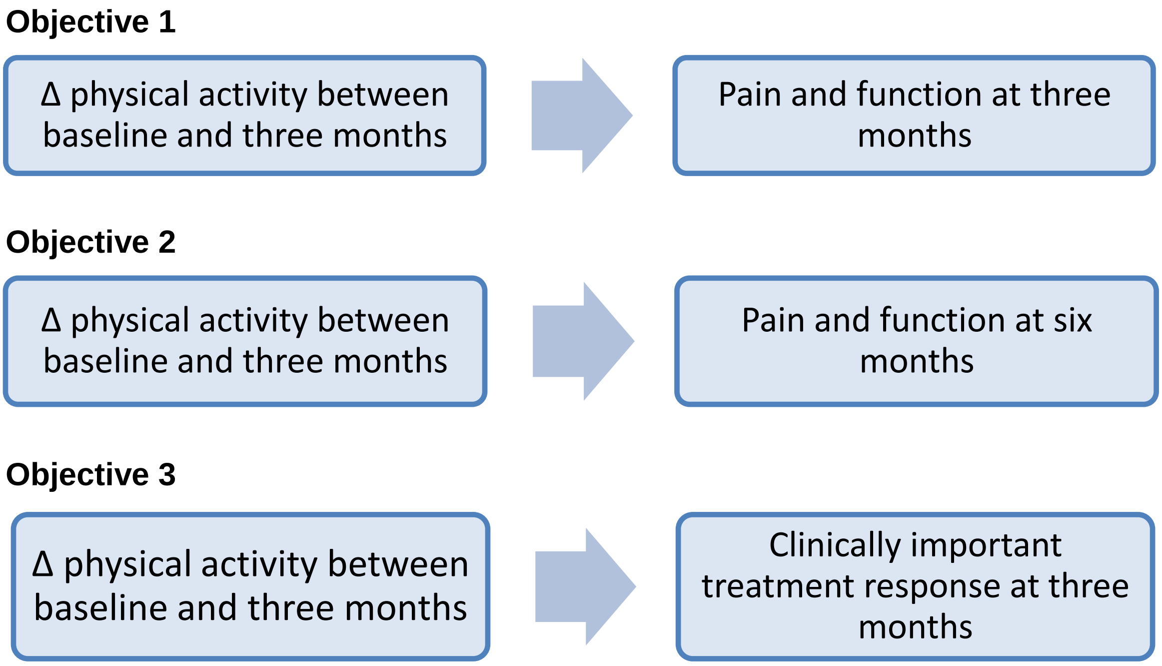
Figure 6.1 Change in physical activity level and clinical outcome



6.3 Causal structure hypotheses for chapter objectives

For objectives 1 to 3, the null hypothesis (H_0) was that change in physical activity level between baseline and three months would not be associated with future pain or physical function at three or six months. The alternate hypothesis (H_1) was that change in physical activity level, from baseline to three months, would be associated with pain and physical function at three and six months. These hypotheses were proposed based on existing literature showing exercise interventions are associated with less pain and higher physical functioning in older adults with knee pain (see chapter 2, section 2.10.1) (Fransen et al, 2015) and that lower pain and physical function have been associated with higher levels of physical activity (chapter 2, section 2.10.3) (Veenhof et al, 2012; Stubbs et al, 2015) (see figure 6.2 for alternate hypotheses).

Figure 6.2 Alternative hypotheses causal structures for chapter objectives



Δ = "change in", Arrows indicate hypothetical causational direction for the research questions in objectives 1-3

6.4 Methods

This section describes the methods and their rationale for the primary data analyses used within this chapter. It is structured by the three chapter objectives with the methods for objective 1 and 2 described together, due to their similarity, followed by the individual description of methods for objective 3. Similar methods and concepts are signposted back to their initial detailed description to avoid unnecessary repetition. Each method section begins by providing a brief overview then introduces the independent and dependent variables utilised before going on to describe univariable analyses and then multivariable model building. Sensitivity analyses for each objective are briefly described following the primary analyses. All data analyses for this chapter were carried out using multiple imputed data from the BEEP dataset using STATA version 13.1. (StataCorp. 2013. Stata

Statistical Software: Release 13. College Station, TX: StataCorp LP). Chapter 4, section 4.3.4 provides the rationale for using multiple imputed data.

6.4.1 Methods to address objectives 1 and 2

In order to investigate whether change in physical activity level between baseline and three months was associated with future pain and physical function at three and six months follow-up (objective 1 and 2 respectively), univariable unadjusted associations were explored initially, followed by adjusted multivariable model building using multiple linear regression.

I) Independent and dependent variables

Dependent variables for objective 1 and 2 were participants' pain and function (measured using the WOMAC pain and function scales at three and six months respectively). Independent variables are shown in table 6.1. The primary independent variable of interest was the absolute change in physical activity level (measured by the PASE). This was calculated by taking the PASE score at three months and subtracting the score at baseline (referred to henceforth throughout this thesis as *"change in physical activity"*). This time period was modelled since it showed the greatest mean change in physical activity level (see table 6.2).

A range of socio-demographic, attitudes and beliefs about physical activity and clinical covariates were also investigated as these may confound the relationships of interest within each objective. These variables were selected based on existing research and their biologic plausibility to act as confounders (see chapter 4, section 4.3.3, IV for further detail).

Table 6.1 Independent variables

Independent variables	Data type	Summary detail
Change variables		
Change in PASE	C	(higher scores=greater increase in activity level)
Change in WOMAC pain*	C	(higher scores=greater pain increase)
Change in WOMAC function*	C	(higher scores=deterioration)
Attitude and beliefs about exercise		
SEE	S	Range 1 to10 (10=highest self-efficacy)
Positive OEE	S	Range 1-5 (5=most positive expectations)
Negative OEE	S	Range 1-5 (5=least negative expectations)
Physical activity level		
PASE (baseline)	S	0-400+ (higher scores=higher physical activity level)
Sociodemographics		
Gender	D	Reference category male
Age	S	45 years and older
BMI	S	Higher scores=higher weight relative to height
Socioeconomic category	C	Three categories, reference professional
Work status	D	Reference working
Partner category	D	Reference no partner
Clinical variables		
WOMAC pain	S	Range 0-20 (20=highest pain)
WOMAC function	S	Range 0-68 (68=poorest function)
WOMAC stiffness	S	Range 0-8 (8=most stiffness)
Pain duaration	C	Four categories, reference <I year duration
Comorbidities	C	Three categories, reference none
Widespread pain	C	Reference no widespread pain
PHQ8 Depression	S	Range 0-24 (24=most depressed)
GAD7 Anxiety	S	Range 0-21 (21=most anxious)
Intervention arm	C	Three categories, reference usual care

Footnote and key: All independent variables measured at baseline except change variables; change scores calculated by subtracting baseline score from score at three months; *=objective 4 only; socioeconomic categories include “professional”, “intermediate” and “manual or routine”; Widespread pain= Manchester Widespread Pain.

Abbreviations: BMI=Body Mass Index; C=Categorical, D=Dichotomous, S Scalar; GAD7=Generalised Anxiety Disorder Questionnaire; OEE=Outcome Expectations for Exercise; PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health Depression Questionnaire; SEE=Self Efficacy for Exercise; WOMAC=Western Ontario and McMaster University OA index.

II) Univariable analyses

Univariable analyses allow an initial crude exploration of the relationships between the independent and dependent variables. They can cautiously be used to provide a precursor step towards generating hypotheses of potential causation and can inform clinical reasoning. They have also been used in the literature to contribute towards variable selection for multivariable model building, however, there is conflicting opinion on utilising them in this way since variables that have non-significant univariable associations may become significant when adjusted for additional covariates in a multivariable model (Szklo & Nieto 2014). Although crude univariable relationships are themselves at high risk of confounding, they are however helpful in understanding confounding by later comparing them to relationships from adjusted models (Szklo & Nieto 2014).

Crude relationships between change in physical activity, sociodemographic and clinical variables with pain and then subsequently function at three and six months follow –up were investigated using simple linear regression. Regression techniques are statistical techniques for estimating the relationship between variables (Szklo & Nieto, 2014). Simple linear regression is a mathematical equation to describe the relationship between two variables using a linear function (straight line) (Marill, 2004). Such modelling can provide statistics from the sample data that allow inferences to be drawn about larger populations (Sim & Wright, 2000; Marill, 2004). Full derivation of this model is described in detail outside of this thesis (Szklo & Nieto, 2014). Simple linear regression output provides information regarding the statistical significance of the association of the independent and dependent variable (p value) and also the magnitude and direction of the association with the dependent variable (β coefficient). In this context, it is superior to correlation which cannot provide information about the relative impact (magnitude) of change in physical activity on clinical outcome (Zou et al, 2003).

A number of assumptions are required for the appropriate use of simple linear regression. Firstly, the dependent variable must be interval or ratio, secondly, there must be a roughly linear relationship between the two variables investigated, thirdly, the variation of individual observed data points around the regression line (i.e. *"residuals"* or model prediction errors) must be constant (*"homoscedasticity"*), fourthly, the variation of data around the regression line must follow a normal distribution at all values of the independent variable, and lastly the independent variable deviation from the regression line should be independent of each other (Marill, 2004; Agresti & Finlay, 2009).

III) Multivariable analyses and model building

The multivariable relationship between change in physical activity, sociodemographics, clinical covariates and clinical outcome of pain and then subsequently function at three and six months was investigated using multiple linear regression. Two separate multivariable models were built for objective 1, with Model 3A investigating the outcome of pain, and Model 3B investigating function at three months. Similarly in answering objective 2, Model 6A investigated pain at six months and Model 6B investigated function at 6 months. Multivariable models such as multiple linear regression can be used to measure associations or predict outcomes of one variable acting on another whilst also controlling for the confounding effects of additional variables by including them within the model (Stoltzfus, 2011).

Confounding was introduced and briefly defined in chapter 3, section 3.3.2 (and is further illustrated in chapter 7, section 7.3.5). In prospective cohort studies, in addition to random differences between comparison groups, variables related to the independent predictor variable of interest may confound the association under study (Szklo & Nieto, 2014) (chapter 4, section 4.5.3). Confounding can be managed in longitudinal cohorts via the common analytical tools of stratification or by multivariable modelling (statistical adjustment) (Szklo & Nieto, 2014). Stratification involves splitting the results according to potential confounders and by so doing controlling for their effect. For example, any confounding effect of gender on the relationship between increase in physical activity and future pain could be explored by carrying out three separate analyses, one on male participants, one on female participants and one on the whole sample then comparing the findings. However, stratification is less well suited to multiple variables, or variables that are not easily categorised, and hence was not utilised within this chapter (Szklo & Nieto, 2014). Statistical adjustment, in multivariable analysis, refers to a series of analytic techniques based on mathematical models, which are used to carry out the estimation of association between an exposure and outcome, while controlling for one or more possible confounding variables (Szklo & Nieto, 2014). Statistical adjustment was selected for the data analysis within this chapter as it has the potential to account for multiple confounding variables that are both categorical and continuous (Katz, 2003).

Multiple linear regression is an expansion of simple linear regression for determining and quantifying the unique contribution of multiple independent variables to a single dependent variable (Katz, 2003). The model provides information regarding both the statistical significance of each individual independent variable, and also the magnitude of the association with the dependent variable (β coefficient), accounting for all other independent variables within the model. Assumptions for this model include those stated for simple linear regression in the above section. In addition, multivariable models need to be correctly specified, i.e. they should include all relevant variables and also fit the data (which means the predicted values should be close to the observed values) (Katz, 2003).

Multiple linear regression model building was carried out using a similar strategy of distinctive steps for objectives 1 and 2. An overview of these steps is provided in the figure 6.3 for clarity whilst detailed justification and rationale for decision-making at each stage is subsequently discussed.

Figure 6.3 Objectives 1 and 2 model building strategy overview

Step 1: Exploration of collinearity within covariates

- Pearson's correlations of continuous sociodemographic and clinical covariates
- Removal of one covariate from pairs of highly correlated variables (Pearson's correlation >0.7) based on clinical importance

↓

Step 2: Initial multiple linear regression model variable entry

- Each initial model included change in physical activity as well as baseline sociodemographics, clinical, attitudes and beliefs about exercise, and BEEP trial intervention arm covariates (remaining from step 1)

↓

Step 3: Iterative model building using backwards elimination

- Non-significant covariates were iteratively eliminated from the model until all remaining covariates were significant
- Change in physical activity, adjustment for baseline pain and BEEP trial intervention arm were held within the model regardless of significance (based on an a priori decision)

↓

Step 4: Diagnostics for final multivariable models

- Post-hoc check for adequate power
- Regression assumption checking diagnostics
- Post-hoc check for collinearity within the model using Variance Inflation Factor

↓

Step 5: Interpretation of models

- β regression coefficients, 95% confidence intervals and statistical significance interpretation
- Discussion of findings

Step 1

The first step in model building was to explore the independent variables for collinearity within the future multivariable model. *"Collinearity"* or *"multicollinearity"* relates to the phenomena whereby independent variables within a regression model are highly correlated with each other, potentially leading to spurious model output results due to explaining the same variance in the dependent variable (Tu et al, 2005). Pearson's correlations between pairs of independent variables were investigated followed by the removal of one variable from each pair of variables that were highly correlated (r of above 0.70). The decision of which of the highly correlated variables to remove was based on perceived clinical importance with the variable considered the least clinically important being removed. For example, in Model 3A, baseline WOMAC pain and stiffness were highly correlated, hence WOMAC stiffness was removed from the models, since stiffness is considered of less clinical importance than pain (Bedson et al, 2007). A further example from Model 3A was that baseline PHQ8 depression and GAD7 anxiety were highly correlated. Although both have been theoretically linked to pain modulation (Linton & Shaw, 2011) and were crudely associated with future pain outcome, GAD7 anxiety was removed as there is a greater body of evidence for the association between depression with knee pain severity in older adults with knee pain (Cruz-Almeida et al, 2013; Collins et al, 2014; Han et al, 2015).

Step 2

The second step was to enter absolute change in physical activity, the primary independent variable of interest, and all remaining baseline independent variables into an initial multiple linear regression model (Kutner, 2005). A priori, absolute change in physical activity was held within the model throughout future model building (since it is of primary interest in answering the research questions) along with the intervention arm variable and the baseline score of the dependent variable under investigation (for example baseline pain in the objective 1 pain Model 3A). Holding the intervention arm variable within the model adjusts for any treatment effect due to the intervention received within the BEEP trial. Adjusting for the baseline clinical severity of the outcome variable in effect ensures that change in clinical outcome (pain or physical function) is modelled (Allison, 1990).

Step 3

Step three involved model building using an author controlled *"backwards elimination"* strategy (as oppose to an automatic computer generated backwards elimination) (Greenland, 1989; Agresti & Finlay, 2009). This involved fitting an initial multivariable model including all the variables from step 2 and removing the variable whose regression coefficient was the most non-significant (largest *p*-value) and then refitting the model. This iterative process was continued until all remaining variables within the model (with the exception of the primary independent variable of interest and those held a priori regardless of statistical significance) were significant. Some authors recommend caution in using variable selection methods for model building based only on variable statistical significance since they may exclude clinically important variables or lead to the inclusion of variables that are not sensible (Greenland, 1989; Agresti & Finlay, 2009), however, since all the covariates included in the model had both theoretic plausibility and supporting research to be potential confounders and key variables relating to the research question were held a priori, this variable selection strategy was deemed appropriate and unlikely to lead to inappropriate variable selection.

Steps 4 and 5

Once the final models were built, post hoc power calculations for sufficient sample size, model assumption tests and collinearity checks were carried out. Adequate sample size is required in regression modelling for both sufficient power to reject the null hypothesis when it is false (*"type II error"*), and for precise estimates of model output independent variable regression coefficients (Maxwell, 2000; Sim & Wright, 2000). To paraphrase, power calculations in regression modelling relate to the ability of the model to detect statistically significant variable coefficients when they exist, and ensure confidence intervals (i.e. the uncertainty) around them are not too large. Regression models that contain too many independent variables for their sample size/outcome events are considered to be *"overfitted"* (Hosmer & Lemeshow, 2000). Overfitting is typically characterised by unrealistically large coefficients and or confidence intervals (Hosmer & Lemeshow, 2000; Menard, 2010). Current literature suggests multiple linear regression models should include around 2 to 15 outcomes per predictor variable to avoid overfitting (Green, 1991; Babyak, 2004; Austin & Steyerberg, 2015). Considering a conservative estimate, based on the 514 fully imputed outcomes in the BEEP dataset, and 15 outcomes per independent variable, the model could include 34 independent variables in the final model. Model assumptions were also checked post hoc by; using scatter plots and best fit lines to check for adequate linearity between independent and dependent variables; using residual versus fitted plots to check for homoscedasticity, and; using histograms of residuals to look for a normal distribution (bell shape with mean of zero) (Kutner, 2005; Agresti & Finlay, 2009) and normal-probability plots to check that the residuals follow a normal distribution throughout the range of values of the independent variables (Kutner et al, 2005;

Regression diagnostics UCLA Statistical Consulting Group. From: http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htmref, accessed: August 2015). A further test to investigate and quantify collinearity was subsequently carried out using the *"variance inflation factor"* (VIF) statistic (O'Brien, 2007). There is some debate in the literature as to what constitutes a cut point for unacceptable collinearity however, scores over 2.5 were considered as a cut off for high collinearity (Kutner et al, 2005; O'Brien, 2007; Allison, 2012 When can you safely ignore multicollinearity? From: http://statisticalhorizons.com/multicollinearity, accessed: July 2015). The final step was to report β coefficients, 95% confidence intervals and statistical significance from the multiple linear regression models and interpret the findings.

0) **Sensitivity analyses**

A number of alternative statistical models were considered for this chapter some of which were carried out as sensitivity analyses. Sensitivity analyses allow data analysis under more than one set of assumptions or models (Sim & Wright, 2000 Haynes et al, 2006). They can be useful as post-hoc tools to further explore or validate primary findings. Within this chapter, sensitivity analyses were used to validate primary findings (for example by using complete case analysis), to explore clinically meaningful categorical independent variables (for example dichotomous important increase in physical activity or not) and to adjust for different independent variables (for example intervention arm variable and WOMAC pain or function variables).

The first sensitivity analysis (Sensitivity analysis I) investigated complete case analysis. Since assumptions were previously made that missing data were missing at random (chapter 4, section 4.3.4), it is expected that the complete case analysis would be very similar to the multiple imputed analyses. Any potential difference may reduce confidence in the primary findings and or imputation process and warrant further exploration of the imputation process and or the data.

A subsequent sensitivity analysis was the minimally important change in physical activity model (Sensitivity analysis II). This analysis involved substituting the continuous absolute change in physical activity variable with a dichotomous *"minimal important physical activity increase"* variable (categorised into *"no"* as the reference and *"yes"* as the alternate category) to see if this predicted clinical outcome. This model is of interest since error in the measurement of the absolute PASE score may be responsible for modest changes in PASE score (Svege et al, 2012; Bolszak et al, 2014). Minimal important change has been defined in various ways within the literature but can primarily be split into distribution based or anchor based methods (de Vet et al, 2006; Revicki et al, 2006, 2008). Anchor methods require either patient input or clinical expertise consensus to determine a clinically important amount of change in the measure of interest or validated comparative measures (for example, accelerometry) or global ratings of improvement by participants (Revicki et al, 2008). Distribution methods include calculating half a standard deviation of the baseline measure value (Norman et al, 2003), using the standard error of measurement (SEM), and intra-class correlation (ICC), which are described in detail outside this thesis (de Vet et al, 2006, 2010, Polit and Yang, 2015). Since the clinical interpretation of the PASE is not intuitive in its scaling, and there was no available anchor (indeed there is no consensus within the literature as to what constitutes a minimal clinically important change in physical activity for older adults with knee pain) distribution methods were considered. However, since calculating the ICC and SEM require repeated measures in the absence of true change in physical activity (which occurred due to the BEEP interventions) only the half standard deviation of the baseline mean PASE score described by Norman and colleagues remained an option (this was calculated as 42). In addition, it was deemed appropriate that any important change score should still be larger than measurement error, hence a surrogate minimal detectable change score (MDC) (i.e. change greater than measurement error) from a sample of older adults with hip pain (87) (Svege et al 2012) was also used and the largest of the two numbers selected as the cut point for minimal important change (i.e. 87).

A further sensitivity analysis involved not adjusting for the intervention arm variable (Sensitivity analysis III). As the BEEP trial tested three physical activity interventions, it was considered important in the primary analysis to a-priori adjust for the intervention arm, which could potentially confound any relationship between change in physical activity and clinical outcome change. However, since there was no statistically significant difference in pain and function between the three intervention groups in the BEEP trial (Hay et al, 2015 under review), sensitivity analyses were carried out for each adjusted regression model without controlling for the intervention arm variable to explore if this altered the model output coefficients.

There is some debate amongst epidemiologists and statisticians as to whether to adjust for the same dependent variable or a surrogate marker of baseline clinical severity since this may lead to over-adjustment (Allison, 1990; Croft and Ogollah personal communication 2014). Although this is more likely to be the case if adjusting for independent measures of clinical severity at more than one time point (*"autocorrelation"* of independent variables) (Kutner, 2005), this uncertainty was addressed in the final sensitivity analysis (Sensitivity analysis IV) which substituted the WOMAC pain baseline adjustment with WOMAC function adjustment in the Model A pain outcome models and vice versa with the Model B function outcome models. By carrying out this sensitivity analysis it is possible to see if the results are altered by adjusting for an alternative baseline clinical severity variable.

6.4.2 Methods to address objective 3

In order to investigate if clinically important treatment response at three months can be predicted by change in physical activity, univariable unadjusted associations were explored initially, followed by adjusted multivariable model building using multiple logistic regression.

I) Predictor and outcome variables

Predictor variables used for objective 4 were identical to objectives 1 and 2 (section 6.4.1), however, OMERACT-OARSI responder criteria (described in detail in chapter 4, section 4.3.3) (Pham et al, 2003) were used as the dichotomous clinical outcome variable rather than WOMAC pain and function. OMERACT-OARSI at three months was selected since this time point is following the period of greatest mean change in physical activity (i.e. baseline to three months- see chapter 4, section 4.4.3)

II) Univariable analyses

Logistic regression was used to investigate the relationships between change in physical activity, attitude and beliefs about physical activity, sociodemographic and clinical variables with dichotomous OMERACT-OARSI criteria. Like linear regression, logistic regression is also a mathematical equation that can be used to describe the relationship between dependent variables and one or more independent variables, however in this model the dependent variable is discrete and dichotomous (Hosmer & Lemeshow, 2000; Menard, 2010). Logistic regression assumes that the relationship between a given value of a predictor variable and the probability of a dichotomous dependent variable is the logistic function (Szklo & Nieto, 2014), in effect, constraining the probability of the dependent variable between 0 and 1 (Katz, 2003). This is of particular use since the antilogarithm of the regression coefficient is equal to the odds ratio (Katz, 2003). The reader is referred to Hosmer and Lemeshow (2000) for detailed derivation of the logistic regression model.

III) Multivariable analyses and model building

The multivariable relationship between change in physical activity, attitudes and beliefs about physical activity, sociodemographics, clinical covariates and OMERACT-OARSI response at three months was investigated using multiple logistic regression. This model expands logistic regression to allow multiple predictor variables to be simultaneously modelled. It has a number of associated assumptions: the outcome variable must be binary; the binary probabilities of the OMERACT-OARSI response must be consistently coded for all variables; the model should be correctly specified; there is an absence of perfect multicollinearity, and; the independent variables are linearly related to the log odds (Hosmer & Lemeshow, 2000; Menard, 2010).

Two separate models were built with the first (Model 3C) holding baseline WOMAC pain in the model (without WOMAC function to avoid collinearity) and the second (Model 3D) holding WOMAC function in the model (without WOMAC function). This was to see if there was any difference in the effect of change in physical activity on OMERACT OARSI response based on differing measures of baseline knee pain clinical severity. The overall model building strategy for both models involved backwards elimination and was similar to the multiple steps carried out for objectives 1 and 2. However, following removal of each covariate after the model at step 2, a likelihood ratio test was carried out comparing the more complex model with the reduced model to ensure the covariates that were eliminated during model building had non-significant odds ratios (Agresti & Finlay, 2009). Likelihood in statistical inference relates to the probability of something given a specific outcome (for example, a OMERACT-OARSI treatment response, given a baseline WOMAC pain score) (Campbell, 2006). To paraphrase, the likelihood ratio tests check that each eliminated variable would not have significantly added to the predictive capabilities of the final multivariable model and is a way of checking the model is correctly specified. Steps 4 and 5 also differed since post hoc power calculation for adequate sample size and model assumption checks were specific to multiple logistic regression.

Several model assumptions were satisfied without formal diagnostic testing, since the dependent OMERACT OARSI responder variable was dichotomous and consistently coded with 0= no response and 1= response, and the elimination of non-significant covariates from the model during model building and likelihood ratio testing was considered to satisfy the *“model correct specification”* assumption. Collinearity checking was carried out by rerunning the final logistic regression models as multiple linear regression models and then checking the VIF as previously described (section 6.4.1, step 4) (Logistic regression diagnostics, UCLA Statistical Consulting Group. From: http://www.ats.ucla.edu/stat/stata/webbooks/logistic/chapter3/statalog3.htm accessed: August 2015). The final model assumption of the independent variables being linearly related to the log odds of outcome was assumed since some texts do not view this as essential (Warner, 2012) and in practice this is normally satisfied without the need for formal assumption testing since even if it is not satisfied the results of misspecification are not severe (Logistic regression diagnostics. UCLA Statistical Consulting Group. From: http://www.ats.ucla.edu/stat/stata/webbooks/logistic/chapter3/statalog3.htm accessed: August 2015).

Logistic regression literature suggests that for each explanatory variable in a model there should be between 10 to 20 outcomes for each binary category with most authors showing 10 to be sufficient (Harrell et al, 1996; Peduzzi et al,1996; Hosmer & Lemeshow, 2000; Menard, 2010; Stoltzfus, 2011). There were 180 participants in the smallest complete case outcome category (number of OMERACT OARSI responders at three months) hence assuming 10 outcomes per variable within this category, no more than 18 predictor variables should be included in the final model to avoid model overfitting. This estimate is likely to be conservative since the analysis was carried out on a multiple imputed data set which would lead to modelling with a greater number of OMERACT-OARSI responders at three months and hence more statistical power.

IV) Sensitivity analyses

Sensitivity analyses were carried out for Models 3C and 3D without adjusting for intervention arm as in objective 1 and 2 (Sensitivity analysis I). Further sensitivity analyses investigated the association between change in physical activity and OMERACT-OARSI response at 6 months adjusting for baseline pain and then subsequently baseline function (Sensitivity analysis II). The following section presents the results for objectives 1 to 3.

6.5 Results

The results are split by objective. Descriptive statistics for the independent and dependent variable change scores are provided initially prior to univariable unadjusted associations between exploratory and dependent variables for each objective together with the adjusted multivariable model and summary results of key sensitivity analyses models. In order to aid the flow of the chapter diagnostic checks of model assumptions and additional detail for sensitivity analyses are reported in Appendix VI.

6.5.1 Descriptive statistics recap

Prior to modelling any potential association between change in an independent variable and a dependent variable it is important to first know if meaningful change took place in the key variables. Table 6.2 below provides a reminder of the key independent and dependent variable statistics over time whilst table 6.3 highlights the magnitude of change in these variables (this information was initially introduced earlier in chapter 4, section 4.4.3).

Table 6.2 Summary statistics from key variables

Variables (range)	Baseline	3 months	6 months
PASE (0-400+)	177.0 (83.3)	192.1 (87.9)	190.5 (89.3)
WOMAC pain (0-20)	8.4 (3.5)	6.7 (3.6)	6.3 (3.9)
WOMAC function (0-68)	28.1 (12.2)	23.6 (12.5)	21.7 (13.7)
OMERACT-OARSI responders (%)	NA	45	52

Footnote: Multiple imputed data. All values are mean scores (standard deviation) except OMERACT-OARSI response which are given in percentages. All scores indicate higher levels of the variable except WOMAC function with higher scores indicating lower functioning.

Abbreviations: OMERACT-OARSI=Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International; PASE=Physical Activity Scale for the Elderly; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Table 6.3 Key variable change scores

Change variable	Mean score (SD)	Range
Change in PASE	15.1 (87.4)	-421.2 to 399.5
Change in WOMAC pain	-1.6 (3.2)	-12 to 12
Change in WOMAC function	-4.5 (10.1)	-41 to 31.6

Footnote: Statistics are based on multiple imputed BEEP dataset; all change is calculated by subtracting the score at baseline from the score at three month follow up; Higher change in PASE scores indicate higher physical activity at three months compared to baseline; Negative change in WOMAC pain and function scores indicate reduced pain and higher function at three months compared to baseline.
Abbreviations: PASE=Physical Activity Scale for the Elderly; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

6.5.2 Objective 1

"Investigate if change in physical activity level between baseline and three months is associated with pain and physical function at three months"

Table 6.4 shows both unadjusted crude univariable associations and adjusted models for pain (Model 3A) and physical function (Model 3B) at three months. Regression coefficients reported are rounded to two decimal places and a score of -0.00 is used to indicate a very small yet negative confidence interval coefficient to highlight the 95% CI crossing zero. For additional clarity, p values and confidence intervals are presented together within this chapter due to the very small ranges of the 95% Cis. Unadjusted change in physical activity, between baseline and three months, was not significantly associated with pain β= 0.00 (-0.00, 0.00) p=0.792 or function at three months β= 0.00 (-0.01, 0.01) p=0.968, however, several other significant unadjusted univariable associations were found. Age, BMI, work status, having a partner, baseline pain, function and stiffness, length of time with knee pain, having two or more comorbidities, widespread pain, depression, anxiety, self-efficacy for exercise, positive and negative outcome expectations were all significantly associated with pain and physical function at three months. Socioeconomic job category was also associated with physical function at three months. The BEEP intervention arm variable was not significantly associated with pain or physical function outcome.

Change in physical activity was also not associated with pain β= 0.00 (-0.00, 0.00) p= 0.406, or physical function β= -0.01 (-0.02, 0.00) p=0.108 at three months when adjusting for age, BMI, baseline pain/ physical function, length of time with knee pain, depression and BEEP treatment arm. Older adults of higher age, worse physical function, higher baseline pain or with knee pain duration lasting over a year and lower mood were more likely to have higher pain and worse physical function at three months regardless of change in physical activity between baseline and three months or intervention arm.

Sensitivity analyses I to IV (as described in section 6.4.1) (using complete case analysis/ adjusted multiple linear regression models for pain and function at three months using the dichotomous minimally important change in physical activity independent variable/ adjusted multiple linear regression models without adjusting for the treatment arm/ adjusting for baseline function instead of baseline pain in the three month pain model, and baseline pain instead of function in the six month function model) all produced similar null findings of no association between change in physical activity and both pain and function at three months (see Appendix VII for results).

Table 6.4 Objective 1: Unadjusted and adjusted Models 3A and 3B (WOMAC pain and function at 3 months)

	WOMAC pain at 3 months (Model 3A)				WOMAC function at 3 months (Model 3B)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig
Change in PA								
Change in PASE*	0.00 (-0.00, 0.00)	0.792	0.00 (-0.00, 0.00)	0.406	0.00 (-0.01, 0.01)	0.968	-0.01 (-0.02, 0.00)	0.108
Sociodemographics								
Gender								
(reference male)	0.29 (-0.36, 0.95)	0.380			1.24 (-1.02, 3.50)	0.281		
Age	0.06 (0.02, 0.09)	0.001	0.05 (0.03, 0.08)	<0.001	0.23 (0.12, 0.35)	<0.001	0.15 (0.06, 0.24)	0.002
Continuous BMI	0.13 (0.08, 0.19)	<0.001	0.06 (0.01, 0.10)	0.023	0.55 (0.35, 0.74)	<0.001	0.21 (0.05, 0.37)	0.010
Socioeconomic class								
(reference professional)								
Intermediate	0.08 (-0.88, 1.03)	0.874			0.49 (-2.80-3.78)	0.770		
Routine/ Manual job	0.66 (-0.18, 1.49)	0.124			3.69 (0.67, 6.71)	0.017		
Currently in paid work								
(reference working)	1.27 (0.63, 1.92)	<0.001			5.31 (3.02, 7.60)	<0.001		
Partner category								
(reference no partner)	-0.89 (-1.66, -0.11)	0.025			-3.79 (-6.47, -1.10)	0.006		
Clinical covariates								
WOMAC pain bl	0.60 (0.52, 0.67)	<0.001	0.52 (0.44, 0.60)	<0.001	1.93 (1.66, 2.21)	<0.001		
WOMAC function bl	0.16 (0.14, 0.18)	<0.001			0.68 (0.61, 0.75)	<0.001	0.60 (0.53, 0.68)	<0.001
WOMAC stiffness bl	0.86 (0.69, 1.03)	<0.001			3.40 (2.83, 3.97)	<0.001		
Pain duration								
(reference <1 year)								
> 1 yr and < 5yrs	1.13 (0.31, 1.94)	0.007	1.06 (0.39, 1.72)	0.002	3.26 (0.34, 6.18)	0.029	2.67 (0.40, 4.94)	0.022
>5 yrs and <10 yrs	2.09 (1.11, 3.07)	<0.001	1.60 (0.80, 2.41)	<0.001	5.64 (2.20, 9.08)	0.001	3.82 (1.15, 6.50)	0.005
>10 yrs	2.07 (1.07, 3.06)	<0.001	1.48 (0.66, 2.31)	<0.001	4.93 (1.46, 8.01)	0.006	3.42 (0.69, 6.15)	0.014

Comorbidities (reference none)								
1 other condition	0.16 (-0.61, 0.92)	0.684			0.70 (-1.99, 3.40)	0.608		
2+ other conditions	1.29 (0.49, 2.08)	0.002			5.72 (2.97, 8.46)	<0.001		
Widespread pain (reference no)	1.15 (0.25, 2.04)	0.012			5.10 (2.09, 8.10)	0.001		
PHQ8 depression	0.19 (0.12, 0.26)	<0.001	0.11 (0.05-0.17)	0.001	0.68 (0.45, 0.91)	<0.001	0.23 (0.03, 0.42)	0.025
GAD7 anxiety	0.16 (0.09, 0.23)	<0.001			0.57 (0.33, 0.81)	<0.001		
SEE	-0.17 (-0.31, -0.03)	0.015			-0.93 (-1.40, -0.45)	<0.001		
Positive OEE	-0.72 (-1.26, -0.18)	0.009			-3.78 (-5.68, -1.89)	<0.001		
Negative OEE	-1.21 (-1.56, -0.85)	<0.001			-4.89 (-6.11, -3.66)	<0.001		
Intervention arm (reference usual physio)								
Individually tailored exercise	0.26 (-0.53, 1.05)	0.520	0.04 (-0.59, 0.67)	0.900	-0.04 (-2.82, -2.74)	0.977	-0.38 (-2.50, 1.74)	0.725
Targeted exercise adherence	0.27 (-0.52, 1.06)	0.500	0.12 (-0.50, 0.75)	0.702	1.56 (-1.21, 4.33)	0.268	0.47 (-1.63, 2.57)	0.661

Key:
White=Unadjusted Models
Blue=Adjusted Model 3A (pain at 3 months model)
Purple=Adjusted Model 3B (physical function at 3 months model)
*Absolute change in PASE calculated by subtracting the baseline score from the score at three months.

Footnotes: Multiple imputed data; multiple linear regression adjusted models selected via backwards elimination holding treatment arm and change in physical activity in the model. Regression coefficients shown are rounded to two decimal places and a score of -0.00 is used to indicate a very small yet negative confidence interval coefficient. Higher scores on self-efficacy for exercise and positive outcome expectancies indicate higher self-efficacy and positive outcome expectancies. Higher score on the negative outcome expectancy scale indicates *less* negative outcome expectancies. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher PASE score indicates higher level of physical activity. Higher PHQ8 depression and GAD7 anxiety scores indicate worse depression and anxiety.

Abbreviations: β= Unstandardized coefficients; bl=baseline; BMI=Body Mass Index; CI=Confidence Interval; ex=exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectations for Exercise (split into positive and negative subscales); PA=Physical Activity level; PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise; WOMAC=Western Ontario and McMaster Osteoarthritis Index; yr=year.

6.5.3 Objective 2

"Investigate if change in physical activity level between baseline and three months is associated with pain and physical function at six months"

Table 6.5 shows both unadjusted crude univariable associations and adjusted models for pain (Model 6A) and physical function (Model 6B) at six months. Unadjusted change in physical activity was not significantly associated with pain β= 0.00 (-0.00, 0.00) p=0.927, or function at six months β= 0.00 (-0.02, 0.02) p=0.987. In terms of pain at six months, several other significant unadjusted univariable associations were found including age, BMI, socioeconomic category, work status, having a partner, baseline pain, function and stiffness, two or more comorbidities, widespread pain, length of time with knee pain, depression and anxiety as well as positive and negative outcome expectancies for exercise. The intervention arm variable was non-significant in both clinical outcome models. In terms of unadjusted univariable associations with physical function at six months, the same variables were associated, with the addition of self-efficacy for exercise.

Change in physical activity also showed no association with pain at six months β= -0.00 (-0.01, 0.00) p=0.254, adjusted for age, BMI, baseline pain, length of time with knee pain, depression and treatment arm within the BEEP trial. Similarly, no association between change in physical activity and physical function at six months was found β= -0.01 (-0.02, 0.00) p=0.108, adjusting for the same variables, with the exception of baseline pain, which was replaced by baseline function. Older adults of higher age and higher baseline pain or worse function, with knee pain duration lasting over a year, and lower mood, were more likely to have higher pain at six months. This was regardless of change in physical activity between baseline and three months and intervention arm.

Sensitivity analyses I to IV (as described in section 6.4.1) all found similar non-significant associations between change in physical activity and clinical outcomes at six months (see Appendix VII for further details).

Table 6.5 Objective 2: Unadjusted and adjusted Models 6A and 6B (WOMAC pain and function at 6 months)

	WOMAC pain at 6 months (Model 6A)				WOMAC function at 6 months (Model 6B)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)		β (95% CI)	Sig
Change in PA								
Change in PASE*	0.00 (-0.00, 0.00)	0.927	0.00 (-0.01, 0.00)	0.254	0.00 (-0.02, 0.02)	0.987	-0.01 (-0.02, 0.00)	0.163
Sociodemographics								
Gender								
(reference male)	0.17 (-0.52, 0.87)	0.621			1.44 (-0.98, 3.86)	0.242		
Age	0.06 (0.03, 0.10)	0.001	0.05 (0.02-0.08)	0.001	0.28 (0.16, 0.40)	<0.001	0.19 (0.09, 0.29)	<0.001
Continuous BMI	0.13 (0.06, 0.19)	<0.001			0.49 (0.28, 0.71)	<0.001		
Socioeconomic class								
(reference professional)								
Intermediate	0.36 (-0.65, 1.37)	0.484			0.40 (-3.18, 3.97)	0.828		
Routine/ Manual job	1.15 (0.22, 2.08)	0.016			4.20 (0.96, 7.440	0.011		
Currently in paid work								
(reference working)	1.09 (0.38, 1.79)	0.003			5.26 (2.82, 7.71)	<0.001		
Partner category					-3.72 (-6.60, -0.84)	0.011		
(reference no partner)	-0.88 (-1.72, -0.03)	0.041						
Clinical covariates								
WOMAC pain bl	0.64 (0.56, 0.73)	<0.001	0.59 (0.51, 0.67)	<0.001	1.97 (1.66, 2.27)	<0.001		
WOMAC function bl	0.17 (0.015, 0.20)	<0.001			0.66 (0.57, 0.74)	<0.001	0.59 (0.50, 0.67)	<0.001
WOMAC stiffness bl	0.87 (0.68, 1.06)	<0.001			3.34 (2.70, 3.97)	<0.001		
Pain duration								
(reference <1 yr)								
>1 yr and <5yrs	1.08 (0.19, 1.97)	0.018	0.96 (0.22, 1.69)	0.011	4.22 (1.15, 7.30)	0.007	3.53 (1.01, 6.05)	0.006
>5 yrs and <10 yrs	2.57 (1.52, 3.62)	<0.001	2.03 (1.17, 2.90)	<0.001	8.50 (4.83, 12.17)	<0.001	6.65 (3.63, 9.67)	<0.001
>10 yrs	2.17 (1.09, 3.25)	<0.001	1.46 (0.56, 2.35)	0.002	6.31 (2.61, 10.01)	0.001	4.57 (1.52, 7.62)	0.003

Comorbidities (reference none)								
1 other condition	0.40 (-0.45, 1.25)	0.355			1.72 (-1.20, 4.64)	0.249		
2+ other conditions	1.21 (0.34, 2.08)	0.006			5.55 (2.55, 8.56)	<0.001		
Widespread pain (reference no)	1.66 (0.71, 2.61)	0.001			6.02 (2.76, 9.28)	<0.001		
PHQ8 depression	0.18 (0.10, 0.25)	<0.001	0.10 (0.04, 0.16)	0.002	0.73 (0.48, 0.98)	<0.001	0.36 (0.14, 0.58)	0.001
GAD7 anxiety	0.15 (0.08, 0.23)	<0.001			0.56 (0.30, 0.82)	<0.001		
SEE	-0.14 (-0.29, 0.01)	0.064			-0.76 (-1.28, -0.24)	0.004		
Positive OEE	-1.13 (1.73, -0.53)	<0.001			-4.62 (-6.68, -2.57)	<0.001		
Negative OEE	-1.12 (-1.52, -0.73)	<0.001			-4.94 (-6.31, -3.58)	<0.001		
Intervention arm (reference usual physio)								
Individually tailored exercise	0.02 (-0.86, 0.90)	0.959	-0.25 (-0.96, 0.47)	0.502	0.86 (-2.14, 3.87)	0.572	0.51 (-1.89, 2.90)	0.678
Targeted exercise adherence	-0.12 (-0.98, 0.74)	0.782	-0.26 (-0.95, 0.44)	0.465	0.08 (-2.93, 3.09)	0.96	-0.72 (-3.13, 1.69)	0.557

Key:
White=Unadjusted Models
Blue=Adjusted Model 6A (pain at 6 months model)
Purple=Adjusted Model 6B (physical function at 6 months model)
*Absolute change in PASE calculated by subtracting the baseline score from the score at three months.

Footnotes: Multiple imputed data, multiple linear regression adjusted models selected via backwards elimination holding treatment arm and change in physical activity in the model. Regression coefficients shown are rounded to two decimal places and a score of -0.00 is used to indicate a very small yet negative confidence interval coefficient. Higher scores on self-efficacy for exercise and positive outcome expectations indicate higher self-efficacy and positive outcome expectations. Higher score on the negative outcome expectancy scale indicates *less* negative outcome expectancies. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher PASE score indicates higher level of physical activity. Higher depression and anxiety scores indicate worse depression and anxiety.

Abbreviations: β=Unstandardized coefficients; bl=baseline; BMI=Body Mass Index; CI=Confidence Interval; ex=Exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectancies for Exercise (split into positive and negative subscales); PA=Physical Activity level; PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise; WOMAC=Western Ontario and McMaster Osteoarthritis Index; yr=year.

6.5.4 Objective 3

"Investigate if change in physical activity level between baseline and three months can predict clinically important treatment response at three months"

Table 6.6 shows both unadjusted univariable associations and adjusted logistic regression models for OMERACT OARSI responder criteria at three months. To recap, the dichotomous OMERACT OARSI responder criteria variable was used to indicate those participants who had experienced clinically important change in pain and or physical function post BEEP trial intervention (chapter 4, section 4.3.3) (Pham et al, 2003). At three months 45% of the participants had met the criteria. Unadjusted change in physical activity was not significantly associated with OMERACT OARSI response at three months OR 1.00 (1.00, 1.00) p=0.358. Significant unadjusted covariate predictors included: age, work status, the length of time with knee pain and baseline pain and function.

In the adjusted Model 3C, including baseline pain level, change in physical activity remained non-significant OR 1.00 (1.00, 1.00) p=0.246, whilst participants with younger age, lower levels of depression, in current employment, with knee pain duration of less than a year, together with higher baseline levels of pain, were more likely to be OMERACT OARSI criteria responders. Model 3D, adjusted for baseline function instead of pain, found similar results with change in physical activity remaining non-significant and being unable to predict clinically important treatment response OR 1.00 (1.00, 1.00) p=0.257. The BEEP intervention arm variable was non-significant in both unadjusted and adjusted models. Sensitivity analyses without holding the BEEP intervention arm and investigating OMERACT-OARSI response at six months gave similar non-significant odds ratios for change in physical activity (see Appendix VII for summary).

Table 6.6 Objective 3: Unadjusted and adjusted Models 3C and 3D (OMERACT OARSI response at 3 months)

	OMERACT OARSI response at three months					
	Unadjusted		Adjusted pain Model (Model 3C)		Adjusted function Model (Model 3D)	
	OR (95% CI)	Sig	OR (95% CI)	Sig	OR (95% CI)	Sig
Clinical covariates						
WOMAC pain bl	1.11 (1.05, 1.18)	<0.001	1.15 (1.08, 1.23)	<0.001		
WOMAC function bl	1.02 (1.00, 1.03)	0.025			1.03 (1.01, 1.05)	0.001
Sociodemographics						
Change in PASE*	1.00 (1.00, 1.00)	0.358	1.00 (1.00, 1.00)	0.246	1.00 (1.00, 1.00)	0.257
Gender						
(reference male)	1.19 (0.82, 1.74)	0.354				
Age	0.97 (0.95, 0.99)	0.008	0.97 (0.94, 0.99)	0.001	0.96 (0.94, 0.98)	0.001
Continuous BMI	1.00 (0.96, 1.03)	0.836				
Socioeconomic category						
(reference professional)						
Intermediate	1.03 (0.59, 1.79)	0.930				
Routine/ Manual job	1.50 (0.91, 2.47)	0.108				
Currently in paid work						
(reference working)	0.55 (0.38, 0.81)	0.003				
Partner category						
(reference no partner)	1.31 (0.83, 2.06)	0.251				
Clinical covariates						
Pain duration						
(reference <1 year)						
> 1 yr and < 5yrs	0.49 (0.30, 0.80)	0.004	0.46 (0.28, 0.78)	0.004	0.47 (0.28, 0.78)	0.004
>5 yrs and <10 yrs	0.36 (0.20, 0.66)	0.001	0.31 (0.17, 0.59)	<0.001	0.33 (0.17, 0.61)	<0.001
>10 yrs	0.64 (0.35, 1.17)	0.145	0.59 (0.32, 1.10)	0.099	0.64 (0.35, 1.19)	0.162

Comorbidities						
(reference none)						
1 other condition	0.96 (0.61, 1.50)	0.850				
2+ other conditions	0.92 (0.58, 1.46)	0.728				
Widespread pain						
(reference no)	1.00 (0.59, 1.67)	0.989				
PHQ8 depression	0.98 (0.95, 1.02)	0.440	0.95 (0.91, 0.99)	0.022	0.95 (0.91, 0.99)	0.024
GAD7 anxiety	1.00 (0.96, 1.04)	0.916				
SEE	1.00 (0.92, 1.08)	0.981				
Positive OEE	1.13 (0.83, 1.55)	0.441				
Negative OEE	0.94 (0.75, 1.16)	0.548				
Intervention arm						
(reference usual physio)						
Individually tailored ex	1.08 (0.70, 1.68)	0.723	1.05 (0.66, 1.68)	0.837	1.10 (0.69, 1.75)	0.687
Targeted ex adherence	1.02 (0.64, 1.62)	0.948	0.95 (0.58, 1.56)	0.830	0.95 (0.58, 1.56)	0.853

Key:
White=Unadjusted Models
Blue=Adjusted Model 3C (OMERACT-OARSI response at 3 months model, adjusted for pain)
Purple=Adjusted Model 3D (OMERACT-OARSI response at 3 month model, adjusted for function)
*Absolute change in PASE calculated by subtracting the baseline score from the score at three months.

Footnotes: Multiple imputed data, multiple logistic regression adjusted models selected via backwards elimination holding treatment arm and change in physical activity in the model. Higher scores on self-efficacy for exercise and positive outcome expectation for exercise scales indicate higher self-efficacy and positive outcome expectations. Higher score on the negative outcome expectation for exercise scale indicates *less* negative outcome expectations. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher PASE score indicates higher level of physical activity. Higher PHQ8 depression and GAD7 anxiety scores indicate worse depression and anxiety.

Abbreviations: β=Unstandardized coefficients; bl=baseline; BMI=Body Mass Index; CI=Confidence Interval; ex=Exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectations for Exercise (split into positive and negative subscales); OMERACT OARSI=Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials; PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise; WOMAC=Western Ontario and McMaster Osteoarthritis Index; yr=year.

6.6 Discussion

This section discusses the key findings from the chapter, compares the results to existing research and identifies methodological strengths and weaknesses before going on to make recommendations for clinical practice and further research.

6.6.1 Key findings

This chapter sought to investigate if change in physical activity behaviour over time is associated with future clinical outcomes in terms of pain and physical function in older adults with knee pain. Although all three intervention groups improved their clinical outcomes, no association was detected with change in physical activity overall. The magnitude of associations was both negligible and non-significant. Small β coefficients were expected given the difference in scale between the PASE (0=400+) and WOMAC pain and function scores (0-20 and 0-68 respectively) (since the PASE scale is larger by approximately a factor of 20 than the WOMAC pain scale). However, even taking this in to account, the magnitude of associations were very small, non-significant and do not appear to be of clinical importance.

The null association findings can be interpreted in four ways which will be discussed and interpreted in turn. Firstly, these findings could indicate that change in general physical activity level is not responsible for change in the knee pain and function in older adults with knee pain, i.e. the null hypothesis is true (which suggests change in general physical activity level is not a mediator for clinical outcome within the BEEP trial). This is supported by the consistent non-significant and negligible β coefficients across all the models (including unadjusted, adjusted and sensitivity analyses models). It is possible that other aspects of physical activity interventions are responsible for improvements in pain and function. For example, it is possible that specific types of physical activity such as strengthening exercises are responsible for clinical improvements rather than physical activity level per se (Knoop et al, 2014) or that psychosocial aspects (sometimes referred to as *"non-specific"* factors) of physical activity interventions play a major role (Gifford, 2002b; Bennell et al, 2010). Outcome expectations, attention and monitoring, the interest and empathy expressed by clinicians and the impressiveness of the intervention may all contribute to improvements in pain and function (Gifford, 2002b; Hall et al, 2010; Bennell et al, 2014) (see chapter 2 section 2.10.2 for further discussion of such factors). Support for this hypothesis is provided within the thesis by analyses showing that baseline positive and negative outcome expectations for exercise were a significant crude predictor of pain and physical function at three and six months (see table 6.4 and 6.5) and externally by a placebo controlled exercise RCT that found no significant difference in clinical outcomes between groups (Bennell et al, 2005).

Secondly, the BEEP trial interventions may not have changed physical activity level sufficiently to detect a statistically significant association with future clinical outcome. This hypothesis is supported by the relatively small mean change in PASE from baseline to three months of just 15 points. The interventions generally targeted therapeutic exercise such as strengthening and walking. Although these types of physical activity are included within the PASE items, they may not have changed sufficiently to make a meaningful increase in overall PASE score due to the relatively crude categorisation of duration and frequency of these activity items. For example, for many participants *"walking outside home"* may not have changed by one or two hours per day (the requisite amount to change PASE score from some baseline walking levels) or equally they may not have changed *"muscle strength activity"* frequency from *"sometimes"* to *"often"* (see Appendix V for further detail regarding the categorisation and scoring of physical activity within the PASE).

Thirdly, it is plausible that some error in measurement may be responsible for the null findings. It is possible that the PASE measure, due to potentially substantial individual measurement errors and inadequate responsiveness, is unable to detect any association between change in physical activity and future clinical outcome if one indeed exists. This hypothesis is supported by the large measurement errors previously reported by studies using the PASE in joint pain populations (Svege et al, 2012; Bolszak et al, 2014) (measurement errors that are likely considerably larger than the mean change in physical activity over time 15.1, since MDC in older adults with hip pain is 87- see section 6.4.1, IV). Whilst responsiveness has not been investigated in older adults with knee pain, and can be defined in different ways (Streiner & Norman, 2008; Mokkink et al, 2010; Polit & Yang, 2015), it is logical that the ability to detect change in physical activity when it has occurred would be reduced by the aforementioned measurement error and the relatively crude categorisation of duration and frequency of PASE items discussed above (which may fail to detect small to modest physical activity changes most likely to occur with the BEEP trial interventions). However, it is of note that Sensitivity analysis II (the minimal important change in PASE models for objectives I and II) also found no association between important change in physical activity and clinical outcome, which is evidence against this argument.

Finally, the modelling of change in physical activity is a challenge. It could be that modelling change in physical activity using an absolute change score between two time-points may compound measurement errors and reduce precision biasing findings towards the null (Streiner & Norman, 2008; Polit & Yang, 2015) (see 6.6.3 for further detailed explanation).

On balance, whilst it is possible that the null hypothesis is true i.e. that change in physical activity is not associated with future clinical outcome, a number of limiting factors may be interacting causing an increased risk of false negative findings and some substantial caution is therefore needed in interpreting the findings. More research is required to further validate the findings by systematically addressing the afore-mentioned limitations (see clinical implementations section for further detail).

A number of covariates were consistently found to be associated with future clinical outcomes of pain and function in multivariable adjusted models for objectives 1 and 2. Poorer clinical outcome at three and six months was associated with higher age, higher pain and worse function at baseline together with pain of duration over a year and higher levels of depression. These variables can be considered prognostic of poorer outcome at three and six months. Since increasing age is both a known risk factor for knee pain onset and progression this finding is expected (Bastick et al, 2015b; Silverwood et al, 2015). It is logical that more severe knee pain and those with worse function at baseline are also more likely to have worse clinical outcome in the future. The presence of pain, of duration over a year, may in theory be associated with more advanced structural OA and central sensitisation that may be associated with poorer future clinical outcome (Woolf, 2011; Fingleton et al, 2015), whilst depression and low mood may modulate pain leading to increased pain perception (Wiech & Tracey, 2009; Strobel et al, 2014).

Objective 3 investigated the association between change in physical activity and OMERACT-OARSI response and found no association. This finding supports those of the first two objectives but is likewise at risk of false negative findings as discussed above. It is of note that increasing age, pain of duration longer than one year and depression all reduced the likelihood of being a treatment responder (consistent with the findings from analyses addressing objectives 1 and 2), whilst those with higher pain and function had a greater likelihood of responding to treatment. Whilst the pain and function finding may appear somewhat counterintuitive, it is likely related to the definition of OMERACT-OARSI response which requires both relative and absolute improvement in these clinical outcomes (absolute improvement may have less chance of occurring in those with low scores at baseline i.e. a *"floor effect"* within the measure see chapter 4, section 4.3.3) (Polit & Yang, 2015).

6.6.2 Comparison to existing research

There is a lack of literature that has looked specifically at the association between change in physical activity and future clinical outcome both within trials and longitudinal cohorts of older adults with knee pain. Change in other factors such as strength, weight, functional self-efficacy and fear of physical activity have however been investigated and shown to be associated with future clinical outcome (see chapter 2, section 10.2 for further detail) (Christensen et al, 2005; Focht et al, 2005; Fitzgerald et al, 2012; Knoop et al, 2014; Runhaar et al, 2015). Cautiously applying the null findings from this study (due to the limitations discussed previously) these factors may be more important mechanisms of action than change in physical activity per se.

Whilst, to the author's knowledge, there is no literature investigating the association between change in physical activity and future clinical outcome, there is mixed evidence for the association between baseline physical activity level and future clinical outcome. Sharma and colleagues (2003) found that higher levels of baseline physical activity measured by the PASE were not significantly associated with good or poor outcome functional outcome. They carried out a prospective longitudinal cohort study investigating the baseline factors that were associated with physical function at three years in older adults with knee pain. They used both multivariable logistic regression and dichotomised outcome into good or poor outcomes using quintiles of WOMAC physical function and individuals' mobility between these groups over time. Conversely, Dunlop and colleagues (2011) found that higher levels of baseline physical activity were associated with greater physical performance at one year. They used the OAI longitudinal cohort data to investigate the association between PASE at baseline and good functional performance at one year. Similar to the Sharma study, they used multiple logistic regression of dichotomised physical performance outcome at one year (based on quintiles of physical function performance and individuals' mobility between these groups over time). These studies provide mixed evidence that physical activity level is associated with future clinical outcome.

6.6.3 Methodological strengths and limitations

This study has a number of strengths, including the large longitudinal sample of 514 older adults with knee pain. This allowed for multivariable modelling with adequate precision and confidence in the various model parameter output estimates (Szklo & Nieto, 2014). Confidence in the findings was further aided by the use of multiple imputation which reduces the chance of imprecision and attrition bias (Sterne et al, 2009). The availability of a large number of theoretically important covariates for multivariable adjustment was also a strength as this reduces the risk of unadjusted confounding on the relationships between change in physical activity and clinical outcome (Szklo & Nieto, 2014). The primary data findings were supported and strengthened by a number of sensitivity analyses including differing clinical covariate adjustment and complete case analyses which gave a consistent and similar picture of a non-significant relationship between change in physical activity and future clinical outcome.

There were a number of study limitations that can be organised into five key topics: factors relating to the measurement properties of the PASE, the use of absolute change scores, issues surrounding adjustment for potential confounding, temporal bias issues surrounding the use of the OMERACT-OARSI response variable and the use of trial data for secondary analysis. Although the PASE is validated in older adult populations (Washburn et al, 1993), including those with joint pain (Martin et al 1999; Svege et al, 2012) and is frequently used within the older adult knee pain literature it is has some clear limitations (as discussed in 6.6.1). Furthermore, as discussed previously (in chapter 2, section 2.7), any self-report measure of physical activity is prone to recall bias, errors in physical activity duration estimation and misclassification of physical activity intensity (Prince et al, 2008; Bassett & John, 2010). PASE also measures the frequency and duration of domestic, work and leisure activity as part of a composite score (Washburn et al, 1993). It is therefore not possible to tell if different types of physical activity change are more or less associated with clinical outcomes, yet it is plausible that some physical activity domains (for example, therapeutic exercise that targets known treatment effect mediators such as quadriceps strengthening) may be associated.

Measuring change is complex and problematic (Polit & Yang, 2015). Although commonly utilised within the literature, absolute change scores calculated by subtracting a score at one point from another are potentially affected by factors that can threaten both their validity and accuracy (Polit & Yang, 2015). Calculating a change score using any measure with imperfect reliability may either magnify a small change, hide a large one, or even reverse the direction of true change (i.e. change scores may be affected by random error rather than real change) (Polit & Yang, 2015). Since the mean change score in the BEEP data between baseline and three months (15) is lower than the MDC (87) in older adults with hip pain we cannot be sure that the change that took place was true change or random error (Polit & Yang, 2015).

Temporal bias is a challenge to the logic of the conclusions regarding the association between change in physical activity and clinical response. Temporal bias occurs when inference about the proper temporal (time) sequence of cause and effect are erroneous (Szklo & Nieto, 2014). The correct temporal sequence is a key consideration in making reasoned judgements about causation, and requires that the exposure of interest occurs prior to the outcome (Hill, 1965). Considering the research question *"are changes in physical activity level associated with future pain and function in older adults with knee pain?"* it is biologically plausible that increases in physical activity could cause improvements in pain and physical function or vice versa. For example, overall increase in physical activity may lead to physiological changes such as quadriceps muscle strengthening that can mediate change in pain (Knoop et al, 2014), yet it also possible that improvements in pain may lead to increased physical activity given that pain severity may act as barrier to physical activity (Hendry et al, 2006; Gyurcsik et al, 2009). Although the primary clinical interest of this thesis is the effect of increased physical activity on pain and physical function, *"reverse causality"* is also considered whereby the presumed outcome is responsible for the exposure of interest (Szklo & Nieto, 2014). For example, clinical outcome *"response"* at three months as measured by the OMERACT-OARSI response criteria, although measured in time after the change in physical activity between baseline and three months, may in fact have occurred at any time-point up to three months (and remained up until the three months when the measure was carried out). This means that any temporal assumptions about change in physical activity happening before clinical outcome response may not be valid.

Potential limitations regarding confounding adjustment include over-adjustment, under-adjustment and imperfect adjustment (Szklo & Nieto, 2014). In all the models over-adjustment may have been a factor as a result of controlling for the baseline value of the dependent variable of interest (for example, adjusting for baseline pain in the adjusted pain at three months model used in objective 1). However, results were similar from all sensitivity analyses irrespective of whether an alternative surrogate clinical severity baseline variable was used (for example, adjusting for baseline function in the adjusted pain at three months Model-sensitivity analysis). Despite adjusting for a broad range of potential confounders, examples of under-adjustment might be the lack of a variable measuring central sensitisation, or the lack of adjustment for co-interventions, such as analgesia use. It is biologically plausible that both of these factors may confound relationships between change in physical activity and future clinical outcomes of pain. The former may be captured in surrogate form through duration of time since pain onset and widespread pain variables but the latter remains unaccounted for. Furthermore, there may be unknown confounders that were not entered into the models. Imperfect adjustment, as a result of confounder categories being too broad, and participants changing categories from those measured at baseline during the 3 to 6 months, may also lead to residual confounding (Szklo & Nieto, 2014). For example, the *"pain duration"* variable does not have a separate category for time periods less than three months which may be clinically different than pain less than a year, whilst an individual may move comorbidity category from that reported at baseline during the three to six month period when the dependent variable is measured. Finally, categorisation of continuous variables (for example, the dichotomous clinically important physical activity change variable used within the sensitivity analyses), although often easier to measure and interpret, will result in loss of information (Altman & Royston, 2006; Szklo & Nieto, 2014) and may bias any associations towards the null.

Components of the model building strategy itself may also have been a limitation. Although the variable selection was carried out by the author in logical iterative steps rather than being a *"black box"* automated procedure, the variable selection process was nevertheless at risk of excluding some variables that were of clinical importance. For example, due to collinearity within the model it was not possible to include both WOMAC pain and function at baseline (both of which are strong independent predictors of future clinical outcomes). Whilst the elements of data driven model building based on covariate statistical significance (section 6.4.1 step 3) excluded some covariates without a full investigation of their interaction effects and may exclude other important variables that may be included in the model due to some other important criteria (such as clinical modifiability) (Kutner, 2005; Agresti & Finlay, 2009). For example, pain duration was associated with future clinical outcome in multivariable models for objectives 1 to 3 (see tables 6.4 to 6.6) however, this is not a target for treatment since it cannot be influenced in clinical practice.

As the data utilised within this chapter was taken from a RCT rather than a prospective cohort study, regression to the mean and specific generalizability issues are also potential limitations (Barnett et al, 2005; Polit & Yang, 2015). The phenomenon of regression to the mean was introduced and described in chapter 4, section 4.5.3. In brief, participants may enter a trial when their symptoms are at a high point but then later clinical improvement changes may occur as a result of the natural course of the syndrome independent of change in physical activity. This phenomenon is challenging to interpret in the context of the association between change in physical activity and clinical outcome but arguably may act like an uncontrolled confounder since it could be non-causally associated with change in physical activity at the start of an exercise RCT and also associated with future clinical outcome.

Finally older adults with knee pain who consented and met inclusion criteria for the BEEP trial investigating exercise are systematically different from the total population of older adults with knee pain (see chapter 4, section 4.5.3 for further detail and discussion). For example, some older adults with knee pain who either did not meet the BEEP trial inclusion criteria (such as those with joint replacements or those residing in nursing homes) or the very frail and old who were unable to attend treatment clinics are likely to be underrepresented in this sample (Foster et al, 2014) which limits the generalisability of the findings to such sub groups.

6.6.4 Clinical implications

Although the BEEP trial interventions all reduced pain and improved physical function, the mechanisms of action for this remain unclear and may not be due to increase in physical activity per se but more likely due to other mechanisms (see chapter 2, section 2.10.2). However, insufficiently active older adults with knee pain should be advised to increase their physical activity levels, in order to achieve the associated benefits (described in chapter 2, section 2.10) with the reassurance that increasing physical activity is not associated with increasing pain or deterioration in function at a group level. These clinical implications offer further support to the safety findings of the systematic review (summarised within chapter 3, section 3.4.6) and can be used to reassure older adults with knee pain who feel that increasing their physical activity will lead to increased pain in the future.

6.6.5 Research Implications

The findings from the analyses within this chapter and the associated methodological limitations provide material for future research. These include investigating additional potential mechanisms of action for change in clinical outcome, investigating the reliability and responsiveness of the PASE in older adults with knee pain and further validating the primary findings using alternative methods to reduce the impact of PASE measurement limitations.

Since factors other than increase in total physical activity may be most important in improving clinical outcomes of pain and physical function, mediation analyses of such plausible factors (that are modifiable) are of clinical interest. For example, hypothesising from the findings of objective 1 and 2, depression was associated with clinical outcome and as it may be improved by regular physical activity it is possible that depression could be a mediator on the causal path between therapeutic exercise intervention and clinical outcome in depressed older adults. Other potential novel mechanisms of action that warrant further investigation are change in attitudes and beliefs about physical activity (since these factors at baseline were crudely associated with future clinical outcomes at three and six months). Considering additional literature, factors related to the therapeutic relationship between health practitioners providing intervention and older adults with knee pain such as rapport, collaboration and empathy (Hall et al, 2010; Bennell et al, 2014) could also be investigated.

In order to further understand if the PASE is a suitable measure for modelling change in physical activity in future studies, the reliability of the PASE could be firstly investigated in older adults with knee pain samples who have not undergone changes in physical activity followed by investigation of responsiveness in older adults with knee pain when true change has taken place (see chapter 9, section 9.9.2 for more detailed discussion) (Polit and Yang, 2015).

In order to reduce the bias and suboptimal sensitivity of the PASE to detect change in physical activity, external validation of the study could theoretically be carried out using minimally invasive and responsive wearable technology containing accelerometry (discussed in chapter 3, section 3.5.8). However, although accelerometry has been shown to have high responsiveness in some populations (Montoye et al, 2014) it also requires responsiveness investigation in older adults with knee pain (Terwee et al, 2011) and has additional limitations of its own including limited ability to pick up common activities for older adults with knee pain such as strengthening activities and swimming as well as suboptimal compliance (see chapter 2, section 2.7 and chapter 4, section 4.3.3).

6.7 Conclusion and chapter summary

This chapter sought to investigate the relationship between change in physical activity and future clinical outcomes of pain and physical function using longitudinal data analysis of the BEEP trial dataset. The primary finding was that change in physical activity from baseline to three months was not associated with clinical outcome at three or six months. There was also no association between change in pain or function and future physical activity at three months. Caution is warranted in interpreting these null findings due to limitations, including unknown responsiveness of the PASE, biases associated with self-report physical activity, limitations of modelling absolute change scores and temporal bias which may have contributed to an increased risk of false negative findings. Regardless of the null findings within this chapter, increasing physical activity should still be recommended for older adults with knee pain, due to its general health benefits and the known clinical improvements in pain and function associated with exercise interventions.

The following chapters investigate the relationship between attitudes and beliefs about physical activity and physical activity level using cross-sectional data analyses of both the BEEP trial and ABC-Knee datasets (chapter 7) and longitudinal data analyses from the BEEP trial dataset (chapter 8).

Chapter 7

The relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain

7.1 Chapter introduction

This chapter comprises Part 3 of this PhD, investigating the relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. It describes regression analyses of cross-sectional BEEP trial baseline data and ABC-knee data (these datasets were previously described in chapters 4 and 5 respectively). The chapter begins by stating the aim and objectives, followed by the analysis methods. It then presents the results split by dataset before a combined discussion of the findings from the two datasets. The chapter concludes with a brief summary and a precursor to the final thesis research question.

7.2 Aim and objectives

This chapter aimed to examine the cross-sectional relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. Specific objectives were to:

1. Investigate univariable associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain.
2. Investigate the univariable associations of sociodemographic and clinical covariates and physical activity level in older adults with knee pain.
3. Investigate the associations between individual attitudes and beliefs about physical activity scales and physical activity level in older adults with knee pain, adjusting for potential confounders.
4. Investigate the combined effect of multiple attitudes and beliefs about physical activity and physical activity level in older adults with knee pain, adjusting for potential confounders.

7.3 Methods

This section describes the selected methods for data analysis within this chapter alongside their rationale. A concise overview of the general methods used in answering the four objectives are provided in figure 7.1 before the section splits into four to address individual chapter objectives. All statistical analyses described within this section were carried out using Stata 13.1 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and complete-case data (see chapter 4, section 4 3.4 and chapter 5, section 5.5.2 for rationale and levels of missing data).

7.3.1 Variable terminology and causality note

Physical activity level is referred to throughout this chapter as the *"dependent variable"* for consistency and clarity with model building. All attitude and belief variables about physical activity are referred to as *"independent variables"*, and all sociodemographic and additional clinical variables are referred to as *"covariates"*. It is fully accepted that although physical activity level is referred to as the *"dependent variable"* and attitudes and beliefs as *"independent"* the relationships being explored are cross-sectional in nature and hence inferring cause and effect is not possible due to a lack of known temporal relationship between the variables (Hill, 1965; Fletcher et al, 2012; Szklo & Nieto, 2014).

7.3.2 Overview of the analyses methods within this chapter

This part of the thesis utilised a range of regression methods and two datasets in order to answer the four research objectives, summarised in figure 7.1 and described in detail below.

Figure 7.1 Overview of methods for each objective

1: Investigate univariable associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain:

- Simple linear regression using BEEP trial data
- Ordinal regression using ABC-Knee data

↓

2: Investigate the univariable associations of sociodemographic and clinical covariates and physical activity level in older adults with knee pain:

- Simple linear regression using BEEP trial data
- Ordinal regression using ABC-Knee data

↓

3. Investigate the associations between individual attitude and belief about physical activity scales and physical activity level in older adults with knee pain, adjusting for potential confounders:

- Multiple linear regression model building using BEEP trial data
- Multivariable ordinal regression model building using ABC-Knee data

↓

4. Investigate the combined effect of multiple attitudes and beliefs about physical activity and physical activity level in older adults with knee pain, adjusting for potential confounders:

- Multiple linear regression model building using BEEP trial data
- Multivariable ordinal regression model building using ABC-Knee data

7.3.3 Independent and dependent variables

Variables capturing attitude and beliefs about physical activity were selected for data analysis from both the BEEP trial and ABC-Knee datasets based on both theoretical plausibility of association with physical activity level and pragmatic availability (chapter 2, section 2.12 to 2.14). Additional sociodemographic, clinical and behavioural covariates were selected based on their potential ability to confound the relationship between attitudes and beliefs about physical activity and physical activity level by being associated with physical activity level and or attitudes and beliefs about physical activity (see section 7.3.5 for further explanation). Covariate selection was informed by previous literature (see chapter 2, section 2.10.3 and 2.12), clinical reasoning and data availability.

I) BEEP trial dataset

The dependent physical activity variable within the BEEP trial dataset was self-report physical activity level, using the PASE. To recap, this continuous scale, between 0 and 400+, measures physical activity level broadly with higher scores indicating higher levels of physical activity (Washburn et al, 1993). Independent variables included exercise self-efficacy using the SEE which is scored between 1 and 10 (Resnick & Jenkins, 2000) and positive OEE and negative OEE scored between 0 and 5 (Resnick, 2005) with higher scores indicating higher self-efficacy and more positive outcome expectations for exercise. These two scales were explored individually rather than in composite form to allow the comparison between positive and negative outcome expectations. Detail on sociodemograpics and clinical covariates were also provided in chapter 4 and are summarised in table 7.1.

Table 7.1 Overview of BEEP baseline variables

Dependent variable	Data type	Summary detail
Physical activity level		
PASE	S	0-400+ (higher scores=higher physical activity level)
Independent variables		
Attitude and beliefs towards exercise		
SEE	S	Range 1 to10 (10=highest self-efficacy)
Positive OEE	S	Range 1-5 (5=most positive expectations)
Negative OEE	S	Range 1-5 (5=least negative expectations)
Sociodemographics		
Gender	D	Reference category male
Age	S	45 years and older
BMI	S	Higher scores=higher weight relative to height
Socioeconomic category	C	Three categories, reference professional
Work status	D	Reference working
Partner category	D	Reference no partner
Clinical		
WOMAC pain	S	Range 0-20 (20=highest pain)
WOMAC function	S	Range 0-68 (68=poorest function
WOMAC stiffness	S	Range 0-8 (8=most stiffness)
Pain duration	C	Four categories, reference <I year duration
Comorbidities	C	Three categories, reference none
Widespread pain	C	Reference no widespread pain
PHQ8 Depression	S	Range 0-24 (24=most depressed)
GAD7 Anxiety	S	Range 0-21 (21=most anxiety)
Treatment intervention arm	C	Three categories, reference usual care

Footnote: All independent variables measured at baseline.

Abbreviations: BMI=Body Mass Index; Data types, C=Categorical with multiple categories, D=Dichotomous, S=Scalar; GAD7=General Anxiety Disorder 7 Questionnaire; OEE=Outcome Expectations for Exercise (positive and negative subscales); PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health depression Questionnaire; SEE=Self-Efficacy for Exercise scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

II) ABC-Knee dataset

The dependent physical activity variable within the ABC-Knee dataset was the STAR. This splits physical activity level into three categories *"inactive"*, *"insufficiently active"* and *"meeting current physical activity guideline recommendations"* (Matthews et al, 2005). Continuous independent variables included: the OPAPAEQ scale which includes attitudes towards physical activity pertaining to tension relief, promotion of health, vigorous exercise and social benefits (Terry et al, 1997) and is scored from 14 to 70; the TSK, which measures movement related fear and injury and is scored between 17 and 68 (Vlaeyen et al, 1995); and the *"other"* subscale of the ASES, which measures arthritis self-efficacy with a focus on physical activity and is scored between 6 and 60. Details about sociodemograpics and clinical covariates were provided previously in chapter 5 and are summarised again here in table 7.2. Given the small number of events within the smallest category of the STAR, it was not possible to model all of the covariates of potential interest in the primary thesis analyses (see 7.3.4 for full explanation). Covariates selected a priori for ABC primary thesis analyses (highlighted in green) and those used in a post hoc sensitivity analysis (in white) are presented together in table 7.2.

Table 7.2 Overview of ABC-Knee variables

Dependent variable	Data type	Summary detail
Physical activity level		
STAR	C	Three categories: *"inactive"*, *"insufficiently active"* and *"meeting current guideline recommendations"*
Independent variables		
Attitude and beliefs about physical activity		
OPAPAEQ	S	Range 14-70 (70=most positive attitudes)
TSK	S	Range 17-68 (68=most fear)
ASES "other"	S	Range 10-100 (100=highest self-efficacy)
Sociodemographics		
Gender	D	Reference category male
Age	S	50 years and older
BMI	S	Higher scores=higher weight relative to height
Socioeconomic category	C	Three categories, reference professional
Partner category	D	Reference no partner
Smoking	C	Reference never
Alcohol	C	Reference
Clinical		
WOMAC pain	S	Range 0-20 (20=highest pain)
WOMAC function	S	Range 0-68 (68=poorest function
WOMAC stiffness	S	Range 0-8 (8=most stiffness)
Days with pain in the last year	D	Reference pain for less than 1 month
Chronic pain grade	D	Reference low disability, low intensity
Comorbidities	C	Three categories, reference none
How often do you feel down?	D	Reference never/ sometimes
How often do you have little interest in doing things?	D	Reference never/ sometimes
Previous advice to exercise for knee pain?	D	Reference yes
Past behaviour		
Used exercise to treat knee pain in the last month	D	Reference yes

Key: Non-highlighted variables used in sensitivity analyses only.
Green highlighted variables used for primary chapter analyses.

Abbreviations: S=Scalar, C=Categorical with multiple categories, D=Dichotomous; STAR=Short Telephone Activity Recall questionnaire; OPAPAEQ=Older Persons Attitudes towards Physical Activity and Exercise Questionnaire; TSK=Tampa Scale for Kinesiophobia; ASES=Arthritis Self-Efficacy Scale; BMI=Body Mass Index; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

7.3.4 Methods to address objective 1

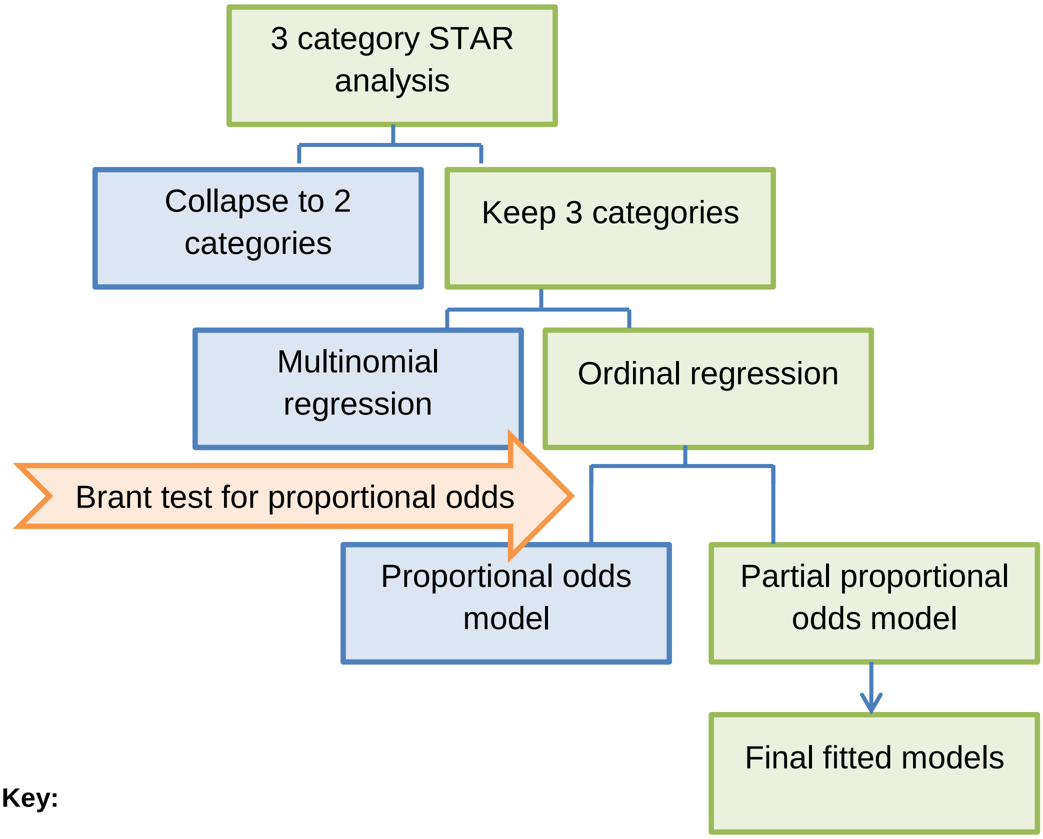
I) BEEP trial dataset methods

In order to investigate the crude associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain, the PASE physical activity variable was regressed on each attitude and belief about physical activity variable in turn using simple linear regression (see table 7.1 for the attitude and belief variables about physical activity and chapter 6, section 6.4.1 for a more detailed description and rationale for selecting simple linear regression). This analysis was also an important first step towards later making inferences regarding confounding (Szklo & Nieto, 2014). Regression assumption diagnostics and model output interpretation were carried out as previously described (see chapter 6, section 6.4.1).

II) ABC-Knee dataset methods

Within the ABC- Knee dataset, the dependent ordinal STAR variable was regressed on individual attitude and belief scalar variables (see table 7.2). A series of decisions were made in choosing the regression model which are schematically represented in figure 7.2. These decisions were driven by both clinical rationale and data fit and are subsequently discussed in turn.

Figure 7.2 STAR regression analysis decision making tree



Key:

Green boxes indicate the chosen decision
Blue boxes indicate options that were considered
Orange arrow indicates a statistical test influencing decision making

Decision 1

The first decision was whether or not to keep the three outcome categories of the STAR. The majority of responders giving complete STAR data (n=579) were categorised as either *"insufficiently active"* (n=298) or *"meeting current physical activity guidelines"* (n=256), whilst only a small number (n=25) were categorised as *"inactive"*; suggesting the data could be well explained by two categories of physical activity. Intuitively the STAR variable could be collapsed into two clinically meaningful dichotomous categories of *"not meeting guideline levels of physical activity"* and *"meeting guideline levels of physical activity"* and modelled using logistic regression (Menard, 2010). However, collapsing dependent variable categories results in loss of information unless there is perfect homogeneity in the categories that are being collapsed (Ananth & Kleinbaum, 1997; Altman & Royston, 2006; Szklo & Nieto, 2014). Indeed, the *"inactive group"* appeared to be a distinctly heterogeneous group from the *"insufficiently active group"* and one that shows similarities in clinical presentation to previous groups who have consulted primary care services for knee pain (Hay et al 2006, Foster et al 2007, chapter 4, section 4.4.2 and chapter 5 section 5.4.4). For example, the *"inactive group"* had markedly higher pain and poorer physical function than the *"insufficiently active group"* (see chapter 5, table 5.4). Hence, it was considered undesirable to lose this clinically unique and important group who may be able to offer more specific insight into primary care consulters and the decision was made to keep the 3 STAR categories (see figure 7.2). However, it is noted that in choosing to keep the three categories of the STAR there was a trade-off of modelling fewer covariates within the later multivariable models for objectives 2 and 3 (to reduce overfit), as well as increased model statistical output and interpretation complexity (Menard, 2010).

Decision 2

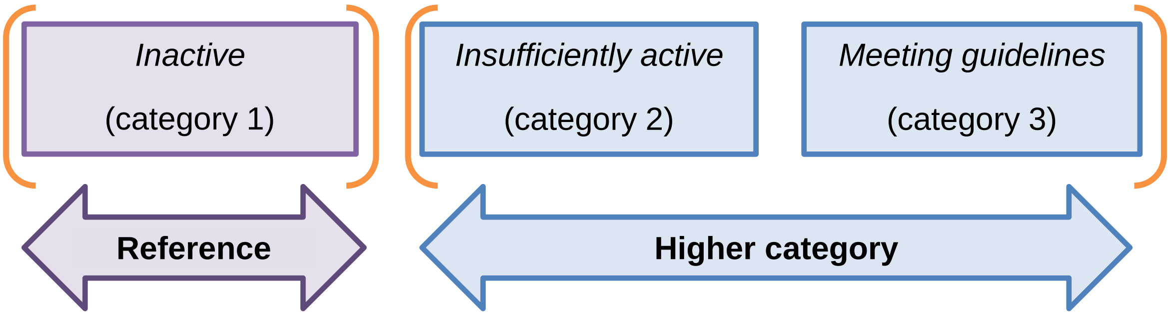
The next decision was whether to use multinomial or ordinal regression modelling. Ordinal regression and multinomial regression models are extensions of the binary logistic regression model (discussed in chapter 6, section 6.4.2) (Hosmer & Lemeshow, 2000). Ordinal regression modelling was selected since it takes into account the ordinal nature of the STAR (hence does not result in information loss) and has less complex model output to interpret (Ananth & Kleinbaum, 1997; Hosmer & Lemeshow, 2000).

Decision 3

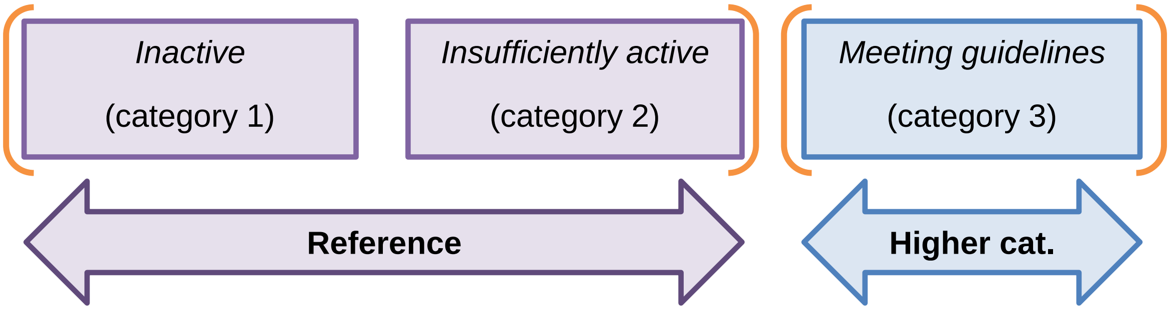
The third decision was which ordinal regression model to choose. Proportional odds (POM) (also known as the *"cumulative logit model"*) and partial proportional odds models (PPOM) are two common options to select between (Ananth & Kleinbaum, 1997). The POM is the most simple to interpret but requires more stringent model assumptions. Figure 7.3 is used to help visualise how these ordinal regression models work and also differentiate them. Full derivation of these models is beyond the scope of this thesis and is provided elsewhere (Ananth & Kleinbaum, 1997; Williams, 2006). In brief, they can be interpreted like two separate logistic regression models as highlighted in figure 7.3 by part A and part B. The first part of the model (part A in figure 7.3) categorises the STAR into *"inactive"* compared to *"insufficiently active and meeting current guideline levels of physical activity"* and the second (part B in figure 7.3) categorises it into *"inactive and insufficiently active"* compared to *"meeting current guideline levels of physical activity"*. Both the POM and PPOM models compare the probability of being in a higher category of the dependent variable compared to a particular reference category given the change of one unit of the independent variable (Mottram et al, 2008). However, the POM assumes that the odds ratios of the two comparisons (parts A and B) are the same (proportional odds) and produces a single set of odds ratios for being in a higher category than either reference category, whilst the PPOM allows for different effects of independent variables at different levels of the dependent STAR category (Lunt, 2005) and may produce more than one set of odds ratios (for part A and part B).

Figure 7.3 Schematic representations of the two component parts of the STAR ordinal regression model

Part A: Category 1 (reference) compared to category 2 and 3



Part B: Category 1 and 2 (reference) compared to category 3



In order to decide which model was most appropriate, the more simple proportional odds model was initially run for each independent variable followed by a Brant test for proportional odds (Williams, 2006).

Brant test for proportional odds

The Brant test works by creating two logistic regression models (part A and part B) and uses a Chi square test for difference to see if the estimated independent variable regression coefficients (prior to conversion into logits) differ for part A and B of the model (Ananth & Kleinbaum, 1997; Williams, 2006). If the proportional odds assumption is not violated, then the proportional odds model restraint is justified (i.e. it is assumed that the effect of the independent variable is the same at each level of the dependent variable) and the proportional odds model is used creating a single logit output (Peterson & Harrell, 1990; Ananth & Kleinbaum, 1997; Williams, 2006). However, if the proportional odds Brant test is violated (i.e. $p<0.05$) then the model was rerun using the PPOM and two separate logit outputs are created for Part A and part B (also known as the generalised ordered logit).

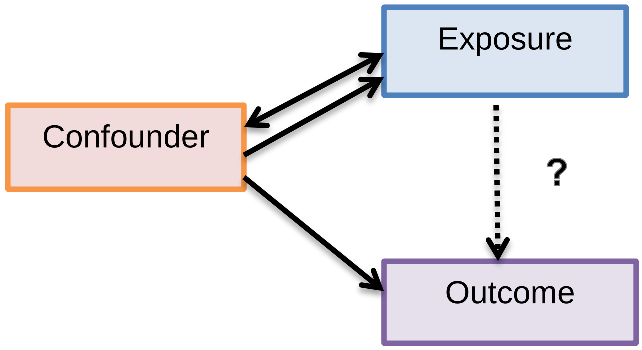
Final model interpretation

Following model fitting, model outputs of independent variable odds ratios for parts A and B of the model (which may be identical if the proportional odds assumption was met) and their 95% confidence intervals and *p* values ($\alpha=0.05$), for statistical significance of independent variable odds ratios being different to 1 were interpreted (Greenland, 1989). Odds ratios greater than 1 indicate more chance of being in a higher category of physical activity given the increase in one unit of the independent variable.

7.3.5 Methods to address objective 2

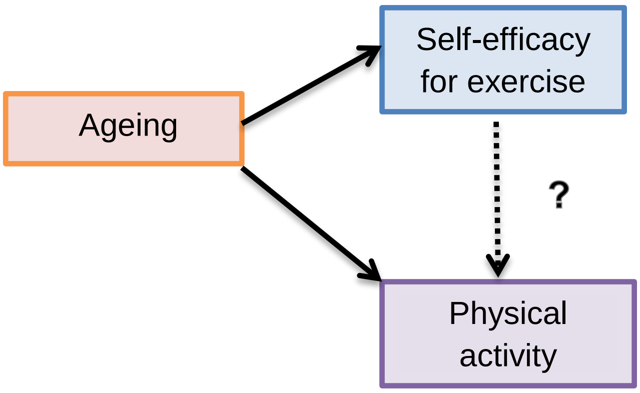
Understanding the univariable relationships between key covariates and physical activity level is of interest within this thesis since these covariates may also influence the relationships between attitudes and beliefs about physical activity and physical activity level. These covariates may act as either confounders (and contribute to non-causal associations between attitudes and beliefs about physical activity and physical activity level) or *"effect modifiers"* and lead to the heterogeneity of association between attitudes and beliefs about physical activity and physical activity level based on their presence and level (Szklo & Nieto, 2014) (due to the focus of the primary thesis research questions, the large number of multivariable models and covariates within this thesis, and the lack of known effect modifiers to investigate, interactions were considered outside the scope of this thesis). Considering a possible confounding example, it is plausible that increased age may act as a confounder of the association between self-efficacy and physical activity since it could cause reduced physical activity due to physiological ageing and associated physical impairment, as well as being associated with reduced self-efficacy due to subjective norms of being less active with ageing. Figure 7.4 shows the general requirements for confounding (Szklo & Nieto, 2014), whilst figure 7.5 depicts the above example.

Figure 7.4 Requirements for confounding between exposure and outcome



A single arrow head indicates a causal relationship, whilst a bidirectional arrow indicates either a causal or non-causal association, and the dotted line indicates the association of interest.

Figure 7.5 A plausible confounding example



A single arrow head indicates a causal relationship, whilst a bidirectional arrow indicates either a causal or non-causal association, and the dotted line indicates the association of interest.

Simple linear and ordinal regressions were carried out regressing self-report physical activity level variables on key covariates from both the BEEP trial and ABC-Knee data sets (see table 7.1 and the variables highlighted in green within table 7.2 for a list of these sociodemographic and clinical covariates). The methods used for these analyses were identical to those described for objective 1.

Within the ABC-Knee dataset, in order not to over-fit subsequent multivariable models, only the covariates deemed to be most theoretically important and repeatedly shown within the literature to be associated with physical activity level and or attitudes and beliefs about physical activity were selected for primary analyses a priori. These included age, gender, function and pain (captured in combined form by the Chronic Pain Grade- CPG) (see chapter 2, section 2.10.3 and 2.12 for supporting literature). Post hoc sensitivity analyses exploring the univariable associations between additional covariates and physical activity level were also carried out (see Appendix VIII).

7.3.6 Methods to address objective 3

In order to investigate the associations between individual attitude and belief scales and physical activity level in older adults with knee pain adjusting for potential confounders, multivariable regression modelling was selected.

I) Model building

Adjusted associations between specific attitudes and beliefs about physical activity and physical activity level were investigated by building six individual regression models (Models A to F), one for each available attitude and belief variable (see table 7.3 below). Multiple linear regression modelling was chosen for the BEEP trial dataset (Models A to C) and partial proportional odds regression modelling for the ABC-Knee data analyses (Models D to F) due to the nature of their physical activity dependent variables. The generic model building strategies for Models A to C and D to F are summarised in figures 7.6 and 7.7 respectively. Since rationale and detailed explanations of multiple linear regression have been described previously (see chapter 6, section 6.4.1) detailed description of regression model building and output interpretation is not provided for Models A to C. However, additional detail for the PPOMs (Models D to F) is provided after figure 7.7.

The decision to initially investigate the available attitude and belief scales in three separate multivariable models for each dataset, rather than a single model, allowed for later comparison of each individual attitude and belief variable with each other (within each dataset). The strategy also reduced the chance of collinearity and over-adjustment. There is potential for collinearity and over-adjustment (as described in section chapter 6, 6.4.1, III) in a combined attitude and belief about physical activity model, since the three independent variables cover overlapping theoretical concepts and may explain much of the same variance in future physical activity level.

Table 7.3 Multivariable models

BEEP multiple linear regression models
Model A: Self Efficacy-for Exercise
Model B: Positive Outcome Expectations for Exercise
Model C: Negative Outcome Expectations for Exercise
ABC-Knee ordinal regression models
Model D: Tampa Scale for Kinesiophobia
Model E: Older Persons Attitudes towards Physical Activity and Exercise
Model F: Arthritis Self-Efficacy “other”

Figure 7.6 Objective 3 Models A to C model building strategy overview

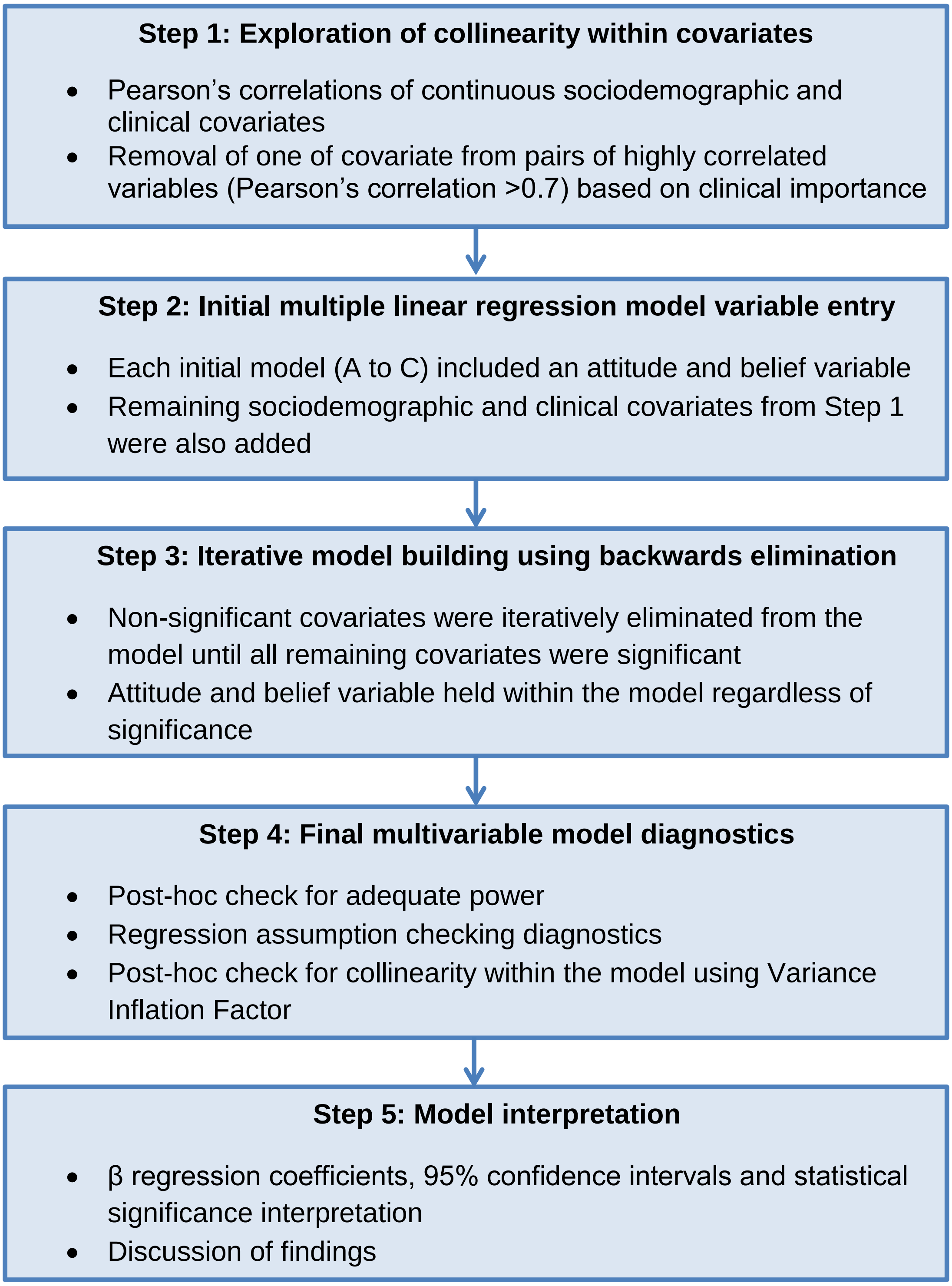


Figure 7.7 Objective 3 Models D to F model building strategy overview

Step 1: A priori selection of salient covariates

- A priori selection of model covariates based on theory and consistency of association with physical activity within older adult with knee pain literature
- Covariates were gender, age, Chronic Pain Grade and previous use of exercise to treat knee pain

↓

Step 2: Partial proportional odds model building

- Each model (D to F) included an attitude and belief variable
- A priori all covariates from Step 1 were held in the model regardless of significance

↓

Step 3: Final multivariable model diagnostics

- Post-hoc check for adequate power
- Assumption checks
- Informal collinearity checks rerunning the model as a multiple linear model and using Variance Inflation Factor

↓

Step 5: Model interpretation

- Model variable odds ratios, 95% confidence intervals and statistical significance interpretation
- Discussion of findings

ABC-Knee dataset Models D to F model building strategy

The partial proportional odds regression models D to F involved unique methodology as summarised in figure 7.7. Following the previously discussed covariate selection criteria, one independent variable together with all four salient covariates were added for the first stage of each model. The *"Gologit-2"* STATA program was used to fit a multivariable PPOM (Williams 2006). This program allows independent variables that satisfy the proportional odds assumption (the previously discussed Brant test) to be modelled using proportional odds and those that do not using generalised ordered logit modelling that allows for flexibility in proportional odds violation (Williams, 2006).

The ordinal regression model output including odds ratios together with 95% confidence intervals and *p* values for statistical significance of each independent variable and remaining model covariates were interpreted as in section 7.3.4. Retrospective power analysis was carried out to ensure that enough data were available to fit the models based on 10 participants in the smallest dependent category per independent variables (Harrell et al, 1996; Peduzzi et al, 1996; Hosmer & Lemeshow, 2000; Menard, 2010; Stoltzfus, 2011).

7.3.7 Methods to address objective 4

In order to investigate the combined effect of multiple attitudes and beliefs about physical activity and physical activity level in older adults with knee pain, adjusting for potential confounders, multivariable regression analysis was carried out simultaneously including all the attitudes and beliefs about physical activity variables. It is theoretically plausible that multiple attitudes and beliefs about physical activity will simultaneously influence and be associated with physical activity level. For example, drawing on social cognition theory in the BEEP dataset, self-efficacy for exercise and outcome expectations for exercise may both be associated with physical activity (Biddle & Mutrie, 2008). Combining multiple attitude and belief about exercise variables and covariates in multivariable models is also of clinical interest because it may help discover which attitude and belief scales are most strongly associated with physical activity level and whether they are more strongly linked with physical activity level than other sociodemographic, clinical and previous behaviour variables.

I) Model building

Two separate multivariable models were built: one for the BEEP data (Model G), and one for the ABC-Knee data (Model H). The BEEP multiple linear regression model and ABC-Knee partial proportional odds model methods were identical to those described for objective 3 in section 7.3.6, except the initial BEEP model included SEE, positive OEE and negative OEE together whilst the ABC-Knee model simultaneously included the TSK, OPAPAEQ and ASES other variables. In addition, a priori within the BEEP model, the three attitudes and beliefs about physical activity variables were considered equally for model backwards elimination since this objective was also interested in whether attitudes and beliefs about physical activity outcompeted other covariates. The BEEP model building was stopped once all non-statistically significant variables were eliminated. In both models, final model output parameters were interpreted and post hoc power calculations with assumptions and collinearity testing carried out as previously described (chapter 6, section 6.4.1, step 5). The following section goes on to present the results from all 4 objectives.

7.4 Results

Results are reported by objective for each dataset separately. BEEP results are presented initially followed by ABC-Knee results. Where possible, tables present the results of multiple objective analyses together. This allows the side-by-side interpretation of crude univariable associations between different attitudes and beliefs about exercise and physical activity level, together with the corresponding covariate estimates. Secondly, it allows unadjusted and multivariable models within the same dataset to be compared side-by-side. Within this chapter, 95% CI without p values are presented for model output statistics since (unlike chapter 6) they allow clear inference regarding statistical significance.

7.4.1 BEEP dataset objective 1

"Investigate the univariable associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain"

Greater self-efficacy for exercise, more positive outcome expectations for exercise and less negative outcome expectations were all significantly associated with higher levels of physical activity (see column one table 7.4). Interpreting the crude results, every extra point on the SEE score was associated with an increase of 5.50 (2.21, 8.20) on the PASE. Similarly for every extra point on the positive OEE and negative OEE scales, there was an associated increase in PASE score by 19.58 (6.85, 32.30) and 20.16 (11.38, 28.94) respectively.

7.4.2 BEEP dataset objective 2

"Investigate the univariable associations of sociodemographic and clinical covariates and physical activity level in older adults with knee pain"

Most sociodemographic and clinical covariates were crudely and significantly associated with physical activity level (see column one table 7.4). However, pain severity, the presence of widespread pain, and having a partner did not reach statistical significance. Considering the sociodemographics that were associated with physical activity, being female β= -18.58 (-33.76, -3.40), of older age β= -2.09 (-2.86, -1.32), higher BMI β= -1.73 (-3.10, -0.36) and not being in employment β= -57.83 (-72.49, -43.17) were all associated with lower PASE physical activity, whilst those in manual occupations had higher levels of physical activity than those employed in professional and management roles.

Considering the clinical variable univariable associations, WOMAC pain, although approaching significance, was not significantly associated with physical activity. However, there was a positive association between higher functioning and higher levels of physical activity β= -1.14 (-1.76, -0.51) (higher WOMAC function scale indicates more functional disability). WOMAC stiffness score was also significantly negatively associated with PASE score β= -5.18 (-9.54, -0.83) (higher WOMAC stiffness scores indicate increased stiffness). Those who had had their knee pain for longer than a year showed trends towards being less physically active, although this only reached statistical significance for knee pain duration of between 5 to 10 years. Having more comorbidities was significantly negatively associated with physical activity level. Having a comorbidity was associated with lower PASE β= -20.56 (-33.83, -2.28), whilst two or more comorbidities compounded the effect β= -48.35 (-66.89, -29.81) (compared to those without comorbidities). Those with widespread pain according to the Manchester widespread pain definition (Hunt et al, 1999) had trends towards lower levels of physical activity. Psychological variables revealed that higher depression and anxiety were also significantly associated with being less physically active. A one point increase on the PHQ8 depression scale and GAD7 anxiety scale was associated with lower PASE scores β= -3.82 (-5.40, -2.24) and β= -1.96 (-3.67, -0.25) points respectively.

7.4.3 BEEP dataset objective 3

"Investigate the associations between individual attitudes and beliefs about physical activity scales and physical activity level in older adults with knee pain, adjusting for potential confounders"

The final adjusted multivariable Models A to C are shown in table 7.4. Self-efficacy for exercise β= 4.14 (0.26, 8.03) and positive outcome expectations for exercise β= 16.71 (1.87, 31.55) remained positively associated with physical activity level in the adjusted Models A and B respectively. However, negative outcome expectations (which were crudely associated with physical activity) were no longer significantly associated within multivariable Model C β=4.47 (-6.39, 15.33).

Socioeconomic status, number of comorbidities and PHQ8 depression were all consistently included in all three multivariable models with somewhat attenuated β coefficients compared to their univariable model βs. However, during model building for Models A to C a number of covariates that were crudely associated with physical activity level were excluded because they were no longer significant within a multivariable model. These included gender, age, BMI, WOMAC function, WOMAC stiffness, duration of time since pain onset and GAD7 anxiety. In addition, WOMAC function, WOMAC stiffness and GAD7 anxiety were all initially removed from model building due to collinearity with WOMAC pain and PHQ8 depression.

7.4.4 BEEP dataset objective 4

"Investigate the combined effect of multiple attitudes and beliefs about physical activity on physical activity level in older adults with knee pain, adjusting for potential confounders"

The final adjusted model was identical to Model B shown in table 7.4. This model was interpreted in section 7.4.3 above. Positive OEE was the only attitude and belief about exercise variable that remained in the final multivariable model, with SEE and negative OEE both being non-significant after backwards elimination model building.

Table 7.4 Objectives 1 to 4: BEEP unadjusted and adjusted Models A to C (PASE physical activity level at baseline)

	Physical activity level (PASE) at baseline							
	Unadjusted		Adjusted model A (SEE)		Adjusted model B (positive OEE)#		Adjusted model C (negative OEE)	
	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig
Attitudes & beliefs								
SEE	5.50 (2.21, 8.20)	0.001	4.14 (0.26, 8.03)	0.037				
Positive OEE	19.58 (6.85, 32.30)	0.003			16.71 (1.87, 31.55)	0.027		
Negative OEE*	20.16 (11.38, 28.94)	<0.001					4.47 (-6.39, 15.33)	0.419
Sociodemographics								
Gender (ref male)	-18.58 (-33.76, -3.40)	0.017						
Age	-2.09 (-2.86, -1.32)	<0.001						
Continuous BMI	-1.73 (-3.10, -0.36)	0.013						
Socio-ec. category (ref professional)								
Intermediate	11.79 (-10.48, 34.06)	0.298	10.28 (-10.96, 31.51)	0.342	10.23 (-10.94, 31.39)	0.343	8.39 (-12.90, 29.68)	0.439
Routine/ Manual job	27.38 (7.05, 47.71)	0.008	28.59 (8.92, 48.27)	0.005	29.20 (9.56, 48.84)	0.004	28.36 (8.47, 48.26)	0.005
Currently in paid work (ref working)	-57.83 (-72.49,-43.17)	0.001	-38.92 (-56.12,-21.73)	<0.001	-37.44 (-54.58,-20.29)	<0.001	-38.51 (-55.86, -21.16)	<0.001
Partner category (ref no partner)	14.71 (-3.65, 33.07)	0.116						
Clinical covariates								
WOMAC pain	-2.11 (-4.28, 0.07)	0.058						
WOMAC function	-1.14 (-1.76, -0.51)	<0.001						
WOMAC stiffness	-5.18 (-9.54, -0.83)	0.02						
Pain duration (ref <1 year)								
> 1 yr and < 5yrs	-19.06 (-38.75, 0.64)	0.058						
>5 yrs and <10 yrs	-31.65 (-55.07, -8.24)	<0.001						

>10 yrs	-16.74 (-40.90, 7.42)	0.174						
Comorbidities (ref none)								
1 other condition	-20.56 (-38.83, -2.28)	0.028	-12.72 (-33.08, 7.65)	0.220	-10.07 (-30.43, 10.30)	0.332	-11.09 (-31.49, 9.31)	0.286
2+ other conditions	-48.35 (-66.89,-29.81)	<0.001	-26.75 (-49.02,-4.49)	0.019	-25.86 (-48.09,-3.62)	0.023	-26.31 (-48.70, -3.93)	0.021
Widespread pain (ref no WSP)	-20.92 (-41.87, 0.04)	0.05						
PHQ8 depression	-3.82 (-5.40, -2.24)	<0.001	-2.59 (-4.47, -0.72)	0.007	-2.93 (-4.74, -1.13)	0.002	-2.91 (-4.80, -1.03)	0.003
GAD7 anxiety	-1.96 (-3.67, -0.25)	0.025						

Key:
White=Unadjusted Models
Blue=Adjusted model A (Self Efficacy for Exercise)
Red=Adjusted Model B (Positive Outcome Expectations for Exercise); #= also represents the multivariable Model G built for objective 4.
Purple=Adjusted Model C (Negative Outcome Expectations for Exercise)

Footnotes: Complete case data, all variables were measured at baseline, multiple linear regression adjusted models selected via backwards elimination holding one of self-efficacy for exercise (Model A) n=338, positive outcome expectations for exercise (Model B) n=339 and negative outcome expectations for exercise (Model C) n=340 within the model. Higher PASE score indicates higher level of physical activity. Higher scores on self-efficacy for exercise and positive outcome expectancies indicate higher self-efficacy and positive outcome expectancies. *Higher score on the negative outcome expectancy scale indicates less negative outcome expectancies. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher depression and anxiety scores indicate worse depression and anxiety

Abbreviations: β=unstandardized coefficient; BMI=Body Mass Index; CI=Confidence Interval; GAD7=Generalised Anxiety Disorder Questionnaire; OEE=Outcome Expectations for Exercise (positive and negative subscales); SEE=Self-Efficacy for Exercise; PHQ8=Personal Health depression Questionnaire; WOMAC=Western Ontario and McMaster Osteoarthritis Index; WSP=Widespread Pain; yr=year.

7.4.5 ABC-Knee dataset objective 1

"Investigate the univariable associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain"

All of the attitudes and beliefs about exercise scales (TSK, OPAPAEQ, and ASES "other") were associated with physical activity level measured by the STAR (table 7.5). Less fear of movement and reinjury, more positive attitudes about exercise and physical activity and higher self-efficacy for physical activity were associated with higher levels of physical activity. The TSK and ASES *"other"* models did not meet the proportional odds assumption (Brant test $p<0.05$), i.e. there is a different effect of both of these scales at differing levels of physical activity. Hence, the proportional odds assumption was relaxed using the partial proportional odds model and two sets of OR output were produced, one for *"inactive"* vs *"insufficiently active and meeting current guidelines"* and one for *"inactive and insufficiently active"* vs *"meeting current recommended guidelines"*. OPAPAEQ met the proportional odds assumption (Brant test p>0.05), hence, only one OR is presented. Interpreting the crude results, for every extra point on the TSK (i.e. increased fear) there was an OR of 0.89 (0.83, 0.94) (less than 1, hence lower likelihood) of being in a higher category of physical activity than in the *"inactive group"*, and an OR of 0.97 (0.95, 0.99) (a lower likelihood) of being in a higher category than in the combined *"inactive and insufficiently active"* categories. These results can also be interpreted as there being an 11% decrease in the odds of being in a higher category of physical activity than the *"inactive group"* and a 3% decrease in the odds of being in a higher category of physical activity than the combined *"inactive and insufficiently active"* categories for every point on the TSK.

For every additional point on the OPAPAEQ (i.e. more positive attitude about physical activity), there was an OR of 1.07 (1.05, 1.10) (greater than 1 and hence higher likelihood) of being in a higher category of physical activity. Alternatively, for every extra point on the OPAPAEQ scale there is a 7% increase in the odds of being in a higher category of physical activity. For every extra point on the ASES *"other"* scale (i.e. increased self-efficacy for physical activity) there was an OR of 1.04 (1.02, 1.06) or 4% increase in the odds of being in a higher category of physical activity than the *"inactive group"* and an OR of 1.01 (1.00, 1.02) or a 1% increase in the odds of being in a higher category than the *"combined inactive and insufficiently active"* categories.

7.4.6 ABC-Knee dataset objective 2

"Investigate the univariable associations of sociodemographic and clinical covariates and physical activity level in older adults with knee pain"

Age, CPG and previous use of exercise to treat knee pain in the last month were all crudely associated with physical activity level (see table 7.5), however, gender was not associated. The gender and previous exercise covariates met the proportional odds assumption (Brant test $p>0.05$) and were fitted using the proportional odds model. Age and CPG did not, and hence were fitted using the partial proportional odds model which produced two sets of OR output (see section 7.3.4 & 7.3.5). No previous use of exercise to treat knee pain was strongly associated with lower levels of physical activity OR 0.56 (0.40, 0.78). Increasing age was associated with lower physical activity, with the effect greater at lower levels of physical activity as indicated by lower ORs for *"inactive"* compared to *"insufficiently active and meeting current guidelines"* OR 0.90 (0.87, 0.94) than *"inactive and insufficiently active"* compared to *"meeting current guidelines"* OR

0.98 (0.96, 1.00). Having a CPG category of II to IV[1] was associated with greater likelihood of being *“inactive”* compared to *“insufficiently active and meeting current guidelines”* OR 0.18 (0.06, 0.51) but was not associated with category of physical activity when *“inactive and insufficiently active”* participants were compared to those *“meeting current guidelines”* OR 0.98 (0.68, 1.39).

Sensitivity analyses investigating additional sociodemographic and clinical covariate univariable associations with physical activity level that were not included in the primary analysis can be found in table form in Appendix VIII. Notable covariates that were significantly associated with physical activity across both parts of the model were WOMAC function and having 2 or more comorbidities. Lower function and 2 or more comorbidities were associated with increased likelihood of being in a lower physical activity level category.

[1] Chronic pain grade I=low disability and low pain intensity, II=low disability and high pain intensity, III=moderate disability and moderately limiting, IV=high disability and severely limiting (Von Korff et al., 1992)

Table 7.5 Objectives 1 and 2: ABC-Knee unadjusted STAR physical activity level associations

Unadjusted STAR physical activity level models				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Attitude and belief scales				
Tampa Scale for Kinesiophobia	0.89 (0.83, 0.94)	<0.001	0.97 (0.95, 0.99)	0.005
Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire	1.07 (1.05, 1.10)	<0.001	-	-
Arthritis Self-Efficacy Other	1.04 (1.02, 1.06)	0.001	1.01 (1.00, 1.02)	0.038
Sociodemographics				
Age	0.90 (0.87, 0.94)	<0.001	0.98 (0.96, 1.00)	0.022
Gender (ref male)				
Female	0.83 (0.60, 1.15)	0.260	-	
Clinical covariates				
Chronic Pain Grade (ref low disability/ low intensity)				
Categories II-IV[c]	0.18 (0.06, 0.51)	0.001	0.98 (0.68, 1.39)	0.895
Used exercise to treat knee pain (ref yes)				
No	0.56 (0.40, 0.78)	0.001	-	

Key:
Highlighted variables did not meet the Brant test for proportional odds *p*<0.05 i.e. have different effects at each level of physical activity hence were fitted relaxing the proportional odds restraint. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash (fitted with proportional odds). [a] =Reference category is "inactive"; [b] =Reference category is "inactive and insufficiently active". [c] =Low disability and high pain intensity/ high disability moderately limiting/ high disability and severely limiting.

Footnotes: Complete case data; Partial proportional odds modelling. Higher Tampa Scale for Kinesiophobia scores indicates greater fear of movement and reinjury. Higher scores on Arthritis Self Efficacy Other scores indicate greater self-efficacy for physical activity. Higher OPAPAEQ score indicates more positive attitudes towards exercise and physical activity. Higher WOMAC scores indicate higher pain, worse function and stiffness.

Abbreviations: CI=Confidence Interval; ref=Reference category; STAR=Short Telephone Activity Recall questionnaire; WOMAC=Western Ontario and McMaster Osteoarthritis Index.

7.4.7 ABC-Knee dataset objective 3

"Investigate the associations between individual attitudes and beliefs about physical activity scales and physical activity level in older adults with knee pain, adjusting for potential confounders"

All three attitudes and beliefs about physical activity variables within models D to F met the proportional odds assumption and were fitted with proportional odds. Model D investigating the adjusted association between the TSK and STAR showed that higher levels of movement-related fear were associated with lower likelihood of being in a higher category of physical activity OR 0.97 (0.95, 0.99) (table 7.6). Model E, investigating the adjusted association between OPAPAEQ and STAR, showed that more positive attitudes about exercise and physical activity relating to vigorous activity, tension release, health outcomes, and social benefits were associated with higher likelihood of being in a higher category of physical activity OR 1.06 (1.03, 1.09) (table 7.7). Model F investigating the ASES "other" scale, showed non-significant trends that higher self-efficacy for physical activity was linked with higher categories of physical activity OR 1.01 (1.00, 1.02) (table 7.8).

Summarising the covariate output from Models D to F, gender and use of exercise to treat knee pain in the previous month met the proportional odds assumption and were modelled using proportional odds, whilst age and CPG did not and were modelled relaxing the proportional odds assumption. Gender was not associated with physical activity level in any of the models, whilst older age was consistently associated with higher likelihood of being *"inactive"* compared to "*insufficiently active and meeting current guidelines"* , but not associated with *"inactive and insufficiently active"* compared to *"meeting current guidelines"*. Categories II to IV of the CPG were not associated with physical activity except within the TSK Model D where it was associated with higher likelihood of being *"inactive"* compared to "*insufficiently active and meeting current guidelines".* Previous exercise behaviour was consistently associated with current level of physical activity in all models, with those who had used exercise to treat knee pain in the previous month more likely to be in a higher category of physical activity level. Post hoc power analysis indicates that Model D to F were at risk of overfitting since they included five variables for just 25 events in the inactive category (Harrell et al, 1996; Peduzzi et al, 1996; Hosmer & Lemeshow, 2000; Menard, 2010; Stoltzfus, 2011)

Table 7.6 Objective 3: ABC-Knee Model D-STAR physical activity level (including TSK)

Adjusted STAR physical activity level				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Attitude and belief scales				
Tampa Scale for Kinesiophobia	0.97 (0.95, 0.99)	0.014	-	-
Sociodemographics				
Gender (ref male)				
Female	0.82 (0.58, 1.16)	0.264	-	-
Age	0.91 (0.87, 0.96)	0.001	0.99 (0.97, 1.01)	0.36
Clinical covariates				
CPG dichotomy (ref I: low disability, low intensity)				
Categories II-IV[c]	0.28 (0.09, 0.91)	0.035	1.21 (0.81, 1.82)	0.35
Used exercise to treat knee pain (ref yes)				
No	0.59 (0.42, 0.84)	0.003	-	

Key:
Highlighted variables did not meet the Brant test for proportional odds *p*<0.05 i.e. have different effects at each level of physical activity hence were fitted relaxing the proportional odds restraint. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash (fitted with proportional odds). [a] =Reference category is “inactive”; [b] =Reference category is “inactive and insufficiently active”; [c] =Low disability and high pain intensity/ high disability moderately limiting/ high disability and severely limiting.

Footnotes: Complete case data n=529; Partial proportional odds modelling. Higher Tampa Scale for Kinesiophobia scores indicates greater fear of movement and reinjury.

Abbreviations: CI=Confidence Interval; ref=Reference category; CPG=Chronic Pain Grade; STAR=Short Telephone Activity Recall questionnaire; TSK=Tampa Scale for Kinesiophobia.

Table 7.7 Objective 3: ABC-Knee Model E-STAR physical activity level (including OPAPAEQ)

Adjusted STAR physical activity level				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Attitude and belief scales				
Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire	1.06 (1.03, 1.09)	<0.001	-	-
Sociodemographics				
Gender (ref male)				
Female	0.90 (0.63, 1.27)	0.519	-	-
Age	0.92 (0.88, 0.97)	0.001	0.99 (0.97, 1.01)	0.492
Clinical covariates				
CPG dichotomy (ref I: low disability, low intensity)				
Categories II-IV[c]	0.34 (0.11, 1.03)	0.058	1.19 (0.80, 1.76)	0.386
Used exercise to treat knee pain (ref yes)				
No	0.65 (0.46, 0.93)	0.02	-	-

Key:
Highlighted variables did not meet the Brant test for proportional odds *p*<0.05 i.e. have different effects at each level of physical activity hence were fitted relaxing the proportional odds restraint. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash (fitted with proportional odds). [a] =Reference category is "inactive"; [b] =Reference category is "inactive and insufficiently active"; [c] =Low disability and high pain intensity/ high disability moderately limiting/ high disability and severely limiting.

Footnotes: Complete case data n=523; Partial proportional odds modelling. Higher OPAPAEQ score indicates more positive attitudes about exercise and physical activity.

Abbreviations: CI= Confidence Interval; ref=Reference category; CPG=Chronic Pain Grade; OPAPAEQ=Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire; STAR=Short Telephone Activity Recall questionnaire.

Table 7.8 Objective 3: ABC-Knee Model F-STAR physical activity level (including ASES "other")

Adjusted STAR physical activity level				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	**p value**	**Odds ratio (95%CI)**	**p value**
Attitude and belief scales				
Arthritis Self Efficacy "Other"	1.01 (1.00, 1.02)	0.052	-	-
Sociodemographics				
Gender (ref male)				
Female	0.91 (0.65, 1.28)	0.580	-	-
Age	0.92 (0.88, 0.96)	0.001	0.99 (0.97, 1.01)	0.354
Clinical covariates				
CPG dichotomy (ref I: low disability, low intensity)				
Categories II-IV[c]	0.35 (0.11, 1.05)	0.06	1.17 (0.78, 1.76)	0.443
Used exercise to treat knee pain (ref yes)				
No	0.57 (0.40, 0.80)	0.001	-	-

Key:
Highlighted variables did not meet the Brant test for proportional odds *p*<0.05 i.e. have different effects at each level of physical activity hence were fitted relaxing the proportional odds restraint. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash (fitted with proportional odds). [a] =Reference category is "inactive"; [b] =Reference category is "inactive and insufficiently active"; [c] =Low disability and high pain intensity/ high disability moderately limiting/ high disability and severely limiting.

Footnotes: Complete case data n=536; Partial proportional odds modelling. Higher scores on Arthritis Self Efficacy Other scores indicate greater self-efficacy for physical activity.

Abbreviations: ASES=Arthritis Self Efficacy Scale; CI=Confidence Interval; ref=Reference category; CPG=Chronic Pain Grade; STAR=Short Telephone Activity Recall questionnaire.

7.4.8 ABC-Knee dataset objective 4

"Investigate the combined effect of multiple attitudes and beliefs about physical activity on physical activity level in older adults with knee pain, adjusting for potential confounders"

All three of the attitudes and beliefs about physical activity variables, together with the gender and previous behaviour covariates, satisfied the proportional odds assumption and were modelled using proportional odds. Age and CPG did not satisfy the assumption and were modelled relaxing the proportional odds assumption. In the combined adjusted attitudes and beliefs about physical activity model, only the OPAPAEQ, age and previous exercise to treat knee pain in the last month variables remained significantly associated with physical activity (table7.9). Higher OPAPAEQ scores OR 1.06 (1.03, 1.09) and previous use of exercise to treat knee pain were both associated with higher levels of physical activity, whilst increasing age was associated with the *"inactive"* group. The TSK, ASES other, gender and CPG variables were not associated with physical activity in the combined Model H. Post hoc power calculation indicated this model was at risk of overfitting since it exceeds recommendations for the number of events per variable with seven variables and just 25 events in the inactive category (Harrell et al, 1996; Peduzzi et al, 1996; Hosmer & Lemeshow, 2000; Menard, 2010; Stoltzfus, 2011).

Table 7.9 Objective 4: ABC-Knee Model H-STAR physical activity level (including combined attitudes and beliefs)

Adjusted ABC-Knee STAR physical activity level				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	**p value**	**Odds ratio (95%CI)**	**p value**
Attitude and belief scales				
Tampa Scale for Kinesiophobia	0.98 (0.95, 1.00)	0.098	-	-
Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire	1.06 (1.03, 1.09)	<0.001	-	-
Arthritis Self Efficacy "Other"	1.00 (0.99, 1.02)	0.573	-	-
Sociodemographics				
Gender (ref male)				
Female	0.86 (0.60, 1.24)	0.422	-	-
Age	0.92 (0.87, 0.97)	0.002	1.00 (0.98, 1.02)	0.691
Clinical covariates				
CPG dichotomy (ref I: low disability, low intensity)				
Categories II-IV[c]	0.32 (0.10, 1.05)	0.06	1.46 (0.95, 2.24)	0.085
Used exercise to treat knee pain (ref yes)				
No	0.68 (0.47, 0.98)	0.04	-	-

Key:
Highlighted variables did not meet the Brant test for proportional odds p<0.05 i.e. have different effects at each level of physical activity hence were fitted relaxing the proportional odds restraint. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash (fitted with proportional odds). [a] =Reference category is "inactive"; [b] =Reference category is "inactive and insufficiently active"; [c] =Low disability and high pain intensity/ high disability moderately limiting/ high disability and severely limiting.

Footnotes: Complete case data n=512; Partial proportional odds modelling. Higher Tampa Scale for Kinesiophobia scores indicate greater fear of movement and reinjury. Higher scores on Arthritis Self Efficacy Other scores indicate greater self-efficacy for physical activity. Higher OPAPAEQ score indicates more positive attitudes towards exercise and physical activity.

Abbreviations: CI=Confidence Interval; ref=Reference category; CPG=Chronic Pain Grade; STAR=Short Telephone Activity Recall questionnaire.

7.5 Discussion

This chapter aimed to investigate the cross-sectional associations between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. This section discusses the findings from the four objectives (see 7.2) using data analyses from both the BEEP trial and ABC-Knee datasets. It begins by summarising the main findings before discussing each objective individually and comparing the findings to existing literature. The strengths and weakness of the methods utilised are evaluated prior to exploration of the clinical and research implications. The chapter concludes with a summary and introduction of chapter 8.

7.5.1 Summary of main findings

This study is the first to quantitatively investigate the relationship between attitudes and beliefs about physical activity and self-reported physical activity levels in older adults with knee pain, whilst also adjusting for covariates. Self-efficacy for exercise, positive outcome expectations for exercise, fear of movement, and a composite scale of physical activity attitudes (relating to vigorous activity, health outcomes, tension release, and social benefits) were all shown to be associated with self-reported activity, after adjusting for sociodemographic and clinical covariates. The findings from model building containing multiple attitude and belief scales, sociodemographics and clinical covariates were that positive outcome expectations about exercise and the composite scale of attitudes about physical activity (OPAPAEQ) were the only attitude and belief variables to remain significant, suggesting these measures to be most strongly associated with physical activity level.

It is not possible to confidently infer if attitudes and beliefs about physical activity are causal of physical activity or vice-versa, or indeed merely associated, since the analyses within this chapter were cross-sectional (Szklo & Nieto, 2014). However, attitudes and beliefs about physical activity may act as barriers to increasing physical activity level in older adults with knee pain (Hendry et al, 2006; Dekker, 2012; Holden et al, 2012; Nicolson et al, 2015) and, drawing on the crude findings from thesis Part 2, existing knee pain and recent low back pain literature, they may plausibly influence the effects of treatment (Fitzgerald et al, 2012; Wertli et al, 2014). Based on the findings, it is plausible that attitudes and beliefs about physical activity may be potentially modifiable targets for interventions aimed at increasing physical activity in insufficiently active older adults with knee pain. Hence, it is logical to consider addressing them alongside more general barriers to exercise such as social and environmental factors (Brittain et al, 2011; Dekker, 2012; Nicolson et al, 2015). However, before firm conclusions and recommendations are made for interventions it is important to investigate the longitudinal relationships between attitudes and beliefs about physical activity and future physical activity level.

I) Crude associations between attitudes, beliefs and physical activity

Univariable associations were found between all of the investigated attitudes and beliefs about physical activity and physical activity level in both the BEEP trial and ABC-Knee datasets (see tables 7.4 and 7.5 respectively). The direction of association was as expected with greater self-efficacy, more positive outcome expectations, less fear of movement and harm, and more positive attitudes about physical activity all being associated with higher levels of physical activity. These findings, although crude and at risk of confounding, suggest that key attitudes and beliefs about physical activity are associated with self-report physical activity level. Crude results are useful in drawing inferences about the association between variables in clinical practice (Szklo and Nieto 2014). For example, knowledge of an individual's outcome expectations for exercise may contribute towards clinical reasoning about likely physical activity levels regardless of whether the relationship between these variables is causal or not.

The magnitude of the associations within the BEEP dataset can be interpreted from the size of the Beta regression coefficients for each attitude and belief variable together with the range of the attitude and belief and physical activity scale. For example, every point increase on the SEE scale (scored from 1-10) was associated with a 5.5 increase in PASE (scored from 0-400+). It is also possible to apply the principles of standardised mean difference (SMD) effect size calculation (Sullivan and Feinn 2012) to estimate the number of points an attitude and belief scale score would have to change to have a small or medium "effect size" on physical activity. For example, taking account of the baseline PASE score standard deviation (83), a three point change on the SEE or a one point change on the positive OEE represented a small effect size on physical activity. Such estimates can aid in the interpretation of the magnitude of crude associations between attitudes and beliefs from the BEEP dataset. Using these estimations it is possible to make the case that the associations are of clinical interest.

Crude associations between covariates and physical activity

A number of sociodemographic characteristics and clinical variables were also crudely associated with physical activity level (see tables 7.4 and 7.5 respectively). Only the primary analyses will be discussed here (although post hoc sensitivity analyses of additional covariates from the ABC-Knee study are available in

Appendix VIII). Increasing age and lower physical function were crudely associated with lower physical activity level in both datasets. However, there were some conflicting findings between the two datasets. Pain severity was not a significant predictor of physical activity level in the BEEP trial dataset analysis but was in the ABC-Knee analysis (when captured in composite form together with function within the CPG). Female gender was associated with lower physical activity within the BEEP trial analysis but not in the ABC-Knee analysis. It is possible that pain severity in a trial sample (who generally have higher levels of pain) is less strongly associated with physical activity level than a community sample or equally it could be that by combining pain with physical function (within the CPG as in the ABC-Knee dataset) it becomes associated with physical activity. The conflicting findings regarding gender may relate to the differences in sensitivity of the physical activity measures between studies since it was significantly associated with the PASE in the BEEP trial dataset but not with the more crude STAR measure within the ABC-knee study.

In addition to the above, higher BMI, professional socioeconomic classification, being unemployed, longer pain duration, greater stiffness, greater number of comorbidities, and higher levels of depression and anxiety were also associated with lower levels of physical activity within the BEEP trial dataset. Previous use of exercise to treat knee pain in the last month was associated with increased likelihood of being in a more active category of physical activity. These are discussed in the subsequent section.

II) Adjusted attitudes, beliefs and physical activity associations

Self-efficacy for exercise and positive outcome expectations for exercise were associated with physical activity level in adjusted Models A and B within the BEEP trial dataset analyses, whilst fear of movement and reinjury and the composite attitudes about physical activity scale were associated with physical activity level in adjusted Models D and E within the ABC-Knee data analyses. These findings are consistent with social cognition and fear avoidance models introduced in chapter 2, section 2.12 (Vlaeyen et al, 1995; Biddle & Mutrie, 2008) and existing qualitative literature (Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012) in suggesting that older adults with knee pain who have the confidence that they can carry out physical activity despite their knee pain, and those who believe it will be enjoyable and or of health benefit, are more likely to carry out higher levels of physical activity. In addition, those who believe that physical activity may cause harm to their knee and fear physical activity, were shown to be less active.

It is of note that negative outcome expectations for exercise were not found to be associated with physical activity in adjusted Model C. This may be because of the strong confounding effect of depression, or that this null finding was due to limitations in the negative outcome expectations for exercise scale, such as insufficient items to discriminate between differing levels of negative outcome expectations within participants.

Inferences about the magnitude of confounding in the relationship between attitudes and beliefs about physical activity and physical activity level can be made by comparing and contrasting the magnitude of crude and adjusted regression coefficients/ odds ratios for attitude and belief variables in models built for objectives 1 and 3. The adjusted regression coefficients for all three attitude and belief scales within the BEEP dataset were attenuated when compared to the crude coefficients (see table 7.4). This suggests that confounding variables were responsible for some of the magnitude of crude association between these variables and physical activity. A similar interpretation can be made from the ABC dataset with odds ratios converging towards 1 for the adjusted associations when compared to the unadjusted associations (see tables 7.5 to 7.8). The Confounding effects appeared most pronounced for negative outcome expectations within the BEEP analyses (see table 7.4). This is perhaps expected, since adjusting for comorbidities and depression, in particular, arguably overlap with negative outcome expectations for exercise and may plausibly explain some of the reduction in main effect of negative outcome expectations. Conceptual overlap of psychological constructs has been demonstrated in other joint pain populations (Campbell et al, 2013). Depression may overlap with negative outcome expectations since it has been conceptualised in similar ways, including cognitively, as negative views of the self and of the world and hopelessness about the future (Beck et al, 1979) as well as emotional distress, negative thinking and motivational deficits (Main et al, 2008).

The two adjusted models for self-efficacy produced conflicting findings. In contrast to Model A (which included the SEE scale), Model F (which included the ASES *"other"* scale) did not find a significant association between self-efficacy for physical activity and physical activity level. This could be because the ASES "other" scale also contains some items that do not relate to self-efficacy for physical activity per se. For example, this scale also contains items measuring self-efficacy for mood, fatigue and frustration (Lorig et al, 1989) (Appendix VI), which may reduce any true association between self-efficacy for physical activity and physical activity level. Limitations regarding measures are considered in more detail in section 7.5.3.

There was a consistent pattern within the final multivariable models for objectives 3 and 4 regarding the covariates that remained associated with physical activity level. These included socioeconomic status, work status, number of comorbidities and depression within the BEEP multivariable models, as well as age and previous use of exercise to treat knee pain in the last month within the ABC-Knee multivariable models. These variables represent some of the more important covariates and may be important predictors of physical activity level in older adults with knee pain. Considering socioeconomic status and work status, older adults who were still working and doing manual jobs were more likely to be physically active. Those remaining in physical work are likely to be younger (not retired), and fitter in order to be working in the first place. Those with more comorbidities and depression were likely to be less active. This finding matches literature from other conditions (Morrato et al, 2007; McNamara et al, 2014). It is not possible to differentiate if comorbidities contribute to lower levels of physical activity directly or if those who were less active are more likely to develop comorbidities. It is likely that both are the case. Depression includes loss of pleasure with activities (NICE, 2009) so it is logical that those who are more depressed also carry out less physical activity. Furthermore physical activity has been advocated as a treatment for reducing depression in the elderly (Mura & Carta, 2013; NICE, 2009), hence older adults who are more physically active are, at least to some extent, protected from depression. Whilst it may seem a truism that previous use of exercise is associated with current physical activity level, this finding is nevertheless important and could tentatively be interpreted that levels of physical activity in this population are relatively habitual (Biddle & Mutrie, 2008).

III) Modelling combined attitudes and beliefs about physical activity

In the physical activity level Models G and H, which were built initially entering combinations of attitude and belief about physical activity variables and covariates, positive outcome expectations for exercise and the composite OPAPAEQ outcompeted other attitude and belief variables and remained significant in the final Models G and H respectively. Hence these two attitude and belief scales may be particularly important in their associations with physical activity level and could be considered as key targets for interventions aimed at increasing physical activity.

7.5.2 Comparisons to existing research

To the author's knowledge, no previous studies have investigated the cross-sectional adjusted association between attitudes and beliefs about physical activity and physical activity level specifically in older adults with knee pain. However, comparisons can be made to more heterogeneous populations with arthritis (Der Ananian et al, 2008; Hutton et al, 2010; Sperber et al, 2014). Self-efficacy for exercise has received the most attention in these studies and there is a relative dearth of literature investigating other attitudes and beliefs about physical activity.

Self-efficacy for exercise has been shown to be associated with physical activity level in a study of adults with arthritis (n=136) (Der Ananian et al, 2008). Der Ananian and colleagues used a cross-sectional design to investigate the factors associated with self-report physical activity level (based on moderate and vigorous physical activity carried out in a usual week). In line with the current findings, they found greater self-efficacy for exercise (Marcus et al, 1992) was associated with a more active category of physical activity (30 minutes or more of moderate intensity exercise or 20 minutes or more of vigorous exercise on at least three days a week), in a multiple logistic regression model adjusting for sociodemographics, clinical, perceived social support to exercise and social interaction variables. These findings agree with those from this chapter.

The most recent study by Sperber and colleagues (2014), used structural equation modelling to explore the relationship between arthritis symptoms, self-efficacy for exercise (Resnick & Jenkins, 2000), and self-reported physical activity level. They used secondary data analysis of older adults with arthritis (n= 339) from a RCT of a lifestyle physical activity programme intervention. They found that self-efficacy for exercise was positively associated with higher levels of self-report physical activity adjusting for pain, fatigue and depression. These findings are also similar to those within the thesis.

Several items relating to attitudes and beliefs about physical activity were also shown to be associated with physical activity level in a large cross-sectional sample of adults with arthritis (n= 1051) (Hutton et al, 2010). Several attitude and belief variables were investigated using multiple logistic regression for their adjusted association with being active (defined by self-report as completing 30 minutes of moderate activity on five or more days a week, or 20 minutes or more of vigorous physical activity on three or more days a week). Items relating to positive and negative outcome expectations were associated with being active and inactive respectively. For example, those with stronger beliefs that *"regular activity will help me live a healthy life"* were more likely to be active, whilst those who had stronger beliefs that *"physical activity is uncomfortable for me"* and *"arthritis or health problems are a barrier"* were more likely to be inactive. Considering self-efficacy for exercise, those who were more confident they could *"be active five days a week"* were more likely to be active. On the theme of kinesiophobia, those who *"worried about the safety of physical activity"* were less likely to be active. Finally, those who were active because they *"enjoyed physical activity"* were more likely to be active. Hence, Hutton et al's (2010) results also supported the key findings within this chapter.

In summary, the findings from the analyses in this chapter are similar to those from heterogeneous populations of adults with arthritis. This has implications for the generalisability of the thesis findings and also adds confidence to the validity of the findings from the BEEP and ABC-Knee data analyses.

I) Theoretical considerations

The direction and significance of associations between attitudes and beliefs about physical activity and physical activity behaviour were in agreement with a range of theories discussed earlier in chapter 2, section 2.12. For example, considering social cognition theory, the findings support the link between outcome expectations for behaviour and self-efficacy for exercise and physical activity behaviour (Bandura 1977, Ogden 2007, Biddle and Mutrie 2008). Pain behaviour models such as the fear avoidance model were also supported with higher levels of kinesiophobia associated with lower levels of physical activity. However, as stated above, the cross-sectional nature of these analyses prevents inferences about determination of behaviour. There was insufficient information regarding social attitudes, beliefs and behaviour to support or refute models such as the biopsychomotor model or more complex ecological models.

7.5.3 Strengths and limitations of the data analyses

A key strength of the analyses within this chapter was the ability to draw on both a trial and a community survey dataset increasing the available variables for investigation and importantly the generalisability of the findings (see chapter 5, section 5.5.2 for further explanation). Both dataset sample sizes were relatively large and also included a wide range of attitudes and beliefs and covariates that had already been identified in the literature to be associated with physical activity level, for example age and physical function (Veenhof et al, 2012; Stubbs et al, 2015). This allowed investigation and adjustment of potential confounding between attitudes and beliefs about physical activity and physical activity level using multivariable modelling. Within the ABC-knee data analysis, selecting PPOM modelling and choosing not to collapse the *“inactive” and “insufficiently active”* groups provides more information and allows independent inferences to be drawn about this clinically at risk and higher disability group.

Some limitations exist that concern both datasets. As stated a priori, the data analyses were cross-sectional therefore it is not possible to make firm conclusions regarding cause and effect, only association. Although complete case data analyses were selected a priori based on the low levels of missing data within key variables and univariable analyses were based on near-complete sample datasets (see chapter 4, section 4.4.1 and chapter 5, section 5.4.2), the multivariable models A to F were based on fewer complete cases. This is due to these Models including a larger number of variables (each with missing data) and hence undergoing increased listwise deletion during analysis. These multivariable analyses hence have less precision and are also at increased risk of bias (Sterne et al, 2009). The level of missing data for ABC-Knee Models D to F, although not ideal, was considered acceptable, firstly because the proportion of missing data was relatively low and secondly, even if the data were not missing at random this would have been unlikely to substantially bias findings about associations between variables. However, due to more concerning levels of listwise deletion in the BEEP Models A to C post-hoc sensitivity analyses were carried out rerunning these models using multiple imputed data to address uncertain confidence in the primary analyses (see Appendix VIII). Since these sensitivity analyses produced similar model output confidence in the validity of the findings from the primary Models A to C is increased (assuming the missing data was missing at random).

A further limitation is the challenge in comparing different attitudes and beliefs about physical activity across heterogeneous regression analyses. In particular comparing from one adjusted model in the BEEP analyses to another in the ABC-Knee analyses is not straight forward, because odds ratios and regression coefficients have different meanings, covariates varied between adjusted models, and the samples have some different characteristics such as pain severity and functional level. Furthermore, each attitude and belief variable scale is heterogeneous in its range and number of items it comprises. Some scales may have more ability to discriminate than others, for example, negative OEE contains only four items and is scored from 1 to 5 (Resnick, 2005), whilst OPAPAEQ includes multiple themes containing multiple items and is scored from 17 to 70 (Terry et al, 1997). Furthermore, model output regression coefficients and odds ratios relate to a one point or category increase in the independent variable and the dependent variable, so the range of the independent variable scale and the type of dependent physical activity variable affects the magnitude of the statistical output, rather than simply the importance of the independent variable (Szklo & Nieto, 2014).

Limitations regarding the validity and clinimetric properties of each attitude and belief and physical activity level measure in older adults with knee pain have previously been discussed (see chapter 4, section 4.5.2; chapter 5, section 5.5.2; chapter 6, section 6.6.3). In particular, the two physical activity level measures (PASE and STAR) and all the attitudes and beliefs scales with the exception of the ASES "other" were not specifically designed for knee pain populations and hence are unable to capture and or offer up some important knee pain specific information. For example, the measures of physical activity level are unable to give specific information regarding salient physical activity such as therapeutic lower limb strengthening exercises. A further example is the negative outcome expectations for exercise scale (Resnick, 2005), which despite containing generic items regarding pain and falls, does not have an item investigating the expectation that exercise will cause *"wear and tear"* to the knee joint, which has been identified in qualitative studies as a potential barrier to regular exercise (Hendry et al, 2006; Holden et al, 2012) and three of its four items had wording that linked directly to physical activity behaviour itself. For example, *"exercise is something I avoid because it may cause me to have pain"* (Appendix VI). Hence, it may have been measuring actual behaviour rather than outcome expectations for that behaviour.

There was the possibility of residual confounding in the multivariable models due to covariates that were not contained within the datasets. For example, considering a broad ecological framework for physical activity and its determinants (Biddle & Mutrie, 2008), it was not possible to adjust for the full range of potential confounders between attitudes and beliefs and physical activity level. For example, no data were available on specific barriers to physical activity such as insufficient time, or environmental factors such as local green spaces and walking distance to local shops, or social factors such as social support which are associated with levels of physical activity (Biddle & Mutrie, 2008; Brittain et al, 2011; Strath et al, 2012; Van Holle et al, 2012; Peeters et al, 2015). Specific to the BEEP dataset, there was no previous physical activity variable to include in multivariable models. Such a variable would likely be strongly associated with both attitude and beliefs towards physical activity and current physical activity behaviour (Ogden, 2007) (ABC-Knee analyses tables 7.6 to 7.9).

There are a number of limitations specific to the ABC-Knee ordinal regression analyses. Firstly, there were relatively low numbers in the physically *"inactive"* physical activity category (n=25). Despite efforts to reduce the number of variables to include in multivariable models, by only including four key covariates from the literature, the retrospective power analyses for multivariable models in objectives 3 and 4 indicated that there was overfit in the models (Menard, 2010). Hence, the models have reduced power to detect significant associations, and greater imprecision in their estimates (Menard, 2010). However, as discussed previously, the decision to keep information on this *"inactive"* category was considered more important, as this group were heterogeneous and of unique clinical interest. Secondly, the STAR physical activity questionnaire was an ordinal measure of physical activity level with just three categories, despite physical activity level being a phenomenon which is intrinsically continuous in nature. Hence the STAR has less statistical power to detect associations with attitudes and beliefs than a continuous physical activity level outcome measure, because it has less ability to discriminate differing levels of physical activity within its three categories (Szklo & Nieto, 2014). Thirdly, although the OPAPAEQ scale was significantly associated with physical activity level, it is not known which component factors have the strongest associations and it is hence challenging to draw focussed clinical inferences from the composite score analyses.

7.5.4 Clinical implications

The analyses from this chapter have shown that key attitudes and beliefs about physical activity are associated with physical activity level, even after adjusting for sociodemographic and clinical covariates. Clinicians should be mindful of this relationship and include the assessment of key attitudes and beliefs about physical activity as part of their assessment of older adults with knee pain (NICE, 2014). These should include self-efficacy for exercise, outcome expectations for exercise, kinesiophobia, and attitudes about the social, health and tension release benefits of physical activity. Clinicians can use this information to aid clinically reasoning regarding patient’s physical activity levels and behaviour.

Attitudes and beliefs about physical activity are likely important in selecting which physical activity is most appropriate for whom (Dekker, 2012). They may be important in collaborative goal setting, building rapport, setting preferred and appropriate physical activity which may in turn contribute to exercise adherence (Jordan et al, 2010, Hall et al 2010). For example, an older adult with high kinesiophobia and low self-efficacy for exercise may be less likely to carry out regular physical activity with a strategy of brief advice to carry out therapeutic exercise and keep active as part of self-management, whilst such advice may be appropriate for an individual with low kinesiophobia, positive outcome expectations for exercise and high self-efficacy for exercise. However, before any firm inferences are made about the potential determinant effects of attitudes and beliefs about physical activity on physical activity level it is important to first investigate if attitudes and beliefs can also predict future physical activity level.

7.5.5 Research implications

The findings from this chapter have research implications for the measurement of attitudes and beliefs about physical activity in joint pain populations, the further cross-sectional investigation of attitudes and beliefs about exercise, and the investigation of longitudinal relationships between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. Since it is often impractical in clinical settings to utilise a battery of scales and the majority of available attitudes and beliefs about physical activity scales were not specifically designed to be used for older adults with joint pain attributed to OA (Terry et al, 1997; Resnick & Jenkins, 2000; Resnick, 2005), and may hence miss some important condition-specific factors, it would be useful to create a single attitudes and beliefs about exercise scale for older adults with joint pain. This could involve data reduction of the existing scales, removal of redundant items and the addition of arthritis specific attitude and belief questions based on existing qualitative work exploring attitudes and beliefs in older adults with knee pain (Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012) or the creation of a new item pool from expert consensus and user input (Streiner and Norman 2008), then item selection through Delphi consensus (Hsu & Sandford, 2007) and factor analysis (Floyd and Widaman 1995).

Physical activity level is a complex phenomenon (Biddle & Mutrie, 2008) and not all potential confounders were available within the datasets. Hence, future investigation of the relationship between attitudes and beliefs about physical activity and physical activity level could adjust for additional social and environmental factors, such as lack of an exercise partner, *"low walkable neighbourhoods"* and lack of local facilities, which may alter the relationship of interest (Dekker, 2012; Strath et al, 2012). In addition, because both samples were taken from a similar sociodemographic of predominantly white adults from similar geographical regions using self-report physical activity level (Foster et al, 2014; Holden et al, 2015), it would be of interest, in generalising these findings, to carry out further external validation in populations with greater ethnic diversity and accelerometer-measured physical activity. The OPAPAEQ was associated with physical activity level in adjusted modelling within this chapter. However, the scale measures several distinct attitude and belief themes; vigorous activity, tension release, health benefits and social benefits of physical activity (Terry et al, 1997). Further investigation of the relationship between these subscale themes and physical activity is warranted to differentiate the key attitudes and beliefs that are associated with physical activity level.

Finally and importantly, in order to draw inferences regarding whether physical activity level in older adults with knee pain is determined by attitudes and beliefs about physical activity, longitudinal data analysis is warranted to see if attitudes and beliefs about physical activity are associated with future physical activity level. If an association is found then attitudes and beliefs about physical activity may also be considered as a potentially modifiable target for intervention.

7.6 Conclusion and chapter summary

This chapter investigated the relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. It did so using regression modelling of baseline data from an exercise intervention RCT and a community survey of older adults with knee pain. Crude associations were found in both samples between all investigated attitude and belief variables and self-report physical activity level. Several attitude and belief scales remained associated in multivariable models after adjusting for sociodemographic and clinical covariates, suggesting these scales to be of potential clinical interest. Self-efficacy for exercise, positive outcome expectations for exercise, kinesiophobia and a composite scale measuring attitudes relating to vigorous exercise, tension release, health outcomes and social benefits of exercise and physical activity were all associated with physical activity level in multivariable models. Multivariable model building using multiple competing attitude and belief variables simultaneously suggested positive outcome expectancies and the aforementioned composite attitude scale to be highly associated with physical activity level.

These quantitative relationship findings are novel in older adults with knee pain and add to the body of evidence on the correlates and factors associated with physical activity level in this population (Veenhof et al, 2012; Stubbs et al, 2015). Although cause and effect cannot be determined from the cross-sectional analyses, the findings warrant further longitudinal investigation to see if attitudes and beliefs about physical activity are associated with future physical activity level. This would firstly help understand the temporal sequence between attitudes and beliefs about physical activity and physical activity level and may also be of use in predicting future physical activity levels following exercise interventions and identifying potentially modifiable targets for intervention. This investigation forms the final analysis part of this thesis and is reported in chapter 8.

Chapter 8

Attitudes and beliefs about physical activity and future physical activity level in older adults with knee pain

8.1 Introduction

This chapter investigates whether attitudes and beliefs about physical activity can predict future physical activity level in older adults with knee pain (Part 4 of this thesis) using longitudinal data analysis of the BEEP dataset. This chapter is important in understanding determinants of physical activity level that are potentially modifiable factors (chapter 2, section 2.15). The chapter begins by stating the aim and objectives of the study before providing a brief rationale for and description of the chosen methods. Results from the analyses are then presented followed by a discussion of the findings and the corresponding implications for future clinical practice and research.

8.2 Aims and objectives

The overall aim of this chapter was to investigate if attitudes and beliefs about physical activity can predict future physical activity level in older adults with knee pain. The individual objectives were to investigate if attitudes and beliefs about physical activity at baseline:

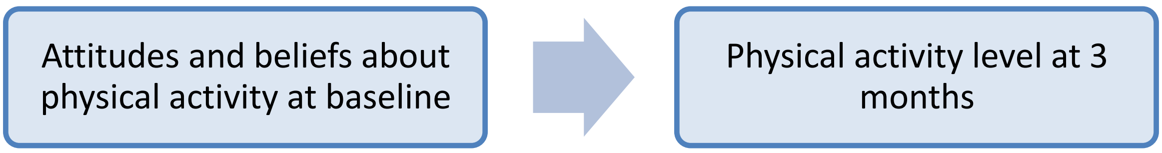
1. Are associated with future physical activity level at three months.
2. Are associated with future physical activity level at six months.
3. Predict clinically important increases in physical activity level from baseline to six months.

8.3 Causal structure hypotheses for chapter objectives

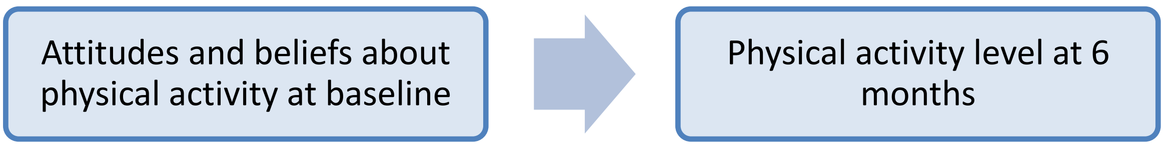
The H_0 for each objective was that there was no association between attitudes and beliefs about physical activity and future physical activity level. The H_1 was that salient attitudes and beliefs about physical activity at baseline would be associated with future physical activity level at both three and six months. The causal structure (figure 8.1) was hypothesised based on previous theory and research in older adults with knee pain (chapter 2, sections 2.12 to 2.14) (Biddle & Mutrie, 2008; Sperber et al, 2014; Peeters et al, 2015) and the findings from the Part 3 of the thesis (see figure 8.1 for causal structure of alternative hypotheses).

Figure 8.1 Alternative hypotheses causal structures for chapter objectives

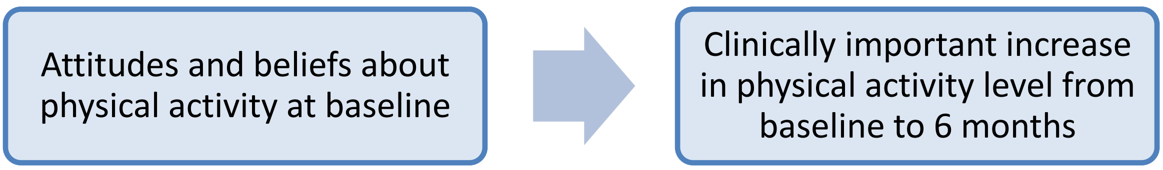
Objective 1



Objective 2



Objective 3



Arrows indicate hypothetical causational direction for the research questions in objectives 1 to 3.

8.4 Methods

This section describes the methods and their rationale for the data analyses used within this part of the PhD. The methods for objectives 1 and 2 are described together, due to their similarity, followed by the methods for objective 3. As previously, when describing methods and concepts that have been introduced in earlier chapters of the thesis, signposts are used to refer the reader back to the initial detailed description. Each objective's methods section begins with a brief overview and introduction to the independent and dependent variables utilised before going on to describe univariable analyses, multivariable model building and sensitivity analyses. All data analyses for this chapter were carried out using STATA and multiple imputed data from the BEEP dataset (see chapter 4, section 4.3.4 for the rationale for using this dataset).

8.4.1 Methods to address objective 1 and 2

In order to investigate if attitudes and beliefs about physical activity at baseline were associated with physical activity level at three and six months respectively linear regression modelling was used. The decision was made to model physical activity level at three and six months for objectives 1 and 2, for similar reasons as stated previously (see chapter 4, section 4.2), for consistency with earlier longitudinal analyses described in Part 2 and because having two separate time-points may also allow inferences as to whether the association between attitudes and beliefs about physical activity at baseline and future physical activity level changes over longer time periods.

I) Independent and dependent variables

The dependent, self-report physical activity level outcome variables for objectives 1 and 2 were the PASE scores at three and six months respectively. The primary independent variables of interest for both objectives 1 and 2 were self-efficacy for exercise (SEE), and positive and negative outcome expectations for exercise scales (OEE) at baseline. Baseline PASE score was included as an independent variable since previous physical activity is known to be a strong predictor of future physical activity behaviour in older adults (McAuley et al, 2007 and thesis Part 3 ABC-Knee analyses). A range of baseline sociodemographic and clinical covariates were also investigated, as these may confound the relationships of interest in the analyses for each objective (discussed previously in chapter 4, section 4.3.3, IV and chapter 7, section 7.3.5). As previously, these variables were selected based on existing research in older adults with joint pain and their potential plausibility to act as confounders through their associations with attitudes and beliefs about physical activity and with future physical activity level (Der Ananian et al, 2008; Hutton et al, 2010; Gyurcsik et al, 2015; Stubbs et al, 2015). These variables are summarised in table 8.1 below whilst further detail on each individual variable was provided previously in chapter 4, section 4.3.3.

Table 8.1 Independent variables

Independent variables	Data type	Summary detail
Attitude and beliefs about exercise		
SEE	S	Range 1 to 10 (10=highest self-efficacy)
Positive OEE	S	Range 1-5 (5=most positive expectations)
Negative OEE	S	Range 1-5 (5=least negative expectations)
Physical activity level		
PASE (baseline)	S	0-400+ (higher scores=higher physical activity level)
Sociodemographics		
Gender	D	Reference category male
Age	S	45 years and older
BMI	S	Higher scores=higher weight relative to height
Socioeconomic category	C	Three categories, reference professional
Work status	D	Reference working
Partner category	D	Reference no partner
Clinical		
WOMAC pain	S	Range 0-20 (20=highest pain)
WOMAC function	S	Range 0-68 (68=poorest function)
WOMAC stiffness	S	Range 0-8 (8=most stiffness)
Pain duration	C	Four categories, reference <1 year duration
Comorbidities	C	Three categories, reference none
Widespread pain	C	Reference no widespread pain
PHQ8 Depression	S	Range 0-24 (24=most depressed)
GAD7 Anxiety	S	Range 0-21 (21=most anxiety)
Intervention arm	C	Three categories, reference usual care

Footnote: All independent variables measured at baseline.

Abbreviations: BMI= Body Mass Index; Data types, C=Categorical with multiple categories, D=Dichotomous, S=Scalar; GAD7=General Anxiety Disorder 7 Questionnaire; OEE=Outcome Expectations for Exercise (positive and negative subscales); PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health depression Questionnaire; SEE=Self-Efficacy for Exercise scale; WOMAC=Western Ontario and McMaster Universities osteoarthritis index.

II) Univariable analyses

Crude relationships between attitudes and beliefs about exercise, socio-demographic and clinical variables at baseline, and physical activity level at three and six months were investigated for objectives 1 and 2 respectively, using simple linear regression (see chapter 6, section 6.4.1 for an introduction to simple linear regression).

III) Multivariable analyses and model building

Multiple linear regression models were built to investigate the relationship between individual scales capturing attitude and beliefs about exercise and future physical activity level at three and six months, adjusting for BEEP intervention arm, baseline physical activity level, socio-demographics and clinical covariates (see chapter 6, section 6.4.1 for an introduction to multiple linear regression and table 8.1 for a list of covariates). Three separate multivariable models were built for both objective 1 and 2 as defined in table 8.2.

Table 8.2 Multivariable models for objective 1 and 2

BEEP multiple linear regression models (PASE at 3 months)
Model 3A: Self Efficacy-for Exercise
Model 3B: Positive Outcome Expectations for Exercise
Model 3C: Negative Outcome Expectations for Exercise
BEEP multiple linear regression models (PASE at 6 months)
Model 6A: Self Efficacy-for Exercise
Model 6B: Positive Outcome Expectations for Exercise
Model 6C: Negative Outcome Expectations for Exercise

Abbreviation: PASE= Physical Activity Scale for the Elderly

The decision to investigate these attitude and belief scales in three separate multivariable models (Models A to C), rather than a single model, was to investigate their independent associations (see chapter 7, section 7.3.7 for full rationale). Multiple linear regression model building for each individual model and objective was carried out using a similar strategy of distinctive steps as utilised in chapter 6, section 6.4.1.

Step 1

Step one investigated the covariates (from table 8.1) for collinearity within the future multivariable model (as described in detail in chapter 6, section 6.4.1).

Sep 2

Step two entered the primary independent attitude and belief variable of interest, for example SEE within model 3A/6A, as well as baseline PASE score, BEEP trial intervention arm, and all the remaining baseline independent sociodemographic and clinical covariates into a multiple linear regression model for PASE at 3/6months respectively. As determined a priori, the attitude and belief variable, baseline PASE score and intervention arm were held in the model throughout. By adjusting for baseline physical activity level, the models take into account the effect of previous physical activity level on future physical activity level, whilst including the intervention arm as a covariate adjusts for any treatment effect on future physical activity level.

Step 3

Step three involved model building, using backwards elimination, to remove independent variables whose β regression coefficients were the most non-significant in the multivariable model (Greenland, 1989). This variable removal process was repeated iteratively, with the exception of the aforementioned variables that were held in the model, until all the variables in the model were significant ($P<0.05$).

Step 4 and 5

Following model building, post hoc power calculations, multiple linear regression model assumption diagnostics and collinearity checks were carried out, as previously described, and model output reported and interpreted (see chapter 6, section 6.4.1 for detail).

IV) Sensitivity analyses

Two sensitivity analyses were carried out. The first used the same methodology as the primary multivariable analyses but using complete case models (Sensitivity analysis I), and the second the used multiple imputed data without holding the intervention arm variable within the models (Sensitivity analysis II). The rationale for these sensitivity analyses is consistent with that provided in previous thesis sensitivity analyses (see chapter 6, section 6.4.1, IV).

8.4.2 Methods to address objective 3

Investigating whether attitudes and beliefs about physical activity at baseline can predict important increases in physical activity level is of interest, since more than half of UK older adults with knee pain have physical activity levels below recommended guidelines (Holden et al, 2015). The time frame between baseline and six months was selected for the dependent variable since six months was the primary outcome point for the BEEP trial and was the longitudinal time-point with the least missing data (see chapter 4, section 4.4.1). In order to investigate if baseline attitudes and beliefs about physical activity at baseline predict important increase in physical activity level between baseline and six months, univariable unadjusted associations were initially explored, followed by adjusted multivariable model building.

I) Independent and dependent variables

Independent variables were the same as selected for objectives 1 and 2 (described previously in section 8.4.1), however, the dependent variable was the dichotomous variable of important increase in physical activity (87 points on the PASE) or not from baseline to six months. This variable was defined in the same way to that described in chapter 6 (section 6.4.1, Sensitivity analysis II), but over a six month period.

II) Univariable analyses

Crude relationships between baseline attitudes and beliefs about physical activity, sociodemographic, and clinical variables, with important increase in physical activity level, between baseline and six months, were investigated using multiple logistic regression (see chapter 6, section 6.4.2 for a detailed introduction to logistic regression).

III) Multivariable model building

Multivariable model building was carried out for three multiple logistic regression models (Models 3AI to 3CI), with each investigating a separate attitude and belief about physical activity scale as previously. A similar strategy of steps for model building was utilised as for objectives 1 and 2, except the dependent variable was the dichotomous clinically important increase in physical activity level between baseline and six months variable (rather than PASE at three or six months). Likelihood ratio testing was also carried out during model building to check the specification of the models as used previously within this thesis during logistic regression model building (see chapter 6, section 6.4.2 for a full description). Following model building, post hoc power calculations, model assumption and collinearity diagnostics were carried out (as described previously in chapter 6, section 6.4.2).

IV) Sensitivity analyses

Three sensitivity analyses were carried out. Sensitivity analysis I and II were carried out using complete case analyses and without holding the BEEP intervention arm during model building (as carried out in objectives 1 and 2). Sensitivity analysis III substituted the dependent variable in the primary analysis with important change in physical activity level from baseline to three months (as defined in chapter 6, section 6.4.1, Sensitivity analyses II).

8.5 Results

The results section begins with a brief recap of descriptive statistics for attitudes and beliefs at baseline and physical activity over time. The main analysis results are then presented split by objective, with univariable unadjusted associations between exploratory and dependent variables reported together with the adjusted multivariable models in both text and table form. Concise summary results of key sensitivity analyses are provided in text. For ease of visual interpretation separate attitude and belief predictor models are shown in varying colours within results tables. The multivariable models investigating self-efficacy for exercise (SEE) are shaded in blue (Models 3A, 6A and 6AI), those investigating positive outcome expectations for exercise (positive OEE) are shaded in red (Models 3B, 6B, 6BI), and those investigating negative outcome expectations (negative OEE) are shaded in purple (Models 3C, 6C and 6CI). In order to aid the flow of the chapter, all checking of model assumptions and additional detail for sensitivity analyses are reported in Appendix IX.

8.5.1 Descriptive statistics revisited

Table 8.3 below provides a reminder of the key independent and dependent variable statistics over time (this information was initially introduced and discussed in chapter 4, section 4.4.3).

Table 8.3 Summary statistics from key variables

Variables (range)	Baseline	3 months	6 months
SEE (0-10)	5.4 (2.3)	5.7 (2.3)	5.6 (2.2)
Positive OEE (1-5)	3.9 (0.6)	4.0 (0.6)	4.0 (0.6)
Negative OEE (1-5)	3.5 (0.8)	3.8 (0.8)	3.8 (0.8)
PASE (0-400+)	177.0 (83.3)	192.1 (87.9)	190.5 (89.3)

Footnote: Multiple imputed data. All values are mean scores (standard deviation) except OMERACT-OARSI response which are given in percentages. All scores indicate higher levels of the variable except Negative OEE with higher scores indicating more positive outcome expectations for exercise.

Abbreviations: OEE=Outcome Expectations for Exercise; PASE=Physical Activity Scale for the Elderly; SEE=Self Efficacy for Exercise.

8.5.2 Objective 1

"Investigate if attitudes and beliefs about physical activity at baseline are associated with future physical activity level at three months"

Table 8.4 shows both unadjusted crude univariable associations and adjusted models for physical activity level at three months. In the unadjusted analyses a number of predictor variables were significantly associated with physical activity level at three months. All three attitude and belief variables crudely predicted physical activity level, with higher levels of self-efficacy for exercise β= 7.28 (3.33, 11.23), more positive outcome expectations for exercise β= 34.55 (20.13, 48.97) and less negative outcome expectations for exercise[2] β= 16.74 (6.51, 26.97) all being associated with higher levels of future physical activity. Baseline level of physical activity was a strong predictor of future physical activity whilst gender,

[2] Higher negative outcome expectations for exercise score indicates less negative outcome expectations for exercise

age, employment status, number of comorbidities and depression at baseline were also significant univariable physical activity predictors. Older adults with knee pain, who were male, more active at baseline, of younger age, working in paid employment and without comorbidities or depression were more likely to have higher physical activity levels at three months. A number of baseline variables were not associated with future physical activity level, including BEEP intervention arm, socioeconomic status, pain duration, widespread nature and severity of pain, function, stiffness, and anxiety.

A number of crude covariate predictors of physical activity level at three months were no longer significant during model building in multivariable Models 3A to 3C and were excluded from the multivariable models. These included gender, age, work status number of comorbidities and depression. The final multivariable Model 3A, holding self-efficacy for exercise and the intervention arm within the model during model building, showed self-efficacy for exercise remained a significant predictor β= 4.95 (1.02, 8.87), together with previous baseline level of physical activity β= 0.49 (0.37, 0.60). Older adults with knee pain, who had higher self-efficacy for exercise, and higher baseline levels of physical activity, had higher levels of physical activity at three months. Model 3B, holding positive outcome expectations for exercise and the intervention arm in the model during model building, showed positive outcome expectations for exercise β= 25.48 (12.33, 38.62) and baseline physical activity β= 0.48 (0.37, 0.59) predicted physical activity level at three months. Older adults with knee pain, who had higher baseline levels of physical activity, and more positive outcome expectations for exercise, had higher physical activity levels at three months. Model 3C, holding negative outcome expectations for exercise and the intervention arm in the model during model building, showed negative outcome expectations for exercise did not predict physical activity level at three months β= 7.40 (-2.46, 17.25), although baseline physical activity level did β= 0.49 (0.38, 0.60). Those with less negative outcome expectations showed non-significant trends towards carrying out higher levels of future physical activity, whilst those with higher baseline levels of physical activity had higher levels of physical activity at three months.

Post hoc power calculations for objectives 1 and 2 revealed all multivariable models were adequately powered, with 514 participants and 15 outcomes per independent variable allowing 34 predictor variables. Sensitivity analyses, including complete-case analyses and multivariable analyses without adjusting for the intervention arm variable, produced similar significant adjusted associations for self-efficacy for exercise and positive outcome expectations, and non-significant multivariable associations for negative outcome expectations (see Appendix IX).

Sensitivity analyses carried out, including complete-case analyses and multivariable analyses without adjusting for the intervention arm variable for Models 3A to 3C, produced similar significant adjusted associations for self-efficacy for exercise and positive outcome expectations, whilst multivariable associations for negative outcome expectations remained non-significant (see Appendix IX).

Table 8.4 Objective 1: Unadjusted and adjusted models 3A to 3C (PASE physical activity level at 3 months)

	Physical activity level (PASE) at 3 months							
	Unadjusted		Adjusted Model 3A (SEE)		Adjusted Model 3B (positive OEE)		Adjusted Model 3C (negative OEE)	
	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig
Attitudes & beliefs								
SEE	7.28 (3.33, 11.23)	<0.001	4.95 (1.02, 8.87)	0.014				
Positive OEE	34.55 (20.13, 48.97)	<0.001			25.48 (12.33, 38.62)	<0.001		
Negative OEE*	16.74 (6.51, 26.97)	0.001					7.40 (-2.46, 17.25)	0.140
Physical activity								
PASE baseline	0.50 (0.39, 0.61)	<0.001	0.49 (0.37, 0.60)	<0.001	0.48 (0.37, 0.59)	<0.001	0.49 (0.38, 0.60)	<0.001
Sociodemographics								
Gender (ref male)	-19.43 (-37.34, -1.51)	0.034						
Age	-1.64 (-2.53, -0.75)	<0.001						
Continuous BMI	-1.34 (-2.92, 0.24)	0.095						
Socio-ec. category (ref professional)								
Intermediate	21.83 (-2.78, 46.44)	0.082						
Routine/ Manual job	12.91 (-10.38, 36.20)	0.276						
Currently in paid work (ref working)	-39.20 (-57.78,-20.63)	<0.001						
Partner category (ref no partner)	19.39 (-0.79, 39.57)	0.060						
Clinical covariates								
WOMAC pain	-0.54 (-3.07, 1.99)	0.675						
WOMAC function	-0.40 (-1.10, 0.29)	0.254						
WOMAC stiffness	-4.36 (-9.34, 0.63)	0.086						
Pain duration (ref <1 year)								

>1 yr and <5yrs	-8.01 (-31.02, 14.99)	0.493						
>5 yrs and <10 yrs	-19.52 (-46.25, 7.20)	0.151						
>10 yrs	-15.30 (-44.82, 14.22)	0.307						
Comorbidities (ref 0)								
1 other condition	-22.96 (-43.00, -2.92)	0.025						
2+ other conditions	-29.43 (-50.58, -8.28)	0.007						
Widespread pain (ref no WSP)	-17.00 (-39.70, 5.70)	0.142						
PHQ8 depression	-1.94 (-3.76, -0.12)	0.036						
GAD7 anxiety	-1.26 (-3.09, 0.57)	0.177						
Intervention arm (ref usual physio)								
Individually tailored exercise	-8.70 (-30.03, 12.63)	0.422	-7.83 (-27.50, 11.84)	0.433	-8.23 (-27.69, 11.23)	0.405	-8.01 (-27.76, 11.74)	0.424
Targeted exercise adherence	-3.72 (-24.64, 17.20)	0.726	-4.49 (-23.71, 14.72)	0.645	-6.61 (-25.81, 12.58)	0.497	-4.45 (-23.99, 15.09)	0.654

Key:
White=Unadjusted Models
Blue=Adjusted Model 3A (including Self Efficacy for Exercise)
Red=Adjusted Model 3B (including Positive Outcome Expectations for Exercise)
Purple=Adjusted Model 3C (including Negative Outcome Expectations for Exercise)

Footnote: multiple imputed data, all independent variables were measured at baseline, multiple linear regression adjusted models selected via backwards elimination holding treatment arm and one of SEE (Model 3A), positive OEE (Model 3B) and negative OEE(Model 3C) within the model. Higher PASE score indicates higher level of physical activity. Higher scores on SEE and positive OEE indicate higher self-efficacy and greater positive outcome expectations for exercise. *Higher score on the negative OEE indicates less negative outcome expectations for exercise. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher depression and anxiety scores indicate worse depression and anxiety.

Abbreviations: β =Unstandardized coefficients; BMI= Body Mass Index; CI=Confidence Interval; ex=Exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectations for Exercise (split into positive and negative subscales); PA=Physical Activity; PASE=Physical Activity Scale in the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise; Socio-ec=Socioeconomic category; WOMAC=Western Ontario and McMaster Osteoarthritis Index; WSP=Widespread Pain; yr=year.

8.5.3 Objective 2

"Investigate if attitudes and beliefs about physical activity at baseline are associated with future physical activity level at six months"

Table 8.5 shows both unadjusted crude univariable associations and adjusted multivariable models for physical activity level at six months. In the unadjusted analyses a number of baseline predictor variables were significantly associated with physical activity level at six months. All three baseline attitudes and beliefs about physical activity variables crudely predicted physical activity level, with higher levels of self-efficacy for exercise β= 6.02 (2.30, 9.75), more positive outcome expectations for exercise β= 25.74 (11.99, 39.49), and fewer negative outcome expectations for exercise β= 11.72 (1.81, 21.64) all being associated with higher levels of physical activity six months later. Baseline level of physical activity was also a strong predictor of future physical activity level, together with age, BMI, employment status, having a partner and having two or more comorbidities. Older adults with knee pain, who were more active at baseline, of younger age, lower BMI, employed, with a partner and less than two comorbidities were more likely to have higher physical activity levels at six months. A number of baseline variables were not associated with future physical activity level including; the BEEP intervention arm, gender, socioeconomic status, duration of knee pain, widespread nature and severity of pain, lower limb function and stiffness nor depression and anxiety.

Model 6A, holding baseline self-efficacy for exercise and BEEP intervention arm within the model during multivariable model building, showed self-efficacy for exercise was a significant predictor of physical activity at six months β= 3.71 (0.26, 7.16), together with baseline level of physical activity β= 0.49 (0.38, 0.59) and age β= -1.07 (-1.88, -0.26). Having greater self-efficacy for exercise was associated with higher levels of physical activity at six months, as was being younger, and having a higher baseline level of physical activity. Model 6B, holding baseline positive outcome expectations for exercise and treatment intervention arm in the model during model building, showed positive outcome expectations for exercise β= 13.93 (1.32, 26.54), baseline physical activity level β= 0.49 (0.38, 0.59) and age β= -0.95 (-1.76, -0.13) predicted physical activity level at six months. Having more positive outcome expectations for exercise at baseline was positively associated with being more physically active at six months, whilst being younger and having a higher baseline level of physical activity was also associated. Model 6C, holding baseline negative outcome expectations for exercise and BEEP intervention arm in the model during model building, showed negative outcome expectations for exercise did not predict physical activity level at six months β= -1.59 (-11.31, 8.13) although, baseline physical activity level β= 0.49 (0.38, 0.59), age β= -1.24 (-2.07, -0.42) and BMI did β= -1.47 (-2.91, -0.03). There was no association between negative outcome expectations and physical activity level at six months, however, younger age was associated with higher physical activity level at six months as was having higher baseline physical activity levels.

Sensitivity analyses comprising complete-case analyses and multivariable analyses without adjusting for the intervention arm variable for Models 6A to 6C, produced similar significant adjusted associations for self-efficacy for exercise and positive outcome expectations, whilst multivariable associations for negative outcome expectations remained non-significant (see Appendix IX).

Table 8.5 Objective 2: Unadjusted and adjusted models 6A to 6C (PASE physical activity level at 6 months)

	Physical activity level (PASE) at 6 months							
	Unadjusted		Adjusted Model 6A (SEE)		Adjusted Model 6B (positive OEE)		Adjusted Model 6C (negative OEE)	
	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig	β (95% CI)	Sig
Attitudes & beliefs								
SEE	6.02 (2.30, 9.75)	0.002	3.71 (0.26, 7.16)	0.035				
Positive OEE	25.74 (11.99, 39.49)	<0.001			13.93 (1.32, 26.54)	0.030		
Negative OEE*	11.72 (1.81, 21.64)	0.021					-1.59 (-11.31, 8.13)	0.747
Physical activity								
PASE baseline	0.53 (0.43, 0.63)	<0.001	0.49 (0.38, 0.59)	<0.001	0.49 (0.38, 0.59)	<0.001	0.49 (0.38, 0.60)	<0.001
Sociodemographics								
Gender (ref male)	-12.58 (-29.04, 3.89)	0.134						
Age	-2.00 (-2.85, -1.15)	<0.001	-1.07 (-1.88, -0.26)	0.010	-0.95 (-1.76, -0.13)	0.023	-1.24 (-2.07, -0.42)	0.003
Continuous BMI	-1.87 (-3.37, -0.37)	0.015					-1.47 (-2.91, -0.03)	0.046
Socio-ec. category (ref professional)								
Intermediate	23.26 (-1.02, 47.54)	0.060						
Routine/ Manual job	14.72 (-9.21, 38.66)	0.226						
Currently in paid work (ref working)	-43.79 (-60.94, -26.63)	<0.001						
Partner category (ref no partner)	20.40 (0.91, 39.90)	0.040						
Clinical covariates								
WOMAC pain	0.45 (-2.22, 3.11)	0.742						
WOMAC function	-0.30 (-1.03, 0.43)	0.419						
WOMAC stiffness	0.26 (-4.63, 5.14)	0.918						
Pain duration (ref <1								

year)								
>1 yr and <5yrs	-4.19 (-26.45, 18.07)	0.711						
>5 yrs and <10 yrs	-13.33 (-38.99, 12.33)	0.307						
>10 yrs	-12.63 (-38.36, 13.10)	0.335						
Comorbidities (ref 0)								
1 other condition	-17.72 (-38.08, 2.64)	0.088						
2+ other conditions	-39.84 (-60.43, -19.26)	<0.001						
Widespread pain (ref no WSP)	-17.77 (-41.25, 5.71)	0.137						
PHQ8 depression	-1.48 (-3.44, 0.49)	0.139						
GAD7 anxiety	0.05 (-2.01, 2.12)	0.959						
Intervention arm (ref usual physio)								
Individually tailored exercise	1.03 (-19.74, 21.79)	0.922	3.59 (-14.88,22.07)	0.702	3.13 (-15.31, 21.58)	0.738	3.63 (-14.87, 22.14)	0.699
Targeted exercise adherence	8.26 (-12.69, 29.21)	0.438	9.16 (-9.74, 28.07)	0.340	7.52 (-11.38, 26.41)	0.434	9.17 (-9.77, 28.11)	0.341

Key: White=Unadjusted Models
Blue=Adjusted Model 6A (including Self Efficacy for Exercise)
Red=Adjusted Model 6B (including Positive Outcome Expectations for Exercise)
Purple=Adjusted Model 6C (including Negative Outcome Expectations for Exercise)

Footnote: Multiple imputed data, all independent variables were measured at baseline, multiple linear regression adjusted models selected via backwards elimination holding treatment arm and one of SEE (Model 6A), positive OEE (Model 6B) and negative OEE (Model 6C) within the model. Higher PASE score indicates higher level of physical activity. Higher scores on SEE and positive OEE indicate higher self-efficacy and greater positive outcome expectations for exercise. *Higher score on the negative OEE indicates less negative outcome expectations for exercise. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher depression and anxiety scores indicate worse depression and anxiety.

Abbreviations: β=Unstandardized coefficients; BMI=Body Mass Index; CI=Confidence Interval; ex=Exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectations for Exercise (split into positive and negative subscales); PA=Physical Activity; PASE=Physical Activity Scale in the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise Questionnaire; Socio-ec=socioeconomic category; WOMAC=Western Ontario and McMaster osteoarthritis index; WSP=Widespread Pain; yr=year.

8.5.4 Objective 3

"Investigate if attitudes and beliefs about physical activity at baseline predict important increase in physical activity level from baseline to six months"

Table 8.6 shows both unadjusted univariable associations and adjusted models for important increase in physical activity level at six months. Only baseline level of physical activity was significantly associated with important increase in physical activity level at six months in the unadjusted models OR 0.99 (0.99, 1.00) p=0.001 and in the adjusted models OR 0.99 (0.99. 1.00) p=0.001. Those with lower baseline physical activity were slightly more likely to increase their physical activity by an important amount. Noting the odds ratios, being higher than 1, for the baseline attitude and belief variables, there were non-significant trends for those with higher self-efficacy for exercise and more positive outcome expectations being more likely to make an important increase in physical activity.

The post hoc power calculation, based on 219 participants in the smallest outcome category (i.e., the number who increased their physical activity by at least an important amount), allowed 21 predictor variables. Hence, the multivariable models were adequately powered (with Models 6AI and 6BI only containing 4 predictor variables and Model 6CI containing 5). Sensitivity analyses I and II found all three attitude and belief models to not be associated with important increase in physical activity (see Appendix IX). However, Sensitivity analysis III, found significant adjusted associations between both self-efficacy for exercise OR 1.19 (1.02, 1.39) and positive outcome expectations for exercise OR 1.81 (95%CI 1.11, 2.96) but not negative outcome expectations for exercise OR 1.39 (95% CI 0.99, 1.96) with important increase in physical activity at three months.

Table 8.6 Objective 3: Unadjusted and adjusted Models 6AI to 6CI (important increase in physical activity level)

	Physical activity level (PASE) important increase at 6 months							
	Unadjusted		Adjusted Model 6AI (SEE)		Adjusted Model 6BI (positive OEE)		Adjusted Model 6CI (negative OEE)	
	OR (95% CI)	Sig	OR (95% CI)	Sig	OR (95% CI)	Sig	OR (95% CI)	Sig
Attitudes & beliefs								
SEE	1.07 (0.96, 1.20)	0.225	1.10 (0.98, 1.24)	0.095				
Positive OEE	1.36 (0.88, 2.10)	0.160			1.54 (0.99, 2.40)	0.056		
Negative OEE	0.97 (0.71, 1.32)	0.842					1.09 (0.79, 1.51)	0.590
Physical activity								
PASE baseline	0.99 (0.99, 1.00)	0.001	0.99 (0.99, 1.00)	0.001	0.99 (0.99, 1.00)	0.001	0.99 (0.99, 1.00)	0.001
Sociodemographics								
Gender (ref male)	0.88 (0.53, 1.47)	0.629						
Age	0.98 (0.96, 1.01)	0.251						
Continuous BMI	0.99 (0.95, 1.04)	0.714						
Socio-ec. category (ref professional)								
Intermediate	1.44 (0.71, 2.92)	0.310						
Routine/ Manual job	0.66 (0.30, 1.44)	0.294						
Currently in paid work (ref working)	0.78 (0.46, 1.32)	0.361						
Partner category (ref no partner)	1.18 (0.63, 2.21)	0.610						
Clinical covariates								
WOMAC pain	1.06 (0.98, 1.15)	0.123						
WOMAC function	1.02 (0.99, 1.04)	0.137						
WOMAC stiffness	1.08 (0.93, 1.25)	0.309						
Pain duration (ref <1								

year)								
>1 yr and <5yrs	0.74 (0.37, 1.47)	0.389						
>5 yrs and <10 yrs	0.98 (0.46, 2.07)	0.956						
>10 yrs	0.98 (0.45, 2.14)	0.960						
Comorbidities (ref 0)								
1 other condition	0.92 (0.49, 1.70)	0.781						
2+ other conditions	0.85 (0.45, 1.62)	0.622						
Widespread pain (ref no WSP)	0.86 (0.41, 1.81)	0.692						
PHQ8 depression	1.03 (0.97, 1.09)	0.309						
GAD7 anxiety	1.03 (0.97, 1.09)	0.303						
Intervention arm (ref usual physio)								
Individually tailored exercise	1.06 (0.55, 2.06)	0.855	1.03 (0.52, 2.04)	0.924	1.04 (0.53, 2.06)	0.903	1.04 (0.53, 2.05)	0.904
Targeted exercise adherence	1.15 (0.58, 2.25)	0.692	1.17 (0.59, 2.32)	0.660	1.15 (0.58, 2.28)	0.691	1.19 (0.60, 2.35)	0.615

Key: White=Unadjusted Models
Blue=Adjusted Model 6AI (Minimally important increase in physical activity model including Self-Efficacy for Exercise)
Red=Adjusted Model 6BI (Minimally important increase in physical activity model including Positive Outcome Expectations for Exercise)
Purple=Adjusted Model 6CI (Minimally important increase in physical activity model including Negative Outcome Expectations for Exercise)

Footnote: Multiple imputed data, all independent variables were measured at baseline, multiple logistic regression adjusted models selected via backwards elimination holding treatment arm and one of SEE (Model 6AI), positive OEE (Model 6BI) and negative OEE (Model 6CI) within the model. Higher scores on the SEE and positive outcome OEE indicate higher self-efficacy and positive outcome expectations for exercise. *Higher score on the negative OEE scale indicates less negative outcome expectations for exercise. Higher WOMAC scores indicate higher pain, worse function and stiffness. Higher depression and anxiety scores indicate worse depression and anxiety. Important increase in physical activity was defined as an increase of 87 PASE points from baseline to six months.

Abbreviations: β=Unstandardized coefficients; BMI=Body Mass Index; CI=Confidence Interval; ex=Exercise; GAD7=Generalised Anxiety Disorder; OEE=Outcome Expectations for Exercise (split into positive and negative subscales); PA=Physical Activity; PASE=Physical Activity Scale for the Elderly; PHQ8=Personal Health Questionnaire; SEE=Self-Efficacy for Exercise; Socio-ec=Socioeconomic Category; WOMAC=Western Ontario and McMaster Osteoarthritis Index; WSP=Widespread Pain; yr=year.

8.6 Discussion

This chapter aimed to investigate whether attitudes and beliefs about physical activity could predict future physical activity level in older adults with knee pain using longitudinal analyses of the BEEP trial dataset. This section summarises and discusses the key findings, comparing the results to existing research and identifies methodological strengths and limitations before going on to make recommendations for clinical practice and further research.

8.6.1 Key findings

Key findings were that baseline self-efficacy for exercise and positive outcome expectations for exercise were positively associated with physical activity three and six months later in both unadjusted and adjusted models. These findings suggest that individuals who have higher confidence in their ability to successfully carry out regular exercise, and believe this will lead to positive health and well-being outcomes, are more likely to carry out higher levels of physical activity in the future. These attitude and belief constructs can hence be used to predict future physical activity levels, and may also be considered for further investigation as potentially modifiable treatment targets to optimise the effectiveness of physical activity interventions for older adults with knee pain.

The estimated magnitude of the adjusted associations between SEE and OEE with PASE score was lower at six months, when compared to three months (as indicated by smaller β coefficients in Models 6A and 6B compared to 3A and 3B). This may be because of the increasing gap between the measurement of the attitudes and beliefs, and the measurement of self-report physical activity level, since attitudes and beliefs can change over time and are more likely to change over longer periods. Furthermore, more BEEP participants were still under the care of a physiotherapist at three months than at six months and change in therapist related factors such as encouragement to exercise could potentially influence the association over time. It is possible that SEE and positive OEE are able to influence physical activity level during a course of treatment (such as physiotherapy led exercise) but over longer time periods, in the absence of external support, they are less able to predict physical activity level. In addition, there may be more life events occurring over longer time periods that confound the relationships between baseline attitudes and beliefs about physical activity and future physical activity level. For example, an individual may be more likely to experience a new comorbidity, which may alter both attitudes and beliefs about physical activity and physical activity levels.

At both three months and six months, the magnitude of associations (Beta regression coefficients) between attitudes and beliefs about physical activity and future physical activity level were attenuated within adjusted models compared to crude models (Tables 8.4 and 8.5). This finding is consistent with the cross-sectional analysis (discussed in chapter 7, section 7.5.1) and suggests that confounding variables explain some of the magnitude of crude association. Indeed, in contrast to the significant adjusted association findings for SEE and positive OEE, no significant adjusted association was found between negative OEE and PASE score at either three or six months (Models 3C and 6C), despite a significant univariable association. In the earlier cross sectional analysis (within chapter 7, section 7.5.1), depression was considered to be a key confounder in the crude relationship between negative OEE and PASE; however, depression was not a significant covariate within adjusted models in this analysis. Negative outcome expectations for exercise may not be predictive when baseline physical activity level is also modelled. It is possible that this important confounding covariate explains the main effect of negative OEE. Given that the wording of the negative OEE scale closely matches physical activity behaviour per se (see Appendix VI), it seems likely that combining the two in a multivariable model explains similar variance in future physical activity level. Sensitivity analyses for objectives 1 and 2, removing the non-significant treatment arm covariate and carrying out complete case analyses, yielded similar findings with regards to the relationships between attitudes and beliefs about exercise and future physical activity thus increasing confidence in the primary results.

Some covariates were found to be associated with future physical activity level in the analyses for objectives 1 and 2. Baseline physical activity level was consistently found to be a significant predictor of future physical activity level in all models at both three and six months. The magnitude of the association also remained very similar across all models. Thus, the analyses show that previous physical behaviour appears to be the most important and consistent predictor of future physical activity behaviour. Although age was crudely associated with physical activity at both three and six months, counterintuitively, it was a significant covariate in predicting physical activity level in all three adjusted models at six months (Models 6A, 6B and 6C) but not in adjusted models at three months (Models 3A, 3B and 3C). The reasons for this are unclear. It may be that, adjusted for other covariates, within the age ranges within the sample, age is a relatively weak predictor that is on the borderline of statistical significance within multivariable models. Baseline BMI was only found to be a significant predictor of future physical activity at six months in Model 6C. In this model, those with a lower BMI at baseline had higher levels of physical activity at six months. It is interesting that BMI was only significant in a multivariable model with a non-significant attitude and belief predictor- perhaps suggesting that the predictive value of this variable is nullified by self-efficacy for exercise and positive outcome expectations.

The BEEP treatment arm variable was not associated with increased future physical activity level, despite one of the three interventions (targeted exercise adherence) including several techniques suggested to facilitate an increase in physical activity level (see Appendix IV for further intervention component detail). This highlights how challenging it is to facilitate important increases in overall levels of physical activity in older adults with knee pain. Physical activity levels appear to be habitual and relatively stable. However, it is also possible that a sub group of older adults within the targeted exercise adherence treatment arm responded and increased their physical activity but that this was balanced at the group level by those who did not. In the future it will be important to identify the most potent behaviour change techniques to inform physical activity interventions.

Since most older adults with knee pain carry out insufficient levels of physical activity, it is of clinical interest to unearth potentially modifiable predictors of clinically important increase in physical activity (investigated in Objective 3). However, although SEE and positive OEE variables were positively associated with clinically important increases in physical activity over six months follow up (as indicated by odds ratios of 1.1 (95% CI 0.98, 1.24) for SEE in Model 6AI and 1.54 (95% CI 0.99, 2.40) for positive OEE in Model 6BI, the confidence intervals included 1 and so the results were not statistically significant. These findings contrast with the findings from the analyses for Objectives 1 and 2. A number of reasons may account for this including; a) information loss in dichotomising a continuous dependent variable; b) important change in physical activity level between baseline and six months may be too long in the future to be associated with baseline attitudes and beliefs; and c) measurement error within the PASE score. As discussed previously in more detail (chapter 6, section 6.6.3), dichotomising any continuous measure makes interpretation simpler but also results in information loss (Altman & Royston, 2006; Szklo & Nieto, 2014). In reality, some individuals may still increase their physical activity, but fall below the threshold for important increase, and be modelled the same as individuals who decrease their activity; hence, findings are biased towards a null association. Secondly, baseline to six months was selected for the time period of the dependent clinically important change variable, since six months was the primary end-point for the BEEP trial. However, as discussed previously, associations between attitudes and beliefs at baseline and physical activity level at six months (Models 6A to 6C) appeared attenuated when compared to those at three months (Models 3A to 3C). Hence, there may have been less chance of finding significant associations between baseline attitudes and beliefs and clinically important increases in physical activity level between baseline and six months, than baseline to three months. Carrying out sensitivity analysis investigating clinically important change from baseline to three months supported this hypothesis, with SEE and positive OEE becoming associated in adjusted models (see Appendix IX, objective 3, Sensitivity analysis III). Finally, any measurement error within the PASE score (as discussed in chapter 6, section 6.6.3) could lead to dependent variable misclassification which would tend to bias any associations towards the null.

The results from objective 3 (Models 6AI to 6AC) suggest, that those who have lower levels of physical activity may have the greatest chance of making important increases in physical activity (since an odds ratio less than 1 suggests that higher baseline PASE scores are associated with less likelihood of clinically important increase in physical activity). Since this subgroup also have higher clinical severity they may represent an ideal initial target for interventions aimed at increasing physical activity level (Peeters et al, 2015; see also chaper 5, section 5.4.4). However, there are also arguments for targeting older adult populations more generally to gain the most far reaching health benefits (Rose, 2001). For example, since previous physical activity level appears one of few important factors in explaining future physical activity level, it can be argued that raising the general physical activity levels across the populations' life-course is the most effective way of increasing future physical activity levels in older adults with knee pain (DOH, 2011). Influencing physical activity at a population level is challenging and considering the ecological model of physical activity may require complex coordinated interventions aimed at a policy, physical environmental and social level as well as those aimed at individuals, organisations and primary care (Biddle & Mutrie, 2008; DOH, 2011).

8.6.2 Comparisons to existing research

To the author's knowledge, this analysis is the first to investigate if attitudes and beliefs about physical activity can predict future physical activity level specifically in older adults with knee pain. Two systematic reviews exist summarising factors associated with physical activity behaviour in older adults with knee pain (Veenhof et al, 2012; Stubbs et al, 2015), however both only found studies investigating cross-sectional associations. These systematic reviews have been discussed earlier in this thesis (in chapter 2, section 2.10.3)

In the absence of studies involving older adults with knee pain specifically, two comparisons can be made with recent longitudinal analyses involving older adults with arthritis more generally, although both investigated change in physical activity level as their dependent variable rather than follow up physical activity level per se. Sperber et al (2014) carried out secondary data analysis of a lifestyle physical activity intervention trial, in 339 older adults with joint pain (of mean age 69 years old) in the US. They investigated the role of symptoms and self-efficacy for exercise in predicting future physical activity level at 20 weeks follow up. They used the self-report Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire (Stewart et al, 2001) and the same SEE scale used within this thesis. Using structural equation modelling, they carried out longitudinal data analysis, which showed an adjusted positive association between change in SEE and change in self-report physical activity level, between baseline and 20 weeks (controlling for change in pain, change in depression, and baseline sociodemographics as well as the intervention arm). A second study investigated the factors associated with increase in self-report physical activity level in insufficiently active older adults with arthritis (of mean age 55) (Peeters et al, 2015). Using a sub sample (n=692) of Australian older adults from a multi-level cohort study that investigated physical activity, they measured longitudinal data at two time points; in 2007 and subsequently in 2009. They investigated the predictive effect of attitudes and beliefs about physical activity (physical activity past experiences, physical activity behavioural intention, self-efficacy for regular physical activity, perceived need and required demand to exercise, motivation to exercise for social and health wellbeing) using logistic regression models. Similar to the Objective 3 primary analysis within this chapter, they found attitude and belief variables were not predictive of dichotomous change in physical activity level. Only previous physical activity experiences and physical activity intention measured in 2007 significantly predicted physical activity level in 2009. It is of note that their analysis is at similar risk of associations being biased towards the null due to information loss in dichotomising physical activity outcome (as discussed previously in chapter 7, section 7.5.3). Furthermore, their time period for change in physical activity level (of two years) was further in the future from baseline than this study (three and six months), which may have served to reduce the potentially predictive effects of attitudes and beliefs measured at baseline. In summary, the majority of literature investigating the relationship between attitudes and beliefs about physical activity and future physical activity level has investigated the longitudinal associations between self-efficacy for exercise and change in physical activity level and, to the authors knowledge, no literature has investigated the longitudinal relationships between outcome expectations for exercise or fear of movement and future physical activity level.

Considering the existing literature for important covariates that were shown to predict future physical activity within the thesis adjusted models, baseline levels of physical activity have previously been shown (in general physical activity literature) to predict future physical activity level (McAuley et al, 2007; Bauman et al, 2012). Furthermore, the analyses from thesis Part 3 also found previous use of exercise to treat knee pain was associated with current physical activity levels (see chapter 7, section 7.5.1). These consistent findings add strength to the hypothesis that previous physical activity level is the most important predictor of future physical activity level. The conflicting findings regarding increasing age as a predictor of lower future physical activity mirrors the existing cross sectional literature that has previously found age to both be associated and not associated with physical activity levels in older adults with knee pain (Veenhof et al, 2012; Stubbs et al, 2015).

I) Theoretical Considerations

The findings support existing theories of social cognition that propose outcome expectations for exercise and self-efficacy for exercise to be antecedents of future physical activity behaviour (Bandura 1977, Biddle and Mutrie 2008). There was insufficient and inconclusive evidence from the findings to support or refute pain behaviour models such as the fear avoidance model or the biopsychomotor model (Miller et al 1991, Sullivan, 2008). This is because the BEEP data set did not include a specific measure of fear of movement, harm and injury or sufficient information regarding attitudes and beliefs about social factors. In addition, although negative outcome expectations for exercise were captured, which may be linked to kinesiophobia, this measure was crudely associated with future physical activity levels but not when significant adjusting for previous behaviour.

8.6.3 Methodological strengths and limitations

Methodological strengths of the research summarised in this chapter included; the sufficiently large sample size for multivariable model building, as confirmed by post hoc sample size calculations; multiple imputation to minimise the impact of missing data (see chapter 4, section 4.3.4 for further discussion); and a broad range of theoretically important covariates to adjust for in multivariable models. In addition, steps were taken to minimise collinearity and over adjustment (as discussed in chapter 6, section 6.6), by carrying out independent multivariable model building for individual attitude and belief variables, checking and removing highly correlated independent variables and post hoc checking of VIF.

By investigating whether attitudes and beliefs about physical activity are associated with physical activity at both three and six months follow-up, it is possible to look for consistency in the patterns of association. For example, confidence in the ability of self-efficacy for exercise to predict future physical activity level is strengthened by finding similar significant associations at the two separate time-points. Furthermore, association findings were also similar after carrying out complete-case and after sensitivity analyses without adjusting for the treatment arm which also increases confidence in the findings.

Limitations in the research methods for this chapter can be split into four key areas: a) missing data from the PASE dependent variable at three and six months; b) outcome measure factors; c) issues with secondary data analysis, including unavailable attitude and belief variables as well as unadjusted confounding; and d) issues regarding generalisability. Although missing data was managed using multiple imputation with the assumption of missingness at random, the levels of missing data for the PASE dependent variable at three and six months was of some concern at 30% and 25% respectively. If any of this missing data was missing not at random then this is a limitation for internal validity of the findings (see chapter 4, section 4.5.2) (Sterne et al, 2009).

Limitations regarding the measurement of physical activity over time using the PASE and the validity of the SEE and OEE measures in older adults with knee pain have been discussed previously in detail (see chapter 4, section 4.3.3, chapter, section 6.6.1 and chapter 7, section 7.5.3 for detail). Another subtle limitation is the discrepancy between the specific behaviour that the attitudes and belief variables relate to i.e. exercise (see Appendix VI for detail on specific item wording) and the outcome behaviour they are predicting i.e. physical activity more generally (including exercise). Social cognitive theory states that predictive relationships between attitudes and beliefs and behaviours are strongest when they all relate to the same specific behaviour and context (Ogden, 2007). This discrepancy in the specificity of behaviour type between predictor and outcome variable may actually bias associations towards the null. Hence the strength of association between attitudes and beliefs towards "*exercise"* and *"physical activity level"* may actually underestimate the true association between attitudes and beliefs about "*physical activity"* more generally and physical activity level.

Secondary data analyses only allow the investigation of variables captured within the dataset used. Chapter 7 identified some important attitudes and beliefs about exercise, measured in the ABC-Knee data, that were associated with physical activity level in the cross-sectional analysis, that were not available for longitudinal analysis in the BEEP data. For example, attitudes and beliefs about the social benefits of physical activity (captured within the OPAPAEQ) were not available for investigation. In addition, other constructs such as physical activity intentions have been identified as predictors of change in physical activity level in other studies (Peeters et al, 2015). These variables may also predict future physical activity level but could not be investigated. Unadjusted confounding, due to unavailable covariates is a further limitation for the analyses (as discussed in detail previously, see chapter 7, section 7.5.3).

The limitation regarding generalisability of the findings from a sample of participants from an exercise trial to all older adults with knee pain has been discussed previously (see chapter 6, section 6.6.3). In addition, exercise trials may potentially exclude those who have the most negative outcome expectations and lowest self-efficacy for exercise, as these individuals would be less likely to enter into the trial in the first place. With regards to the findings of this chapter, this selection bias may alter the range of attitude and belief scores from the true scores in the broader population of older adults with knee pain (although mean attitude and belief scores did appear roughly comparable to both trial and non-trial samples chapter 4, section 4.5.1) .

8.6.4 Clinical implications

The findings from this chapter show that some attitudes and beliefs about physical activity, including self-efficacy for exercise and positive outcome expectations for exercise, are associated with future physical activity level in older adults with knee pain taking part in a trial testing exercise interventions. Furthermore, previous physical activity level has been further confirmed as a strong predictor of future physical activity level. Clinicians should be made aware of these important associations as they are some of the few predictors of longer term physical activity levels. Key attitudes and beliefs about physical activity should form part of clinical assessment (tools such as the SEE and OEE may be helpful in this regard until more pain tailored concise screening tools are available) and in addition clinicians should elicit information regarding current and previous physical activity levels (reinforcing the clinical recommendations from Part 3 of the thesis, chapter 7, section 7.5.4). This information can then be utilised to predict future physical activity level and to target treatment aimed at facilitating increase in physical activity level. Although age and previous physical activity levels are unmodifiable once an older adult with knee pain consults in primary care, attitudes and beliefs about physical activity are potentially modifiable through treatment.

Clinicians should both encourage therapeutic exercise and regular physical activity and directly target specific attitudes and beliefs about physical activity using tailored techniques based on each older adult with knee pain's attitude and belief profile from assessment. For example, in addressing individuals without positive outcome expectations for exercise, clinicians should provide reassurance and education regarding the benefits and safety of therapeutic exercise (reinforcing the clinical recommendations from Part 1 of the thesis, discussed in chapter 3, section 3.5.7). Whilst in order to address low self-efficacy for exercise, clinicians can employ techniques such as valued goal acquisition, vicarious experience of other older adults with knee pain successfully carrying out physical activity, and physical activity behaviour shaping with positive reinforcement and encouragement from clinicians and *"important others"* (Bandura, 2004; Ashford et al, 2010; Michie et al, 2013; Marks, 2014; Sperber et al, 2014). However, it is noted that research is required in the further development and optimisation of such interventions in older adults with knee pain as discussed below (Brand et al 2013).

8.6.5 Research implications

The findings from this chapter have research implications for further investigation into additional important attitudes and beliefs about physical activity, longer-term behaviour prediction, the stability of attitudes and beliefs about physical activity over time, the reduction of attitude and belief scales to formats practical for use in busy clinical settings, the design of interventions for influencing attitudes and beliefs about physical activity, and the external validation of the findings.

Investigating the relationship between additional key attitudes and beliefs about physical activity (that are potentially modifiable) and future physical activity levels is of interest since such research could highlight further targets for interventions aimed at increasing physical activity levels. Considering the findings from thesis Part 3 together with existing research (Holla et al 2014), fear of pain, movement and harm warrants further investigation for its association with future physical activity level since this was associated with physical activity level in the ABC-Knee study. Perceived social support and perceived subjective norms regarding exercise and physical activity are also theoretically important in social cognition theory and may help predict physical activity level (Ogden, 2007; Biddle & Mutrie, 2008), whilst fear of falling also warrants investigation since it is both common in older adults with knee pain and linked to physical activity level in older adults generally (Hornyak et al, 2013; Fransen et al, 2014).

It is unclear if attitudes and beliefs about physical activity can predict physical activity level over follow up periods longer than six months and if they are changeable or relatively stable. Gaining insight into these issues would help understand their clinical importance. For example, if they can predict physical activity level over the longer term (especially in periods without intervention support) they may have more lasting clinical and general health benefits. However, if attitudes and beliefs about physical activity only change by small amounts they may not have a meaningful effect on physical activity levels (and hence not be important targets for intervention).

In order to practically maximise the assessment and addressing of salient attitudes and beliefs about exercise within clinical outpatient settings, the creation of a concise single attitude and belief about physical activity in older adults with joint pain scale is warranted (see chapter 7, section 7.5.5 for further detail). A further option would be to design a composite physical activity prediction scale including key attitudes and beliefs and additional important determinants of future physical activity such as previous physical activity behaviour, age and perhaps BMI, comorbidities and work status. This physical activity prediction scale could potentially be utilised to identify sub groups of older adults with pain into different treatment groups based on likelihood of future physical activity level (using data driven cut-points) (Streiner & Norman, 2008). Whilst modifiable scale items could inform targeted physical activity interventions based on the modifiable risk factors (Hill et al, 2008, Foster et al, 2013).

There is a need to design and trial interventions that combine both therapeutic exercise components and psychologically informed components that target change in key attitudes and beliefs about physical activity (Brand et al 2013; see section 8.6.4). The therapeutic exercise component may involve lower limb strengthening and or aerobic exercise (Uthman et al, 2013; Juhl et al, 2014), whilst the component targeting attitudes and beliefs could be informed by theory (such as self-efficacy, social cognition and behaviour change theories) (Bandura, 2004; Ashford et al, 2010; Michie et al, 2013) and components of other musculoskeletal pain interventions that have successfully changed key attitudes and beliefs such as kinesiophobia and self-efficacy for exercise. Cognitive Behaviour Therapy (CBT), Acceptance and Commitment Therapy (ACT) and Behavioural Graded Activity all show potential for being able to influence kinesiophobia, self-efficacy or physical activity behaviour (Ashford et al, 2010; Bailey et al 2010; Pisters et al 2010; Monticone et al, 2014).

Finally, it is unknown if the attitudes and beliefs about physical activity of older adults with knee pain in the community can predict future physical activity level in the absence of a physical activity intervention. This information could help clinicians predict which older adults with knee pain are likely to be physically active independent of intervention and which need additional support (potentially contributing to future stratified care). The external validity of the findings could be further explored by carrying out similar research using both self-report and accelerometer-measured physical activity in observational prospective cohorts of older adults with knee pain and comparing the results to these RCT secondary data analyses.

8.7 Conclusion and chapter summary

This chapter investigated whether attitudes and beliefs about physical activity can predict future levels of physical activity. Higher self-efficacy for exercise, more positive outcome expectations and less negative outcome expectations for exercise were all crudely associated with higher levels of self-report physical activity at three and six months follow-up. Self-efficacy and positive outcome expectations for exercise remained associated with self-report physical activity level in multivariable adjusted models at both time-points, but not when the outcome was dichotomised into clinically important increase or not. Consistent with existing research, previous physical activity level was also a significant predictor of future physical activity level. In addition, those with lower baseline levels of physical activity had a greater likelihood of making a clinically important change in physical activity following BEEP interventions. The findings from this section suggest that self-efficacy and positive outcome expectations for exercise may be important intervention targets.

The final chapter of this thesis summarises this body of work, highlighting the main findings, its original contributions to the literature, strengths and limitations before concluding on key clinical and research recommendations for the future in relation to the thesis aim of informing future interventions for older adults with knee pain.

Chapter 9

Synthesis of thesis findings

9.1 Chapter introduction

This chapter recaps the thesis rationale and aims, summarises the key findings and discusses implications for clinical practice and future research. General thesis limitations that relate to multiple parts of the thesis are discussed before making overarching conclusions about this body of research.

9.2 Thesis rationale

Despite the unequivocal health benefits, including pain reduction and physical function improvement, associated with regular physical activity for older adults with knee pain (Warburton et al, 2010; Autenrieth et al, 2013; Fransen et al, 2015), there is uncertainty from such older adults regarding the long-term safety of physical activity which influences actual physical activity behaviour (Hendry et al, 2006; Holden et al, 2012). The safety of long-term physical activity has not been systematically reviewed whilst the mechanisms of action for improvements in pain and function with physical activity are not fully understood and it is unclear if change in physical activity level changes future clinical outcomes (Bennell et al, 2011; Runhaar et al, 2015). Furthermore, the majority of older adults with knee pain do not meet recommended levels of physical activity; hence are unlikely to gain the associated benefits (Wallis et al, 2013; Holden et al, 2015). Both physical activity uptake and long-term adherence are suboptimal and problematic in this population (Pisters et al, 2007; Jordan et al, 2010; Bennell & Hinman, 2011; Dekker, 2012; Holden et al, 2015) therefore understanding the factors linked to physical activity behaviour in older adults with knee pain is a research priority (Rankin et al, 2012; Holden et al, 2015). Attitudes and beliefs about physical activity are theoretically likely to play a significant role in explaining physical activity level (Biddle & Mutrie, 2008; Main et al, 2008; Nicolson et al, 2015).

Several attitudes and beliefs about physical activity that may influence physical activity behaviour in older adults with knee pain have been identified, such as uncertainty over safety (Hendry et al, 2006; Holden et al, 2012; Nicolson et al, 2015), yet prior to this thesis, their relationships with physical activity level had not previously been quantitatively modelled in older adults with knee pain. Multivariable modelling allows the magnitude of association between attitudes and beliefs about physical activity and physical activity level to be estimated whilst also adjusting for covariates that may confound the relationship (Szklo & Nieto, 2014). Quantitative understanding of the salient attitudes and beliefs about physical activity and their relationship with physical activity level could help inform interventions targeted at increasing physical activity in older adults with knee pain.

9.3 Thesis aims and research questions revisited

This thesis investigated attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. In doing so, it investigated factors that may aid design of future interventions aimed at increasing physical activity level and improving clinical outcomes in older adults with knee pain. The first part of the thesis aimed to address the uncertainty over the safety of long-term physical activity by systematically reviewing the published literature. Part 2 then sought to increase understanding of the mechanisms of action for physical activity interventions by investigating if changes in physical activity level per se were associated with changes in clinical outcomes in terms of pain and physical function within a previous RCT. Finally, in order to better understand the relationship between attitudes and beliefs about physical activity and physical activity level the cross-sectional and longitudinal relationships between key attitudes and beliefs and self-report physical activity level were investigated in Parts 3 and 4 respectively.

9.4 Key findings

Key findings from the thesis are highlighted and summarised within box 9.1.

9.5 Synthesis and evaluation of thesis findings with existing literature

This thesis has contributed to the evaluation of the benefits and harms of physical activity in older adults with knee pain. The systematic review found long-term physical activity, in the form of therapeutic exercise, to be safe for most older adults with knee pain. This finding can also be cautiously triangulated with the finding that increasing physical activity level was not associated with increase in pain or functional decline in thesis Part 2. Synthesising the evidence, the overall picture is one of relatively few harms associated with physical activity and therapeutic exercise for older adults with knee pain. These few harms can be weighed against the known benefits of higher levels of physical activity, such as reduced mortality and morbidity (Warburton et al, 2006; DOH, 2011), to support both general and joint pain specific guideline recommendations for regular physical activity for older adults with knee pain (Chodzko-Zajko et al, 2009; DOH, 2011; Fernandes et al, 2013; McAlindon et al, 2014; NICE, 2014).

Box 9.1 Key thesis findings

Part 1: Is long-term physical activity safe for older adults with knee pain?

- Long-term therapeutic exercise is likely safe for the vast majority of older adults with knee pain. Most evidence related to low impact moderate intensity therapeutic exercise
- Adverse events were only explicitly reported in 21 of 48 included trials. There were no reported severe adverse events associated with exercise interventions, whilst moderate adverse events such as falls were very rare (ranging from 0 to 6% of exercise participants). A minority (ranging from 0 to 22%) of older adults with knee pain within exercise interventions experience mild adverse events such as mild or temporary increases in pain
- There is a dearth of evidence relating to long term OA imaging evidence regarding progression of OA and total knee replacement frequency associated with physical activity
- There was insufficient evidence to draw conclusions on other types of physical activity including high impact therapeutic exercise, occupational activity, travel activity and sport

Part 2: Are changes in physical activity level associated with future clinical outcomes in terms of pain and function in older adults with knee pain?

- Only small mean change in physical activity level was available for modelling
- Change in physical activity was not associated with change in pain or physical function
- Likewise, change in pain and physical function were not associated with change in physical activity level
- Change in physical activity level may therefore not mediate clinical outcome in older adults with knee pain
- However, the reliability and likely sub optimal responsiveness of the Physical Activity Scale for the Elderly make it a questionable option for modelling change in physical activity level in future studies

Part 3: Are attitudes and beliefs about physical activity associated with physical activity level in older adults with knee pain?

- Several attitude and beliefs about physical activity were found to be associated with self-report physical activity level in adjusted models, including self-efficacy for exercise, outcome expectations, kinesiophobia, and a composite scale including aspects of outcome expectations, beliefs about vigorous exercise, enjoyment and social benefits
- Cross-sectional relationships were found between attitudes and beliefs about exercise and physical activity level in both exercise trial and community survey datasets
- A number of sociodemographic and clinical variables were also associated with physical activity, including socioeconomic category, employment status, number of comorbidities, age, chronic pain grade and previous use of therapeutic exercise to treat knee pain

Part 4: Can attitudes and beliefs about physical activity predict future physical activity level in older adults with knee pain?

- Attitudes and beliefs about physical activity can predict future self-report physical activity
- Baseline positive outcome expectations and self-efficacy for exercise were associated with self-report physical activity level at three and six months in adjusted models
- The magnitude of association between attitude and belief variables and physical activity level decreased in the six month physical activity level models compared to the three month models suggesting attitudes and beliefs about physical activity are weaker predictors of future physical activity level over longer time periods
- Past physical activity level was a consistent predictor of future physical activity level

These findings are clinically important since many older adults with knee pain, and some of the clinicians who manage them, do not believe that keeping active and carrying out regular therapeutic exercise is appropriate or safe condition management (Hendry et al, 2006; Holden et al, 2009, 2012; Cottrell et al, 2010; Poitras et al, 2010). The thesis findings could be used to challenge such attitudes and beliefs with the goal of increasing the recommendation and application of regular physical activity for older adults with knee pain. Furthermore, in the absence of a cure, regular physical activity appears to have a favourable safety profile when compared to other common condition management options for older adults with knee pain such as paracetamol and NSAIDS (Abdulla et al, 2013; Machado et al, 2015; Mallen & Hay, 2015; Richette et al, 2015). This reinforces physical activity as a core treatment for this population (NICE, 2014).

Part 2 of the thesis did not show change in physical activity level per se to be associated with future clinical outcomes of pain and physical function. Although there were a number of methodological limitations that increased the risk of a false negative association, this finding can be cautiously interpreted to suggest that other components of physical activity are the active mechanisms of action for pain reduction and physical function improvement within physical activity interventions (see chapter 2, section 2.10.2).

The thesis has also added further insight into the important relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain. Several attitudes and beliefs about physical activity were found to be associated with self-report physical activity level in both cross-sectional and longitudinal multivariable adjusted analyses. Combining these findings provides quantitative evidence that adds to existing qualitative and mixed method research that attitudes and beliefs about physical activity are importantly linked to actual levels of physical activity (Campbell et al, 2001; Hendry et al, 2006; Petursdottir et al, 2010; Holden et al, 2012, 2015). Self-efficacy and positive outcome expectations for exercise, fear of movement and harm, and a composite scale measuring physical activity attitudes about vigorous exercise, health outcomes, social benefits and tension release were all found to be significantly associated with physical activity level. The findings from this thesis suggest that these attitudes and beliefs about physical activity are key correlates of physical activity level. Whilst the findings from Part 4 of this thesis suggest self-efficacy and positive outcome expectations for exercise may tentatively be considered as potential determinants of physical activity level since they have association, dose response, theoretical plausibility and the correct temporal order (Hill, 1965; Szklo & Nieto, 2014), this statement is made with the caveat that physical activity behaviour in older adults with knee pain is a complex phenomenon with multiple interacting facilitators and barriers (Biddle & Mutrie, 2008; Dekker, 2012; Nicolson et al, 2015) and the methods used within this thesis remain at risk of residual confounding (Szklo & Nieto, 2014). Salient attitudes and beliefs about physical activity, such as self-efficacy and positive outcome expectations for exercise are clinically relevant since they can both predict future levels of physical activity and may be potentially modifiable. Hence, if they can be shown to be sufficiently changeable they may be suitable targets for interventions aimed at increasing physical activity in older adults with knee pain (Baron & Kenny, 1986; Sallis et al, 2000; Sperber, 2014; Runhaar et al, 2015).

9.6 Applications to the wider joint pain literature

Some of the findings from this thesis may also be applied, with caution, to other adult joint pain literature. For example, although there is a dearth of published literature exploring the attitudes and beliefs about physical activity of older adults with hip and foot pain attributed to OA (Petursdottir et al, 2010; Cuperus et al, 2013), it is perhaps likely that these populations share similar attitudes and beliefs about physical activity to older adults with knee pain due to general pain and physical activity socially constructed lay beliefs (Crombie et al, 2004; Biddle & Mutrie, 2008; Foster et al, 2008; Main et al, 2008) (in addition to some mutually exclusive illness perceptions). Hence, the salient attitudes and beliefs about physical activity within this thesis may also have similar associations with physical activity level and predictive value within these populations. Interestingly, positive outcome expectation and higher self-efficacy for physical activity have also been associated with higher physical activity in other cross-sectional joint pain populations such as adults with rheumatoid arthritis (RA) (Ehrlich-Jones et al, 2011). Hence, regardless of the differing aetiology of OA and RA, it may be possible to cautiously infer that self-efficacy and outcome expectations for exercise may also be important predictors of future physical activity in this heterogeneous clinical population. The thesis findings may also have important implications in other common and disabling musculoskeletal conditions associated with low levels of physical activity, such as chronic low back pain. Indeed, the extent to which there is a core set of salient attitudes and beliefs about physical activity for musculoskeletal joint pain populations generally warrants further investigation for practical general application in healthcare settings.

Whilst the safety findings from this thesis appear encouraging for other joint pain attributed to OA, it is uncertain if the safety of therapeutic exercise may also be extrapolated to pain in other weight bearing joints, such as the hip and foot joints in older adults. This is because although these types of joint pain share many aspects of aetiology and some sociodemographics with older adults with knee pain (Zhang & Jordan, 2010; Thomas et al, 2015) they also have unique prognostic factors and biomechanical factors that may interact with physical activity in a different way to older adults with knee pain (Wright et al, 2009; Bennell & Hinman, 2011; Bastick et al, 2015b). It is hence important to systematically review the safety literature pertaining to these joints independently before reaching a robust conclusion.

9.7 General thesis limitations

Whilst a number of specific limitations have been described within previous chapters, some key issues affected multiple thesis analyses, including the use of secondary analyses, imperfect measures of physical activity level, unadjusted confounding and the generalisability of the thesis findings. Since the analyses within this thesis were based on existing studies the variables available for analyses were only those used within the original datasets. For example, it would have been useful to compare the findings from Parts 2 to 4 with those obtained from accelerometry (which is considered to be at less risk of recall, social desirability bias and misclassification errors than self-report physical activity) (Prince et al 2008). In addition, since not all potential confounding variables were available in the datasets there is a risk of unadjusted confounding. For example, ecological models of physical activity suggest wider social, environmental and government policy factors may all influence physical activity alongside personal factors (Biddle & Mutrie, 2008), yet when modelling physical activity in thesis Parts 3 and 4 there were no environmental or government policy variables available for consideration in model building. Finally, the results from the BEEP trial dataset for Parts 2 to 4 were taken from older adults with knee pain who consented to take part in a physical activity intervention trial and may not be representative of all older adults with knee pain since, for example, the oldest and most frail older adults and those who do not wish to undergo physical activity interventions were underrepresented (Bartlett et al, 2005; Peat et al, 2006b) (chapter 4, section 4.4.2).

9.8 Thesis clinical recommendations

Clinical recommendations for older adults with knee pain and the healthcare clinicians who manage them can be made from the novel findings within this thesis and supported by existing research. It is recommended that clinicians who manage older adults with knee pain are educated regarding the safety profile and benefits of regular physical activity for older adults with knee pain. It addition, it is recommended that clinicians be made aware that attitudes and beliefs about physical activity and previous physical activity behaviour are associated with physical activity level and are important predictors of future physical activity level. Translating this into practice, the thesis findings support existing NICE guidelines (2014) recommending that clinical assessment of older adults with knee pain include current and previous physical activity level as well as exploration of key attitudes and beliefs about physical activity (NICE, 2014) such as outcome expectations, self-efficacy for physical activity and kinesiophobia. Drawing on the author's clinical opinion and wider pain literature it is advised that clinicians are mindful that adopting a pain contingent condition management strategy may in fact contribute to iatrogenic fears that hurt means harm and that regular physical activity may not be safe (Main et al 2008). Indeed, extrapolating from the available evidence within the systematic review in Part one such fears of activity being unsafe appear unsubstantiated and hence could be minimised since they may act as barriers to regular physical activity.

It is suggested that clinicians target physical activity increases indirectly by addressing attitudes and beliefs about physical activity (that may act as potential barriers or facilitators to physical activity) and directly by recommending regular physical activity and therapeutic exercise (including lower limb strengthening and aerobic exercise) (Brand et al, 2013; Fransen et al, 2015). Older adults with knee pain can be reassured that long-term therapeutic exercise is likely to be safe in the vast majority of cases. They can be educated that increasing physical activity levels is not associated with increased knee pain, reduced function, progression of OA on imaging or increased risk of TKR, but that the majority of individuals who carry out long-term therapeutic exercise will experience improvements in pain and physical function as well as general health benefits (Warburton et al, 2010; Fransen et al, 2015). Reassurance can be provided that it is normal for a minority of older adults with knee pain to experience mild or temporary increases in pain with physical activity but that this is not necessarily a sign of harm or associated with progression of OA.

In addition, the thesis findings support existing studies suggesting that older adults with knee pain are more likely to carry out and increase physical activity if they enjoy it, find it socially rewarding and believe they can successfully carry it out (Hendry et al, 2006; Holden et al, 2012). Hence, building on previous literature it is recommended patients and clinicians be involved in collaborative goal setting

(Hall et al, 2010), with incremental increases in activity from a baseline that is achievable and should have choice in the types of physical activity they carry out (Jordan et al, 2010; Hochberg et al, 2012; Fernandes et al, 2013).

It is advised that clinicians tailor their treatment to each patient's specific profile of attitudes and beliefs about physical activity. For example, patients who hold negative and fearful outcome expectations for physical activity or low self-efficacy for physical activity could potentially be managed by using condition education and reassurance, valued achievable goal setting, positive feedback on physical activity behaviour, vicarious experience of similar others carrying out physical activity, graded exposure of physical activity, cognitive behavioural therapy or acceptance and commitment therapy in those with chronic pain (Gifford, 2006; Main et al, 2008; Ashford et al, 2010; Bailey et al, 2010; Monticone et al, 2014). Such interventions need further development and testing (see section 9.9.5).

9.9 Research recommendations

A number of research implications have been suggested within earlier chapters. This section seeks to evaluate the key implications for future research from this thesis and summarises the top five research areas which the author believes could help inform physical activity understanding and interventions for older adults with knee pain.

9.9.1 Areas for further understanding the safety of physical activity

The findings from Part 1 highlighted a number of areas for further research into the safety of long-term physical activity for older adults with knee pain. A key recommendation for future physical activity interventions is the explicit monitoring and reporting of adverse events including a clear statement about the lack of adverse events in the cases that no adverse events were detected. It is recommended that trial authors should provide information on the type, frequency and severity of adverse events attributable to exercise including exacerbations of pain during exercise (Ioannidis et al 2004 Schulz et al 2010). This information will reduce the risk of bias in physical activity safety conclusions due to selective reporting.

There is a gap in the literature regarding the safety of long-term physical activity research other than low impact therapeutic exercise and a relative underrepresentation of specific *"at risk"* groups of older adults with knee pain within RCTs (such as the frail and most elderly and those with cardiovascular disease). Knowledge of the safety of additional types of activities and specific at risk subgroups would aid clinicians in providing confident physical activity advice and may in turn aid physical activity behaviour choices in older adults with knee pain. Whilst recent research is beginning to increase knowledge regarding the safety of high impact physical activity (Multanen et al, 2014; Lo et al, 2015) (see chapter 3, section 3.5.5), there remains a lack of research investigating the safety of occupational activity, travel activity and sport in older adults with knee pain.

Further observational studies of older adults with or at high risk of knee pain are perhaps best placed to investigate the safety of these additional types of physical activity. However, for these studies to be valid it is important that adequate measures of long-term physical activity are recorded and sufficient follow-up is available to reach robust conclusions on long-term safety outcomes such as structural OA progression on imaging (including the patella femoral joint) or progression to TKR (see chapter 3, section 3.3.2 & 3.5.4). Novel phase one dose-response trials of specific physical activities (Wallis et al 2015) may also offer initial safety evidence from small sub groups of adults underrepresented within the systematic review (such as the frail elderly, those with a history of falls or those with a previous cardiac event) partaking in specific activities without the need for large and expensive cohort studies or trials.

9.9.2 Clinimetric properties of the PASE in older adults with knee pain

This research has highlighted limitations of current physical activity measures commonly used for older adults with knee pain, namely questionable intra-rater reliability and responsiveness. Although there is some research exploring the validity and reliability of the PASE for older adults with other joint pain and following joint replacement (Svege et al, 2012, Bolszak et al 2014), to date the reliability and responsiveness of the PASE in older adults with knee pain has not been investigated. Hence, to increase the confidence in the findings from Parts 2 and 4 of this thesis and to inform decision making in selecting optimal physical activity measures in future studies exploring physical activity (especially studies requiring repeated measures and change in physical activity), further PASE clinimetric research is required in older adults with knee pain.

9.9.3 Replication and exploration of additional mechanisms of action

The limited change in physical activity levels within the BEEP dataset and concern over the reliability and responsiveness of the PASE for calculating absolute change in physical activity level may warrant further investigation into the relationship between change in physical activity level over time and future clinical outcome of pain and physical function in older adults with knee pain (thesis Part 2). Such analysis could add confidence in or raise concerns regarding the null association findings. Future analyses could consider the use of direct measures of physical activity level, such as accelerometry which are not at risk of recall bias, may have superior responsiveness properties and allow the break-down of changes in some specific types of physical activity (such as differing cardiovascular intensities) (Prince et al, 2008; Montoye et al, 2014). However, it is noted existing direct measures also have their own unique limitations (see chapter 2, section 2.7).

Additional novel potential mechanisms of action for physical activity interventions worthy of future investigation include, change in attitudes and beliefs about physical activity, change in depression in depressed sub groups, and therapeutic relationship factors of empathy, rapport and clinical collaboration (Hall et al 2010, Bennell et al 2014).

9.9.4 Designing a brief attitudes and beliefs about physical activity scale for older adults with joint pain

Most of the attitudes and beliefs about physical activity scales utilised within this thesis were not specifically designed for older adults with joint pain. Furthermore, it is not practical in many clinical settings to use several attitude and belief about physical activity scales. Hence, there is a clinical need for a single concise attitude and belief about physical activity scale tailored to older adult populations with joint pain. This could be utilised to aid clinical reasoning of likely future physical activity levels and to inform potentially modifiable targets for treatment.

Arguably the most appropriate method would be to develop a new scale item pool specifically tailored to joint pain in older adults (informed by the findings of this thesis, existing research, expert and patient consensus), then use data reduction processes such as Delphi methods (Hsu & Sandford, 2007) and factor analysis to create a scale (Streiner & Norman, 2008) which could be tested for psychometric properties in a sample of older adults with joint pain.

9.9.5 Key recommendations for future physical activity interventions

Based on the findings from this thesis, there is a need to design and test a physical activity intervention that both targets increasing physical activity levels directly and indirectly by addressing key attitudes and beliefs about physical activity.

Recommendation 1: Important measures

Attitudes and beliefs about physical activity and current and previous physical activity levels should be assessed at baseline along with sociodemographics and clinical severity. Measuring attitudes and beliefs about physical activity at baseline and over time using a novel composite scale (see section 9.9.4) could help identify targets for individually tailored intervention (and allow future mediation analyses investigating mechanisms of action) (Baron & Kenny, 1986; Mansell et al, 2014; Sperber et al, 2014; Runhaar et al, 2015). Following reliability and responsiveness testing of the PASE (see section 9.9.2) and minimally invasive accelerometry in older adults with knee pain (see chapter 3, section 3.5.8), a decision on the optimum repeated measure of physical activity level can be made.

Recommendation 2: Intervention components

Intervention should be tailored to the individual, considering baseline physical abilities, comorbidities, current physical activity level and attitudes and beliefs about physical activity. Enjoyable low impact and moderate intensity physical activity interventions tailored to the individual’s preference and baseline abilities that include lower limb strengthening and aerobic exercise together with social interaction, support and collaborative achievable goal setting are recommended as core components (Jordan et al, 2010, NICE 2014). Older adults with knee pain should also be educated regarding the safety of low impact, moderate intensity exercise and the likely positive clinical outcomes associated with regular long-term physical activity. Reassurance should be offered to those with fear of movement and harm that mild increase in pain with physical activity, although experienced in a minority, is likely temporary and not representative of harm. Cognitive behavioural therapy, ACT, behaviour change and social cognition theories may help inform intervention components targeting key attitudes and beliefs about physical activity and physical activity increase in insufficiently active older adults.

Recommendation 3: Stratification of care

Finally, in order to match the most appropriate and cost-effective physical activity interventions to individual older adults with knee pain, it may be possible to stratify care based on prognostic factors for future physical activity levels including modifiable attitudes and beliefs about physical activity (Hill et al 2008, Foster et al, 2013). For example, older adults with positive outcome expectations, high self-efficacy for exercise who enjoy exercise, have low fear of movement and harm may be managed successfully with simple advice regarding self-management, therapeutic exercise, regular physical activity and signposting to local facilities, whilst insufficiently active older adults with negative outcome expectations for exercise, low self-efficacy for exercise, fear of movement and harm, who do not enjoy exercise may require more comprehensive, psychologically informed interventions as discussed above. Such hypotheses could be tested with RCT methodology alongside cost-effectiveness analysis comparing stratified care to usual care.

9.9 Thesis conclusion

This thesis has made a novel contribution to the field of physical activity for older adults with knee pain as highlighted below.

Box 9.2 Thesis novelty

1. **The first systematic review to specifically investigate the safety of physical activity behaviour in older adults with knee pain by synthesising multiple safety outcome domains.**

2. **The first study to investigate if change in physical activity per se is associated with clinical outcome in older adults with knee pain.**

3. **The first study to quantitatively investigate the cross-sectional and longitudinal relationship between attitudes and beliefs about physical activity and physical activity level in older adults with knee pain.**

It has confirmed the safety of long-term therapeutic exercise for the majority of older adults with knee pain which can help reassure both older adults with knee pain and the clinicians who manage them. Hence, with knowledge dissemination, there is the potential to reduce a key barrier to regular physical activity. It has shown that increase in physical activity level per se may not be associated with changes in clinical outcome within a physical activity RCT suggesting that other mediating factors account for the mechanisms of treatment effect, but also that increasing physical activity level does not lead to pain increase at a group level which can reassure clinicians recommending increases in physical activity. It has also shown a number of attitudes and beliefs about physical activity to be related to current and future physical activity level. In particular, greater self-efficacy beliefs about physical activity and positive outcome expectations were associated with higher future levels of physical activity, suggesting that these attitude and belief factors may be both key predictors of future physical activity level and also potential targets for intervention. In addition, a number of suggestions for future research in the field and clinical recommendations have also been made integrating the thesis findings with existing knowledge. Therefore this thesis has important implications for older adults with knee pain, the clinicians who manage them and also future research that aims to increase physical activity levels and ultimately improve health outcomes in older adults with knee pain.

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Appendices

Appendix I: Systematic review study eligibility and data extraction form

Review ID		
Reviewer		
Date of form completion		
Study ID		
First author, Year of study publication		
Country of origin/ language.		

Study eligibility	Yes	Unclear	No
Q1. Is the study a full text, peer reviewed, RCT OR case control OR prospective cohort?			
	Go to next question		Exclude
Q2. Are all (or an independently analysed subgroup) of the participants adults with knee pain and mean age over 45 OR adults with knee OA? (OA can be by radiographic or clinical criteria)			
	Go to next question		Exclude
Q3. Was the intervention or exposure some form of exercise or physical activity carried out explicitly over 3 months or longer? (NB HEPs are included whilst advice to exercise alone is excluded. See additional guidance sheet)			
	Go to next question		Exclude
Q4. Did the study measure one or more of the following primary safety related outcomes: • Self-reported pain • Self-reported function • Adverse events (e.g. falls, injuries etc.) • Biomarker outcomes of osteoarthritis progression from: radiographic reduced joint space/ Kellgren-Lawrence score, MRI cartilage volume, joint space narrowing, bone marrow lesions, synovitis (crepitus and effusion excluded). AND/ OR one of the secondary outcomes: • Progression to total knee replacement • Analgesia use			
Final decision/ Reason	Include	Unclear	Exclude

Appendix II: Risk of bias tool selection pilot

Two separate risk of bias tools were utilised within this Phd, for RCTs and observational studies due to these different study types being at risk of bias from mutually exclusive factors. For example, observational study findings may be at risk of bias from unadjusted confounding, whilst this is less likely to be a factor in RCTs, since the randomisation process distributes known and unknown confounding factors into both treatment groups, hence negating their effect on outcomes (Szklo & Nieto, 2014).

Since there is no gold standard risk of bias tool for use in judging risk of bias of included studies within systematic reviews (Sanderson et al, 2007; Higgins & Green, 2009), a number of tools were piloted. In order to pilot a pragmatic number of risk of bias tools, two tools were selected for RCTs and two tools for observational studies based on existing recommendations within the literature, and on the tools commonly used in existing systematic reviews.

For observational studies, Sanderson et al (2007) suggest that a tool should include three fundamental domains; appropriate selection of participants, appropriate measurement of variables and appropriate control of confounding. The Newcastle-Ottawa Scale tool (Wells et al, 2007. From http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed: November 2012) and modified QUIPS tool (Hayden et al, 2013) satisfy these criteria have been used in existing systematic reviews and were selected for piloting. For RCTs, the Cochrane Collaboration recommends assessing six fundamental domains; selection bias, performance bias, attrition bias, detection bias, reporting bias and "*other sources of bias*". Their most recent tool is a domain based evaluation tool (Higgins et al, 2011). It was piloted together with the commonly utilised and concise Jadad score (Jadad et al, 1996). Both tools include risk of bias domains that have been shown in the literature to be associated to biased results in previous studies (Jadad et al, 1996, Higgins & Green, 2009, Hartling et al, 2009).

The pilot involved two researchers (JQ and NF) using the tool on a purposive sample of three studies (RCTs and observational studies), before making a decision on the final tool selection. The decision was made to use the Cochrane risk of bias tool and the modified QUIPS tool within the systematic review. The primary reason for the selection of these two tools was that they were more comprehensive in covering a broad range of risk of bias domains (Higgins & Green, 2009). Strengths and limitations of each of the piloted tools are summarised in the two tables overleaf.

Table A2-1: Evaluation of piloted RCT risk of bias tools

Cochrane risk of bias tool	Jadad scale tool
Strengths	
• Domain based judgement avoids quantifying a subjective concept • Empirical support for domain components • Comprehensive assessment of multiple risk of bias domains • Flexibility with “other sources of bias” domain • Peer reviewed in construction • Recommended by Cochrane	• Very quick to complete • Commonly utilised in the literature • Empirical evidence support for components • Peer reviewed in construction
Limitations	
• Time consuming to complete • Is at risk of different risk of bias domain judgement conclusions from different reviewers	• Scale score weighting is difficult to justify • No assessment of allocation concealment or reporting bias • Poor scale score discrimination potential

Table A2-2: Evaluation of piloted observational study risk of bias tools

Modified QUIPs tool	Newcastle-Ottawa Scale
Strengths	
• Domain based risk of bias tool • Developed by mixed academic and clinical working group with feedback from multiple review groups. • Median k statistic inter-rater agreement of 0.75 • Peer reviewed	• Very quick to complete • Simple scoring criteria hence likely high inter-rater scoring agreement • Commonly utilised in the literature
Limitations	
• Time consuming to complete • Requires baseline knowledge in the reviewer (for example regarding key confounders) • Confusing “double negative” (question 12)	• Scale score weighting is difficult to justify • Inadequate handling of confounding bias • Not fully validated and published in a peer reviewed journal

QUIPs=Quality in prognostic study tool for risk of bias in observational studies.

Appendix III: Risk of bias tools scoring guidance

Cochrane RCT risk of bias tool

The Cochrane RCT risk of bias tool is split into 6 bias domains with 7 judgements. Each judgement is categorised as either "low risk" of bias, "high risk" of bias or "unclear risk" of bias. Category and judgement is provided by Higgins et al (2011) and can be found on line in further detail (Criteria for judging risk of bias. From: http://handbook.cochrane.org/chapter_8/table_8_5_d_criteria_for_judging_risk_of_bias_in_the_risk_of.htm, accessed: December 2012)

Modified QUIPs risk of bias tool

The table below is modified from Hayden et al (2013), and displays the assessed bias domains within observational studies for the modified QUIPS tool. It also highlights issues to consider when judging whether an observational study is at "low risk", "moderate risk" or "high risk" of bias for each domain.

Table A3-3: Bias domains and issues to consider in judging modified QUIPS risk of bias (modified from Hayden et al 2013)

Biases	Issues to consider for judging overall rating of "Risk of bias"
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**
Source of target population	The source population or population of interest is adequately described for key characteristics.
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)
Recruitment period	Period of recruitment is adequately described
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).
Adequate study participation	There is adequate participation in the study by eligible individuals
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-completing participants).**
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics.
	There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analysed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**

Biases	Issues to consider for judging overall rating of "Risk of bias"
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.
3. Prognostic Factor Measurement	**Goal: To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).**
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.
PF Measurement Summary	***PF*** **is adequately measured in study participants to sufficiently limit potential bias.**
4. Outcome Measurement	**Goal: To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).**
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.
Outcome Measurement Summary	***Outcome of interest*** **is adequately measured in study participants to sufficiently limit potential bias.**

Biases	Issues to consider for judging overall rating of "Risk of bias"
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.
5. Study Confounding	**Goal: To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).**
Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model), are measured.
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**
6. Statistical Analysis and Reporting	**Goal: To judge the risk of bias related to the statistical analysis and presentation of results.**
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.
	The selected statistical model is adequate for the design of the study.
Reporting of results	There is no selective reporting of results.
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**

Appendix IV: BEEP adherence enhancing tool kit

Section 1-Information for physiotherapists

- Instructions for using the adherence enhancing toolkit
- Background information about exercise, knee pain in older adults and adherence

CD containing: electronic version of the Toolkit

Section 2-Educational aids

- The BEEP advice and information leaflet
- TENS/ Medication/ walking guides
- Intensities for common activities
- Exercise and chronic conditions
- Useful website addresses for patient information
- Examples of other information leaflets
- Frequently asked questions
- Instructions for PhysioTools

Section 3-Behavioural aids

- Pedometer instructions and pedometers
- PhysioTools software
- Visual feedback chart
- Reminder postcard
- Graded activity sheet
- Physical activity diary
- Knee exercise diary
- How to measure heart rate guide

Section 4-Cognitive behavioural aids

- Questions to elicit health related beliefs
- Identifying barriers/ facilitators to exercise
- SMART goal setting
- Exercise and physical activity contracts
- Rulers (readiness ruler, confidence ruler, importance ruler)
- Set-back plan sheet

Section 5-local lifestyle change opportunities

- Exercise and physical activity opportunities in the local area (developed for local areas by participating physiotherapists)

(From Foster et al (2014) supplementary material with permission).

Appendix V: PASE and STAR Physical activity scale detail

Physical Activity Scale for the Elderly (PASE) scale (Washburn et al, 1993):

- Designed to measure self-report physical activity in older adults.
- Measures occupational/ household & leisure activities in the previous week
- PASE scores are calculated based on the frequency and weighting for 12 different types of physical activity (see below)

Table A5-1: PASE scoring form (modified from Washburn et al, 1993)

PASE item	Type of activity	Activity weight	Activity frequency	Weight times frequency
Leisure activities				
2	Walk outside home	20	a.	
3	Light sport/ recreational activities	21	a.	
4	Moderate sport/ recreational activities	23	a.	
5	Strenuous sport/ recreational activities	23	a.	
6	Muscle strength/ endurance activities	30	a.	
Household activity				
7	Light housework	25	b.	
8	Heavy housework or chores	25	b.	
9a	Home repairs	30	b.	
9b	Lawn work or yard care	36	b.	
9c	Outdoor gardening	20	b.	
9d	Caring for another person	35	b.	
Occupational work				
10	Work for pay or as volunteer	21	c.	
		PASE score total		

Activity frequency values: a= use hours per day conversion table below**;** b= 1=activity reported in the past week, 0=activity not reported**;** c= Divide work hours reported in question 10 by seven, if no work hours or job is predominantly sedentary, then activity frequency =0

Table A5-2: PASE activity time to hours per day conversion table

Days of activity	Hours per day of activity	Hours per day
0. Never		0
1. Seldom	1. less than 1 hour	0.11
	2. 1-2 hours	0.32
	3. 2-4 hours	0.64
	4. More than four hours	1.07
2. Sometimes	1. less than 1 hour	0.25
	2. 1-2 hours	0.75
	3. 2-4 hours	1.50
	4. More than four hours	2.50
3. Often	1. less than 1 hour	0.43
	2. 1-2 hours	1.29
	3. 2-4 hours	2.57
	4. More than four hours	4.29

Modified Short Telephone Activity Recall (STAR) questionnaire (Matthews et al, 2005)

- Self-report physical activity
- Based on three questions relating to the quantity and frequency of moderate and vigorous physical activity
- Individuals are categorised into *"inactive"*, *"insufficiently active"* and *"meeting guideline recommendations of physical activity"*
- *"Meeting recommendations"* was defined as moderate intensity activity for 5 days per week and 30 minutes per day or vigorous activity 3 days a week and 20 minutes per day
- *"Insufficient"* was defined as some moderate or vigorous activity but not of sufficient duration or frequency to meet recommendations
- *"inactive"* was defined as reporting no moderate or vigorous physical activity

Full wording of the modified STAR questions are provided overleaf.

Modified STAR Questions (Matthews et al, 2005 with permission)

We are interested in the activities that you do at home, at work, for leisure or exercise, or for any other reason.

1) In a usual week, how often do you do **moderate** activities for at least 10 minutes at a time?

By ***moderate*** *activities we mean activities such as bicycling, raking leaves, mowing the lawn, vacuuming the house, or walking for exercise or transport.*

(Please put a cross in one box only)

Never………………………………….. ☐→**please go to 3)**
Occasionally or 1 to 3 times a month….. ☐
Once or twice a week……………………. ☐
Three or four times a week…………….. ☐
Five or more times a week………………. ☐

2) On days when you do **moderate** activities for at least 10 minutes at a time, on average how much total time do you spend each day doing these activities? (please put a cross in one box only)

10-20 minutes………… ☐
20-30 minutes………☐
30-40 minutes………… ☐
40-50 minutes………☐
50-60 minutes………… ☐
60 minutes or over….☐

Please state what kind of **moderate** activities you do:
…………………………………………………………………………………………
…………………………………………………………………………………………

3) In a usual week, how often do you do **vigorous** activities for at least 20 minutes at a time?

By ***vigorous*** *activities we mean activities or exercise such as running, aerobics, or heavy garden work.*

(Please put a cross in one box only)

Never……………………………………… ☐→**please go to next question**
Occasionally or 1 to 3 times a month…. ☐
Once or twice a week……………………. ☐
Three or four times a week…………….. ☐
Five or more times a week……………… ☐

Please state what kind of **vigorous** activities you do:
…………………………………………………………………………………………
…………………………………………………………………………………………

Appendix VI: Thesis attitude and belief scale item detail

BEEP attitude and belief scales:

Self-Efficacy for Exercise (SEE) (Resnick & Jenkins, 2000)

- Assesses individual's self-efficacy for exercise
- The scale is based on self-efficacy theory
- The scale measures individuals confidence that they could exercise three times a week for 20 minutes based on various scenarios
- The self-efficacy for exercise scale contains 9 items
- The scale is scored based on the mean score from the 9 items and ranges from 0-10
- Validated in older adults (mean age 85)

Table A6-1 SEE items (modified from Resnick & Jenkins, 2000 with permission)

How confident are you right now that you could exercise three times per week for 20 minutes if:
1.The weather was bothering you
2.You were bored by the program of activity
3.You felt pain when exercising
4.You had to exercise alone
5.You did not enjoy it
6.You were too busy with other activities
7.You felt tired
8.You felt stressed
9.You felt depressed

Each item is scored from 0-10 with; Not confident=0, Very confident =10

Outcome Expectations for Exercise (OEE 2) (Resnick, 2005)

- Assesses individual's outcome expectations for exercise
- The scale is based on self-efficacy and social cognition theories
- The scale is split into two sub scales; the *"positive outcome expectation scale"* and the *"negative outcome expectation scale"*
- The positive outcome expectation scale contains 9 items and the negative outcome expectation scale contains 4 items
- Both scales are scored based on the mean response of the items within them and are scored from 1-5 more positive outcome expectations for exercise are indicated by higher scores
- Validated in older adults (mean age 88)
- Both scales are correlated

Table A6-2 OEE 2 items (modified from Resnick 2005 with permission)

Item	SA	A	N	D	SD
Positive outcome expectations for exercise subscale					
1.Exercise makes me feel better physically					
2.Exercise makes my mood better in general					
3.Exercise helps me feel less tired					
4.Exercise makes my muscles stronger					
5.Exercise is an activity that I enjoy doing					
6.Exercise gives me a sense of personal accomplishment					
7.Exercise makes me alert mentally					
8.Exercise improves my endurance in performing my daily activities					
9.Exercise helps to strengthen my bones					
Negative outcome expectations for exercise subscale					
1.Exercise is something I avoid because it causes me to be short of breath					
2.Exercise is something I avoid because it may cause me to have pain					
3.Exercise makes me fearful that I will fall or get hurt					
4.Exercise places too much stress on my heart so I avoid it					

SA=strongly agree; A=agree; N=neutral; D=disagree; SD=strongly disagree
Positive outcome expectations for exercise item scoring: strongly agree=5, agree=4, neutral=3, disagree=2, strongly disagree=1; Negative outcome expectations scoring: strongly agree=1, agree=2, neutral=3, disagree=4, strongly disagree=5

ABC-Knee scales:

Tampa Scale for Kinesiophobia (TSK) (Miller et al, 1991, Vlaeyen et al, 1995)

- Assesses an individual's fear of movement/ (re)injury
- The version used was the original 17 item version
- Each item indicates whether individuals strongly disagree, somewhat disagree, somewhat agree, or strongly agree with statements relating to kinesiophobia
- The scale ranges from 17-68 with higher scores indicating higher levels of kinesiophobia
- Originally designed for older adults with back pain but validated in knee pain populations (Heuts et al, 2004)

Table A6-3 TSK (modified from Vlaeyen et al, 1995 with permission)

Item	SD	D	A	SA
1. I'm afraid that I might injure myself if I exercise				
2. If I were to try to overcome it, my pain would increase				
3. My body is telling me I have something dangerously wrong				
4.My pain would probably be relieved if I were to exercise				
5.People aren't taking my medical condition seriously enough				
6.My condition has put my body at risk for the rest of my life				
7.Pain always means I have injured my body				
8.Just because something aggravates my pain does not mean it is dangerous				
9.I am afraid I may injure myself accidently				
10.Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening				
11.I wouldn't have this much pain if there wasn't something potentially dangerous going on in my body				
12.Although my condition is painful, I would be better off if I were physically active				
13.Pain lets me know when to stop exercising so that I stop injuring myself				
14.It's really not safe for a person with a condition like mine to be physically active				
15.I can't do all the things normal people do because it's too easy for me to get injured				
16.Even though something is causing me a lot of pain, I don't think it is actually dangerous				
17.No one should have to exercise when he/ she is in pain				

SD=strongly disagree; D=somewhat disagree; A=somewhat agree; SD=strongly disagree
TSK scoring: SD=1; D=2; A=3; SA=4. Items 4, 8, 12 & 16 reverse scored.

Arthritis Self-Efficacy Scale (ASES) (Lorig et al, 1989)

- Assesses the self-efficacy regarding pain, function and *"other"*
- Only the "other" sub scale relates predominantly to physical activity and was including in this thesis
- This "other" subscale is built up of 6 items, three of which address physical activity directly
- The subscale was scored from 10-100 with higher scores indicating greater self-efficacy for physical activity
- Validated in older adults arthritis (predominantly with OA)

Table A6-4: ASES "other" items (modified from Lorig et al, 1989)

How certain are you that you can now perform the following activities or tasks?
1. How certain are you that you can control your fatigue?
2. How certain are you that you can regulate your activity so as to be active without aggravating your arthritis?
3. How certain are you that you can do something to help yourself feel better if you are feeling blue?
4. As compared with other people with arthritis like yours, how certain are you that you can manage arthritis pain during your daily activities?
5. How certain are you that you can manage your arthritis symptoms so that you can do the things that you enjoy doing?
6. How certain are you that you can deal with the frustration of arthritis?

10=very uncertain and 100=very certain, higher scores indicate greater self-efficacy

Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire (OPAPAEQ) (Terry et al, 1997)

- Assesses attitudes towards physical activity
- Based on 14 items split up to themes of *"tension release"*, *"health promotion"*, *"vigorous exercise"* and *"social benefits"*.
- Each item is a statement about physical activity- individuals score based on how much they agree or disagree with the statement
- Scored from 14-70 (summing individual item scores) with higher scores indicating more positive attitudes towards physical activity
- Validated in adults 50 years old and older

Table A6-5 OPAPAEQ items (modified from Terry et al, 1997)

Item	SA	A	N	D	SD
1.Exercising with other people in the same age range is socially beneficial					
2.Physical exercise, undertaken with common sense and good judgement, is essential to good health					
3.Exercise helps to work off emotional tensions and anxieties					
4.Associating with others in physical activity is fun					
5.Regular vigorous exercise is necessary for good health					
6.Developing one's physical skills leads to mental relaxation and relief from tension					
7.Physical exercise is important in helping a person gain and maintain all-round health					
8.Participation in physical recreation is a satisfying and enriching use of leisure time					
9.vigorous daily exercise is ***not*** necessary to maintain one's general health *					
10.Physical activity in some form is an excellent remedy for the tense, irritable, and anxious person					
11.Physical exercise is beneficial to the human body					
12.physical activity releases the tension of the individual participant					
13.Regular physical activity makes one feel better					
14.Vigorous exercise is necessary to maintain one's general health					

Key
SA=strongly agree; A=agree; N=neutral; D=disagree; SD=strongly disagree;
green=*"social benefits"* theme items
white=*"health promotion"* theme items
red=*"tension release"* theme items
purple*=*"health promotion"* theme items (item 9 scored in reverse)

OPAPAEQ item scoring: strongly agree=5, agree=4, neutral=3, disagree=2, strongly disagree=1

Appendix VII: Model assumptions and sensitivity analyses for chapter 6

Model assumptions introduction

Chapter 6 utilised multiple linear regression modelling for Objectives 1, 2 and 4 and multiple logistic regression for Objective 3. This Appendix is organised so that the assumptions for multiple linear regression are addressed together, followed by the assumptions for multiple logistic regression. In the interest of brevity and focal interest, only a purposeful sample assumption checks for selected multivariable models are presented here. These models were selected because they address focal thesis research questions and or provided notable output.

Objective 1, 2 and 4 multiple linear regression assumptions methods

Multiple linear regression models have a number of assumptions which are listed below (Marill, 2004, Kutner et al, 2005, Agresti & Finlay, 2009):

1. **The dependent variable is interval or ratio**
2. **There must be a roughly linear relationship between the dependent and independent variables investigated**
3. **The variation of individual observed data points around the regression line must be constant ("homoscedasticity")**
4. **The variation of data around the regression line (residuals) must follow a normal distribution at all values of the independent variable**
5. **The independent variable deviation from the regression line should be independent of each other**

The dataset for the analyses within chapter 6 and 8 were multiple imputed. Given the initial assumptions for using multiple imputation (i.e. data missing at random), it is expected that the assumptions tested on the complete case and on imputed datasets should be similar. In order to increase confidence in this, a pilot was carried out testing assumptions on a multivariable model on the complete case data and then subsequently on two randomly selected imputed datasets (see "Imputation assumption pilot" in Appendix IX). Given the consistent findings from this pilot, subsequent model assumptions were carried out on complete case data only with the expectation that these assumptions would also hold valid for the multiple imputed dataset models.

Generic assumption checking methods:

Assumption 1: Considering the assumptions in order, assumption 1 was satisfied without the need for formal statistical testing since the change in physical activity dependent variable (absolute change in PASE score from baseline to three months) is continuous.

Assumption 2: In order to satisfy a roughly linear relationship between the independent and dependent variables (assumption 2), *"scatter plots"* were created, with an approximate line of best fit added, plotting model independent variables (e.g. change in physical activity) against dependent variables (e.g. pain and function at three and six months for Objectives 1 and 2 respectively and plotting change in pain and function against physical activity at three months) (Agresti & Finlay, 2009) (see figure A7-1 below). Linear relationships are shown by a roughly straight line of the plotted points.

Assumption 3: Homoscedasticity (assumption 3) was checked by plotting a scatter plot of standardised predicted values against standardised residuals (Regression diagnostics UCLA Statistical Consulting Group. From: http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htmref accessed: August 2015). Standardized residuals called *"studentized residuals"* are calculated by dividing a residual by the standard deviation of the residuals (Agresti & Finlay, 2009). For the homoscedasticity assumption to be satisfied the data points should be roughly equal about the predicted value line without any *"funnelling"* of the points.

Assumption 4: Normal variation of data around the regression line (assumption 4) was checked by looking at the normality of standardised regression residuals using a histogram of the studentized residuals (Kutner et al, 2005). In addition normal probability plots were checked that compare the residuals against the expected values under normality. A plot that is roughly linear is considered to satisfy the assumption (Kutner et al, 2005).

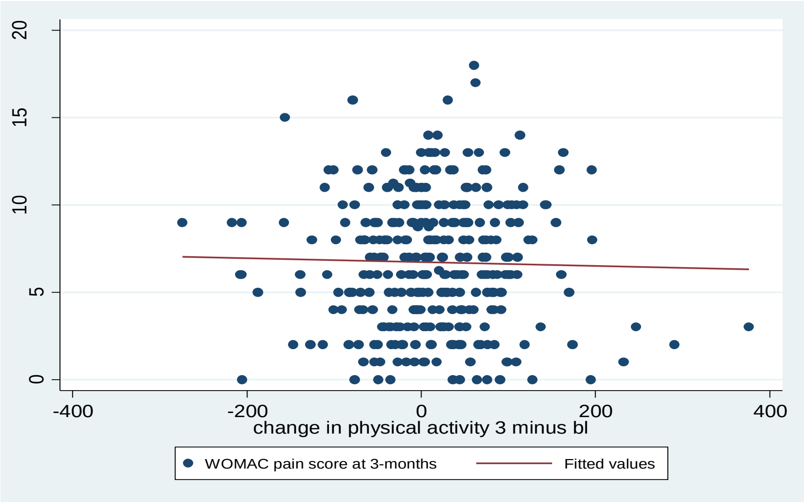
Assumption 5: Finally, the independence of independent variable deviation (residuals) from the regression line was assumed since the participants were independent of each other.

Assumption checking examples 1 and 2: Models 3A and 3B

The model assumptions for these models were selected for presentation here since there was a possibility of the models failing the homoscedasticity assumption and they show the negligible correlation between change in physical activity measured by the PASE and future clinical outcome. Other multiple linear regression models (Models 6A, 6B, 3E and 3F) were also considered to be satisfactory in fitting model assumptions (assumption checking not shown).

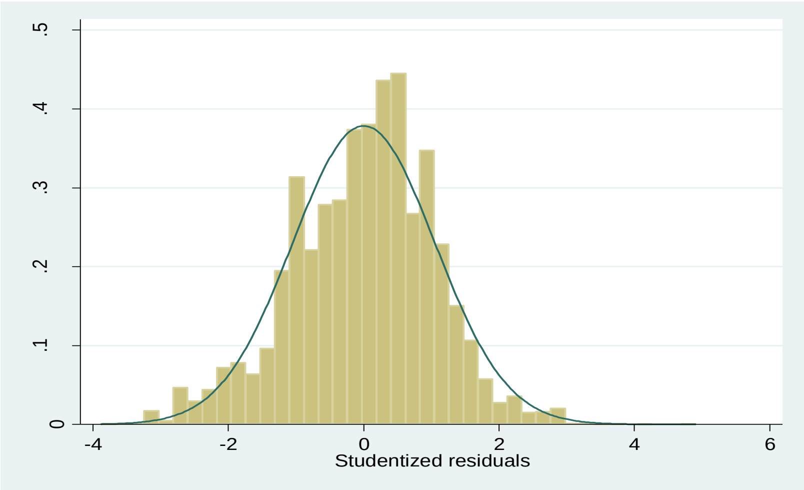
Pain at three months (Model 3A)

Model 3A scatter plot of change in physical activity and future pain



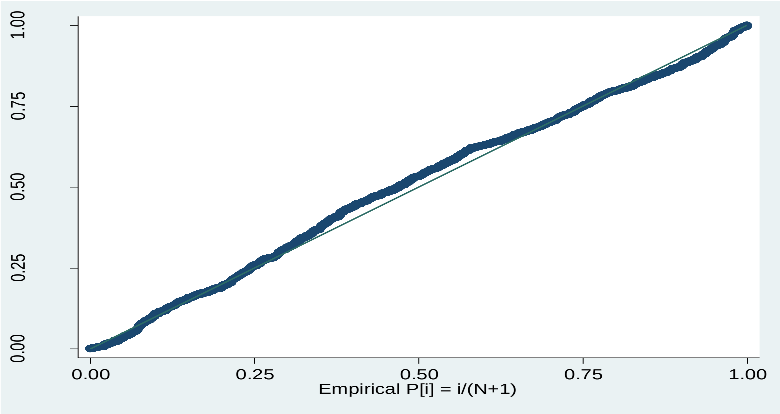
Checking assumption 2, the scatter plot though shows a roughly linear relationship and there is no evidence of a curvilinear relationship, although the correlation appears negligible.

Model 3A histogram of studentized residuals



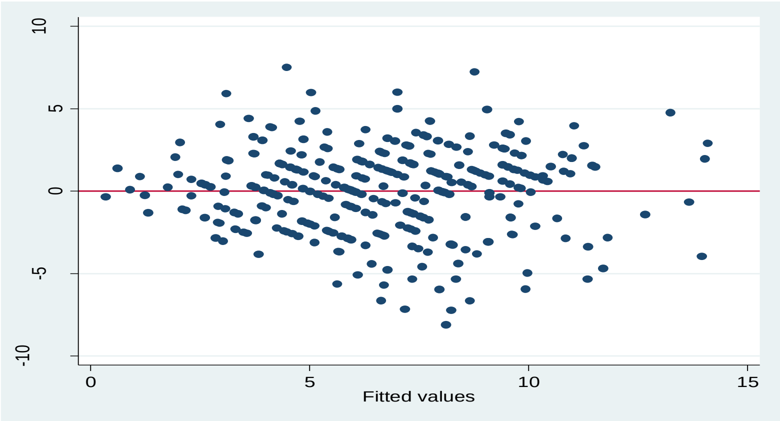
Checking assumption 3, the histogram above suggests a roughly normal distribution of residuals as indicated by the bell shaped distribution.

Model 3A normal probability (p-p) plot



The p-p plot showed a roughly straight line suggesting a normal distribution of residuals.

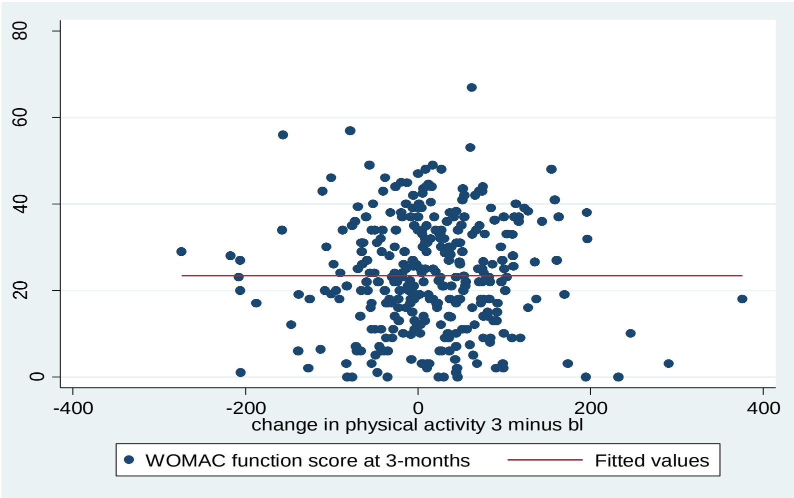
Model 3A residual versus fitted plot



Although the residuals were roughly spread about a mean of zero there did appear to be a potential funnelling on the left hand side of the plot suggesting the residuals may not be homoscedastic. Hence, further statistical testing for heteroscedasticity were carried out using Cameron and Trivedi's test which gave a non-significant statistic (chi square 59.33, 56 df, p=0.355) confirming the residuals were acceptably homoscedastic (Regression diagnostics UCLA Statistical Consulting Group. From: http://www.ats.ucla.edu/stat/stata/webbooks/reg/chapter2/statareg2.htmref accessed: August 2015)

Model 3B WOMAC function at three months further example

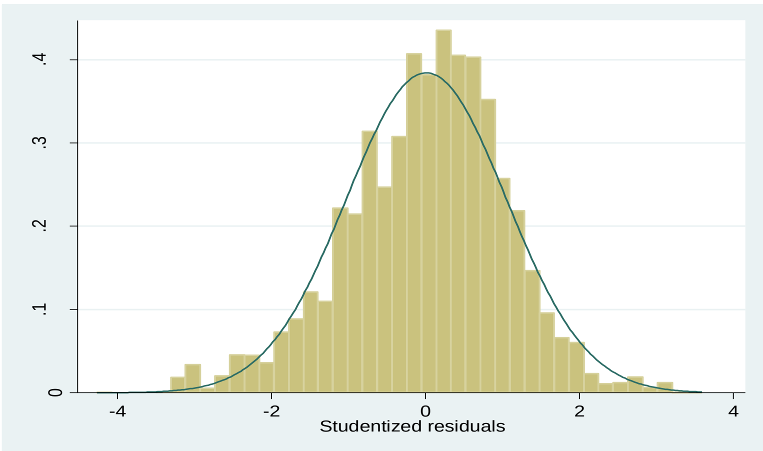
Model 3B scatter plot of change in physical activity and future function



Although there was no clear correlation the data did not look curvilinear.

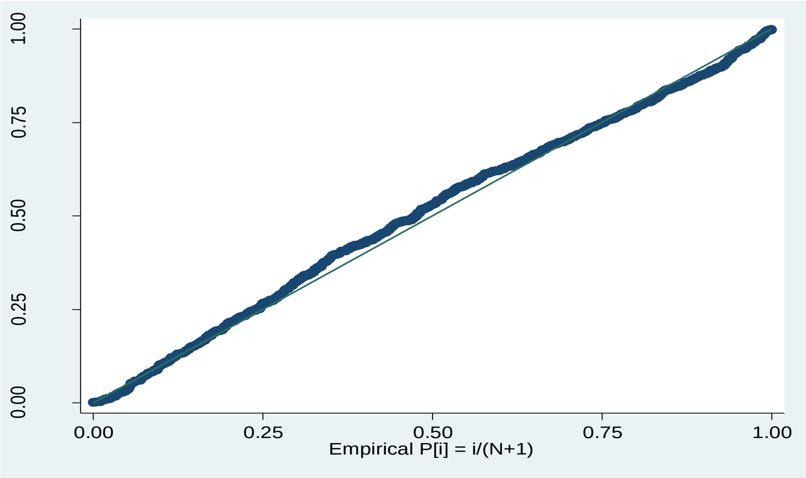
Model 3B

Histogram of studentized residuals



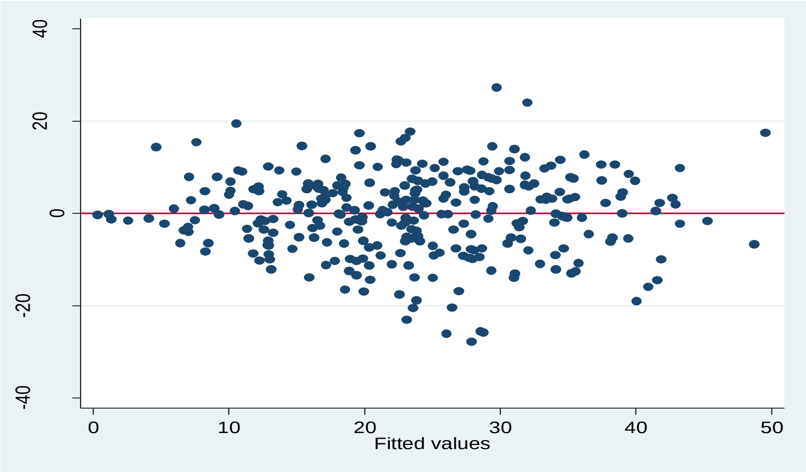
Checking assumption 3, the histogram above suggests a roughly normal distribution of residuals.

Model 3B normal probability (p-p) plot



The p-p plots showed a roughly straight line suggesting a normal distribution of residuals.

Model 3B residual versus fitted plot



Once more, the residuals appeared to funnel towards the left side of the plot. Hence, further statistical testing was carried out to check for heteroscedasticity using the Cameron and Trivedi test. The test was non-significant (chi square 62.94, 56 df, p=0.2443) suggesting that the model residuals were sufficiently homoscedastic.

Objective 3 multiple logistic regression assumptions (Hosmer & Lemeshow, 2000)

1. The dependent variable must be binary
2. The binary dependent variable probabilities must be correctly coded
3. The model should be correctly specified
4. Each residual must be independent
5. The independent variables are linearly related to the log odds of the dependent variable

Considering these assumptions in order, assumption one was satisfied since OMERACT OARSI response is dichotomous. OMERACT OARSI dependent variable was consistently coded with 0=no response and 1=response. The model was assumed to be correctly specified with all relevant variables included as a result of the backwards elimination strategy of non-significant independent variables and iterative likelihood ratio checking after elimination of each covariate. Although it is possible that other confounders may exist that were not included in the BEEP trial dataset and hence final multivariable models, this was accepted as a limitation (see chapter 6, section 6.6.3 for further discussion). It is noted the intervention arm regression odds ratio was non-significant yet was included in the final model, however, this was considered theoretically appropriate a priori and sensitivity analyses excluding it did not change the independent variables included in the final model. Although there is error associated with the absolute change in physical activity measure this was considered as a limitation. Independence of residuals was ensured by having independent participants giving data. Assumption 5 that the independent variables were related linearly to the log odds of the dependent variable was assumed without graphical checking (see chapter 6, section 6.4.2 for rationale).

Chapter 6 Sensitivity analyses

Sensitivity analyses for each objective are presented. In the interest of brevity and focus only key adjusted primary independent variable statistics are presented.

Objective 1: *"Investigate if change in physical activity level between baseline and three months is associated with pain and physical function at three month follow up"*

Sensitivity Analysis I: Complete case analyses

Model 3A (WOMAC pain at three months) adjusted regression coefficient for change in physical activity, β = -0.001 (95% CI -0.005, 0.003)

Model 3B (WOMAC function at three months) adjusted regression coefficient for change in physical activity, β = -0.010 (95% CI -0.023, 0.003)

Sensitivity analysis II: Important change in physical activity

Model 3A (WOMAC pain at three months) adjusted regression coefficient for change in physical activity, β=-0.043 (95% CI -0.795, 0.709)

Model 3B (WOMAC function at three months) adjusted regression coefficient for change in physical activity, β=-0.477 (95%CI -3.015, 2.061)

Sensitivity analysis III: No intervention arm variable

Model 3A (WOMAC pain at three months) adjusted regression coefficient for change in physical activity, β =-0.001 (95% CI -0.005, 0.002)

Model 3B (WOMAC function at three months) adjusted regression coefficient for change in physical activity, β =-0.009 (95% CI -0.019, 0.002)

Sensitivity analysis IV: Changing baseline clinical adjustment

Model 3A (WOMAC pain at three months) adjusted regression coefficient for change in physical activity (adjusted for baseline function), β =-0.002 (95%CI -0.005, 0.002)

Model 3B (WOMAC function at three months) adjusted regression coefficient for change in physical activity (adjusted for baseline pain), β =-0.007 (95%CI -0.019, 0.005)

Objective 2 ***"Investigate if change in physical activity level between baseline and three months is associated with pain and physical function at six months follow up"***

Sensitivity Analysis I: Complete case analyses

Model 6A (WOMAC pain at six months) adjusted regression coefficient for change in physical activity, β = -0.001 (95%CI -0.005, 0.004)

Model 6B (WOMAC function at six months) adjusted regression coefficient for change in physical activity, β = -0.003 (95%CI -0.018, 0.012)

Sensitivity analysis II: Important change in physical activity

Model 6A (WOMAC pain at six months) adjusted regression coefficient for change in physical activity, β=-0.201 (95%CI -1.102, 0.699).

Model 6B (WOMAC function at six months) adjusted regression coefficient for change in physical activity, β=-0.987 (95%CI -4.134, 2.160)

Sensitivity analysis III: No intervention arm variable

Model 6A (WOMAC pain at six months) adjusted regression coefficient for change in physical activity, β =-0.002 (95%CI -0.006, 0.002).

Model 6B (WOMAC function at six months) adjusted regression coefficient for change in physical activity, β =-0.009 (95%CI -0.022, 0.004)

Sensitivity analysis IV: Changing baseline clinical adjustment

Model 6A (WOMAC pain at six months) adjusted regression coefficient for change in physical activity (adjusted for baseline function), β =-0.003 (95%CI -0.007, 0.002).

Model 6B (WOMAC function at six months) adjusted regression coefficient for change in physical activity (adjusted for baseline pain), β =-0.007 (95%CI -0.021, 0.006)

Objective 3: *"Investigate if change in physical activity level between baseline and three months can predict clinically important treatment response at three month follow up"*

Sensitivity analysis I: No intervention arm variable

Model 3C/D (OMERACT OARSI response at 3 months) adjusted odds ratio for change in physical activity, OR= 1.002 (95%CI 0.999, 1.004)

Sensitivity analysis II: OMERACT-OARSI response at 6 month

OMERACT OARSI Model at 6 months. Adjusted odds ratio for change in physical activity, OR= 1.001 (95%CI 0.998, 1.004)

(NB the two above sensitivity analyses odds ratios are identical to three decimal places adjusting for either baseline WOMAC pain or WOMAC function in the model)

Objective 4: *"Investigate if change in pain and physical function between baseline and three months are associated with physical activity level at three month follow up"*

Sensitivity Analysis I: No intervention arm variable

Model 3E (physical activity at 3 months) adjusted regression coefficient for change in pain, β = -1.27 (95%CI-3.67, 1.13)

Model 3F (physical activity at 3 months) adjusted regression coefficient for change in function, β = -0.66 (95%CI -1.42, 0.09)

Appendix VIII: Model assumptions and sensitivity analyses for chapter 7

Multiple linear regression assumptions and diagnostics for BEEP dataset models were carried out as in Appendix VII. ABC-Knee ordinal regression model assumptions were as described for logistic regression models in Appendix VII except that the dependent variable was ordinal in nature rather than binary for the dependent ordinal STAR variable (Menard et al, 2010).

Assumption checking for multiple linear regression models A-C

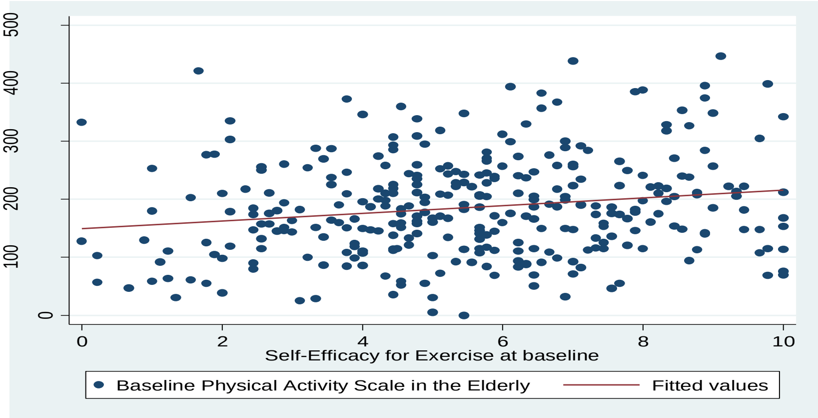
The three BEEP multivariable models investigating individual attitudes and beliefs about physical activity are presented together for ease of comparison (see overleaf). Each model was considered satisfactory in meeting assumptions for multiple linear regression (see previous reasoning in Appendix VII).

Assumptions for ABC partial proportional odds models D to F.

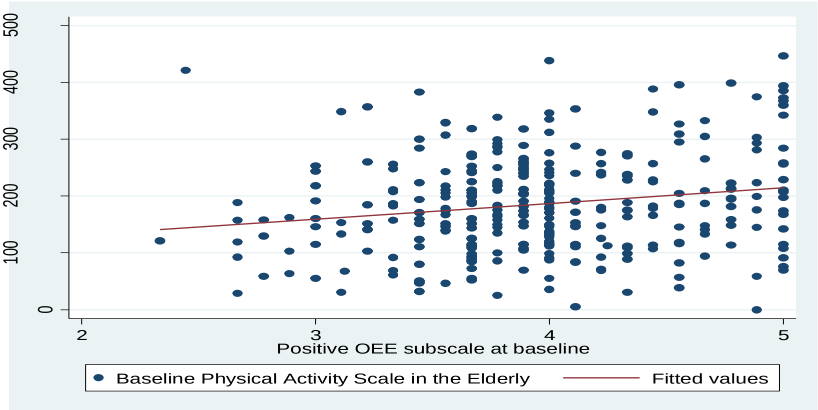
The ordinal dependent variable was correctly and consistently coded. Correct specification of models was assumed since the independent variables were considered to be those most important from the published literature (chapter 7, section 7.3.4). However, since it was only possible to adjust for a few independent variables in each model due to the risk of overfitting it is possible that some clinically important variables were not included in the models. This is an accepted limitation. The Gologit 2 program used in STATA (Williams, 2006) automatically checks the proportional odds assumption and produces variable proportional odds output where this is justified. (chapter 7, section 7.3.5 to 7 provides a detailed account of how the Partial proportional odds model works).

Assumption checking: Models A, B and C

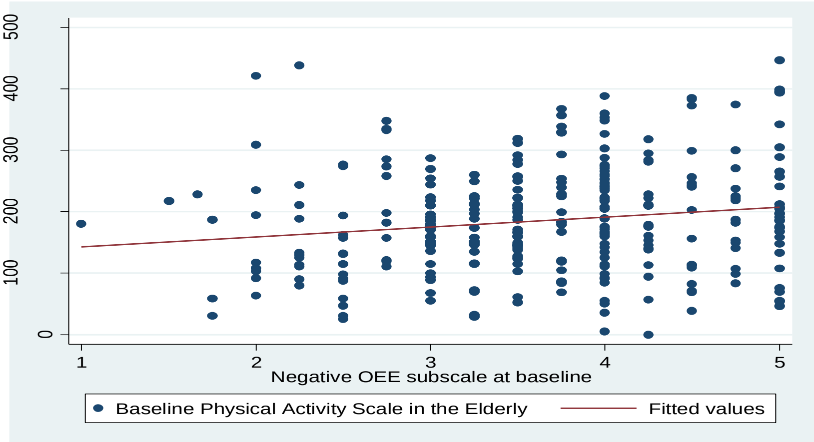
Model A (Physical activity model including SEE) scatterplot



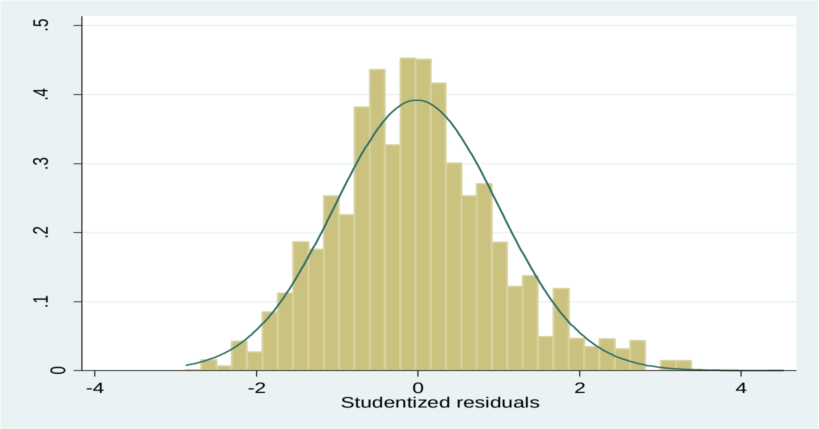
Model B (Physical activity model including positive OEE) scatterplot



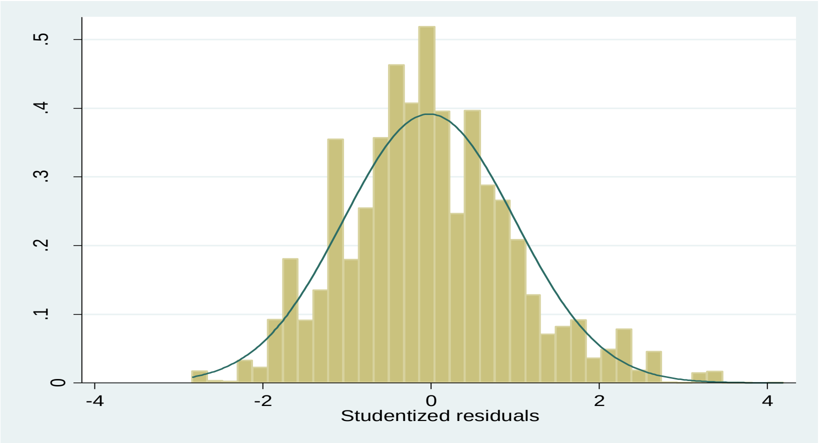
Model C (Physical activity model including negative OEE) scatterplot



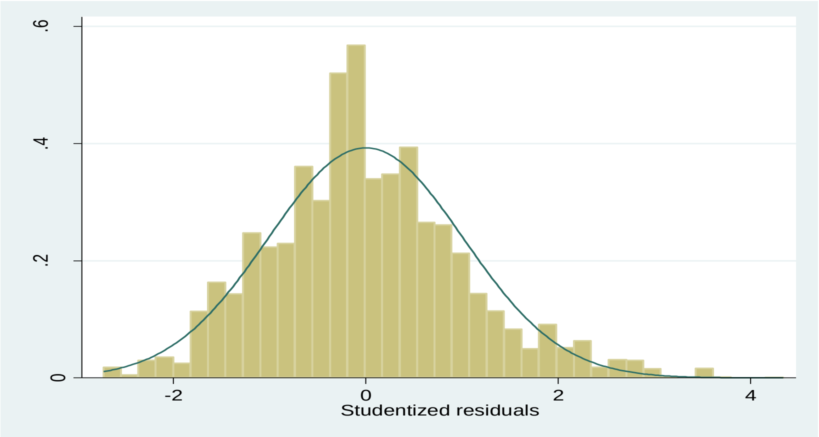
Model A histogram of studentized residuals



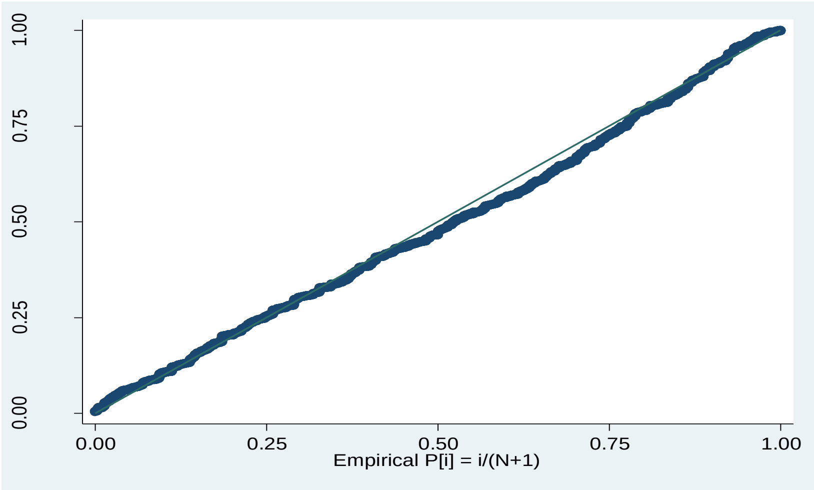
Model B histogram of studentized residuals



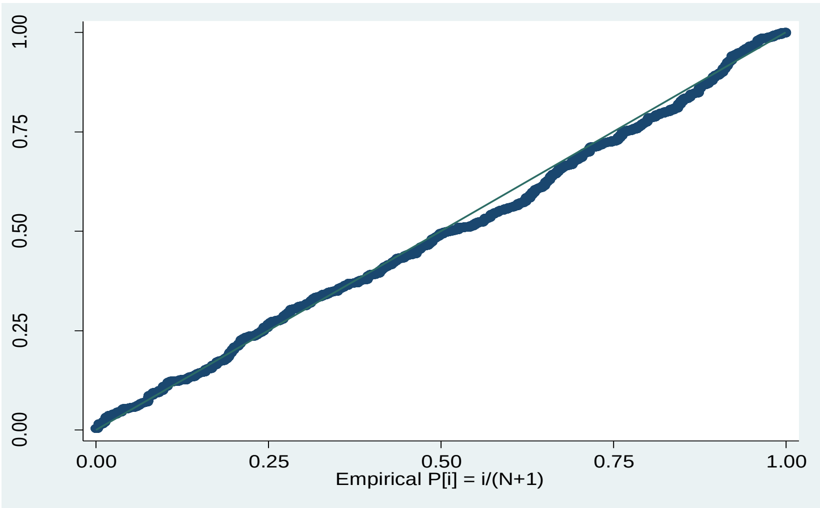
Model C histogram of studentized residuals



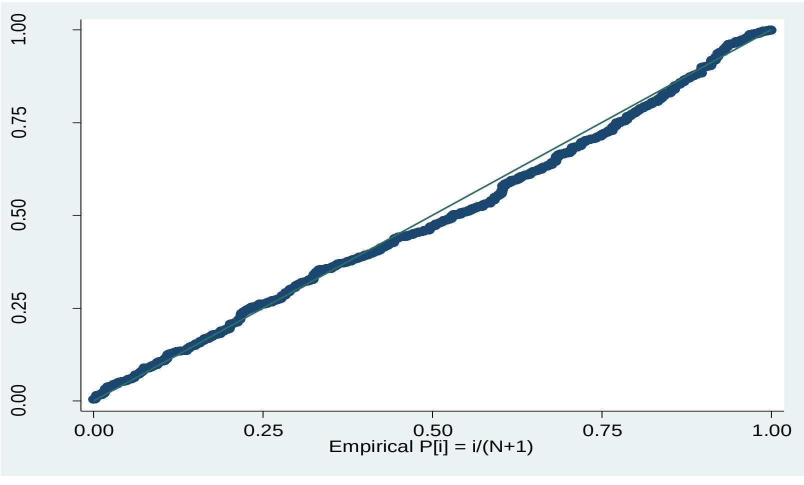
Model A Normal probability (p-p) plot



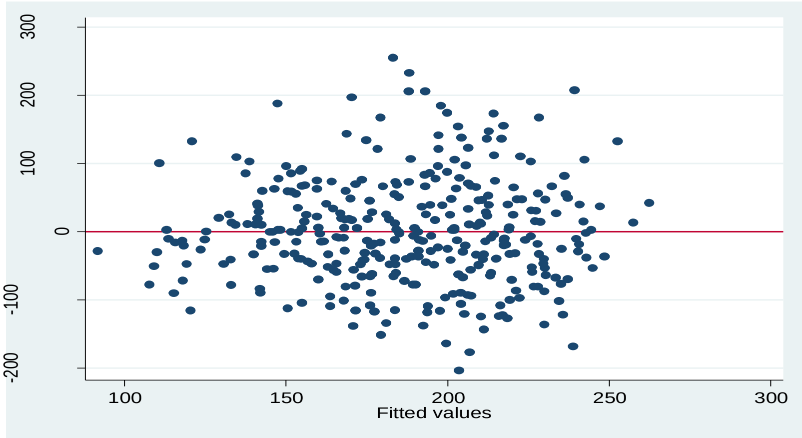
Model B Normal probability (p-p) plot



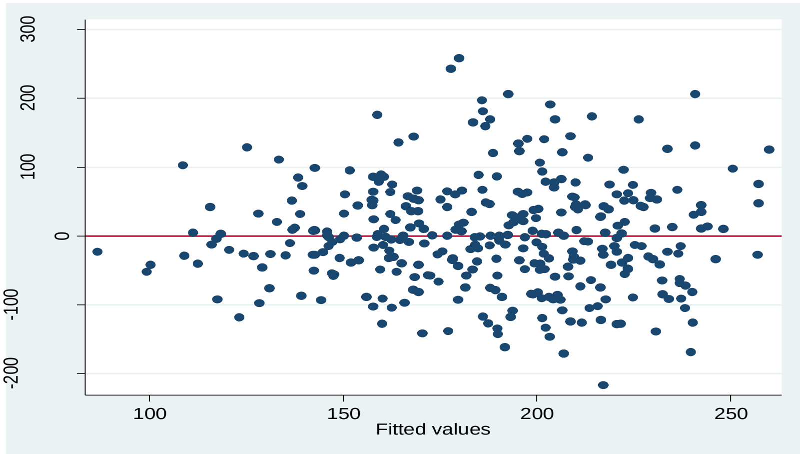
Model C Normal probability (p-p) plot



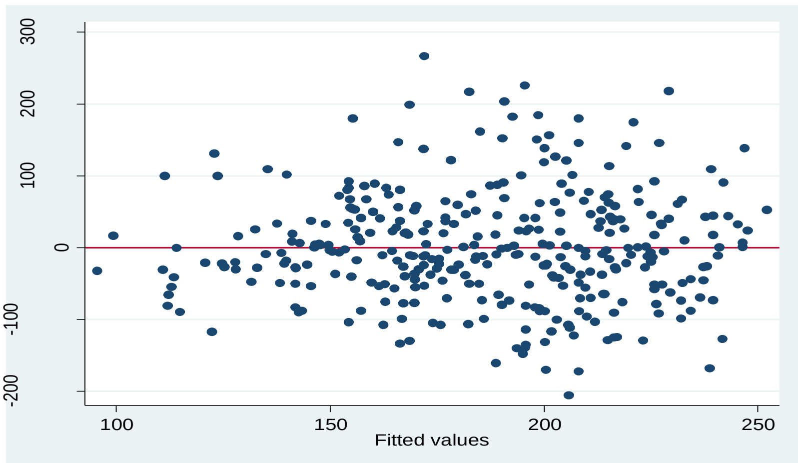
Model A residual versus fitted values plot for homoscedasticity



Model B residual versus fitted values plot for homoscedasticity



Model C residual versus fitted values plot for homoscedasticity



Chapter 7 Sensitivity analyses

Sensitivity analyses for each objective are presented below.

Objective 1 & 2

"Explore crude univariable associations between attitudes and beliefs about physical activity/ sociodemographics and clinical covariates and physical activity level in older adults with knee pain"

Sensitivity analysis I: Post hoc full univariable investigation of the ABC dataset

This sensitivity analysis involved the additional investigation of univariable relationships between all potentially relevant ABC-Knee covariates and physical activity. The results are presented in table format over the two subsequent pages.

Objective 3 & 4: *"Investigate the associations between individual attitudes and beliefs about physical activity scales and physical activity level in older adults with knee pain, adjusting for potential confounders"*

Note: including either WOMAC pain or WOMAC function at step two of BEEP dataset multivariable model building resulted in identical final models for Objective 3 and 4 (as shown in chapter 7, table 7.4).

Post hoc Sensitivity analysis I: Multiple imputed BEEP Models A to C

Model A (PASE at baseline) adjusted regression coefficient for baseline SEE, β= 4.03 (95% CI 0.18, 7.88)

Model B (PASE at baseline) adjusted regression coefficient for baseline positive OEE, β= 17.44 (95% CI 2.77, 32.12)

Model C (PASE at baseline) adjusted regression coefficient for baseline negative OEE, β= 5.43 (95% CI -5.32, 16.03)

Sensitivity analysis I ABC-Knee dataset post hoc univariable physical activity models using additional variables

Univariable associations with physical activity category (STAR) page one of two				
	Insufficiently active and meeting current guidelines[a]		Meeting current guidelines[b]	
	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Attitude and belief scales				
Tampa Scale of Kinesiophobia	0.89 (0.83-0.94)	<0.001	0.97 (0.95-0.99)	0.005
Arthritis Self-Efficacy Other	1.04 (1.02-1.06)	0.001	1.01 (1.00-1.02)	0.038
Older Persons' Attitudes towards Physical Activity and Exercise Questionnaire	1.07 (1.05-1.10)	<0.001	-	-
Sociodemographics				
Age	0.90 (0.87-0.94)	<0.001	0.98 (0.96-1.00)	0.022
Gender (ref male)				
Female	0.83 (0.60-1.15)	0.260	-	
BMI	0.96 (0.93-1.00)	0.310	-	
Partner (ref single)				
With partner	1.50 (1.03-2.18)	0.034	-	
Socioeconomic status (ref professional)				
Intermediate	0.75 (0.16-3.39)	0.704	1.31 (0.83-2.08)	0.240
Routine/ manual	0.30 (0.09-0.95)	0.041	1.05 (0.70-1.57)	0.827
Smoking status (ref never smoked)				
Previous smoker	0.85 (0.61-1.20)	0.358	-	
Current smoker	0.91 (0.51-1.62)	0.761	-	
Alcohol use (ref never/ yearly)				
Weekly/ monthly	2.05 (0.85-4.96)	0.111	0.91 (0.59-1.39)	0.657
Daily/ most days	4.72 (1.27-17.51)	0.02	0.98 (0.61-1.55)	0.917
Clinical covariates				
WOMAC pain	0.78 (0.71-0.86)	<0.001	0.97 (0.93-1.01)	0.114
WOMAC function	0.93 (0.91-0.96)	<0.001	0.99 (0.98-1.00)	0.031

Unadjusted univariable associations with physical activity category (STAR) page two of two				
	Insufficiently active and meeting current guidelines[a]		**Meeting current guidelines**[b]	
	Odds ratio (95%CI)	**p value**	**Odds ratio (95%CI)**	**p value**
WOMAC stiffness	0.65 (0.52-0.80)	<0.001	0.91 (0.84-1.00)	0.038
Chronic Pain Grade (ref low disability/ low intensity)	0.18 (0.06-0.51)	0.001	0.98 (0.68-1.39)	0.895
N. of days with pain in the previous year (ref <3months)				
≥3 months	0.16 (0.05-0.47)	0.001	0.74 (0.53-1.04)	0.087
Comorbidities (ref none)				
One	1.78 (0.44-7.23)	0.417	0.96 (0.66-1.41)	0.844
Two or more	0.24 (0.09-0.63)	0.004	0.53 (0.35-0.82)	0.004
Feel down (ref never/sometimes)				
Often/always	0.88 (0.68-1.13)	0.320	-	
Little interest in things (ref never/sometimes)				
Often/always	0.84 (0.63-1.12)	0.240	-	
Advised to exercise to treat knee pain (ref yes)				
No	2.57 (1.03-6.40)	0.042	0.74 (0.52-1.05)	0.087
Used exercise to treat knee pain (ref yes)				
No	0.56 (0.40-0.78)	0.001	-	

Footnotes: Complete case data; ordinal regression partial proportional odds modelling. Highlighted variables did not meet the Brant test for proportional odds *p*<0.05 (significance not shown) i.e. have different effects at each level of physical activity hence the generalised ordered logit model was used. None highlighted variables met the assumption of proportional odds hence odds ratios are considered acceptable across both physical activity comparisons as indicated by a dash hence the proportional odds model was used. [a]Reference category is “inactive”; [b]Reference category is “inactive and insufficiently active”;

Higher Tampa Scale of Kinesiophobia scores indicate greater fear of movement and reinjury. Higher scores on Arthritis Self Efficacy Other scores indicate greater self-efficacy for physical activity. Higher OPAPAEQ score indicates more positive attitudes towards exercise and physical. Higher WOMAC scores indicate higher pain, worse function and stiffness.

Abbreviations: CI= confidence interval; N.= number; ref=reference category; STAR= Short Telephone Activity Recall questionnaire; WOMAC=Western Ontario and McMaster osteoarthritis index.

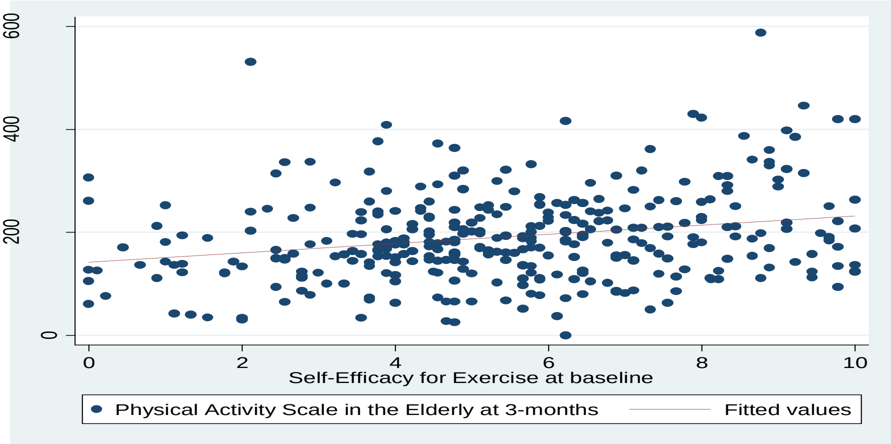
Appendix IX: Model assumptions and sensitivity analyses for chapter 8

Multiple linear regression and multiple logistic regression assumptions were the same as stated in Appendix VII. All thesis models were considered to roughly fit model assumptions. Only selected models are presented here that formed a pilot comparing Model 3A assumption diagnostics carried out on a complete case dataset to those on two separate randomly selected dataset imputations (as previously described in Appendix VII).

Pilot: complete case compared to imputed dataset assumption diagnostics

For ease of comparison each complete case assumption test is presented side by side with each of the two imputed dataset assumption tests (imputation data set 7 of 25 and 14 of 25). Three scatter plots are compared followed by the histograms, partial probability plots and residual versus fitted plots (Kutner et al, 2005) (figures shown on the subsequent page). Since each of the three sets of model assumptions were sufficiently similar it was judged that complete case analyses assumptions would be a satisfactory approximation for models built from the multiple imputed dataset. Hence all multivariable thesis model assumptions were carried out on the complete case dataset regardless of whether the original models were built from imputed data or not. It also offered some basic reassurance that the imputed data appeared to be reasonable estimations from the complete case data

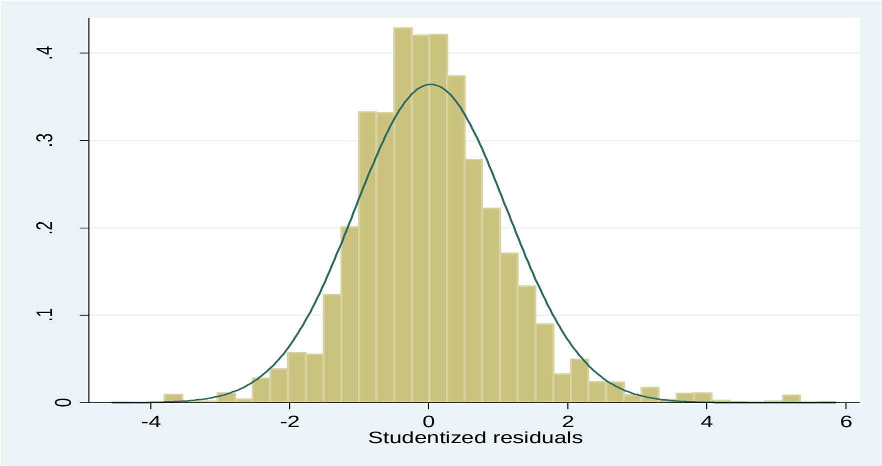
Model 3A Scatter plot of SEE against PASE at 3months *(complete case)*



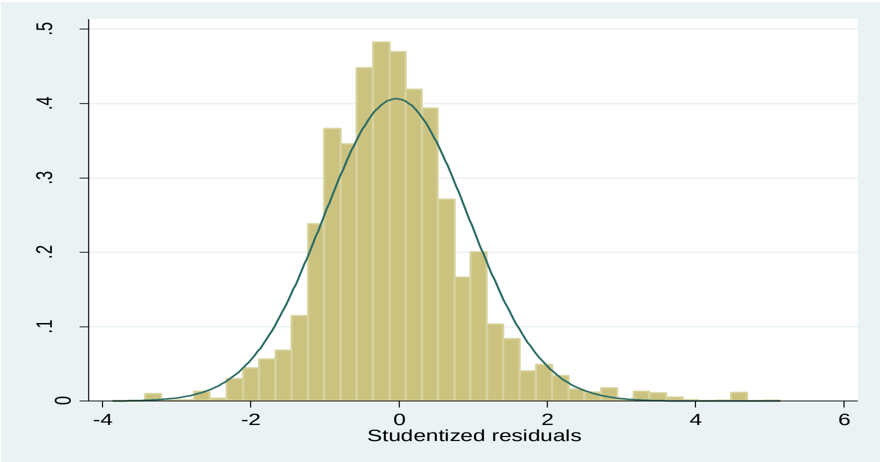
Model 3A Scatter plot of SEE against PASE at 3months *(imputation 7)*

Model 3A Scatter plot of SEE against PASE at 3months *(imputation 14)*

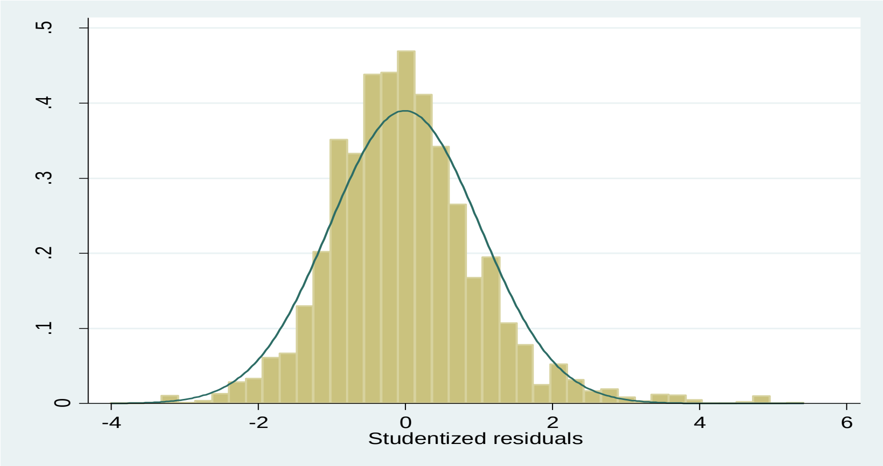
Model 3A Histogram of studentized residuals *(complete case)*



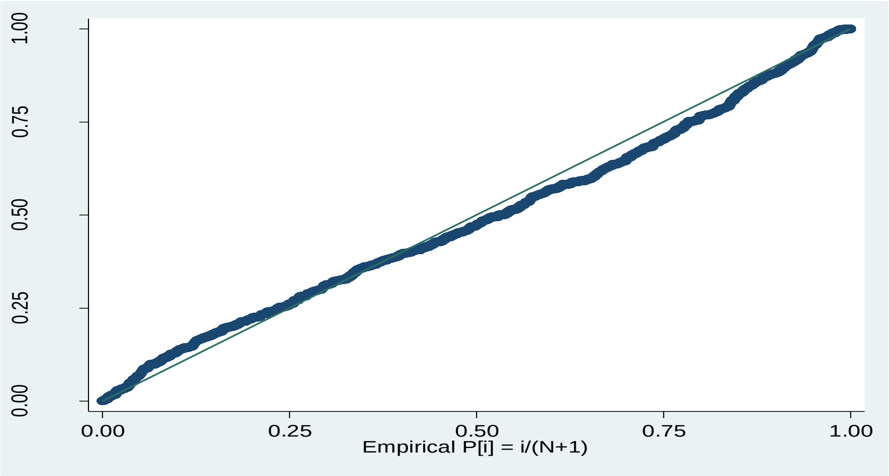
Model 3A Histogram of studentized residuals *(imputation 7)*



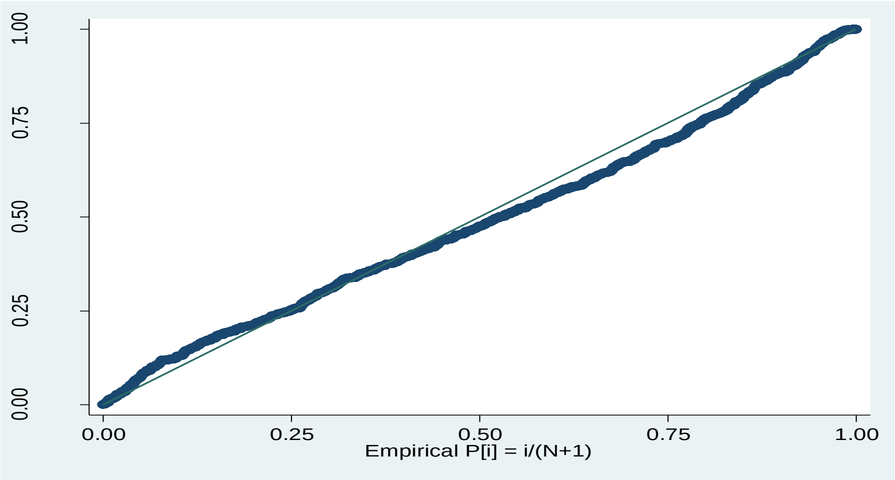
Model 3A Histogram of studentized residuals *(imputation 14)*



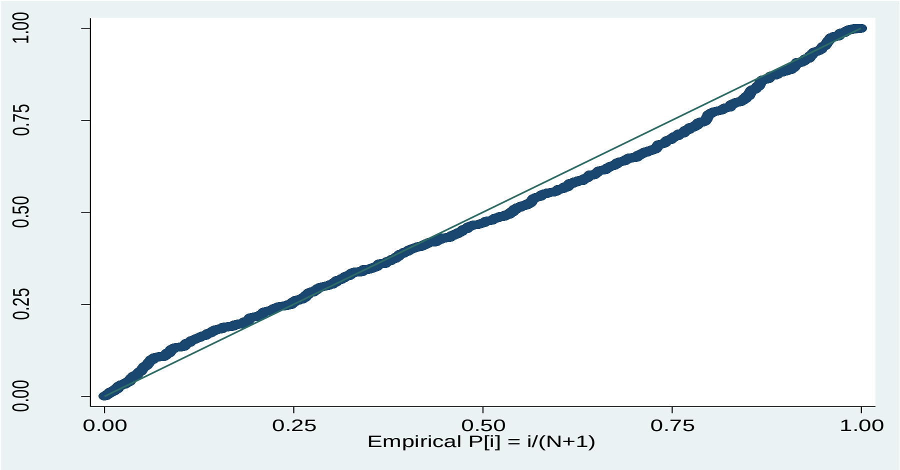
Model 3A Normal probability (p-p) plot *(complete case)*



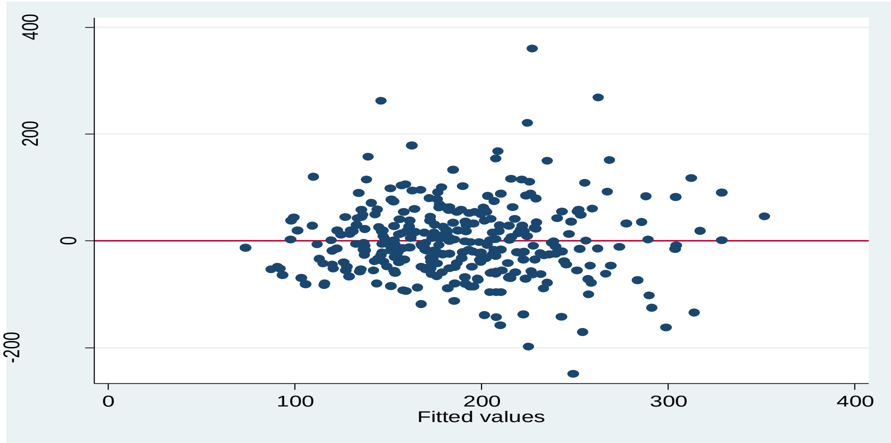
Model 3A Normal probability (p-p) plot *(imputation 7)*



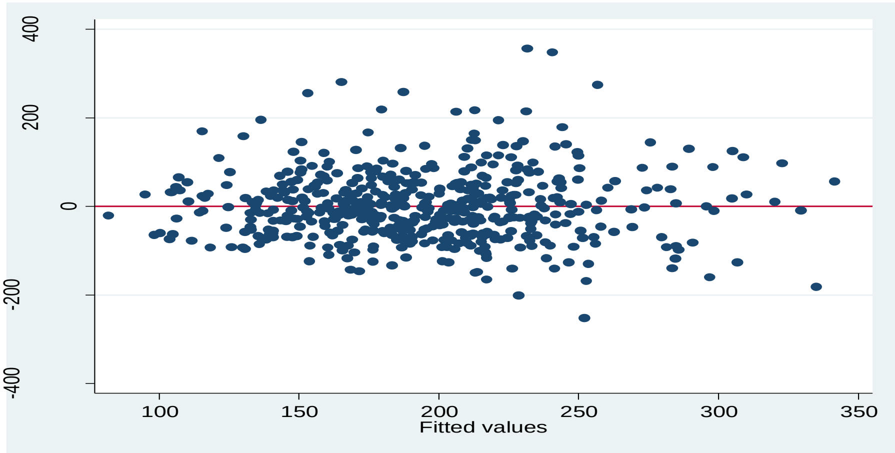
Model 3A Normal probability (p-p) plot *(imputation 14)*



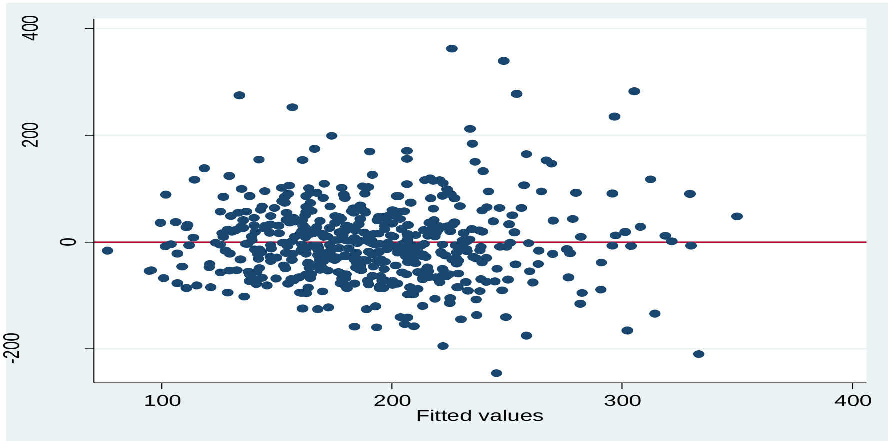
Model 3A residual versus fitted plot *(complete case)*



Model 3A residual versus fitted plot *(imputation 7)*



Model 3A residual versus fitted plot *(imputation 14)*



Chapter 8 Sensitivity analyses

Sensitivity analyses for each objective are presented. As previously in Appendices VI and VII only key adjusted primary independent variable statistics are presented here.

Objective 1: *"Investigate if attitudes and beliefs about physical activity at baseline are associated with future physical activity level at three months"*

Sensitivity Analysis I: Complete case analyses

Model 3A (PASE at three months) adjusted regression coefficient for baseline SEE, β= 4.84 (95% CI 1.44, 8.23)

Model 3B (PASE at three months) adjusted regression coefficient for baseline positive OEE, β= 21.05 (95% CI 7.40, 34.69)

Model 3C (PASE at three months) adjusted regression coefficient for baseline negative OEE, β= 5.50 (95% CI -3.84, 14.84)

Sensitivity analysis II: No intervention arm variable

Model 3A (PASE at three months) adjusted regression coefficient for baseline SEE, β= 4.86 (95% CI 1.03, 8.91)

Model 3B (PASE at three months) adjusted regression coefficient for baseline positive OEE, β= 25.42 (95% CI 12.28, 38.56)

Model 3C (PASE physical activity at three months) adjusted regression coefficient for baseline negative OEE, β= 7.45 (95% CI -2.41, 17.30)

Objective 2: *"Investigate if attitudes and beliefs about physical activity at baseline are associated with future physical activity level at six months"*

Sensitivity Analysis I: Complete case analyses

Model 6A (PASE at six months) adjusted regression coefficient for baseline SEE, β= 5.42 (95% CI 2.05, 8.80)

Model 6B (PASE at six months) adjusted regression coefficient for baseline positive OEE, β= 15.60 (95% CI 2.51, 28.68)

Model 6C (PASE at six months) adjusted regression coefficient for baseline negative OEE, β= 1.90 (95% CI -8.09, 11.90)

Sensitivity analysis II: No intervention arm variable

Model 6A (PASE at six months) adjusted regression coefficient for baseline SEE, β= 3.63 (95% CI 0.19, 7.08)

Model 6B (PASE at six months) adjusted regression coefficient for baseline positive OEE, β= 14.12 (95% CI 1.52, 26.71)

Model 6C (PASE at six months) adjusted regression coefficient for baseline negative OEE, β= -1.91 (95% CI -11.60, 7.79)

Objective 3: *"Investigate if attitudes and beliefs about physical activity at baseline predict important increase in physical activity level from baseline to six months"*

Sensitivity Analysis I: Complete case analyses

Model 6AI (PASE important change from baseline to six months) adjusted odds ratio for baseline SEE, OR= 1.00 (95% CI 0.92, 1.09)

Model 6BI (PASE important change from baseline to six months) adjusted odds ratio for baseline positive OEE, OR= 1.03 (95% CI 0.75, 1.43)

Model 6CI (PASE important change from baseline to six months) adjusted odds ratio for baseline negative OEE, OR= 0.89 (95% CI 0.71, 1.12)

Sensitivity analysis II: No intervention arm variable

Model 6AI (PASE important change from baseline to six months) adjusted odds ratio for baseline SEE, OR= 1.11 (95% CI 0.98, 1.24)

Model 6BI (PASE important change from baseline to six months) adjusted odds ratio for baseline positive OEE, OR= 1.55 (95% CI 0.99, 2.41)

Model 6CI (PASE important change from baseline to six months) adjusted odds ratio for baseline negative OEE, OR= 1.08 (95% CI 0.79, 1.50)

Sensitivity analysis III: Important change in physical activity between baseline and three months

Model 3AI (PASE important change from baseline to three months) adjusted odds ratio for baseline SEE, OR= 1.19 (95% CI 1.02, 1.39)

Model 3BI (PASE important change from baseline to three months) adjusted odds ratio for baseline positive OEE, OR= 1.81 (95% CI 1.11, 2.96)

Model 3CI (PASE important change from baseline to three months) adjusted odds ratio for baseline negative OEE, OR= 1.39 (95% CI 0.99, 1.96)