The association between gout and psychological co-morbidity: results from a prospective cohort study

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Honesty declaration

I certify that:

An academic honesty form has been signed and submitted to Keele Post Graduate Research as part of the completion and submission of this thesis. All work carried out in this thesis is my own or referenced appropriately. Where support, opinion, advice, or direct contribution was carried out by others (such as dual screening) that directly impacted the thesis content, this has been clearly documented. This thesis has not been submitted for any other degree or professional qualification.

Jordan Higgs ……. **Date: 27th January 2023**

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Jordan Higgs

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List of abbreviations and search strategy command lines

Abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
BL	Baseline
BMI	Body mass index
BSR	British Society for Rheumatology
CBT	Cognitive behavioural therapy
CHB	Conor Henry-Blake
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CRP	C-reactive protein
DALY	Disability-adjusted life years
DAMP	Damage associated molecular pattern
DP	Decimal place
DSM5/DSMV	Diagnostic and Statistical Manual of Mental Disorders 5
DST	Dexamethasone suppression test
ECT	Electroconvulsive therapy
EQ-5D	EuroQol Five Dimensional
ER	Ed Roddy
ESR	Erythrocyte sedimentation rate
EULAR	European league against rheumatism
GAD	Generalised anxiety disorder
GAD-7	Generalised anxiety disorder -7
GDS-SF	Geriatric depression Scale - Short Form
GIS	Gout impact scale
GP	General Practice
GR	Glucocorticoid receptor
HADS	Hospital Anxiety and depression Scale

HAMD	Hamilton Depression Rating Scale
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
HRQOL	Health related quality of life
ICD-9	International classification of Diseases
IL-	Interleukin
IMD	Index of Multiple Deprivation
IPQ-R	Illness perception questionnaire (revised)
IQR	Interquartile range
JH	Jordan Higgs
JJ	Jo Jordan
LC	Lorna Clarson
MA	Monoamine
MSU	Monosodium urate
Mϕ	Macrophage
NA	Not applicable
NALP3	NACHT, LRR and PYD domains-containing protein 3
NC	Nadia Corp
NHS	National Health Service
NICE	National institute for Health and Care Excellence
NOS	Newcastle-Ottawa Scale
NSAID	Non-steroidal anti-inflammatory drug
OB	Opeyemi Babatunde
OCD	Obsessive compulsive disorder
OR	Odds ratio
NRS (pain)	Numerical Rating Scale
PAMP	Pathogen associated molecular pattern
PCRN	Primary Care Research Network
pH	Power of Hydrogen
PHQ-9	Patient health questionnaire 9

PICOS	Population, Item/exposure of interest, Comparator group, Outcomes of interest and Setting/Study design
PRR	Pattern recognition receptors
PYs	Person years
QoL	Quality of life
RA	Rheumatoid Arthritis
RB	Ram Bajpai
Ref	Reference
RR	Relative risk
SD/STD	Standard deviation
SF-36	Short form 36
SM	Sara Muller
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPSS	Statistical Package for the Social Sciences
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
sU	Serum urate
T2DM	Type 2 diabetes mellitus
TCA	Tricyclic antidepressant
TNFα	Tumour necrosis factor alpha
ULT	Urate lowering therapy
URAT1	Urate Transporter 1
WCC	White cell count
WHO	World health organisation
WMN	West midlands north
XO	Xanthine oxidase inhibitor
Y1, Y3, Y5	Year 1, Year 3, Year 5

Search strategy command line meanings

Exp = explode

* = truncate

? = wildcard

Adjn = adjacent where n is a number

.kf = key word

.ti = title

.ab = abstract

OR = combining searches so that one or the other or both can appear

AND = combining searches so that both searches must appear, not one or the other

NOT = search results will not contain this

MeSH = Medical Subject Heading. This is controlled vocabulary

Abstract

Gout is associated with an increased risk of both physical-health co-morbidities and a reduction in physical health-related quality of life. However, the association between gout and psychological co-morbidity (depression and anxiety) has received little attention. A systematic review of the existing knowledge between gout and psychological co-morbidity was conducted. Then, a secondary analysis of a five-year prospective cohort study was performed to determine the prevalence, incidence, and gout characteristics associated with psychological co-morbidity.

The systematic review included 15 articles: all examined depression, whereas seven reported on anxiety, in people with gout. The prevalence of depression (11.8 to 49.4%), and anxiety (5.3 to 22.9%) was common. Depression incidence varied (3.13 to 25.50 per 1000 person-years), whereas anxiety incidence was 15.2 per 1000 person-years. Greater flare frequency, and having more joints affected were associated with psychological co-morbidity.

The secondary analysis comprised 1184 baseline responders with gout, 411 by five years. The prevalence of depression and anxiety peaked at 12.6% and 10.0%, respectively. Over five years, one in twelve developed new-onset anxiety, and one in eleven developed new-onset depression. A baseline history of oligo- or poly-articular gout flares were associated with developing anxiety (OR 2.31, 95% CI: 1.26 to 4.23). However, flare frequency, gout duration, or allopurinol use were not. Allopurinol use at baseline was associated with developing depression (OR 1.93, 95% CI: 1.01 to 3.69). However, flare frequency, gout duration, or oligo- or poly-articular gout were not.

Psychological co-morbidity is common in people living with gout; clinicians should be aware of this mental health need and the characteristics identified associated with increased risk of psychological co-morbidity to focus surveillance and maximise holistic care. Further studies into gout and psychological co-morbidity (particularly of prospective design and featuring anxiety) are recommended to further strengthen and elucidate these findings.

Chapter 1 - Introduction

Gout is a crystal arthropathy and the most common inflammatory arthritis. In the UK, the burden of gout is increasing as the prevalence and incidence continue to rise (Kuo et al., 2015). In addition, gout is associated with an increased risk of numerous physical health co-morbidities (Choi, Hyon K. et al., 2007); however, the association between gout and psychological co-morbidity has been less well researched. This chapter covers the aims, objectives, and thesis format.

1.1 Aims

This thesis aims to establish the existing knowledge base of psychological co-morbidity (anxiety and depression) in people living with gout, and explore the epidemiology and associations between gout and psychological co-morbidity in people living with gout in UK primary care.

1.2 Objectives

The objectives of this thesis were:

1. To perform a systematic review of gout and psychological co-morbidity to identify the prevalence/incidence of, and characteristics associated with psychological co-morbidity in people living with gout
2. To perform a secondary analysis of a 5-year prospective cohort study to identify the prevalence/incidence of, and gout characteristics associated with psychological co-morbidity in people with gout in UK primary care

1.3 Thesis format

The thesis format is as follows: initially, pertinent background information to gout, anxiety and depression is presented. The background chapter is followed by a systematic review (SR) into gout and psychological co-morbidity (anxiety and depression). The SR chapter is self-containing and includes the justification, methods, results, and discussion of findings. Following the SR chapter, a methodology chapter is presented, which details the secondary analysis methods of the prospective cohort study. Next is the results (of the secondary analysis) chapter. Lastly, the discussion chapter summarises the principal findings of the secondary analysis and compares these to the existing literature in conjunction with the systematic review. Strengths, weaknesses, and limitations are discussed, as well as implications for clinicians and future research.

This chapter covers the aims, objectives, and thesis format. The next chapter will provide background information about the pathophysiology, epidemiology, signs and symptoms, and management of gout, depression, and anxiety. Finally, potential relationships between gout and psychological co-morbidity are discussed.

Chapter 2 - Background

Gout is a long-term health condition that has been recognised for thousands of years. It reduces physical health-related quality of life and is associated with an increased risk of a multitude of co-morbidities such as chronic kidney disease, hypertension, glucose intolerance, and myocardial infarction. Anxiety and depression are common mental health conditions. Long-term health conditions are associated with an increased risk of developing anxiety or depression. However, the association between gout and psychological co-morbidity (depression and anxiety) has received little attention, and there is a paucity of research exploring this relationship. This chapter will provide background information about the pathophysiology, epidemiology, signs and symptoms, and management of gout, depression, and anxiety. Finally, potential relationships between gout and psychological co-morbidity are discussed.

2.1 Gout

2.1.1 Gout pathophysiology

Gout is the manifestation of monosodium urate (MSU) precipitation in and around joints following persistent hyperuricaemia. Urate (uric acid) is a naturally occurring metabolite synthesised as the end-product of purine metabolism. This pathway's penultimate and final stages convert hypoxanthine to xanthine, and xanthine to urate, by the enzyme xanthine oxidase (Desai, Steiger & Anders, 2017). Urate is predominantly excreted by the kidneys (66%), the rest by the gastrointestinal tract (Maiuolo et al., 2016). Hyperuricaemia occurs because of renal under-excretion in 90% of people with gout and overproduction in 10%.

As urate exceeds its solubility limits (supersaturation), MSU crystal formation occurs and may lead to gout flares (Desai, Steiger & Anders, 2017). However, supersaturation alone is insufficient to cause gout flares by itself as only up to one-third of hyperuricaemic patients have evidence of MSU crystal deposition (Ragab, G., Elshahaly & Bardin, 2017; Pineda et al., 2011; Puig

et al., 2008). A variety of biological factors influence urate solubility and hence MSU crystal formation, such as synovial pH, temperature, and trauma, although the exact mechanism that triggers flares has not been elucidated (Zhang, Yuqing et al., 2006; Ragab, Gaafar, Elshahaly & Bardin, 2017; Dalbeth, Haskard, 2005a; Abhishek et al., 2017).

When the immune system recognises MSU crystals, a strong inflammatory response is evoked, causing rubor (redness), calor (heat), tumor (swelling) and dolor (pain) (Cronstein, Terkeltaub, 2006; Freire, Van Dyke, 2013). This quintessential inflammatory response is due to MSU crystals being recognised by pathogen- and damage-associated molecular pattern (PAMP or DAMP) pattern recognition receptors (PRRs). Mast cell degranulation occurs early on, releasing histamine, leading to vasodilatation, and increased vascular permeability, causing an itching sensation and an outward appearance of rubor, calor, dolor and tumor. NACHT, LRR and PYD domains-containing protein 3 (NALP3) is a PRR found mainly within macrophages (Mϕs). Thus, NALP3 plays a principal role in gout flares. NALP3 PRRs recognise MSU crystals forming an inflammasome within Mϕs, upregulating pro-inflammatory cytokines such as IL-1β and TNFα. IL-1β and TNFα cause leucocyte extravasation and chemotaxis to the flare site and is assisted by vasodilation and increased vascular permeability from histamine release. Following this, there is a dramatic influx of neutrophils to the site, further increasing inflammation (Dalbeth, Haskard, 2005b; Branco, Anna Cláudia Calvielli Castelo et al., 2018; Suresh, 2005; El Ridi, Tallima, 2017).

2.1.2 Gout epidemiology

Gout is a highly prevalent condition and the most common inflammatory arthritis. In the UK, the prevalence of gout has been increasing: Lifetime prevalence was reported as 2.6 per 1000 in 1975, rising to 9.5 per 1000 by 1993 (Currie, 1979; Harris, Lloyd & Lewis, 1995). More recently, Kuo et al. (2015) reported the prevalence of gout to be 2.49% in 2012 within the UK, with gout being four times more common in men than women, 3.97% vs 1.05% respectively. Between 1997 and 2012,

the prevalence of gout increased by 63.9%, from approximately 1.50% to 2.49%. Gout incidence was 1.77 per 1000 person-years in 2012. Like prevalence, the incidence of gout was also higher in men than women, 2.58 vs 0.99 per 1000 person-years, respectively. There was a 29.6% increase in incidence during the study period from approximately 1.37 to 1.77 per 1000 person-years (1997 to 2012) (Kuo et al., 2015). Furthermore, unplanned hospital admissions due to gout increased by 58.4% over ten years (2006/7 -2016/17), from 7.6 to 12.5 admissions per 100,000 of the population (Russell et al., 2020).

Outside of the UK, gout prevalence ranges from 0.1% (Nigeria) to 6.8% (Australia). Eastern nations such as China and South Kora have a prevalence of 1.1% or lower, whereas western nations such as Canada and the USA had a prevalence of 3.8 to 3.9% (Rai et al., 2017; Chen-Xu et al., 2019; Dehlin, Jacobsson & Roddy, 2020).

2.1.3 Gout signs and symptoms

Hyperuricaemia is the precursor stage and the most critical risk factor for gout. The physiological saturation threshold of urate in serum occurs around 6.8mg/dl (~400µmol/l). Therefore, hyperuricaemia is defined as a serum urate (sU) level above 6.8mg/dl. Asymptomatic hyperuricaemia describes the occurrence of hyperuricaemia in a person who has never had symptomatic gout.

The first presentation of gout is typically monoarthritic, with approximately 55-75% of flares occurring in the first metatarsophalangeal joint (podagra) (Roddy, E., 2011). Ankle, midfoot, elbow, knee (gonagra), and hand (chiagra) joints are also common sites of flares (Underwood, 2006). Lower limb involvement is more common than the upper limb. The flare site usually displays the hallmarks of inflammation, namely swelling, erythema, tenderness, and heat, which may lead to loss of function of the affected joint due to extreme pain or swelling (Ciaccia, 2011). Pain is typically severe and typically reaches peak intensity in less than 24 hours (Rees, Doherty,

2014). Some patients report a prodromal itch in the area before a gout flare occurs, which is most likely due to mast cell degranulation and histamine release. Due to the inflammatory nature of a gout flare, a fever may be present. Flares are followed by asymptomatic (inter-critical) periods. If under-treated, tophaceous gout may occur. The length of time this inter-critical period lasts before the next flare or tophi occurrence is mainly dependent on treatment efficacy (Suresh, 2005).

Tophaceous gout is the accumulation and deposition of MSU crystals over time that fails to self-resolve, often leaving a visually evident and palpable mass. Clinically apparent tophi are painless white solid nodules located under cutaneal tissues. Classical locations include the first metatarsophalangeal joint, pinna of the ear, Achilles tendon, interphalangeal joints and olecranon bursa and are typically a consequence of under-or un-treated gout (Chhana, Dalbeth, 2015). Tophi are not permanent structures and can be reversed by appropriate urate-lowering therapy (ULT). However, tophi can have permanent consequences, such as joint destruction, bony erosion, loss of joint mobility, and deformity (Ragab, G., Elshahaly & Bardin, 2017).

2.1.4 Gout risk and protective factors

A risk factor increases the chance of developing a condition, whereas a protective factor reduces the chance of disease manifesting. There is a multitude of modifiable and non-modifiable risk factors associated with gout. However, hyperuricaemia is undeniably the single most important risk factor for developing and preserving gout, though most people with hyperuricaemia do not show signs of gout (Sun et al., 2018).

Historically, gout has been associated with an affluent lifestyle that was rich in meat and alcohol consumption. Although meat and certain types of alcohol do increase risk, the cause of gout is often multifactorial. Therefore, it would be incorrect to maintain the perception that the development of gout is solely dietary. Excessive seafood, alcohol, and fructose consumption all

increase the risk of developing gout (Choi, Hyon K. et al., 2004). Alcoholic drinks, particularly beer, contain purines (guanine) and thus increase urate load (MacFarlane, Kim, 2014). Choi, Liu and Curhan (2005) studied pure-rich foods, protein and dairy products and their relationship with sU: As total meat and seafood intake increased, so did sU. Conversely, as dairy intake increased, sU levels decreased. It was also noted that those who consumed milk, or yoghurt, at least once a day, had lower sU ($p < 0.001$) (Choi, Hyon K., Liu & Curhan, 2005).

Vitamin C has a uricosuric effect (Gao et al., 2008). Choi, Gao and Curhan (2009) found a relative risk (RR) of 0.55 for incident gout in subjects taking 1500mg/day of vitamin C vs subjects with an intake of <250mg/day, although participants were all healthcare professionals, so may not be a representative sample of the total population (Choi, H. K., Gao & Curhan, 2009).

A prospective cohort study of male health professionals reported a decreased risk of incident gout in patients taking 1500mg/day of vitamin C (RR 0.55, 95% CI: 0.38 to 0.80) than those with less than 250mg/day. Cherries have been shown to be beneficial in gout flare prevention (Zhang, Yuqing et al., 2012). The evidence of cherries benefits in gout is more limited than with vitamin C, though there are ongoing trials (Lamb et al., 2020). Potential mechanisms include antioxidant and anti-inflammatory suppressing cytokine production, one in vitro study finding cherry juice concentrate inhibited IL-1β by 60% from monocytes exposed to MSU crystals. Two weeks of tart cherry juice treatment in an animal (rat) model led to a 20% decrease of sU in hyperuricaemic animals (Collins, Saag & Singh, 2019).

Chatzipavlou et al. (2014) reported that eight weeks of a Mediterranean diet decreased sU from 9.12 to 6.2mg/dl in hyperuricaemic participants and that no gout flares occurred during the study period in the treatment group (Chatzipavlou et al., 2014).

A systematic review of 11 observational studies studying the association between consumption of coffee and hyperuricaemia or gout showed an inverse relationship between coffee consumption and incident gout (RR 0.43, 95% CI: 0.31 to 0.59). However, there was no

evidence for a relationship between coffee intake and sU levels or hyperuricaemia (Zhang, Yi et al., 2016).

Gout risk increases with age in both males and females and is rare before 20 in either sex. For males, there is a linear increase in prevalence until approximately 75-79 years of age. Whereas in females, there is a shallow increase until around 55-59 and then a steeper increase until 85-89 years of age. This coincides with menopause which has an average age of onset in the UK of 51 (Sarri et al., 2015). Oestrogen, which is lost with the onset of menopause, is uricosuric and protective of gout. Post-menopausal women have an adjusted RR of 1.26 for gout compared with premenopausal counterparts. Being male is a risk factor, having a higher prevalence and incidence of gout than females (Singh, J. A., 2013; Hak et al., 2010).

Ethnicity can also contribute to the risk of developing or severity of gout. For example, new Zealanders of Māori descent have over double (6.4%) the prevalence of gout vs New Zealanders of European descent (2.9%) (Klemp et al., 1997). In the National Health and Nutrition Examination Survey 2007-2008, black ethnic people were found to have a 25% higher prevalence of gout vs white ethnicity at 5.0% vs 4.0%, despite African Americans sharing the same genes associated with hyperuricaemia (Zhu, Pandya & Choi, 2011; Singh, J. A., 2013). Hollis-Moffatt et al. (2011) reported that a variant (rs3733591) of the SLC2A9 gene, which encodes for glucose as well as urate transporters, could be a marker for severe gout in specific populations such as Han Chinese (Hollis-Moffatt et al., 2011).

There are several co-morbid conditions associated with gout. Choi et al. (2005) found that higher adiposity (BMI of >25) and weight gain were risk factors for gout vs counterparts with body mass index between 21 - 22.9. It was also worth noting that weight loss was protective (Choi, H. K. et al., 2005). A systematic review by Evans et al. (2018) reported a pooled RR of 2.84 for obese individuals compared to non-obese. Hypertension and diuretic use were also highlighted as independent risk factors, with pooled adjusted RRs of 2.11 (95% CI: 1.64 to 2.72) and 2.39 (95%

CI: 1.57 to 3.65), respectively (Evans et al., 2018). Metabolic syndrome is also associated with gout (Choi, Hyon K. et al., 2007). Choi et al. (2007) defined metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III, requiring three or more of the following: Abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, and high fasting glucose. Individual components of metabolic syndrome, such as obesity and hypertension, are associated with developing gout, and high sU levels are a risk factor for metabolic syndrome (Jeong, Suh, 2019). As urate is predominantly excreted from the kidneys and under excretion is the cause of 90% of gout, chronic kidney disease is a risk factor for gout. Wang, Bhole and Krishnan (2015) reported a hazard ratio (HR) of 1.61 (95% CI: 1.17 to 2.21) for incident gout in chronic kidney disease (CKD) after adjusting for age, alcohol, smoking, hypertension, diabetes, and body mass index (Wang, W., Bhole & Krishnan, 2015).

Numerous medications are known risk factors for hyperuricaemia and gout. Cytotoxic drugs such as chemotherapy can lead to hyperuricaemia through cellular death and purine generation. Diuretics induce uric acid re-absorption. Low dose aspirin and anti-tubercular drugs pyrazinamide and ethambutol increase sU load by similar mechanisms (Ben Salem et al., 2016). Both aspirin and pyrazinamide increase sU re-absorption by stimulating URAT1. URAT1 is a renal urate transporter responsible for transferring urate from the nephron lumen back into the capillary blood (Ben Salem et al., 2017).

Certain statins have been found to exhibit urate-lowering qualities. For example, a 3-year study of patients with chronic heart disease and metabolic syndrome found statin therapy reduced sU levels by 8.9% vs baselines, whereas sU levels increased by 4.3% for those not on statin therapy (Athyros et al., 2006). Further to this, a 2016 systematic review of nine articles that investigated the impact of statin therapy on plasma uric acid levels found atorvastatin and simvastatin, but not pravastatin or rosuvastatin, caused a significant reduction in plasma sU levels (Derosa et al., 2016).

2.1.5 Gout diagnosis and investigations

The gold standard diagnostic investigation for gout is joint or tophus aspiration. Identification of strongly negative birefringent needle-shaped MSU crystals by polarised light microscopy confirms a diagnosis of gout with high sensitivity and specificity (Richette, Pascal et al., 2018). In addition, blood tests such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white cell count (WCC) are often elevated (Ruggiero et al., 2006). However, most people with gout symptoms present to primary care where joint or tophus aspiration are not routinely available.

Up to 89% of general practitioners make a clinical diagnosis of gout based upon the presence of typical symptoms and history and a low index of suspicion of other conditions such as septic arthritis (Owens, Whelan & McCarthy, 2008).

Septic arthritis also commonly presents as a monoarthritic painful, hot and swollen joint, and is an important differential diagnosis to consider due to a high mortality rate ranging from 3 to 25%, and potential for co-occurrence in patients with crystal arthropathies (Kennedy, N. et al., 2015; Long, Koyfman & Gottlieb, 2019). Therefore, when suspecting septic arthritis, joint aspiration is mandatory as it can show the presence or absence of infectious organisms and identify MSU crystals (Long, Koyfman & Gottlieb, 2019).

X-ray imaging is of limited diagnostic use as there may be no radiographic features in early disease. In later disease, “punched out” erosions with sclerotic margins or asymmetrical soft tissue swelling may be present. With ultrasound imaging, a double contour sign may be visible. A double contour sign is the presence of a second silhouette, above the first silhouette (created by cartilage). This second silhouette is due to the echogenicity from the deposition of MSU crystals on articular cartilage (Chowalloor, Siew & Keen, 2014; Perez-Ruiz et al., 2009).

Serum urate levels are not diagnostic for gout, as people with gout can have normal or raised serum urate levels, and people without gout can have raised urate levels. For instance, in 25 to 49% of flares, sU levels are normal due to increased renal excretion of urate during the acute

inflammatory response, lowering serum urate levels (potentially within the reference range) during a flare. However, when the flare resolves, serum urate levels rise again (Min, Kim, 2020).

2.1.6 Gout management – flares

Medical management of gout flares includes pharmacological and non-pharmacological options. The main aim is to rapidly reduce severe pain, swelling, and inflammation associated with the gout flare.

Non-pharmacological management may include advising the patient to rest and elevate the limb, avoid trauma to the affected joint, and keep the afflicted area cool with ice (Schlesinger et al., 2002). In addition, specialist equipment may be available, e.g., for podagra, a bed cage may be beneficial; this helps stop bed sheets resting on flare site, reducing discomfort (Mallen et al., 2017; Underwood, 2006).

First-line pharmacological management typically comprises NSAIDs or low-dose colchicine for pain relief (Wechalekar et al., 2014). However, there is no evidence to suggest any individual NSAID is more effective than another or colchicine (Roddy, E. et al., 2020). Gastroprotection may be co-prescribed with NSAIDs to minimise the risk of gastric injury/ulcers. Common side effects of colchicine are abdominal pain and diarrhoea (20 to 45%). A recent trial found that almost half (45.9%) of participants on low dose colchicine experience diarrhoea, compared with only 20% on naproxen, despite no significant difference in average pain relief over the first week (Roddy, E. et al., 2020). However, colchicine may be preferential over NSAIDs in certain circumstances, such as people on anticoagulants or who have chronic kidney disease (Blairon et al., 2020; Johnson, Seideman & Day, 1993).

If NSAIDs and colchicine are ineffective or contraindicated, oral steroids may be used (Prasad, Ewigman, 2008). Paracetamol can be added as an adjunct for pain/fever relief. Urate

lowering therapy (ULT) should not be stopped or started during a flare because ULT lowers sU and brings about the partial dissolution of MSU crystals, which are then shed into joint space, where a flare can be triggered. More invasive options are available such as intra -muscular and -articular steroid injections, depending on severity, clinical setting, and appropriateness (Burns, Wortmann, 2012). For example, when a large joint is affected, an intra-articular injection may be suitable. An advantage of this treatment option is that joint aspiration can also occur, allowing light microscopy and microscopical gout diagnosis.

Where there is a failure to respond to the above options, IL-1 inhibitors such as canakinumab and anakinra may occasionally be used in specialist settings. However, these medications are costly and not NICE approved in the UK. For instance, one dose of canakinumab costs £9927.80 vs £1.49 for a 40mg steroid dose (NICE, 2013; Elmi et al., 2019).

2.1.7 Gout management - Long term

Long term gout management comprises lifestyle adjustments and pharmacology (Chaichian, Chohan & Becker, 2014). Advice around weight loss, increasing exercise, diet, alcohol consumption, and increasing fluid intake should be discussed to help minimise purine load, reduce urate levels, and lessen the risk of future flares (Mallen et al., 2017; Underwood, 2006).

The pharmacological management of gout centres around urate-lowering therapy (Chaichian, Chohan & Becker, 2014). ULT is not recommended for asymptomatic hyperuricaemia (Li et al., 2017). Instead, treat-to-target strategies in symptomatic patients are recommended by both the European League against Rheumatism (EULAR) (sU <360 µmol/l) and the British Society for Rheumatology (BSR) (sU <300 µmol/l) (Hui et al., 2017; Richette, P. et al., 2017). Previously, indications to initiate ULT included recurrent flares (2 or more in 12 months), tophi, urate nephropathy or renal urate stones. However, the BSR published an updated guideline in 2017 which recommended ULT be discussed and offered at the diagnosis of gout, with the aims to

improve patients' understanding of gout and its long-term management, patient autonomy and compliance, and treat the disease early, reducing avoidable sequelae (Hui et al., 2017; Doherty et al., 2018).

There are two main classes of ULT: xanthine oxidase (XO) inhibitors and uricosurics. XO inhibitors work by preventing the metabolism of hypoxanthine to xanthine, and xanthine to urate. Uricosurics increase the ability of the kidney to excrete urate. In the UK, allopurinol is the first-line XO inhibitor recommended for long term management of gout (Chao, Terkeltaub, 2009). Febuxostat, another NICE approved XO inhibitor, has been approved by NICE if allopurinol is not tolerated (Choi, Hyon et al., 2018). Febuxostat (at 80 or 120mg) is more efficacious at lowering sU levels than allopurinol (at 300mg) (Becker et al., 2005). However, febuxostat is more costly than allopurinol (Liu et al., 2019; Cutolo, Cimmino & Perez-Ruiz, 2017). It is worth noting that there is not a standard dose of allopurinol, as the medication is individually titrated to achieve the sU target. This individually customisable approach to medical management enables people living with gout to have a more personal and effective treatment plan. However, a lack of clinician awareness of treat to target management can lead to inadequate sU monitoring, which means treatment targets are often not accomplished (Aung, Myung & FitzGerald, 2017).

Uricosurics, such as benzbromarone, sulfinpyrazone and probenecid, enhance renal urate excretion. Uricosurics achieve this by suppressing the URAT1 transporter, which is responsible for urate re-absorption from the renal tubule (Terkeltaub, Bushinsky & Becker, 2006). Typically, uricosurics are used as adjuvants alongside allopurinol or febuxostat if these are ineffective, or as monotherapy, if allopurinol and febuxostat are contraindicated or not tolerated (Hui et al., 2017). A Cochrane review identified two studies (Reinders et al. 2009 & Perez-Ruiz et al. 1999) that compared benzbromarone treatment to allopurinol and its effect on sU levels (Kydd et al., 2014). The pooled results of Reinders et al. 2009 and Perez-Ruiz et al. 1999 found that that 74% of participants achieved a normal sU level after four months of benzbromarone treatment,

compared with 60% on allopurinol. However, this review stated 4% of those taking benzbromarone had a gout flare, whereas none of the allopurinol participants did (Kydd et al., 2014).

Starting ULT of any kind commonly triggers a gout flare. For this reason, when initiating ULT, co-prescribing prophylactic gout flare medication (such as NSAIDs or colchicine) should be considered (Wortmann et al., 2010). In addition, the risk of ULT induced flares should be explained to patients to avoid the impression that they are getting flares despite ULT, as this may lead to the incorrect conclusion that ULT is not working, which may affect their adherence to the medication.

Serum urate levels are monitored for ULT titration. EULAR guidelines recommend reducing sU to <360µmol/l, or <300 µmol/l in those with severe gout, whereas BSR recommends lowering sU to <300µmol/l, and if a clinical cure is achieved, consider reducing ULT so that ULT is between 300 to 360µmol/l (Hui et al., 2017; Richette, P. et al., 2017).

Screening for, investigation of, and diagnosing co-morbidities may be carried out simultaneously. Screening for co-morbidities is important as some increase the risk of developing and maintaining gout. Therefore, managing these co-morbidities may help in gout management. For example, chronic kidney disease, hyperlipidaemia, glucose intolerance and hypertension are common gout co-morbidities, thus checking kidney function, lipid profile, glucose levels, and blood pressure may be prudent (Bardin, Richette, 2017).

2.1.8 Gout prognosis

Despite gout being a curable condition, it is often undertreated. Proudman et al. (2019) reported that gout flares were associated with reduced physical health-related quality of life and that approximately 50% of the study population who experienced frequent (≥2 in the past 12 months) gout flares were not receiving allopurinol treatment. A substantial portion of those receiving

allopurinol still had frequent flares, signifying under-treatment. Kuo et al. (2015) reported that only 18.6% of people with incident gout received ULT within six months of diagnosis in 2012 in primary care (Kuo et al., 2015). Undertreatment may lead to additional flares, tophi development, and a reduction in quality of life (Golenbiewski, Keenan, 2019; Proudman et al., 2019). If allowed to progress to tophi development, there may be permanent joint destruction irrespective of the resolution of tophi via adequate ULT therapy. Gout is also an independent risk factor for cardiovascular mortality, and as previously mentioned and reported by Proudman et al. (2019), Chandrate et al. (2013) also found that gout impairs physical health-related quality of life (Rahimi-Sakak et al., 2019; Chandratre, P. et al., 2013). However, there has been less work undertaken into the relationship between gout and psychological health-related quality of life or psychological co-morbidity, despite other inflammatory arthropathies having increased psychological co-morbidity (Jacob, Rockel & Kostev, 2017)

2.2 Depression

2.2.1 Depression background

Mood disorders are common, widespread, and debilitating mental health conditions characterised by either depressed or elevated mood. Mood disorders can be split into two: unipolar or bipolar depression. Unipolar depressive disorders include major depression, disruptive mood dysregulation disorder, persistent depressive disorder (dysthymia), and premenstrual dysphoric disorder (Spijker, Claes, 2014). Bipolar disorders include bipolar disorder and cyclothymia (Spijker, Claes, 2014). Unipolar depression and bipolar depression differ by the absence (unipolar) or presence (bipolar) of mania or elevated mood in conjunction with depression. As the Patient Health Questionnaire 9 (PHQ-9), defined later in section 2.2.5, was used to gather data for this thesis, this section and thesis will primarily focus on major depression, so other depressive disorders are not described.

Simply being low in mood is different to a medical diagnosis of depression. Feeling down or sad is a normal human emotion, often brought about by challenging life events. Depression can manifest as a discrete incident or become a recurrent chronic disorder. A persistent low mood for two weeks or longer characterises the diagnosis of major depression. It is often accompanied by somatic symptoms such as insomnia or hypersomnia, weight change and psychomotor retardation, and psychological symptoms such as diminished interest and thoughts of death (Ng, How & Ng, 2016). Depending on the number of symptoms present, depression can be characterised by severity such as mild, moderate, and severe. This classification can help guide management (Tolentino, Schmidt, 2018).

Depression is a common diagnosis; it is both the most common mood disorder and mental health condition. Depression significantly impacts quality of life (QoL), and with a high prevalence, it is an important medical challenge to tackle (Hofmann et al., 2017). Depression is commonly identified and managed in primary care, either by general practitioners or (self or clinician) referral to community services. However, it is often under-recognised and managed (Wittchen, Mühlig & Beesdo, 2003). More complex cases may require specialist care input from services within secondary or tertiary care settings.

2.2.2 Depression pathophysiology

There are several hypotheses for the cause and progression of depression, such as the monoamine (MA) hypothesis. The MA hypothesis revolves around the theory that depression is caused by the depletion of MAs such as serotonin, dopamine, and noradrenaline in central nervous system synapses. However, rather than MAs being the cause of depression, they may be a downstream effect of other abnormalities. For example, Tafet et al. (2001) found that cortisol increases gene expression for a serotonin transporter (Tafet et al., 2001). Cortisol, colloquially referred to as the 'stress' hormone, is produced in response to physically or mentally stressful stimuli. This cascade

of events starts with the amygdala becoming stimulated by fearful or emotional events. These extreme events activate the hypothalamus, sympathetic nervous system, and hypothalamic-pituitary-adrenal (HPA) axis, causing the release of adrenaline and cortisol. People with depression are often found to have higher circulating cortisol levels, suggesting a potential dysfunction of the HPA axis; therefore, increasing cortisol may increase serotonin transport and reduce synaptic serotonin levels (Hasler, 2010).

Another hypothesis centres around the role of inflammation in the pathogenesis of depression. Depressed individuals have been shown to have increased levels of pro-inflammatory cytokines such as TNFα and various interleukins (Amodeo, Trusso & Fagiolini, 2017). Interestingly, it has also been shown that some antidepressant medications, such as the Selective Noradrenaline Reuptake inhibitor (SNRI) venlafaxine, can have immunomodulatory activity leading to an anti-inflammatory effect (Lee, C. H., Giuliani, 2019). Furthermore, patients who have received cytokine therapy for chronic infective hepatitis are at risk of developing a depressive-like illness (Bonaccorso et al., 2001). However, the link between increased pro-inflammatory cytokines and depression remains poorly understood.

2.2.3 Depression epidemiology

Depression is a globally prevalent condition and a significant healthcare burden. Smith et al. (2013) identified a lifetime prevalence of 25.8% for major depression in 130,000 eligible participants registered in the UK biobank (Smith et al., 2013). In a cohort study conducted by McDougall et al. (2007) in older people (65 and over) in England and Wales, the prevalence of depression was 9.7% and was more common in women (10.4%) compared to men (6.5%) (McDougall et al., 2007).

Lim et al. (2018) investigated the prevalence of depression across 30 countries between 1994 to 2014. When grouped by continent, the highest point prevalence of depression was found

in South America (20.6%), whereas the lowest was Australia (7.3%). Europe's pooled prevalence was 11.9% (Lim et al., 2018).

2.2.4 Depression signs and symptoms

According to the DSM-V criteria for major depression, five symptoms must be present for at least two weeks, including at least one of the following core symptoms: low mood and loss of interest or pleasure (Ng, How & Ng, 2016). The remaining non-core symptoms include weight loss/gain or change of appetite, insomnia/hypersomnia, fatigue or loss of energy, feeling of worthlessness or guilt, lack of concentration or focus, psychomotor retardation, and suicidal ideation or thoughts of death (Kennedy, S. H., 2008). In addition to these diagnostic symptoms, depressed individuals may withdraw from social situations or isolate themselves. Finally, a subset of individuals with depression may experience false perceptions, hallucinations or paranoia and receive a diagnosis of psychotic depression (Gaudiano, Dalrymple & Zimmerman, 2009).

2.2.5 Investigations and diagnosis

The diagnosis of depression is usually made based on patient history and validated questionnaires. However, in the 1980s and 90s, there was an interest in cortisol levels/response as a potential diagnostic or prognostic indicator for depression. Hayes et al. 1983, found that 40 to 70% of inpatients and 20-50% of outpatients diagnosed with depression had abnormal dexamethasone suppression tests (DSTs) compared to non-depressed counterparts (Hayes, Ettigi, 1983). However, the DST does not play a role in current depressive illness diagnosis or management, and there are currently no diagnostic laboratory tests for depression.

The Patient Health Questionnaire 9 (PHQ-9) is a validated tool designed to diagnose major depression and identify the severity (Kroenke, Spitzer & Williams, 2001). This questionnaire

comprises nine questions that focus on the DSM criteria for depression, as mentioned in the depression signs and symptoms section. Each question can be answered and scored as the following: “Not at all” 0, “Several Days” 1, “More than half the days” 2, and “Nearly every day” 3. Therefore, the possible score ranges from 0 to 27 and can be categorised as:

- 0 – 4, no or subclinical depression
- 5 – 9, mild depression
- 10 – 14, moderate depression
- 15 – 19, moderately severe depression
- 20 – 27, severe depression

2.2.6 Depression risk and protective factors

Depression has been associated with many modifiable risk factors such as long-term conditions, medications, substance misuse, physical inactivity, social well-being, deprivation, and inequality (Meng et al., 2017).

A variety of long-term conditions have been associated with depression. There is evidence that type two diabetes mellitus (T2DM) is a risk factor for depression with a RR of 1.15 (95% CI: 1.02 to 1.30) (Mezuk et al., 2009). A systematic review that investigated the putative association between diabetes and depression found depression was a risk factor for T2DM, with a pooled RR of 1.60 (95% CI: 1.37 to 1.88) (Alzoubi et al., 2018). Hughes et al. (2020) found that poor sleep quality and depression were prevalent in people living with rheumatoid arthritis. An increased tender joint count was associated with poor sleep and depression (Hughes et al., 2020). Furthermore, Jacob, Rockel and Kostev (2017) found that approximately 30% of people living with rheumatoid arthritis (RA) develop depression within five years of their RA diagnosis, and women had an HR of 1.61 (95% CI: 1.42 to 1.84) vs men (Jacob, Rockel & Kostev, 2017).

Iatrogenic depression caused by prescribed (depressogenic) medication has been reported and recognised for some time. For example, reserpine, an antihypertensive medication approved in the 1950s, was found to induce depressive symptoms. Its mechanism of action as an antihypertensive cause a reduction of monoamines, and this discovery helped lead to the monoamine hypothesis of depression. Other commonly used medications that carry this potential side effect include corticosteroids, progesterone implants and varenicline (Rogers, Pies, 2008). However, the exact mechanisms by which these medications increase depression risk have yet to be elucidated.

The relationship between substance misuse and depression is complex and likely to be bidirectional. For example, individuals who misuse alcohol are 3.7 times more likely to have major depression. In addition, alcohol intoxication has been shown to cause depressive symptoms, whilst periods of abstinence decrease them (McHugh, Weiss, 2019). However, it has been suggested that people suffering from depression may turn to alcohol as a coping mechanism, or that social dysfunction or the financial implications of alcohol misuse may contribute to the development of depression, rather than the pharmacological effects of alcohol itself (Conner, Pinquart & Gamble, 2009).

Just as physical inactivity has been identified as a risk factor for depression, living an active life can be protective, as it can reduce both mortality and depressive symptoms. For example, using the Nurses' Health Study, a prospective cohort study of 121,700 US female registered nurses aged 46 to 71 in 1992, Lucas et al. (2011) found that between 1992 and 2000, there was an age-adjusted RR of 0.65 (95% CI: 0.57 to 0.74) for developing depression in participants who did over 90 minutes of daily exercise (Lucas et al., 2011).

A systematic review of studies that examined the association between income inequality and depression found a pooled RR for developing depression of 1.19 (95% CI: 1.07 to 1.31) in populations with higher income inequality vs lower; income equality was measured by the Gini

Co-efficient in 21 of 26 included studies (Patel, V. et al., 2018). In addition, other social factors such as high neighbourhood poverty (RR 1.20, 95% CI: 1.05 to 1.36) and high homicide rates (RR 1.09, 95% CI: 1.02 to 1.17) have been associated with symptoms of depression. Neighbourhood poverty levels were assigned by the percentage of households with a 1km walking radius from the participant's house below the federal poverty line. Homicide levels were assigned by downloading homicide map data and generating the one-year rate of homicides per 100,000 people living within the same 1km walking radius (Joshi et al., 2017).

Non-modifiable risk factors for depression include sex and age. Females and younger adults (age 18 to 65) have increased prevalence compared to males and older adults (65+), respectively. The global prevalence of depression was estimated as 1.7 times greater in women (5.5%) vs men (3.2%) in 2010. In Canada, in 2012, the prevalence of depression was 1.6 times greater in women (5.8%) than men (3.6%) (Albert, 2015). Kessler et al. 2011 looked at age differences in major depression and found the lifetime prevalence estimate of depression in all ages to be 19.2%, but ages 35 to 49 years had the greatest prevalence (22.7%) versus those aged ≥65 had the lowest prevalence (9.5%). Women had 1.5 times higher lifetime prevalence across all ages (22.9%) vs men (15.1%) (Kessler et al., 2010).

2.2.7 Depression management

The management of depression can be guided by severity; in mild depression (PHQ-9 score <10), self-help techniques such as books (audio or written) or cognitive behavioural therapy (CBT) worksheets provided by counsellors or psychologists are recommended by the NHS for stress, anxiety, and depression (NHS, 2018). If these self-help techniques fail to resolve mild depression, low-intensity CBT or talking therapies can be initiated. Pharmacological therapies are often recommended for moderate to severe depression (PHQ-9 score ≥10) alongside more intense talk therapies (Park, Zarate, 2019). This approach is the stepped care model, tailoring management to

the patients' needs as their care requirements move up or down (Meeuwissen et al., 2008). In addition to talking therapies, there are support groups and charities that can address social aspects of living with, or the consequences of, depression.

First-line medications are typically Selective Serotonin Reuptake Inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) due to their lower side-effect profile when compared with older antidepressant classes such as Tricyclic antidepressants (TCAs) (Gautam et al., 2017). SSRIs, SNRIs and TCAs increase monoamine levels in synaptic spaces by inhibiting their reuptake (Sangkuhl, Klein & Altman, 2009). These medications often take at least two to four weeks to work, and there may be a paradoxical rise in depressive symptoms or suicidal ideation before an improvement is seen. In the case of treatment-resistant depression, augmentation with mood stabilisers, such as lithium or atypical antipsychotics, may be trialled (Al-Harbi, 2012; Voineskos, Daskalakis & Blumberger, 2020). The National Institute for Health and Care Excellence (NICE) suggests using electroconvulsive therapy (ECT) for severe or life-threatening depression where a rapid response is sought (such as catatonic patients) or other treatments have failed. NICE recommends not to use ECT routinely for people with moderate depression, but that it may be considered if multiple treatments have failed (NICE, 2020b). More recently, Esketamine (structurally related to ketamine) has been licenced for treatment-resistant depression in America and noted for its' more immediate effects than traditional pharmacological agents (Kraus et al., 2019; Corriger, Pickering, 2019). However, this treatment option was rejected by NICE in January 2020 in the UK. It is also significantly more costly than other antidepressants (NICE, 2020a).

2.2.8 Depression prognosis

Burcusa and Lacono (2007) conducted a review into the recurrence of depression. They reported that people with a history of depression would, on average, have five to nine episodes of

depression throughout their life and that half of the people who recover from their first depressive episode go on to have more (Burcusa, Iacono, 2007). Risk factors associated with depression recurrence can include childhood maltreatment, residual depressive symptoms, and co-morbid anxiety (Buckman et al., 2018). The World Health Organisation (WHO) predict that major depression will be the leading cause of disease burden by 2030 internationally (Lépine, Briley, 2011). Depression is a significant cause of disability and the 4th most common cause of loss of DALYs (disability-adjusted life years) in the world. Despite being a recognisable and treatable condition with modifiable risk factors, depression is often underdiagnosed and undertreated. Although many do recover or manage their depression, a proportion of people with depression attempt suicide. The risk of suicide is 15 times higher in depressed individuals, and up to two-thirds of suicide attempts are linked to depression. The lifetime risk of suicide due to depression is 3.5% (Blair-West, Mellsop & Eyeson-Annan, 1997). In 2018 there were over 6500 deaths recorded by suicide (11.2 deaths per 100,000) in the UK (ONS, 2019). With better identification, quicker initiation of management, and altering modifiable risk factors, the prognosis for individuals suffering from depression could be significantly improved, reducing the burden of depression on the healthcare system.

2.3 Anxiety

2.3.1 Anxiety background

Anxiety disorders, much like depression, are a common and often debilitating category of mental health conditions characterised by a predominant feeling of anxiety, worry or doom. This group of mental health disorders includes generalised anxiety disorder (GAD), phobias, panic disorder, agoraphobia, social anxiety disorder, and obsessive-compulsive disorder (OCD) (Ströhle, Gensichen & Domschke, 2018).

Feeling anxious or worried is a natural emotion, often brought on by everyday life events such as health issues, exams, financial pressures, or relationship issues. As with depression, anxiety can manifest as a discrete incident or become a recurrent chronic disorder.

GAD is described as anxiety due to nonspecific triggers for at least six months, invoking excessive fear or overwhelming anxiety. In addition, anxiety is associated with psychological, social, and physical symptoms such as difficulty concentrating, irritability, self-isolation, sleep disturbances, muscle tension and palpitations (Munir, Takov, 2021). The WHO stated anxiety disorders are the 6th most significant contributor to years lived with disability and has a global 12-month prevalence of 3.6%. As the General Anxiety Disorder 7 (GAD-7) questionnaire, defined later in section 2.3.4, was used to gather data for this thesis, this section and thesis will primarily focus on general anxiety disorder, so other anxiety disorders are not described.

2.3.2 Anxiety pathophysiology

The precise mechanism that causes anxiety is unknown. However, the hypotheses previously mentioned concerning depression pathophysiology (section 2.2.2) have also been implicated in the development of anxiety: cortisol abnormalities, dysregulation of monoamines (MAs), and raised circulating inflammatory molecules.

Stressful and traumatic events, particularly if prolonged or at a younger age, are risk factors for developing GAD (Blanco et al., 2014). Cortisol, a glucocorticoid, is released in reaction to stressful stimuli via activation of the HPA axis and is a normal physiological response. Abnormal cortisol levels and responses have been reported in subjects with mental conditions, such as GAD. Wang et al. (2017) studied cortisol levels and response in 64 patients with current GAD and 65 healthy counterparts. In GAD patients, but not controls, cortisol levels were elevated, and peripheral glucocorticoid receptor (GR) sensitivity was diminished. GR sensitivity correlated with anxiety symptoms (Wang, Wei et al., 2017).

Furthermore, Lenze et al. (2011) studied the effect of SSRI treatment (escitalopram) vs placebo on elevated cortisol levels in patients with GAD. After 12 weeks of escitalopram treatment, there was a statistically significant reduction in both peak and total cortisol levels vs the placebo group. However, the authors noted that whilst the finding of escitalopram's effect on cortisol levels is important, the clinical benefit of lowering cortisol levels in relation to GAD was not explored (Lenze et al., 2011).

Cortisol has been shown to increase gene expression for a serotonin transporter (Tafet et al., 2001). Thus, serotonin, a monoamine, has been implicated in the pathogenesis of GAD. Despite the evidence around serotonin levels being inconclusive, SSRIs (which increase synaptic serotonin levels by inhibiting their re-uptake) remain a first-line pharmacological treatment due to their efficacy in reducing the symptoms, severity, and presence of anxiety.

In a case-control study of 54 patients with GAD, Hou et al. (2017) found a significant increase in pro-inflammatory molecules such as IL-10 and TNFα compared to the control group, as well as a reduction of anti-inflammatory molecules independent of the presence or severity of depression (Hou et al., 2017). In addition, as previously stated, it has been shown that some anxiolytic medications, such as the SNRI venlafaxine, can have immunomodulatory activity leading to an anti-inflammatory effect.

2.3.3 Anxiety epidemiology

The WHO reported that anxiety disorders are the 6th largest contributor to years lived with disability, had a global 12-month prevalence of 3.6% in 2015 and form a significant healthcare burden (WHO, 2017). A 9-year UK population-based cohort study by Remes et al. (2018) found that 2.2% of participants had GAD (Remes et al., 2018). Watterson et al. (2017) reported a lifetime prevalence of GAD as 8.7% in Canada, with a 12-month prevalence of 2.6% (Watterson et al., 2017).

2.3.4 Anxiety signs, symptoms, and diagnosis

Much like depression, GAD is a clinical diagnosis made based on history, signs and symptoms. The DSM-V diagnostic criteria for GAD is excessive anxiety and worry most days for at least six months (Locke, Kirst & Shultz, 2015). At least three or more of the following should also be present: restlessness or feeling on edge, easily fatigued, difficulty concentrating, irritability, muscle tension, sleep disturbances. These thoughts, feelings or physical symptoms should be significant enough to impair daily living (Locke, Kirst & Shultz, 2015).

There are several validated questionnaires and tools which can aid clinicians in making a diagnosis of GAD. The General Anxiety Disorder 7 (GAD-7) questionnaire comprises seven questions that focus on the DSM-IV criteria for GAD as mentioned above. Each question can be answered and scored as the following: “Not at all” 0, “Several Days” 1, “More than half the days” 2, and “Nearly every day” 3. Therefore, possible scores range from 0 to 21. The score can be used to diagnose GAD, as well as identify the severity (Williams, 2014):

- 0 – 4 no or subclinical GAD
- 5 – 9 mild GAD
- 10 – 14 moderate GAD
- 15 - 21 severe GAD

2.3.5 Anxiety risk and protective factors

As with depression, there are several modifiable and non-modifiable risk factors associated with GAD. Modifiable factors include previous mental illness, socioeconomic circumstances, and medications. Non-modifiable factors include sex, family history, age, trauma, and genetics (Blanco et al., 2014).

A systematic review that examined panic and general anxiety disorders by Monreno-Peral et al. (2014) reported that a previous history of mental health problems, including but not limited to major depression, were significantly associated with GAD (Moreno-Peral et al., 2014). A Canadian study of a national health survey with over 25,000 participants found that having a low household income (defined as <$30,000 – approximately £19,000 in 2012) was a significant risk factor for GAD (OR 3.2, 95% CI: 2.3 to 4.5) (Watterson et al., 2017). A review by Ciriaco et al. (2013) of psychiatric complications of corticosteroid use identified a study by Bolanos et al. (2004) that reported two to four per cent of corticosteroid users developed depression, anxiety, or apathy over 6 months on a dose of 7.5mg/day of prednisone (Ciriaco et al., 2013).

Grant et al. (2009) found that being female increased the risk of all anxiety disorders (except social phobia), including GAD (Grant et al., 2009). Watterson et al. (2017) investigated the epidemiology of, and risk factors for GAD and reported increased risk of GAD in being: Female (OR 1.6, 95% CI: 1.3 to 2.1), middle-aged (35-54) (OR 1.6, 95% CI: 1.0 to 2.7), widowed or divorced (OR 1.9, 95% CI: 1.4 to 2.6), being unemployed (OR 1.9, 95% CI: 1.5 to 2.5), born in Canada (OR 2.0, 95% CI: 1.4 to 2.8) (Watterson et al., 2017).

2.3.6 Anxiety management

The management of GAD follows a similar stepped care model as depression: As GAD severity increases or decreases, management can be stepped up or down to be tailored to the patient's specific needs (Meuldijk, Wuthrich, 2019). For mild GAD (GAD-7 score <10), self-help techniques, CBT worksheets, books or audio written/recorded by counsellors or psychologists and exercise are recommended by the NHS for anxiety (NHS, 2018). If these self-help techniques fail to resolve mild GAD, low-intensity CBT or other talking therapies can be initiated. For moderate to severe GAD (GAD-7 score ≥10), pharmacological therapies are often recommended alongside more intense talking therapies (Munir, Takov, 2021).

SSRIs or SNRI are first-line medications for anxiety, similar to depression. These medications can take from two to four weeks to reduce anxiety levels, and there may be a paradoxical rise in anxiety before an improvement is seen. If required, short term use of beta-blockers for physical symptoms can be co-prescribed; if beta-blockers are contraindicated, buspirone can be used, although this may cause drowsiness and concentration difficulties (Patel, D. R. et al., 2018). Buspirone is an anxiolytic that acts as an agnostic on serotonin receptors.

2.4 Gout and psychological co-morbidity (anxiety and depression)

There are few studies in this area, as the predominant focus of research into gout and co-morbidity has been physical, rather than psychological, health.

There are several possible mechanisms by which gout could predispose to anxiety and depression. As discussed, inflammation has been postulated to play a role in the aetiology of anxiety and depression. Specific pro-inflammatory molecules, such as TNFα and IL-1β, are upregulated in individuals with anxiety or depression. These molecules are also crucial in the inflammatory response in a gout flare.

Other conditions that cause pain, joint damage and impaired mobility may increase the risk of depression. For instance, Jacob, Rockel and Kostev (2017) have shown that in rheumatoid arthritis (RA), another inflammatory arthritis, depression develops in up to 30% of patients within five years of diagnosis (Jacob, Rockel & Kostev, 2017). As gout shares many similarities to RA, both being long term inflammatory conditions associated with disability and loss of quality of life, it is feasible a similar risk of depression may occur in gout. Furthermore, TNFa is also a critical pro-inflammatory cytokine in both gout and RA.

In addition to the inflammatory nature of gout flares, flares are also intensely painful and stressful incidents. Stressful and traumatic events are risk factors for developing anxiety, and

anxiety is a risk factor for developing depression (Blanco et al., 2014; Moreno-Peral et al., 2014). Thus, it is also plausible that the uncertainty and lack of predictability of when flares will occur could contribute to feelings of anxiety.

There is a relationship between alcohol misuse and depression, and high alcohol consumption (particularly beer) is a risk factor for developing gout.

Despite these shared risk factors and potential pathophysiological mechanisms, the evidence of an association between gout and anxiety and depression remains inconclusive: Prior et al. (2015) reported similar consultation rates for anxiety or depression in people living with gout in the UK to age, gender and year of consultation matched counterparts without gout. However, in a cross-sectional study of people living with gout as well as anxiety and depression, gout characteristics such as flare frequency and having had oligo- or poly-articular gout flares were associated with depression (PHQ-9 score ≥10), but not anxiety (GAD-7 score ≥10) (Prior et al., 2015b; Prior et al., 2016).

In summary, gout, anxiety, and depression are common conditions. There is a credible rationale to expect gout to be associated with depression or anxiety. However, this possible association has received less attention than the associations between gout and physical co-morbidities. This thesis comprises a systematic review (SR) of previous studies of gout and anxiety and depression, and an original cohort study of the course of anxiety and depression in people living with gout over five years. The next chapter will provide the methods, results, discussion and conclusion of the systematic review.

This chapter covered the pertinent background information regarding gout and psychological co-morbidity (anxiety and depression), their possible associations and justification for the systematic review and secondary analysis of the cohort study in this thesis. The next chapter presents the systematic review into the epidemiology and associations of gout and psychological co-morbidity, containing the methods, results, and discussion.

Chapter 3 - Systematic review

The previous chapter covered pertinent background information regarding gout and psychological co-morbidity (anxiety and depression), their possible associations and justification for this thesis. This chapter will describe the methods utilised for this systematic review, including protocol development, PICOS (Population, Item/exposure of interest, Comparator group, Outcomes of interest and Setting/Study design) eligibility criteria, the search strategy, search terms, databases used, screening process, quality appraisal, results and discussion of the findings.

3.1 Systematic review methods

3.1.1 Overview and justification

A systematic review is a reproducible way of methodically reviewing primary research to help answer specified questions. The key characteristics of a systematic review include stated objectives or questions, background to the subject as to why the review is justified, and detailed eligibility and exclusion criteria. Furthermore, it details what search methods (such as search terms and databases) were used, how search results were handled, quality assessment of included articles and how data were synthesised.

The review process should be sufficiently transparent and robust to allow any reader to follow each step to yield the same search results and included full-text articles, thus minimising bias. However, the utility of a systematic review goes beyond trying to answer the pre-defined questions. It can summarise knowledge from multiple different sources and collate it into one succinct document. This provides researchers and clinicians with high-quality up-to-date information, which can help shape their practice. It also provides a base for the direction of future study or which areas are under-researched. An often-overlooked aspect of systematics reviews is

the ability to highlight what research has already been conducted in a field, thus minimising the chance of duplication.

3.2 Protocol

The author (JH) devised a systematic review protocol with the assistance of both academic supervisors (LC and ER) and the systematic review team (OB, NC and JJ). A systematic review protocol and support template was used to help guide this process. A blank copy of the 'Systematic Review Protocol & Support Template' is attached in the appendix.

3.3 Aims

The primary aim was to identify the prevalence and incidence of psychological co-morbidity (anxiety and depression) in people living with gout and (where provided) compared to non-gout control subjects. The secondary aim was to identify specific characteristics, e.g., frequency of gout flares, number of joints affected, sociodemographic factors, or co-morbidities associated with psychological co-morbidity in people living with gout.

3.4 Methods

3.4.1 Eligibility criteria

3.4.1.1 Inclusion criteria

Utilising the PICOS format (Population, Item/exposure of interest, Comparator group, Outcomes of interest and Setting/Study design), inclusion criteria were formulated.

The population of interest was human adults aged ≥18 years old with a diagnosis of gout. Studies containing populations with other conditions and gout were deemed to meet inclusion criteria if subgroup analysis of the gout sufferers had occurred.

The exposure of interest was gout. The preferred methods of diagnosing gout were clinical diagnosis, medical record review, or the gold standard method of diagnosing gout, monosodium urate (MSU) crystal identification. However, self-report was acceptable. These aspects were taken into consideration during quality appraisal.

Studies without comparator groups were included, although studies with sex- and age-matched non-gout control groups were preferred. These differences were highlighted during quality appraisal and reflected in quality appraisal scoring.

The outcomes (aims), as stated in section 3.3, were the prevalence or incidence of psychological co-morbidity (anxiety and depression) in people living with gout and (where provided) compared to non-gout control subjects; and factors associated with psychological co-morbidity in people living with gout, such as gout characteristics, sociodemographic factors or co-morbidity.

Studies that were undertaken in any care setting, including population-based studies, were acceptable. As the primary outcome was to identify epidemiological estimates such as prevalence and incidence, primary quantitative epidemiological studies of any study design were eligible for inclusion.

3.4.1.2 Exclusion criteria

Articles were excluded if they met any of the following conditions:

- Participants <18 years of age
- Non-English language studies for which a translation could not be obtained
- Case reports or case series
- Editorials, letters, conference abstracts or posters where a full article had not been published

- Reviews, including systematic reviews, although reference checking of topic relevant reviews was undertaken
- Articles where a full text could not be found during the screening process
- Qualitative studies
- Animal studies

3.4.2 Database interfaces and databases

The author (JH) used three database interfaces (Ovid®, Web of Science and EBSCO) to search eight databases from the date of inception to October 2019. First, databases AMED, Embase® and MEDLINE® were searched independently via Ovid®. Next, the database Web of Science Core Collection was searched via Web of Science. Finally, databases APA PsychINfo, APA PsycARTICLES, Ageline and CINAHL Plus were collated into one search via EBSCO's database interface. A short description of each database interface and database follows below in Table 3.1.

Table 3.1 Description of database interfaces and databases								
Database interface	**Ovid®**							
Description	Ovid Technologies Inc. (Ovid®) was originally developed in the 1980's as a way of accessing the MEDLINE® database. It now offers online access to a range of databases and the current iteration of the interface is called OvidSP. It primarily focuses on biomedical and health science databases. This interface was used to search **MEDLINE®**, **AMED**, and **Embase®** databases.							
	↓							
Databases	**MEDLINE®**		**AMED**		**Embase®**			
Description	MEDLINE® contains over 25 million references with a predominant interest in life sciences, biomedicine and medicine. The U.S. National Library of Medicine® (NLM) upholds it and thus has predominantly American coverage.		The Allied and Complementary Medicine Database (AMED) contains over 500 journals and focuses on alternative and complementary medicine. It has a predominantly European coverage, as the Health Care Information Service of the British Library produces it.		Embase® focuses primarily on biomedical literature. It contains almost 8,500 journals, including approximately 2900 that are not on MEDLINE®.			
Database interface	**Web of Science**							
Description	Web of Science is a subscription-based online database interface. It covers numerous disciplines including biomedical and health sciences, but also arts and humanities. This interface was used to search the Web of Science: **Core Collection** database**.**							
	↓							
Databases	**Web of Science: Core Collection**							
Description	Web of Science: Core Collection has over 21,000 journals, books and conference proceedings. A wide variety of subjects are covered, but particularly biomedical sciences and social sciences.							
Database interface	**EBSCO**							
Description	EBSCO (EBSCOhost) offers access to numerous databases depending on subscription package. It covers core medical and life sciences, but also social sciences, music, computer sciences and much more. This interface was used to search **APA PsycARTICLES**, **APA PsychInfo**, **CINAHL Plus** and **AgeLine** databases.							
	↓							
Databases	**APA PsycARTICLES**		**APA PsychInfo**		**CINAHL plus with full-text**		**AgeLine**	
Description	The American Psychological Association (APA), the Canadian Psychological Association and Hogrefe Publishing group publishes PsycARTICLES. It contains over 70 peer-reviewed full-text journals with a focus on psychology, psychiatry and related medicine.		In contrast to PsycARTICLES, PsycInfo mainly contains citations and abstracts rather than full-text articles. However, it also references books, reports and dissertations containing over 2500 journals in psychology, psychiatry and related medicine. Many articles from PsycARTICLES are also found within PsychInfo but for completeness, both were searched as to not miss any relevant materials.		CINAHL (Cumulative Index to Nursing and Allied Health Literature) plus predominantly covers nursing and biomedicine related journals. It has over six million records and over 5000 indexed journals. In additional to peer-reviewed articles, it also contains healthcare books, dissertations and conference proceedings.		AgeLine focuses on gerontological research. It covers topics including medicine, nursing and other allied health professions in people aged 50 and older. It contains over 180,000 records.

3.4.3 Search strategy

Following consultation with the systematic review (SR) team and a pilot search (via MEDLINE®), the author (JH) searched the databases from the date of inception to October 2019. The pilot search involved generating suitable search terminology and reviewing the results for appropriateness. Search terminology was revised with the help of the SR team. The pilot search was validated by successfully identifying a relevant article known to meet all eligibility criteria previously identified during the literature search for the background section.

3.4.4 Search terminology

The same keywords were used for all databases. However, some databases used different syntaxes. Where possible, the corresponding syntax was used for uniformity. Search terms fell into two categories: gout, and psychological co-morbidity (anxiety and depression). Gout related keywords included terms such as "gout*"[1], "hyperuric?emi*"[2] , as well as Mesh Heading "Gout" in MEDLINE® (or other database equivalents). Headings were exploded to contain all subheadings. The same approach was taken for psychological co-morbidity by generating a list of anxiety and depression keywords or phrases and exploding subject headings. The results within categories were combined using the Boolean operator OR to sum them into one search line. The sum of gout related words and psychological co-morbidity related terms were then combined using the Boolean operator AND to only yield articles that satisfied at least one term from both categories. Studies labelled as animal only, and not human, were also excluded by a search term. Table 3.2 gives an overview of the search terms used for MEDLINE ® and the number of results returned.

[1] An asterisk (*) denotes truncation. For example, "gout*" will return results containing the word gout, as well as gouty.

[2] A question mark (?) denotes a wild card. For "hyperuric?emi*" the '?' will allow both UK and US variations of the word to be returned, combining this with the '*' means hyperuricaemia, hyperuricemia, hyperuricaemic and hyperuricemic will all be returned.

No search filters or limits were applied, and all databases were searched from the date of their inception.

Table 3.2 - Medline® search strategy

Gout terms

Search Number	Search Term	Results
1	exp Gout/	11851
2	gout*.kf,ti,ab.	12543
3	hyperuric?emi*.kf,ti,ab.	7160
4	toph*.kf,ti,ab.	1852
5	(monosodium adj3 urate).kf,ti,ab.	1160
6	(sodium adj3 urate).kf,ti,ab.	279
7	(crystal* adj3 arth*).kf,ti,ab.	750
8	podagra.kf,ti,ab.	117

Psychological co-morbidity terms

Anxiety			Depression		
Search Number	**Search term**	**Results**	**Search Number**	**Search term**	**Results**
10	exp Anxiety Disorders/	77412	15	Depression/	112420
11	exp Anxiety/	80739	16	exp Mood Disorder/	118157
12	anxi*.kf,ti,ab.	168290	17	depress*.kf,ti,ab.	388673
13	worr*.kf,ti,ab.	18045	18	mood*.kf,ti,ab.	62153
14	panic*.kf,ti,ab.	16598	19	sad*.kf,ti,ab.	20168
			20	unhapp*.kf,ti,ab.	1605

			21	hopeless*.kf,ti,ab.	4874

Boolean operator terms		
Search Number	**Search Term**	**Results**
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	21312
22	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	634119
23	9 and 22	194
24	exp animals/ not human/	4634845
25	23 not 24	176

3.4.5 Search result management

The search results were imported and collated in RefWorks. RefWorks is a web-based reference management interface. RefWorks' duplicate search function was used to identify and remove exact duplicates. The remaining articles were exported into Rayyan, a free web-based application set up by the Qatar Computing Research Institute to perform systematic reviews. Using Rayyan's similarity checker, articles with high resemblance to others were flagged for manual review by the author (JH). Any duplicates (by comparison of title, abstract, authors, and year of publication) were removed.

3.4.6 Screening

After duplicates were removed in RefWorks and Rayyan, screening against eligibility criteria began. This was split into two phases, title with abstract, and full-text screening. The author (JH), second reviewer (CHB), and the supervisory team (LC and ER) participated at different stages, as detailed below.

3.4.6.1 Title and abstract screening

Article title and abstracts were initially screened by the author (JH) using Rayyan's highlight function against exclusion criteria. Keywords or phrases like 'In this systematic review' or 'This case series' were identified, and after a manual review of the highlighted articles title or abstract, were excluded. This approach allowed brevity of the screening process whilst maintaining a high level of reliability and bias reduction. Once articles that had met obvious exclusion criteria were removed, the remaining articles' titles and abstracts were dual-screened by the author (JH) and the second reviewer (CHB). Articles where inclusion or exclusion was agreed by both the author (JH) and the second reviewer (CHB), were retained or removed respectively for full-text screening. Any disparity in outcome was reviewed by a third reviewer from the supervisory team (LC). Any articles with missing abstracts were retained for full-text review unless the title noted clear exclusion criteria. A final list of articles for full-text review was then generated.

3.4.6.2 Full-text screening

Full-texts of eligible articles were manually searched for by the author (JH) via electronic databases, Google Scholar, and Google search engine. Cross-checking of title, abstract, authors and year of publications was carried out to ascertain a match. Once full-text articles were identified, they were uploaded into the corresponding title/abstract file on Rayyan for ease of use by other reviewers. Where full-text articles could not be identified, authors were emailed directly. If a full text was provided, it was screened. Articles that were found to be conference/meeting abstracts only were excluded if a corresponding full-text peer-reviewed paper had not been published. Where no full-text could be found, articles were excluded. All full-text articles were reviewed by two reviewers, the author (JH) and either LC or ER. Any conflicts were adjudicated by the opposite reviewer (LC or ER), and a final decision for inclusion or exclusion was made.

3.4.6.3 Other sources

References lists of included articles were checked to identify any articles that had not have been found during the initial search. Any articles found would be screened against the same eligibility criteria listed above.

3.4.7 Quality appraisal

The Newcastle-Ottawa Scale (NOS) was used for the quality assessment of the included full-text articles. This was carried out by the author (JH). The NOS was devised to quality assess non-randomised control studies, specifically cohort and case-control studies. There are three components to the NOS, which differ slightly according to study design: for cohort studies, the three components assessed are selection, comparability and exposure; whilst for case-control and cross-sectional studies, the three components assessed are selection, comparability and outcome. Table 3.3 describes the specific questions and options for scoring each study design and the criteria by which a "star" is awarded for robust methodology. The questions that are awarded a star are pre-determined by the NOS. The NOS first section has a maximum of four stars, the second two stars, and the third three stars, with a total combined maximum score of nine stars. A standard criterion for what constitutes a high-, fair-, or low-quality study from the NOS has not been unanimously agreed upon (Islam et al., 2016). Islam et al. (2016) assigned the score ≥7 to be high-quality. Following this, cut-offs for high-, fair-, and low-quality studies were agreed upon by the supervisory team. A global score of ≥7 (stars) was deemed high quality, scores ranging from 4 to 6 were fair quality, and scores of ≤3 were low quality. Any uncertainty about scoring was discussed with the supervisory team (LC and ER) for clarification and a final decision. Results were tabulated and then colour coded so global scores groups can be understood at a glance. In the results tables, questions where a star was awarded are shown as green. Questions where no star was awarded are red. The global score is also colour coded: high-quality green, fair-quality amber, and low-quality red.

Table 3.3 Newcastle Ottawa Scale for each study type								
	Category							
	Selection				Comparability	Exposure		
Study type	Question 1	Question 2	Question 3	Question 4	Question 1	Question 1	Question 2	Question 3
Case-control	**Is the case definition (gout diagnosis) adequate?**	**Representativeness of the cases**	**Selection of Controls**	**Definition of Controls**	**Comparability of cases and controls on the basis of the design or analysis**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-Response rate**
Options	a) yes, with independent validation * b) yes, e.g. record linkage or based on self-reports c) no description	a) consecutive or obviously representative series of cases* b) potential for selection biases or not stated	a) community controls* b) hospital controls c) no description	a) no history of disease (endpoint)* b) no description of source	a) Study controls for age* b) Study controls for additional factor gender*	a) secure record (e.g. surgical records)* b) structured interview where blind to case/control status* c) interview not blinded to case/control status d) written self-report or medical record only e) no description	a) yes* b) no	a) same rate for both groups* b) non respondents described c) rate different and no designation
	Selection				**Comparability**	**Outcome**		
Cohort	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**
Options	a) truly representative of the average 18+ year old living with gout in the community* b) somewhat representative of the average 18+ year old living with gout in the community* c) selected group of users e.g. nurses, volunteers d) no description of the derivation of the cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non-exposed cohort	a) secure record (e.g. surgical records)* b) structured interview* c) written self-report d) no description	a) yes* b) no	a) Study controls for age* b) Study controls for additional factor gender*	a) independent blind assessment* b) record linkage* c) self-report d) no description	a) yes (>6 months) b) no	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost >95% follow up, or description provided of those lost* c) follow up rate <80% and no description of those lost d) no statement

Table 3.3 continued

	Selection				Comparability	Outcome	
Cross-sectional	**Representativeness of the sample**	**Sample size**	**Non-respondents**	**Ascertainment of the exposure (risk factor)**	**The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled**	**Assessment of the outcome**	**Statistical test**
Options	a) Truly representative of the average 18+ year old living with gout in the community* (all subjects or random sampling) b) Somewhat representative of the average 18+ year old living with gout in the community* c) Selected group of users d) No description of the sampling strategy	a) Justified and satisfactory * b) Not justified	a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory* b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory c) No description of the response rate or the characteristics of the responders and the non-responders.	a) Validated measurement tool. * b) Non-validated measurement tool, but the tool is available or described c) No description of the measurement tool	a) Study controls for age* b) Study controls for additional factor gender*	a) Independent blind assessment and/or validated measurement tool ** b) Record linkage* c) Self report d) No description	a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and/or the probability level (p value)* b) The statistical test is not appropriate, not described, or incomplete

Notes

An asterisk (*) at the end of an answer denotes it would gain a 'star'. Only the single most appropriate answer will be selected per question, **except** for question 1 of the comparability section where a) and/or b) or neither answer can be chosen. Answer A for question 1 in the outcome category for Cross-sectional studies can received two stars (**).

3.4.8 Data extraction

Data were extracted into a Microsoft Excel spreadsheet. A draft spreadsheet was tested to ensure its suitability for capturing the appropriate data by extracting data from three random articles. Once this was confirmed, data from the remaining articles were extracted. The following information was captured:

- First author
- Year of publication
- Country of study
- Study design
- Average age, mean (±1 SD) or median (IQR)
- Sex distribution, number or percentage of males and females
- Sample size
- Study population
- Method of gout ascertainment
- Method of anxiety or depression ascertainment
- Prevalence or incidence of anxiety or depression in people living with gout
- Estimates of the association between gout and anxiety or depression, e.g. odds ratio, hazard ratios
- Characteristics associated with anxiety or depression within people living with gout

3.4.9 Data validation

The second reviewer (CHB) extracted data from 4 (27%) articles independently. This was compared against the data the author (JH) extracted. All incongruity was discussed. An error rate of >10% would

trigger double extraction of all articles. If required, the supervisory team (LC and ER) resolved any remaining conflicts.

3.4.10 Data analysis

3.4.10.1 Narrative review

All included articles were analysed and described narratively. A narrative review is a way of reporting results from a systematic review predominantly via text instead of statistics. Tables and graphs are still utilised, but the 'story' of the data is conveyed by writing.

3.5 Results

3.5.1 Search results

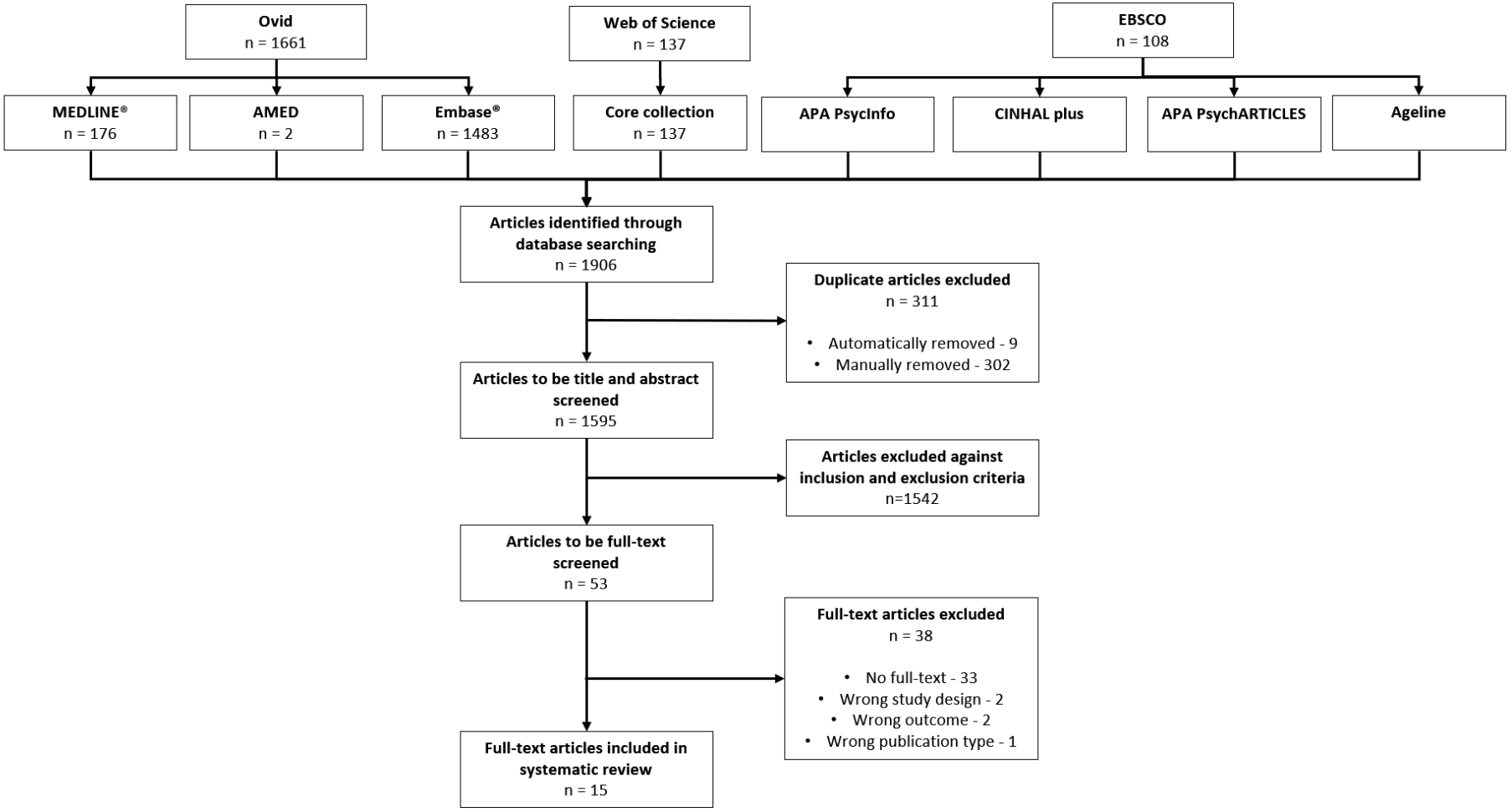
The systematic search identified 1906 articles.

Articles returned by the web interface and corresponding databases:

- **Ovid**: MEDLINE® 176, AMED 2, Embase® 1483 (**1661** combined)
- **Web of Science**: Core collection **137**
- **EBSCO**: APA PsycInfo, APA PsycARTICLES, Ageline and CINHAL Plus full-text (**108** combined)

An overview of this process is outlined in Figure 3.1 which follows the PRISMA statement

Figure 3.1 PRISMA flow diagram of article search



EBSCO automatically removed nine duplicate articles. This left 1897 articles to be imported into RefWorks. No exact duplicates were identified using Refworks exact duplicate checker. Therefore, 1897 articles were imported into Rayyan. Using Rayyan's similarity checker, a further 302 duplicate articles were manually reviewed and removed.

The remaining 1595 articles were title and abstract screened by the author (JH), of which 1453 articles explicitly did not meet eligibility criteria and were removed. The remaining 142 articles were dual-title and abstract screened, resulting in 39 articles included for full-text screening, 79 were excluded, and 25 conflicts arose between the two reviewers. The third reviewer (LC) screened these 25 conflicts, 14 were included and 11 excluded. This left 53 articles to be full-text screened.

Of the 53 articles full-text screened, 33 were automatically excluded as the full-text could not be located. This was most commonly (30 out of 33) due to being a conference abstract or poster. The remaining 20 articles had their full-text dual-screened by the author (JH) and the third (LC) or fourth reviewer (ER). After dual screening, 14 were included, five were excluded, with one conflict. The fourth reviewer screened the conflict, and it was retained. Of the five excluded studies, two were the wrong study design (qualitative only), two did not have anxiety or depression as outcomes, and one was a book. Consequently, 15 full-text articles were included in the systematic review.

3.5.2 Data extraction

Two pairs of studies used the same data sources: Fu et al. (2017) and Fu et al. (2018), and Roddy et al. (2015) and Prior et al. (2016). Data were extracted from all studies and presented in tables individually, including from both sets of studies with duplicate data sources, and presented separately.

3.5.3 Study characteristics

Table 3.4 - Study characteristics											
First Author, Surname	**Year of publication**	**Country of study**	**Study design**	**Study population**	**Age, years ± 1 STD**	**Sex split, %**	**Sample size, n**	**Gout assessment**	**Depression assessment**	**Anxiety assessment**	**Quality assessment score - NOS (stars)**
Wang	2010	Taiwan	Cross-sectional	Community	Gout NA Comparators NA	Gout Male 67.9% Female 32.1% Comparators Male 54.8% Female 45.2%	Total = 3970 Gout = 305 Comparators = 3665	Self-report	GDS-SF	NA	5
Mak	2011	Singapore	Cross-sectional	Secondary care	Gout 58.2 ± 14.9 Comparators 42.75 ± 14.0***	Gout Male 90% Female 10% Comparators Male 13% Female 87%	Total = 111 Gout = 50 Comparators = 61	ACR classification criteria	HADS-depression	HADS-anxiety	3
Prior	2015	UK	Cohort	Primary care	Gout 63 ±16 Comparator Unknown	Gout Male 76% Female 24% Comparator Unknown	Total =8445 Gout = 1689 Comparators = 6756	Read codes	Read codes	Read codes	8
Changchien	2015	Taiwan	Cohort	Population (National health insurance programme)	Gout 49.3 ±16 Comparator 48 ±16.2	Gout Male 80.2% Female 19.8% Comparator Male 80.2% Female 19.8%	Total = 102,150 Gout = 34,050 Comparators = 68,100	ICD-9	ICD-9	NA	9

Spaetgens	2015	Netherlands	Cross-sectional	Secondary care	Gout 65.8 ± 10.5 Comparators Unknown**	Gout Male 85.5% Female 14.5% Comparators Unknown**	Total 110 Gout = 110 Comparators = Unknown**	Hospital records	EQ-5D	EQ-5D	4
Roddy	2015	UK	Cross-sectional	Primary care	Gout 65.6 ± 12.5 Comparators NA	Gout Male 83.6% Female 16.4% Comparator N/A	Total =1184 Gout = 1184 Comparators = N/A	Read codes	PHQ-9	GAD-7	5
Kim	2015	USA	Cross-sectional	Population (National health survey)	NA	Gout Male 63.9% Female 36.1% Comparators Male 42.8% Female 57.2%	Total = 2266 Gout = 82 Comparators = 2184	Self-report	PHQ-9	NA	6
Kuo	2016	UK	Case-control	Primary care	Gout 62.2 ± 15.1 Comparators Unknown	Gout Male 72.49% Female 27.52% Comparators Male 72.49% Female 27.51%	Total = 78,222 Gout = 39111 Comparators = 39111	Read codes	Read codes	NA	8
Prior	2016	UK	Cross-sectional	Primary care	Gout 65.6 ± 12.5 Comparators NA	Gout Male 83.6% Female 16.4% Comparator N/A	Total = 1184 Gout = 1184 Comparators = N/A	Read codes	PHQ-9	GAD-7	7

Fu	2017	China	Case-control	Secondary care	Gout 53.18 ± 15.77 Comparators 51.21 ± 13.48	Gout Male 94.7% Female 5.3% Comparators Male 94% Female 6%	Total = 458 Gout = 226 Comparators = 232	ACR classification criteria	PHQ-9	GAD-7	8
Fu	2018	China	Case-control	Secondary care	Gout 53.18 ± 15.77 Comparators 51.21 ± 13.48	Gout Male 94.7% Female 5.3% Comparators Male 94% Female 6%	Total = 458 Gout = 226 Comparators = 232	ACR classification criteria	PHQ-9	GAD-7	8
Singh	2018	USA	Cohort	Medicare database	Combined 75.9 ± 7.4	Combined Male 29.7% Female 70.3%	Total = 142,596 Gout = 7218 Comparators = 135,378	ICD-9	ICD-9	NA	8
Nguyen	2019	Australia	Cohort	Community (Residential care facility)	Gout Males: 86 (79-90) * Female: 87 (83-92)* Comparators Males: 84 (77-89)* Female: 87 (82-92)*	Gout Male 47% Female 53% Comparators Male 68.7% Female 31.3%	Total = 11,548 Gout = 1232 Comparators = 10,316	Electronic health records	Electronic health records	NA	4
Zhou	2019	China	Cross-sectional	Secondary care	Gout 61.9±10.9 Comparators 62.3 ± 8.2	Gout Male 81.2% Female 18.8% Comparators Male 58% Female 42%	Total = 386 Gout = 186 Comparators = 200	ACR classification criteria	HAMD-17 + DSM5 clinical psychologist interview	NA	7
Lee	2019	Singapore	Cross-sectional	Secondary care	Gout 52.2 ± 16.08 Comparators NA	Gout Male 92.1% Female 7.9% Comparators NA	Total = 267 Gout = 267 Comparators = NA	ACR classification criteria	EQ-5D	EQ-5D	3

Notes
*Median + IQR. **Age and gender matched general public. *** SLE controls. Abbreviations in abbreviations list at start of document.

3.5.4 Study outcome data

Table 3.5 Depression and anxiety prevalence					
		Depression		Anxiety	
First Author	Year of publication	Gout, %	Comparator, %	Gout, %	Comparator, %
Wang	2010	11.8%	9.7%	NA	NA
Mak	2011	20.0%	10.0%	6.00%	10.00%
Kim	2015	22.5%	12.5%	NA	NA
Roddy**	2015	26.7%	NA	22.9%	NA
Spaetgens***	2015	17.9%	19.1%	NA	NA
Kuo	2016	12.1%	11.5%	NA	NA
Prior**	2016	12.6%	NA	10.0%	NA
Fu*	2017	15.0%	6.0%	5.3%	4.3%
Fu*	2018	15.0%	6.0%	5.3%	4.3%
Lee***	2018	17.2%	NA	NA	NA
Nguyen	2019	49.4%	49.6%	NA	NA
Zhou	2019	17.2%	Unknown	NA	NA

Notes
*Same data source. **Same data source; Roddy 2015 includes mild depression/anxiety. ***Anxiety and Depression prevalence combined. Abbreviations in abbreviations list at start of document.

Table 3.6 Incidence of depression and anxiety					
		Depression		Anxiety	
First Author	Year of publication	Gout, per 1000 PYs	Comparator, per 1000 PYs	Gout, per 1000 PYs	Comparator, per 1000 PYs
Singh	2018	25.50	14.30	NA	NA
Prior	2015	10.80	10.00	15.20	16.20
Changchien	2015	3.13	2.60	NA	NA
Abbreviations in abbreviations list at start of document.					

3.5.5 Quality appraisal

Quality appraisal was carried out using the Newcastle-Ottawa Scale (NOS). Tabulated summaries are provided in Tables 3.7 to 3.9. The studies are categorised by study design. The two pairs of studies that used the same data sources were independently quality appraised. This was done on the information presented in the full-text articles irrespective of the information provided in the other paper.

3.5.6 NOS table

The letter denotes the option chosen from Table 3.3 (earlier) for each particular question. For the main table: **green** cells mean a star was awarded, whereas red means no star was awarded. For the total stars awarded column 0-3 (**red**) = poor quality, 4-6 (**amber**) = fair quality, and 7-9 (**green**) = good quality.

Table 3.7 NOS Case-control summary										
	Selection				Comparability		Exposure			
First author, year	Adequate case definition	Representativeness of the cases	Selection of Controls	Definition of controls	Comparability of cases and controls based on the design or analysis		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	Total stars awarded (Max = 9)
Kuo, 2016	b	a	a	a	a	b	a	a	a	8
Fu, 2017	a	a	b	a	a	b	a	a	a	8
Fu, 2018	a	a	c	a	a	b	a	a	a	8

Table 3.8 NOS Cohort summary										
	Selection				Comparability		Outcome			
First author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total stars awarded (Max = 9)
Prior, 2015	b	a	a	a	a	b	b	b	a	8
Changchien, 2015	a	a	a	a	a	b	b	a	a	9
Nguyen, 2019	c	a	a	b	-	-	b	b	a	4
Singh, 2018	c	a	a	a	a	b	b	a	a	8

Table 3.9 NOS Cross-sectional summary										
	Selection				Comparability		Outcome			
First author, year	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled		Assessment of the outcome		Sufficient statistical test	Total stars awarded (Max = 9)
Wang, 2010	c	b	b	b	a	b	a		a	5
Mak, 2011	c	b	c	a	-	-	a		b	3
Spaetgens, 2015	b	b	a	c	a	b	c	-	b	4
Kim, 2015	b	a	c	c	a	-	a		a	6
Roddy, 2015	b	b	a	b	-	-	a		a	5
Prior, 2016	b	b	a	b	a	b	a		a	7
Lee, 2019	b	b	b	a	-	-	c	-	a	3
Zhou, 2019	c	b	a	a	a	b	a		a	7

3.5.7 NOS results narrative

3.5.7.1 Case-control studies

Three (20%) of the 15 studies were case-control studies (Fu et al., 2017; Fu et al., 2018; Kuo et al., 2016). Kuo et al. (2016) and Fu et al. (2017;2018) all scored three out of four stars in the Selection section. Fu et al. (2017;2018) did not use controls purely from the community, and Kuo et al. (2016) did not use a validated tool to ascertain gout diagnosis. All three papers received three stars in the Comparability section due to adjusting for age and gender as part of the study design or analysis. All three studies were awarded three stars in the Exposure section. This was due to using secure records as their method of ascertainment of the exposure and using the same method of ascertainment for both cases and controls. All case-control studies achieved high-quality appraisal scores of eight out of nine stars.

3.5.7.2 Cohort studies

Out of the 15 included articles, four (27%) were cohort studies (Prior et al., 2015a; Singh, Jasvinder, Cleveland, 2018; Changchien et al., 2015; Nguyen et al., 2019). Two studies used samples of select users who may not truly represent the average person living with gout and thus did not gain a star (Singh, Jasvinder, Cleveland, 2018; Nguyen et al., 2019). However, all four (100%) drew non-exposed participants from the same community. All four used secure medical records to ascertain the exposure (gout). Three articles demonstrated that the outcome (anxiety or depression) was not present at study inception (Prior et al., 2015a; Singh, Jasvinder, Cleveland, 2018; Changchien et al., 2015). Changechien et al. (2015) and Prior et al. (2015) were awarded the maximum of four stars in this section. Singh and Cleveland (2018) scored three stars, and Nguyen (2019) was awarded two stars in this section. Three of the four studies scored full marks (2 stars) in the comparability section by controlling for age and gender (Prior et al., 2015a; Singh, Jasvinder, Cleveland, 2018; Changchien et al., 2015). Nguyen (2019) received no stars in this section. Two

papers scored full marks (3 stars) in the exposure category (Singh, Jasvinder, Cleveland, 2018; Changchien et al., 2015). All four articles' methods of ascertaining the psychological co-morbidity and adequacy of follow up gained a star each. Nguyen (2019) and Prior et al. (2015) did not state a sufficient follow-up period. Changechien et al. (2015), Prior et al. (2015) and Singh and Cleveland (2018) achieved high-quality scorings of nine, eight, and eight, respectively. Nguyen (2019) received four stars overall, equating to fair quality.

3.5.7.3 Cross-sectional studies

Eight (53%) of the 15 included full-text papers were cross-sectional studies (Wang, Jiunn-Kae, Su & Chou, 2010; Mak et al., 2011; Spaetgens et al., 2015; Roddy et al., 2015; Prior et al., 2016; Zhou et al., 2019; Lee, W. et al., 2019; Kim, Shin & Song, 2015). No article received four stars in the selection section. Wang, Su and Chou (2010) scored no stars in this category. Mak et al. (2011) scored one star as they used a select group of users as their sample, did not justify their sample size, and did not describe respondent vs non-respondent characteristics. The remaining six papers scored two stars in this section. Only one of the eight articles gained a star for justifying sample size (Kim, Shin & Song, 2015). Three articles gained a star for using a validated measurement tool to ascertain the diagnosis of gout (Lee, W. et al., 2019; Mak et al., 2011; Zhou et al., 2019). Three articles received no stars in the comparability section as they did not control for age or gender (Lee, W. et al., 2019; Mak et al., 2011; Roddy et al., 2015). Wang, Su and Chou (2010), Prior et al. (2016), Spaetgens et al. (2015), and Zhou et al. (2019) scored two stars in this section. Kim et al. (2015) received one star for controlling for age. Five studies were awarded three stars in the outcome category. This was because they used a validated measurement tool or independent blind assessment method to ascertain psychological co-morbidity and provided appropriate statistical tests to measure any associations (Wang, Jiunn-Kae, Su & Chou, 2010; Kim, Shin & Song, 2015; Roddy et al., 2015; Zhou et al., 2019). Lee et al. (2019) scored one star in this section as they

used appropriate statistical measurements but did not use a validated tool or record linkage to identify psychological co-morbidity. Spaetgens et al. (2015) scored no stars in this section as they used self-report outcome assessment and did not describe statistical tests appropriately. Prior et al. (2016) and Zhou et al. (2019) were deemed high-quality, with seven stars awarded overall. Kim et al. (2015), Wang, Su and Chou (2010), Roddy et al. (2015), and Spaetgens et al. (2015) received fair quality appraisals with scores of six, five, five, and four, respectively. Lee et al. (2019) and Mak et al. (2011) received poor quality appraisals, both with three stars overall.

3.5.8 Narrative review of results

3.5.8.1 Case-control studies characteristics

Three case-control studies were identified; all were awarded eight out of nine stars during quality appraisal (Fu et al., 2017; Fu et al., 2018; Kuo et al., 2016). However, it is worth noting that Fu et al. (2017) and Fu et al. (2018) used the same source data. Kuo et al. (2016) was based in the UK and used the Clinical Practice Research Datalink (CPRD) which is an extensive primary care consultation database, whilst Fu et al. (2017;2018) was based in China and recruited participants from a secondary care setting. Fu et al. (2017;2018) gout participants had a mean age of 53 years, whereas, in Kuo et al. (2016) it was 63 years. The gout participants in Kuo et al. (2016) were 72.5% male, whereas in Fu et al. (2017;2018) they were 94.7% male. The samples sizes varied considerably between studies, Kuo et al. (2016) used 39,111 gout participants and age- and sex-matched these 1:1 (gout:non-gout comparator) for a total of 78,222 participants. Fu et al. (2017;2018) had 458 participants, comprising 226 gout participants age- and sex-matched to 232 comparators. Kuo et al. (2016) found controls from the same community as cases, whereas Fu et al. (2017;2018) found controls from cases' family members and other hospital patients.

The mode of ascertainment of gout diagnosis differed between the three studies. Kuo et al. (2016) utilised Read codes and searched the Clinical Practice Research Datalink (CPRD)

database. On the other hand, Fu et al. (2017;2018) required patients to fulfil the American College of Rheumatology (ACR) 1977 gout classification criteria. In addition, Fu et al. (2017;2018) measured depression and anxiety, which were ascertained using the PHQ-9 and GAD-7 tools, respectively, whereas Kuo et al. (2016) identified depression using Read codes.

3.5.8.2 Cohort studies characteristics

There were four cohort studies identified, Nguyen et al. (2019) receiving four, Singh and Cleveland (2018) eight, Prior et al. (2015) eight, and Changchien et al. (2015) nine stars on the NOS (Table 3.8). Nguyen et al. (2019) used a community sample from residential care facilities in Australia, Prior et al. (2015) a primary care database, and Singh and Cleveland (2018) and Changchien (2015 used national health insurance databases in the USA and Taiwan respectively. The population in Changchien et al. (2015) was younger (mean age 49.3 years) than those of Prior et al. (2015) (mean age 63 years), Singh and Cleveland (2018) (mean age 75.9) and Nguyen et al. (2019) (median age 86 in males and 87 in females). In addition, Changchien et al. (2015) and Prior et al. (2015) had high proportions of male gout participants at 80.2% and 86%, respectively. In contrast, less than half of the gout study population were male in Nguyen et al. (2019) and Singh and Cleveland (2018), 47% and 29.7%, respectively.

All four studies used a form of electronic health record to identify gout patients (Changchien et al., 2015; Singh, Jasvinder, Cleveland, 2018; Prior et al., 2015a; Nguyen et al., 2019). The non-gout comparators cohorts were all selected from the same source as the gout participants in each study. In addition, Nguyen et al. (2019) had non-age- or non-sex-matched comparators. The remaining three studies used age- and sex-matched comparators (Changchien et al., 2015; Singh, Jasvinder, Cleveland, 2018; Prior et al., 2015a). Three studies included depression (Changchien et al., 2015; Singh, Jasvinder, Cleveland, 2018; Nguyen et al., 2019),

whereas Prior et al. (2015) studied depression and anxiety. Each study used the same method to ascertain exposure and outcome within their study.

3.5.8.3 Cross-sectional studies characteristics

Eight of the studies identified were cross-sectional and received from three to seven stars during quality appraisal with the NOS (Wang, Jiunn-Kae, Su & Chou, 2010; Mak et al., 2011; Spaetgens et al., 2015; Roddy et al., 2015; Prior et al., 2016; Zhou et al., 2019; Lee, W. et al., 2019; Kim, Shin & Song, 2015). Prior et al. (2016) and Roddy et al. (2016) were based in the UK, Lee et al. (2019) and Mak et al. (2011) were based in Singapore, Wang, Su and Chou (2010) Taiwan, Spaetgens (2015) in the Netherlands, Zhou et al. (2019) China, and Kim et al. (2015) in the USA. Four studies obtained participants from secondary care (Wang, Jiunn-Kae, Su & Chou, 2010; Spaetgens et al., 2015; Zhou et al., 2019; Lee, W. et al., 2019), two from primary care (Prior et al., 2016; Roddy et al., 2015), and two via community survey (Kim, Shin & Song, 2015; Wang, Jiunn-Kae, Su & Chou, 2010). Prior et al. (2016) and Roddy et al. (2015) used the same data source. The mean age of gout participants ranged from 52.2 years to 65.8 years in six studies; two studies did not provide this data. In six studies, the proportion of male participants was over 80% (range 81.2% to 92.1%), in two studies it was lower (63.9% and 67.9%) (Wang, Jiunn-Kae, Su & Chou, 2010; Mak et al., 2011; Spaetgens et al., 2015; Roddy et al., 2015; Prior et al., 2016; Zhou et al., 2019; Lee, W. et al., 2019; Kim, Shin & Song, 2015).

Mak et al. (2011), Zhou et al. (2019), and Lee et al. (2019) ascertained gout status according to the clinical application of the ACR gout criteria (Neogi et al., 2015). Wang, Su and Chou (2010) and Kim et al. (2015) identified gout status via participant self-report. Spaetgens et al. (2015) identified gout participants via secondary care electronic health records. Roddy et al. (2015) and Prior et al. (2016) utilised Read codes to identify gout participants.

Three studies had no comparator group (Prior et al., 2016; Roddy et al., 2015; Lee, W. et al., 2019). Spaetgens et al. (2015) used age- and sex-matched general-public but did not state at what ratio or total number. The remaining four studies stated the number of comparators (Wang, Jiunn-Kae, Su & Chou, 2010; Mak et al., 2011; Zhou et al., 2019; Kim, Shin & Song, 2015).

Six studies reported the prevalence of depression in gout participants (Wang, Jiunn-Kae, Su & Chou, 2010; Mak et al., 2011; Roddy et al., 2015; Prior et al., 2016; Zhou et al., 2019; Kim, Shin & Song, 2015). Three studies reported the prevalence of anxiety in the gout participants (Roddy et al., 2015; Prior et al., 2016; Mak et al., 2011). Lee et al. (2019) and Spaetgens et al. (2015) reported a combined prevalence of depression and anxiety. Three studies used the PHQ-9 to ascertain depression (Prior et al., 2016; Roddy et al., 2015; Kim, Shin & Song, 2015), two studies used the EQ-5D (Spaetgens et al., 2015; Lee, W. et al., 2019), one used the GDS-SF (Wang, Jiunn-Kae, Su & Chou, 2010), and one used the HADS-depression tool (Mak et al., 2011). Zhou et al. (2019) used the HAMD-17 and clinical psychologist interview to ascertain depression status. To ascertain anxiety status, two studies used GAD-7 (Prior et al., 2016; Roddy et al., 2015), two studies used EQ-5D (Lee, W. et al., 2019; Spaetgens et al., 2015), and one used HADS-anxiety (Mak et al., 2011).

3.5.8.4 Prevalence of anxiety and depression in people with gout

Fu et al. (2017;2018) and Kuo et al. (2016) reported the prevalence of depression in people with gout to be 15% (vs comparators 6%), and 12.1% (vs comparators 11.45%), respectively. The prevalence of depression reported in Nguyen et al. (2019) was substantially higher in both people with gout and non-gout comparators at 49.35% and 49.61%, respectively. Kim et al. (2015) reported the prevalence of depression as 22.50% in people with gout vs 12.50% in non-gout comparators. When stratifying by sex, 11.0% of males with gout had depression vs 9.50% of male non-gout comparators. Depression in females with gout was reported as 40.6% vs 14.8% in female

non-gout comparators. Wang, Su and Chou (2010) reported depression prevalence in people with gout as 11.8% vs 9.7% in non-gout comparators. Mak et al. (2011) reported the prevalence of depression in gout participants to be 20% vs 10% in non-gout comparators. However, the controls in this study were age- and sex-matched to SLE participants, not the gout cohort. Roddy et al. (2015) used the PHQ-9 and categorised results into no depression (0-4), mild (5-9), moderate (10-14), moderate-severe (15-19) and severe depression (20-27). Including mild depression (PHQ-9 score ≥5), 26.7% of gout participants had depression. Prior et al. (2016) used the same data source as Roddy et al. (2015) but reported that 12.60% of people with gout had depression, defined as a PHQ-9 score of ≥10. Zhou et al. (2019) defined depression as a score of ≥7 on the Hamilton depression scale (HAMD-17) and reported depression prevalence as 17.2% in people with gout.

Fu et al. (2017;2018) reported the prevalence of anxiety in people with gout to be 5.3% vs 4.3% in comparators. Mak et al. (2011) reported a similar prevalence of anxiety (6.0%) in people with gout, but higher (10%) in non-gout comparators. However, as for depression, the controls in this study were age- and sex-matched to SLE participants of this study, rather than matched to people with gout. Roddy et al. (2015) used the GAD-7 and categorised results into no anxiety (0-4), mild (5-9), moderate (10-14), and severe (15-21). Including mild anxiety (GAD-7 ≥5), 22.90% of people with gout had anxiety. Prior et al. (2016) used the same data source as Roddy et al. (2015) and found that 10.0% of people with gout had anxiety defined as a GAD-7 score of ≥10.

Two studies reported the combined prevalence of anxiety and depression in gout participants; Lee et al. (2019) 17.20% and Spaetgens et al. (2019) 17.90%.

3.5.8.5 Incidence of anxiety and depression in people with gout

Three studies reported incidence (per 1000 person-years). For depression in people with gout vs comparators, Singh and Cleveland (2018) reported an incidence of 25.5 vs 14.3, Prior et al. (2015) reported 10.8 vs 10.0, and Changchien et al. (2015) 3.13 vs 2.6, per 1000 person-years. Prior et al.

(2015) reported the incidence of anxiety within gout participants as 15.2 vs 16.2 per 1000 person-years of comparators.

3.5.8.6 Associations between gout, anxiety or depression

Kuo et al. (2016) found a positive association between depression and incident gout. In adjusted models, participants with depression 1 and 10 years before gout diagnosis had ORs of 1.09 (95% CI: 1.04 to 1.15) and 1.11 (95% CI: 1.01 to 1.22) respectively to develop incident gout. The cumulative probability of depression after diagnosis of gout was 24.74% at ten years vs 20.59% in non-gout comparators, and there were increased odds of incident depression after a gout diagnosis (OR 1.19, 95% CI: 1.12 to 1.26).

Changchien et al. (2015) reported a hazard ratio (HR) for incident depression in people with gout (vs non-gout comparators) of 1.18 (95% CI: 1.07 to 1.29) after adjustment for age, sex, co-morbidities, and medication.

Prior et al. (2015) reported that people with gout did not have increased odds of anxiety (HR 1.01, CI 95%: 0.87 to 1.16) or depression (HR 0.87, 95% CI: 0.73 to 1.05).

Kim et al. (2015) identified increased odds for depression in people with gout when adjusted for self-reported co-morbid conditions and metabolic biomarkers (OR 2.65, 95% CI: 1.39 to 5.04). In addition, stratified by sex, females with gout had increased odds of depression (OR 5.0, 95% CI: 1.26 to 19.82), whereas males with gout did not (OR 1.43, 95% CI: 0.57 to 3.55).

Wang, Su and Chou (2010) adjusted for age, sex, marital status, educational level, living arrangement, diabetes mellitus, hypertension, cardiovascular disease, stroke, gouty arthritis, mini-mental state examination. After adjustment, there was no association between gout and depression (OR 1.02, 95%CI: 0.62 to 1.70). However, when stratified by sex, females with gout had increased odds of developing depression (OR 2.46, 95% CI: 1.27 to 4.79), whereas males with gout did not (OR 0.42, 95% CI: 0.18 to 1.04).

3.5.8.7 Characteristics associated with people who have gout and anxiety or depression in people with gout

Fu et al. (2018) stratified the gout population by depression (PHQ-9 of ≥10) or not, and anxiety (GAD-7 of ≥10) or not. People with gout and depression had lower education duration, higher corticosteroid use, more tender joints, and more tophi than those with gout but not depression. There was a positive association between HAQ-DI (OR 3.623, 95% CI: 1.605 to 8.176) and the number of tophi (OR 1.742, 95%CI: 1.048 to 2.895) and depression in people with gout. People with gout and anxiety had lower education duration and were more likely to have nephropathy than those with gout and no anxiety.

Changchien et al. (2015) identified individual variables associated with increased odds of incident depression in people with gout (vs non-gout comparators) were: being male (HR 1.20, 95% CI: 1.07 to 1.34), being younger; ≤34 years old (HR 1.53, 95% CI: 1.23 to 1.91), aged 35-49 (HR 1.26, 95% CI: 1.05 to 1.50), having no co-morbidity (HR 1.23, 95% CI: 1.08 to 1.39), not using NSAIDs (HR 1.21, 95% CI: 1.08-1.36), not using prednisolone (HR 1.21, 95% CI: 1.10 to 1.33).

Furthermore, Changchien et al. (2015) reported that people with gout who were not taking anti-gout treatment (including colchicine, xanthine oxidase inhibitors, and uricosurics) had increased odds of incident depression (HR 1.51, 95% CI: 1.34 to 1.70) compared to those taking anti-gout medication. A protective association was found between people with gout treated with colchicine, xanthine oxidase inhibitor or uricosuric agents, and incident depression (HR 0.70, 95% CI: 0.55 to 0.88).

Singh and Cleveland (2018) reported three different adjusted multivariable models for HRs using the Charlson-Romano co-morbidity score as a continuous variable, categorical variable, and individual co-morbidities[3], all of which were also adjusted for medications, cardiovascular

[3]Each of the 17 Charlson–Romano co-morbidities, and additionally adjusted for hypertension, hyperlipidaemia, and coronary artery disease.

disease and urate-lowering therapy. Utilising the third model (adjusting for individual co-morbidities), the following characteristics were associated with future incident depression in people aged 65 or over with gout, older age groups 75-84 years (HR 1.24, 95% CI: 1.22 to 1.25) and ≥85 years, (HR 1.58, 95% CI: 1.56 to 1.61), being female (HR 1.73, 95% CI: 1.71 to 1.75), black race (HR 0.60, 95% CI: 0.59-0.62), and another race to white or black (HR 0.65, 95% CI: 0.63 to 0.66).

Roddy et al. (2015) reported that people with gout that had mild (OR 3.02, 95% CI: 1.78 to 5.11), moderately-severe (OR 3.41, 95% CI: 1.22 to 9.57) and severe depression (OR 4.55, 95% CI: 1.22 to 17.18) was associated with foot pain[4] in the last month. Furthermore, people with gout and mild (OR 3.27, 95% CI: 1.80 to 5.97), moderately-severe (OR 4.16, 95% CI: 1.28 to 13.51), and severe depression (OR 8.81, 95% CI: 2.04 to 38.01), were also associated with disabling foot pain[5]. There was no association found between any degree of anxiety and foot pain in the last month, or disabling foot pain.

Prior et al. (2016) found an association between ≥3 gout flares within 12 months (OR 2.67, 95% CI: 1.6 to 4.4), and having a history of oligo/polyarticular gout (OR 1.63, 95% CI: 1.1 to 2.4), and anxiety in people with gout. However, after adjustment (for age, gender, deprivation status, BMI, co-morbidities, alcohol consumption and gout characteristics), anxiety was not associated with gout flare frequency or history of oligo/polyarticular gout. Oligo/polyarticular gout was associated with depression (OR 2.01, 95% CI: 1.2 to 3.3) in people with gout during multivariable analysis. When stratified by allopurinol use, both use (OR 2.64, 95% CI: 1.0 to 6.8) and non-use (OR 2.09, 95% CI: 1.1 to 4.0) of allopurinol and having oligo/polyarticular gout was associated with

[4] Foot pain was defined as reporting any pain, aching or stiffness in the feet on most or all days in the past month.

[5] Disabling foot pain was defined as reporting foot pain in the last month (as defined above) and reporting at least one of the ten items of the MFPDI function construct as occurring on most or every day(s), e.g. avoiding walking outside at all, or for long distances.

depression. People with gout who use allopurinol and have ≥3 gout flares over 12 months was associated with depression (OR 2.87, 95% CI: 1.2 to 6.6).

Zhou et al. (2019) identified that people with gout and depression were more likely to have ≥3 gout flares per 12 months, gout flares in multiple joints, and lower serum vitamin D levels (46.4 ±19 vs 57 ±17). In addition, multivariable regression analysis of people with gout showed serum vitamin D levels ≤40.0nmol/L (OR 3.833, 95% CI: 1.406 to 110.453), frequent gout flares (OR 6.136, 95% CI: 1.737 to 21.674) and gout flares in multiple joints (OR 4.454, 95% CI: 1.468 to 13.512), were associated with increased odds of developing depression.

Lee et al. (2019) identified people with gout who had anxiety or depression problems vs those without had higher overall gout concern (83.2 vs 64.5), more gout medication side effects (73.9 vs 63.1), higher unmet gout treatment needs (46.4 vs 35.4), worse well-being during gout flares (70.5 vs 55.8), and greater gout concern during flares (72.8 vs 57.1).

3.6 Discussion of results

This systematic review of the occurrence of psychological morbidity in people with gout identified 15 articles for inclusion. All studies examined the occurrence of depression in people with gout, whereas only seven examined the occurrence of anxiety. Most (eight) studies were cross-sectional, meaning the temporal direction of associations could not be determined. Furthermore, most (seven) studies recruited people with gout from secondary care, despite people with gout being more commonly managed in a primary care setting. Anxiety or depression are commonly co-morbid in people with gout, typically affecting one or two out of every ten people with gout. Additionally, the prevalence of anxiety and depression in people with gout was typically higher than in control groups without gout. Finally, gout characteristics, female sex and low vitamin D levels, were associated with psychological co-morbidity in people with gout across multiple studies, such as flare frequency, the number of joints affected, and gout management.

The prevalence of depression in people with gout ranged between 11.8% to 26.7% in all studies but one. Nguyen et al. (2019) found a prevalence of depression of 49.4%, which may be explained by the older age, care setting (old age residential care facility), and a higher proportion of females in the study population.

The prevalence of anxiety ranged from 5.3% to 10.0% in all studies but one, Roddy et al. (2015) [22.9%]. Roddy et al. (2015) defined anxiety as a GAD-7 score of ≥5, which includes mild anxiety, which likely explains why the prevalence is higher in this study than in other studies. The prevalence of depression and anxiety in people with gout are similar to those reported in people with rheumatoid arthritis (RA), another common inflammatory arthritis. For example, Katchamart et al. (2020) identified that 14.5% of people with RA had some degree of anxiety, and Engelbrecht reported that 22.8% of people have moderate or worse depression. Furthermore, periodic screening for depression in people with RA has been suggested (ElSherbiny, ElSayed Saad, 2020). However, routine screening for psychological co-morbidity is yet to be suggested in people with gout.

There was a paucity of studies reporting the incidence of anxiety (one article) and depression (three articles) in people with gout. Furthermore, the incidence of depression in people with gout varied. These studies took place on different continents where the culture around reporting or identifying mental health conditions may vary, and participants were recruited in various ways, national databases vs primary care, and age eligibility criteria being different. Nevertheless, the incidence of depression was consistently higher in people with gout than non-gout comparators. Interestingly, the single study that reported incidence of anxiety found a marginally lower incidence in people with gout than non-gout comparators.

A plethora of characteristics has been associated with depression in people with gout. Several studies have identified the same or similar features, such as greater frequency of gout flares, having more joints affected, sex (female), age (both being much older, or much younger),

ethnicity (non-white or non-black), and gout treatment (untreated associated with increased risk, and being treated as a protective factor).

The clarity of documentation of the methodology used to perform this systematic review is a key strength of this systematic review. For instance, search terms, syntax, and databases searched have all been listed so that this systematic review can be independently replicated to a high level of precision to yield the same results, corroborating its validity. Furthermore, the search strategy, screening, and extraction processes were done in conjunction with the systematic review team, second, third and fourth reviewers to maximise search results and minimise bias.

A further strength of this systematic review was the high quality of studies included. Typically, studies were fair to good quality: All case-control studies were of good quality, and all but one cohort study was of good quality. On the other hand, cross-sectional studies contained the lowest quality studies, though these lower quality studies did not affect the overall interpretation of this systematic review.

The short time scale available to complete this systematic review was a limitation. Due to this, studies were limited to the English language only as there was insufficient time to request translations. Although multiple full-text articles could not be located for full-text screening in the time available, it is feasible with more time. Additional full-texts could have been located and potentially included (if eligible). In addition, the second reviewer performed data extraction on a subset of articles rather than all 15 for brevity. A high level of congruity was achieved between the first and second reviewers across the dual extracted studies, though with more time, total dual extraction would further minimise the opportunity for data extraction errors to arise.

An unavoidable limitation of this review is the small number of studies identified in the published literature. In addition, the heterogeneity of included studies may limit the generalisability of the results reported. For instance, there were noticeable disparities in

demographics (participants aged ≥18 vs aged ≥65) and geographical location (primarily European or Asian, with no studies were conducted in Africa).

A limitation of any systematic review is publication bias. Publication bias occurs when the outcome of research (often negative or null findings) affects its ability to be published, either directly by the author/s or when manuscripts are submitted for review. A way of assessing publication bias is via funnel plots. Funnel plots are graphical representation for indicating publication bias. Funnel plots assume that well conducted, large, accurate studies will plot near the average (middle of the funnel), whereas studies with lower precision will tend to either side of the average, creating a funnel shape. If the shape deviates from a funnel, there may be publication bias. Assessing publication bias was beyond the scope of this thesis, so it is not possible to comment whether it may have played a role. A systematic review of studies of anxiety and depression in gout by Howren et al. (2020), this study is discussed later in section 6.3, featured funnel plots, which suggested studies of depression in gout may be subject to publication bias, although there were only 4 studies.

A limitation of the systematic review performed during this thesis was the use of a narrative review compared with meta-analysis (as Howren et al. (2020) performed) or a narrative synthesis. A narrative review, as described in the systematic review chapter, is a broad textual based method to summarise findings. A more standardised type of narrative review in systematic reviews is a narrative synthesis. Since inception of the work described in this thesis, reporting guidelines of synthesis without meta-analysis (SWiM) in systematic reviews has been published by Campbell et al (2020). This provides guidance on how to perform synthesis of data describing intervention effects without meta-analysis in a more organised, transparent, and repeatable fashion, which help readability, reliability and reduce error or bias (Campbell et al., 2020).

During the article search phase, a systematic review on a similar topic was identified (Lin, Zhang & Ma, 2018). As it was secondary research, it did not meet eligibility criteria and was

omitted. Lin, Zhang and Ma (2018) identified seven articles that studied gout and depression, but not their determinants. Of the seven included articles, four were not included in my systematic review. The full-text could not be located for two studies during the search time frame of the systematic review (Branco, J. C. et al., 2016; DiBonaventura et al., 2012). The remaining two other studies were excluded during title and abstract search as they appeared to focus on a different outcome, erectile dysfunction (Hsu, Lin & Kao, 2015; Chen et al., 2015). Furthermore, after subgroup analysis according to study types study quality the association between people with gout and depression persisted, Zhang and Ma's (2018) meta-analysis found an association between people with gout and depression (pooled adjusted OR 1.19, 95% CI: 1.11 to 1.29). This appears to be the first meta-analysis into gout and depression. However, they did not include any cohort studies, or studies with gout and anxiety.

The findings of my systematic review highlight several areas where knowledge is still lacking. Incidence of psychological co-morbidity (depression or anxiety) in people with gout was infrequently studied, and there was a general sparsity of research into people with gout and anxiety. Of the studies that did examine anxiety in people with gout, few studies examined associations between anxiety and gout. Furthermore, most studies were cross-sectional, and only four studies were prospective cohort studies, limiting interpretation of the temporal direction of associations. Therefore, further prospective cohort studies are needed to examine the incidence and determinants of anxiety and depression in people with gout.

The systematic review performed justified and shaped the secondary analysis conducted in this thesis. The prevalence and incidence of anxiety and depression in people with gout will be reported to add to the existing (but limited) knowledge base. Gout characteristics associated with depression have been identified, informing the associations to be assessed in the subsequent cohort analysis. In particular, antigout medication and gout characteristics (flare frequency). The

data analysed in this thesis will be from a 5-year prospective cohort study; the temporal aspect of the study design may allow causality to be assessed.

3.8 Conclusion

This systematic review identified a small number of published studies that emphasise the high burden of psychological co-morbidity present in people with gout. Overall, there appears to be an association between gout and depression, and multiple gout characteristics have been reported to increase the odds of having co-morbid depression. However, due to limitations of cross-sectional study designs, the temporal associations of gout and psychological co-morbidity remains to be elucidated. Further studies investigating the prevalence, incidence and characteristics associated with anxiety and depression in people with gout are required to discern these relationships. This knowledge can be used to inform clinical practice, screen for psychological co-morbidity where appropriate and better patient care.

This chapter presented the systematic review of the epidemiology and associations of gout and psychological co-morbidity, containing the methods, results, and discussion. The next chapter describes the methodology of the original cohort study and the methods used in this thesis to describe the prevalence and incidence of psychological co-morbidity (anxiety and depression) in people living with gout and explore associations between gout characteristics and psychological co-morbidity.

Chapter 4 – Methods

The previous chapter presented the systematic review of gout and psychological co-morbidity which detailed the prevalence/incidence of, and characteristics associated with psychological co-morbidity in people living with gout. The systematic review chapter was self-containing and featured the methods, results, and discussion. The systematic review highlighted the paucity of published studies (particularly of prospective design) of psychological co-morbidity in people with gout. This chapter will describe the methods employed in a cohort study to identify the prevalence/incidence of, and gout characteristics associated with psychological co-morbidity in people with gout in UK primary care. It is in two parts: (1) the methods of the secondary analysis carried out for this thesis and (2) the methodology of the cohort study from which data were derived.

4.1 Secondary Analysis: The associations between gout and psychological co-morbidity

The objectives of this chapter were examined by undertaking a secondary analysis of data from the cohort described above.

4.1.1 Objectives

The objectives of this thesis were to perform a secondary analysis of a 5-year prospective cohort study to identify the prevalence/incidence of, and gout characteristics associated with psychological co-morbidity in people with gout in UK primary care.

4.1.2 Design

This analysis used cohort study data collected at baseline, 12-, 36- and 60-months follow-up. A cohort study is a type of observational study where participants are followed forwards in time following exposure to a hypothesised risk factor, to identify the occurrence of an outcome. There are strengths and weaknesses to cohort study designs. The main benefit from a cohort study is the temporal element, which allows the directionality of the relationship between an exposure and outcome to be determined. Other advantages include being able to study multiple outcomes and exposures, and identify incidence. The main limitations of cohort studies are that they are not suitable to study rare outcomes, and due to being followed up over time, loss to follow-up.

4.1.3 Data request

This analysis requested data for use via a written data request form following Keele Clinical Trials Unit Standard Operating Procedures. Only data determined to be relevant to the research objectives were requested. Table 4.1 below shows the variables and corresponding time points that were requested.

Table 4.1 precise data requested

Questionnaire Variable ID	Variable description	Timepoints
Questionnaire data		
a1	How many attacks[6] of gout have you had in the last 12 months? Response: 0, 1, 2, 3, 4, or ≥5	BL, Y1, Y3, Y5
a2	Age of first diagnosis of gout	BL

[6] Flare is now the preferred term to attack (Bursill et al., 2019). However, attack was the term used in the study questionnaires and hence is retained here to correctly represent the questionnaire content.

	Response (in years):	
a3	Are you having an attack of gout at the present? Response: Yes or no	BL, Y1, Y3, Y5
a4	Have you ever had any gout in more than one joint at the same time? (History of oligo/polyarticular attacks) Response: Yes or no	BL, Y1, Y3, Y5
a5 (a5_1)	Do you currently take a tablet called allopurinol for gout? Response: Yes or no	BL, Y1, Y3, Y5
a5_2	If yes, please indicate the dose below Response: 50, 100, 200, 300, 400, 500, 600, 700, 800, 900mg, or Don't know	BL, Y1, Y3, Y5
a5_3	Other dose Response (please specify):	BL, Y1, Y3, Y5
c7_a to c7_i	Co-morbidities – Diabetes, Stroke, High blood pressure, TIA or mini stroke, High levels of cholesterol, fats or lipids in your blood, Kidney failure, Heart attach, Kidney stones, Angina Response: Yes or no	BL
d1_a to d2	PHQ: items, score and categories	BL, Y1, Y3, Y5
d3_a to d3_g	GAD: items, score and categories	BL, Y1, Y3, Y5
f1_a to f1_b	Which of the following best describes your current situation?	BL, Y1, Y3, Y5
f2	Have you taken time off work during the last 6 months because of gout?	BL, Y1, Y3, Y5
g2	Are you Male or Female Response: (tick box)	BL

g3	What is your relationship status	BL
g4_a to g4_b	Did you go on from school to full-time education or university? + If yes age	BL
g5	Is your ethnic origin? Response: White UK/European, Asian, Afro Caribbean, African, Chinese, or Other.	BL
g6_a to g6_c	What is your height? Response: (answer in feet, inches or cm)	BL
g7_a to g7_c	What is your weight? Response: (answer in stones, lbs or kgs)	BL
g8	About how often do you drink alcohol Response: Daily/almost daily, 3-4 times per week, 1-2 times per week, 1-3 times per month, special occasions, never.	BL
g9_a to g9_c	In an average week how many….do you drink? a. Small glasses (175 ml) of wine do you drink (there are roughly 6 glasses per bottle? b. Pints of beer do you drink (includes bitter, lager, stout and ale)? c. Measures of spirits do you drink (includes Whiskey)? Response: (number)	BL
Non-questionnaire data requested		
	IMD	BL
	Age	BL
BL = Baseline. Y1 = Year 1 (12-month) follow-up. Y3 = Year 3 (36-month) follow-up. Y5 = Year 5 (60-month) follow-up.		

4.1.4 Sampling frame

All baseline participants were eligible for inclusion in this study.

4.1.5 Questionnaire domains

Questionnaire domains relevant to this thesis were: gout, general health (co-morbidities), mood (GAD-7 and PHQ-9), gout and work, and demographics. These were then split into exposures/co-variables and outcomes.

4.1.5.1 Exposures/co-variables

Respondents were asked about gout characteristics. Table 4.1 above provides the possible response options:

- How many attacks[7] of gout have you had in the last 12 months?
- How old were you when you were first diagnosed with gout?
- Are you having an attack of gout at present?
- Have you ever had gout in more than one joint at the same time?
- Do you currently take a tablet called allopurinol for gout?
- If yes (to taking allopurinol), please indicate the dose

Respondents were asked if they had ever been diagnosed with or treated for various co-morbidities in the baseline questionnaire: Diabetes, Stroke, High blood pressure, TIA or mini-stroke, High levels of cholesterol, fats or lipids in your blood, Kidney failure, Heart attack, Kidney

[7] As previously mentioned, flare is now the preferred term to attack (Bursill et al., 2019). However, attack was the term used in the study questionnaires and hence is retained here to correctly represent the questionnaire content.

stones, Angina. Respondents were asked if they had ever been diagnosed with, or treated for, these conditions.

Demographic information, such as date of birth, gender, height, weight, and ethnic origin, were asked. Socioeconomic data included questions related to alcohol consumption, relationship status, work situation and attending higher education. The original protocol states that smoking status will be collected at baseline (Chandratre et al., 2012). However, this was not included in the final questionnaires. Deprivation was assigned by the Index of Multiple Deprivation (IMD). IMD is a measure of relative deprivation created by the Ministry of Housing, Communities & Local Government. It is constructed around the following seven domains (and their weighting to the final score): income (22.5%), employment (22.5%), education (13.5%), health and disability (13.5%), crime (9.3%), barriers to living services (9.3%), and living environment (9.3%) (Dibben et al., 2007). An area of England is assigned a score based on these domains and ranked from 1 (most deprived area) to 32,844 (least deprived area). Participants' addresses, specifically postal codes, were used to assign an IMD rank.

4.1.5.2 Outcomes: Anxiety and Depression

GAD-7 and PHQ-9 assessed psychological co-morbidity (anxiety and depression). Both GAD-7 and PHQ-9 are validated tools capable of diagnosing and measuring the severity of generalised anxiety disorder and major depression, respectively (Kroenke, Spitzer & Williams, 2001; Spitzer et al., 2006). This approach allows the severity of psychological co-morbidity to be evaluated objectively from each participant's self-report score, rather than assessing the presence or absence of diagnosed anxiety or depression or their treatment.

4.1.6 Data handling

I had no access to the original study master files, such as those that could link participant survey IDs to identifiable information. Despite this, after successfully requesting and receiving the study data, I stored the anonymised data in a password-protected folder for added security.

The data was provided in an SPSS® file format. The majority of data had been pre-cleaned by the original study staff. Data that had not been cleaned was manually reviewed and cleaned by the author (JH), under guidance from the statisticians (RB and SM).

4.1.7 Sampling

All 1184 participants who responded at baseline and consented to the original cohort study were included in this analysis. When reporting baseline characteristics, anxiety and depression prevalence, all respondents at each time point were included. When analysing new-onset anxiety, participants with a baseline GAD-7 score of ≥10 were excluded. When analysing new-onset depression, participants with a baseline PHQ-9 score of ≥10 were excluded.

4.1.8 Statistical analysis

Analysis of the cleaned dataset was undertaken in SPSS. Descriptive statistics, such as the mean, mode, and percentages, were used to describe the characteristics of participants at baseline, gout-specific characteristics at each time point, and point prevalence of anxiety, and depression at each time point. Where appropriate, means were reported with the one standard deviation figure. The mean and percentages were reported to one decimal place (DP).

To identify associations between gout characteristics and new-onset psychological co-morbidity, binary logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Initially, crude analysis of the association between exposures and outcomes was

undertaken without adjustment. Subsequent exposures were adjusted for age, gender, and IMD. Odds ratios (ORs) were reported with 95% confidence intervals (CI).

Gout duration was calculated by subtracting the age at gout diagnosis from the current age. Validated questionnaires, PHQ-9 and GAD-7, were summated and then classified into validated categorical groups (Kroenke, Spitzer & Williams, 2001; Spitzer et al., 2006). For depression, PHQ-9 scores and severity were:

- 0-4 (non to minimal)
- 5-9 (mild)
- 10-14 (moderate)
- 15-19 (moderately severe)
- 20-27 (severe)

For anxiety, GAD-7 scores and severity were:

- 0-4 (non to minimal)
- 5-9 (mild)
- 10-14 (moderate)
- 15-21 (severe)

Gout duration and flare frequency (in the last 12 months) were split into the same groupings used by Prior et al. (2016): ≤2, 3-8, 9-17, and ≥18 years and 0, 1-2, ≥3 flares, respectively. After deprivation status was assigned at baseline via participant postal code and the corresponding IMD rank, participants' deprivation status was categorised into tertiles. BMI was calculated from height and weight and then categorised into the following groups:

- <25.0kg/m^2 = normal
- 25.0 to 29.9kg/m^2 = overweight
- 30.0 to 34.9kg/m^2 = obese
- ≥35.0kg/m^2 = morbidly obese

All analysis was performed within SPSS® to minimise manual errors. Results were then imported into Microsoft Excel to create results tables. Anxiety was defined as having a GAD-7 score of ≥10. Depression was defined as having a PHQ-9 score of ≥10. The frequency and point prevalence of anxiety and depression at baseline, 12-months, 36-months, and 60-months was calculated.

4.1.8.1 Main analysis – new-onset psychological co-morbidity

The term "new-onset" was preferred to simply 'incident' as the original study criteria did not explicitly exclude people with gout who previously had anxiety or depression, therefore true lifetime incident anxiety or depression could not be ascertained.

To identify new-onset anxiety or depression, participants who scored ≥10 in the GAD-7 (i.e., had anxiety) at baseline were excluded from the anxiety analysis. Equally, participants who scored ≥10 in the PHQ-9 (i.e., had depression) at baseline were excluded from the depression analysis. The remaining participants were eligible for the main and sensitivity analysis.

The exposures of interest were gout characteristics at baseline: frequency of gout flare over the last 12 months, history of oligo- or poly-articular flares, gout duration, and allopurinol use. The outcomes of interest were new-onset anxiety, and new-onset depression (as defined above). Crude analysis was undertaken, followed by adjustment (of age, gender and deprivation) using binary logistic regression.

The main analysis of new-onset psychological co-morbidity required participants to have completed the relevant outcome (GAD-7 for new-onset anxiety, PHQ-9 for new-onset depression) during at least one follow-up time-point. The frequency and incidence of new-onset anxiety and depression were calculated at 12, 36 and 60 months.

4.1.8.2 Sensitivity analysis – new-onset psychological co-morbidity

The sensitivity analysis was performed to explore the effect of attrition on the findings. This analysis was identical to the main analysis except participants had to complete the GAD-7 and PHQ-9 during every follow-up time-point, rather than at least one.

This chapter described the methodology of the original cohort study and the methods used in this thesis to describe the prevalence and incidence of psychological co-morbidity (anxiety and depression) in people living with gout and explore associations between gout characteristics and psychological co-morbidity. The next chapter will report the results of the analysis of data from a prospective cohort study conducted as part of this thesis. This included baseline characteristics, the point prevalence of psychological co-morbidity, new onset of psychological co-morbidity, and associations between gout characteristics and new-onset psychological co-morbidity.

4.2 Cohort study overview

This was a prospective cohort study. Ethical approval was granted by the North West- Liverpool East Research Ethics Committee (Reference number 12/NW/0297). The study protocol and baseline findings have previously been published (Chandratre et al., 2012; Prior et al., 2016).

4.2.1 Objectives

The original primary objectives of the cohort study were three-fold (Chandratre et al., 2012):

1. To describe the spectrum of HRQOL in patients with gout and its distribution by demographic, socio-economic and anthropometric characteristics
2. To describe the prevalence, onset, persistence and progression of chronic foot problems in gout over 3 years

3. To examine:
    a) Cross-sectional associations between poor HRQOL and gout disease characteristics and treatment, chronic foot problems, co-morbidities, and psychosocial factors in gout
    b) Change in HRQOL in gout over 3 years and determine which of the associated factors may predict deterioration or recovery

4.2.2 Design

The observational prospective cohort study comprised of six phases:

1. Baseline questionnaire
2. Medical record review
3. 6-month follow-up questionnaire
4. 12-month follow-up questionnaire
5. 24-month follow-up questionnaire
6. 36-month follow-up questionnaire

Ethics committee approval was later obtained for an amendment to add additional follow-up questionnaires at 48 and 60 months.

4.2.3 Sampling frame

4.2.3.1 Inclusion criteria

Patients aged ≥18 who were registered with 20 general practices in the West Midlands, England, who had a Read code for gout during the previous two years or prescription for colchicine or allopurinol.

4.2.3.2 Exclusion criteria

Patients were ineligible if they were aged <18 years, unable to complete the questionnaires in English, or were considered vulnerable, such as having a significant cognitive impairment or severe enduring mental illness.

4.2.4 Patient identification and communication

The West Midlands North (WMN) Primary Care Research Network (PCRN) identified participants fulfilling the inclusion criteria by an electronic search of primary care records in 20 participating general practices. Read codes for a consultation for gout or a prescription for allopurinol or colchicine within the last two years were used to identify patients. The following Gout-related Read codes (terms) were used:

- C34 (Gout)
- N023 (Gouty arthritis)
- EGTON 227 (Gout NOS)
- OX2740G (GOUT acute/ox)
- 1443 (H/O: gout)
- EMISR4QG01 (Gouty tophi + Gout NOS)
- 2D52 (O/E – auricle of ear – tophi)
- 669 (Gout monitoring)

The lead general practitioner in each practice identified potentially vulnerable patients who were omitted from the mailing list. This list was screened for deceased patients, or those who had left the practice, before mailing the baseline survey, thus minimising insensitive patient contact. The remaining eligible patients were mailed information about the study, consent form, baseline survey and pre-paid return envelope. After two weeks, a reminder postcard was mailed to non-responders. A further questionnaire was mailed to non-responders after another two weeks.

Consent to access patient GP records for the period two years before study enrolment and through the 5-year follow-up phase, was requested. Data collected from the medical record included gout consultations, co-morbidities, prescriptions, and referrals.

4.2.5 The baseline questionnaire

The questionnaire contained seven sections: gout symptoms and treatment, how gout affects daily life, general health (co-morbidities and physical function), mood (depression and anxiety), foot and joint pain, work situation, and demographics. The parts of the questionnaire relevant to this thesis are discussed in more detail in section 4.2.5. Table 4.1 summarises the information collected at each time point.

Table 4.2 summary of questionnaire domains and questions at corresponding time points								
Questionnaire		**Timepoint**						
Domain	**Questions**	**Baseline**	**6 months**	**12 months**	**24 months**	**36 months**	**48 months**	**60 months**
Gout	Gout flare frequency	x	x	x	x	x	x	x
	Age at gout diagnosis	x	x	x	x	x	x	x
	Current flare	x	x	x	x	x	x	x
	History of Oligo/polyarticular gout	x	x	x	x	x	x	x
	Currently Taking allopurinol	x	x	x	x	x	x	x
Gout and daily life	GIS	x	x	x	x	x	x	x
	IPQ-R	x	x	x	x	x	x	x
General health	SF-36	x	x	x	x	x	x	x
	HAQ-DI	x	x	x	x	x	x	x
	Pain NRS	x	x	x	x	x	x	x
	Global health assessment	x	x	x	x	x	x	x
	Co-morbidities	x						
Mood	GAD-7	x		x		x		x
	PHQ-9	x		x		x		x
Foot and joint pain	Hallux valgus	x		x		x		x
	Foot pain	x		x		x		x
	Foot pain location	x		x		x		x
	Foot function	x		x		x		x
	Foot consultations	x		x		x		x
	Joint pain	x		x		x		x
Gout and work	Employment status	x		x		x		x
	Time off due to gout	x		x		x		x
	Ability to work due to gout	x		x		x		x
	Ability to work due to joint issues	x		x		x		x
Demographics	Date of birth	x						
	Sex	x						
	Relationship status	x						
	Education	x						
	Ethnic origin	x						
	Height	x		x		x		x
	Weight	x		x		x		x
	Alcohol consumption	x						
	Smoking status	x						

Abbreviations: (GIS) Gout Impact Scale, (IPQ-R) Illness Perception Questionnaire-Revised, (SF-36) Short form-36, (HAQ-DI) Health Assessment Questionnaire-Disability index, (NRS) Numeric Rating Scale, (GAD-7) General Anxiety Disorder-7, (PHQ-9) Patient Health Questionnaire-9

4.2.6 Data handling

Trained members of staff processed completed questionnaires, and raw data were inputted into a study database. Approximately 10% of questionnaires were checked randomly by another study team member against the database to assess the quality and accuracy of data entry. Data cleaning took place before analysis.

4.2.7 Follow-up

Participants were mailed follow-up questionnaires at 6-, 12-, 24-, 36-, 48- and 60-month post-recruitment. Pre-paid return envelopes were supplied. Not all questions within each domain were repeated at every follow-up time point; for instance, gender and ethnicity were asked at baseline only, whereas height and weight were asked at every timepoint. PHQ-9 and GAD-7 were collected only at baseline, 12-, 36- and 60- months. Table 4.2 above summarises questions from each domain and the timepoint they are asked at. The same reminder process was followed as at baseline.

4.2.8 Sample size

As reported by Chandratre et al. (2012) in the study protocol paper, a sample size of 882 would allow the smallest meaningful difference in HRQOL of 0.2 standard deviation units to be detected between two groups (441 subjects per group) defined in terms of frequency of gout attacks (<2 attacks, ≥two attacks per year) using a linear mixed model (significance 0.05, power 90%, autocorrelation 0.8). Allowing for 70% response at baseline and 30% dropout over the follow-up period would require 1800 people with gout to be contacted at baseline (Chandratre et al., 2012).

Chapter 5 - Results

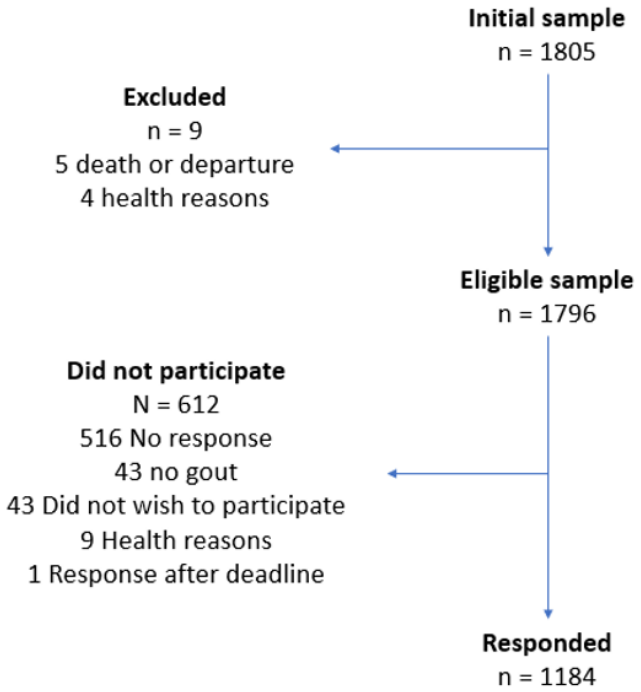
The previous chapter described the methodology of the original cohort study and the methods used in the secondary analysis to identify the prevalence/incidence of, and gout characteristics associated with new-onset psychological co-morbidity in people with gout in UK primary care. This chapter will report the findings of the secondary analysis.

5.1 Results

5.1.1 Sample response

As previously reported, the mailed population comprised 1805 people living with gout registered with one of 20 participating general practices in the West Midlands (Roddy et al., 2015). One recipient was excluded before mailing the baseline questionnaires due to death or departure. A further eight recipients were excluded during mailing due to death, departure, or health reasons. This left 1796 eligible respondents, of which 1184 (66%) returned the baseline questionnaire. A flow chart of the sample response is shown in Figure 5.1. below. Over 90% (1076) consented to medical record review (Roddy et al., 2015). Non-responders to the baseline questionnaire were younger (60.1 vs 65.6 years) and less likely to be males (77.8%) vs. responders (83.6%) (Roddy et al., 2015).

Figure 5.1 Flow chart of sample response



5.1.2 Baseline characteristics

Baseline characteristics have previously been reported by Prior et al. (2016), Chandratre et al. (2018) and Roddy et al. (2015), and are summarised in Table 5.1, along with responder vs non-responder characteristics at follow-up. The mean age was 65.6 years. Nine hundred and ninety (83.6%) were male, 809 (69.4%) married, 1126 (97.6%) white UK/European, 896 overweight or obese (80.4%), and 538 fully retired (47.4%). Two hundred and seventy-three drank alcohol daily (23.4%), and 870 did not attend further education (77.7%). The most common co-morbidity was hypertension 731 (61.7%), followed by hyperlipidaemia 508 (42.9%) and then diabetes mellitus 205 (17.3%) (Prior et al., 2016; Roddy et al., 2015; Chandratre, Priyanka et al., 2018).

Gout specific characteristics are summarised in Table 5.2. At baseline, the mean age of gout diagnosis was 53.4 years and the mean duration of gout was 11.9 years. Seven hundred and twenty-five (64.6%) participants reported having at least one gout flare in the 12 months preceding baseline, 436 (38.5%) had ever had an oligo- or poly-articular flare, and 630 (56.3%) were taking allopurinol. The most common dose of allopurinol was 300mg (48.9%).

The point prevalence of anxiety and depression at baseline have previously been reported by Prior et al. 2016. At baseline, 1094 (92.4%) completed the GAD-7, with 109 (10.0%) scoring ≥10, and 1042 (88.0%) completed the PHQ-9, with 131 (12.6%) scoring ≥10 (Table 5.3).

Table 5.1 Baseline characteristics and comparison of baseline characteristics of responders vs nonresponders at future follow-up								
	Baseline	12 months		36 months		60 months	
	Responders (n=1184)	Responders (n=721)	Non-responders (n=463)	Responders (n = 605)	Non-responders (n=579)	Responders (n=411)	Non-responders (n=773)
Age (mean [SD]) n = 1184	65.6 (12.5)	65.4 (11.7)	66.0 (13.7)	64.6 (11.5)	66.7 (13.4)	64.0 (10.7)	66.5 (13.3)
Gender (male [%]) n = 1184	990 (83.6%)	629 (87.2%)	361 (78.0%)	541 (89.4%)	449 (75.5%)	378 (92.0%)	612 (79.2%)
Relationship status n = 1165							
Married	809 (69.4%)	495 (69.5%)	314 (69.3%)	432 (72.1%)	377 (66.6%)	304 (74.9%)	505 (66.5%)
Widowed	114 (9.8%)	67 (9.4%)	47 (10.4%)	45 (7.5%)	69 (12.2%)	20 (4.9%)	94 (12.4%)
Co-habiting	73 (6.3%)	43 (6.0%)	30 (6.6%)	37 (6.2%)	36 (6.4%)	25 (6.2%)	48 (6.3%)
Divorced	69 (5.9%)	45 6.3%)	24 (5.3%)	34 (5.7%)	35 (6.2%)	22 (5.4%)	47 (6.2%)
Separated	22 (1.9%)	14 (2.0%)	8 (1.8%)	9 (1.5%)	13 (2.3%)	6 (1.5%)	16 (2.1%)
Single	78 (6.7%)	48 (6.7%)	30 (6.6%)	42 (7.0%)	36 (6.4%)	29 (7.1%)	49 (6.5%
Ethnic origin (White UK/European) n = 1154	1126 (97.6%)	698 (98.2%)	428 (96.6%)	589 (98.3%)	537 (96.8%)	400 (98.5%)	726 (97.1%)
Deprivation (IMD - tertiles)							
Least	384 (32.4%)	241 (33.4%)	143 (30.9%)	192 (31.7%)	192 (33.2%)	137 (33.3%)	247 (32.0%)
Middle	398 (33.6%)	265 (36.8%)	133 (28.7%)	236 (39.0%)	162 (28.0%)	165 (40.1%)	233 (30.1%)
Most	402 (34.0%)	215 (29.8%)	187 (40.4%)	177 (29.3%)	225 (38.9%)	109 (26.5%)	293 (37.9%)
Attended further education n = 1119							
Yes	249 (22.3%)	175 (25.2%)	74 (17.4%)	157 (26.9%)	92 (17.2%)	107 (26.8%)	142 (19.7%)
If yes - age finished (mean [SD]) n =247	20.4 (8.5)	20.6 (7.4)	19.9 (10.8)	20.6 (7.8)	20.0 (9.7)	21.6 (8.3)	19.5 (8.6)
BMI n = 1113							
<25	222 (19.9%)	136 (19.7%)	86 (20.3%)	108 (18.6%)	114 (21.5%)	74 (18.8%)	148 (20.6%)
25.0 - <30.0	511 (45.9%)	323 (46.9%)	188 (44.3%)	262 (45.0%)	249 (46.9%)	191 (48.5)	320 (44.5%)
30.0 - <35.0	258 (23.2%)	159 (23.1%)	99 (23.3%)	146 (25.1%)	112 (21.1%)	89 (22.6%)	169 (23.5%)
>35	122 (11.0%)	71 (10.3%)	51 (12.0%)	66 (11.3%)	56 (10.5%)	40 (10.2%)	82 (11.4%)
Alcohol consumption n = 1167							
Daily/almost daily	273 (23.4%)	182 (25.5%)	91 (20.1%)	163 (27.1%)	110 (19.5%)	107 (26.2%)	166 (21.9%)
3-4 times per week	263 (22.5%)	163 (22.8%)	100 (22.1%)	139 (23.1%)	124 (21.9%)	106 (26.0%)	157 (20.7%)
1-2 times per week	254 (21.8%)	156 (21.8%)	98 (21.7%)	132 (21.9%)	122 (21.6%)	87 (21.3%)	167 (22.0%)
1-3 times per month	109 (9.3%)	71 (9.9%)	38 (8.4%)	60 (10.0%)	49 (8.7%)	43 (10.5%)	66 (8.7%)
Special occasions	155 (13.3%)	86 (12.0%)	69 (15.3%)	62 (10.3%)	93 (16.5%)	36 (8.8%)	119 (15.7%)
Never	113 (9.7%)	57 (8.0%)	56 (12.4%)	46 (7.6%)	67 (11.9%)	29 (7.1%)	84 (11.1%)

Table 5.1 Continued									
	Baseline		**12 months**			**36 months**			**60 months**
	Responders (n=1184)		**Responders (n=721)**	**Non-responders (n=463)**		**Responders (n = 605)**	**Non-responders (n=579)**		**Responders (n=411)**	**Non-responders (n=773)**
Co-morbidity n = 1184										
Angina	147 (12.4%)		85 (11.8%)	62 (13.4%)		68 (11.2%)	79 (13.6)		41 (10.0%)	106 (13.7%)
Diabetes mellitus	205 (17.3%)		118 (16.4%)	87 (18.8%)		94 (15.5%)	111 (19.2%)		59 (14.4%)	149 (18.9%)
hyperlipidaemia	508 (42.9%)		315 (43.7%)	193 (41.7%)		274 (45.3%)	234 (40.4%)		177 (43.1%)	331 (42.8%)
hypertension	731 (61.7%)		440 (61.0%)	291 (62.9%)		364 (60.2%)	367 (63.4%)		230 (56.0%)	501 (64.8%)
Kidney failure	56 (4.7%)		36 (5.0%)	20 (4.3%)		21 (3.5%)	35 (6.0%)		15 (3.6%)	41 (5.3%)
Kidney stones	81 (6.8%)		48 (6.7%)	33 (7.1%)		45 (7.4%)	36 (6.2%)		36 (8.8%)	45 (5.8%)
Myocardial infarction	119 (10.1%)		70 (9.7%)	49 (10.6%)		49 (8.1%)	70 (12.1%)		32 (7.8%)	87 (11.3%)
Stroke	37 (3.1%)		24 (3.3%)	13 (2.8%)		14 (2.3%)	23 (4.0%)		7 (1.7%)	30 (3.9%)
Tia	62 (5.2%)		33 (4.6%)	29 (6.3%)		30 (5.0%)	32 (5.5%)		23 (5.6%)	39 (5.0%)
Current work status n = 1136										
Working full-time in a paid job	316 (27.8%)		197 (28.0%)	119 (27.5%)		179 (30.4%)	137 (25.0%)		129 (31.9%)	187 (25.5%)
Working part-time in a paid job	77 (6.8%)		54 (7.7%)	23 (5.3%)		48 (8.2%)	29 (5.3%)		39 (9.7%)	38 (5.2%)
Fully retired	538 (47.4%)		324 (46.1%)	214 (49.4%)		244 (41.5%)	294 (53.6%)		158 (39.1%)	380 (51.9%)
GAD-7 n = 1094	109 (10.0%)		60 (8.8%)	49 (11.9%)		47 (8.2%)	62 (12.0%)		23 (5.8%)	86 (12.4%)
PHQ-9 n = 1042	131 (12.6%)		77 (11.8%)	54 (13.8%)		59 (10.5%)	72 (14.9%)		30 (7.7%)	101 (15.5%)

5.1.3 Follow-up

Characteristics of responders and non-responders at 12 and 36 months described below have been published previously (Watson et al., 2020). Characteristics at 60 months were analysed for the first time by the author (JH) specifically for this thesis. At all follow-up time-points, responders were younger, less likely to be male, and less likely to have anxiety or depression than non-responders. Amongst responders, fewer responders reported having at least one flare in the preceding 12 months at each follow-up time-point than at baseline (baseline 64.6%, follow-ups 41.0-45.3%). The proportion of responders reporting ever having had an oligo- or poly-articular flare did not appear to change over time. Amongst responders, the proportion reporting taking allopurinol increased gradually from 56.3% at baseline to 68.9% at 60 months.

At 12 months, 721 participants responded (mean age 65.4 years, 87.2% male). Non-responders (n=463) were older (66.0 years), and less likely to be male (78.0%). In responders, in the preceding 12 months, 296 (42.3%) reported having at least one gout flare, 299 (42.7%) ever having oligo- or poly-articular flares, and 435 (62.9%) taking allopurinol. The most common dose of allopurinol was 300mg (50.0%).

At 36 months, 605 participants responded (mean age 64.6 years, 89.4% male). Non-responders (n=579) were older (66.7 years), and less likely to be males (77.5%). In responders, in the preceding 12 months, 263 (45.3%) reported having at least one gout flare, 239 (40.9%), ever having oligo- or poly-articular flares, and 377 (65.7%) taking allopurinol. The most common dose of allopurinol was 300mg (50.3%).

At 60 months, 411 participants responded (mean age 64.0 years, 92.0% male). Non-responders (n=773) were older (66.5 years), and less likely to be males (79.2%). In responders, in the preceding 12 months, 164 (41.0%) reported having at least one gout flare, 158 (39.4%) ever having oligo- or poly-articular flares, and 273 (68.9%) taking allopurinol. The most common dose of allopurinol was 300mg (49.4%).

Table 5.2 Gout specific characteristics per time point								
	Baseline (n = 1184)		1 Year (n =721)		3 Years (n = 605)		5 Years (n = 411)	
	Question respondents, n	Answer frequency, n (%)	Question respondents, n	Answer frequency, n (%)	Question respondents, n	Answer frequency, n (%)	Question respondents, n	Answer frequency, n (%)
Age of first diagnosis of gout (Years - mean [SD])	1098	53.4 (15.9)						
Gout duration (mean [SD])	1095	11.9 (21.1)						
Gout flares in last 12 months	1123		701		580		400	
0		398 (35.4%)		405 (57.8%)		317 (54.7%)		236 (59%)
1 - 2		418 (37.2%)		188 (26.9%)		154 (26.6%)		98 (24.5%)
≥3		307 (27.3%)		108 (15.4%)		109 (18.8%)		66 (16.6%)
Currently experiencing a gout flare (yes)	1135	132 (11.6%)	701	64 (9.1%)	584	53 (9.1%)	400	34 (8.5%)
Ever experienced gout in more than one joint (yes)	1131	436 (38.5%)	700	299 (42.7%)	585	239 (40.9%)	401	158 (39.4%)
Currently using allopurinol (yes)	1120	630 (56.3%)	692	435 (62.9%)	574	377 (65.7%)	396	273 (68.9%)
Allopurinol dose (mode dose - range: 50mg to 900mg)	618		426		379		271	
Modal dose		300mg (48.9%)		300mg (50.0%)		300mg (50.3%)		300mg (49.4%)
2nd most common		100mg (34.3%)		100mg (30.8%)		100mg (29.3%)		100mg (29.5%)
3rd most common		200mg (9.5%)		200mg (9.4%)		200mg (10.9%)		200mg (10.3%)
Figures are n (%) unless stated otherwise.								

Table 5.3 Point prevalence of anxiety and depression per time point								
	Baseline (n = 1184)		1 Year (n =721)		3 Years (n = 605)		5 Years (n = 411)	
	Question respondents, n (%)	Anxiety (GAD-7) or depression (PHQ-9), n (%)	Question respondents, n (%)	Anxiety (GAD-7) or depression (PHQ-9), n (%)	Question respondents, n (%)	Anxiety (GAD-7) or depression (PHQ-9), n (%)	Question respondents, n (%)	Anxiety (GAD-7) or depression (PHQ-9), n (%)
GAD-7	1094 (92.4%)	109 (10.0%)	685 (95.0%)	61 (8.5%)	582 (96.2%)	49 (8.4%)	392 (95.4%)	26 (6.6%)
PHQ-9	1042 (88.0%)	131 (12.6%)	680 (94.3%)	81 (11.9%)	564 (93.2%)	63 (11.2%)	394 (95.9%)	38 (9.6%)
Figures are n (%) unless stated otherwise.								

5.1.5 Follow-up: Point prevalence of psychological co-morbidity

GAD-7 and PHQ-9 were completed by 685 (95.0%) and 680 (94.3%) responders respectively at 12 months, 582 (96.2%) and 564 (93.2%) at 36 months, and 392 (95.4%) and 394 (95.9%) at 60 months. The highest point prevalence of both anxiety and depression was seen at baseline and the lowest at 60 months. The point prevalence of both anxiety and depression amongst responders got gradually lower over time. The point prevalence of anxiety was 8.5% (n=61) at 12 months, 8.4% (n=49) at 36 months, and 6.6% (n=26) at 60 months. The point prevalence of depression was 11.9% (n=81) at 12 months, 11.2% (n=63) at 36 months, and 9.6% (n=38) at 60 months

5.1.6 Main analysis

5.1.6.1 New-onset anxiety

A total of 656 respondents who did not report anxiety (GAD-7 <10) at baseline completed the GAD-7 during at least one follow-up time-point. Of these, 7.5% (n=49) reported onset of anxiety (GAD-7 ≥10) (table 5.4). On univariable and adjusted multivariable analyses, having a history of oligo- or poly-articular gout flares were associated with new-onset anxiety (OR 2.44, 95% 1.34 to 4.44; 2.31, 1.26 to 4.23, respectively). No other gout characteristics were associated with the onset of anxiety on crude or multivariable analysis.

5.1.6.2 New-onset depression

In total, 609 respondents who did not report depression (PHQ-9 <10) at baseline completed the PHQ-9 during at least one follow-up time-point. Of these, 9.2% (n=56) reported onset of depression (PHQ-9 ≥10) (Table 5.5). Univariable and adjusted multivariable analyses found that having a history of gout flares in the preceding 12 months and oligo- or poly-articular gout preceding baseline was not associated with the onset of depression. On adjusted multivariable

analysis, gout duration of 9-17 years (OR 2.69, 1.05 to 6.90) and allopurinol use (OR 1.93, 95% CI: 1.01 to 3.69) were associated with the onset of depression. No other gout characteristics were associated with the onset of depression on crude or multivariable analyses.

Table 5.4 Associations between gout characteristics and developing anxiety (GAD ≥10); participants who completed a GAD questionnaire at at least one follow-up timepoint

	Developed new-onset anxiety				Crude OR (95% CI)	Adjusted OR (95% CI)
	No	%	Yes	%		(Age, gender, and deprivation)
Frequency of gout flares over the last 12 months						
n = 632						
0	226	95%	13	5%	Ref	Ref
1-2	220	92%	19	8%	1.50 (0.72 to 3.11)	1.32 (0.63 to 2.78)
≥3	138	90%	16	10%	2.02 (0.94 to 4.32)	1.75 (0.80 to 3.81)
Total	584	92%	48	8%		
Oligo- or poly-articular gout						
n = 632						
No	371	95%	20	5%	Ref	Ref
Yes	213	88%	28	12%	**2.44 (1.34 to 4.44)[a]**	**2.31 (1.26 to 4.23)[a]**
Total	584	92%	48	8%		
Gout duration (years)						
n = 619						
≤2	145	93%	11	7%	Ref	Ref
3-8	143	91%	14	9%	1.29 (0.57 to 2.94)	1.41 (0.61 to 3.28)
9-17	130	93%	10	7%	1.01 (0.42 to 2.47)	1.31 (0.52 to 3.27)
≥18	154	93%	12	7%	1.03 (0.44 to 2.40)	1.44 (0.59 to 3.51)
Total	572	92%	47	8%		
Allopurinol use (at baseline)						
n = 626						
No	237	94%	15	6%	Ref	Ref
Yes	343	92%	31	8%	1.43 (0.75 to 2.70)	1.58 (0.82 to 3.04)
Total	580	93%	46	7%		

[a] *P* ≤ 0.05

Table 5.5 Associations between gout characteristics and developing depression (PHQ ≥10); participants who completed a PHQ questionnaire at at least one follow-up timepoint

	Developed new-onset depression				Crude OR (95% CI)	Adjusted OR (95% CI)
	No	%	Yes	%		(Age, gender, and deprivation)
Frequency of gout flares over the last 12 months						
n = 587						
0	215	94%	14	6%	Ref	Ref
1-2	196	89%	25	11%	1.96 (0.99 to 3.88)	2.00 (0.997 to 4.00)
≥3	124	91%	13	9%	1.61 (0.73 to 3.54)	1.59 (0.72 to 3.55)
Total	535	91%	52	9%		
Oligo- or poly-articular gout						
n = 587						
No	343	92%	28	8%	Reg	Ref
Yes	192	89%	24	11%	1.53 (0.86 to 2.72)	1.55 (0.86 to 2.77)
Total	535	91%	52	9%		
Gout duration (years)						
n = 576						
≤2	132	94%	8	6%	Ref	Ref
3-8	135	90%	15	10%	1.83 (0.75 to 4.47)	2.03 (0.82 to 5.06)
9-17	115	89%	14	11%	2.01 (0.81 to 4.96)	**2.69 (1.05 to 6.90)[a]**
≥18	143	91%	14	9%	1.62 (0.66 to 3.97)	2.28 (0.89 to 5.88)
Total	525	91%	51	9%		
Allopurinol use (at baseline)						
n =580						
No	212	94%	14	6%	Ref	Ref
Yes	316	89%	38	11%	1.82 (0.96 to 3.44)	**1.93 (1.01 to 3.69)[a]**
Total	528	91%	52	9%		

[a] ***P* ≤ 0.05**

5.1.7 Sensitivity analysis

5.1.7.1 New-onset anxiety

A total of 311 respondents who did not report anxiety (GAD-7 <10) at baseline completed the GAD-7 at every follow-up time-point. Of these, 8.4% (n=26) reported an onset of anxiety (GAD-7 ≥10) during the follow-up period (Table 5.6). On univariable analysis, having a history of oligo- or poly-articular gout flares were associated with an increased risk of the onset of anxiety (OR 2.40, 95%CI 1.05 to 5.49). However, this association attenuated and lost statistical significance on multivariable adjustment. No other gout characteristics were associated with the onset of anxiety on crude or multivariable analysis.

5.1.7.2 New-onset depression

In total, 300 respondents who did not report depression (PHQ-9 <10) at baseline completed the PHQ-9 at every follow-up time-point. Of these, 9.3% (n=28) reported onset of depression (PHQ-9 ≥10) in the follow-up period (Table 5.7). No gout characteristics were associated with the onset of depression on crude or multivariable anal

Table 5.6 Associations between gout characteristics and developing anxiety (GAD ≥10); participants who completed a GAD questionnaire at all follow-up timepoints

	Developed new-onset anxiety				Crude OR (95% CI)	Adjusted OR (95% CI)
	No	%	Yes	%		(Age, gender, and deprivation)
Frequency of gout flares over the last 12 months						
n = 302						
0	111	95%	6	5%	Ref	Ref
1-2	109	90%	12	10%	2.04 (0.74 to 5.62)	1.88 (0.66 to 5.39)
≥3	57	89%	7	11%	2.27 (0.73 to 7.08)	1.73 (0.51 to 5.83)
Total	277	92%	25	8%		
Oligo- or poly-articular gout						
n = 302						
No	181	94%	11	6%	Ref	Ref
Yes	96	87%	14	13%	**2.40 (1.05 to 5.49)[a]**	2.20 (0.93 to 5.22)
Total	277	92%	25	8%		
Gout duration (years)						
n = 296						
≤2	67	93%	5	7%	Ref	Ref
3-8	60	88%	8	12%	1.79 (0.55 to 5.76)	1.80 (0.50 to 6.47)
9-17	65	92%	6	8%	1.24 (0.36 to 4.25)	1.84 (0.48 to 7.05)
≥18	79	93%	6	7%	1.02 (0.30 to 3.48)	1.63 (0.42 to 6.30)
Total	271	92%	25	8%		
Allopurinol use (at baseline)						
n = 300						
No	108	94%	7	6%	Ref	Ref
Yes	167	90%	18	10%	1.66 (0.67 to 4.12)	1.79 (0.69 to 4.66)
Total	275	92%	25	8%		

[a] ***P* ≤ 0.05**

Table 5.7 Associations between gout characteristics and developing depression (PHQ ≥10); participants who completed a PHQ questionnaire at all follow-up timepoints

	Developed new-onset depression				Crude OR (95% CI)	Adjusted OR (95% CI)
	No	%	Yes	%		(Age, gender, and deprivation)
Frequency of gout flares over the last 12 months						
n = 292						
0	103	94%	7	6%	Ref	Ref
1-2	106	87%	16	13%	2.22 (0.88 to 5.62)	2.18 (0.84 to 5.65)
≥3	56	93%	4	7%	1.05 (0.30 to 3.75)	0.81 (0.22 to 2.99)
Total	265	91%	27	9%		
Oligo- or poly-articular gout						
n = 293						
No	178	91%	18	9%	Reg	Ref
Yes	88	91%	9	9%	1.01 (0.44 to 2.34)	0.99 (0.42 to 2.34)
Total	266	91%	27	9%		
Gout duration (years)						
n = 288						
≤2	70	95%	4	5%	Ref	Ref
3-8	62	91%	6	9%	1.69 (0.46 to 6.28)	1.86 (0.47 to 7.36)
9-17	60	87%	9	13%	2.63 (0.77 to 8.96)	3.61 (0.96 to 13.54)
≥18	69	90%	8	10%	2.03 (0.58 to 7.05)	3.10 (0.80 to 11.95)
Total	261	91%	27	9%		
Allopurinol use (at baseline)						
n = 288						
No	106	94%	7	6%	Ref	Ref
Yes	155	89%	20	11%	1.95 (0.80 to 4.78)	1.97 (0.79 to 4.93)
Total	261	91%	27	9%		

[a] ***P* ≤ 0.05**

This chapter reported the results of the analysis of data from a prospective cohort study conducted as part of this thesis. The next chapter will discuss these findings and their implications for clinical practice and future research.

Chapter 6 – Discussion

The previous chapter reported the results of the analysis of data from the prospective cohort study. This chapter will summarise the principal findings of the prospective cohort study. These will be compared with existing literature in conjunction with the systematic review reported in chapter 3. Next, the strengths, weaknesses and limitations of this study are discussed. This is followed by implications for clinicians, future research, and a summative conclusion.

6.1 Discussion

The first objective of this thesis was to establish the existing knowledge base about psychological co-morbidity (anxiety and depression) in people with gout by performing a systematic review. The identification of the existing data concerning the prevalence and incidence of psychological co-morbidity in people with gout, and associations between psychological co-morbidity and gout helped shape the objectives for empirical data analysis. The detailed findings of the systematic review are discussed in section 3.8. The second objective of this thesis was to analyse data from a primary care-based five-year prospective cohort study to determine the prevalence and incidence of psychological co-morbidity in people living with gout, and identify associations between gout characteristics and new-onset psychological co-morbidity.

6.2 Study

6.2.1 Summary of study results

Psychological co-morbidity was common in people with gout during the five-year study period. The point prevalence of anxiety and depression were 10.0% and 12.6% respectively at baseline, as reported previously by Roddy et al. (2015), Prior et al. (2016) and Chandratre et al (2018), and then decreased gradually over time to 6.6%% and 9.6% respectively by the end of the five-year

follow-up period. Over this period, one in twelve people with gout who did not have anxiety at baseline developed anxiety, and one in 11 without depression at baseline developed depression. On crude and adjusted analyses, having a baseline history of oligo- or poly-articular gout flares was associated with greater odds of developing anxiety in people with gout. Baseline flare frequency, gout duration and allopurinol use were not associated with developing anxiety in people with gout. On adjusted analysis, having a baseline history of allopurinol use and a gout duration of 9 to 17 years (at baseline) were associated with greater odds of developing depression in people with gout. Baseline flare frequency and oligo- or poly-articular gout were not associated with developing depression in people with gout.

6.2.2 Comparison of results with the existing literature

The point prevalence of anxiety identified in this study is higher than that identified in the systematic review. Fu et al. (2017;2018) and Mak et al. (2011) reported a point prevalence of 5.3% and 6.0% in people living with gout in southeast Asia. The higher prevalence could be due to geographical, cultural, or ethnic differences. For example, Fu et al. (2017;2018) and Mak et al. (2011) were undertaken in south-east Asia, whereas this study was conducted in the UK, where participants were predominantly white UK/European ethnicity. There may also be differences in (mental) health-seeking behaviour or stigma between countries or cultures, affecting willingness to participate or reporting questions around mental well-being. Lauber and Rössler (2007) reported widespread stigmatisation and discrimination towards people with mental illness in Asia, and that psychological symptoms are seen as socially disadvantageous, negatively affecting health-seeking behaviours (Lauber, Rössler, 2007). Furthermore, Fu et al. (2017;2018) and Mak et al. (2011) used different instruments to assess anxiety. Mak et al. 2011 used the HADS-anxiety subscale, whereas Fu et al. (2017;2018) and this study utilised GAD-7. HADS-Anxiety was explicitly designed to help identify anxiety in a secondary care setting (Bocéréan, Dupret, 2014). In contrast,

GAD-7 is typically used in primary care and is therefore suitable for use in the primary care setting of this study.

The prevalence of depression was similar to that reported by the one UK study identified in the systematic review (Kuo et al., 2016). Kuo reported a prevalence of diagnosed depression of 12.1% (vs non-gout controls 10.4%) in people ten years before gout diagnosis in UK primary care using Clinical Practice Research Datalink (CPRD) data. The CPRD contains 12 million health records of individuals in the UK. Kuo et al. (2016) identified 39,111 individuals with incident gout between 1997 and 2005 via Read code. The mean age was 62.2±15.1 years, and 72.5% were male. The main finding was that people with gout have poorer pre-existing health at diagnosis and that risk of incident co-morbidity continues to rise following diagnosis. Two other UK studies, Prior et al. 2016 and Roddy et al. 2015, utilised baseline data from the same study as reported in this thesis. The prevalence of both anxiety and depression decreased over time. Possible explanations for this are that people living with gout adjust to having anxiety or depression over time or received treatment and can better manage their mental health. Another possible explanation is that participants without anxiety or depression could have been more likely to respond to follow-up questionnaires than those with anxiety or depression.

Over the five-year study period, 7.5% and 9.2% of people with gout developed new-onset anxiety and new-onset depression, respectively. The systematic review identified only three studies that reported the incidence of anxiety or depression in people with gout (Singh, Jasvinder, Cleveland, 2018; Prior et al., 2015a; Changchien et al., 2015). All three studies reported the incidence of depression, whereas only Prior et al. (2015) reported the incidence of anxiety. However, the incidence was reported per 1000 person-years in each of these studies, so comparing these estimates to this study is not possible.

Across the five-year follow-up period, having a baseline history of oligo- or polyarticular gout flares at baseline was associated with new-onset anxiety on univariable analysis, which is

consistent with the cross-sectional findings of Prior et al. (2016) and Zhou et al. (2019). Having a baseline history of gout duration for nine to 17 years and allopurinol use were associated with new-onset depression. No other gout duration groups (three to eight, or ≥18 years) were associated with new-onset depression, so this may be a spurious result as there was no evidence of a dose-dependent effect of greater incidence with longer gout duration.

Furthermore, in contrast to the finding in this study that allopurinol use was associated with the onset of depression, in a nationwide cohort study, Changchien et al. (2015) reported that people with gout who were not taking anti-gout treatment (including colchicine, xanthine oxidase inhibitors, and uricosurics) had greater odds of incident depression compared to those taking anti-gout medication. Additionally, Changchien et al. (2015) described a protective association between people with gout who took any gout medication (colchicine, xanthine oxidase inhibitor, or uricosuric agents) and incident depression. Thus, there are two credible possibilities to explain the counter-intuitive finding that allopurinol use increases the risk of depression. Firstly, confounding by indication: People who are prescribed allopurinol are likely to have more severe gout, and the severity of gout may predispose them to depression rather than taking allopurinol. Secondly, ULT is often sub-optimally used: if flare frequency (and other gout characteristics) is associated with anxiety or depression in people with gout, it would be expected that allopurinol treatment would reduce the onset of anxiety or depression by preventing flares. However, the opposite association was seen. Allopurinol use in this primary care-based study was likely sub-optimal. Previous studies have shown that only a minority of people with gout prescribed allopurinol in UK primary care have the dose increased sufficiently to achieve a target serum urate level (Cottrell et al., 2013; Roddy, E., Zhang & Doherty, 2007). Moreover, 90% of people in this study received 300mg or less of allopurinol. In the Doherty trial, the mean dose in the nurse-led care arm (>90% of whom achieved a target serum urate level) was 460mg per day (Doherty et al., 2018). Therefore, it seems likely that the people receiving allopurinol in this study were dosed insufficiently to achieve a target serum urate level and prevent gout flares. This could explain why

allopurinol use was associated with greater, rather than lower, odds of new-onset anxiety or depression.

6.2.3 Strengths, weaknesses, and limitations

The systematic review highlighted that there are few prospective cohort studies of gout, psychological co-morbidity, and their associations. Therefore, a key strength of this thesis is its prospective cohort study design, which allows temporal aspects of these associations to be explored. Furthermore, the sample population was from primary care (rather than secondary or tertiary care), which represents most people with gout, as the majority are managed entirely in primary care. The length of follow-up was up to five years which allowed an adequate amount of time for psychological co-morbidity to manifest. Furthermore, psychological co-morbidity was assessed using recognised validated tools capable of diagnosing and identifying the severity of anxiety and depression.

A weakness of this study was that participants' GAD-7 or PHQ-9 scores before baseline were unknown. This meant that it was not possible to report the true incidence of new psychological co-morbidity. Instead, participants with anxiety or depression at baseline were excluded from the main and sensitivity analyses, and subsequent onset of anxiety or depression was reported, rather than definite first incidence.

This study was a secondary analysis of data from a pre-existing prospective cohort study. Participants were identified in primary care by Read code (clinical diagnosis) rather than identifying MSU crystals on synovial fluid microscopy (the gold standard method of gout diagnosis) or validated classification criteria. However, Meier and Jick (1997) reported the positive predictive value of GP diagnosis of gout to be 90% (Meier, Jick, 1997). Furthermore, Watson, Muller and Roddy (2019) reported that a primary care diagnosis (identified by Read code) had a positive predictive value of 80% compared with the 1977 ARA gout classification criteria and a primary

care diagnostic rule (Wallace et al., 1977; Janssens et al., 2010; Watson, Muller & Roddy, 2019). Participants were also identified by prescriptions for allopurinol or colchicine, which raises the possibility that people identified by allopurinol or colchicine use could have been prescribed these medications for other indications and not have gout. Allopurinol is used to treat people with uric acid renal stones and to prevent acute hyperuricaemia and tumour lysis syndrome in people receiving chemotherapy. Colchicine is licenced for prophylaxis of Mediterranean fever and used off-licence for acute calcium pyrophosphate crystal arthritis (formerly known as pseudogout). However, Watson et al. (2020) and Bajpai et al. (2021) reported that no participants in this cohort identified by prescription only had a Read code for these other indications (Bajpai et al., 2021; Watson et al., 2020). Furthermore, as discussed above, the analyses of the association of allopurinol with anxiety and depression did not account for confounding by indication or suboptimal dosing.

The ethnicity of the study population was predominantly white UK/European. However, further research is needed to explore the possibility that the associations identified in this thesis would not hold true in predominantly non-white non-European populations.

As with all cohort studies incorporating follow-up at multiple time points, attrition is inevitable, which risks non-response bias. However, the proportions reporting new-onset anxiety and depression in the sensitivity analysis undertaken in those who returned questionnaires at all follow-up time-points did not differ substantially from the main analysis, providing reassurance. However, it is worth noting that although the magnitude of the ORs remained similar the 95% CI were wide, which is most likely a reflection of the smaller sample size in the sensitivity analysis, and lower statistical power. This meant that factors associated with new-onset anxiety (oligo- or poly-articular gout) and new-onset depression (gout duration & allopurinol use) in the main analysis were no longer significant in the sensitivity analysis.

In this cohort, the point prevalence of both anxiety and depression decreased over time. As those lost to follow-up did not complete a GAD-7 or PHQ-9, it is not possible to know if the burden of psychological co-morbidity was higher in non-responders vs responders at those specific time points. However, looking at follow-up responders vs non-responders and comparing their baseline characteristics, non-responders were more likely to be male, older, not using allopurinol and have a higher prevalence of psychological co-morbidity.

The sample size was derived during the original prospective cohort study set-up and was based on the association between gout flares and change in health-related quality of life. Over a five-year follow-up period, there were only 49 and 56 outcomes in the main analyses for anxiety and depression, respectively (26 and 28 respectively in the sensitivity analysis). This limited the number of covariables that could be assessed. The 95% confidence intervals were wide, which may reflect sample size and outcome frequency. Whilst the magnitude of the odds ratios suggests associations between having a history of oligo- and polyarticular gout flares, greater flare frequency and allopurinol use and future psychological co-morbidity in people with gout, the study is likely to have been underpowered.

As this study was a secondary analysis, it was not possible to examine covariables of interest that had not been collected in the original study. For instance, the systematic review highlighted that low vitamin D levels might be associated with depression in people with gout.

Allopurinol use was associated with greater odds of new-onset depression; however, this may be confounded by indication. There are statistical techniques that could account for this, such as propensity score methodology, but these were considered to be beyond the scope of this thesis. Furthermore, it is likely that allopurinol was sub-optimally dosed in this study. Unfortunately, only a minority of serum urate levels were available in the medical record at baseline, so it was unfeasible to explore this further.

6.2.4 Implications for clinical practice

Psychological co-morbidity was common with approximately one in ten people with gout affected in this study. Therefore, clinicians should be aware of the burden of anxiety and depression in people with gout and which gout characteristics are associated with increased risk of anxiety and depression (having a history of oligo- and poly-articular gout, and allopurinol use). Identifying gout characteristics that increase the odds of developing new-onset psychological co-morbidity provides clinicians with more exact information to monitor people more closely with gout who have those characteristics for risk of developing psychological co-morbidity. Furthermore, it enables clinicians to warn people with newly diagnosed gout that these characteristics may put them at higher risk of future psychological co-morbidity and empower patients to self-monitor and present if symptoms occur. As previously mentioned, the association of allopurinol use with increased odds of new-onset psychological co-morbidity may be due to confounding by indication or undertreatment, if the latter this gives further impetus to clinicians to make sure treatment targets are followed. Clinicians should consider the mental health needs of people with gout, especially as gout, anxiety and depression are all commonly treated in primary care, streamlining dissemination of information, monitoring and management. Another potential benefit of informing both clinicians and people living with gout of psychological co-morbidity being common is that it may result in anxiety or depression being identified sooner and potentially at a less severe stage.

6.2.5 Implications for future research

A baseline history of oligo- and poly-articular gout and allopurinol use were associated with the onset of psychological co-morbidity. However, as highlighted above, incidence could not be measured due to the original study design. This meant that it was not possible to report the true incidence of psychological co-morbidity. Therefore, further studies which exclude people living

with gout who had previous psychological co-morbidity from enrolment would be beneficial to identify the true incidence of psychological co-morbidity in gout and identify any associations. Furthermore, the exact mechanisms linking gout and psychological co-morbidity remain unclear.

Further research is required to understand the association between allopurinol use and developing psychological co-morbidity, as antigout medication has been previously shown to be protective against incident depression in Changchien et al. (2015). In contrast, in this study, allopurinol use was associated with the onset of depression. Gout severity may be associated with anxiety and depression, so better managed gout (most commonly with allopurinol) would be expected to be less associated with anxiety and depression. However, this study did not address confounding by indication in its design. If allopurinol use is suboptimal and the dose is not titrated to reduce the serum urate level below target, potential beneficial effects of allopurinol may not be seen. Therefore, future research is needed to explore the effect of allopurinol on psychological co-morbidity in people with gout, either by addressing confounding by indication in the design of observational studies or by including anxiety and depression as outcome measures in randomised trials.

6.3 Systematic review and meta-analysis

In 2020, Howren et al. published a systematic review and meta-analysis examining the epidemiology of depression and anxiety (Howren et al., 2021). As this was published after completing the systematic review in this thesis, it was not included in the systematic review chapter (3). Howren et al. (2020) included 20 articles, of which 12 were present in the systematic review in this thesis. Of the additional eight that were not included, three of them featured in the 2018 systematic review by Lin et al. examining gout and depression. The reasons for excluding these papers from the systematic review undertaken as part of this thesis have been discussed previously in the systematic review chapter. Of the five other articles included in Howren et al.

(2021) which are not included in the systematic review in this thesis: two articles were not found by the search terms, no full-text could be found for two abstracts during the search phase time window, and one was rejected during the title and abstract review for not having the outcomes of interest in this thesis, depression or anxiety, focussing on erectile dysfunction instead. There were also four papers included in this systematic review that were not present: Nguyen et al. (2019), Spaetgens et al. (2015), Roddy et al. (2015), and Lee et al. (2019).

The meta-analysis performed by Howren et al. 2020 estimated an OR of 1.29 (1.07 to 1.56) between gout and depression, and 1.29 (0.96 to 1.73) between gout and anxiety, and a pooled hazard ratio of 1.17 (1.01 to 1.36) for incident depression. Similar to the systematic review in this thesis, flare frequency was associated with depression, in addition to oligo- or polyarticular gout flares and the number of tophi. Howren et al. (2020) concluded that depression and anxiety are significantly associated with gout. The paucity of research around people living with gout and anxiety was also noted, strengthening the justification for the study undertaken in this thesis.

6.4 Conclusion

This five-year prospective cohort study has identified that psychological co-morbidity is common in people living with gout within UK primary care. Oligo- and poly-articular gout flares, history of gout, and allopurinol use, were associated with greater odds of onset of psychological co-morbidity in people living with gout. Due to limitations of study design, incident anxiety and depression could not be studied. Therefore, further large-scale studies that exclude people living with gout with previous psychological co-morbidity from enrolment should be pursued and assess confounding by indication to understand the link between allopurinol use and psychological co-morbidity development. Implications for future practise include clinicians being more aware of the mental health needs of people with gout, as psychological co-morbidity is common. The identification of specific gout characteristics which increase the odds of developing new-onset psychological co-morbidity also provides clinicians with more information on which patients may need closer monitoring.

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Appendix

Arthritis Research UK Primary Care Centre

Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. A copy of this completed form will be available via the intranet to help others carrying out reviews in the future and to avoid duplicating work already undertaken in the Centre. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review and items should be adapted to fit the type of review that is being undertaken.

The template has been updated to include all the items from the PRISMA-P checklist (http://www.prisma-statement.org/Extensions/Protocols.aspx). All systematic reviews should be registered with PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/) unless the review is methodological.

Please complete the form in as much detail as possible for your review and email to Opeyemi Babatunde, o.babatunde@ keele.ac.uk

Title of the review	The association between gout and psychological co-morbidity
First reviewer	Jordan Higgs (JH)
Other reviewers (with role/contribution in the review)	Lorna Clarson (LC) – academic supervisor, and additional reviewer for dispute resolution (SR team) – methodological support, and advice (OB, NC, JJ) Connor Henry-Blake (CHB) - second reviewer Edward Roddy (ER) – academic and clinical input
Clinical Portfolio Group	Inflammatory programme
Funding source	Intercalated MPhil project
PROSPERO registration number	NA

Amendments to the protocol	NA

Background to review

Brief introduction to the subject of the review, including rationale for undertaking the review and overall aim

Gout is the manifestation of monosodium urate (MSU) precipitation in and around joint space following a hyperuricemic state. Hyperuricemia is caused by either over-production and/or under-excretion of urate, and as urate reaches the limits of its solubility (supersaturation), MSU crystal formation may occur (Desai, Steiger & Anders, 2017). However, supersaturation alone is not sufficient to develop gout, as only 5% of hyperuremic patients advance to MSU crystal deposition, and the exact trigger of this phenomena is yet to be elucidated (Ragab, Elshahaly & Bardin, 2017). When the host's immune system recognises MSU crystals a strong inflammatory response is evoked causing red, inflamed, oedematous and painful attacks in the affected area, characteristic of an acute gouty episode (Wertheimer, Morlock & Becker, 2013). Within the UK, gout is highly prevalent affecting up to 4.9 per 1000, and is the most common inflammatory arthritis (Roddy, Doherty, 2010). In a cohort of gout sufferers, attacks become frequent and persist over many years leading to joint destruction and tophi build up in soft tissues, leading to chronic gouty arthritis. This causes significant chronic pain, disfigurement and disability (Desai, Steiger & Anders, 2017). Outside of the direct musculoskeletal ramifications of gout, a plethora of other bodily systems can be affected, such as renal and cardiovascular systems, often negatively impacting on physical quality of life (Chandratre et al., 2013, Edwards, 2008). However, the evidence relating to the effect of gout on psychological health, specifically anxiety and depression, has been conflicting and this putative association is not well understood (Prior et al., 2015, Fu et al., 2018).

Anxiety and depression are both common mental health conditions, with 19.7% of ≥16 year olds displaying symptoms of anxiety or depression (Evans, J., Macrory, I., & Randall, C, 2016). Anxiety is the sensation of worry or unease usually due to tentative outcomes. When this anxious state begins to interfere with daily living, an anxiety disorder can be formally diagnosed if found to fulfil International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Common symptoms include trouble relaxing and feeling as if something terrible might happen, or feeling on edge and not being able to control worrying thoughts. Some patients also experience physical symptoms such as palpitations, shortness of breath and chest pain (Barton et al., 2014). Depression, like anxiety, can be a normal emotional response to a challenging life event, such as following bereavement. Clinical depression occurs when a collection of symptoms such as low mood, anhedonia, and low energy levels persist for 2 weeks or more and impairs normal function (Kennedy, 2008). Clinically, both anxiety and depression are managed in a similar manner, with self-help and talking therapies, such as Cognitive Behavioural Therapy (CBT), the mainstay of treatment. Pharmacological therapy, typically Selective Serotonin Reuptake Inhibitors (SSRIs), can also be supplemented in to support other treatment options in persistent or more severe cases (National Collaborating Centre for Mental Health, (UK), 2010).

Jacob, Rockel and Kostev (2017) have shown in rheumatoid arthritis (RA), another inflammatory arthritis, depression develops in up to 30% of patients within 5 years of diagnosis (Jacob, Rockel & Kostev, 2017). As gout shares many similarities to RA, it is feasible

similar may occur. Therefore, the main aim of this review is to establish the existing knowledge-base, incidence/prevalence of, and characteristics or prognostic factors pertaining to psychological co-morbidity within gout patients.

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2. Specific objectives/questions the review will address
The main objective of this review is to summarise existing knowledge regarding gout and psychological co-morbidity (anxiety and depression). Where such data is available three further sub-objectives will be explored: Identify the prevalence and incidence of psychological co-morbidity within gout Relative risk, odds ratio and hazard ratio of psychological co-morbidity within gout Identify if any characteristics have been associated with psychological co-morbidity within gout patients

3. a) Eligibility Criteria for including studies in the review If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading	
Population, or participants and conditions of interest	Any human adult (≥18 years old) with a diagnosis of gout
Interventions/Exposure/item of interest	Psychological co-morbidity (depression and/or anxiety)
Comparisons or control groups, if any	Where applicable non-gout comparators
Outcomes of interest	Prevalence and/or incidence of psychological co-morbidity (anxiety or depression) within gout sufferers Relative risk, odd ratio and/or hazard ratio of psychological co-morbidity within gout sufferers Characteristics associated with psychological co-morbidity development
Setting	Any care setting including population-based studies
Study designs	Primary studies of any study design except qualitative only

3. b) Criteria for excluding studies not covered in inclusion criteria Any specific populations excluded, date range, language, whether abstracts or full text available, etc	
Non-English language studies for which a translation cannot be obtained Case reports, or case series Editorials or letters Conference abstracts or posters Reviews: check relevant systematic reviews only for included studies Papers where full text cannot be found during full text screening	
4. Search methods	
Electronic databases & websites Please list all databases that are to be searched and include the interface (eg NHS HDAS, EBSCO, OVID etc) and date ranges searched for each. NB All search strategies should be reviewed by Jo Jordan or Nadia Corp BEFORE searching begins	Ovid from inception to present: AMED (Allied and Complementary Medicine) Embase MEDLINE(R) Web of science Core collection from date of inception to present: Science Citation Index Expanded Conference Proceedings Citation Index- Science EBSCO from date of inception to present: PsycINFO AgeLine CINAHL Plus with full text PsycARTICLES
Other methods used for identifying relevant research i.e. contacting experts and reference checking, citation tracking	Reference checking

Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.	

5. Methods of review	
How will search results be managed & documented? ie which reference management software, how duplicates dealt with	A systematic review management software will be used for search result management. Following database extraction, and import, duplicate references will be removed. Results will be exported from each database into refworks, any exact duplicates will be removed at this stage. Results will then be collated and exported to rayyan. Any titles that are a close match, as highlighted by Rayyans % similarity, will be manually reviewed and marked as a duplicate (and deleted) or marked as not a duplicate (and retained).
Selection process Number of reviewers, how agreements to be reached and disagreements dealt with, etc.	3 Reviewers will be involved in the selection process. Reviewer 1 (JH) will perform the literature search and title screening. Reviewers 1 (JH) & 2 (CHB) abstract screening, and full text screening. Reviewer 3 (LC) will assist with disputed items.
Quality assessment Tools or checklists used with references or URLs, was this piloted? Is it to be carried out at same time as data extraction?	Included studies will be quality assessed using the Newcastle-Ottawa tool.
How is data to be extracted? What information is to be collected on each included study? If databases or forms on Word or Excel are used, were these piloted and how is this recorded and by how many reviewers?	The following information will be collected and compiled into an excel spreadsheet following a pilot search to confirm appropriateness: year of publication country setting study design method of gout diagnosis age of participants sex how was psychological comorbidity assessed and defined, epidemiological data: incidence/prevalence

	statistical data: relative risk, odds ratio, hazard ratio any listed characteristics with an effect on psychological comorbidity
Outcomes to be extracted & hierarchy/priority of measures ie which measure is preferred and if that is not available which is next in order of preference?	Outcomes of interest: epidemiological data: incidence, prevalence, relative risk, odds ratio, and/or hazard ratio (adjusted or unadjusted) of psychological comorbidity (depression and/or anxiety) within gout sufferers any listed prognostic factors associated with psychological co-morbidity (depression and/or anxiety) in gout sufferers
Narrative synthesis Details of what methods, how synthesis will be done and by whom. Is the Narrative Synthesis Framework to be used?	A narrative synthesis will be carried out by JH to summarise the appropriate available evidence describing key characteristics for each study in the same way so fair comparisons can be made. Studies may be grouped upon similarity of design or outcome.
Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.	If sufficient quantitative data is collected and not excessively heterogeneous a meta-analysis will be conducted, otherwise these data will be described in the narrative synthesis.
Will the overall strength of evidence be assessed? If so, how? ie GRADE?	N/A

6. Presentation of results

Outputs from review Papers and target journals, conference presentations, reports, etc	Rheumatology, British Journal of General Practice, Journal of Rheumatology, Arthritis Care and Research. Conference: SAPC North

7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	Sept to Oct w2
Literature searching	Oct w3 to w4
Screening	Nov w1 to w2
Quality appraisal	Nov w3 to w4
Data extraction	Nov w3 to w4
Synthesis	Dec w1 to w4
Writing up	Dec to May

Support – please state if advice/training or personnel required at each stage	
SR overview	Advice/training provided by LC, ER and SR team.
Protocol development	Advice/training provided by LC and ER; protocol written by JH.
Literature searching	Advice/training provided by the SR team JH to undertake systematic review course. JH to perform search. CHB to assist.
Quality appraisal	Support/training as above. JH and CHB to perform independently. LC to assist in dispute resolution.
Data Extraction	Support/training as above. JH and CHB.

Synthesis	Support/training as above. JH.
Writing up	Support/training as above. JH.

Please send your completed protocol to Opeyemi (see email below) as we would like to put examples on the Intranet.

The systematic review team are available to answer any queries or give advice on completing your review. Systematic review workshops are run at least once a year, or can be arranged on an ad hoc basis if needed by a group. Presentations from previous workshops can be found on the Centre's Intranet.

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