

CHRONIC PAIN IN THE UNITED KINGDOM AND ASSOCIATED CARDIOVASCULAR DISEASE

Alan Fayaz

*Imperial College London
Department of Surgery and Cancer*

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ABSTRACT

Prior to the studies presented in this thesis there was no widely accepted estimate for the prevalence of chronic pain in the United Kingdom, little understanding of the biological consequences of chronic pain (as compared to its psychological and social impact), and unresolved issues about the possible influence of chronic pain on cardiovascular outcomes.

I have used meta-analysis to summarise prevalence estimates for a range of chronic pain phenotypes, demonstrating that just over 43% of the adult population experience pain with a duration of 3 months or greater. This figure is considerably higher than estimates often quoted in public and scientific forums. I have also outlined the impact of chronic pain on cardiovascular health through a systematic review of existing evidence, suggesting that chronic pain may be associated with cardiovascular disease and cardiovascular mortality.

However, existing studies took an inconsistent and incomplete approach in their adjustment for potentially confounding factors, so it cannot be concluded that these associations are causal. I have therefore supplemented existing evidence with analysis of data from a large national survey of the population of England, adjusting for a comprehensive list of potentially confounding variables. My study shows that participants reporting chronic pain are 55% more likely to experience cardiac disease than those without

pain, and that this risk increases systematically in-line with increasing chronic pain intensity.

In summary, I have demonstrated that chronic pain affects a much greater proportion of the adult population on the United Kingdom than previously estimated. Furthermore, adults reporting chronic pain, in particular those most severely affected, may be at significantly increased risk of cardiac disease. Future studies should focus on determining whether reducing the impact of chronic pain can improve cardiac health.

DECLARATION OF ORIGINALITY

I hereby confirm that the work presented in this thesis is original and my own. Where contributions have been made, or information has been derived from other sources, this has been appropriately referenced.

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Dedicating time to research activities can be expensive, and I could not have afforded to complete my Thesis without financial contributions along the way.

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PUBLICATIONS ARISING FROM THIS THESIS

Fayaz A, Croft P, Langford RM, Donaldson LJ, Jones GT. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*. 2016;6(6).

Fayaz A, Ayis SAM, Panesar S, Langford R, Donaldson L. Assessing the relationship between chronic pain and cardiovascular disease: A systematic review and meta-analysis. *Scandinavian Journal of Pain*. 2016 Oct;13:76-90.

Fayaz A, Watt HC, Langford RM, Donaldson LJ. The Association Between Chronic Pain and Cardiac Disease: A Cross-sectional Population Study. *The Clinical journal of pain*. 2016;32(12):1062-8.

For Simin and Amir ...

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LIST OF ABBREVIATIONS

CI	Confidence intervals
CP	Chronic pain
CPG	Chronic pain grade
CGPS	Chronic pain grade scale
CV	Cardiovascular
CVD	Cardiovascular disease
CWP	Chronic widespread pain
FM	Fibromyalgia
HSE	Health Survey England
HR	Hazard ratio
OR	Odds ratio
NSAIDS	Non-steroidal anti-inflammatory drugs
SMR	Standardised mortality ratio
UK	United Kingdom
USA	United States of America

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THESIS OVERVIEW

Chronic pain is a potentially disabling condition. The impact of chronic pain on social and psychological wellbeing is well recognised. In contrast the biological consequences of chronic pain are often underestimated. My thesis aims to better qualify the burden of chronic pain in the United Kingdom: exploring, in particular, the possibility of an increased risk of cardiac disease in patients with chronic pain.

AIMS OF THESIS

To establish reliable estimates for the prevalence of chronic pain and chronic widespread pain in the United Kingdom

To review the evidence-base for an association between chronic pain and cardiovascular disease

To examine population-level data in order to understand the basis, and importance, of the association between chronic pain and cardiovascular disease

INTRODUCTION

Chronic pain (as defined below) is costly, at an individual and societal level.

In the United States of America direct (healthcare) and indirect (loss of productivity) costs attributable to chronic pain conditions have been estimated at \$560 to \$635 billion (£403 to 458 billion), outstripping costs relating to cancer and heart disease combined (\$552 billion) (1). In the United Kingdom a national audit, commissioned by the Healthcare Quality Improvement Partnership, found that two-thirds of chronic pain patients surveyed had visited their general practitioner three or more times over a six month period for help with their pain, and up to 20% had attended an emergency department for pain management over a similar period (2).

Chronic pain is associated with psychosocial and physiological morbidity. Observational studies have reported a greater occurrence of anxiety and depression amongst cohorts reporting chronic pain, when compared to general populations (3-6). Chronic pain has been linked to impaired memory (7), cognition (7), sleep (8-10) and sexual function (11, 12). Adults reporting chronic pain are more likely to be unemployed or from low socio-economic backgrounds (13-16). It is perhaps not surprising that chronic pain patients attest to low scores for quality of life, that are comparable to people living with Parkinson's Disease (17) and terminal cancer (18). Suicidal ideation and suicide attempts are also commoner amongst those reporting chronic pain (19).

Chronic pain is a silent epidemic; a global public health problem that rarely achieves the publicity of other long-term conditions such as cancer and cardiovascular disease. The First National Pain Summit, held in the United Kingdom, highlighted the paucity of evidence about the burden of chronic pain. (20). Furthermore, whilst the psychological and social impact of chronic pain has been studied, very little is understood about the potential biological consequences.

The impact of chronic pain at a national level requires access to reliable and contemporaneous prevalence estimates. Globally, it is reported that one in five primary care patients experience persistent pain; this is a figure generated from pooled survey data collected in 15 regions across Asia, Africa, Europe, and the Americas (21). However, prevalence estimates in individual countries range from 10% to 55% according to the geographical location and methodology (22-26). Two particular sources of data have been used to estimate the burden of chronic pain in the United Kingdom. The first, a survey of 8610 residents in England, found that 31% to 37% of respondents reported pain in one or more body regions, for a period of three months or longer (15); the second, a European telephone survey, found that one in five adults had experienced moderate to severe pain, several times a week, lasting for six months or more (27). Both studies have major limitations: in the first, data were gathered from residents of England only, and in the second study, only 300 households sampled were in the United Kingdom whilst much of the data on individuals was collected, by proxy, through the primary respondents.

In the first part of my Thesis, I will address these shortcomings through a systematic review and meta-analysis of recent, and nationally representative population studies in order to generate pooled estimates for different chronic pain phenotypes.

The idea that chronic pain is related to an increased risk of cardiovascular disease first arose in the mid-, to late, 20th century. Longitudinal studies had found an apparent association between low back pain and the subsequent development of vascular diseases including angina pectoris (28), intermittent claudication (28, 29) and myocardial infarction (30). Furthermore, post-mortem and clinical studies had demonstrated that atheromatous lesions of the aorta and lumbar arteries appeared to be associated with an increased lifetime incidence of low back pain. These studies led to some authors suggesting that chronic lower back pain was a symptom of lumbar-vascular disease; in the way that angina may be indicative of cardio-vascular disease (31, 32). However, more recent reports have pointed to an augmented risk of cardiovascular diseases amongst a wider spectrum of chronic pain conditions including chronic neuropathic pain (33), widespread pain (34, 35) and fibromyalgia (36, 37).

Whilst chronic pain and cardiovascular disease share common risk factors (38, 39), the chronic stress that accompanies pain itself may be a risk factor for heart disease. Indeed, there are research findings that chronic pain is

linked to dysfunction of the autonomic nervous system, the inflammatory system and endothelial processes (40-46). All these are known to play a part in the pathophysiology of cardiovascular disease.

There are a number of plausible ways to explain an independent association between chronic pain and cardiovascular disease. First, the biological response to acute pain includes activation of the sympathetic nervous system, often in proportion to the size and duration of the nociceptive stimulus. This increases peripheral resistance, heart rate and stroke volume with a consequential rise in blood pressure. These effects may contribute to the (protective) reduction in pain sensitivity that has been demonstrated both clinically and experimentally (47). As pain shifts from acute to chronic (41), the balance of this relationship appears to reverse. There are persistent and maladaptive responses of baroreceptors to ascending nociceptive signals, such that this could lead to increased blood pressure as well as greater cardiovascular risk and mortality (41, 48). Second, there is an inflammatory theory of pain causation. Fractaline is one of only two chemokines that exist in both soluble and membrane-bound forms. Its expression is strongly associated with central nervous system inflammation, and its interaction with the fractaline receptor is believed to play a key role in neuronal interaction in the dorsal horn during pain transmission (42). Fractaline has also been associated with the development of atherosclerotic plaques. In fact, animal studies have pointed to the cardio-protective action of Acetylsalicylic Acid being mediated through reduction of fractaline expression.

Given the complex interplay between processing of somato-sensory signals, and contextual information from centers in the brain associated with anxiety, fear and arousal, it is conceivable that the negative biological responses to pain are actually mediated through neuro-physiological systems that are not pain specific. Hypervigilance is defined as an “enhanced state of sensory sensitivity accompanied by an exaggerated scan, or search, for threatening information” (49). Hypervigilance is more prominent in widespread pain conditions such as Fibromyalgia (50), with which there is the strongest evidence for autonomic instability. Hypervigilance also correlates well with pain intensity, anxiety, distress and emotional disability (51). Anxiety, depression and hypervigilance can be measured (52), and consequently, controlled for in the assessment of a direct link between chronic pain and cardiovascular disease. However, to attempt to tease out the physio-emotional factors that could be contributing to negative outcomes may undermine the definition of pain itself. Pain is an unpleasant sensory and *emotional* experience. The difference between pain and nociception (the neural response to potentially harmful stimuli) is in fact this integration of sensory information to higher centres of the brain responsible for vigilance and arousal.

In the second part of my Thesis, I will search and analyse the evidence base for an association between chronic pain and cardiovascular disease that is

independent of commonly shared risk factors. I will summarise published evidence narratively and, where appropriate, through meta-analysis.

In the last part of my Thesis, I intend to support the findings of my review through high-level statistical analysis of cross-sectional data from a large national survey of the population of England.

METHODS

Definitions of terms

Chronic pain: Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” by the International Association for the Study of Pain (53). The emphasis on subjectivity is important. It obviates the need to identify a stimulus, and allows for the reporting of pain in the absence of overt pathophysiological changes. *Chronic* pain is defined as pain that persists beyond the accepted time of healing (54) which, for practical purposes, is a period of three to six months following the initiation of symptoms (53). This seemingly arbitrary temporal separation between acute and chronic pain probably represents a functional transition from protective mechanisms to more maladaptive neuro-behavioural processes, with the potential for significant harm and distress.

Chronic Widespread Pain: A subset of people reporting chronic pain experience it in more than one distinct body area. The American College of Rheumatology has defined chronic widespread pain as chronic pain (pain of duration 3 months or longer) occurring in three or more distinct body areas: above and below the waist, on the left and right side of the body, and including the axial spine. The definition emerged during the identification of diagnostic criteria for fibromyalgia. Fibromyalgia sufferers represent a subset of chronic widespread pain patients in whom fatigue, cognitive

impairment and sleep disturbance are dominant features (55). Adults with chronic widespread pain and fibromyalgia report greater pain severity, interference with function, impairment of capacity to work, and poorer quality of life than those with regional pain syndromes (56, 57).

Chronic Pain Disability Grade: The number of pain sites is not the only surrogate measure of pain severity. The Chronic Pain Grade Scale (CPGS) developed by Von Korff and colleagues is a validated, bi-directional tool that assesses the severity of chronic pain, based on its characteristics and the impact on a person's activities (58, 59). The scale uses a severity score based on participants' subjective assessment of their: current pain; worst and average pain over previous six months; pain related disability and pain interference with social and work related activity. An algorithm divides respondents into: low disability, low intensity chronic pain (Grade I); low disability, high intensity chronic pain (Grade II); high disability, moderately limiting chronic pain (Grade III); and high disability, severely limiting chronic pain (Grade IV).

Neuropathic pain: Previously referred to as “pain initiated or caused by a primary lesion or dysfunction in the nervous system”, neuropathic pain was redefined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system”, in 2008 (60). The change in taxonomy has helped to differentiate neuropathic pain from chronic nociceptive pain, which may also be driven by dysfunctions (in processing) of

the nervous system. The gold standard for diagnosis of neuropathic pain remains clinical assessment, but various screening tools have been developed to facilitate identification of pain with neuropathic features (61, 62). The tools use pain descriptors (LANSS, NPQ, PainDETECT, DN4) and bedside examination (LANSS, DN4) to predict the likelihood of neuropathic pain; predictive sensitivity for the tools range between 66% and 91%, and specificity varies between 74% and 94% (61). The LANSS has also been modified and validated as a self-report questionnaire with a positive predictive value of 76% (63). However, these screening tools have not been developed, or validated, specifically for use in population studies. The 2008 classification system stratifies pain symptoms into the following outcomes: (1) unlikely to be neuropathic, (2) possible neuropathic; (3) probable neuropathic or (4) definite neuropathic pain. In order to fulfil the criteria of 'probable' or 'definite' neuropathic pain, a physical examination and/or diagnostic imaging is required. This is clearly not practical at a population level. Furthermore, in order to reliably classify symptoms as 'possible' neuropathic pain a history of a credible neurological lesion, and neuro-anatomical plausibility is required. Therefore, the context in which pain symptoms occur is highly important, and given the lack of specificity of 'neuropathic' pain descriptors (such as burning or sharp), cross-sectional estimates are likely to over-estimate the prevalence of pain with neuropathic features.

Establishing the prevalence of chronic pain in the United Kingdom

I synthesised existing data on the prevalence of various chronic pain phenotypes in the United Kingdom by searching the electronic databases Medline (inception to 31st May 2015) and Embase (1980 to 31st May 2015) via the Ovid portal. I have presented the list of the medical subject headings and free-text terms used in Appendix 1(a). I supplemented these results with a manual search of the bibliographies of shortlisted review and original study articles. In addition, I approached a number of field experts to identify additional viable studies from the grey literature.

I included all study formats reporting point or period prevalence estimates, from general population samples, for the following pain phenotypes: (i) *chronic pain*: defined as pain in one or more body locations, lasting for a period of three months or longer; (ii) *chronic widespread pain*: defined in accordance with the American College of Rheumatology (ACR) 1990 guidelines as pain in the axial skeleton and two contralateral limbs, lasting for a period of three months or longer (55); (iii) *fibromyalgia*: defined in relation to either the 1990 or 2010 ACR criteria as ‘widespread’ pain, lasting for a period of three months or longer, in association with tender-points or somatic symptoms as described in their respective protocols (55, 64), and; (iv) *neuropathic pain*: defined as pain in one or more body locations, lasting for a period of three months or longer, with predominantly neuropathic features (as defined by a validated neuropathic-pain screening tool).

I did not include studies presenting data relating exclusively to specific body regions (for example chronic pelvic pain only, or chronic lower back pain only) in the review, as they were likely to underestimate the prevalence of (non site-specific) chronic pain. Where case-control studies were identified, they had to be nested within a cohort to allow for calculation of prevalence estimates. I included studies based in general practice on the proviso that they used the population registers of the practices as a sampling frame of the general population.

In order to provide contemporaneous and representative estimates I excluded studies if they: (i) presented data collected prior to 1990; (ii) presented international prevalence estimates where data from the United Kingdom was not independently retrievable; (iii) presented data obtained from United Kingdom populations that were not deemed to be representative of the general population (for example estimates of neuropathic pain in diabetic patients, or chronic pain prevalence within specific migrant populations); or (iv) presented data on a study population that had already been included in the analysis. In the case of follow-up studies, estimates from the baseline studies were preferentially included in the review, unless the follow-up study provided data on additional parameters that were not available from the earlier publication.

I screened all the articles by title initially, and subsequently by abstract. I then analysed shortlisted studies by reference to the full-text, to determine

their eligibility. In order to minimise investigator bias an independent clinician-researcher verified the screening process. We resolved any disagreements about suitability through arbitration or by deferring to a third clinician-researcher. I extracted data using a collection tool piloted on a small sample of population studies. Data extraction was also verified by one of the two clinician-researchers independently. I extracted data on population characteristics, response rates (where possible adjusted to reflect the viable survey denominator), crude prevalence estimates (number of cases divided by the sample size), age and/or sex adjusted prevalence estimates and, where provided, estimates stratified by age, by gender or by pain severity. Where age/sex standardised data were available, I used these figures preferentially in the meta-analysis. I did not contact authors directly for missing information.

I appraised the articles using a risk of bias tool developed specifically for prevalence studies (65). This tool consists of ten items addressing the external validity (risk of selection and nonresponse bias), as well as the internal validity (risk of measurement bias, and bias related to the data analysis) of observational studies in order to generate an overall risk of bias assessment. Studies that were deemed to be at 'high risk of bias' were removed. The use of the risk of bias assessment in the systematic review is further discussed below.

I incorporated estimates for the prevalence of chronic pain and chronic widespread pain that were not restricted to age-specific or gender-specific cohorts into a meta-analysis. The standard errors (SE) for prevalence (p) estimates were derived from the equation $\sqrt{[(p*(1-p))/n]}$, where n = number of participants with *completed* data in survey. Data were synthesised using StataSE v13 for Mac. Studies were weighted according to the prevalence effect size and the inverse of the study variance in order to generate an I² value, serving as a measure of heterogeneity amongst the studies. A random effects model was used to generate summary prevalence data, displayed (on forest plots) with 95% confidence intervals. Where number of studies and variation in the characteristics was sufficient (calendar year of survey and geographical location), stratified analysis of the survey prevalence figures was presented.

The results of this review are presented in Chapter I.

Quantifying the association between chronic pain and cardiovascular disease

In the first part of my thesis, I established summary estimates for the prevalence of important chronic pain phenotypes in the United Kingdom. These data will help to quantify the societal burden of chronic pain for policy makers, medical professionals and the public. In the subsequent analyses I addressed the potential biological consequences of chronic pain by attempting to quantify the association between chronic pain and cardiovascular disease.

I searched major electronic databases MEDLINE (via Ovid), EMBASE (via Ovid), Psycinfo (via Ovid), Cochrane and Web of Science from 1947 to December 5th 2015 for studies examining the association between chronic pain and cardiovascular disease. I have presented examples of the search strategies in Appendix 2(a). I supplemented my search results with a manual inspection of the bibliographies of the shortlisted study and review articles. In addition, I approached a number of field experts to identify additional, potentially viable, studies from the grey literature. Finally, I performed parallel searches of ProQuest (a web-based information suppository), in order to access unpublished academic work and grey literature that could be relevant.

I included English language studies examining the relationship between chronic pain (defined as pain with a duration lasting greater than three

months) and (i) *cardiac disease* (myocardial ischemia or myocardial infarction), (ii) *cerebrovascular disease*, (iii) *cardiovascular mortality*, or (iv) any combination of the above.

I excluded search results that were presented as letters, case studies, or foreign language articles (although I inspected their respective bibliographies to ensure full coverage of the subject matter).

I submitted the shortlisted studies to quality appraisal and risk of bias assessment using the relevant version of the Critical Appraisal Skills Programme tool for cohort (66) and case-control studies (67). For the assessment of risk of bias in cross-sectional studies I used a tool developed by Hoy and colleagues (65); this has been discussed in greater detail as part of my review of chronic pain prevalence estimates. I evaluated each study against criteria from the appropriate checklists. Another clinician-researcher subsequently scored the shortlisted papers in order to obtain an independent appraisal of the literature. We settled any discrepancies in the scores awarded through arbitration.

I performed the data extraction using a pre-defined tool designed to summarise the following: the demographic information for each study; the nature of the variables compared; the outcome measures used; and the confounders that were accounted for during any regression analyses. Where possible, I retrieved raw counts of the measured cardiovascular outcomes

amongst exposure groups (chronic pain) and control groups (no chronic pain). Manipulation of the raw data allowed me to generate unadjusted odds ratios (OR) and confidence intervals (CI) for the purpose of meta-analysis. Where data was not immediately available from the publication I attempted to contact the corresponding authors for access to the original study data.

I performed a meta-analysis, combining data from individual studies. I pooled studies that investigated similar association variables and also reported comparable outcome measures. A decision as to which pain phenotypes (number of pain sites, severity of pain) were amenable to meta-analysis was made post-hoc although the plan to pool comparable data was outlined 'a-priori' in the study protocol (68).

I synthesised the data using StataSE version 13 for Mac (69). In order to account for anticipated heterogeneity between the studies, I used a random effects model. This model applies relatively less weight to larger studies (70). A (post-hoc) review of the studies included in the meta-analysis allowed me to identify factors that potentially contributed to statistical heterogeneity. The impact of these factors was subsequently quantified by sensitivity analysis. Finally, I supplemented the data synthesis with a narrative summary evaluating the impact of pain phenotype (number of pain sites, severity of pain) and the role of confounding variables on the association between chronic pain and cardiovascular outcomes. The confounding

variables addressed in my review were limited to those factors that study authors had elected to account for in their respective statistical models.

The results of the systematic review and meta-analysis are presented in Chapter II.

Data analysis

In the final part of my thesis, I used data from a large national survey of the population of England to supplement the findings from my systematic review.

In the preceding review I had established some of the limitations of existing studies. I was therefore able to tailor my data analysis to better quantify the strength of the association between chronic pain and cardiovascular disease.

I extracted data for my study from the Health Survey for England; an annual survey collecting information on various aspects of physical health, lifestyle behaviors, social care and mental health from a representative sample of the population of England (71). This survey was first instructed in 1991, and the 21st chapter (collected in 2011) is the first to include data specifically about chronic pain symptoms. Detailed explanation of the construct of the survey have been published elsewhere (71). In principle, data are gathered through interviews with respondents randomly selected from post-code allocated sampling units across the country. Objective measures of health such as height, weight and blood pressure are then recorded alongside pre-specified demographics relating to health and social care. Ethical approval for the 2011 survey was obtained from the Oxford A Research Ethics Committee (reference number 10/H0604/56).

The survey organisers approached participants from 8992 private households to achieve a nationally representative sample of the English population. Households were selected through a process of stratified

sampling from 562 geographical sampling units. A total of 10,617 (8,610 adults) participants were interviewed, achieving a household response rate of 66%. From this cohort 5,715 participants also had a nurse visit allowing further questioning, collection of various anthropomorphic measurements and, where appropriate, blood and salivary samples. Data from interview and nurse visits, of approximately 10% of productive households, were recalled and reviewed as part of quality control measures to minimise bias in data collection.

Dependent variables: Participants were considered to have cardiac disease if they responded 'Yes' to either of the following questions: (i) "Were you told by a doctor that you had Angina?" (ii) "Were you told by a doctor that you had a Heart Attack (including myocardial infarction or coronary thrombosis)?"

I generated a supplementary variable ("cardiac last year") from responses to the above questions, in which a doctor had given the diagnosis of 'Angina' or 'Heart Attack' in the year leading up to the survey (albeit not necessarily given for the first time in this preceding year).

Independent variables: Participants were considered to fulfill the criteria for chronic pain if they responded "Yes" to both of the following questions: (i) "Are you currently troubled by pain or discomfort, either all the time or on and off?" (ii) "Have you had this pain or discomfort for more than 3 months?"

Pain disability grade was assessed at interviews using responses to the 'Chronic Pain Grade Scale' (CPGS). For the purposes of the statistical analysis grades III and IV were collectively used to represent high-disability chronic pain, while grades I and II were grouped to represent low-disability chronic pain. This grouping is consistent with previously published studies addressing cardiovascular outcomes in chronic pain patients (72, 73). Pain score severity was taken as an average of participants' current pain score (ranging from 0-10), worst pain score in previous six-months, and average pain score in the previous six months. A mean score of 5 or above represented 'higher average chronic pain score' (58). Pain distribution was classified according to the number of body sites in which chronic pain was reported; participants were offered up to seven body locations including back, neck/shoulder, head/face/dental, stomach/abdominal, limbs, chest or 'other'. Participants reporting chronic pain in four or more distinct body areas were considered to have 'chronic widespread pain' although I acknowledge this definition is not strictly adherent to the American College of Rheumatologists standard (64). In order to prevent bias from Angina being categorized as chronic pain in the chest area, data from all participants reporting chronic pain in the chest area were excluded from the statistical analysis.

Confounding variables: Age, gender and Income were obtained directly from the core survey questions. The latter was used as a measure of social class,

calculated by applying a McClement score to each household (integrating number, age and relationships of adults and children in household) and dividing the total household income by this score. Subjects were grouped into the following quintiles: <£11,676.65, £11,676.66-£19,117.65, £19,117.66-£27,704.92, £27,704.93-£47,794.11, and >£47,794.12. The effect of smoking was accounted for by dividing subjects into one of three groups: a) never-regular smokers, b) ex-regular smokers or c) current smokers. Body mass index was derived from validated height and weight measurements and participants were separated into quintiles: <18.5, 18.5-24.9, 25-29.9, 30-39.9 and >40. Participants were classified as hypertensive or diabetic if they reported ever receiving these diagnoses directly from a physician. Anxiety and depression were gauged as part of the general health questionnaire with subjects self-reporting as 'not anxious or depressed', 'moderately anxious or depressed' or 'extremely anxious or depressed'. Regular use of NSAIDS was included if the participant had a regular prescription for any drug coded under section 10.01.01 in the British National Formulary, allowing me to differentiate between NSAIDS taken for analgesic purposes and those taken for cardiovascular disease (e.g. Aspirin).

Statistical analysis: I processed the data using STATA SE (version 13). I performed serial logistic regression analyses addressing the association between cardiac disease and (i) *chronic pain*, (ii) *chronic pain distribution* (iii) *chronic pain disability*, and (iv) *average chronic pain score*. The process was then repeated using 'cardiac last year' as the dependent variable. Initially I

included the full complement of confounding variables in the regression models. Subsequently, I removed non-significant variables in a step-wise fashion, in order to generate the final models for the analysis. Removing non-significant confounding variables allowed me to include larger sample sizes in the final analyses, since data was not complete for some variables. To this effect I removed BMI and regular NSAIDS from all regression models, and anxiety and depression from models analyzing cardiac disease by chronic pain distribution and by chronic pain disability. I removed smoking from all models using cardiac disease in the last year as the dependent variable, and diabetes from the regression model analyzing cardiac disease in the last year against chronic pain disability. Results of the regression analysis are presented in Chapter III.

Strengths and weaknesses of observational studies

The use of systematic reviews to collate published evidence is becoming increasingly relevant in epidemiological research (74). Synthesising data from observational studies may be particularly useful in the assessment of risk factors and diseases where access to data from controlled trials is either not available or not feasible (for example, where outcomes are rare, or exposure to the risk factor would be considered unethical in the experimental setting).

The pooling of research outside the constraints of well-designed randomised controlled trials may be limited by 'heterogeneity'. Heterogeneity amongst studies may occur as a result of variations in study design, methodology, statistical analysis and quality of reporting (74-77). For such reasons, researchers have questioned the validity of inferences made through the synthesis of observational studies (77-79). Furthermore, meta-analyses of studies based on observational data are prone to the same limitations attributable to the syntheses of randomised controlled trials, in particular of publication bias (80, 81). Limitations aside there are many examples where the synthesis of observational data has helped improve our understanding of diseases and their associated risks. The Burden of Disease project aims to obtain 'best estimates' of disease prevalence, through pooling of global data. These estimates may be based on a small number of studies, of varying methodological quality, resulting in pooled outcomes with high levels of heterogeneity (82, 83). Nonetheless, the pooled outcomes are generally

accepted as useful qualifiers of disease burden that have the potential to direct further research and the allocation of resources.

As part of my Thesis I have presented the results of two systematic reviews pooling data derived predominantly from observational studies. I have also presented high-level regression analyses of data collected as part of a large survey of the population of England.

The following sections describe how I chose my study design so as to mitigate the limitations of observational data.

Improving the GRADE of evidence: The authors of the “Grades of Recommendation, Assessment, Development, and Evaluation” (GRADE) Working Group recommend that grading of outcomes derived from observational studies be scored as ‘low’, i.e.: “further research is very likely to have an important impact on our confidence in the estimate of effect, and is likely to change the estimate” (84). However, the working group acknowledge that the grade of evidence may be increased if synthesis of the data is able to demonstrate a strong evidence of association, or evidence of a dose response gradient. The authors have also recognize the role of confounding in assessing the validity of study outcomes; exclusion of potentially confounding variables, and/or the demonstration that such variables alter the strength of the associations in question, are considered acceptable levers to increase the grade of evidence based on observational

studies. These guidelines were influential in the design of the analytical chapters in my thesis. I used a systematic review to identify potential confounding variables in the association between chronic pain and cardiovascular disease (Chapter II). Subsequently, I ensured that these variables were accounted for during my analysis of the data from the Health Survey England (Chapter III). While I acknowledge that it is not possible to make judgments about causation or directionality given the limitations outlined above, readers may feel a greater confidence in the validity of the results given the demonstration of a dose-response gradient.

Reporting bias: The validity of conclusions derived from meta-analyses depends on the ability of researchers to access, and include, all the relevant evidence. Reporting bias is a measure of the barriers that may systematically influence which data is available for synthesis in reviews (85). Publication bias, the observed trait that studies with positive outcomes and/or larger effect sizes are more likely to be published, is a recognised contributor to reporting bias. The mechanisms are multiple; publishers may be more inclined to accept studies that are considered to be of greater ‘impact’ and authors may be less enthusiastic, or reluctant to pursue publication of studies with negative results (86). Other contributors to reporting bias include language bias, citation bias and time-lag bias, all of which may influence access to data that would influence review outcomes (85).

Reporting bias may be presented visually using a Funnel plot, in which the standard error of individual studies is plotted against the outcome effect size.

Asymmetry in the scatter plot suggest reporting bias, which may be further quantified through statistical manipulation of the plot (Egger's test). For my meta-analysis of cardiovascular outcomes in chronic pain it was not practical to measure reporting bias, as the outcome measures I used for pooling were often derived by manipulation of the raw data (to minimise the impact of heterogeneity in study methods). Therefore, the data did not always reflect the outcomes authors had submitted for publication. Accepting the premise that most reviews will be subject to reporting bias, I have attempted to minimise the impact by accessing the grey literature as detailed in the methods section.

Quality appraisal and risk of bias assessment: Assessment of methodological quality has been used extensively in the context of systematic review methods as part of the critical appraisal of included studies (87, 88). There is, however, no gold standard for the assessment of quality in studies reporting disease prevalence estimates (65, 89). A systematic review of quality appraisal tools available for the analysis of observational studies concluded that many were unable to differentiate poor reporting from poor methodological quality (89). Of the five tools that were created specifically for studies of disease prevalence little information was provided with regards to their development, reliability or validity, and most of the appraisals relied heavily on subjective judgments in responding to questions and/or grading of responses (89).

Current best practice guidelines for reporting of systematic reviews draw a distinction between the assessment of methodological quality and the assessment of risk of bias. The latter is considered to be a better measure of the extent to which results of included studies should be believed (76, 87). A 'bias' is a systematic error, or deviation from the truth, which may lead to underestimation or overestimation of the true outcome, and consequently contribute to the heterogeneity observed amongst studies that present otherwise comparable outcomes (87). Bias differs from 'imprecision', whereby multiple replications of the same study would still produce different effect estimates as a result of sampling variation.

For the purposes of my review of chronic pain prevalence (Chapter I) I used a tool that was developed specifically to assess the risk of bias in prevalence studies (65). The tool is a modification of a checklist that was used to assess study quality in a systematic review of the prevalence of low back pain (90). In order to establish the face validity of the tool the authors collated a list of relevant criteria for assessing risk of bias in prevalence studies based on: (i) a peer-reviewed literature-search of existing tools; (ii) recommendations from previous reviews of study assessment tools; and (iii) comparison with checklists that were considered to be of 'good quality' in previous reviews. Finally they undertook a series of consensus exercises with a cohort of musculoskeletal epidemiologists from the Global Burden of Disease 2010 'Low Back and Neck Pain expert group' to generate a more refined list of core criteria complementing those in the original checklist. Once developed, the

tool was found to be easy to apply and demonstrated high inter-rater agreement (65).

Whilst the use of some form of quality appraisal tool is commonplace in systematic review methodology, there is no consensus regarding the appropriate response to study stratification by quality or risk of bias (88).

In my analysis of prevalence estimates, I classified the shortlisted studies into low, medium or high risk of bias, using the aforementioned bias tool. In keeping with my *á priori* methodology plan, I excluded studies deemed to be at high risk of bias from the data synthesis. An alternative approach, and one which is endorsed by the Cochrane study group, is to use sensitivity analysis in estimating the impact of quality on the outcomes measured by pooling study data before and after exclusion of the high risk of bias studies (87). This approach would allow review authors to establish the impact of the high risk of bias studies on pooled outcomes, in particular the impact on statistical measures of heterogeneity. A meaningful increase in the heterogeneity of pooled studies might therefore justify exclusion of the high risk of bias studies. In my analyses, pooled estimates for chronic pain prevalence and chronic widespread pain prevalence using only the medium-risk and low-risk of bias studies already demonstrated very high (>90%) heterogeneity. Therefore, a sensitivity analysis with the addition of high-risk of bias studies would not have been informative.

Statistical heterogeneity: Previous studies attempting to pool data on chronic pain and chronic widespread pain prevalence have been restricted by variations in case definition, study methodology and populations sampled (91-93). These limitations apply equally to studies attempting to quantify the association between chronic pain and cardiovascular disease (94, 95). Systematic reviews bring together a collection of studies that vary methodologically. It is therefore useful to quantify the degree to which there are genuine differences in the underlying studies (heterogeneity), i.e.: differences that may not be explained by random sampling or chance alone. By convention heterogeneity is considered to be low, moderate, and high at I^2 values above 25%, 50%, and 75% respectively (75). High levels of heterogeneity may undermine the process of pooling study outcomes, and some authors have suggested abandoning meta-analysis under these circumstances. However, such purism has been challenged (96). Increasingly investigators will allow pooling of data despite high levels of heterogeneity, in particular where available data make it possible to investigate the possible source of variation through sensitivity analyses and the use of meta-regression. Referring back to In the Global Burden of Disease studies: where heterogeneity is encountered, and after the potential covariates that may have impacted on the differing outcomes have been explored, the assumption is that the studies have ultimately been measuring the same phenomenon, albeit with varying quality (82). I used a similar rational to justify the pooling of prevalence estimates in my analysis of the prevalence of chronic pain in the United Kingdom.

Confounding and regression analysis: A limitation of studies that are based on observational data is the potential for confounders to influence the results. This concern may be addressed through the process of randomization in clinical trials. Following my review of the existing evidence for an association between chronic pain and cardiovascular diseases (Chapter II) I was able to conclude that no single study had satisfactorily considered the spectrum of potentially confounding variables in their statistical models. It was therefore imperative for me to identify and correct for these factors during my analysis of the data from the Health Survey England (Chapter III). In my analyses, I corrected for up to 11 potentially confounding variables (gender, income, age, body mass index, smoking history, hypertension, diabetes, use of non-steroidal anti-inflammatory drugs, anxiety and depression). Despite the inclusion of multiple comparators I elected to retain a statistical significance level of 0.05. In making multiple comparisons the probability of a Type I error (incorrectly rejecting the null hypothesis) increases as the number of comparators increases. Adjusting the P-value for the individual comparisons is an insurance policy against Type I errors. Unfortunately adjustment of the significance level come at the cost of increasing Type II error (falsely accepting the null hypothesis). Correction may be appropriate in the analysis of large volumes of random data. However, there is also reasonable support against the process of adjustment (for multiple comparisons) if there is a clinical or physiological context within which the associations are plausible (97).

Another concern with the inclusion of multiple variables from cross-sectional data is the impact this may have on the quality and quantity of data available. As the number of measured variables increases so do the number of participants with incomplete data. Exclusion of incomplete data reduces the power of the study and also increases the probability of responder bias. In order to maximise the power of my study I used a stepwise regression process. Following the inclusion of all 11 confounding variables in the analysis, I manually removed the variables that were not statistically significant, one at a time, in order of least significance. I repeated this process until the model included only the confounders that were statistically significant.

CHAPTER I: THE PREVALENCE OF CHRONIC PAIN IN THE UNITED KINGDOM, A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES.

Chapter overview

There is no consensus about the burden of pain in the United Kingdom. In the following section I collate and pool existing data on the prevalence of chronic pain phenotypes to produce accurate and contemporary population estimates.

I searched for and found 1737 articles; 19 of these studies matched my inclusion criteria. These presented data from 139,933 adult residents of the United Kingdom. The prevalence of chronic pain, derived from seven studies, ranged from 35.0% to 51.3% (pooled estimate 43.5%, 95% confidence intervals 38.4% - 48.6%). The prevalence of moderate-severely disabling chronic pain (Von Korff Grades III/IV), based on four studies, ranged from 10.4%-14.3%. Twelve studies stratified chronic pain prevalence by age group. These studies showed that chronic pain increased with age: from 14.3% in 18-25 year olds, to 62% in the over 75 year age group, although the prevalence of chronic pain in young people (18-39 year olds) may be as high as 30%. I summarised reported prevalence estimates for chronic widespread pain (pooled estimate 14.2%, 95% CI 12.3% - 16.1%; five studies), chronic neuropathic pain (8.2% to 8.9%; two studies) and fibromyalgia (5.4%; one study). Chronic pain was more common in female than male participants, across all measured phenotypes.

Introduction

Chronic pain, represented by conditions such as low back pain and osteoarthritis, has recently been highlighted as one of the most prominent causes of disability worldwide by the Global Burden of Disease reviews (98). At the same time national governments have started to recognise that chronic pain represents a major priority and challenge for their public health and social care systems through production of national strategies and convening of Pain Summits in countries including UK, USA and Australia (99-102). Such initiatives emphasise the importance of accurate population-based estimates of chronic pain in helping to drive and inform policies of prevention and care, needs assessments, and surveillance of the impact of interventions, as has happened for other long-term conditions such as cancer and cardiovascular disease.

Despite several high profile national reports highlighting the significance of chronic pain in the United Kingdom (UK) (15, 17, 102, 103), there is little consensus regarding the burden of pain in this country. One estimate suggests that up to 8 million people in the UK live with chronic pain (102), in keeping with a telephone survey of residents across Europe in which 13% of the UK population reported pain of moderate to severe intensity, lasting for a period of greater than six months (27). Estimates based on definitions more closely aligned with that of the International Association of the Study of Pain: “pain that persists beyond normal tissue healing time, which is assumed to be 3 months” (53) have been considerably higher than those quoted from the

European telephone survey (15, 27). The purpose of this chapter was to process existing data on the population prevalence of various chronic pain phenotypes, in order to produce much needed, accurate and contemporary national estimates.

Methods

I devised a protocol for my systematic review in accordance with the PRISMA guidelines (104). The protocol has been registered, and published on PROSPERO (CRD: 42014012993) (105). I have presented a detailed summary of the methods used to generate the summary estimates for chronic pain phenotypes earlier in the Thesis. In summary: I searched major electronic databases for articles, published after 1990, reporting population-based prevalence estimates of chronic pain (pain lasting greater than three months), chronic widespread pain, fibromyalgia and chronic neuropathic pain. I used meta-analysis to derive pooled prevalence estimates for chronic pain and chronic widespread pain.

Results

After removal of duplicates the initial search generated 1726 studies. From this cohort, I reviewed 87 full-text articles for eligibility assessment. I identified a further 11 articles through parallel searches, as described in the methods section. I have included flowcharts of the screening and selection processes under Appendices 1(b) and 1(c).

Of the twenty-five papers shortlisted for detailed analysis I excluded six on the basis of high risk of bias. One reasons for excluding articles were the use of non-standardised definitions of chronic pain phenotypes (106, 107) (case definition and period prevalence risk). I also excluded studies that surveyed adults that I did not feel were representative of the general population (108-111) (study population and sampling frame risk). A breakdown of the risk of bias scoring, for both included and excluded articles is presented under Appendix 1(d).

I included 19 articles for synthesis in the review: 13 cross-sectional studies, 4 cohort studies and 2 case control studies nested in population cohorts.

Collectively the articles present prevalence data on 139,933 residents of the United Kingdom. The baseline characteristics of included studies are presented in Table 1. I was only able to perform meta-analysis using two of the study phenotypes: chronic pain and chronic widespread pain.

Table 1: Overview of studies included in systematic review of the prevalence of chronic pain phenotypes

Study	Study design	Sample source	Sample size	Response rate (Corrected)	Male (n)	Age range (Mean)	Prevalence estimates included in systematic review						Method for data retrieval	Risk of Bias	Primary aim
							CP	CWP	FM	NeP	CPG	Age			
Beasley et al. (2014)	Cross-sectional	2 GP practices in UK	14680 ¹	-	-	-	*	*					Postal questionnaire	Moderate	To see if the distribution of reported pain sites has any association with a number of potential risk markers
Macfarlane et al. (2009)	Cohort	GB Birth cohort	12069	78.0%	49.4% (3918)	45		*					Interview and examination	Moderate	To determine to what extent the reporting of pain in adulthood varies by adult socioeconomic status
Gale et al. (2012)	Cohort	GB Birth cohort	11971	78.3%	49.2% (3399)	45 (45)		*					Questionnaire	Low	To investigate the relationship between intelligence in childhood and risk of CWP in adulthood
Smith et al. (2004)	Cross-sectional	UK RCP OCP study	11797	85.4%	0%	-	*					*	Postal questionnaire	Moderate	To examine the prevalence and factors associated with CP among women still in the RCoGP OCP Study
Croft et al. (2003)	Case Control nested in Cohort	UK RCP OCP study	11797	85.4%	(0)	(55)		*					Questionnaire	Low	To identify associations between illness episodes and future pain complaints
Jones et al. (2007)	Cohort	GB Birth cohort	10453	89.7%	-	44-46 (45)		*					Postal questionnaire	Low	To examine whether children with common symptoms experience an increased risk of CWP as adults
Torrance et al. (2013)	Cross-sectional	10 GP practices, 5 locations across England and Scotland	10000	44.5% (47.0%)	42.9% (1846)	>18 (53)	*			*	*	*	Postal questionnaire	Moderate	To estimate the proportion of NeP in the population that is "refractory"
Bridges (2013)	Cross sectional	Postcodes across England	8599 ¹	(66.0%)	44.4% (3817)	16-100	*				*	*	Interview	Moderate	To determine the prevalence of chronic pain
Vandenkerkhof et al. (2011)	Case Control nested in Cohort	UK Birth cohort (England, Scotland and Wales)	8572 ¹	-	-	45 (45)	*	*					Postal questionnaire	Moderate	To examine the relationship between diet and lifestyle, and CWP
Torrance et al. (2006)	Cross-sectional	6 GP practices (Grampian,	6000	50.0% (52.4%)	44.4% (1333)	18-96 (50)	*			*	*		Postal questionnaire	Moderate	To improve the understanding of chronic pain with neuropathic features using

													epidemiologic research
Elliott et al. (1999)	Cross-sectional	Leeds, London) 29 GP practices across Grampian, Scotland	5036	71.6% (82.3%)	48.3% (1741)	>25	*			*	Postal questionnaire	Low	To quantify and describe the prevalence and distribution of CP in the community
Smith et al.² (2001)	Cross-sectional	29 GP practices across Grampian, Scotland	4611	78.2% (82.3%)	48.3%	>25			*		Postal questionnaire	Moderate	To describe the prevalence and distribution in the community of CP defined as 'significant' and 'severe'
Jones et al. (2015)	Cross-sectional	Grampian NHS register	4600	34.9% (36.3%)	45.0%	>25 (55)		*			Postal questionnaire	Moderate	To determine the population prevalence of FM
Aggarwal et al. (2006)	Cross-sectional	1 GP practice in Manchester	4200	59.6% (72.0%)	45% (1035)	18-75 (Mdn = 48)		*			Postal questionnaire	Moderate	To investigate the co-occurrence, in the general population, of syndromes that are frequently unexplained
Parsons et al. (2007)	Cross-sectional	16 GP practices across SE England	4171	60% (62.0%)	44.0% (1073)	18-102 (52)	*			*	Postal questionnaire	Moderate	To measure the prevalence and troublesomeness of musculoskeletal pain in different body locations and age groups
Macfarlane et al. (2010)	Cross-sectional	3 GP practices across NW England	3950	69.9% (80.3%)	41.1% (1020)	25-65 (Mdn = 54)		*			Postal questionnaire	Moderate	To determine whether the report of pain is influenced by meteorological conditions
Macfarlane et al. (1999)	Cross-sectional	1 GP practice in Manchester	3004	65.0% (75.0%)	42.8% (835)	18-65		*		*	Postal questionnaire	Moderate	To determine whether psychological symptoms and mental disorder are an intrinsic part of the CWP syndrome
Mallen et al. (2005)	Cross-sectional	3 GP practices in North Staffordshire	2389	35.9% (37.0%)	-	18-25	*			*	Postal questionnaire	Moderate	To establish the prevalence of severely disabling CP in young adults
Croft et al. (1993)	Cross-sectional	2 GP practices in Cheshire	2034	66% (75.0%)	43.0% (572)	20-85 (Mdn = 46)	*	*		*	Postal questionnaire	Moderate	To establish the prevalence of CWP and associated symptoms in a general population sample

Abbreviations: CP (chronic pain), CPG (chronic pain grade), CWP (chronic widespread pain), GP (General practitioner), FM (fibromyalgia), Mdn (median), n (number), NeP (neuropathic pain)

¹n = population responded (denominator not stated) ²Population sample is a duplicate from Elliot et al. therefore only age stratified prevalence estimates have been included

Chronic pain prevalence: Ten studies presented prevalence data for chronic pain, two of which were from age-restricted cohorts and the latter are therefore excluded from the national synthesis: a United Kingdom (England, Scotland and Wales) birth cohort of residents aged 45 years (112), and a survey of 18-25 year olds from the North Staffordshire region (113). One study drew participants from a cohort of women previously enrolled in a national study looking at the long term effects of the oral contraceptive pill (114), and therefore did not present any pain prevalence data for males. The remaining seven articles reported data on general population samples from various regions across the United Kingdom (15, 63, 115-119). Male participants comprised between 41.4% and 49.5% of the survey respondents. The reported prevalence of chronic pain in the United Kingdom ranged from 35.0% to 51.3% (Table 2); pooled estimate 43.5%, 95% confidence interval [CI] 38.4% - 48.5%. I have presented a forest plot of the studies included in the meta-analysis, arranged by date order in Figure 1. The forest plot demonstrates high variability among the pooled studies (I^2 98.9%, $p=0.00$).

Where gender was specified, the prevalence was consistently higher in female participants (37.0% to 51.8%) than in male participants (31.0% to 48.9%).

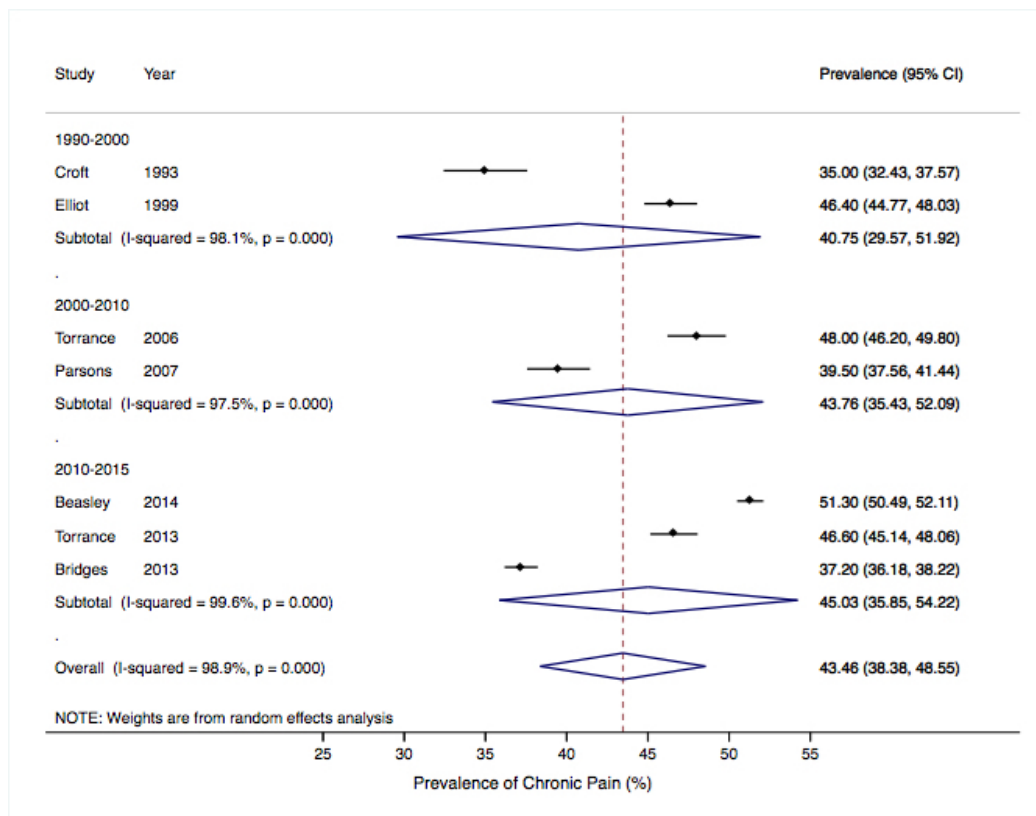
Table 2: Studies reporting estimates for chronic pain prevalence

Study	Pain Definition	Sample size (response)	Male (n)	Age range (Mean)	Prevalence total [95% CI] (n)	Prevalence in males [95% CI]	Prevalence in females [95% CI]
<i>Studies excluded from meta-analysis</i>							
Smith et al. (2004)	Aches or pains in previous 1/12, lasting >3/12	11797 (85.4%)	0%	-	-	-	38.40%
Mallen et al. (2005)	Pain in the previous 6/12, lasting for >3/12	2389 (37.0%)	-	18-25	14.3% (119)		
Vandenkerkhof et al. (2011)	Aches or pains in previous 1/12, lasting >3/12	8572 ¹	-	45 (45)	53.3% (4573)	-	-
<i>Studies reporting data from 1990-2000</i>							
Croft et al. (1993)	Pain in previous 1/12, lasting >3/12	2034 (75.0%)	43.0% (572)	20-85 (Mdn = 46)	35.0%	-	-
Elliott et al. (1999)	Current pain or discomfort, present for >3/12	5036 (82.3%)	48.3% (1741)	>25	46.4 ² (1817)	48.9% [37.0-61.4%]	51.8% [41.8-61.0%]
<i>Studies reporting data from 2001-2009</i>							
Torrance et al. (2006)	Current pain or discomfort, present for >3/12	6000 (52.4%)	44.4% (1333)	18-96 (50)	48.0% (1420)	-	-
Parsons et al. (2007)	Current pain, present for >3/12	4171 (62.0%)	44.0% (1073)	18-102 (52)	39.5% ⁴ (966)	37.2% ⁴	41.3% ⁴
<i>Studies reporting data from 2010-2015</i>							
Beasley et al. (2014)	Pain lasting >3/12		-	-	51.3% (7536)	-	-
Torrance et al. (2013)	Currently troubled by pain or discomfort, present for >3/12	10000 (47.0%)	42.9% (1846)	>18 (53)	46.6 ² (2202)	45.0% ³	47.9% ³
Bridges (2013)	Current pain, present for >3/12	8599 (66.0%)	44.4% (3817)	16-100	37.2% (3202)	31.0%	37.0%

Abbreviations: CI (confidence intervals), Mdn (median), n (number)

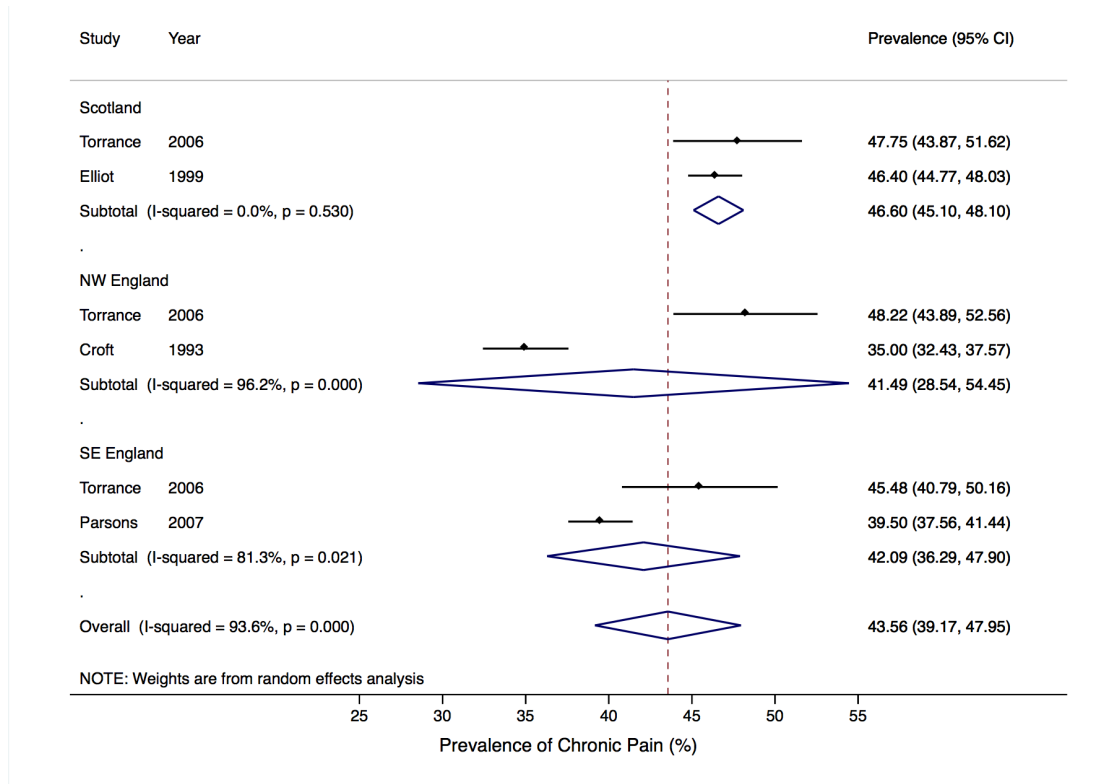
¹n = population responded (denominator not stated). ² Age/gender adjusted estimate. ³ Gender estimates were calculated from a smaller data-set of 4306 participants. ⁴ Presented figures have been derived from tabulated data presented in article

Figure 1: Pooled estimates for chronic pain prevalence by date of publication



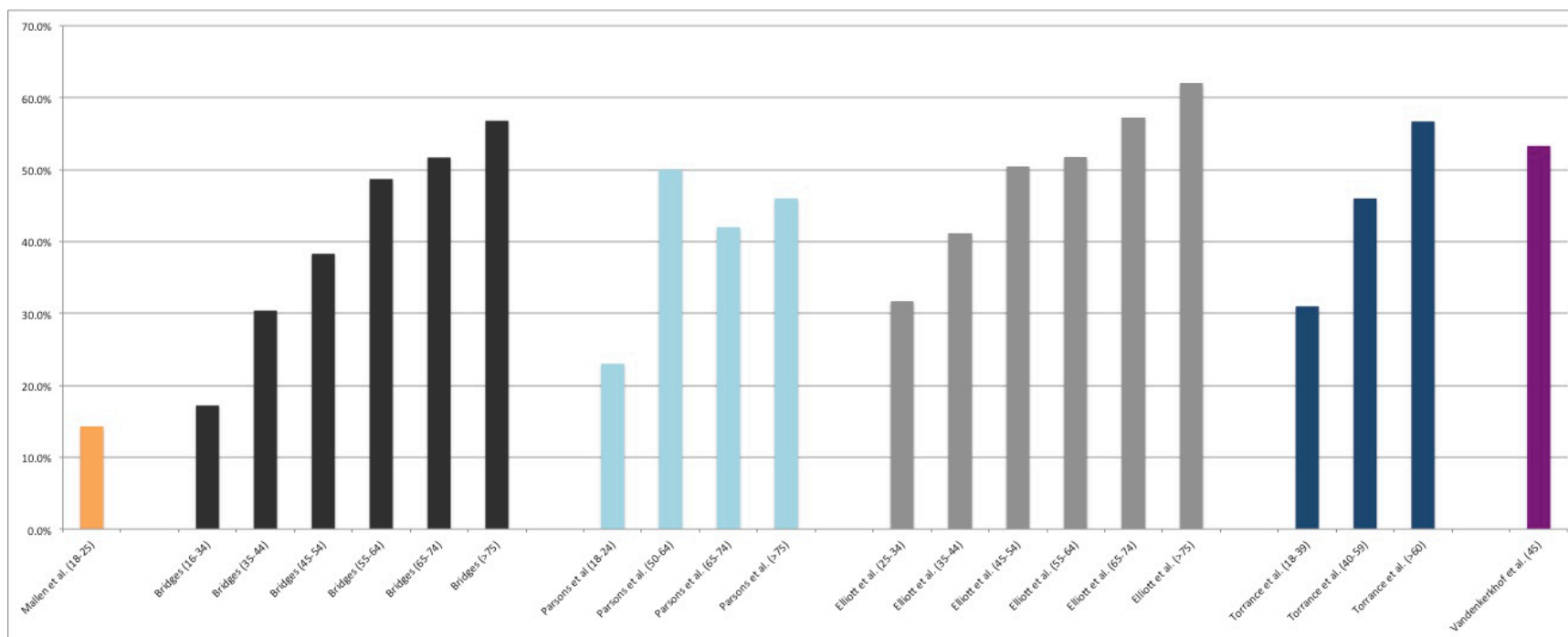
Exploration of sources of heterogeneity: I explored potential sources of heterogeneity through stratified analysis of the included studies. The gender and age distributions did not vary enough amongst the studies to justify different categories, nor was there significant variability in survey methodology. However, pooling of estimates according to publication date suggests an increase in chronic pain prevalence over time: 40.8% (95% CI 29.8-51.9) across studies published between 1990-2000; 43.8% (95% CI 35.4-52.1) from studies published between 2000-2010; increasing to 45.0% (95% CI 35.8-54.2) from studies published after 2010 (Figure 1). Differences were also apparent with geography: three studies included in the chronic pain meta-analysis presented data from distinct geographical locations: Scotland (Grampian) (63), SE England (116) and NW England (Cheshire) (117) respectively; one additional study presented stratified estimates for all three areas (118). There was some evidence of geographical variation ranging from 41.5% (95% CI 28.5-54.5) in NW England, to 46.6% (95% CI 45.1-48.1) in Scotland (Figure 2), although there are too few studies to draw any firm conclusions.

Figure 2: Pooled estimates for chronic pain prevalence by geographical region



Chronic pain prevalence by age: Twelve studies presented data stratified by age groups: chronic pain in seven studies (15, 63, 112-115, 117), chronic widespread pain in six studies (112, 116, 120-123), and neuropathic pain in one study (115). Age strata did not overlap precisely across the studies, making synthesis of the data impractical. Within studies, chronic pain prevalence increased steadily with age from a low of 14.3% in 18-25 year olds (113) to a peak of 62% in the over 75 age group (63). A single exception to this trend was observed in one instance where reported pain prevalence amongst 50-64 year olds was higher than that reported in the older age strata (117). Two of the five articles presenting data in the youngest age-strata (18-39 year olds) reported prevalence estimates greater than 30% (63, 115). The data for chronic pain has been tabulated in Figure 3. Similar patterns of increasing prevalence with age were demonstrated in studies looking at chronic widespread pain and neuropathic pain, with one single exception. In this instance the prevalence of chronic widespread pain in 65-74 year olds was lower than the prevalence in the 55-64 year old bracket; stratification by gender demonstrates that the observed drop is due to reduced pain reporting by male participants in the 65-74 year old age bracket (116). The prevalence of chronic widespread pain ranged from 6.8% in 18-32 year olds (121) to a peak of 21% in the over 75 age group (116). Neuropathic pain prevalence by age was reported in a single study demonstrating increasing pain prevalence: 6.3%, 9.7% and 10.4% in 18-39 year olds, 40-59 year olds and over 60 year olds respectively.

Figure 3: Chronic pain prevalence by age strata



Chronic pain severity: Four articles presented data on chronic pain prevalence that were stratified according to pain severity (15, 115, 117, 124). Authors defined pain severity using the ‘Chronic Pain Grade Scale’ (CPGS) tool developed by Von Korff and colleagues (58). This tool has been validated for use in chronic pain research (59). I have summarised the results in Table 3. The national prevalence of moderately limiting, high disability pain (Grade III) ranged from 4.7% to 6.5%, and that of highly limiting, high disability pain (Grade IV) from 5.7% to 7.8% of the total population. Combining these two groups: between 10.4% and 14.3% of the population of the United Kingdom report severely disabling chronic pain that is either moderately or severely limiting (Von Korff Grades III and IV, respectively).

One article presented data on chronic neuropathic pain severity estimating that 1.8% to 2.6% of the population experience Grades III and IV chronic neuropathic pain, respectively (115).

Table 3: Studies reporting prevalence estimates for moderate or severe chronic pain

Study	Pain measure	CPGS Grade III	CPGS Grade III by gender	CPGC Grade IV [95% CI]	CPGS Grade IV by gender [95% CI]
Smith et al (2001)	Chronic pain	-	-	6.3% [5.9-6.7%] 5.7% [4.9-6.5%] ²	M = 5.7% [4.6-6.8%] F = 6.9% [5.7-8.1%]
Torrance et al (2013)	Chronic pain	6.2%	-	6.0%	-
Parsons et al (2007)	Chronic pain	6.5%	-	7.8%	-
Bridges¹ (2013)	Chronic pain	4.7%	M = 3.9% F = 5.2%	7.2%	M = 6.5% F = 7.7%
Torrance et al (2013)	Neuropathic pain	1.8%	-	2.6%	-

Abbreviations: Chronic pain grade scale (CPGS), Confidence interval (CI), Female (F), Male (M)

¹Gender stratified prevalence estimates from Bridges (2013) have been retrieved by access to the raw data

²estimates adjusted to sampling frame

Chronic widespread pain prevalence: Ten studies presented prevalence data for chronic widespread pain. I excluded four studies that surveyed age-restricted birth cohorts of the British population (112, 120, 122, 123), as well as one study that reported estimates from a gender restricted cohort (125) from the pooled analysis. The remaining five articles reported data on samples representative of the general population from various regions across the United Kingdom (116, 119, 121, 126, 127). I have reproduced prevalence estimates from all ten studies in Table 4. I have also presented pooled data in a forest plot (Figure 4). The plot demonstrates high variability amongst the included studies (I^2 91.5%, $p=0.00$).

The reported prevalence of chronic widespread pain ranged from 11.2% to 16.5% (pooled estimate 14.2%, 95% CI 12.3% - 16.1%). Prevalence estimates were again higher in female (12.3% to 17.9%) than in male participants (9.0% to 14.1%).

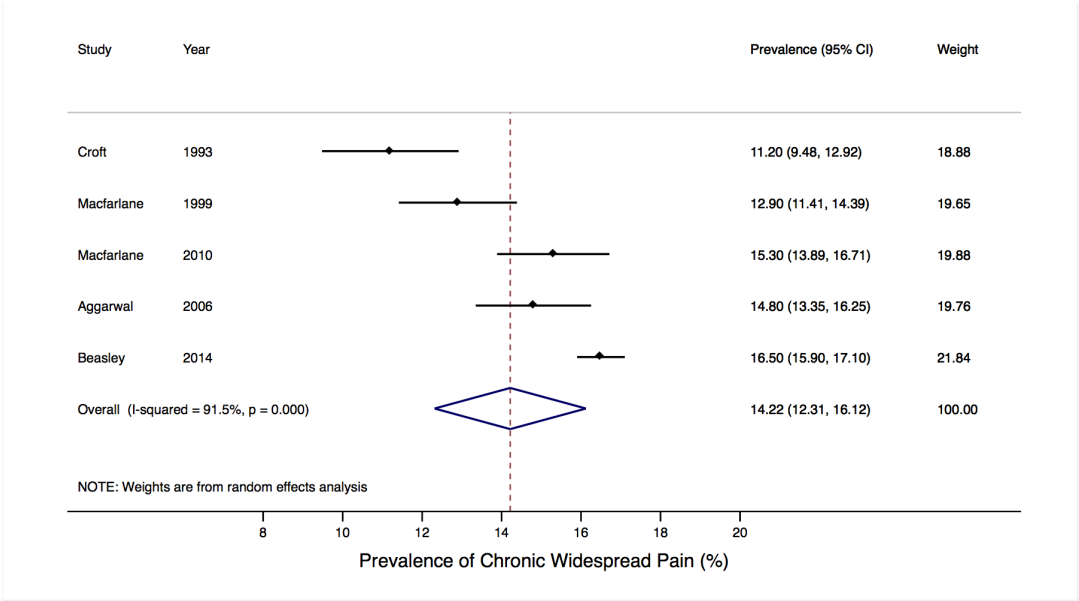
Table 4: Studies reporting prevalence estimates for chronic widespread pain

Study	Pain Definition	Sample size	Male (n)	Age range (Mean)	Prevalence total (n)	Prevalence in males	Prevalence in females
Studies excluded from meta-analysis							
Croft et al. (2003)	ACR in the past 1/12 for >3/12	11797	(0)	(55)	-	-	12.30%
Jones et al. (2007)	ACR in the past 1/12 for >3/12	10453	-	44-46 (45)	12.2%	11.8%	12.7%
Macfarlane et al. (2009)	ACR in the past 1/12 for >3/12	12069	49.4% (3918)	45	11.8%	-	-
Vandenkerkhof et al. (2011)	ACR in the past 1/12 for >3/12	8572 ¹	-	45 (45)	12.3% (1056)	12.0%	13.0%
Gale et al. (2012)	ACR in the past 1/12 for >3/12	11971	49.2% (3399)	45 (45)	14.4% (993)	14.1%	14.7%
Studies included in meta-analysis							
Macfarlane et al. (1999)	ACR in the past 1/12 for >3/12	3004	42.8% (835)	18-65	12.9% (252)	10.5%	14.7%
Croft et al. (1993)	ACR in the past 1/12 for >3/12	2034	43.0% (572)	20-85 (Mdn = 46)	11.2 ² (164)	9.40%	15.60%
Aggarwal et al. (2006)	ACR for >3/12	4200	45% (1035)	18-75 (Mdn = 48)	14.8% (340)	9.0%	17.9%
Macfarlane et al. (2010)	ACR in the past 1/12 for >3/12	3950	41.1% (1020)	25-65 (Mdn = 54)	15.3% (381)	-	-
Beasley et al. (2014)	ACR in the past 1/12 for >3/12	14680 ¹	-	-	16.5%	-	-

Abbreviations: ACR (American College of Rheumatology), Mdn (median), n (number)

¹n = population responded (denominator not stated). ² Age/gender adjusted estimate

Figure 4: Pooled estimates for chronic widespread pain prevalence



Chronic neuropathic pain prevalence: Two studies, from the selection presenting data on chronic pain, also screened participants for features predictive of neuropathic pain. The authors defined neuropathic pain as a score of 12 or greater on the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire. The studies estimated the prevalence of chronic neuropathic pain based on responses from 16,000 residents registered with general practitioner (GP) surgeries across England and Scotland. They report this as 8.9% and 8.2% in their respective studies (115, 118). Estimates for chronic neuropathic pain prevalence were higher in female participants (9.2% to 10.2%) than in males (6.7% to 7.9%).

Fibromyalgia prevalence: Only one study (128) provided comprehensive data from populations representative of the general population. This may reflect the evolving awareness and acceptance of this condition, and the practical restrictions of formally diagnosing a patient with fibromyalgia (requiring a history and examination in order to exclude alternative causes for widespread pain, and to establish the presence of the defined criteria (55)). This study used a modification of the ACR (2010) preliminary diagnostic criteria for fibromyalgia which relies on self-reported pain and somatic symptoms, and was developed specifically for use in epidemiological studies (129). The authors estimated the population prevalence of fibromyalgia to be 5.4% (95% CI 4.7–6.1) (128). A small proportion of respondents to the survey (2.4% of the source population) were invited for clinical examinations in order ascertain prevalence rates of fibromyalgia using the conventional

diagnostic criteria developed in 1990. The authors then weighted these figures back to the target population in order to generate 'general population' estimates, against which the modified research criteria could be compared. However, the methodology used to generate the latter prevalence estimates was subject to a greater risk of bias. I have therefore only included figures based on the modified criteria, and derived from the larger (source) population, in this review.

CHAPTER II: ASSESSING THE RELATIONSHIP BETWEEN CHRONIC PAIN AND CARDIOVASCULAR DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Chapter overview

Chronic pain is a potentially disabling condition affecting approximately 43% of the population of the United Kingdom (see Chapter I), through impaired physical function and quality of life. It may also be associated with an increased prevalence of cardiovascular disease. I have performed a systematic review and meta-analysis to better define the association between chronic pain and cardiovascular health.

Twenty-five studies matched my predefined inclusion criteria. I have synthesized the data from these studies in my review, demonstrating statistically significant associations between chronic pain and mortality from cardiovascular disease: pooled odds ratio (OR) 1.20, 95% confidence intervals (CI) 1.05-1.36; chronic pain and cardiac disease: pooled OR 1.73, 95% CI 1.42-2.04; and chronic pain and cerebrovascular disease: pooled OR 1.81, 95% CI 1.51-2.10. I have also found evidence supporting a dose-response gradient in this relationship, with greater pain intensity and distribution producing a stronger association with cardiovascular outcomes.

Introduction

Claims of a causal link between back pain and cardiovascular disease appear in studies as far back as 1950 (130). The pathological rationale for this was based on the idea that back pain may result from atherosclerotic disease of the lumbar arteries (131). However, more recent evidence points to an effect across a spectrum of chronic pain conditions including pelvic pain, neuropathic pain and fibromyalgia (33, 37, 132).

Whilst chronic pain and cardiovascular disease share common risk factors (smoking, increasing age, depression), the chronic stress associated with pain may itself be a risk factor for heart disease. A causal association is supported by findings that chronic pain is associated with dysfunction of the autonomic nervous system, the inflammatory system and endothelial processes; all of which play a part in the pathophysiology of cardiovascular disease (40-46).

The aim of this chapter was to review the evidence for a link between chronic pain and cardiovascular disease. Where possible, I have qualified the strength of this association by pooling data as part of a meta-analysis. I have provided further support for an association by establishing a dose-response gradient (whereby increasing pain severity results in greater cardiovascular disease). Finally, I have attempted to evaluate the extent to which potentially confounding variables may contribute to this association.

Methods

I devised a protocol for this systematic review in line with the Meta-analysis of Observation Studies in Epidemiology (MOOSE) guidelines (74). The protocol was registered on PROSPERO (CRD: 42013006585) (68) prior to commencing the searches. I have presented a detailed summary of the methods for this review earlier in this Thesis. In summary: I searched major electronic databases for articles reporting strengths of association between chronic pain (pain in any part of the body excluding migraine, for a period of three months or longer) and cardiovascular disease. I used meta-analysis to pool data reporting strengths of association between: chronic pain and cardiac disease, chronic pain and cerebrovascular disease, and chronic pain and cardiovascular mortality. Finally, I have assessed the impact of chronic pain severity and chronic pain distribution (number of body regions affected), as well as the influence of confounding variables on the strength of this relationship; this analysis has been presented as a narrative review.

Results

The searches generated 11,141 studies, of which 1,155 were duplicates. After reviewing article titles and abstracts I shortlisted 31 full text articles for detailed appraisal against the inclusion criteria, resulting in the exclusion of a further six articles. I subjected the remaining 25 studies (12 cohorts studies, 9 cross-sectional studies and 4 case-control studies) to the quality appraisal process outlined in the Methods section. I have summarised the selection process in Appendix 2(b). I have presented the defining characteristics of the studies in Table 5.

Chronic pain and cardiovascular mortality (3 studies; total 'n'=23148): One study reported a borderline significant association between chronic pain and circulatory system deaths, using unadjusted data from a population of primary care patients in Scotland: Hazard Ratio (HR) 1.26, 95% Confidence Intervals (CI) 1.0-1.59 (72). However, the relationship became statistically insignificant following the addition of potentially confounding factors in the analysis: HR 0.86, (95% CI 0.65-1.14). Two remaining studies did not present crude outcomes, but reported statistically insignificant associations between chronic pain and mortality from cardiovascular disease after adjustment for potentially confounding factors; Odds Ratio (OR) 0.95 (95% CI 0.63-1.44) from a cohort of women enrolled in a National Contraceptive Study in Great Britain (133); Relative Risk (RR) 1.0 (95% CI 0.8-1.2) amongst participants from a nationally representative sample from the population of Finland (134).

Table 5: Overview of studies included in the systematic review of the association between chronic pain and cardiovascular disease

Article	Population description	Sample 'n' % Included	Age (average) % Female	Pain Measures (Prevalence)	CV Measures (Prevalence)	Association unadjusted/adjusted for non-modifiable confounders only (95% CI)	Association adjusted for remaining confounders (95% CI)	Confounders accounted	Quality
Conway et al. 2014 United Kingdom <i>[Cross-sectional]</i>	Nationally representative population sample (from Scottish Family Health study)	12881	Not given Not given	CP (36.3%) Severe CP [CPGS III/IV] (6.1%)	Rose Angina CVD [Self reported cardiac disease + use of cardiac drugs]	CP and Rose Angina, OR 3.42 (2.98-3.92); CP and CVD, OR 1.46 (1.30-1.64). Severe CP and Rose Angina OR 4.4 (3.7-5.2)		Age, Gender	Low
Cote et al. 2000 Canada <i>[Cross-sectional]</i>	Nationally representative population sample	2184 51.8%	20-69 53.4%	Severe neck pain [CPGS III/IV] (4.8%)	CVD [Disorders with moderate/severe impact on health] (4.1%)		Severe neck pain vs. Grade 0 neck pain and CVD, OR 5.66 (1.29-24.87)	Age, sex, education, headache, digestive disorders, LBP, smoking, vehicular collision with neck injury	Low
Ha et al. 2014 South Korea <i>[Cross-sectional]</i>	Nationally representative population sample	31705 43.7%	20-89 56.1%	CLBP [LBP >3/12] (16.6%)	CVD [Cardiac infarction and angina] (2.1%) CVA (2.0%)	CLBP and CVD, OR M 2.09 (1.32-3.30) F 2.43 (1.64-3.60); CLBP and CVA, OR M 1.74 (1.02-2.97), F 2.14 (1.41-3.24)	CLBP and CVD, OR M 2.16 (1.34-3.49) F 2.26 (1.51-3.38); CLBP and CVA, OR M 1.53 (0.91-2.58), F 1.95 (1.28-2.97)	Age, income, education, BMI, exercise habits, occupation	Moderate
Makela et al. 1991 Finland <i>[Cross-sectional]</i>	Nationally representative population sample (from Min-Finland Health Study)	8000 90.2%	>29 54.5%	Chronic neck pain [>3/12] (M 9.5% F 13.5%)	CVD [Abnormal clinical findings, including HTN] (28.8%)	Chronic neck pain and CVD, OR 1.37 (1.16-1.61)	Chronic neck pain and CVD, OR 1.18 (0.98-1.42)	Age, sex, obesity, DM, smoking, physical stress at work, any mental disorder, other (various) chronic MSK pain, any respiratory disorder.	Low
Ohayon et al. 2012 Germany <i>[Cross-sectional]</i>	Residents randomly sampled from telephone directory	3786 79.5%	15-100 51.4%	CP exc NeP [pain >3 days a week for >3/12] (18.4%) CNeP (6.5%)	Heart disease CVA	CP (excluding NeP) and Heart disease OR 1.6 (1.0-2.4); NeP and Heart disease, OR 2.5 (1.5-4.2). CP (excluding NeP) and CVA OR 1.1 (0.6-2.0); NeP and CVA, OR 2.5 (1.3-4.7)		Age, Sex	Moderate
Parsons et al. 2015 United Kingdom <i>[Cross-sectional]</i>	Adults randomly selected from 8 General practices in Scotland and England	45994 33.0%	>24 (56) 57.0%	Any Pain [>1/day] Severe CP [CPGS IV]	Angina (3.5%) Heart attack (3.7%)	Severe CP vs. Grade 0 CP and Heart attack, OR 3.87 (2.58-5.80); Severe CP vs. Grade 0 CP and Angina, OR 3.57 (3.40-5.32)	Severe CP vs. Grade 0 CP and Heart attack, OR 2.47 (1.43-4.28); Severe CP vs. Grade 0 CP and Angina, OR 3.17 (1.71-5.85)	Age, sex, BMI, DM, HTN, smoking, activity, depression, alcohol consumption	Moderate
Ryan et al. 2014 England <i>[Cross-sectional]</i>	Nationally representative population sample	8947 59.8%	>44 54.3%	Chronic MSK pain [ICD coded chronic MSK disease with current pain] (21.2%)	CVD [All ICD causes of circulatory disease, including HTN]	CMP and CVD >65 age, OR 2.39 (1.95-2.94); CMP and CVD 45-65 age, OR 1.71 (1.36-2.14)	CMP and CVD >65 age, OR 1.83 (1.45-2.30); CMP and CVD 45-65 age, OR 1.27 (0.98-1.66)	Age, gender, social status, BMI, smoking, subjective sedentary behaviour, anxiety, depression, diet, alcohol MSK medication, endocrine and metabolic conditions	Low

Svensson et al. 1983 Sweden <i>[Cross-sectional]</i>	National census of men aged 40-47	940 76.2%	40-47 0.0%	Severe CLBP [LBP occurring daily or >2x/week] (16%)	Angina (6.0%) Claudication (7.4%)	Prevalence of angina if severe LBP 9.5% vs. no LBP 3.3% (p 0.05-0.1); Prevalence of claudication if LBP 16.2% vs. no LBP 3.6% (p <0.001)	Only claudication remained significantly associated with severe LBP after further adjustment	Smoking, physical activity, worry/tension, fatigue, perception of stress, shortness of breath on exertion	Low
Von Korff et al. 2005 United States <i>[Cross-sectional]</i>	Nationally representative population sample (from National comorbidity survey)	9282 61.3%	>17 58.2%	Chronic spinal [back or neck] pain (19%)	Heart attack (4.0%) CVA (4.3%)		Heart attack if chronic spinal pain, OR 0.9 (0.6-1.4) vs. general population; Stroke if chronic spinal pain vs. general population, OR 1.5 (1.1-2.1)	Age, sex, education, ethnicity.	Low
Ablin et al. 2009 Israel <i>[Case-control]</i>	93 patients post cardiac catheterization, 51 healthy volunteer controls	144	42-83 54.8%	FM [ACR 1990] Point tenderness FIQ Score	CAD [Angiographic] Composite cardiac severity score [LVF and CAD]	Prevalence of FM if CAD (33.3%) vs. no CAD (6%)	Tenderness and CAD, r = 0.46 (p = 0.019); FIQ and CAD, r = 0.354 (p = 0.005). Composite cardiac score and FIQ/tenderness, r = 0.354 (p 0.005)	Age, gender, BMI, DM, HTN, smoking, angiotensin converting enzyme inhibitor, insulin and diuretic use	Moderate
Cho et al. 2010 Korea <i>[Case-control]</i>	Females with FM from specialist clinics, 20 age-matched healthy controls	50	42-66 (48) 100.0%	FM [ACR 1990] FIQ Score	Global LV Strain [On 2 Dimensional echocardiography]	Measure of LV strain if FIQ>50 vs. FIQ<50 vs. no FM, -18.6 vs. -22.7 vs. -22.82 (+/- 3.09, 1.46, 9.62)	LV strain and FIQ >50, r = 0.68 (p<0.01)	None. However, controls were matched for age, gender and depression	Moderate
Keller et al. 2012 Taiwan <i>[Case-control]</i>	9269 patients diagnosed with BPS/ICC 46345 matched controls (from Insurance bank)	55614	>17 (50) 81.8%	BPS/ICC [ICD coded]	IHD Stroke		BPS/IC and IHD, OR 1.85 (1.61-2.23); BPS/IC and Stroke, OR 1.68 (1.57-1.79)	Sex, age group, monthly income and geographic region	Moderate
Pontari et al. 2005 United States <i>[Case-control]</i>	463 men with CPPS/CP and 121 asymptomatic age-matched controls	584	20-88 (43) 0.0%	CPPS/CP [Pain in the pelvic region >3/12]	CVD [Self report, raised cholesterol, CAD, arrhythmia, HTN]		CP/CPPS and CVD, OR 7.15 (p = 0.009)	Income and psychiatric disease. However, controls were also matched for age, gender, smoking, education and employment	Moderate
Andersson 2009 Sweden <i>[Cohort]</i>	Random population sample from two municipalities in Sweden	1812 90.0%	25-74 50.4%	CP [>3/12] (55.2%) CWP [Pain in >4 distinct body areas >3/12] (9.4%)	CV deaths [ICD coded] over 13.5 years	CRP and CVD, HR 1.27 (0.76-2.10), CWP and CVD, HR 2.17 (1.12-4.21)	CWP and CVD, HR no longer significant after further adjustment (results not shown)	Age, gender, education, living alone, club membership, employment, smoking, physical activity, BMI, insomnia, anxiety and perception of stress	Moderate
Chen et al. 2014 Taiwan <i>[Matched cohort]</i>	1291 females with BPS/IC, and 3760 matched controls	4512	>17 (47) 100.0%	BPS/ICC [ICD coded]	CVD [ICD coded for IHDx and unspecified CVD] over 3 years	BPS/IC and CVD, HR 2.28 (1.58-3.27)	BPS/IC and CVD, HR 1.65 (1.09-2.48)	Age, income, DM, HTN, High cholesterol, geographical region, chronic kidney disease, urinary tract infection, bladder outlet obstruction, (n) physician visits	Moderate

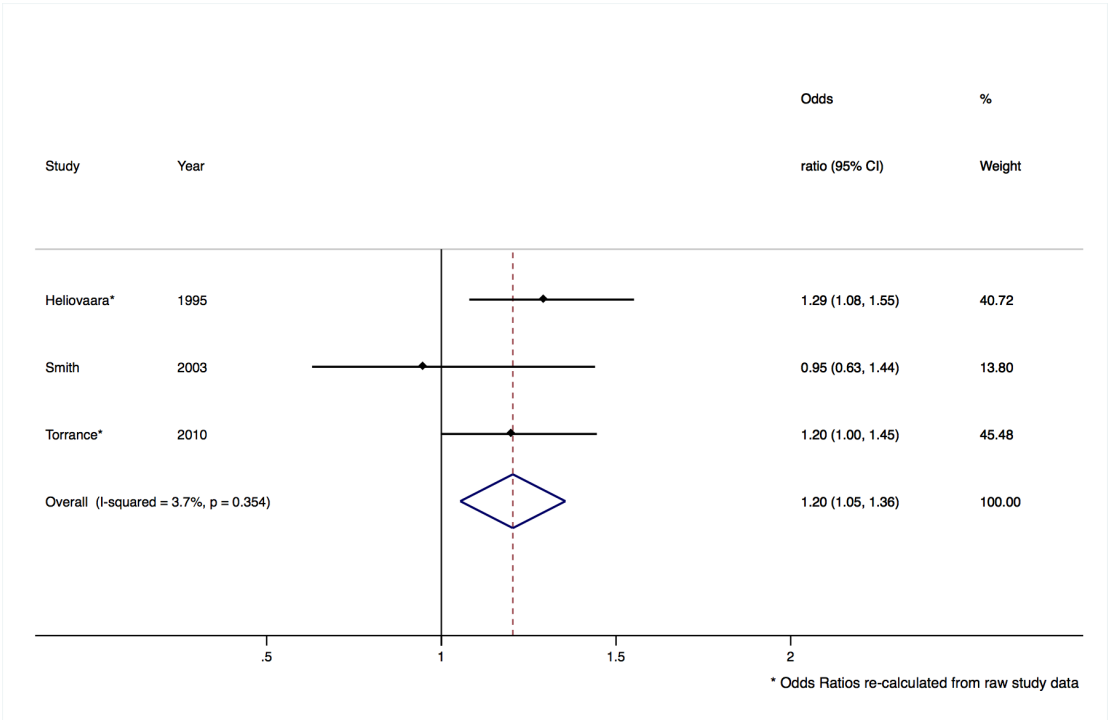
Dreyer et al. 2010 Denmark <i>[Cohort]</i>	Patients referred to Copenhagen Hospital rheumatology service	1361 83.2%	>18 100.0%	FM [ACR 1990]	Death from IHD and CVA [ICD coded] over an average 3.9 years	Deaths from IHD too few to allow analysis. Deaths from CVA if FM; SMR 3.8 (1.2-8.8) times higher than expected for Danish women		None	Moderate
Heliovaara et al. 1995 Finland <i>[Cohort]</i>	Nationally representative population sample	8000 90.2%	>28 54.5%	CLBP [Pain for 3/12 + signs on clinical examination] (17%)	Any CV mortality or Coronary mortality [ICD 8 coded] over 12-14 years		CV Mortality if CLBP, RR 1.0 (0.8-1.2); Coronary Mortality if CLBP, RR 1.0 (0.8-1.3)	Age, sex, smoking	Moderate
Kadam et al. 2005 United Kingdom <i>[Cohort]</i>	Patients registered with a semi-urban general practice in North-East England	3968 57.9%	18-75 53.4%	CRP [<4 areas, for >3/12] (25.9%) CWP [ACR 1990] (8%)	CVD [from primary care codes, may include HTN] over 3 years (14.3%)		CRP and CVD, RR 1.0 (0.8-1.4); CWP and CVD, RR 1.65 (1.1-2.4)	Age, sex, social deprivation, anxiety and depression	Moderate
Lindgren et al. 2010 Sweden <i>[Cohort]</i>	Nationally representative population sample	3928 58.0%	20-74 (47) 53.2%	CRP [<4 areas, for >3/12] (24.5%) CWP [ACR 1990] (12.5%)	CVD [ICD 10 codes for stroke and IHD] for 8.9 years (6.3%)		CRP and CVD, OR 1.6 (1.0-2.4); CWP and CVD, OR 1.9 (1.2-3.1)	Age, sex, SE status, smoking, follow-up time	Moderate
Mease et al. 2010 United States <i>[Matched cohort]</i>	764786 FM patients and 707721 matched controls (from insurance register)	1472507	Not given Not given	FM medicated FM unmedicated	CVD TIA CAD	FM medicated vs. no FM and CVD, IRR 1.19 (p<0.001); FM untreated vs. no FM and CVD IRR 1.35 (p<0.001). FM medicated vs. FM unmedicated and CVD, IRR 2.02 (p<0.001)	Risks remained significant after adjustment for confounders	Not clear. However, control group were matched for age and gender	Low
Smith et al. 2003 United Kingdom <i>[Cohort]</i>	Nationally representative population sample (from Contraception Study)	11797 85.4%	(56) 100.0%	CP [>3/12] (38.4%)	CV mortality [ICD 8 coded, including mortality from HTN] over 7 years (1.1%)		CP and CV Mortality, OR 0.95 (0.63-1.44)	Age, social class, smoking	Moderate
Su et al. 2015 Taiwan <i>[Cohort]</i>	61,612 patients with FM and 184,834 matched controls (from insurance database)	246446	(44) 59.30%	FM [ICD 9 codes for Myositis/Myalgia + treatment >3/12]	CAD: Acute coronary syndrome, angina, IHD, and coronary atherosclerosis	FM and CAD, IRR of 1.64 (95% CI 1.61–1.68) (age and sex matched)	FM and CAD, HR of 1.47 (95% CI 1.43–1.51)	Age, gender, occupation, monthly income, "comorbidities of traditional cardiovascular risk factors", depression, and anxiety	Moderate
Torrance et al. 2010 Scotland <i>[Cohort]</i>	Patients from 29 general practices in Scotland (50% selected based on analgesic prescription)	6940 84.3%	>24 52.7%	CP [>3/12] (12.1% - 36.3%) Severe CP [CPGS III/IV]	All circulatory system deaths [ICD 10 coded] over ten years	CP and Circulatory system mortality, HR 1.26 (1.0-1.59); Severe CP and Circulatory system mortality, HR 2.11 (1.59-2.80)	CP and Circulatory system mortality, HR 0.86 (0.65-1.14); Severe CP and Circulatory system mortality, HR 1.68 (1.20-2.35)	Age, sex, education, housing, long term illnesses	Moderate
Tsai et al. 2015 Taiwan <i>[Matched cohort]</i>	3420 with FM and 10260 matched controls (from insurance database)	13680	>19 55.9%	FM [ICD 9 codes for Myositis/Myalgia + treatment >3/12]	CAD events [new PCI and CABG procedures] over 8.6 years (1.2%)	FM and CAD, HR 2.11 (1.48-3.00)	FM and CAD, HR 1.97 (1.36-2.85)	Age, sex, obesity, DM, HTN, anxiety, depression, NSAIDS, opioids, CV drugs, number of cardiology visits	Moderate

Zhu et al. 2007 Australia <i>[Cohort]</i>	Elderly Australian women (from national Osteoporosis study)	1484	70-85 100.0%	Frequent LBP [daily pain over previous year] (21.8%)	Coronary events [death/new diagnosis of IHD or angina] over 5 years (8.4%)	Frequent LBP and coronary heart events, HR 2.13 (1.35-3.34) when compared to infrequent LBP. Adjusted for Age	Severe LBP and coronary heart events, HR 2.13 (1.32-3.44) when compared to infrequent LBP	Age, BMI, DM, HTN, smoking, analgesic use, raised cholesterol, CVD	Moderate
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Abbreviations: American college of Rheumatology (ACR), Bladder pain syndrome/interstitial cystitis(BPS/IC), Body mass index (BMI), Cardiovascular (CV), Cardiovascular disease (CVD), Cerebrovascular accident (CVA), Confidence intervals (CI), Coronary artery disease (CAD), Chronic pain (CP), Chronic regional pain (CRP), Chronic widespread pain (CWP), Diabetes Mellitus (DM), Fibromyalgia (FM), Fibromyalgia impact questionnaire (FIQ), Chronic Pain Grade Scale (CPGS), Hazard ration (HR), Hypertension (HTN), Incidence risk ratio (IRR), International classification of diseases (ICD), Ischemic heart disease (IHD), Left ventricular failure (LVF), Musculoskeletal (MSK), Myocardial infarction (MI), Non-Steroidal anti-inflammatory drugs (NSAIDS), Odds ration (OR), Osteoarthritis (OA), Percutaneous coronary intervention (PCI), Relative risk (RR), Standardized mortality ration (SMR)

A meta-analysis using the unadjusted or, where these were not extractable, the least adjusted outcomes from these studies, demonstrated a statistically significant association between chronic pain and mortality from cardiovascular disease (Figure 5): pooled OR 1.20 (95% CI 1.05-1.36), I^2 3.7% (p 0.35). I performed a sensitivity analysis by removing the one study that had made adjustments for confounding variables (133) (age, smoking and social class). Following the removal of this study, the pooled estimate [OR 1.25 (95% CI 1.08-1.41), I^2 0% (p = 0.58)] remained significant and fairly similar to the initial results.

Figure 5: Chronic pain and cardiovascular mortality meta-analysis



Chronic widespread pain and cardiovascular mortality (2 studies, total 'n'=2878): A Swedish population study reported increased mortality from cardiovascular causes amongst respondents with chronic widespread pain compared to those without pain: HR 2.17 (95% CI 1.12-4.21), following adjustment for age and sex. The reported association lost statistical significance after further adjustment for life-style confounding variables that included smoking and physical activity. However the adjusted HR was not formally reported (135). A Danish study comparing Fibromyalgia patients from a Rheumatology clinic with adults from the general population reported significantly increased mortality from cerebrovascular accidents in the pain group; SMR 3.8 (95% CI 1.2-8.8) (136). However, the authors did not adjust the statistical models to account for the influence of potentially confounding variables.

Chronic pain severity and cardiovascular mortality (2 studies, total 'n'=7035): One study measured the impact of pain severity, qualified using the Chronic Pain Grade Scale (CPGS), on the association with cardiovascular mortality. The authors demonstrated that severe pain (CPGS grades III-IV) remained significantly associated with mortality from cardiovascular disease even after correction for confounding variables HR 1.68 (95% CI 1.20-2.35) (72). Another study demonstrated that increased frequency of pain symptoms amongst Australian women reporting chronic lower back pain was associated with an increase in the occurrence of coronary events (including death from coronary heart disease) over a 5-year follow-up period; HR for daily back

pain 2.13 (1.32-3.44) when compared to infrequent/no back pain, after adjustments for confounding variables (137).

Chronic pain and cardiovascular diseases (9 studies, total 'n'=118497): Almost all of the studies reporting associations between chronic pain and cardiac disease (n=7), cerebrovascular disease (n=4) or both combined (n=3) demonstrated statistically significant associations between the respective variables (6, 33, 132, 138-143). Effect sizes ranged from OR 1.37 (95% CI 1.16-1.61) for the association between chronic neck pain and cardiovascular disease amongst a nationally representative sample of the population of Finland, to OR 7.15 (p = 0.009) for the association between chronic pelvic pain syndrome and self-reported cardiovascular diseases amongst a cohort of men from the United States (132, 142). Following the introduction of confounding variables into the analyses, statistical significance was lost entirely in only one study (142), and in subsets of participants in three other studies (those aged below 65 in one study, male participants reporting stroke in another study and participants reporting cardiac disease but not stroke in a third study) (6, 140, 143). Full details of the study outcomes are presented in Table 5.

Two studies that used matched controls in their analysis (132, 138) were excluded from pooling, as it was not possible to reliably extract comparable outcome measures. I performed a meta-analysis, using the least adjusted outcomes from the remaining studies. This demonstrated a statistically significant association between chronic pain and cardiac disease: pooled OR

1.73 (95% CI 1.42-2.04), I^2 87.0% ($p < 0.001$) as well as cerebrovascular disease: pooled OR 1.81 (95% CI 1.51-2.10), I^2 83.3% ($p < 0.001$) (Figures 6 and Figure 7).

In most studies Hypertension was adjusted for as a potentially confounding variable. However, in three studies, Hypertension was measured as a primary cardiovascular outcome (thereby contributing to 'cardiovascular disease' burden) (34, 142, 143). I performed a sensitivity analysis by excluding these studies. The removal of these studies did not alter the significance of the pooled outcomes: cardiac disease pooled OR 1.75 (95% CI 1.30-2.21), I^2 87.7% ($p < 0.001$); cerebrovascular disease pooled OR 1.94 (95% CI 1.39-2.50), I^2 79.8% ($p = 0.002$).

Figure 6: Chronic pain and cardiac disease meta-analysis

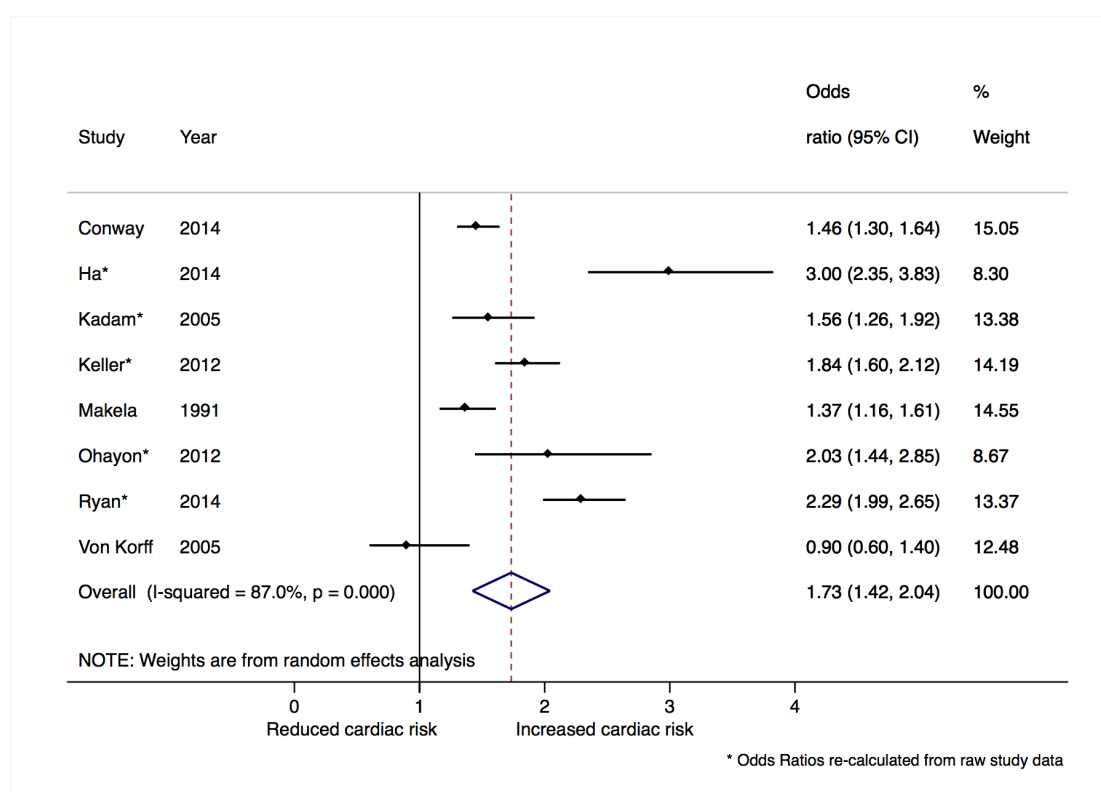
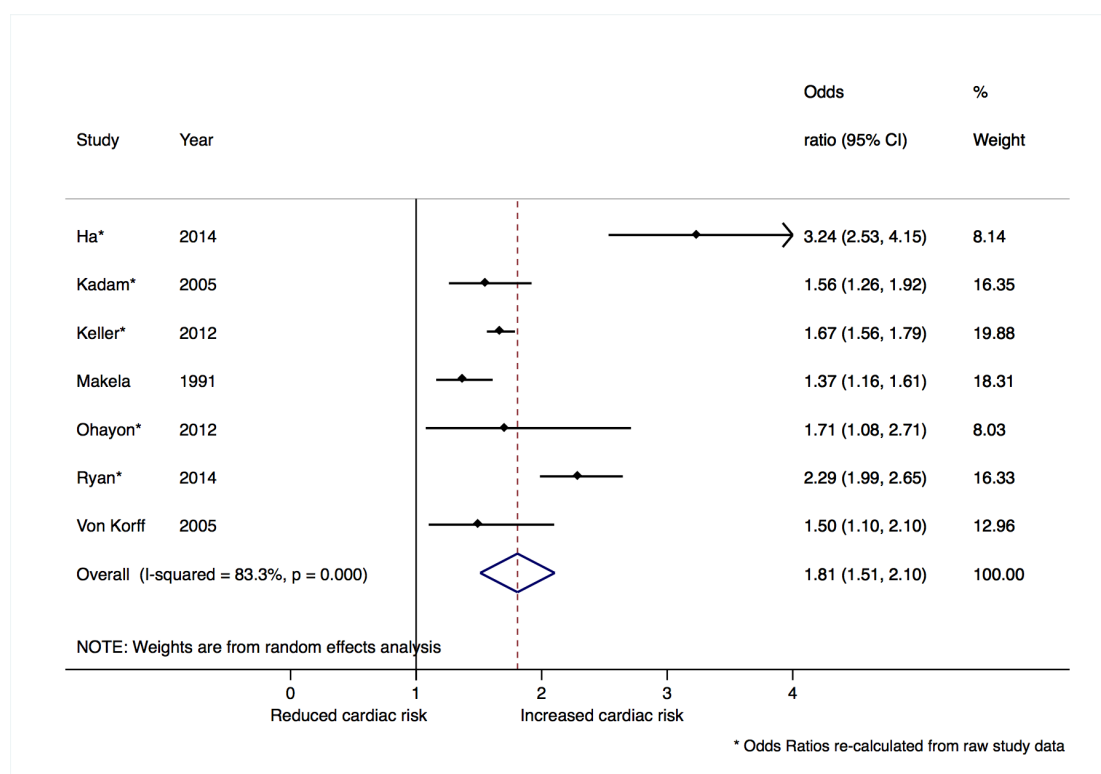


Figure 7: Chronic pain and cerebrovascular meta-analysis



Chronic widespread pain and cardiovascular diseases (7 studies, total 'n'=1737858): All seven studies demonstrated statistically significant associations between chronic widespread pain or fibromyalgia and cardiovascular outcomes, before and after correction for potentially confounding variables (34, 35, 37, 144-147). In two studies participants reporting chronic widespread pain and chronic regional pain were compared (in turn) with pain free cohorts (34, 35). In both studies the outcome measure was greater for the widespread pain cohort than for the regional pain cohorts, and in one study statistical significance was lost for the regional pain cohort (but not the widespread pain cohort) after adjustments were made for confounding variables (34).

Chronic pain severity and cardiovascular diseases (7 studies, total 'n'=1506715): In the studies various methods were used to quantify the severity of pain phenotypes: higher Von Korff pain 'Chronic Pain Grade' (73, 139), presence of neuropathic symptoms (33), scores on numerical pain rating scales (148), frequency of symptoms (137, 149), and qualification based on medication taken for symptoms (146). In all instances the strength of association was greater in the 'more severe' chronic pain group. However, in one instance neither outcome was statistically significant after correction for confounding variables (149). The relevant study results are summarised in Table 6.

Table 6: Chronic pain and cardiovascular disease: a summary of the severity measures used

Study	Severity Measure	High Severity Outcome Measure (95% CI)	Low Severity Outcome Measure (95% CI)	Control group
Conway	Chronic Pain Grade (I-IV)	Grades III-IV CP and Rose Angina OR 4.4 (3.7-5.2)	All CP and Rose Angina, OR 3.42 (2.98-3.92)	No chronic pain
Cote	Chronic Pain Grade (I-IV)	Grades III-IV chronic neck pain and CVD, OR 5.66 (1.29-24.87)	Grades II chronic neck pain and CVD 1.21 (0.33-4.47)	No chronic pain
Mease	Medicated FM vs. non medicated FM	FM subjects taking medication and CVD, IRR 2.02 (p<0.001)	N/A	Unmedicated FM subjects
Ohayon	Neuropathic pain vs. non neuropathic pain	NeP and Heart disease, OR 2.5 (1.5-4.2); NeP and CVA, OR 2.5 (1.3-4.7)	Non NeP CP and Heart disease OR 1.6 (1.0-2.4); Non NeP CP and CVA OR 1.1 (0.6-2.0)	No chronic pain
Parsons	Numeric pain score (1-5)	Chronic pain score 5/5 and Heart attack, OR 3.87 (2.58-5.80); or Angina, OR 3.57 (3.40-5.32)	Chronic pain score 3/5 and Heart attack, OR 1.50 (0.95, 2.38); or Angina, OR 2.01 (1.30-3.09)	Chronic pain score 1/5
Svensson	Frequency of pain symptoms	Prevalence of angina if weekly LBP 9.5%	Prevalence of angina if monthly LBP 8.5%	no LBP 3.3%
Zhu	Frequency of pain symptoms	Daily LBP and coronary heart events, HR 2.13 (1.35-3.34)	Monthly LBP and coronary heart events, HR 1.78 (1.15-2.75)	Infrequent LBP (<1/month)

Abbreviations: CI (confidence intervals), CP (chronic pain), CVA (cerebrovascular accident), CVD (cardiovascular disease), FM (Fibromyalgia), LBP (low back pain), NeP (neuropathic pain), OR (odds ratio)

Exclusions (n=6 studies): I excluded three studies from the review because the duration of pain symptoms did not meet the criteria for chronicity: pain in the past month lasting greater than one week (150); pain in the past month lasting a day or longer (151); or any pain, ache or tenderness on movement in one or more joints during the last month (150). One study (an Abstract) reported data already included in the review under a different first author (152). Finally, two studies addressed the risk of cardiovascular diseases amongst participants meeting the American College of Rheumatology (ACR) definition for Fibromyalgia. I excluded both studies as the Fibromyalgia and Control groups had a similar prevalence of non-specific chronic pain conditions (36, 153).

Quality: I have included a breakdown of the quality scoring for each study under Appendix 2(c). I did not consider any of the included studies to be 'High' Quality, although in general the longitudinal (cohort and case control) studies fared better than the cross-sectional/population studies. The main weakness across both groups of studies was the inadequate inclusion of potentially confounding variables in the statistical modelling; only two of the studies included general analgesic use as a potential confounding risk factor (137, 143); only one study specifically addressed the impact of Non-Steroidal anti Inflammatory Drugs (NSAIDs) (37). I have presented a breakdown of the Quality scores in Table 7.

Table 7: Summary of confounding variables accounted for in the review papers

Authors	Age	Sex	Status	Anxiety	Depression	Smoking	BMI	Diabetes	HTN	Mobility	NSAIDS	Quality	Study Showed a link?
<i>Ablin</i>	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	Moderate	Yes
<i>Andersson</i>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Moderate	Yes, with confounding
<i>Chen</i>	Yes	N/A	Yes	No	No	No	No	Yes	Yes	No	No	Moderate	Yes
<i>Cho</i>	M	M	No	No	M	No	No	No	No	No	No	Moderate	Yes
<i>Conway</i>	Yes	Yes	No	No	No	No	No	No	No	No	No	Low	Yes
<i>Cote</i>	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	Low	Yes
<i>Dreyer</i>	No	No	No	No	No	No	No	No	No	No	No	Moderate	Yes
<i>Ha</i>	Yes	No	Yes	No	No	No	Yes	No	No	Yes	No	Moderate	Yes
<i>Heliovaara</i>	Yes	Yes	No	No	No	Yes	No	No	No	No	No	Moderate	No
<i>Kadam</i>	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Moderate	Yes
<i>Keller</i>	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Moderate	Yes
<i>Lindgren</i>	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No	Moderate	Yes
<i>Makela</i>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Low	Yes, with confounding
<i>Mease</i>	M	M	No	No	No	No	No	No	No	No	No	Low	Yes
<i>Ohayon</i>	Yes	Yes	No	No	No	No	No	No	No	No	No	Moderate	Yes
<i>Parsons</i>	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Moderate	Yes
<i>Pontari</i>	M	M	Yes	Yes	No	M	No	No	No	No	No	Moderate	Yes
<i>Ryan</i>	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Low	Yes
<i>Smith</i>	Yes	N/A	Yes	No	No	Yes	No	No	No	No	No	Moderate	No
<i>Su</i>	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Moderate	Yes
<i>Svensson</i>	No	N/A	Yes	Yes	No	Yes	No	No	No	Yes	No	Low	Yes, with confounding
<i>Torrance</i>	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Moderate	Yes, with confounding
<i>Tsai</i>	M	M	No	M	M	No	No	M	M	No	M	Moderate	Yes
<i>Von Korff</i>	Yes	Yes	Yes	No	No	No	No	No	No	No	No	Low	Yes, with confounding
<i>Zhu</i>	Yes	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate	Yes

M = Matched control groups

N/A = Not Applicable

Abbreviations: BMI (Body mass index), HTN (Hypertension), NSAIDS (Non-steroidal anti-inflammatory drugs)

CHAPTER III: THE ASSOCIATION BETWEEN CHRONIC PAIN AND CARDIAC DISEASE: A CROSS-SECTIONAL POPULATION STUDY

Chapter overview

In the preceding chapter I discussed how chronic pain might increase the risk of cardiac disease. However, the extent to which confounding variables account for this association is yet to be satisfactorily established. In the following section of my Thesis I have examined the possibility for an *independent* association between these two variables.

I analyzed data from 8596 residents of the United Kingdom in order to establish the strength of the association between chronic pain and cardiovascular disease.

Participants reporting chronic pain (n=3023) were more likely to experience cardiac disease than those without pain: odds ratio (OR) 1.55, 95% confidence interval (CI) 1.15-2.07. Subsets of participants fulfilling various criteria for high-intensity chronic pain demonstrated stronger associations with cardiac disease than those with low intensity chronic pain, suggesting a 'dose-response' gradient to the relationship: chronic widespread pain OR 3.3 (95% CI 1.42-7.68); higher-disability chronic pain OR 2.35 (95% CI 1.71-3.23); higher average chronic pain score OR 1.95 (95% CI 1.40-2.71).

Adjustment for regular prescription of non-steroidal anti-inflammatory drugs did not significantly alter the association of chronic pain with cardiac disease.

Introduction

A late 20th Century study reporting that farmers with a history of back pain had an almost five-times greater risk of death from ischaemic heart disease than those without pain raised interest in the possibility of an association between chronic pain and cardiovascular disease (30). A more recent study, using data from a large population survey in England, demonstrated a significantly higher prevalence of cardiac disease in adults (aged 65 and over) who also reported chronic pain (154). This study was limited by the use of surrogates for chronic pain, derived by combining a diagnosis of long-term musculoskeletal conditions with self-reported moderate or severe pain on the day of the survey. While it may not be possible to establish the directionality of an association based on data from cross-sectional studies, there is additional evidence from longitudinal studies suggesting that chronic pain may be a precursor of cardiovascular morbidity (35, 37, 137, 138, 146). Further support for a link between these variables comes from research focusing on pathogenesis. For example, atherosclerosis of the lumbar arteries has been shown to be the forerunner of lower back pain (155), whilst widespread chronic pain has been implicated in alterations of endothelial function (156, 157), hypothalamo-pituitary axis (158) and autonomic nervous system functioning (43, 44, 159, 160).

Some authors have sought to validate a causal relationship between chronic pain and cardiovascular disease by demonstrating a dose-response gradient. In 2000, Cote and colleagues reported that the presence of high-grade

chronic neck pain, defined according to 'Chronic Pain Grade Scale' questionnaire, was more likely to be associated with cardiovascular conditions moderately or severely impacting health than either intermediate grade chronic pain or low grade chronic pain (73). Other authors have shown that the number of pain sites may be relevant to the degree of cardiovascular morbidity by comparing outcomes amongst cohorts of patients reporting chronic widespread pain with those reporting only chronic regional pain (34, 135). Claims that the risk of cardiovascular disease is proportional to the duration, severity or distribution of chronic pain need to be balanced against the understanding that these studies were entirely based on observational data, with little consistency in the terminology used to define pain symptoms and/or cardiovascular indices.

In the previous chapter I summarised the existing evidence in support of an association between chronic pain and cardiovascular disease. However, the ability to establish causation was hampered by the failure of authors to comprehensively address the role of potentially confounding variables, in particular the regular use of non-steroidal anti-inflammatory drugs (NSAIDS) that have well-publicized negative effects on cardiovascular health (161).

In this chapter I have used national data, collected as part of the Health Survey for England (HSE) to explore the hypothesis that chronic pain is independently associated with cardiac disease and that this augmented risk is proportional to the intensity of pain symptoms.

Methods

I have presented details of the methods used to generate outcome measures for the association between chronic pain and cardiovascular disease earlier in this Thesis. In summary: I applied logistic regression analysis to data from 8596 adults surveyed in a population study of the health of the population of England. I quantified the strengths of the association between cardiac disease (angina and/or myocardial infarction) and chronic pain (pain lasting greater than three months). As part of the regression analysis I accounted for ten pre-selected potentially confounding variables: age, gender, income, body mass index, smoking history, hypertension, diabetes, self-reported anxiety and depression and finally regular prescriptions for NSAIDs.

Results

I have presented the characteristics of the study population in Table 8 and Table 9. In total 8610 adults participated in the survey. However, completed data for questions on cardiac disease and chronic pain prevalence were only available from 8596 participants (male = 3815, female = 4781). The median age of survey respondents with completed data was 49 years.

The prevalence of cardiac disease was 5.5% (n = 471). Just over a third of those with cardiac disease (n = 164) were diagnosed in the year leading up to the survey. In both instances male participants reported cardiac disease more frequently than did female participants. Over 35% of respondents (n=3023) reported chronic pain symptoms. Chronic pain symptoms were more common in female participants than in male participants (38% vs. 33%).

Table 8: Participant demographics by chronic pain status and severity

Variable	"n"	"n"=male (%)	Age mean (SD)	Age Range	"n" with Cardiac (%)	"n" with Cardiac last year [§] (%)
Total survey adults	8610	3822 (44)	49.64 (18.7)	16-100	471 (5.5)	164 (1.9)
Cardiac disease						
No	8136	3537 (43)	48 (18.3)	16-100	-	-
Yes	471	283 (60)	70 (12.1)	27-96	-	-
Yes (last year only)[§]	164	97 (59)	70.1 (11.9)	31-94	-	-
Chronic pain						
No	5397	2510 (46)	45.5 (18.3)	16-100	152 (2.8)	27 (0.5)
Yes	3023	1225 (41)	56.6 (17.2)	16-97	249 (8.2)	87 (2.9)
Pain distribution*						
Regional chronic pain (1-3 sites)	2950	1208 (41)	56.6 (17.3)	16-97	238 (8)	81 (2.8)
Widespread chronic pain (>3 sites)	71	15 (21)	56.5 (16.6)	19-87	11 (15)	6 (8.7)
Pain disability**						
Low disability (grade I-II)	2081	863 (41)	55.1 (17.1)	16-97	122 (5.9)	38 (1.8)
High disability (grade III-IV)	913	346 (37)	59.8 (17.0)	16-96	125 (13.7)	48 (5.3)
Pain score severity*						
Low (average pain score 1-4)	1416	652 (46)	54.9 (17.4)	16-97	75 (5.3)	21 (1.5)
High (average pain score >4)	1537	552 (35)	58 (17.0)	16-95	170 (10.8)	64 (4.1)

n (number), *SD* (standard deviation)

[§]A subgroup analysis was performed on subjects who were diagnosed with cardiac disease in the year leading up to the survey

*Pain disability was derived from the 'Chronic pain grade scale' Questionnaire

*Numbers in complementary categories may not add up to total number of patients because of missing data

Table 9: Distribution of confounding variables by chronic pain status

	Chronic Pain Status		Cardiac Disease Status	
	Yes (n=3023) n (%)	No (n=5397) n (%)	Yes (n=471) n (%)	No (n=8136) n (%)
Gender				
Male	2510 (46)	1225 (41)	283 (60)	3537 (43)
Female	2887 (54)	1798 (59)	188 (40)	4599 (57)
Income				
>£47794.12	1011 (24)	407 (17)	77 (22)	1124 (17)
>£27704.92	953 (23)	442 (18)	115 (33)	1303 (20)
<=£47794.12				
>£19117.65	798 (19)	525 (21)	89 (26)	1268 (20)
<=£27704.92				
>£11676.65	798 (19)	577 (24)	38 (11)	1369 (21)
<=£19117.65				
<=£11676.65	662 (16)	496 (20)	26 (8)	1402 (22)
Age				
16-29	1212 (22)	216 (7)	1 (0)	1444 (18)
30-39	1048 (19)	319 (11)	4 (1)	1379 (17)
40-49	1045 (19)	533 (18)	23 (5)	1580 (19)
50-59	735 (14)	555 (18)	55 (12)	1276 (16)
60-69	707 (13)	640 (21)	116 (25)	1267 (16)
70-79	434 (8)	454 (15)	159 (34)	766 (9)
>80	216 (4)	306 (10)	113 (24)	424 (5)
Body Mass Index				
<18.5	80 (2)	28 (1)	4 (1)	107 (2)
18.5-24.9	1728 (39)	673 (28)	64 (18)	2375 (36)
25-29.9	1692 (38)	930 (38)	136 (39)	2524 (38)
30-39.9	888 (20)	704 (29)	136 (39)	1505 (23)
>40	85 (2)	96 (4)	9 (3)	177 (3)
Smoking history				
Never regular	3015 (56)	1378 (46)	185 (39)	4286 (53)
Ex-regular	1260 (24)	1029 (34)	212 (45)	2139 (27)
Regular	1067 (20)	601 (20)	72 (15)	1635 (20)
Raised blood pressure				
Yes	1116 (21)	1149 (38)	167 (36)	6086 (75)
No	4278 (79)	1872 (62)	303 (64)	2044 (25)
Diabetes Mellitus				
Yes	5153 (95)	2728 (90)	345 (73)	7677 (95)
No	243 (5)	290 (10)	126 (27)	446 (5)
Self-reported anxiety/depression				
None	3815 (80)	1681 (62)	223 (59)	5336 (74)
Moderate	859 (18)	893 (5)	132 (35)	1691 (23)
Extreme	76 (2)	98 (4)	20 (5)	172 (2)
NSAID prescription				
Yes	46 (1)	204 (7)	452 (96)	7895 (97)
No	5351 (99)	2819 (93)	19 (4)	241 (3)

Chronic pain and cardiac disease: Cardiac disease (angina or myocardial infarction) occurred more frequently amongst participants reporting chronic pain, with an odds ratio (OR) of 1.87 (95% confidence intervals [CI] 1.51-2.34), after adjusting for the non-modifiable risk factors age and gender. Table 10 shows the results of a logistic regression analysis in which the association between chronic pain and cardiac disease was tested alongside the full complement of modifiable and non-modifiable confounding variables. Body mass index and NSAIDS were not independently associated with cardiac disease and were removed from the final model. In fact, the estimated OR for cardiac disease amongst users of NSAIDS was always 1.00 or less than 1.00 in all models of risk factors for cardiac disease including chronic pain or chronic pain by severity and other confounding variables. I therefore did not adjust for the use of NSAIDS in the final models presented in Table 11 and Table 12.

The final models report ORs and CIs adjusted for only the statistically significant confounding factors. The data confirm that adults with chronic pain are more likely to report cardiac disease than those without pain, OR 1.55 (95% CI 1.15-2.07). The odds of cardiac disease in the presence of chronic pain were greater when cardiac disease was restricted to the final year of the study, OR 3.20 (95% CI 1.65-6.18). The results did not differ much if adjustment was made for all potential confounding variables, OR 2.87 (95% CI 1.45-5.67).

Table 10: Chronic pain and cardiac disease, adjusting for all confounding variables

	OR	p-value	95% CI
Chronic pain	1.45	0.02	1.06-2.00
NSAID prescription	1.00	1.00	0.53-1.89
Gender (female)	0.48	< 0.001	0.35-0.66
Income			
>£47794.12	1.00	-	-
>£27704.92			
≤£47794.12	1.23	0.51	0.66-2.29
>£19117.65			
≤£27704.92	1.52	0.15	0.87-2.66
>£11676.65			
≤£19117.65	1.74	0.05	1.00-3.03
≤£11676.65	1.76	0.06	0.98-3.17
Age			
16-29	1.00	-	-
30-39	2.78	0.38	0.29-26.95
40-49	6.85	0.07	0.87-53.96
50-59	19.11	0.004	2.56-142.93
60-69	42.51	< 0.001	5.80-311.80
70-79	76.24	< 0.001	10.34-526.31
>80	92.50	< 0.001	12.19-701.61
BMI			
<18.5	1.00	-	-
18.5-24.9	0.48	0.27	0.13-1.76
25-29.9	0.58	0.40	0.16-2.06
30-39.9	0.71	0.59	0.20-2.53
>40	0.56	0.45	0.12-2.56
Smoking history			
Never regular	1.00	-	-
Ex-regular	1.13	0.47	0.81-1.59
Regular	1.62	0.03	1.05-2.52
Raised blood pressure	1.77	< 0.001	1.28-2.43
Diabetes Mellitus	1.76	0.01	1.17-2.63
Self-reported anxiety/depression			
None	1.00	-	-
Moderate	1.28	0.16	0.91-1.79
Extreme	1.23	0.68	0.46-3.27

OR (odds ratio), se (standard error), CI (confidence intervals), NSAIDS (non-steroidal anti-inflammatory drugs), BMI (body mass index)

Table 11: Cardiac disease against chronic pain status and intensity, correcting for statistically significant confounders only

	OR	p-value	95% CI
Chronic pain status			
No chronic pain	1.00	-	-
Chronic pain*	1.55	< 0.001	1.15-2.07
Chronic pain distribution			
No chronic pain	1.00	-	-
Regional chronic pain (1-3 sites) [†]	1.45	0.01	1.12-1.89
Widespread chronic pain (>3 sites) [†]	3.30	0.01	1.42-7.68
Chronic pain disability			
No chronic pain	1.00	-	-
Low disability (grade I-II) [‡]	1.11	0.48	0.82-1.51
High disability (grade III-IV) [‡]	2.35	< 0.001	1.71-3.23
Chronic pain score severity			
No chronic pain	1.00	-	-
Low (average pain score 1-4) [§]	1.09	0.65	1.75-1.60
High (average pain score >4) [§]	1.95	< 0.001	1.40-2.71

OR (odds ratio), se (standard error), CI (confidence intervals)

*adjusted for gender, income, age, smoking, blood pressure, diabetes, and self-reported anxiety/depression

[†]adjusted for gender, income, age, smoking, blood pressure and diabetes

[‡]adjusted for gender, income, age, smoking, blood pressure and diabetes

[§]adjusted for gender, income, age, smoking, blood pressure, diabetes, and self-reported anxiety/depression

Table 12: Cardiac disease restricted to the final year of the survey against chronic pain status and intensity, correcting for statistically significant confounders only

	OR	p-value	95% CI
Chronic pain status			
No chronic pain	1.00	-	-
Chronic pain*	3.20	0.001	1.65-6.18
Chronic pain distribution			
No chronic pain	1.00	-	-
Regional chronic pain (1-3 sites) [†]	3.10	0.001	1.60-6.02
Widespread chronic pain (>3 sites) [†]	7.11	0.003	1.92-26.32
Chronic pain disability			
No chronic pain	1.00	-	-
Low disability (grade I-II) [‡]	1.93	0.08	0.92-4.08
High disability (grade III-IV) [‡]	6.70	< 0.001	3.26-13.75
Chronic pain score severity			
No chronic pain	1.00	-	-
Low (average pain score 1-4) [§]	2.05	0.08	0.92-4.56
High (average pain score >4) [§]	4.13	< 0.001	2.05-8.33

OR (odds ratio), se (standard error), CI (confidence intervals)

* adjusted for gender, income, age, blood pressure, diabetes, and self-reported anxiety/depression

[†] adjusted for gender, income, age, blood pressure, diabetes, and self-reported anxiety/depression

[‡] adjusted for gender, income, age, blood pressure, and self-reported anxiety/depression

[§] adjusted for gender, income, age, blood pressure, diabetes, and self-reported anxiety/depression

Cardiac disease by chronic pain distribution: A sub-set (71 people) of those who had reported chronic pain experienced it in four or more distinct body areas (meeting my a-priori criteria for chronic widespread pain). This tally approximated to 2.3% of the chronic pain cohort (Table 1). There were significantly fewer male participants reporting chronic pain, who met the criteria for chronic widespread pain than females (1.2% vs. 3.1%). Cardiac disease was significantly more common in participants reporting chronic regional pain (1-3 sites) and those reporting chronic widespread pain, when compared to participants with no chronic pain. However, the odds of cardiac disease was more than doubled in the chronic widespread pain group as compared to the chronic regional pain group OR 3.30 (95% CI 1.42-7.68) vs. OR 1.45 (95% CI 1.12-1.89), respectively. Similar proportions were evident in the “cardiac-last-year” model (Table 5).

Cardiac disease by chronic pain disability: Almost twice as many chronic pain sufferers were classified as having low-disability chronic pain (CPGS I and II) than high-disability chronic pain (CPGS grades III and IV). Only high-disability pain was statistically significantly associated with cardiac disease after correction for confounding variables OR 2.35 (95% CI 1.71 – 3.23) and OR 6.70 (95% CI 3.26-13.75) for cardiac disease and cardiac disease in the last year, respectively.

Cardiac disease by chronic pain score severity: Just over half of the participants with chronic pain reported average chronic pain scores greater than or equal

to 5/10. Again, a statistically significant association with cardiac disease was only apparent in the cohort reporting higher average chronic pain scores. The odds for this association were more than doubled when outcomes were restricted to the final year of the survey OR 4.13 (95% CI 2.05-8.33) vs. OR 1.95 (95% CI 1.40-2.71).

Excluded participants: Participants excluded from the statistical model accounting for the full complement of confounding variables were marginally older, wealthier, and more likely to be prescribed NSAIDS but less often hypertensive and diabetic than were included participants (Appendix 3). With progressive removal on non-significant variables the proportion of 'excluded' participants were reduced; consequently the study population more closely represented the survey population.

DISCUSSION

Chronic pain appears to affect between one-third and one-half of the population of the United Kingdom, corresponding to just under 28 million adults. This figure is likely to increase further in line with an ageing population. Furthermore, adult populations reporting chronic pain, particularly those most severely affected, may be at significantly increased risk of cardiac disease.

The prevalence of chronic pain in the United Kingdom

Based on the best quality studies of general population samples, I have estimated the prevalence of chronic pain in the United Kingdom to be 43.5%. This equates to just under 28 million people (referencing population statistics from 2013). Chronic pain prevalence rises steadily with increasing age, affecting up to 62% of the population over the age of 75. Therefore, the burden of chronic pain may increase further still, in line with an ageing population, if the incidence remains unaltered. I have also summarised the proportion of patients reporting severe pain; weighted averages for chronic widespread pain suggest that 14.2% of the population may be affected. I have demonstrated that between 10.4% and 14.3% of the population report chronic pain that is either moderately or severely limiting (Von Korff Grades III and IV). This estimate corresponds to an estimated median of 7.9 million people in the UK population with this category of chronic pain.

The estimate of 43.5% (28 million people) in the UK with chronic pain is considerably higher than a previously quoted figure of 7.8 million people with 'chronic pain' (102) based on data from a telephone-based Pain in Europe survey (27). However, the European survey looked only at moderate to severe pain, and figures from that survey are more directly comparable with, and similar to, my summary estimates for moderate-and-severely limiting chronic pain.

I used a definition for chronic pain in my systematic review described in terms of symptom duration (pain present for a period of 3 months or greater). It could reasonably be argued that this measure is not reflective of the societal burden of the condition. For example, it may be that a proportion of 'chronic pain' reporters are highly functioning individuals with little restriction in day-to-day activity, and limited reliance on health services. Many people living with chronic inflammatory or degenerative conditions, in their milder forms, would fall into this category. However, it is of interest that even amongst the youngest population age groups (18-39 year olds), where chronic degenerative conditions are less likely to occur, prevalence estimates for chronic pain as high as 30% have been reported (Figure 3). This would suggest a greater burden on the 'working' population than might be anticipated.

Further evidence for the potential impact of chronic pain is provided by the Global Burden of Disease study (162, 163). The project uses available data on

the prevalence and severity of over 300 diseases to provide proportionate estimates of the 'Years Lived in Disability' (YLD) attributable to each disease. The prominence of pain conditions has been remarkable, with tension-type headaches, migraine, low back and neck pain often cited in the list of the most frequently occurring chronic diseases globally (164). More impressive, however, is the impact pain conditions have had on populations in both developed and developing countries. Since inception of the project in 1990, low back pain has consistently been highlighted as the single greatest cause of YLD globally. Furthermore, in the most recent analysis, low back pain and migraine featured in the list of top-ten most disabling conditions in every one of the 195 countries surveyed (165).

The uncomfortable reality of growing, and ageing, populations is that chronic pain conditions will continue to represent significant public health concerns, and measures aimed at containing the impact of such conditions will need to be prioritised.

To my knowledge my meta-analysis is the first study attempting to synthesise prevalence data on chronic pain phenotypes specifically from the United Kingdom. In order to strengthen my findings, I have attempted to limit the impact of clinical and methodological heterogeneity by imposing fairly strict selection criteria from the outset of the review. I have also been selective about the studies that were permitted to enter the meta-analysis by excluding problematic studies after appraisal of study quality and risk of bias. At the expense of sensitivity, the selection criteria have generated data

comparable enough to permit synthesis and meta-analysis of the two most prominent pain phenotypes (chronic pain and chronic widespread pain). The tests for statistical heterogeneity amongst the articles included in the meta-analyses still demonstrated substantial variability between studies (I^2 98.9% and 95.2% for chronic pain and chronic widespread pain, respectively). However, there was limited opportunity to investigate sources of this variability due to the small number of studies included, and the lack of recorded characteristics showing variability between studies. A stratified analysis grouped by calendar year of survey suggested this as one potential source of systematic variation between studies: prevalence increasing with time. Further analysis, grouping studies by location of study population suggested this as another potential source. Notably, pooled prevalence estimates for Scotland appear to be higher than those reported elsewhere in the United Kingdom. Geographical variations of this sort may reflect the inherent differences in the populations chosen for sampling. Whilst baseline demographics for Scotland are comparable with those of the UK, census estimates suggest that populations in Scotland are likely to report poorer health outcomes, shorter life expectancy and lower household income when compared to those in England and Wales (166). I can speculate that differences in age structure, levels of deprivation and urban/rural differences could be contributing to differences between study populations, as may variation in the distribution of known risk factors and confounders. However, without access to individual participant data it is not possible to control fully for these factors.

Furthermore, methodological variations (such as the definitions used, questioning formats and response rates) may also account for the regional differences in prevalence estimates. It is worth noting that the authors most frequently associated with pain epidemiology research in the UK are based in academic institutions in Scotland, and certainly the low statistical heterogeneity following pooling of studies from Scotland ($I^2 = 0$), suggests greater regional consistency with regards to study methodology. However, firm conclusions in this regard are limited by the few studies available in which to make robust comparisons, and the marked heterogeneity within the groups. No other stratified analyses by study were possible.

Another limitation of my review was the quality of the studies available for synthesis. Fewer than half of the 19 included studies were primarily designed to produce prevalence data (Table 1), and this was reflected in the variability of reporting of important variables: population denominators and response rates were not always identifiable, in particular where the survey measured multiple outcomes; participant demographics were not always displayed; and there were occasional numerical discrepancies between the data presented in the study abstract, main text and results tables. I had excluded six studies from the review on the grounds of a higher than acceptable risk of bias; three of these studies provided data that could potentially have been incorporated into my meta-analysis of chronic pain prevalence. I acknowledge that there exist different approaches regarding the application of quality appraisal in systematic literature reviews (88), and these have been discussed in greater

depth earlier in my Thesis. However, my a priori approach was that rigorous quality assessment would be used to select only those studies meeting a minimum standard (105).

Whilst it is possible that references from the grey literature have been missed, I am reassured that a recent systematic review of chronic widespread pain surveys (167) did not identify any eligible UK papers which had not been included at some stage of my literature search.

My thesis demonstrates how a systematic review of published surveys carried out in one country, with exclusion of studies at high risk of bias, can provide population prevalence estimates for different pain conditions of the sort required by national policy strategies for prevention and care of chronic pain. Despite the high level of heterogeneity between study outcomes, my summary estimates (population prevalence of 43.5%) is comparable with those from international surveys and reviews. For example in the United States, the Institute of Medicine estimated the prevalence of chronic pain in the United States of America to be 40%, affecting an estimated 100 million people (100). The World Health Organisation has produces similar estimates from surveys across developed (37%) and developing (41%) countries (168), despite between-country variability, and to the estimate from this review here (43%). Surveys of more severe chronic disabling pain in America (169), Europe (170) and elsewhere (171) estimate similar prevalence figures to those found in my study (around 12%). I conclude that my estimates can be

used in national and local prevalence calculations of chronic pain prevalence, to inform, for example, planning of community pain services and targets for prevention.

The association between chronic pain and cardiovascular diseases

Through my searches I identified 25 studies that explore the relationship between chronic pain and cardiovascular disease and/or cardiovascular mortality. Pooling of available data has demonstrated statistically significant associations between chronic pain and mortality from cardiovascular diseases, OR 1.21 (95% CI 1.05-1.36); chronic pain and cardiac disease, OR 1.77 (95% CI 1.47-2.07); and chronic pain and cerebrovascular disease, OR 1.81 (95% CI 1.51-2.10). In these analyses, all associations between chronic pain phenotypes and cardiovascular outcomes (cardiac disease, cerebrovascular disease and cardiovascular mortality) appeared to be stronger (i.e. larger effect size), and the associations in these subgroups appeared to be more independent of confounding effect, when subgroups with increasing pain distribution and/or increasing pain severity were selectively analysed.

A recent meta-analysis demonstrated increases in cardiovascular related deaths amongst populations with chronic pain (pooled OR 1.09, 95% CI 0.84-1.41) and chronic widespread pain (pooled OR 1.17, 95% CI 0.89-1.63) that were not statistically significant (94). A different study, published after my systematic review, used data from a national Biobank to demonstrate that

participants meeting the criteria for chronic widespread pain have an increased risk of cardiovascular related deaths, when compared with participants reporting no pain (172). The association remained statistically significant even after adjustment for potentially confounding variables, OR 1.99 (95% CI 1.41 - 2.80). The same authors subsequently performed an updated meta-analysis combining their results with data from other studies addressing the risk of cardiovascular mortality in participants with chronic widespread pain. Pooled results demonstrated a positive association that was not statistically significant MMR 1.63 (95% CI 0.98 - 2.70). However, in both meta-analyses the authors included studies where pain symptoms in the exposure groups were not exclusively 'chronic', and would likely bias the pooled results towards the Null Hypothesis.

I have constructed this review in accordance with guidance published by the Meta-analysis of Observation Studies in Epidemiology (MOOSE) consortium (74). I have used standardized definitions for chronic pain phenotypes, determined a priori, in an attempt to limit bias that may arise during retrieval, analysis and interpretation of available evidence. To my knowledge this is the first review article that attempts to rigorously address the impact that the chronicity of pain symptoms has on the risk of cardiovascular disease and cardiovascular mortality.

All the data collated in my review were extracted from observational studies. The hypothesis under question does not lend itself to analysis through the

more robust methodology of randomised controlled trials. I am therefore restricted in my ability to draw firm conclusions regarding causality and directionality between the two variables. Studies varied markedly in design and methodology, often using non-standardised definition of chronic pain and widespread pain, and selecting cardiovascular outcomes that were not directly comparable. For example, some studies included hypertensive disease as a cardiovascular outcome (34, 132, 133, 142, 143) while others included hypertension as a confounding variable (137, 138, 144, 148). These limitations are reflected in the quality appraisal and risk-of-bias assessment for both longitudinal and cross-sectional studies in this review. Through a search of the literature I have identified 11 variables that may be independently associated with chronic pain and cardiovascular disease: age, gender, socio-economic status, smoking, body mass index, depression, anxiety, mobility, hypertension, diabetes and use of non-steroidal anti-inflammatory drugs (NSAID) (161, 173, 174). Co-occurrence of one or more of these risk factors may account for part of the associations identified in the meta-analysis of unadjusted outcomes. While most of the authors acknowledged the potential for confounding in their analyses there was little consistency with regards to the choice of variables included in the statistical models. None of the authors attempted to adjust for all 11 variables outlined above, and only three studies acknowledged the potential role of NSAIDs. Such heterogeneity has made it impossible to perform a meaningful pooling of data for comparison *after* adjustment for confounders. It is likely that confounding plays a significant role in the association between chronic pain

and mortality from cardiovascular disease, with all three of the reported associations losing statistical significance after adjustment (72, 133, 134). Studies addressing the risk of cardiovascular morbidity (cardiac and cerebrovascular disease) were less affected by confounding, providing a firmer basis for claims of an independent link between these variables and chronic pain. Studies focussing on subsets of participants with severe or widespread chronic pain were the most likely to demonstrate a statistically significant association after adjustment; suggesting that there may be a dose-response gradient for this association.

It is clear from my review that further research is warranted, designed to acknowledge (and powered to account for) the role of the potentially confounding factors outlined above - in particular to assess the impact of NSAIDs. The aim of the final chapter of my theses was to address some of the shortcoming in the existing evidence base. Using data from a well-constructed national survey of the population of England I have demonstrated that participants reporting chronic pain symptoms were 55% more likely to experience cardiac disease than those not reporting chronic pain, after adjustment for confounding variables. This figure is comparable to the increase frequency of cardiovascular events observed with other modifiable risk factors such as smoking (OR 2.87), Diabetes Mellitus (OR 2.37) and Hypertension (OR 1.91) (175).

A key brief in my analyses was to strengthen my findings through demonstration of a dose-response gradient in the relationship between the measured variables. In my study, I used three different indices for pain intensity: chronic pain distribution, chronic pain disability and average chronic pain score. The results indicate that cardiac risk increases markedly in line with chronic pain intensity, irrespective of the measure used.

These results are consistent with published studies citing statistically significant increases in cardio-vascular morbidity, ranging from 18% to 83% (142, 174, 176), that are also most pronounced in populations with higher-intensity chronic pain (34, 135). However, as outlined earlier in this chapter, confounding variables were not consistently or comprehensively accounted for in the statistical models used in prior studies. I have adjusted for a wide range of potentially confounding cardiovascular risk factors including: age, gender, socio-economic status, body mass index, diabetes, hypertension, smoking, anxiety, depression and regular use of non-steroidal anti-inflammatory drugs (NSAIDS). To my knowledge this is the first study to account for the use of these drugs as a confounding variable in the association between chronic pain and cardiovascular disease.

In my analysis, I found that the regular use of NSAIDS was independently associated with both chronic pain and cardiac disease. However, it was not a statistical confounder in the association between chronic pain and cardiac disease (Table 3). Interestingly, when logistic regression analysis was used to

quantify the association between regular prescription for NSAIDS and the presence of cardiac disease, adding chronic pain to the model (as a potential confounder) does in fact remove statistical significance. While it would be simplistic to surmise that the cardiac risk attributable to regular use of NSAIDS could be explained entirely by co-existing chronic pain, the data highlight the complex interplay between these three factors in clinical practice; reaffirming the need to carefully balance the overall cardiac risk against the potential analgesic benefit NSAIDS could provide in chronic pain patients. For example, it is conceivable that: following a limited course of NSAID therapy, in selected individuals, the provision of effective analgesia (and thereby improved mobility, activity and potentially reducing cardiovascular risk directly attributable to chronic pain severity as discussed above) might counter-act the augmented cardiovascular risk associated with these agents.

My study has been based on observational data from a national survey. Self-reporting of chronic physical conditions has previously been shown to demonstrate moderate to high agreement with data from medical records (177), and I feel the large, nationally representative sample size adds robustness to the analysis, as do the quality control measures used by the Health Survey for England to validate the data. However, an important limitation of my data analysis was that anxiety and depression were not measured using well-validated assessments tools. Instead, participants were asked whether they feel depressed or anxious, moderately depressed or

anxious, or severely depressed or anxious, and I cannot really differentiate if participants were really having serious and potentially harmful depressive symptoms, or just showing some distress. There was also no specific assessment of post-traumatic stress disorder. Post-traumatic stress disorder has been linked with both chronic pain and cardiovascular disease (178, 179), and would have ideally been adjusted for as a confounding variable in the statistical analysis. In some instances, the questioning format used in the survey was more restrictive than I would have liked, and the coding of prescription drugs did not allow me to identify the anti-depressant medicines or opioid analgesics used by participants, some of which may be associated with an increased risk of cardiovascular events (180, 181). Furthermore, the data on medication usage were limited to prescription drugs, therefore I was not able to account for over-the-counter use of NSAIDS, nor could I identify the dose or quantity of the drugs actually taken by study participants. Future research could benefit from targeted questionnaires asking about exposure to over-the-counter NSAID use (182, 183). Self-reported drug utilization may be subject to recall bias, in particular when exposure periods extends over several years, and misclassification bias given the complex and varied terminology used to refer popular NSAIDs. In countries where state legislature allows for re-imbursement of over-the-counter medication, a more objective assessment of drug exposure could be established through accessing of nationalized data (184). While these options were not available for my study, I am reassured by the fact that the cardiovascular side-effects of NSAIDs are more commonly associated with high doses of prescription

medication (Diclofenac), than over-the-counter preparations (Ibuprofen) (185).

As the data source is cross-sectional, I am limited in my ability to attribute directionality. For example, it is possible that in some instances cardiac disease preceded or perhaps even predisposed to chronic pain, as would be the case with chronic chest pain. In order to address this issue I excluded participants who reported chronic pain symptoms in the chest area from the analyses. Additionally, I ran parallel regression analyses, restricting the cardiovascular outcome to the last year of the survey. The demonstration that all the study outcomes remained statistically significant was reassuring. In fact, in all instances the likelihood of cardiac disease actually increased in the restricted outcome set, with a greater than 7-fold increased risk in participants reporting chronic widespread pain than those without pain.

Population estimates from the prevalence of chronic pain in the United Kingdom range from 35% to 51% (116, 119), with up to 16% of the general population reporting chronic widespread pain (119). Similar figures have been quoted from studies looking at the prevalence of severe chronic pain in European countries (170). Extrapolation of the results of this study highlights a fairly underpublicized public health concern. While I am unable to establish causality in the absence of further support from longitudinal studies, I can acknowledge that chronic pain populations, in particular those most severely

affected, are likely to benefit from regular assessment of cardiac risk, and targeted measures to reduce this risk.

SUMMARY AND DIRECTION FOR FUTURE WORK

The greater use of prevalence estimates for chronic pain will enable its impact on the population to be assessed and tracked over time.

The strength of the association between chronic pain and cardiovascular disease represents a substantial public health concern that must lead to action to raise public and healthcare professional awareness.

My studies lend weight to the argument that chronic pain should be considered an independent disease state, with potentially harmful biological consequences.

Future work streams that have been discussed in this thesis will create greater scope for ameliorating cardiac risk in chronic pain patients.

Global attitudes to chronic pain are changing; there is a greater appreciation that chronic pain can represent a disease in its own right, with potential for significant psychological and social morbidity. Whilst some aspects of disability are better recognised, little is known about the long-term biological or physiological consequences of living with chronic pain. In comparison to more high-profile long-term conditions such as cancer and cardiovascular disease, chronic pain is a silent epidemic.

Prior to the studies presented in this thesis, there was no widely accepted estimate for the prevalence of chronic pain in the United Kingdom, little understanding of the biological consequences of chronic pain (as compared to its psychological and social impact), and unresolved concerns about the possible influence of chronic pain on cardiovascular outcomes.

I have used the best available data to demonstrate that chronic pain affects between one-third and one-half of the population of the United Kingdom: a figure that is likely to increase, over time, as the population ages further. Such prevalence data do not, in themselves, define the need for care or offer targets for prevention. However, good prevalence data could be the bedrock for policy-makers to give greater priority to this important cause of distress and disability that affects the lives of so many people. My experience in working with such data has shown that future population studies must adhere to standardised methods for collecting and presenting observational data. The guidance produced by the Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) group (186) is a good starting point for this more rigorous and consistent approach.

There is mounting evidence that chronic stress or inflammation may provide a biologically plausible pathway from pain to cardiovascular damage. My studies highlight a possible dose-response relationship between chronic pain and cardiovascular disease. This finding is supported by other observational studies from different countries (73, 137, 139, 146, 148, 149), but their weakness has been the consistent failure to establish the impact of confounding variables. I have addressed this shortcoming by demonstrating an increased prevalence of cardiovascular disease amongst survey participants reporting chronic pain; this finding was statistically significant even after correcting for a comprehensive list of potentially confounding cardiovascular risk factors.

My studies support the hypothesis that chronic pain is an independent, and potentially modifiable, risk factor for cardiac disease. Thus, I have drawn attention to a possible causal association between two common sources of illness, disability, and death, that is of public health importance. An important direction for future research, triggered by my findings, is to explore whether reducing the severity of chronic pain (through improved pain control and reduction of symptom intensity) will protect against cardiovascular morbidity and mortality.

LIST OF APPENDICES

- 1 (a) List of search terms used for systematic review of Pain Prevalence
- 1 (b) Screening flowchart for systematic review of Pain Prevalence
- 1 (c) Flow Diagram of searches in systematic review of Pain Prevalence
- 1 (d) Risk of Bias Scores for articles from systematic review of Pain
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- 2 (a) List of search terms used for systematic review of Pain and CV
associations
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- 2 (c) Quality Scores for articles from systematic review of Pain and CV
associations

- 3 Key participant characteristics for included and excluded participants

Appendix 1(a): List of search terms used for systematic review

Search terms for Embase (via Ovid): 1988 to 14th May 2015

1. prevalence.ab,ti.
2. occurrence.ab,ti.
3. burden.ab,ti.
4. prevalence/
5. 1 or 2 or 3 or 4
6. (chronic adj5 pain).ab,ti.
7. fibromyalgia.ab,ti.
8. (chronic adj5 (headache or migraine)).ab,ti.
9. Chronic Pain/
10. Fibromyalgia/
11. neuropathic pain.ab,ti.
12. Neuropathic pain /
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. United Kingdom.ab,ti.
15. Great Britain.ab,ti.
16. British.ab,ti.
17. (England or Ireland or Scotland or Wales or London).ab,ti.
18. (English or Irish or Scottish or Welsh).ab,ti.
19. (NHS or National Health Service).ab,ti.
20. (general practice or general practitioner or primary care or community).ab,ti.
21. exp United Kingdom/
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 5 and 13 and 22

1381 records found (of which 40 were duplicates)

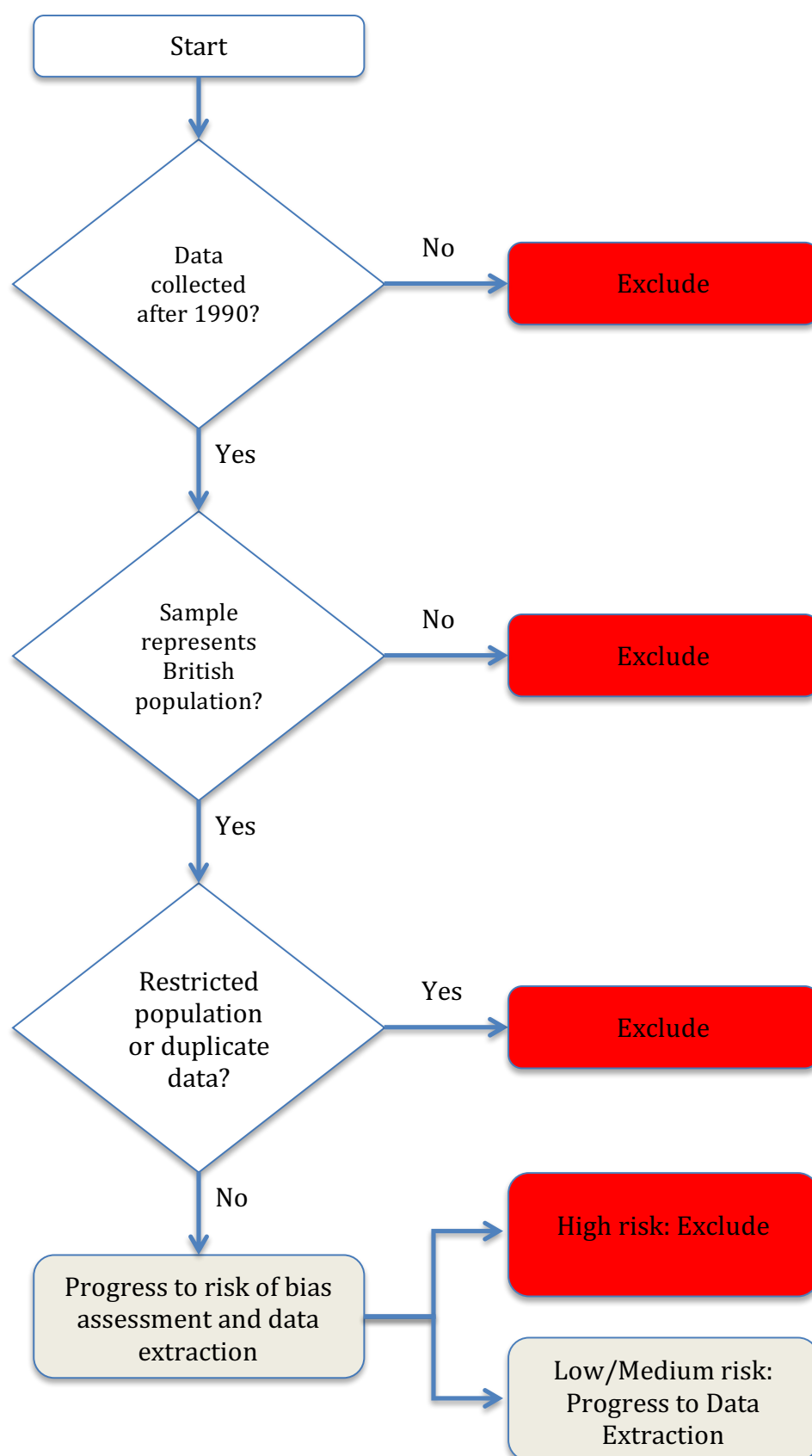
Search terms for Medline (via Ovid): 1948 to 14th May 2015

1. prevalence.ab,ti.
2. occurrence.ab,ti.
3. burden.ab,ti.
4. Prevalence/
5. (chronic adj5 pain).ab,ti.
6. fibromyalgia.ab,ti.
7. (chronic adj5 (headache or migraine)).ab,ti.
8. exp Chronic Pain/
9. exp Fibromyalgia/
10. exp Neuralgia/
11. neuropathic pain.ab,ti.
12. 1 or 2 or 3 or 4
13. 5 or 6 or 7 or 8 or 9 or 10 or 11
14. United Kingdom.ab,ti.
15. Great Britain.ab,ti.
16. British.ab,ti.
17. (England or Ireland or Scotland or Wales or London).ab,ti.
18. (English or Irish or Scottish or Welsh).ab,ti.
19. (NHS or National Health Service).ab,ti.
20. (general practice or general practitioner or primary care or community).ab,ti.
21. exp Great Britain/
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 12 and 13 and 22

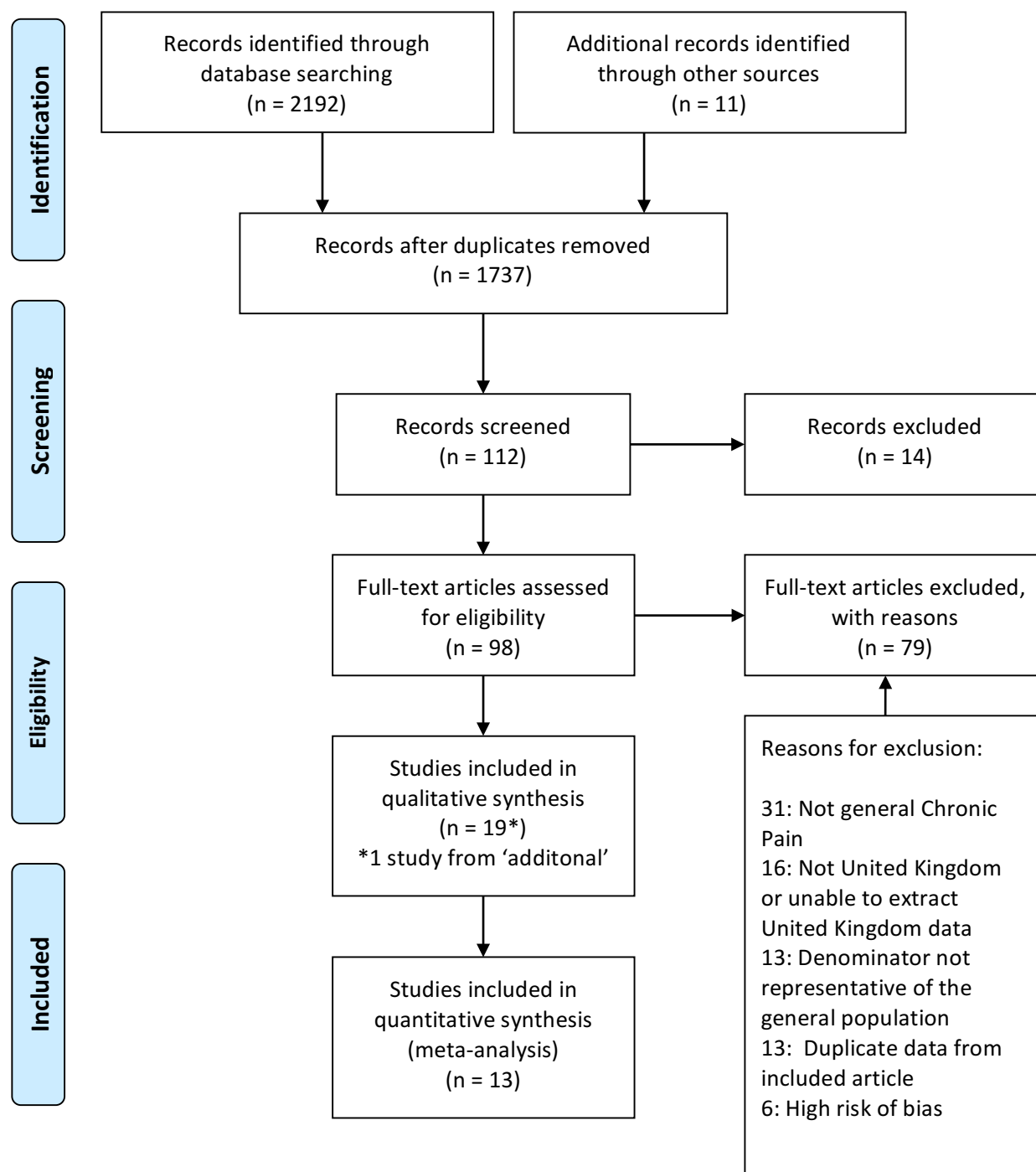
891 records found (of which 40 were duplicates)

When combined = 2192 references of which a further 466 were duplicates

Appendix 1(b): Screening flowchart for Systematic review



Appendix 1(c): Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 1(d): Risk of Bias Scores for screened articles

Author	Date	Overall Risk of Bias	External validity risk	Study pptn risk	Sampling frame risk	Selection method risk	Response rate risk	Internal validity risk	Data collection risk	Case definition risk	Valid instrument risk	Consistency of collection risk	Prevalence period risk	Consistency of numbers risk
<i>Included studies:</i>														
Aggarwal et al.	2006	Moderate	High	High	Low	Low	High	Moderate	Low	Low	Low	High	High	Low
Beasley et al.	2014	Moderate	High	Low	High	Low	High	Moderate	Low	Low	Low	Low	High	Low
Bridges et al.	2013	Moderate	Moderate	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Croft et al.	2003	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Croft et al.	1993	Moderate	High	High	High	High	High	Low	Low	Low	Low	Low	Low	Low
Elliott et al.	1999	Low	Moderate	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Gale et al.	2012	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Jones et al.	2007	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Jones et al.	2015	Moderate	High	Low	Low	High	High	Moderate	Low	Low	Low	High	Low	Low
Macfarlane et al.	1999	Moderate	Moderate	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Macfarlane et al.	2009	Moderate	Moderate	High	Low	Low	High	Moderate	Low	Low	Low	Low	Low	High
Macfarlane et al.	2010	Moderate	High	High	High	Low	High	Low	Low	Low	Low	Low	Low	Low
Mallen et al.	2005	Moderate	Moderate	High	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
Parsons et al.	2007	Moderate	Low	Low	Low	Low	Low	Moderate	Low	Low	Low	Low	Low	High
Smith et al.	2001	Moderate	Moderate	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Smith et al.	2004	Moderate	Moderate	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low
Torrance et al.	2013	Moderate	Moderate	Low	Low	Low	High	Moderate	Low	High	Low	Low	High	High
Torrance et al.	2006	Moderate	Moderate	Low	High	Low	High	Moderate	Low	High	Low	Low	Low	Low
Vandenkerkhof et al.	2011	Moderate	Moderate	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low
<i>Excluded studies:</i>														
Bowsher et al.	1991	High	High	High	High	High	High	High	High	Low	Low	High	High	High
Gajria et al.	2011	High	Moderate	High	Low	Low	Low	High	High	High	High	Low	High	High

Gureje et al.	1998	High	High	High	High	High	High	Moderate	Low	High	Low	Low	High	Low
Macfarlane et al.	2009	High	High	High	High	High	High	Low	Low	Low	Low	Low	Low	Low
Martin et al.	2014	High	High	Low	Low	High	High	Moderate	Low	Low	Low	Low	High	Low
Nicholl et al.	2014	High	High	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low

Appendix 2(a): Search terms used for review

Search terms used for Embase (via Ovid)

1947 to 2015 July 17

1. Chronic Pain.ab,ti.
2. widespread pain.ab,ti.
3. fibromyalgia.ab,ti.
4. (chronic adj5 pain).ti,ab.
5. exp Chronic Pain/
6. exp Fibromyalgia/
7. cardiovascular disease.ti,ab.
8. myocardial infarction.ti,ab.
9. angina.ti,ab.
10. stroke.ti,ab.
11. ischemic heart disease?.ti,ab.
12. atherosclerosis.ti,ab.
13. cardiovascular morbidity.ti,ab.
14. cardiovascular mortality.ti,ab.
15. exp heart muscle ischemia/
16. exp heart infarction/
17. exp cerebrovascular accident/
18. exp cardiovascular disease/
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 1 or 2 or 3 or 4 or 5 or 6
21. 19 and 20

8691 results generated

Search terms used for MEDLINE (via Ovid)

1946 to Present

1. Chronic Pain.ab,ti.
2. widespread pain.ab,ti.
3. fibromyalgia.ab,ti.
4. (chronic adj5 pain).ti,ab.
5. exp Chronic Pain/
6. exp Fibromyalgia/
7. cardiovascular disease.ab,ti.
8. myocardial infarction.ab,ti.
9. angina.ab,ti.
10. stroke.ab,ti.
11. ischemic heart disease?.ab,ti.
12. atherosclerosis.ab,ti.
13. cardiovascular morbidity.ab,ti.
14. cardiovascular mortality.ab,ti.
15. exp Myocardial Ischemia/ or exp Coronary Disease/ or exp Myocardial Infarction/
16. exp Stroke/
17. exp cardiovascular disease/
18. 1 or 2 or 3 or 4 or 5 or 6
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
20. 18 and 19

2024 results generated

Cochrane search terms

1. "chronic pain*":ab,ti
2. "widespread pain*":ab,ti
3. fibromyalgia:ab,ti
4. MeSH descriptor [Chronic Pain] this term only
5. MeSH descriptor [Fibromyalgia] this term only
6. 1 or 2 or 3 or 4 or 5
7. "cardiovascular disease*":ab,ti
8. "myocardial infarction":ab,ti
9. angina:ab,ti
10. stroke*:ab,ti
11. "heart disease*":ab,ti
12. "cardiovascular mortality":ab,ti
13. "cardiovascular morbidity":ab,ti
14. atherosclerosis:ab,ti
15. MeSH descriptor [Cardiovascular Diseases] this term only
16. MeSH descriptor [Stroke] this term only
17. MeSH descriptor [Myocardial Infarction] this term only
18. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
39. 6 and 18

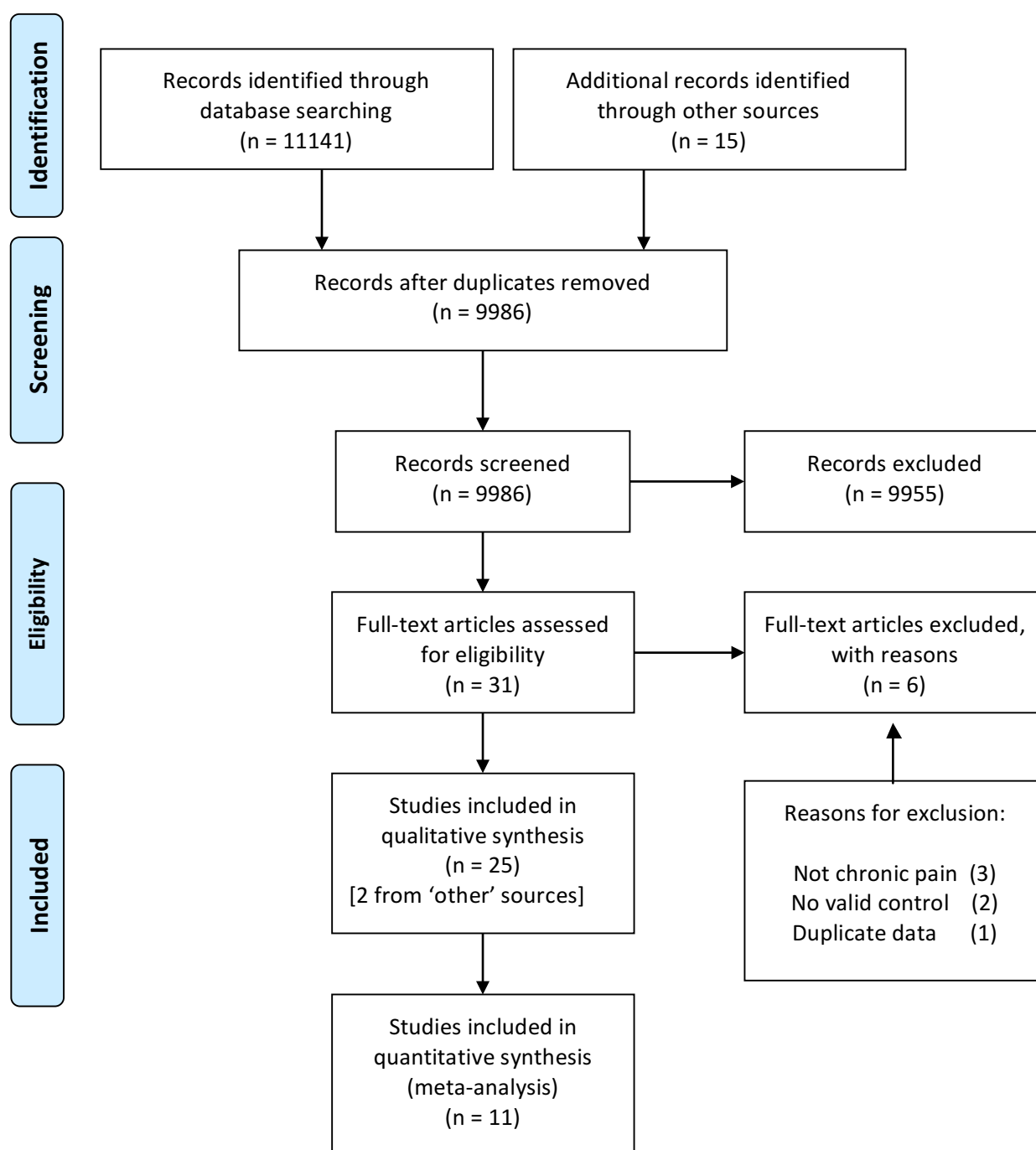
Citations returned = 35

Web of Science search terms

1. "chronic pain" or "widespread pain" or "severe pain" or "persistent pain" or "back pain" or fibromyalgia
2. "cardiovascular disease\$" or "myocardial infarction" or "angina pectoris" or stroke\$ or atherosclero* or "Coronary Disease\$" or "heart disease\$" or "heart failure\$" or "left ventricular dysfunction" or "metabolic syndrome"
3. 1 and 2

Citations returned = 67

Appendix 2(b): Flow Diagram of article selection



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2(c): Quality scores for studies from CP and CVD association review

Critical Appraisal Skills Programme tool for Cohort studies

Article	1	2	3	4	5	6	7	8	9	Score	Comments
Andersson	✓	✓	✓	✓	✗	✓	✓	✗	✗	Moderate	Inadequate confounding, pain prevalence did not vary significantly with age or gender
Chen	✓	✓	✓	✓	✗	✓	✓	✗	✓	Moderate	Inadequate confounding, low incidence of cardiovascular events
Dreyer	✓	✓	✗	✓	✗	✗	✗	✓	✓	Moderate	Inadequate confounding, controls not defined, low incidence of cardiovascular events
Heliovaara	✓	✓	✓	✗	✗	✓	✓	✓	✓	Moderate	Inadequate confounding, ICD codes not quoted, therefore cardiovascular outcomes unclear
Kadam	✓	✓	✓	?	✗	✓	✗	✓	✓	Moderate	Inadequate confounding, outcomes not clearly defined, may include Hypertension
Lindgren	✓	✓	✓	✓	✗	✓	✓	✓	✓	Moderate	Inadequate confounding
Mease	✓	✓	✗	?	✗	?	✗	✓	✓	Low	Inadequate confounding, controls not defined, study group identified by third party diagnosis
Smith	✓	✓	✓	?	✗	✓	✓	✗	✗	Moderate	Inadequate confounding, female only, outcomes includes mortality from HTN
Torrance	✓	✓	✓	?	✗	✓	✓	✓	✓	Moderate	Inadequate confounding, outcomes not clearly defined, may include Hypertension related deaths
Tsai	✓	✓	✓	✓	✓	✓	✓	✓	✓	Moderate	Exposure generated from insurance records (not direct from subjects) but supplemented with medication hx.
Wolfe	✓	✓	✗	✓	✗	?	✓	✗	✓	Low	Inadequate confounding Control group were OA patients who are likely to have chronic pain too.
Zhu	✓	✓	✓	✓	✓	✓	✓	✗	✓	Moderate	Female only population, elderly - results may not be translatable to wider population

Scoring tool

- 1 Did the study address a clearly focused issue?
- 2 Was the cohort recruited in an acceptable way?
- 3 Was the exposure accurately measured to minimise bias?
- 4 Was the outcome accurately measured to minimise bias?
- 5 Have the authors identified all important confounding factors?
- 6 Was the follow up of subjects complete?
- 7 Do you believe the results?
- 8 Can the results be applied to the local population?
- 9 Do the results of this study fit with other available evidence?

Critical Appraisal Skills Programme tool for Case Control studies

Article	1	2	3	4	5	6	7	8	9	10	11	Score	Comments
Ablin	✓	✓	✓	✓	X	X	?	?	✓	✓	✓	Moderate	Exposure not qualified, inadequate confounding, numerical inconsistencies, CI not presented
Cho	✓	✓	✓	✓	✓	X	?	?	✓	X	✓	Moderate	Inadequate confounding, small and homogeneous population
Hesler	✓	✓	✓	✓	X	?	X	X	X	X	X	Low	Surrogate FM definition, confounding unclear - match for baseline CVD?
Keller	✓	✓	✓	✓	X	X	X	X	✓	X	✓	Moderate	Inadequate confounding, third party data collection, homogeneous population
Pontari	✓	✓	✓	✓	✓	X	?	?	✓	✓	✓	Moderate	Inadequate confounding, outcome includes hypertension

Scoring tool

- 1 Did the study address a clearly focused issue?
- 2 Did the authors use an appropriate method to answer their question?
- 3 Were the cases recruited in an acceptable way?
- 4 Were the controls selected in an acceptable way?
- 5 Was the exposure accurately measured to minimise bias?
- 6 Was the outcome accurately measured to minimise bias?
- 7 Have the authors taken account of the potential confounding factors?
- 8 Do you believe the results?
- 9 Can the results be applied to the local population?
- 10 Do the results of this study fit with other available evidence?

Risk of Bias assessment of Cross-sectional studies

Article	1	2	3	4	5	6	7	8	9	10	11	12	Bias	Quality ¹	Comments
Conway	?	?	?	?	H	L	?	L	L	?	L	M	High	Low	Data from abstract only, many parameters not outlined fully
Cote	L	L	L	H	M	L	H	L	L	L	H	H	High	Low	Not clear what CVD were but Hypertension included separate. Not clear what pain duration was, Huge CI
Ha	L	L	H	H	H	L	L	?	L	L	H	M	Moderate	Moderate	Low inclusion rate from survey population, overall lower outcome prevalence than expected
Makela	L	L	L	L	L	L	H	L	L	L	L	H	High	Low	Overall reasonable quality, but outcome likely to include HTN and confounders included OA/CLBP
Ohayaon	L	H	H	L	H	H	H	L	L	L	L	M	Moderate	Moderate	Sampling method restricted to telephone users and responders, inadequate confounding
Parsons	L	L	L	H	M	L	H	L	L	L	L	M	Moderate	Moderate	Low survey response rate, the period of pain is not fully defined
Ryan	L	H	L	?	H	L	H	L	L	L	L	H	High	Low	Outcomes restricted to older age groups, surrogates for CP, CVD outcomes include HTN
Svensson	L	H	H	L	H	L	H	L	L	H	H	H	High	Low	Inadequate confounding, males only, restricted age group, data irregularities, not necessarily CP
Von Korff	L	L	H	H	H	L	H	L	H	L	L	M	High	Low	Selection biased towards mental illness, chronicity based on self-assessment, confounders unclear

Scoring tool

- 1 Was the study's target population a close representation of the national population?
- 2 Was the sampling frame a true or close representation of the target population?
- 3 Was some form of random selection used to select the sample?
- 4 Was the likelihood of non-response bias minimal?
- 5 External validity score
- 6 Were data collected directly from the subjects (as opposed to a proxy)?
- 7 Was an acceptable case definition used in the study?
- 8 Was the study instrument that measured the parameter of interest shown to have reliability and validity?
- 9 Was the same mode of data collection used for all subjects?
- 10 Was the length of the shortest prevalence period for the parameter of interest appropriate?
- 11 Were the numerator and denominator for the parameter of interest appropriate?
- 12 Internal validity score

Key

- High H
Low L
Moderate M
Can't tell ?

¹Taken as reciprocal of bias score

Appendix 3: Key participant characteristics for included and excluded participants

	Included (n=5283) Mean Age = 48.3		Excluded (n=3225)* Mean Age = 51.6		p-value
	"n"	%	"n"	%	
Gender					0.088
Male	2387	45	1396	43	
Female	2896	55	1829	57	
Income					0.000
>£47794.12	853	16	319	22	
>£27704.92 <=£47794.12	1062	20	321	23	
>£19117.65 <=£27704.92	1073	20	261	18	
>£11676.65 <=£19117.65	1145	22	256	18	
<=£11676.65	1150	22	271	19	
Body Mass Index					0.033
<18.5	82	2	26	2	
18.5-24.9	1790	34	624	38	
25-29.9	2046	39	584	35	
30-39.9	1120	23	382	23	
>40	145	3	37	2	
Smoking history					0.891
Never regular	2768	52	1661	53	
Ex-regular	1452	28	866	28	
Regular	1063	20	620	20	
Raised blood pressure					0.000
Yes	3929	74	2261	70	
No	1354	26	959	30	
Diabetes Mellitus					0.000
Yes	5001	95	2937	91	
No	282	5	275	9	
Self-reported anxiety/depression					0.130
None	3926	74	1588	72	
Moderate	1237	23	541	25	
Extreme	120	2	63	3	
NSAID prescription					0.015
Yes	5108	97	3148	98	
No	175	3	77	2	

*Describes the demographics from participants excluded when the full complement of confounding variables were included in the statistical analysis. With progressive removal on non-significant variables the proportion of 'excluded' participants was reduced

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