THE RELATIONSHIP BETWEEN MUSCULOSKELETAL CONDITIONS AND CHRONIC DISEASE, AND THE MANAGEMENT OF LIFESTYLE RISK FACTORS

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DECLARATIONS

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Amanda Williams reports no conflict of interest.

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PREFACE

This thesis is arranged in eight chapters, written so that each chapter can be read independently. Chapter One is an introduction to the thesis. It provides a summary of the relevant literature on musculoskeletal conditions and introduces the studies that form this thesis. Chapter Two is a systematic review of cohort studies that investigate whether common musculoskeletal conditions increase the risk of developing non-communicable chronic diseases. This chapter is currently under review at *BMC Medicine.* Chapter Three describes the study protocol (Part A) and statistical analysis plan (Part B) for a healthy lifestyle intervention for patients with chronic low back pain, who are overweight or obese. The statistical analysis plan also includes a second randomised controlled trial (RCT) of a healthy lifestyle intervention for patients with knee osteoarthritis, because the two trials were conducted together as part of a cohort multiple RCT. The study protocol is presented as published in *BMC Musculoskeletal Disorders* and the statistical analysis plan is presented as published in *Brazilian Journal of Physiotherapy*. Chapter Four outlines the results of the RCT detailed in Chapter Three. This chapter is presented as published in *PAIN.* Chapter Five describes an a priori protocol for a mediation analysis of aggregate data from the two trials outlined above, one for chronic low back pain and one for knee osteoarthritis. The mediation analysis protocol is presented as published in *BMJ Open*. Chapter Six outlines the findings of the mediation analysis outlined in Chapter Five. Chapter Seven is an economic evaluation of a healthy lifestyle intervention for patients with chronic low back pain. Chapter Six and Seven are published on the preprint server, bioRxiv. These chapters are currently under review at *Clinical Rehabilitation* and *European Journal of Pain*, respectively. Finally, Chapter Eight provides a summary of the principle findings of the thesis, describes implications of these findings and proposes directions for future research.

Each chapter contains its own reference list and relevant supplementary material. Ethical approval for all studies included in this thesis was obtained from the Hunter New England Human Research Ethics Committee and the University of Newcastle Human Research Ethics committee.

ABSTRACT

Musculoskeletal conditions, such as spinal pain and osteoarthritis (OA) have a high global burden. Although evidence suggests that musculoskeletal conditions are linked with both chronic diseases and lifestyle risk factors, there are significant evidence gaps in our understanding of these relationships. This thesis attempts to explore the relationship between musculoskeletal conditions and chronic diseases and assess the management of lifestyle risk factors in patients with common musculoskeletal conditions including chronic low back pain and knee OA.

Chronic diseases and musculoskeletal conditions have a significant global burden and frequently co-occur. Emerging evidence suggests musculoskeletal conditions may contribute to the development of chronic disease and several mechanisms have been proposed to explain these links. However, the available studies have not been systematically synthesised, and longitudinal relationships have not been assessed. In Chapter Two, a systematic review was performed to investigate whether the most common musculoskeletal conditions contribute to the development of non-communicable chronic diseases. Electronic databases were searched for cohort studies reporting adjusted estimates of the association between musculoskeletal conditions (neck or back pain or osteoarthritis of the knee or hip) and subsequent development of chronic disease (cardiovascular disease, cancer, diabetes, chronic respiratory disease or obesity). Thirteen eligible cohort studies following 3,086,612 people were identified. In the primary meta-analysis of adjusted estimates, osteoarthritis was the exposure in eight studies and back pain in two studies and cardiovascular disease was the outcome in eight studies, cancer in one study, and diabetes in one study. Pooled adjusted estimates from these ten studies showed that people with a musculoskeletal condition, have a 17% increase in the risk of developing a chronic disease, compared to people without a musculoskeletal condition (hazard ratio 1.17, 95%CI 1.13 to 1.22; I^2 52%, total n=2,686,113). The meta-analysis found musculoskeletal conditions may increase the risk of chronic disease. The results highlight that musculoskeletal conditions could be important in the prevention of chronic disease.

There is evidence to suggest that the persistence of low back pain is linked to lifestyle risk factors, such as overweight and obesity. Although there is widespread suggestion that managing lifestyle risks such as weight, should be part of management for patients with low back pain, there is currently no evidence about the effectiveness of lifestyle management to guide clinical practice. Chapter Three presents a study protocol (Part A) and statistical analysis plan (Part B) for the first high quality randomised controlled trial (RCT) testing whether targeting lifestyle risk factors could improve outcomes for patients with chronic low back pain. Eligible patients (n=160) were randomly allocated, using a central concealed random allocation process, to receive advice and education and referral to a 6-month telephone-based healthy lifestyle coaching service, or usual care. Chapter Four presents the results of the trial and showed that there were no differences between groups for pain intensity over six months (area under the curve, mean difference 6.5, 95%CI -8.0 to 21.0; p=0.38) or any secondary outcome. The lifestyle intervention did not reduce self-reported weight, the hypothesised mechanism to influence important patient outcomes such as pain and disability. The results suggest that clinical education and advice coupled with referral to generic, non-disease specific telephone-based healthy lifestyle coaching may not adequately support patients with chronic low back pain.

Standard analyses of RCTs estimate whether an intervention is effective or not. However, these analyses cannot provide explanations for how an intervention works, or why it does not work. Causal mediation analysis of RCTs can be used to determine if intervention effects worked through the hypothesised targets or if they are explained by other mechanisms. When there are no intervention effects, causal mediation analysis can help to determine if changing the targets is likely to lead to the outcome of interest. Chapter Five and Six presents an a priori protocol and results of a causal mediation analysis, respectively, of aggregated data from two RCTs; one which included 160 patients with chronic low back pain (the RCT presented in Chapters Three and Four), and another which included 120 patients with knee OA. In both trials the intervention consisted of brief advice and referral to a 6-month telephone-based healthy lifestyle coaching service. In the back pain trial participants were also offered a single physiotherapy

consultation. The hypothesised primary mediator was self-reported weight and alternative mediators were diet, physical activity and pain beliefs. Outcomes were pain, disability and quality of life (QoL). Data were analysed using causal mediation analysis with sensitivity analyses for sequential ignorability. The intervention had no effect on pain intensity, disability or physical QoL. The intervention significantly improved mental QoL however, the intervention effect was not channeled via the selected mediators. The intervention did not reduce weight, or the alternative mediators (diet, physical activity, pain beliefs), and these mediators were not associated with the outcomes (with one exception; poor diet was associated with lower mental QoL). Although clinical guidelines advocate focusing on lifestyle risk factors and erroneous pain beliefs in patients with chronic low back pain or knee OA, there is uncertainty about whether they are causes of pain, disability, and poor QoL. These findings suggest that addressing lifestyle risk factors and erroneous pain beliefs may not be appropriate targets to improve pain, disability and quality of life in these patients.

Decision makers often have limited funds and are required to choose between health care interventions. Economic analysis of RCTs provide decision makers with information to help guide allocation of scarce resources. Chapter Six presents an economic evaluation of a healthy lifestyle intervention for patients with chronic low back pain, compared with usual care (the RCT presented in Chapters Three and Four). The primary outcome was quality-adjusted life years (QALYs). Secondary outcomes were pain intensity, disability, weight, and body mass index. Costs included intervention costs, healthcare utilisation costs and work absenteeism costs. The primary analysis was conducted from the societal perspective and included all of these cost categories. Mean total costs were lower in the intervention group than the control group (-$614, 95%CI -3133 to 255). For all outcomes, the intervention was on average less expensive and more effective than usual care and the probability of the intervention being cost-effective compared to usual care was relatively high (i.e. 0.81) at a willingness-to-pay of $0/unit of effect. For QALYs, this probability increased to 0.90 at a willingness-to-pay of $17,000/QALY and reached a maximum of 0.96 at $67,000/QALY. However, the probability of cost-effectiveness was not as favourable among

sensitivity analyses. These findings suggest that the healthy lifestyle intervention seems to be cost-effective from the societal perspective. However, variability in the sensitivity analyses indicate caution is needed when interpreting these findings.

Overall, the studies included in this thesis have advanced the evidence-base regarding the relationship between musculoskeletal conditions and chronic disease, and the management of lifestyle risk factors. A systematic review of the literature suggests that musculoskeletal conditions should be considered in the prevention of chronic disease. However, a better understanding of the relationships between musculoskeletal conditions and chronic diseases is required to support inclusion of musculoskeletal conditions in the current chronic disease prevention agenda. To improve understanding about causal relationships, use of contemporary analytical methods in the assessment of longitudinal data is needed. Other aspects of this thesis explore management of lifestyle risk factors in patients with musculoskeletal conditions. Using existing population health services might be a scalable and cost-effective model to support clinicians to provide lifestyle-focused care for patients with musculoskeletal conditions. However, in their generic form, they do appear to produce clinically meaningful benefit to patients. Given the high prevalence of musculoskeletal conditions, a dedicated line of research would be warranted to support adaptation of available services for patients with musculoskeletal conditions and concomitant health risks. To maximise knowledge gained from the investment in research, clinical trialists should routinely plan and use supplementary analyses, such as causal mediation analyses and economic evaluations, in addition to standard analyses of treatment effectiveness. These methods of analysis extend knowledge from RCTs to guide intervention refinement and can inform decisions about resource allocation for clinical or policy decision-makers.

CHAPTER ONE

Thesis introduction

1.1 Overview

Musculoskeletal conditions, such as spinal pain and osteoarthritis (OA) have a large global burden. Spinal pain and OA are highly prevalent and are among the leading causes of disability. People with these conditions commonly suffer from high levels of pain, leading to adverse physical, psychological and social effects. In economic terms, healthcare expenditure and indirect costs associated with the conditions are substantial. Evidence suggests that spinal pain and OA are linked with other non-communicable diseases, but there is little knowledge of the characteristics of this relationship. Further, there is evidence to suggest that lifestyle risk factors such as excess weight, physical inactivity, and poor diet, are associated with the chronicity of spinal pain and OA. For knee OA, there are data showing that weight loss can reduce pain and disability; however, for chronic low back pain there is currently no evidence to support such a treatment approach.

1.2 Common types of musculoskeletal conditions

Musculoskeletal conditions are generally characterised by pain and functional impairment of the musculoskeletal system, including bones, muscles and joints.[1] They include, but are not limited to, conditions such as low back pain, neck pain, OA, rheumatoid arthritis, gout and osteoporosis. Of these, the most common and burdensome conditions are low back pain, neck pain and OA. The research in this thesis focuses on these common musculoskeletal conditions.

Low back pain is defined as pain occurring between the 12th rib (bottom of the rib cage) and the inferior gluteal folds (buttock crease), with or without leg pain.[2,3] An episode of low back pain is described by de Vet et al. as low back pain lasting more than 24 hours, preceded by a pain-free period of at least 30 days.[4] Low back pain episodes are typically classified by the duration of symptoms, with acute low back pain defined as pain lasting less than six weeks since onset, sub-acute as six to twelve weeks since onset, and chronic low back pain as 12 weeks or longer.[2,5] Clinical practice guidelines recommend that patients presenting to care with low back pain should be triaged into one of three categories, these include low back pain attributed to specific spinal pathology (fracture, malignancy, infection, axial spondyloarthritis and cauda equina syndrome); radicular syndromes (radicular pain, radiculopathy and spinal stenosis) and non-specific

low back pain (the remaining cases which for symptoms cannot be reliably attributed to a specific cause).[6,7] Of these three classifications, non-specific low back pain encompasses 85-95% of presentations for care.[6,7] This thesis concerns non-specific low back pain.

Neck pain is defined by the Bone and Joint Decade 2000-2010 Task Force, as pain occurring in the neck region, between the superior nuchal line (approximately mid-ear) to the spine of the scapula (the shoulder blades) with or without radiation to the head, trunk, and upper limbs.[8] Aside from anatomical location, neck pain is classified according to duration as per low back pain.[9] Differential diagnoses include specific pathologies (e.g. cervical fracture or myelopathy); nerve root compromise, and non-specific neck pain (when symptoms cannot be reliably attributed to a specific cause).[9] Similar to low back pain, non-specific neck pain comprises the majority of presentations.[10] This thesis concerns non-specific neck pain. The term 'spinal pain' encompasses low back and neck pain, and will be used throughout this thesis to collectively refer to low back and neck pain.

OA is defined by the Osteoarthritis Research Society International, as a disorder involving movable joints that starts as abnormal joint tissue metabolism followed by changes to the joint itself, which may include cartilage degradation, loss of joint space, bone reshaping, osteophyte formation, joint inflammation and loss of normal joint function.[11] OA can occur in any joint, including the joints of the knee, hip, hand, foot and spine.[12] As the clinical significance of degenerative changes to the spinal joints is unknown, spinal pain is typically referred to as non-specific back/neck pain rather than 'spinal OA'.[13] OA of the knee and hip are the most common and burdensome types of OA,[14,15] the research in this thesis is concerned with knee and hip OA, with a larger focus on knee OA. Diagnosis of knee and hip OA includes differentiating between clinical OA and clinical plus radiological OA.[16–18] Clinical classification is based on the presence of symptoms (i.e. pain and stiffness) and findings of a physical examination (i.e. bony tenderness or enlargement).[16–18] Clinical and radiological OA may include loss of joint space and the presence of osteophytes at joint margins determined via imaging.[16–18] In practice, consideration of radiographic findings alone are not

recommended for diagnosis as there is poor correlation between symptoms and radiographic findings; that is radiological joint findings are common in the absence of pain.[19] Additional classification of OA includes defining it as primary or secondary OA.[16] Primary OA is described as OA that has no known cause, whereas secondary OA can be attributed to another cause or condition including, repeated joint trauma, abnormal joints at birth, gout or rheumatoid arthritis.[16]

1.3 Prevalence of spinal pain and OA

Spinal pain and OA are highly prevalent. Globally, there were more than 748 and 301 million cases of spinal pain and OA respectively, in 2016.[15] Over a lifetime, up to 84% of people will experience low back pain,[20] around 50% will experience neck pain[21] and over 40% will be diagnosed with OA.[22] Systematic reviews report that the prevalence of spinal pain is higher in females than males, and prevalence peaks in middle age.[9,23] Similarly, OA is more common in females than males, however prevalence increases beyond middle age.[1] OA of the knee is the highest contributor to the total prevalence of OA, followed by OA of the hip.[14]

1.4 Burden of spinal pain and OA

1.4.1 Individual burden

The individual burden of spinal pain and OA is commonly described in terms of the disruption to an individual's daily life. Adverse physical, psychological and social impacts are common.[24] Pain from these conditions may interfere with activities of daily living, lead to sleep disturbance and physical fatigue.[25–29] Pain and functional impairment arising from spinal pain and OA may also contribute to or exacerbate mental health issues, such as symptoms of anxiety and depression.[24–28] People with these conditions also often report impact on social life, reduction in participation in leisure activities, feelings of isolation, problems with relationships, work problems and financial concerns.[26,28–30] Additionally, health-related quality of life, a measure that summarises the impact of conditions on a person's overall well-being,[24] is consistently lower in people that have spinal pain and OA, than those that do not have these conditions.[31–34]

1.4.2 Societal burden

Collectively, spinal pain and OA comprised 17.1% of the total global burden in terms of years lived with disability (YLDs), according to the Global Burden of Disease Study 2016.[15] Low back pain, neck pain and OA are ranked 1st, 6th and 12th respectively among all causes of YLDs.[15] Disability adjusted life years (DALYs) is a measure that includes the number of years lost to death or disability.[35] Although, spinal pain and OA do not directly lead to death, they are among the leading causes of DALYs.[35] Combined, 4.3% of DALYs from all causes were attributed to spinal pain and OA in 2016.[35] Spinal pain ranked 4th among the leading causes of DALYs, behind ischemic heart disease, cerebrovascular disease and low respiratory infection.[35] Notably, the global burden of spinal pain and OA is increasing over time. Between 2006 and 2016, total DALYs increased by 19.3% and 31.5% for spinal pain and OA respectively.[35]

1.4.3 Economic burden

Spinal pain and OA have a large societal economic impact. Economic costs are generally reported in terms of 'direct' and 'indirect' costs. Direct costs include physician services, hospital costs, medications and diagnostic imaging; indirect costs include those due to lost work productivity such as absenteeism, presenteeism, reduced tax revenue, superannuation loss, welfare payments, carer costs and impact on gross domestic product.[12,36] In Australia and the United Kingdom, estimates of annual total costs (i.e. direct and indirect costs) of low back pain, were $9.2 billion,[37] and £12.3 billion,[38] respectively. For neck pain, estimated annual total costs were $0.7 billion in the Netherlands, equating to 0.1% of the gross domestic product (GDP).[39] In all of these estimates, the majority of costs were attributed to productivity losses.[37–39] In Australia, productivity losses from spinal disorders were estimated at $4.8 billion in annual individual earnings, $622 million in additional welfare payments, $497 million in government taxation revenue, and $2.9 billion in lost GDP.[40] The costs of OA are even more substantial. The total costs of OA in 2008 was estimated at $23.1 billion in Australia, an increase of 63.6% from 2005.[41] In the UK and US, OA accounts for an estimated 1-2.5% of the GDP.[42] The majority of costs for OA are also attributed to productivity losses.[26]

1.5 Spinal pain, OA and chronic diseases

Chronic non-communicable diseases (hereafter referred to as chronic diseases), are responsible for the majority of deaths worldwide. For example, cardiovascular disease, cancer, diabetes and chronic respiratory diseases accounted for 31.2 million of 56 million global deaths in 2012.[43]

An emerging body of research indicates that chronic diseases frequently co-occur with musculoskeletal conditions, particularly spinal pain and OA.[44] While the direction of the relationship is unclear, there is some evidence to suggest that spinal pain and OA may contribute to the development of chronic disease. For example, Jordan and colleagues demonstrated that those with back pain had more than double the risk of developing cancer over a ten year period, than those without back pain.[45] There is also evidence to suggest that those with OA are more likely to develop cardiovascular disease, compared to people without OA.[46,47] One plausible explanation for these relationships is that pain and disability, caused by spinal pain and OA, may limit participation in physical activity and contribute to weight gain[48,49] and other lifestyle risk factors[50–53] for chronic disease. Further, common management approaches for spinal pain and OA are linked to increased risk of cardiovascular-specific mortality, for example the use of non-steroidal anti-inflammatory drugs.[54] However, given that these relationships are based on data from observational studies, it is possible that the apparent relationships are a result of confounding.

Although independent studies have examined the association between spinal pain, OA and chronic diseases,[46,47,52,54] these studies have not been systematically synthesised. To understand if spinal pain and OA truly cause the onset of chronic diseases, the included studies need to be examined for temporal precedence and measurement bias as well as assessed for use of methods that facilitate causal inference such as structural identification of confounders with directed acyclic graphs or instrumental variable analysis. These methods are necessary because there may be other reasons for statistical associations between musculoskeletal pain and chronic disease such as reverse causation and coincidence. If musculoskeletal pain were demonstrated to be a causal factor, this would provide justification for targeting spinal pain and OA in chronic disease prevention strategies.

Chapter Two of this thesis reviews the evidence investigating the association between spinal pain and OA, and the development of chronic diseases.

1.6 Spinal pain, OA and lifestyle risk factors

Lifestyle risk factors are modifiable factors that increase the risk and progression of chronic diseases, common examples include excess weight, poor diet, physical inactivity, smoking and alcohol consumption.[50] Evidence from observational studies suggests that lifestyle risk factors, in particular excess weight, also influence persistence of spinal pain and progression of OA.[48,55–60] For example, a meta-analysis of cohort studies showed that the odds of developing chronic low back pain was 43% (95% CI: 1.28, 1.60) higher for overweight or obese individuals, than non-overweight individuals.[48] Similarly, in one prospective study, the odds of developing chronic neck pain was 40% (95% CI: 1.1, 1.8) higher for obese individuals compared to non-overweight individuals.[60] For knee OA, a recent meta-analysis showed that being either overweight (95% CI: 1.57, 2.20) or obese (95% CI: 2.15, 3.28) doubles a person's risk of developing knee OA when compared to non-overweight controls.[58] Additionally, a meta-analysis demonstrated that a 5-unit increase in BMI is associated with a 35% (95% CI: 1.21, 1.51) increased risk of knee OA.[59] Given that poor diet, physical inactivity and alcohol consumption are key drivers of excess body weight, these lifestyle risk factors are also likely to contribute to the chronicity of low back pain, neck pain and OA.[61,62] Moreover, independent of weight, low levels of physical activity have been shown to influence the chronicity of low back pain[63] and contribute to poorer physical function in people with knee OA.[64]

Weight loss has been shown to be beneficial in the management of knee OA.[65,66] A meta-analysis of four randomised controlled trials (RCTs) including 454 patients showed that behavioural weight loss interventions lead to moderate improvements in pain and physical function for patients with knee OA who were overweight or obese (pooled effect sizes (ES) 0.2, 95% CI: 0, 0.39 and 0.23, 95% CI: 0.04, 0.42, respectively).[65] Furthermore, patients with knee OA who achieve at least a 5% weight loss experience a significant reduction in disability

(ES=0.34).[65] These data have led to the inclusion of weight loss as a core treatment in current knee OA clinical guidelines for people who are overweight or obese.[67] In contrast to knee OA, no RCTs have been conducted to establish if lifestyle interventions improve pain and disability in patients with low back pain. It is plausible that targeting lifestyle risk factors as part of low back pain management could be beneficial however, more research is needed.

1.7 Lifestyle-focused care for low back pain

1.7.1 Theoretical mechanisms of lifestyle-focused care for low back pain

There are several theories as to why targeting lifestyle risk factors could improve patient-reported outcomes such as pain and disability for people with low back pain. Proposed mechanisms include mechanical, metabolic and psychosocial factors.[68] In terms of mechanical factors, reducing excess weight may improve low back pain by reduced load and excessive stress on the spine and back, and by improving associated movement dysfunction and ambulation.[68,69] Weight loss may also influence low back pain by improving metabolic systems. Excess weight is associated with low-grade systemic inflammation, poor circulation, central nervous system changes, and development of neuropathic disorders, which are all known contributors to the pain experience.[68–70] Reducing excess weight may also improve psychosocial factors that are thought to exacerbate the pain experience. For example, weight loss may reduce emotional distress, improve anxiety and depression, or positively influence the patient's social environment.[68,70] Increased physical activity and a better diet (i.e. less energy-dense nutrient-poor foods), may influence these processes by contributing to weight loss.[70] Further, independent to weight loss, improvements in physical activity and diet are thought to reduce inflammation, reduce emotional distress and improve anxiety and depression.[69,71,72] Increased physical activity may also improve important patient outcomes by a number of other mechanisms. These include; increased strength and conditioning, improved self-efficacy, reduced fear of specific movements, increased pain coping and reduced inappropriate pain beliefs.[73,74] Although discussed independently, it is plausible that targeting lifestyle risk factors in patients with low back pain will activate several of these mechanisms simultaneously.

1.7.2 Evidence of potential benefits of lifestyle-focused care for low back pain

There is some evidence to suggest that improving lifestyle risk factors in patients with low back pain improves patient-reported outcomes. A pre-post study of a 52-week medically supervised weight loss program found a statistically significant weight loss of 15.3kg (95% CI: 7.8, 22.8) was associated with a significant improvement in disability (Oswestry Disability Index, baseline 31.9±17.7, follow-up 27.1±20.9).[75] The program included two phases, each of six months duration. In phase one participants attended three-hour weekly group educational sessions including topics on healthy eating, physical activity and behaviour change. Additionally, phase one included dietary restrictions, beginning with a liquid replacement diet (~3780kJ/d) in weeks 2-13, followed by a gradual transition over weeks 14-17 to a solid food diet of ~5040-6300kJ/d for the remaining weeks of phase one. Phase two (weeks 27-53) included the continuation of the solid food diet and monthly group sessions to maintain behaviour changes.[75] Although encouraging, this study has a high risk of bias due to the study design. High quality RCTs are needed to determine whether targeting lifestyle risk factors is beneficial for the management of low back pain.

1.7.3 Provision of lifestyle-focused care to patients with low back pain

Despite the evidence suggesting that targeting lifestyle risk factors may improve important patient-reported outcomes in patients with low back pain, patients do not typically receive lifestyle-focused care. A cross-sectional analysis of 780 patients awaiting specialist consultation for musculoskeletal pain, including chronic low back pain, found that the majority of patients (85%) were overweight or obese and none met Australian guideline recommendations for levels of physical activity or serves of fruits and vegetables. Almost all patients (93%) reported interest in addressing lifestyle risk factors, however, only 30% had received any advice and none believe that they could action that advice.[76] Given that there is currently no evidence on how to provide lifestyle-focused care to patients with low back pain, it is not surprising that patients are not receiving this type of care.

Lifestyle interventions for patients with musculoskeletal conditions have been delivered using a variety of modalities such as face-to-face consultations,

telephone support, provision of education materials or a combination of these.[65,66,77,78] Telephone-based interventions provide direct verbal patient-provider contact, can be delivered remotely and are preferred by patients.[76,79] Given the large number of patients with low back pain, development of scalable interventions is a particularly important consideration for this population group. Using telephone-based population health services alongside clinical services is a novel approach that could ensure that all patients with low back pain receive care that addresses their lifestyle risk factors, when present. In Australia, there are existing telephone-based population health services that could help to provide this care for patients with low back pain, including The New South Wales Get Healthy Service and Quitline. The New South Wales Get Healthy Service is a telephone-based health coaching service that supports individuals to modify eating behaviours, increase physical activity and achieve and maintain a healthy weight.[80] Integrating this population health service with appropriate clinical care (e.g. guideline recommended advice and reassurance)[81] would increase the capacity of the health system to provide lifestyle-focused care. Providing care that addresses lifestyle risk factors has the potential to improve not only patient outcomes related to low back pain, but also general health. To establish the effectiveness of such an approach high quality RCTs are required.

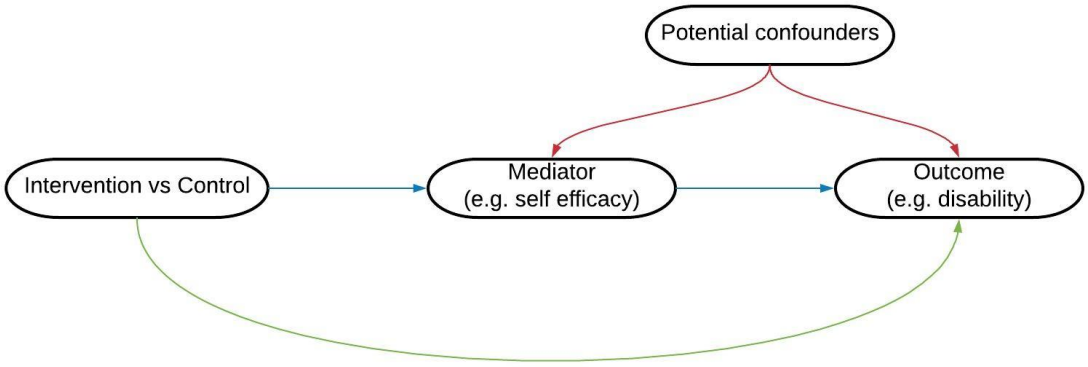
Chapter Three of this thesis presents a study protocol (Part A) and a statistical analysis plan (Part B) for a healthy lifestyle intervention that integrates clinical and population health services for patients with chronic low back pain, who are overweight or obese. The statistical analysis plan also includes a second RCT of a healthy lifestyle intervention for patients with knee osteoarthritis, because the two trials were conducted together as part of a cohort multiple RCT. Chapter Four reports the effectiveness of the intervention for patients with chronic low back pain.

1.8 Understanding causal mechanisms of treatments

Most low back pain or knee OA treatments do not directly target patient-reported outcomes such as pain and disability, they target factors hypothesised to be causes of the outcome of interest.[82,83] Often, treatments are expected to exert their effects on the outcome(s) through an indirect pathway, a ‘causal

mechanism'.[82] For example, Fordham and colleagues tested advice plus a cognitive-behavioural intervention, versus advice alone, in patients with low back pain.[84] In this example, one hypothesis was that the cognitive-behavioural intervention would improve disability by increasing pain self-efficacy.[84]

Figure 1. A single mediator model depicted by a directed acyclic graph. Blue lines represent indirect effects (mechanism of interest). Green lines represent direct effects (direct effect of treatment on outcome plus all unspecified indirect effects). Red lines represent possible effects that could induce confounding for indirect and direct effects.



Causal mediation analyses of RCTs aim to understand causal mechanisms of treatments.[85] Specifically, if a treatment is effective, mediation analyses help determine if the intervention exerted its effect on the patient outcome by changing a specific treatment target. Conversely, if the treatment is ineffective, mediation analyses can determine where the causal mechanism broke down. That is, by determining whether the treatment failed to influence the hypothesised treatment targets, or whether the targets were not causes of the outcome, or both.[82,83] This information can be used to refine treatments with the aim of improving their efficacy and efficiency. For example, intervention components that modulate treatment targets that are causes of patient outcomes can be prioritised, and targets that are not causes of patient outcomes can be abandoned.[82]

To date, there are only few causal mediation analyses of low back pain or knee OA treatments.[82] For low back pain, there are no causal mediation analyses of

lifestyle interventions because there are no RCTs. The majority of mediation analyses of low back pain studies have assessed hypothesised targets of psychological interventions for reducing patient disability.[82,86] In these studies, commonly identified hypothesised targets included pain self-efficacy, fear-avoidance and pain catastrophizing.[82,86] For knee OA, despite evidence suggesting that lifestyle interventions can improve pain and disability, there is a paucity of causal mediation analyses testing this assumption. To my knowledge only one previous study of a lifestyle intervention in patients with knee OA has undertaken causal mediation analyses. Foy et al. found that in adults with knee pain and diabetes, who were overweight or obese, a mean weight reduction of 8.2 kg explained 98% of the intervention effect on disability.[84] For all other lifestyle interventions for knee OA patients, in the absence of causal mediation analyses, one can only assume that the intervention worked through the treatment targets, however, it is possible that these interventions worked via different causal mechanisms. Identifying targets that are causes of important patient outcomes is needed to refine existing treatments and devise new treatments, as such, evaluations of RCTs should routinely include causal mediation analyses.

Chapter Five of this thesis presents a protocol of a causal mediation analysis of two healthy lifestyle interventions for patients with chronic low back pain and knee OA, who are overweight or obese, and Chapter Six presents the results of the causal mediation analysis.

1.9 Economic analyses of randomised controlled trials

Policy or decision makers work in a resource limited environment and are required to choose between healthcare interventions.[87] Economic analyses of RCTs compare costs in relation to clinical effects, allowing an assessment of whether a treatment is cost-effective, relative to another treatment.[87,88] This information can be used to prioritise available healthcare interventions and guide allocation of resources.[87] Economic evaluations of RCTs enable the comparison of costs between two courses of action, allowing assessment of which treatment option results in less costs to society and/or the health system.[87] Pragmatic RCTs are ideal for facilitating economic analyses, as an intervention can be compared to current practice and costs are evaluated under real world conditions.[87]

A recently published study mapped the available economic evidence for various chronic low back pain treatment options.[89] The study found that systematic review evidence was available for 17% of low back pain treatments, evidence from individual studies was available for 22% of low back pain treatments, and for 61% of treatment approaches no economic evaluations have been conducted.[89] The majority of available economic evidence was for activity and physical treatments, psychological and multidisciplinary interventions and surgical treatments.[89] For decision makers to decide between available interventions a broad range of treatments need to be evaluated. Ideally, economic evidence would be available for all treatments.[89]

Chapter Seven is an economic evaluation of a healthy lifestyle intervention for patients with chronic low back pain, who are overweight or obese.

1.10 Summary

Musculoskeletal conditions such as spinal pain and OA are common conditions that place significant burden on individuals, health systems and economies globally. Although evidence suggests that musculoskeletal conditions are linked with chronic diseases and lifestyle risk factors, there are significant evidence gaps in the understanding of these relationships. For instance, there is evidence suggesting that musculoskeletal conditions play a role in the development of chronic diseases, however, this evidence has not been systematically synthesised nor critically appraised. Targeting lifestyle risk factors for the management of musculoskeletal conditions is another area worthy of investigation and is lacking for chronic low back pain.

1.11 Aims of this thesis

This thesis attempts to explore the relationship between musculoskeletal conditions and chronic diseases and assess the management of lifestyle risk factors in patients with common musculoskeletal conditions including chronic low back pain and knee OA.

Specific aims are to:

- Review the evidence of the association between spinal pain and OA, and the development of chronic diseases (Chapter Two)
- Describe a protocol and statistical analysis plan to test the effectiveness of a healthy lifestyle intervention for patients with chronic low back pain, who are overweight or obese (Chapter Three)
- Evaluate the effectiveness of a healthy lifestyle intervention for patients with chronic low back pain, who are overweight or obese (Chapter Four)
- Describe a protocol to test the causal mechanisms of a healthy lifestyle intervention for patients with chronic low back pain or knee OA, who are overweight or obese (Chapter Five)
- Evaluate the causal mechanisms of a healthy lifestyle intervention for patients with chronic low back pain or knee OA, who are overweight or obese (Chapter Six)
- Conduct an economic evaluation of a healthy lifestyle intervention for patients with chronic low back pain, who are overweight or obese (Chapter Seven)

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CHAPTER TWO

Musculoskeletal conditions may increase the risk of chronic disease: A systematic review and meta-analysis of cohort studies

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I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: "Musculoskeletal conditions may increase the risk of chronic disease: A systematic review and meta-analysis of cohort studies," in the following ways:

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Musculoskeletal conditions may increase the risk of chronic disease: A systematic review and meta-analysis of cohort studies

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Abstract

Background

Chronic diseases and musculoskeletal conditions have a significant global burden and frequently co-occur. Musculoskeletal conditions may contribute to the development of chronic disease; however, this has not been systematically synthesised. We aimed to investigate whether the most common musculoskeletal conditions, neck or back pain or osteoarthritis of the knee or hip contribute to the development of chronic disease.

Methods

We searched CINAHL, Embase, Medline, Medline in Process, PsycINFO, Scopus and Web of Science to February 08, 2018, for cohort studies reporting adjusted estimates of the association between baseline musculoskeletal conditions (neck or back pain or osteoarthritis of the knee or hip) and subsequent diagnosis of a chronic disease (cardiovascular disease, cancer, diabetes, chronic respiratory disease or obesity). Two independent reviewers performed data extraction and assessed study quality. Adjusted hazard ratios were pooled using the generic inverse variance method in random effect models, regardless of the type of musculoskeletal condition or chronic disease. PROSPERO: CRD42016039519.

Results

There were 13 cohort studies following 3,086,612 people. In the primary meta-analysis of adjusted estimates osteoarthritis was the exposure in eight studies and back pain in two studies and cardiovascular disease was the outcome in eight studies, cancer in one study, and diabetes in one study. Pooled adjusted estimates from these ten studies showed that people with a musculoskeletal condition have a 17% increase in the rate of developing a chronic disease compared to people without a musculoskeletal condition (hazard ratio 1.17, 95% confidence interval 1.13 to 1.22; I^2 52%, total n=2,686,113).

Conclusions

This meta-analysis found musculoskeletal conditions may increase the risk of chronic disease. In particular, osteoarthritis appears to increase the risk of developing cardiovascular disease. Prevention and early treatment of musculoskeletal conditions and targeting associated chronic disease risk factors

in people with long standing musculoskeletal conditions may play a role in preventing other chronic diseases. However, greater understanding about why musculoskeletal conditions may increase the risk of chronic disease is needed.

Introduction

Non-communicable chronic diseases are responsible for a significant global burden. Cardiovascular disease, cancer, diabetes and chronic respiratory diseases ranked among the leading causes of global disability-adjusted life years (DALYs) in 2015.[1] Together, these conditions were responsible for over 31 million of 56 million deaths worldwide in 2012.[2] Obesity, now also considered a chronic disease,[3] also contributes to a high rate of morbidity and all-cause mortality.[2]

Another significant source of the global disease burden is from musculoskeletal conditions, specifically neck and back pain as well as osteoarthritis (OA) of the knee and/or hip. Neck and back pain ranks fourth among the leading causes of DALYs, and elderly people with neck and back pain or OA die sooner than those without.[1,4,5] When considering only years lived with disability (YLDs), neck and back pain, as well as OA, rank 1st and 13th respectively among all causes of global YLDs and together accounted for 13.6% of YLDs in 2015.[6]

Evidence shows that chronic diseases and musculoskeletal conditions frequently co-occur,[7] and importantly, people with musculoskeletal conditions are reported to have roughly twofold chance of having chronic disease of other body systems, such as heart disease, neurological disorders, gastric ulcers, and endocrine disorders.[8] Several mechanisms have been proposed to explain these links. Chronic inflammation associated with OA has been hypothesised to increase the risk of cardiovascular disease, diabetes and cancer.[5] Pain and disability from musculoskeletal conditions can also limit participation in physical activity, or may influence other risk factors for chronic diseases, for example weight gain or poor sleep.[5,8–11] Similarly, pain management approaches which are widely used for back pain and OA, for example, the use of non-steroidal anti-inflammatory drugs (NSAIDs), are known to increase the risk of cardiovascular events and mortality.[5] These hypotheses suggest musculoskeletal pain may play a role in the subsequent development of other chronic diseases.

Despite the suggested link between musculoskeletal conditions and chronic diseases,[5,9,12,13] to the best of our knowledge the available studies have not been systematically synthesised, and a direct longitudinal relationship has not been

considered. To determine if the most common and burdensome musculoskeletal conditions (neck or back pain, or OA of the knee or hip) increased the development of chronic disease (cardiovascular disease, cancer, diabetes, chronic respiratory disease and obesity) we conducted a systematic review and meta-analysis of longitudinal cohort studies reporting adjusted estimates of the association between these musculoskeletal conditions and the development of chronic disease.

Methods

The systematic review protocol was prospectively registered with Prospero on 24th May 2016 (PROSPERO 2016: CRD42016039519). The systematic review adheres to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.[14]

Study eligibility

We included longitudinal cohort studies that estimated a direct association between baseline neck or back pain, or OA of the knee or hip (i.e. exposure) and subsequent diagnosis of a chronic disease (cardiovascular disease, cancer, diabetes, chronic respiratory disease or obesity) over any follow up length (i.e. outcome). We did not aim to identify studies of mechanisms or specific causal factors for chronic disease such as treatment provided (e.g. NSAIDs) or features of pain (e.g. disabling pain). Studies with mixed populations of musculoskeletal conditions were included where separate data was provided for the conditions of interest, or where at least 75% of 'musculoskeletal conditions' reported were one of or a combination of neck or back pain, or OA of the knee or hip. Studies assessing specific forms of OA other than knee or hip (e.g. hand/wrist, foot etc.) were excluded. We included any study that assessed 'osteoarthritis' broadly (i.e. did not define the type of OA) as we expected knee and hip OA would constitute the majority of participants, as these are the most prevalent forms of osteoarthritis.[15] We included all neck or back pain and OA, defined as clinical, self-reported, and diagnoses with or without imaging. There were no restrictions on the study setting, participant age, length of follow-up, publication type (e.g.

abstracts from conference proceedings, dissertations), publication date or language.

Data sources and search strategy

We searched CINAHL, Embase, Medline, Medline in Process, PsycINFO, Scopus and Web of Science for eligible studies. Databases were searched from inception to 08 February, 2018. The search used key terms as subject headings and text words to identify; i) neck or back pain, or OA of the knee or hip, and ii) chronic diseases (cardiovascular disease, cancer, diabetes, chronic respiratory disease or obesity) along with terms for chronic disease, and morbidity (see Additional file one Table S1). The search strategy was reviewed and performed by an information specialist. We manually searched the reference lists of included studies to identify further studies. All references were stored in Endnote X7 software.

Study selection

Before screening, duplicates were removed using the duplicate removal function in Endnote X7 software. After removing duplicates, pairs of review authors independently screened studies for inclusion based on title and abstract (AW, SK, KO, SY, ER, CW). For studies not excluded at this step, each full text retrieved was screened independently by pairs of review authors to determine final inclusion (AW, SK, KO, CW). Consensus was used to resolve any disagreements and a third reviewer was consulted when required (SK, CW). Studies reported in a language other than English were read within a two month period after the search was conducted, by a colleague or collaborator of the author team who was a native speaker in that language, to determine if they met inclusion criteria.

Data abstraction

Relevant information was extracted from included studies by one author and checked for accuracy and omissions by a second author (AW, KO). Discrepancies were resolved by discussion. The following study characteristic information was extracted into nine categories outlined in Additional file one Table S2: study source and country, population description, number of patients with a

musculoskeletal condition, age, sex, measure of musculoskeletal condition, measure of chronic disease, follow-up time and adjustment for any covariates. All information was extracted directly into the table. Outcome data (i.e. estimates of the association between a musculoskeletal condition and a chronic disease) were extracted into Microsoft Excel 2013 and then those estimates used in meta-analyses were stored in RevMan5 software for analysis.[16]

Risk of bias assessment

Risk of bias was assessed using a modified version of the Quality in Prognosis Studies (QUIPS) tool for assessing studies of prognostic factors.[17] For this review we were interested in assessing a risk factor or exposure that increases the likelihood of developing a disease, in this case a musculoskeletal condition, rather than a prognostic factor that influences outcome from or course of a disease. Thus, we amended the 'prognostic factor' domain in QUIPS to reflect this. The following six domains were considered: study participation, study attrition, risk factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Each domain was assessed as having high, moderate or low risk of bias. Overall risk of bias was also assessed for each study, the designers of the QUIPS tool recommend that this is done by determining which domains (of the six) are most important and assigning low risk if a study is low in those domains.[17] In line with this recommendation, we categorised a study as 'low risk of bias' when the risk of bias was rated low on at least four of the six domains, and was rated low for both study attrition and study confounding. Two authors independently assessed each study (AW, SK). Consensus was used to resolve any disagreement and a third reviewer was consulted when required (CW).

Data synthesis

We calculated pooled hazard ratios of the effect of the exposure (musculoskeletal condition) on the outcome (chronic disease) and 95% confidence intervals using the generic inverse variance method.[18] We used random effect models to incorporate heterogeneity between studies.[19] Not all studies reported hazard ratios and 95% confidence intervals. Despite being modelled under different

assumptions, incidence rate ratios are considered approximations of hazard ratios and therefore, were included in the meta-analysis.[20] Where the incidence rate and number of events were reported these data were used to calculate the incidence rate ratio and standard error respectively. Where the number of events was not reported, we attempted to contact authors for further data. Where authors did not respond to contact attempts, we estimated the standard error using the number of events derived from available data. The number of events was calculated using the number of patient years per group and the incidence rate per group. The patient years per group was calculated using the total number of people in each group (those with the musculoskeletal condition and those without), and the mean years of follow-up.

In the primary meta-analysis, we pooled estimates from all musculoskeletal conditions and chronic diseases. We pooled estimates using the most adjusted estimates from each study. Where possible, we also reported pooled estimates by musculoskeletal condition and by chronic disease. We undertook a secondary analysis using unadjusted estimates from each study.

Where there was more than one article reporting on the same patient sample, we included the data that was most clinically homogenous with the other included studies or included the more comprehensive exposure or outcome (i.e. all cancer rather than a specific cancer). If several estimates were reported from one study (e.g. men and women) where possible we combined estimates using a fixed effects model to generate one estimate for the sample. When combining several estimates from within a study was not appropriate (i.e. where the unexposed group would be counted twice), we chose a single estimate based on clinical homogeneity with other studies in the meta-analysis, the less selective sample, or interpretability of the clinical measures.

We used sensitivity analyses to test whether the primary adjusted meta-analysis was affected by overall risk of bias. This involved performing a meta-analysis including only studies at low risk of bias determined by the QUIPS tool, and comparing the pooled estimate with the primary analysis. We also used sensitivity analyses to assess whether the primary adjusted meta-analysis was affected by our decisions to choose between different exposures or outcomes reported within

the one study. This involved performing meta-analyses whereby, the alternative reported estimate was substituted in for our original choice, and comparing the pooled estimates with the primary analysis.

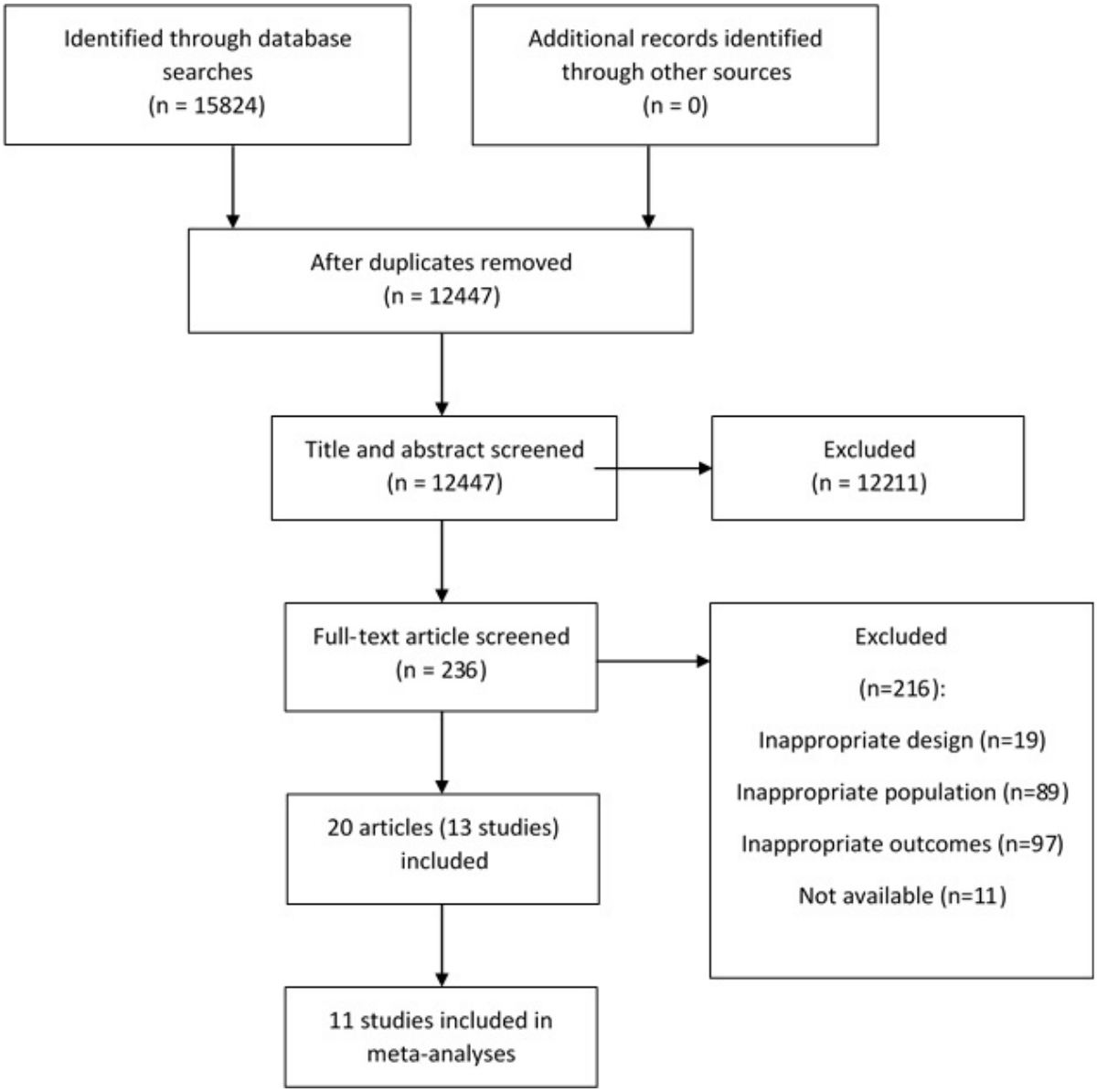
The impact of heterogeneity between studies was assessed using the I^2 statistic with ≥50% considered substantial. Funnel plots to identify small-study effects were planned for analyses including at least 10 estimates.[21] All analyses were conducted using RevMan5 software.[16]

Results

Study selection

The search identified 15,824 articles of which 12,447 remained after removal of duplicates. There were 236 articles that remained after title and abstract screening, of these 205 were excluded after assessment of the full text. Eleven abstracts were excluded as the full text or sufficient data were not available, confirmed by correspondence with authors or no response to contact attempts. Two abstracts with sufficient data and information to assess inclusion were included in the review. This left 20 articles[9,12,13,22–38] that met the criteria for inclusion in the review. The 20 articles reported on 13 studies, there was sufficient data reported from 11 studies to be included in meta-analyses (Figure 1).

Figure 1. Flow diagram of study selection



Study characteristics

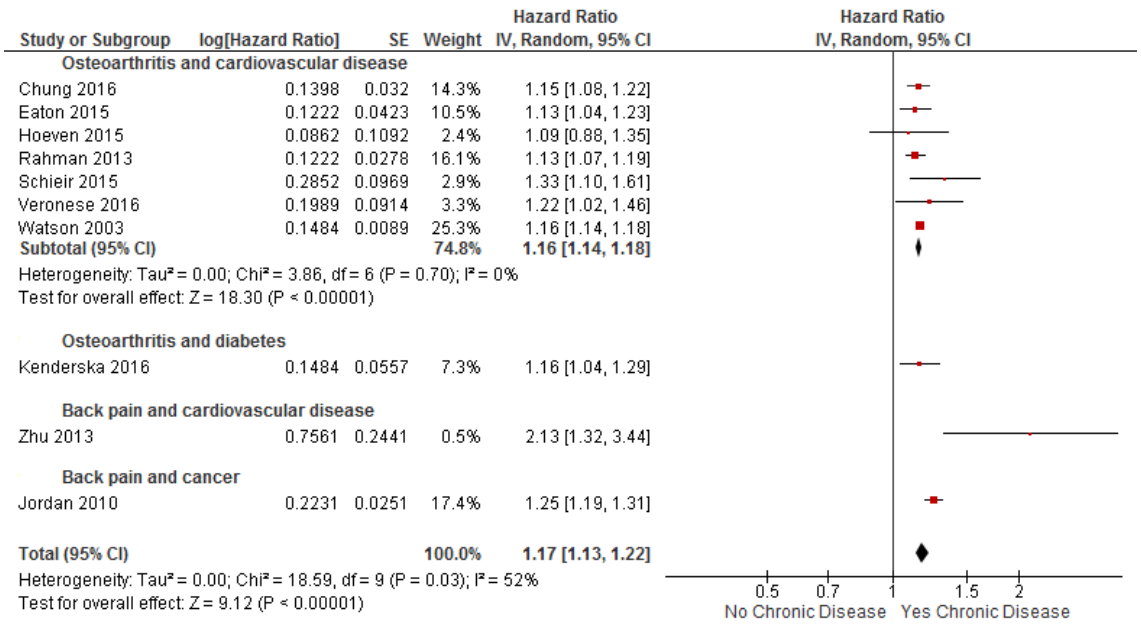
The 13 studies included data from a total of 3,086,612 persons (mean follow-up range 4 to 16 years).[9,12,13,22,24–26,29,31,35–38] Of those studies that reported a mean participant age, seven reported a mean of >50 years,[12,13,22,24,29,31,38] and three studies reported a mean of >70 years.[9,35,37] Four studies were from Canada,[13,31,35,36] two from the United Kingdom[29,38] and one from either the United States of America,[25] Taiwan,[22] the Netherlands,[12] Italy,[37] Spain,[24] Australia[9] or Norway.[26] All studies were published in English. The musculoskeletal condition (exposure) was general OA in seven studies,[13,22,25,35–38] knee OA in three

studies,[12,31,37] hip OA in three studies,[12,31,37] back pain in four studies[9,24,26,29] and neck pain in one study.[29] The chronic disease (outcome) was cardiovascular disease in nine studies,[9,12,13,22,25,35–38] cancer in one study,[29] diabetes in three studies[24,31,33] and obesity in one study.[26] All studies excluded participants who reported the outcome of interest at baseline. Descriptive data for all studies are provided in Additional file one Table S2.

Risk of chronic disease from musculoskeletal conditions

The 11 studies with sufficient data for meta-analysis reported ten adjusted estimates from a total of 2,686,113 persons[9,12,13,22,25,29,31,36–38] and five unadjusted estimates from a total of 612,873 persons.[13,22,25,35,37] The primary meta-analysis of adjusted estimates (Figure 2) showed a statistically significant increased risk of chronic disease incidence from musculoskeletal conditions (hazard ratio 1.17, 95% confidence interval 1.13 to 1.22, I^2 52%, ten studies). Studies most often adjusted for age, sex, body mass index, hypertension, diabetes, hyperlipidaemia and smoking. A full list of adjustment variables per study are outlined in Additional file one Table S2. The unadjusted meta-analysis demonstrated a larger, statistically significant association (hazard ratio 1.39, 95% confidence interval 1.23 to 1.58, I^2 94%, five studies).

Figure 2. Meta-analysis of adjusted estimates of the association between musculoskeletal conditions and chronic disease

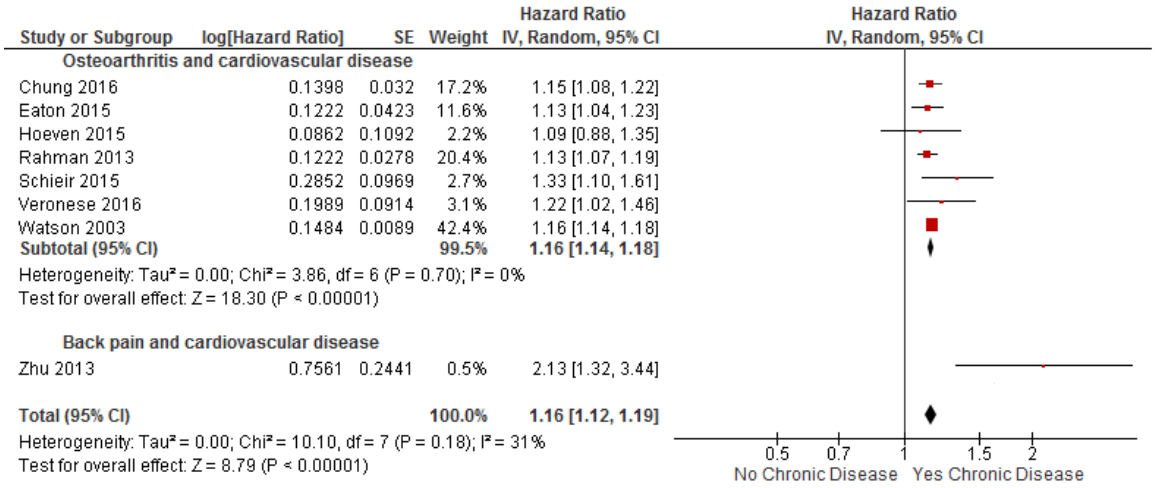


Analyses by condition

Combining all studies with adjusted estimates that assessed OA as the exposure revealed a statistically significant increased risk of chronic disease (hazard ratio 1.16, 95% confidence interval 1.14 to 1.18, I^2 0%, eight studies). Seven of the eight studies that included OA as the exposure assessed the increased risk of cardiovascular disease.[12,13,22,25,36–38] Removal of the remaining study that assessed the increased risk of diabetes[31] did not change the results (Figure 2). Combining the two studies with adjusted estimates that assessed OA as the exposure and diabetes as the outcome revealed a statistically significant increased risk of diabetes (hazard ratio 1.16, 95% confidence interval 1.11 to 1.22, I^2 0%, two studies).[31,33] We were unable to perform analysis by back or neck pain due to the limited number of included studies of these conditions. Two individual studies of back pain found that those with back pain had an increased risk of cardiovascular disease[9] (hazard ratio 2.13, 95% confidence interval 1.32 to 3.44) and cancer[29] (hazard ratio 1.25, 95% confidence interval 1.19 to 1.32), compared to people without back pain. The one study that assessed neck pain found that those with neck pain had an increased risk of cancer[29] (hazard ratio 1.20, 95% confidence interval 1.09 to 1.31), compared to people without neck pain.

Combining all musculoskeletal conditions as the exposure and cardiovascular disease as the outcome revealed a statistically significant increased risk of cardiovascular disease (hazard ratio 1.16, 95% confidence interval 1.12 to 1.19, I^2 31%, eight studies) (Figure 3). We were unable to perform analyses by other chronic diseases (cancer, chronic respiratory disease, diabetes or obesity) due to insufficient number of included studies of these conditions.

Figure 3. Meta-analysis of adjusted estimates of the association between musculoskeletal conditions and cardiovascular disease



Risk of Bias assessment

Of the 13 included studies, 10% (n=8) of the six domains showed a high risk of bias, 23% (n=18) showed moderate risk, and 67% (n=52) low risk of bias. Risk of bias was highest in the 'study confounding' domain with three studies at high risk[29,35,38] and four at moderate risk.[9,13,24,25] Of the ten studies included in the primary meta-analysis of adjusted estimates, three had an overall low risk of bias.[12,22,31]

Sensitivity analyses

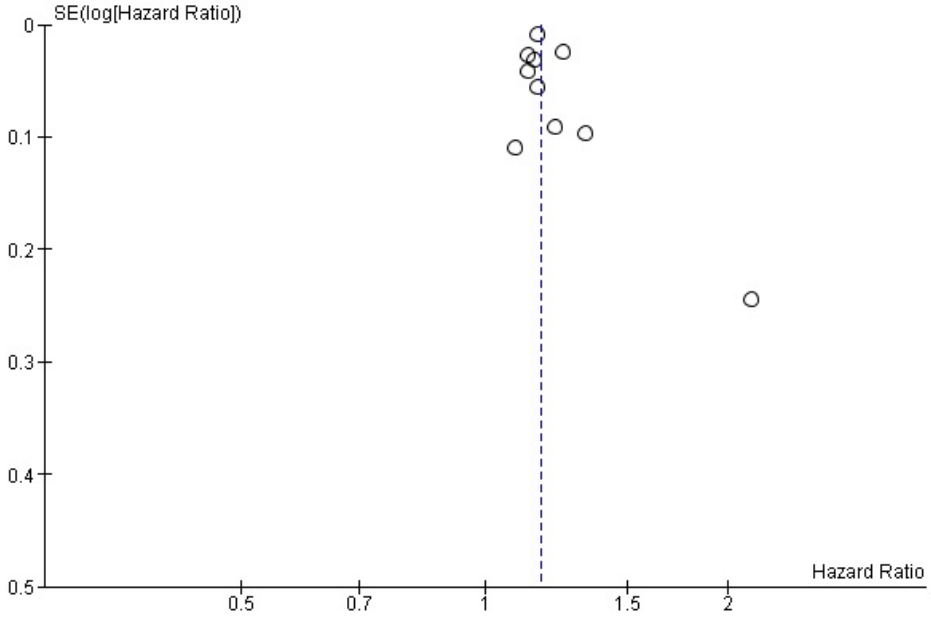
Sensitivity analysis including the three low risk of bias studies, demonstrated a statistically significant association between musculoskeletal conditions and chronic disease (hazard ratio 1.15, 95% confidence interval 1.09 to 1.21, I^2 0%). These studies all assessed OA, two assessed cardiovascular disease[12,22] and one diabetes.[31]

We conducted sensitivity analyses of the primary adjusted meta-analysis whereby, we substituted in an alternative exposure (i.e. general OA vs. hip OA only vs. knee OA only) or outcome (i.e. cardiovascular disease vs. diabetes) from five studies[12,13,29,31,37] where multiple exposures or outcomes were reported. In all cases, using the alternative estimate did not alter the pooled hazard ratio by more than 0.2 and all estimates remained significant.

Substantial heterogeneity (I^2 52%) was present in the primary meta-analysis of adjusted estimates. Sensitivity analysis exploring this found that when the two studies of back pain were removed and only studies of OA remained, heterogeneity dropped to 0%.

Inspection of the funnel plot for the primary adjusted meta-analysis showed that the plot was symmetrical aside from one small-study outlier. Removal of the outlier[9] did not change the pooled estimate (Figure 4).

Figure 4. Funnel plot for adjusted estimates of the association between musculoskeletal conditions and chronic disease



Discussion

This systematic review and meta-analysis including data from 2,686,113 persons showed that people with a musculoskeletal condition have a 17% increase in the risk of developing a chronic disease compared to people without a musculoskeletal condition. Most studies included OA as the exposure and cardiovascular disease as the outcome; analysis of these studies revealed that people who reported OA have a 16% increase in the risk of developing cardiovascular disease, compared to people without OA. Two individual studies concerning back pain and one of neck pain, reported that those with back pain had an increased risk of cardiovascular disease, and those with back or neck pain had an increased the risk of cancer. While our review question ultimately sought

to assess a causal connection between common musculoskeletal conditions and chronic disease, we cannot draw strong conclusions due to poor adjustment, the analysis methods employed by the included studies, and a lack of studies investigating conditions other than OA and cardiovascular disease.

To the best of our knowledge, this is the first attempt at a meta-analysis of longitudinal cohort studies that estimates the risk of developing a chronic disease in people with highly prevalent and burdensome musculoskeletal conditions, neck or back pain, or osteoarthritis of the knee or hip. This review was prospectively registered with the International prospective register of systematic reviews (PROSPERO) and has been reported following the MOOSE reporting guidelines. We used a comprehensive search strategy, studies were not limited by publication date or language and we assessed risk of bias using a specific tool for observational studies. We reported analyses by condition, and conducted sensitivity analyses of studies that had low risk of bias and for studies that reported multiple exposures or outcomes, all of which provided very similar, and precise estimates, to that of the primary analysis.

The lack of sufficient low-bias studies to confidently test the full hypothesis represent major limitations on the strength of conclusions about the general hypothesis about musculoskeletal conditions. While there is more confidence that OA increases the risk of cardiovascular disease, the lack of studies assessing other conditions limits generalisability of our results. Due to the small number of included studies we were unable to assess the effect of various study characteristics (e.g. age, gender, variation in the measurement of the exposure and outcome etc.) on the observed estimates. Studies in the review neither assessed latent exposure to musculoskeletal conditions. It is possible that participants who reported no musculoskeletal condition at baseline (i.e. unexposed), developed a musculoskeletal condition during follow up (i.e. became exposed), but we could not assess this from the included studies. Although, it is not clear if adjusting for this exposure would attenuate or amplify our estimate. Finally, while our assessment of funnel plots suggested there was no evidence of small-study effects, we do not know the influence of the 11 studies for which a full text was not available.

Our intention was to synthesise studies that used methods enabling an assessment of causal effects. To do this, we restricted inclusion to longitudinal cohort studies to assess temporal relationships, and prioritised adjusted estimates over crude estimates to account for potential confounding. We did not find studies that satisfied all of Bradford Hill's suggested criteria for casual inference (e.g. none estimated dose-response effects); nor did we find studies that used contemporary causal inference methods for observational data (e.g. a structured identification approach for selection of confounding variables[39,40] or assessment of the effects of unmeasured or residual confounders).[41–43] As such, we are unable to infer a strong causal connection between musculoskeletal conditions and chronic diseases.

There is evidence to suggest that the relationships found in this review are biologically plausible, meaning that there are possible mechanisms by which musculoskeletal conditions may contribute to the development of chronic disease. For example, there is evidence to suggest that chronic inflammation from OA may increase the risk of cardiovascular disease.[5] Further, pain and disability from these conditions can often limit participation in physical activity and lead to higher weight gain, both recognised risk factors for cardiovascular disease and cancer.[5,8,9] However, none of the included studies assessed possible causal mechanisms. While we did not intend to study mechanisms of the effect, our review provides useful evidence for one direction of accumulation of multimorbidity in people with chronic disease.

Our review focused on the most common and burdensome musculoskeletal conditions showing they may play a role in the development of chronic disease. Most of the evidence to date focuses on OA. Given the high burden of back and neck pain, further research is required to examine the causal effects of these conditions on chronic diseases. Since it is impractical and unethical to randomise individuals to disease states (i.e. musculoskeletal conditions) better use of observational data is required. To facilitate assessment of causal effects, contemporary analysis methods that more accurately identify and account for confounders should be considered alongside observational data. These might include structural identification of confounders with directed acyclic graphs,

matching on propensity scores, or the application of instrumental variable analysis to eliminate the effects of residual confounders.[44] In the context of policy and clinical practice, our findings suggest that considering musculoskeletal conditions in the prevention of chronic disease may be important. However, to inform this, it would be useful to formally identify the mechanisms by which musculoskeletal conditions could cause chronic disease. Understanding how musculoskeletal conditions interact with other co-existing risk factors could further inform targeted intervention strategies to reduce chronic diseases. Certainly, future trials that assess the feasibility and efficacy of targeting musculoskeletal conditions in chronic disease preventive strategies are warranted.

Conclusions

This review found that musculoskeletal conditions may increase the risk of subsequent chronic disease. In particular, meta-analysis of over 2 million people shows OA increases the risk of developing cardiovascular disease. The results suggest that prevention and early effective treatment of musculoskeletal conditions such as OA, back and neck pain may play a role in preventing other chronic diseases. Typical targets for chronic disease prevention currently include lifestyle risk factors such as poor diet, physical inactivity, alcohol consumption and smoking,[45] but currently musculoskeletal conditions are largely ignored. Considering their high global burden, addressing musculoskeletal conditions via public health strategies may have an impact on other chronic diseases such as cardiovascular disease.

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Additional file one

Table S1. Search strategy

Database: MEDLINE
Search Strategy:

#	Searches	Results
1	exp Overweight/	160682
2	exp Obesity/	158483
3	Obes*.tw.	183304
4	Body Mass Index/	92290
5	Abdominal Fat/	1951
	Combined at Set 39	
6	exp Osteoarthritis/	47474
7	exp Back Pain/	31134
8	Neck Pain/	5027
9	(backache or neckache).tw.	1965
10	Musculoskeletal Pain/	1311
11	Sciatica/	4441
12	Neuralgia/	9508
13	(dorsalgia or cervicalgia).tw.	124
14	((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) adj3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)).tw.	128911
15	(osteoarthr* or osteo arthr*).tw.	44030
16	Coxarthr*.tw.	1600
17	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	206206
18	exp Cardiovascular Diseases/	2005418
19	exp Cerebrovascular Disorders/	302083
20	Cardiovascular.tw.	286290
21	Coronary.tw.	304158
22	Cerebrovascular.tw.	38667
23	(arteriosclero* or artherosclero*).tw.	13919
	Combined at set 40	
24	exp Neoplasms/	2790625
25	exp Respiratory Tract Diseases/	1131784
26	exp Diabetes Mellitus/	342867
27	IDDM.tw.	6752
28	NIDDM.tw.	6787
29	MODY.tw.	884

30	glucose intoleran*.tw.	7895
31	(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.	11924
32	((typ* I or typ* II) adj6 diabet*).tw.	14080
33	(insulin* depend* or insulin?depend*).tw.	28196
34	exp Insulin Resistance/	62175
35	(T1DM or T2DM).tw.	8812
	Combined at Set 41	
36	exp Cohort Studies/	1504401
37	(cohort adj (analys* or stud*)).tw.	100608
38	36 or 37	1523206
39	1 or 2 or 3 or 4 or 5	274880
40	18 or 19 or 20 or 21 or 22 or 23	2182009
41	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	395388
42	**17 and 38 and (39 or 40 or 24 or 25 or 41)**	**5075**

Database: Embase Classic + Embase
Search Strategy:

#	**Searches**	**Results**
1	Overweight.mp.	66652
2	exp obesity/	356737
3	Obes*.tw.	294232
4	body mass/	230331
5	abdominal fat/	3824
6	1 or 2 or 3 or 4 or 5	556494
7	exp osteoarthritis/	99445
8	exp backache/	79712
9	neck pain/	15234
10	(backache or neckache).tw.	3043
11	musculoskeletal pain/	6369
12	sciatica/	780
13	neuralgia/	8988
14	(dorsalgia or cervicalgia).tw.	254
15	((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) adj3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)).tw.	196438
16	(osteoarthr* or osteo arthr*).tw.	69330
17	Coxarthr*.tw.	2692
18	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	344871

19	exp cardiovascular disease/	3499892
20	exp cerebrovascular disease/	454290
21	Cardiovascular.tw.	450368
22	Coronary.tw.	455986
23	Cerebrovascular.tw.	59187
24	(arteriosclero* or artherosclero*).tw.	25707
25	19 or 20 or 21 or 22 or 23 or 24	3703937
26	exp neoplasm/	3848545
27	exp respiratory tract disease/	2044455
28	exp diabetes mellitus/	712474
29	IDDM.tw.	7586
30	NIDDM.tw.	7803
31	MODY.tw.	1462
32	glucose intoleran*.tw.	11690
33	(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.	13818
34	((typ* I or typ* II) adj6 diabet*).tw.	21103
35	(insulin* depend* or insulin?depend*).tw.	33156
36	insulin resistance/	90992
37	(T1DM or T2DM).tw.	21464
38	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	766800
39	cohort analysis/	220966
40	(cohort adj (analys* or stud*)).tw.	152667
41	((followup or follow up or longitudinal or prospective or retrospective) adj (analys* or stud*)).tw.	524320
42	39 or 40 or 41	769164
43	**18 and 42 and (6 or 25 or 26 or 27 or 38)**	**5328**

Database: PsycINFO
Search Strategy:

#	**Searches**	**Results**
1	exp overweight/	19257
2	obesity/	18315
3	Obes*.tw.	28742
4	Body Mass Index/	3648
5	Body Fat/ or Abdominal Fat.mp.	1354
6	1 or 2 or 3 or 4 or 5	32471
7	Back Pain/	3118
8	(backache or neckache).tw.	128

9	exp Neuralgia/	795
10	(dorsalgia or cervicalgia or Sciatica).tw.	137
11	((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) adj3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)).tw.	16756
12	(osteoarthr* or osteo arthr*).tw.	1418
13	Coxarthr*.tw.	9
14	7 or 8 or 9 or 10 or 11 or 12 or 13	18797
15	exp cerebrovascular disorders/	21180
16	exp Cardiovascular Disorders/	48654
17	Cardiovascular.tw.	22481
18	Coronary.tw.	8901
19	Cerebrovascular.tw.	5067
20	(arteriosclero* or artherosclero*).tw.	675
21	15 or 16 or 17 or 18 or 19 or 20	68454
22	exp neoplasms/	39555
23	exp respiratory tract disorders/	11830
24	exp Diabetes Mellitus/	4332
25	IDDM.tw.	243
26	NIDDM.tw.	94
27	MODY.tw.	27
28	glucose intoleran*.tw.	270
29	(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.	270
30	((typ* I or typ* II) adj6 diabet*).tw.	906
31	(insulin* depend* or insulin?depend*).tw.	1032
32	exp Resistance/ and exp Insulin/	173
33	(T1DM or T2DM).tw.	577
34	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	5914
35	(cohort adj (analys* or stud*)).tw.	13534
36	((followup or follow up or longitudinal or prospective or retrospective) adj (analys* or stud*)).tw.	72436
37	35 or 36	84439
38	**14 and 37 and (6 or 21 or 22 or 23 or 34)**	**77**

Database: MEDLINE In-Process & Other Non-Indexed Citations
Search Strategy:

#	Searches	Results
1	Overweight.mp.	5562

2	obes*.mp.	22159
3	Body Mass Index.mp.	13320
4	Abdominal Fat.mp.	434
5	1 or 2 or 3 or 4	31248
6	(backache or neckache).tw.	172
7	(dorsalgia or cervicalgia or sciatica or Neuralgia).tw.	1108
8	((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) adj3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)).tw.	15365
9	(osteoarthr* or osteo arthr*).tw.	4558
10	Coxarthr*.tw.	37
11	6 or 7 or 8 or 9 or 10	20023
12	Cardiovascular.tw.	27608
13	Coronary.tw.	18829
14	Cerebrovascular.tw.	2839
15	(arteriosclero* or artherosclero*).tw.	414
16	12 or 13 or 14 or 15	44811
17	(neoplasm* or cancer*).tw.	114262
18	(Respirat* or lung*).tw.	54981
19	Diabetes.tw.	34841
20	IDDM.tw.	71
21	NIDDM.tw.	121
22	MODY.tw.	70
23	glucose intoleran*.tw.	567
24	(non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.	220
25	((typ* I or typ* II) adj6 diabet*).tw.	927
26	(insulin* depend* or insulin?depend*).tw.	555
27	(Insulin adj2 Resist*).tw.	5658
28	(T1DM or T2DM).tw.	2372
29	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	38123
30	(cohort adj (analys* or stud*)).tw.	13478
31	((followup or follow up or longitudinal or prospective or retrospective) adj (analys* or stud*)).tw.	32442
32	30 or 31	44858
33	**11 and 32 and (5 or 16 or 17 or 18 or 29)**	**180**

Database: CINAHL
Search Strategy:

#	Query	Results
S43	**S17 and S42 and (S6 or S24 or S25 or S26 or S37)**	**1,615**
S42	S38 OR S39 OR S40 OR S41	335,884
S41	(MH "Retrospective Panel Studies")	142
S40	(MH "Prospective Studies+")	281,749
S39	TI (((followup or follow up or longitudinal or prospective or retrospective) n1 (analys* or stud*))) OR AB (((followup or follow up or longitudinal or prospective or retrospective) n1 (analys* or stud*)))	99,701
S38	TI ((cohort n1 (analys* or stud*))) OR AB ((cohort n1 (analys* or stud*)))	38,348
S37	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	123,146
S36	TI ((T1DM or T2DM)) OR AB ((T1DM or T2DM))	2,211
S35	(MH "Insulin Resistance+")	18,367
S34	TI ((insulin* depend* or insulin?depend*)) OR AB ((insulin* depend* or insulin?depend*))	2,370
S33	TI (((typ* I or typ* II) n6 diabet*)) OR AB (((typ* I or typ* II) n6 diabet*))	1,632
S32	TI ((non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*)) OR AB ((non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*))	888
S31	(MH "Glucose Intolerance")	2,295
S30	TI MODY OR AB MODY	219
S29	TI NIDDM OR AB NIDDM	607
S28	TI IDDM OR AB IDDM	500
S27	(MH "Diabetes Mellitus+")	109,105
S26	(MH "Respiratory Tract Diseases+")	193,894
S25	(MH "Neoplasms+")	343,517
S24	S18 OR S19 OR S20 OR S21 OR S22 OR S23	423,185
S23	TI ((arteriosclero* or artherosclero*)) OR AB ((arteriosclero* or artherosclero*))	475
S22	TI Cerebrovascular OR AB Cerebrovascular	5,631
S21	TI Coronary OR AB Coronary	48,182
S20	TI Cardiovascular OR AB Cardiovascular	57,198
S19	(MH "Cerebrovascular Disorders+")	70,895
S18	(MH "Cardiovascular Diseases+")	388,522
S17	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	84,544
S16	TI Coxarthr* OR AB Coxarthr*	37
S15	TI ((osteoarthr* or osteo arthr*)) OR AB ((osteoarthr* or osteo arthr*))	13,203
S14	TI (((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) n3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*))) OR AB (((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) n3 (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)))	54,485
S13	TI ((dorsalgia or cervicalgia)) OR AB ((dorsalgia or cervicalgia))	44

S12	(MH "Neuralgia")	2,563
S11	(MH "Sciatica")	1,176
S10	TI ((backache or neckache)) OR AB ((backache or neckache))	269
S9	(MH "Neck Pain")	4,447
S8	(MH "Back Pain+")	21,327
S7	(MH "Osteoarthritis+")	18,222
S6	S1 OR S2 OR S3 OR S4 OR S5	112,360
S5	(MH "Abdominal Fat")	1,088
S4	(MH "Body Mass Index")	54,204
S3	TI Obes* OR AB Obes*	48,636
S2	(MH "Obesity+")	64,317
S1	"Overweight"	14,236

Database: SCOPUS
Search Strategy:

ALL((Osteoarthr* or "osteo arthr*" or backache* or neckache* or sciatica or neuralgia or dorsalgia or cervicalgia or ((Cervical Vertebrae or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) and (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)) or coaxarthr*) AND (cohort or followup or follow up or longitudinal or prospective or retrospective) AND (Overweight or obes* or "Body mass index" or "abdominal fat" or cardiovascular or cerebrovascular or coronary or arteriosclero* or artherosclero* or neoplasm* or cancer* or respirat* or lung* or diabet* or iddm or niddm or mody or "glucose intoleran*" or insulin* or noninsulin or "type 1" or "type 2" of t1dm or t2dm))

Database: WEB OF SCIENCE
Search Strategy:

TITLE: ((Osteoarthr* or "osteo arthr*" or backache* or neckache* or sciatica or neuralgia or dorsalgia or cervicalgia or ((“Cervical Vertebrae” or back or knee* or neck or spin* or hip* or lumb* or joint* or musculoske*) and (pain* or ache* or aching or complaint* or stiff* or dysfunction* or disabil* or trauma* or disorder* or injur*)) or coaxarthr*)) AND TITLE: ((cohort or followup or “follow up” or longitudinal or prospective or retrospective))AND TITLE: ((Overweight or obes* or "Body mass index" or "abdominal fat" or cardiovascular or cerebrovascular or coronary or arteriosclero* or artherosclero* or neoplasm* or cancer* or respiratory or lung* or diabet* or iddm or niddm or mody or "glucose intoleran*" or insulin* or noninsulin or "type 1" or "type 2" of t1dm or t2dm))

Table S2. Characteristics of included studies

Source (Country)	Population Description	Patients with MSK, No./Total No. (%)♯	Age, y♯	Men, No. (%)♯	Measure of MSK	Measure of Chronic Disease	Follow-up time, y	Adjustment variables
Chung et al, 2016 (Taiwan) (22, 23)	National Health Insurance Research Database (covers 99% of residents & 96% of healthcare institutions Taiwan)	46,042/92,084 (50)	Mean (SD) 60.6 (14.1)	37740 (41)	OA (OA ICD9 codes at more than 3 healthcare visits)	CVD (ACS diagnosis, ICD9 codes)	Mean OA 8.0 ± 1.5 Mean Control 7.9 ± 1.7	Age, sex, comorbidities (HTN, DM, hyperlipidaemia, stroke and congestive heart failure)
Dario et al, 2017* (Spain) (24)	Adult twins from the Murcia Twin Registry, born 1940-1966 in the Murcia region	675/2096 (32)	Mean (SD) 53.6 (7.3)†	940 (45)†	LBP (self-reported chronic LBP from the Spanish National Health Survey, LBP persisting for ≥6 months including seasonal or recurrent episodes)	Diabetes (self-reported diabetes from the Spanish National Health Survey confirmed by diagnosis by physician recorded in healthcare records)	Mean NR Total follow-up 2-4	Age, sex, BMI, smoking, physical activity
Eaton et al, 2015 (USA) (25)	Postmenopausal women; Women's Health Initiative	40,421/96,047 (42)	NR	0 (0)	OA (self-reported OA & self-reported joint pain)	CVD (MI and CHD mortality, medical records & death certificate)	NR	Age, race, SES (income, education), CHD risk factors (DM, hyperlipidemia, HTN, smoking, family history of CHD, BMI), Lifestyle risk factors (physical acitivity, total calories/day, alternative healthy eating index, alcohol), medications (aspirin, NSAIDs, beta-blockers,

								statins), access to care (personal physician, insurance, modified Charlson co-morbidity index), psychosocial risk factors (marital status, social support, social strain, depression)
Heuch et al, 2013* (Norway) (26)	Residents 30-69yrs in county of Nord-Trondelag (HUNT 2 & HUNT 3)	6568/25450 (26)	Range 30-69	11402 (45)	LBP (self-reported chronic LBP, LBP persisting for ≥3 months during the past yr)	Obesity (BMI divided into 3 groups: <25, 25-29.9, 30+)	Mean NR Total follow-up 11	Age, education, work status, physical activity at work & in leisure time, smoking, blood pressure, lipid levels, time between last meal & blood sampling, BMI at baseline.
Hoeven et al, 2015 (Netherlands) (12, 27-28)	Residents 55yrs+ in Ommoord district, Rotterdam for at least 1yr	336/4648 (7)	Mean 67.6 ± 7.9	1813 (39)	Knee OA, Hip OA (radiographic [K&L score ≥2] & joint complaints in last month)	CVD (Total CVD: MI, surgical or percutaneous revascularisation, coronary mortality, stroke [ischaemic & haemorrhagic], GP medical records confirmed by patient's physician)	Median 14.4	Age, sex, BMI, DM, HTN, total chol. HDL chol. Ratio, smoking
Jordan et al, 2010 (UK) (29,30)	Persons 50yrs+ from the General Practice Research Database (covering ~5% of the UK population)	9259/49513 (19)	Mean (SD) Back 65.0 (10.9) Mean (SD) controls 66.5 (10.8)	Back 4223 (46) Controls 18145 (45)	Back pain, neck pain (at least 1 consult for back or neck pain, Read or Oxmis Code)	Cancer (consult for malignant or pre-malignant neoplasm, Read or Oxmis Code)	Median Back 9.7 Median Controls 9.4	Age & sex standardised
Kendzerska et al, 2016	Cohort of residents 55yrs+	2431/16362 (15)	Median 68‡	6381 (39)‡	Knee OA, Hip OA (self-reported	Diabetes (diagnosis as defined in health	Median 13	Age, sex, BMI, income, pre-existing comorbidities (CVD, HTN), prior primary care exposure

(Canada) (31, 32)					symptomatic OA, swelling, pain, or stiffness in any joint lasting ≥6 weeks in the past 3 months, and indication on a joint homunculus that a knee or hip was 'troublesome')	administration data)		
Rahman et al, 2013 (Canada) (13, 33,34)	Random representative sample of all individuals 20yrs+ in the MSP or British Columbia	12745/49 631 (26)	Mean OA 58.2 ± 14.5 Mean controls 57.5 ± 14.3	OA patients 5098 (40) Controls 15123 (41)	OA (diagnosis by health professional ICD9/10 codes)	CVD, Diabetes (hospital discharge records ICD9/10 codes)	Mean 13	History of DM HTN, hyperlipidemia, COPD, Charlson score, BMI, and SES
Ray et al, 2005 (Canada) (35)	Provincial health care administrative databases of 1.5 million senior residents 65yrs+ of Ontario	172953/3 72953 (46)	Mean (SD) OA 74.9 (6.8) Mean controls (SD) 74.7 (7.0)	OA 67429 (39) Controls 82574 (41)	OA (hospital records ICD9 codes)	CVD (diagnosis or surgical treatment of coronary artery disease, stroke, PAD or aneurysm or dissection of the aorta, healthcare database records ICD9 codes)	Mean NR Total follow-up 7	Unadjusted analyses only
Schieir et al, 2015 (Canada) (36)	Participants 18yrs+, National Population Health Survey	NR/12591 (NR)	Mean 43.0 (0.2)	5728 (45)	Arthritis (self-reported arthritis excluding RA	CVD (Heart disease, self-reported health professional diagnosis, or	Mean NR Total follow-up 16	Age, education, high blood pressure, DM, BMI, smoking, physical activity, other chronic conditions and use of pain relievers

					and fibromyalgia)	heart disease death ICD10 codes, cause of death confirmed against death database)		
Veronese et al, 2016 (Italy) (37)	Participants 65yrs+ from the Progetto Veneto Anziano cohort study	1336/2158 (62)	Mean 75.4 ± 7.6	805 (37)	OA, Knee OA, Hip OA (medical history, clinical records, previous radiographic reports, OA-related pain, and examination of movement)	CVD (CAD, stroke, TIA, heart failure, PAD, CVD-related hospitalisation, CVD-related death, physical examination, medical history, ICD9 codes)	Mean 4.4 ± 1.2	Age, sex, waist-to-hip ratio, education level, baseline COPD, atrial fibrillation, HTN, DM, baseline low-dose aspirin, antihypertensives, and NSAIDs, number of medications, smoking, ADLs, Mini-Mental State Exam, Geriatric Depression scale score, glycosylated hemoglobin levels, total cholesterol, serum uric acid, estimated GFR and erythrocyte sedimentation rate, ankle brachial index, Short Physical Performance Battery, hand grip strength
Watson et al, 2003 (UK) (38)	Persons 40yrs+ from the General Practice Research Database (covering ~6% of the UK population)	163274/2361918 (7)	Mean (SD) men 54.5 (13.7)‖ Mean (SD) women 57.2 (15.1)‖	1106064 (47)	OA (patient record for diagnosis of OA)	CVD (All vascular events, patient records of fatal or nonfatal MI or cerebrovascular event, or sudden/unexplained death)	Mean men 4.7 Mean women 4.8	Age & sex standardised
Zhu et al, 2013 (Australia) (9)	Participants 70-85yrs from the Calcium Intake Fracture Outcome	323/1161 (29)	Mean Daily back pain 75.1 ± 2.7	0 (0)	Back pain (self-reported daily back pain)	CVD (CHD: Ischemic heart disease and angina ICD10 codes, self-report patient diary with	Mean NR Total follow-up 5	Baseline age, BMI, smoking history, analgesia use, DM, CVD, hypercholesterolemia & HTN

	Random selection of women 70yrs+ on the western Australia electoral roll	Mean Infrequent back pain 75.3 ± 2.7					healthcare professional assistance & hospital morbidity data system & primary care physician records)	

*Not included in the meta-analyses

♯ Data is presented on the exposure included in the primary adjusted meta-analysis unless otherwise indicated

† For whole sample including participants with Chronic LBP, Neck pain, Spinal pain and No LBP, Neck pain or Spinal pain

‡ For whole sample including participants with Knee OA, Hip OA and No OA

‖ For whole sample including participants with Osteoarthritis, Rheumatoid Arthritis and No arthritis

Abbreviations: SD= standard deviation, OA= osteoarthritis, ICD= International Classification of Diseases codes, CVD=cardiovascular disease, ACS= acute coronary syndrome, HTN= hypertension, DM= diabetes, LBP= low back pain, NR= not reported, MI- myocardial infarction, CHD= coronary heart disease, SES= socioeconomic status, BMI= body mass index, NSAIDs=nonsteroidal anti-inflammatory drugs, yrs= years, K&L score= Kellgren and Lawrence scale, GP=general practitioner, chol.=cholesterol, HDL= high density lipoprotein, MSP=Medical Services Plan, COPD= chronic obstructive pulmonary disease, PAD= peripheral artery disease, RA= rheumatoid arthritis, CAD=coronary artery disease, TIA= transient ischemic attack, ADLs= activities of daily living, GFR= glomerular filtration rate.

CHAPTER THREE

Part A: Study protocol

A randomised controlled trial of a lifestyle behavioural intervention for patients with chronic low back pain, who are overweight or obese

Chapter Three Part A is a published paper:

Williams A, Wiggers J, O'Brien KM, Wolfenden L, Yoong S, Campbell E, Robson E, McAuley J, Haskins R, Kamper SJ, Williams CM: A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol. *BMC Musculoskeletal Disorders.* 2016; 17(1):70. doi:10.1186/s12891-016-0922-1.

CO-AUTHOR STATEMENT FOR CHAPTER THREE PART A

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: “A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol,” in the following ways:

• Conception and design of the research

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STUDY PROTOCOL Open Access

A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol

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Abstract

Background: Low back pain is a highly prevalent condition with a significant global burden. Management of lifestyle factors such as overweight and obesity may improve low back pain patient outcomes. Currently there are no randomised controlled trials that have been conducted to assess the effectiveness of lifestyle behavioural interventions in managing low back pain. The aim of this trial is to determine if a telephone-based lifestyle behavioural intervention is effective in reducing pain intensity in overweight or obese patients with low back pain, compared to usual care.

Methods/Design: A randomised controlled trial will be conducted with patients waiting for an outpatient consultation with an orthopaedic surgeon at a public tertiary referral hospital within New South Wales, Australia for chronic low back pain. Patients will be randomly allocated in a 1:1 ratio to receive a lifestyle behavioural intervention (intervention group) or continue with usual care (control group). After baseline data collection, patients in the intervention group will receive a clinical consultation followed by a 6-month telephone-based lifestyle behavioural intervention (10 individually tailored sessions over a 6-month period) and patients in the control group will continue with usual care. Participants will be followed for 26 weeks and asked to undertake three self-reported questionnaires at baseline (pre-randomisation), week 6 and 26 post randomisation to collect primary and secondary outcome data. The study requires a sample of 80 participants per group to detect a 1.5 point difference in pain intensity (primary outcome) 26 weeks post randomisation. The primary outcome, pain intensity, will be measured using a 0–10 numerical rating scale.

Discussion: The study will provide robust evidence regarding the effectiveness of a lifestyle behavioural intervention in reducing pain intensity in overweight or obese patients with low back pain and inform management of these patients.

Trial registration number: Australian New Zealand Clinical Trials Registry, ACTRN12615000478516, Registered 14/05/2015.

Keywords: Low back pain, Obesity, Lifestyle, Telephone, Randomised controlled trial, Protocol

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Background

Low back pain is a common condition and poses significant burden to individuals and society. Globally, the median point prevalence of low back pain has been reported to be 15 % [1] and the global lifetime prevalence as high as 84 % [2]. The latest Global Burden of Disease Study (2013) reported over 651 million cases of low back pain in 2013, which is the leading cause of disability measured [3]. As a consequence, low back pain represents a considerable economic burden. Direct costs of care are reported to be more than $AU4.7 billion in Australia (2012 values), more than £1.6 billion in the United Kingdom (1998 values) and as much as $US90 billion in the United States (1998 values) [4, 5].

While the aetiology of low back pain remains unclear, it is now widely accepted that effective treatment for low back pain requires consideration of the psychological and behavioural factors. Several lifestyle behavioural factors are reported to be associated with an increased prevalence and persistence of low back pain including weight, sleep disturbance, psychological distress, and beliefs. Among the most compelling evidence is the association between overweight and obesity and low back pain [6, 7]. One meta-analysis which included 33 cross-sectional and cohort studies, found significant associations between overweight or obesity and a range of low back pain outcomes. Data from the cohort studies showed that overweight or obesity is associated with an increased 12-month prevalence of low back pain ($n = 6828$; OR 1.21, 95 % CI: 1.07, 1.37), increased risk of chronic low back pain (defined as longer than 3 months in duration; OR 1.43, 95 % CI: 1.28, 1.60), and higher rates of health care seeking for low back pain (OR 1.56, 95 % CI: 1.46, 1.67) [7]. Similar associations have been reported for body mass index (BMI) [8]. While the association between physical activity and diet and low back pain is less consistent, these are key drivers of weight gain [9]. Certainly, patients with low back pain who are overweight or obese, are likely to have more complex health needs requiring focus on a holistic lifestyle and behavioural approach to management.

Given these widely reported associations between lifestyle behavioural factors and low back pain, it is suggested that targeting these as part of low back pain management could improve patient outcomes [7, 10, 11]. While international guidelines for weight management recommend behavioural modification interventions as the preferred approach to managing weight loss and healthy lifestyle there is limited evidence to guide such care in patients with low back pain [9]. Several systematic reviews have found no randomised controlled trials (RCT) reporting the effectiveness of lifestyle behavioural interventions in managing persistent low back pain [10, 12]. To the author's knowledge only one pre-post study of a 52 week medically supervised weight loss program for obese patients with low back pain has been conducted. The study found a statistically significant weight loss of 15.3 kg (95 % CI: 7.8, 22.8) was associated with a significant improvement in pain related disability (Oswestry Disability Index (ODI) baseline 31.9 ± 17.7, follow-up 27.1 ± 20.9, $p = 0.009$) [13]. While promising, there is a need to test the effectiveness of lifestyle behavioural interventions on low back pain outcomes in robust RCTs.

Given the large numbers of patients who suffer from low back pain and are overweight or obese [6, 7], an important consideration is to provide cost effective interventions that are accessible to a large proportion of overweight patients at relatively lower cost to patients. Telephone-based interventions as a treatment delivery modality has potential to provide greater access to treatment for patients, and overcomes barriers to accessing continued care, including time and travel requirements to attend face-to-face appointments, and flexible scheduling of contact [14]. Importantly, telephone-based interventions that include behavioural modification and adjunct psychological strategies are consistently shown to be as effective as face-to-face interventions in achieving weight loss [15, 16]. For the key determinants of weight loss; physical activity and diet modification, telephone-based interventions have also been shown to be more cost-effective compared to clinical face-to-face practices [14].

The primary objective of the study is to determine if a telephone-based lifestyle behavioural intervention is effective in reducing pain intensity in overweight or obese patients with low back pain, compared to usual care. Secondary objectives are to investigate if the intervention improves key secondary outcomes: disability and function, anthropometry (weight, BMI, waist circumference), quality of life, diet, physical activity and health care utilisation, compared to usual care.

Methods

Study design and setting

The study will employ a parallel group randomised controlled design (Fig. 1), as part of a cohort multiple RCT [17]. This pragmatic design utilises participants from our existing cohort of routine service; patients are randomised to be offered a new clinical intervention (intervention group) or to remain part of the cohort (control group). The control group is not aware of the intervention trial and thus act as a real world usual care comparison. This protocol adheres to the requirements of the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) guidelines and is prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000478516). The trial will be undertaken in the Hunter New England Local Health District, New South Wales (NSW), Australia. Ethical approval has been obtained from the Hunter New England Human Research Ethics Committee

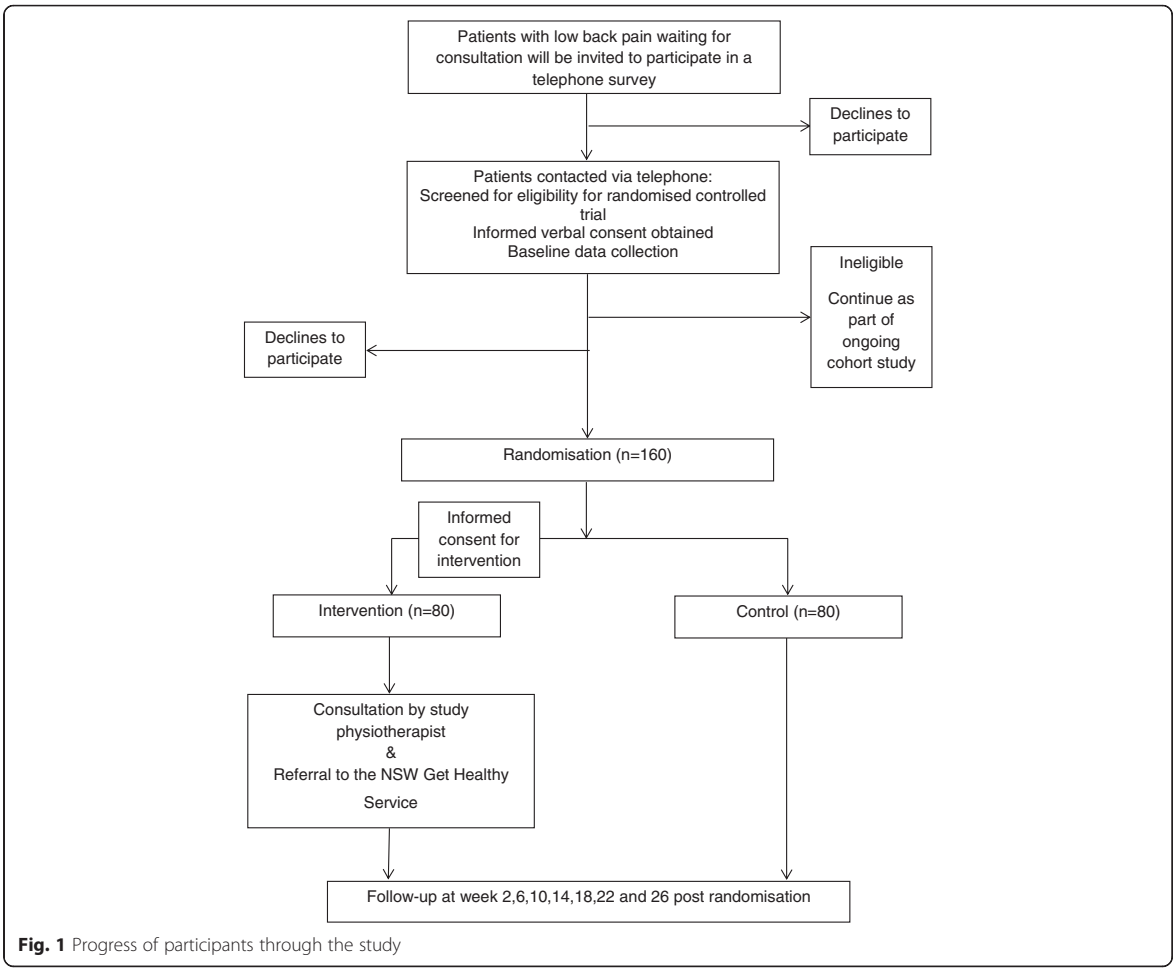

Fig. 1 Progress of participants through the study

(approval No. 13/12/11/5.18) and the University of Newcastle Human Research Ethics Committee (approval No. H-2015-0043).

Population and recruitment

One hundred and sixty patients waiting for an outpatient orthopaedic consultation at a public tertiary referral hospital within NSW for non-specific low back pain will be recruited. All patients over 18 years of age waiting for an outpatient consultation for low back pain will be sent an information letter to invite participation in a telephone survey as part of the ongoing cohort study. Patients will be asked to contact the researchers if they do not wish to participate or can refuse upon receipt of the telephone call. Patients consenting to the telephone survey will then be screened for eligibility for the RCT by a trained interviewer, invited to participate if eligible for the study and asked to complete the baseline survey at the time of the call.

To be eligible participants must meet the following criteria:

- Chronic low back pain defined as: pain in the lower back (i.e. between the 12th rib and buttock crease) with/without leg pain and a duration of longer than 3 months since the onset of pain [18];
- Aged 18 years or older;
- Classified as overweight or obese with a BMI of ≥27 kg/m^2 and <40 kg/m^2 – based on self-reported weight and height;
- Have access to and can use a telephone;
- Low back pain severe enough to cause at least average low back pain intensity ≥3 of 10 on a 0–10 numerical rating scale (NRS) in the last week or

moderate level of interference in activities of daily living (adaptation of item 8 on SF36).

Patients will be excluded if they meet the following criteria:

- Known or suspected serious pathology as the underlying cause of back pain (e.g. fracture, cancer, infection, inflammatory arthritis, cauda equine syndrome);
- A previous history of obesity surgery;
- Currently participating in any prescribed, medically supervised or commercial weight loss program;
- Back surgery in the last 6 months or booked in for surgery in the next 6 months;
- Unable to comply with the study protocol that requires them to, adapt meals or exercise, due to non-independent living arrangements;
- Any medical or physical impairment, apart from back pain, precluding safe participation in exercise such as uncontrolled hypertension, or morbid obesity (BMI ≥40);
- Cannot speak and read English sufficiently to complete the study procedures.

Randomisation and blinding

A randomisation schedule will be created a priori by an independent investigator using SAS 9.3 through the SURVEYSELECT procedure. Consenting patients who are eligible for the trial will be allocated, in a 1:1 allocation ratio, to either receive the lifestyle behavioural intervention at that time (intervention group) or remain as part of the cohort and be told they will be offered clinical services in 6 months (control group). To randomise patients, a trained interviewer will open a sealed opaque envelope containing group allocation. A staff member not involved in the study will prepare the envelopes. Patient progress through the study is outlined in Fig. 1.

All outcome assessors will be blind to group allocation.

Treatments

Intervention group

Patients randomised to the intervention group will be provided brief advice and education about the benefits of weight loss and physical activity for their conditions by trained telephone interviewers. Participants will then be invited to attend a one hour consultation with the study physiotherapist at Hunter New England Population Health, NSW, Australia and referred to the NSW Get Healthy Information and Coaching Service (GHS) [19, 20].

Consultation

The consultation will involve a low back pain clinical assessment and detailed low back pain education based on principles recommended by clinical practice guidelines. The consultation will also apply behaviour change techniques to support a healthy lifestyle and weight management for low back pain. This intervention content was informed by Self Determination Theory (SDT) [21, 22]. According to SDT autonomous behaviour rather than behaviour controlled by rewards, punishments or self-imposed pressures is more likely to result in long lasting behaviour change [22]. The constructs deemed integral in SDT to develop autonomous motivation include increasing 1) perceived competence (increase interest, enjoyment and importance) and 2) self-regulation (increase ability to direct behaviour to act in your long term best interest and in line with your values) [22]. The specific techniques used in the consultation to address these key constructs include: i) provision of education and reassurance to correct inappropriate pain beliefs and improve self-efficacy for self-management (i.e. provide information about the about the nature of the condition, that persistent low back pain is multifactorial with multiple influences and not usually the result of pathological damage), ii) acknowledging the consequences of unhealthy lifestyle factors (overweight, inactivity, poor diet, alcohol misuse, smoking, poor sleep) on low back pain, iii) provide general encouragement and examples of how improving lifestyle factors can influence pain outcomes and quality of life, iv) prompt commitment from the participant, v) acknowledge that monitoring of behaviours will be conducted throughout the program, vi) setting graded tasks to adopt better physical functioning and healthy behaviour (e.g. begin walking 30 min daily), vii) encourage self-monitoring of goals, viii) present the NSW GHS as a way to support ongoing behaviour change to improve low back pain and general health, ix) acknowledge general barriers that may reduce motivation to change lifestyle and adherence to the program (e.g. acknowledge fluctuating nature of condition and that high levels of pain are the result of a complex interaction of factors not just the result of increased activity, and discourage use of pain as a guide for progression of activity).

Lifestyle behavioural intervention - The NSW Get Healthy Service

Following the consultation, patients randomised to the intervention group will be referred to the established GHS [19]. The referral to the GHS will be provided to the service on the participants' behalf. The GHS is a free telephone-based government funded service to support individuals to modify their eating behaviours, increase their physical activity, reduce alcohol consumption and maintain a healthy weight or reduce their weight. The service was developed in response to evidence supporting the efficacy of telephone-based behaviour modification interventions and facilitates the translation of this evidence into a population wide approach [19]. A pre-

post study assessing the effectiveness of the GHS in the general population reported significant reductions in weight, BMI, and waist circumference, and significant improvements in physical activity and nutrition-related behaviours [19].

The GHS service involves 10 individually tailored coaching calls delivered over a 6 month period by a qualified health professional including dieticians, exercise physiologists and psychologists [19]. The support provided is based on national guidelines including the Australian Guide to Healthy Eating and National Physical Activity Guidelines [19, 23], utilises motivational interviewing principles [19, 24], addresses health-related psychological blocks with Socratic questioning [25], and applies self-regulation principles including goal setting, overcoming barriers and creating sustainable changes [19]. The program is individually tailored to each patient with content targeted to address individual patient goals throughout the 6 months and phone calls scheduled according to the patient's preferences. These aspects are determined by the patient and health coach together, however calls are generally provided on a tapered schedule, with a higher intensity of calls ($n = 6$) made within the first three months of the program [19]. This schedule facilitates initiation of behaviour change in the first three months and maintenance and prevention of relapse in the second half of the program. In addition to the health coaching calls, participants receive an information booklet that provides additional information to support them during the program to achieve their goals, a coaching journal to record goals and actions, and access to online services to help track their progress. Medical clearance from a general practitioner will be obtained when required, as per existing service protocols [19].

All health coaches, regardless of multidisciplinary background, receive training to ensure they meet the requirements of the service and to promote consistency across the program. The service conducts audits of coaching quality as part of its quality improvement practices. To ensure the GHS health coaching is relevant for low back pain participants, health coaches will be provided additional training by a study investigator (CW) in evidence-based management for low back pain (2 h interactive training session) and provided with information resources to guide specific advice to be provided to study participants. The training session includes the topics of diagnosis, prognosis and evidence-based management strategies including the role of a healthy lifestyle and weight loss. The information provided is contained within international clinical practice guidelines for low back pain. Resources also detail guideline recommended advice about the nature of the condition, the diagnosis, prognosis and evidence-based treatments, as well as common misconceptions about back pain and its management.

Control group

Participants randomised to the control group will continue on the usual care pathway and take part in data collection during the 6 month intervention period. Currently no active management of low back pain patients waiting for an outpatient orthopaedic consultation occurs. Control group patients will be informed that a face-to-face appointment to determine the need for further care will be available in 6 months.

Data collection

Participants will be followed for 6 months (26 weeks) and be asked to complete three self-reported questionnaires at baseline (pre-randomisation), week 6 and 26 weeks post randomisation to collect primary and secondary outcome data. All participants will be mailed a questionnaire one week prior to the 6 and 26 week time point and then asked to provide responses in one of two ways: via telephone or returned postal questionnaire. The baseline questionnaire will be completed via telephone only. Participants will also be asked to record the primary outcome 'pain intensity' at week 2, 10, 14, 18 and 22. Participants will be asked to provide these data via telephone or reply to text message, whichever their preference. During the 26 week telephone survey participants will be asked to attend a follow up clinic appointment (intervention group) or initial clinical appointment (control group) with a health professional.

Measures

Baseline demographic characteristics

The following demographic items will be collected at baseline: age, Aboriginal and/or Torres Strait Islander status, employment status, country of origin, highest level of education, health insurance status and medical conditions. Length of time waiting for consultation (days) and triage classification will be obtained from hospital records.

Primary outcome

Pain intensity Pain intensity will be measured using a 0–10 NRS, as the average pain over the last week where zero indicates 'no pain' and ten indicates the 'worst possible pain' [26]. Pain intensity will be collected at baseline, at 2, 6, 10, 14, 18, 22 and 26 weeks post randomisation (see Table 1). The NRS is a valid and reliable measure of pain intensity in adults with low back pain [27].

Secondary outcomes

The secondary outcomes include: low back pain disability, using the Roland Morris Disability Questionnaire (RMDQ) [28]; self-reported weight (kg); objective weight (kg) measured to the nearest 0.1 kg by a trained assessor using

Table 1 Trial Measures

Outcome	Domain	Measures	Time point (weeks)
Primary	Pain intensity	Pain intensity over the previous week as measured by the 0–10 Numerical Rating Scale (NRS) [26]	0, 2, 6, 10, 14, 18, 22, 26
Secondary	Disability	Roland Morris Disability Questionnaire (RMDQ) [28]	0, 6, 26
	Self-reported weight	Self-reported weight (kg)	0, 6, 26
	Objective weight	Measured to the nearest 0.1 kg [29]	0[a], 26
	BMI	Calculated as weight/height squared (kg/m^2)	0[a], 26
	Waist circumference	Measured to the nearest 0.1 cm [29]	26
	Quality of life	Short Form 12 version 2 (SF12.v2) [30]	0, 6, 26
	Perceived change in condition	Global Perceived Effect Scale [43]	6, 26
	Psychological distress	Depression, Anxiety and Stress Scale-21 (DASS-21) [31]	0, 26
	Sleep quality	Item 6 of the Pittsburgh sleep quality index [32]	0, 6, 26
	Health behaviours	Physical Activity measured using the Active Australia Survey [33]	0, 6, 26
		Dietary intake measured using a short food frequency questionnaire [34]	0, 6, 26
		Alcohol Consumption measured using the alcohol use disorders identification test (AUDIT) [35]	0, 6, 26
		Self-reported smoking status [36]	0, 6, 26
	Health care utilisation	Medication use for low back pain	0, 6, 26
		Visits for low back pain – type and number of sessions	0, 6, 26
		Attended orthopaedic consultation, received surgery	26
	Pain attitudes	Survey of Pain Attitudes (SOPA) [38]	0, 6, 26
	Fear Avoidance	Fear Avoidance Beliefs Questionnaire (FABQ) [39]	0, 26
	Economic	Quality of life (SF12.v2)	0, 6, 26
		Health care utilisation (including estimated out of pocket cost)	
		Absenteeism (days off normal work due to lower back pain in the past 6 weeks)	

GHS: Get Healthy Information and Coaching Service; [a]Intervention group only

International Society for the Advancement of Kinanthropometry (ISAK) procedures [29]; BMI calculated as weight /height squared (kg/m^2); waist circumference measured at 26 weeks post randomisation taken at the level of the narrowest point between the inferior rib border and the iliac crest by trained assessors using a flexible tape measure to the nearest 0.1 cm [29]; quality of life assessed using the 12-item Short Form Health Survey version 2 (SF-12.v2) [30]; global perceived change in condition measured using the Global Perceived Effect Scale (–5 to 5 scale) [29]; psychological distress using the Depression, Anxiety and Stress Scale-21 (DASS-21) [31]; sleep quality measured using item 6 of the Pittsburgh Sleep Quality Index [32]; health behaviours including physical activity reported as the frequency and total minutes of spent participating in physical activity measured by the Active Australia Survey [33], dietary intake measured by a short food frequency questionnaire (FFQ) [34], alcohol consumption measured using the Alcohol Use Disorders Identification Test (AUDIT) [35] and self-reported current smoking status [36]; health care utilisation including medication use, type of health services utilised for low back pain and the number of sessions [37]; and attitudes and beliefs measured by the Survey of Pain Attitudes (SOPA) [38] and the Fear Avoidance Beliefs Questionnaire (FABQ) [39]. See Table 1 for data collection time points for secondary outcomes.

Intervention and data integrity

The delivery of the intervention will be assessed using attendance records for the physiotherapy consultation and data regarding delivery of the GHS intervention including, commencement and number, length, timing of coaching calls and achievement of identified goals which will be provided by the GHS. Patient reported receipt of care (as well as additional care) will be collected at all secondary collection time points. Participants will be monitored for adverse events throughout the intervention period. All adverse events will be recorded and serious adverse events will be assessed and managed on a case-by-case basis according to Good Clinical Practice (GCP) guidelines [40]. Trial data integrity will be monitored by regularly scrutinising data files for omissions and errors. Manually entered data (i.e. data not recorded directly by participant) will be double entered

and the source of any inconsistencies will be explored and resolved in consultation with the lead investigator (CW). Data will be stored on password protected files, with access given to approved researchers only.

Sample size

Sample size was calculated using Stata sample size calculator. Using a standard deviation of 2.3, a two-sided alpha of 0.025 (to account for multiple outcomes of interest – pain and weight) [41] and allowing for 15 % loss to follow up, a sample of 80 participants per group will provide 90 % power to detect a clinically meaningful difference of 1.5 in pain intensity (pain numerical rating scale) between intervention and control groups at 26 weeks post randomisation. This sample also provides power 80 % to detect a 6 % reduction in weight in the underlying sampling population and based on evidence from other musculoskeletal conditions is hypothesized to lead to a clinically meaningful reduction in pain [42].

Statistical analysis

Primary outcomes analysis

Between group differences in pain intensity will be assessed using linear mixed models, with random intercepts for individuals to account for correlation of repeated measures. We will obtain estimates of the effect of the intervention and 95 % confidence intervals by constructing linear contrasts to compare the adjusted mean change in outcome from baseline to each time point between the treatment and control groups. Dummy coded variables representing group allocation will be used to ensure blinding of the analyses. Missing data will be assessed for randomness if this is more than 10 %.

Secondary outcomes analysis

Linear mixed models will be used to assess treatment effects on secondary outcomes as per the primary outcome. We will compare the adjusted mean change (continuous variables) or difference in proportions (dichotomous variables) in outcome from baseline to each time point between the treatment and control groups.

An economic evaluation will also be undertaken. We will develop costing models from the perspective of the health service and broader societal perspective. These models will utilize data regarding patient quality of life (SF12v2), health care and community services use, work absenteeism. We will calculate costs based on published normative data and estimated out of pocket costs reported by participants. We will also investigate the mechanisms underlying the intervention using causal mediation analysis and include the following measures at baseline, 6 weeks and 6 months: pain attitudes (SOPA), fear avoidance beliefs (FABQ) and symptoms of psychological distress (DASS 21), weight loss (kg), health behaviours (physical activity (MVPA), diet, alcohol, smoking, sleep quality).

Discussion

This is the first RCT designed to evaluate the effectiveness of a lifestyle behavioural intervention for low back pain patients who are overweight or obese. The results will inform care pathways by providing robust evidence about the effectiveness of such management for overweight patients with low back pain.

Abbreviations

BMI: Body Mass Index; RCT: Randomised controlled trial; ODI: Oswestry Disability Index; SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials; NSW: New South Wales; NRS: Numerical rating scale; GHS: NSW Get Healthy Information and Coaching Service; RMDQ: Roland Morris Disability Questionnaire; ISAK: International Society for the Advancement of Kinanthropometry; SF12.v2: Short Form Healthy Survey version 2; DASS-21: Depression Anxiety Stress Scale-21; FFQ: Food Frequency Questionnaire; AUDIT: Alcohol Use Disorders Identification Test; SOPA: Survey of Pain Attitudes; FABQ: Fear Avoidance Beliefs Questionnaire; GCP: Good Clinical Practice; HMRI: Hunter Medical Research Institute.

Competing interests

The authors declare that there are no competing interests.

Author's contributions

AW, CW, KO, JW, LW, SY, LC were responsible for the design of the study. CW and JW procured funding. All authors contributed to developing the intervention and data collection protocols and materials, and reviewing, editing, and approving the final version of the paper. AW drafted the manuscript and all authors have contributed to the manuscript. All authors have read and approved the final manuscript.

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CHAPTER THREE

Part B: Statistical analysis plan

A randomised controlled trial of a lifestyle behavioural intervention for patients with chronic low back pain, who are overweight or obese

Chapter Three Part B is a published paper:

O'Brien KM, **Williams A**, Wiggers J, Wolfenden L, Yoong S, Campbell E, Kamper SJ, McAuley J, Attia J, Oldmeadow C, Williams CM: Effectiveness of a healthy lifestyle intervention for low back pain and osteoarthritis of the knee: protocol and statistical analysis plan for two randomised controlled trials. *Brazilian Journal of Physical Therapy.* 2016; 20(5):477-89. doi: 10.1590/bjpt-rbf.2014.0189.

CO-AUTHOR STATEMENT FOR CHAPTER THREE PART B

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: “Effectiveness of a healthy lifestyle intervention for low back pain and osteoarthritis of the knee: protocol and statistical analysis plan for two randomised controlled trials,” in the following ways:

• Conception and design of the research

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protocol

BJPT Brazilian Journal of Physical Therapy

Effectiveness of a healthy lifestyle intervention for low back pain and osteoarthritis of the knee: protocol and statistical analysis plan for two randomised controlled trials

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ABSTRACT | **Background:** These trials are the first randomised controlled trials of telephone-based weight management and healthy lifestyle interventions for low back pain and knee osteoarthritis. This article describes the protocol and statistical analysis plan. **Method:** These trials are parallel randomised controlled trials that investigate and compare the effect of a telephone-based weight management and healthy lifestyle intervention for improving pain intensity in overweight or obese patients with low back pain or knee osteoarthritis. The analysis plan was finalised prior to initiation of analyses. All data collected as part of the trial were reviewed, without stratification by group, and classified by baseline characteristics, process of care and trial outcomes. Trial outcomes were classified as primary and secondary outcomes. Appropriate descriptive statistics and statistical testing of between-group differences, where relevant, have been planned and described. **Conclusions:** A protocol for standard analyses was developed for the results of two randomised controlled trials. This protocol describes the data, and the pre-determined statistical tests of relevant outcome measures. The plan demonstrates transparent and verifiable use of the data collected. This *a priori* protocol will be followed to ensure rigorous standards of data analysis are strictly adhered to.

Keywords: low back pain; knee osteoarthritis; lifestyle; telephone; randomised controlled trial; statistical analysis plan.

Trial Registration: Both trials were prospectively registered with the Australian New Zealand Clinical Trials Registry (trial one: ACTRN12615000478516 and trial two: ACTRN12615000490572).

BULLET POINTS

- Lifestyle factors such as overweight and obesity are associated with low back pain and osteoarthritis. However, accessible interventions aiming to support patients with low back pain or osteoarthritis to manage lifestyle factors have not been tested in high quality trials.
- The two trials determine the effectiveness of telephone-based healthy lifestyle interventions for low back pain and osteoarthritis of the knee.
- This protocol comprehensively describes key trial methodology relating to data capture, management and pre-determined statistical analyses.
- Such protocols are important in raising the validity of physical therapy research as they demonstrate transparent and verifiable use of the data collected and ensure rigorous standards of data analysis are strictly adhered to.

HOW TO CITE THIS ARTICLE

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Introduction

This protocol describes the first randomised controlled trials (RCT) of telephone-based weight management and healthy lifestyle interventions for low back pain and knee osteoarthritis. Here we describe the protocol and pre-determined statistical analysis plan, for both trials (trial one: *low back pain* and trial two: *knee osteoarthritis*). The protocol and statistical analysis plan was finalised prior to analysing the data and will be adhered to in analysing the data from the trials. All study investigators signed and approved the statistical analysis plan in May 2016. Participant recruitment for both trials was completed in October 2015, and final participant follow-up was completed in May 2016. Following data integrity checks the database will be locked (June 2016). The statistical analyses specified in the statistical analysis plan will be performed in June 2016.

Study overview

Study design and setting

These trials were established as part of a cohort multiple RCT design[1], whereby participants from our existing cohort of patients referred for an outpatient orthopaedic consultation at a public tertiary referral hospital within NSW Australia, were randomised to be offered a new clinical intervention (intervention group) or remain as part of the cohort (control group). Both trials were prospectively registered with the Australian New Zealand Clinical Trials Registry (trial one: ACTRN12615000478516, and trial two: ACTRN12615000490572) and full study protocols for each trial have been published elsewhere[2,3]. These trials were approved by the Hunter New England Health Human Research Ethics Committee (13/12/11/5.18), Wallsend NSW, Australia and the University of Newcastle Human Research Ethics Committee (H-2015-0043), Newcastle, Australia.

Participants and recruitment

Patients with non-specific low back pain (trial one, n=160) or knee osteoarthritis (trial two, n=120) were recruited. Participants in the intervention group of both trials were provided with brief advice and education about the benefits of weight loss and physical activity for their conditions by trained telephone interviewers. Additionally, participants in the intervention group of trial one (low back pain) were provided with an initial consultation with the study physical therapist. The consultation involved a low back pain clinical assessment and detailed low back pain education based on clinical practice guidelines. Behavioural change techniques were also utilised to support a healthy lifestyle and weight management for low back pain. There was no baseline clinical assessment for participants of trial two (knee osteoarthritis).

Following baseline data collection, participants in the intervention groups of both trials were referred to the NSW Get Healthy Information and Coaching Service (GHS). The GHS is a free, telephone-based government funded service to support individuals to modify their eating behaviours, increase their physical activity, reduce alcohol consumption and achieve or maintain a healthy weight[4]. The GHS has been shown to be effective in the general population and involves 10 individually tailored coaching calls delivered over a 6-month period by a university-qualified health professional. The support provided is based on national guidelines and utilises motivational interviewing[4]. All health coaches were provided with training by a study investigator (CW) in evidence-based management for low back pain and knee osteoarthritis.

Participants in the control group received any usual care offered to them by their treating clinician during the six month intervention period, and participated in data collection. Follow-up lasted for 26 weeks (6 months).

Inclusion/exclusion criteria

Patients were eligible for inclusion in the trials if all of the following criteria were met:

- Trial one condition definition: chronic low back pain defined as pain in the lower back (i.e. between the 12th rib and buttock crease) with/without leg pain and duration of longer than 3 months since the onset of pain[5];
- Trial two condition definition: complaint of pain in the knee due to knee osteoarthritis (as per referral) lasting longer than 3 months;
- Aged 18 years or older;
- Classified as overweight or obese with a self-reported body mass index (BMI) $\geq 27 kg/m^2$ and $<40 kg/m^2$;
- Have access to and can use a telephone; and
- Have back or knee pain, for each trial respectively, severe enough to cause at least average pain intensity ≥ 3 of 10 on a 0–10 numerical rating scale (NRS)[6] in the last week or moderate level of interference in activities of daily living (adaptation of item 8 on SF36)[7].

Patients were excluded if they met the following criteria:

- Known or suspected serious pathology as the underlying cause of back pain or knee osteoarthritis, for each trial respectively, (e.g. fracture, cancer, infection, inflammatory arthritis, infection, cauda equine syndrome);
- A previous history of obesity surgery;
- Current participation in any prescribed, medically supervised or commercial weight loss program;
- Back or knee surgery, for each trial respectively, in the last 6 months or booked in for surgery in the next 6 months;
- Unable to walk unaided;
- Unable to comply with the study protocol that requires them to, adapt meals or exercise, due to non-independent living arrangements;
- Any medical or physical impairment, apart from back pain or knee osteoarthritis for each trial respectively, precluding safe participation in exercise such as uncontrolled hypertension, or morbid obesity (BMI≥40); and
- Unable to speak and read English sufficiently to complete the study procedures.

Unblinding

The analysis plan was written and approved prior to analysis of data and blind to group status. Dummy coded variables representing group allocation will be used to ensure blinding of statistician(s) undertaking the analysis.

Objectives

The primary objective of both trials is to establish if:

Trial one: pain education and referral to a telephone-based weight management and healthy lifestyle intervention improves pain intensity in patients with *low back pain*, who are overweight or obese, compared to usual care.

Trial two: referral to a telephone-based weight management and healthy lifestyle intervention improves pain intensity in patients with *knee osteoarthritis*, who are overweight or obese compared to usual care.

Secondary aims of the two trials is to establish if the telephone interventions lead to reductions in disability, weight, BMI, waist circumference, alcohol consumption, and smoking prevalence, and improvement in quality of life, emotional distress, sleep quality, physical activity, diet, pain attitudes and beliefs, perceived change in condition and change in health care and medication use.

A separate analysis plan will be detailed for health economic analyses and is not included in this manuscript.

Definition of outcome variables

Participant demographics and baseline characteristics

Baseline data includes: age, gender, Aboriginal and/or Torres Strait Islander status, employment status, country of origin, highest level of education, health insurance status, other co-existing medical conditions needing medication, and pain duration (how long have you been troubled with your pain). Length of time waiting for consultation (days) and triage classification will be obtained from hospital records. In Australia, patients referred for orthopaedic consultation are categorised according to urgency of consultation: urgent – to be seen within 30 days; semi-urgent – to be seen within 90 days; and non-urgent – to be seen within 12 months[8]. See Table 1 for details.

Primary outcome

The primary outcomes are average weekly back pain intensity (trial one) and average weekly knee pain intensity (trial two), measured over the course of follow up.

Participants were asked to report the "average pain intensity experienced in their back (trial one) or knee (trial two) over the past week, on a 0 to 10 NRS, where 0 was 'no pain' and 10 was the 'worst possible pain'"[6]. These pain intensity scores were measured at baseline, at 2, 6, 10, 14, 18, 22 and 26 weeks. Average weekly (back or knee) pain intensity is defined as the Area under the Curve (AUC) of the pain intensity trajectory, over the follow up period. The AUC for each participant will be computed using the trapezoid rule.

Secondary outcomes

The secondary outcomes include:

- Physical disability and function, measured in trial one using the Roland Morris Disability Questionnaire (RMDQ)[9] 0-24 scale and measured in trial two using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 0-96 scale[10];

Table 1. Demographic and baseline characteristics.

	Intervention	Control
Demographic		
Age (years)	mean (SD)	mean (SD)
Gender (male)	n/N (%)	n/N (%)
Aboriginal and/or Torres Strait Islander status	n/N (%)	n/N (%)
Employment status		
Employed	n/N (%)	n/N (%)
Unemployed	n/N (%)	n/N (%)
Retired	n/N (%)	n/N (%)
Can't work (health reasons)	n/N (%)	n/N (%)
Country of origin (Australia)	n/N (%)	n/N (%)
Highest level of education		
>High school	n/N (%)	n/N (%)
Private health insurance	n/N (%)	n/N (%)
Other co-existing medical conditions needing medication	n/N (%)	n/N (%)
Length of time waiting for consultation (days)	mean (SD)	mean (SD)
Triage classification		
Non-urgent	n/N (%)	n/N (%)
Semi-urgent	n/N (%)	n/N (%)
Baseline characteristics		
Pain intensity (NRS)	mean (SD)	mean (SD)
Pain duration (how long have you been troubled with your pain)	mean (SD)	mean (SD)
Disability and function (Trial 1: RMDQ / Trial 2: WOMAC)	mean (SD)	mean (SD)
Subjective weight	mean (SD)	mean (SD)
BMI	mean (SD)	mean (SD)
Quality of Life (SF12.v2)		
Physical component score (PCS)	mean (SD)	mean (SD)
Mental component score (MCS)	mean (SD)	mean (SD)
Emotional distress (DASS-21)	mean (SD)	mean (SD)
Poor sleep quality (item 6, Pittsburgh Sleep Quality Index)	n/N (%)	n/N (%)
Physical activity (mins MVPA/week)	mean (SD)	mean (SD)
Diet		
Fruit (serves)	n/N (%)	n/N (%)
Vegetables (serves)	n/N (%)	n/N (%)
Discretionary foods (serves)	n/N (%)	n/N (%)
Alcohol consumption (AUDIT)	mean (SD)	mean (SD)
Smoking prevalence	n/N (%)	n/N (%)
Pain attitudes (SOPA)	mean (SD)	mean (SD)
Fear avoidance beliefs (FABQ)	mean (SD)	mean (SD)
Health care utilisation		
Medication use for back or knee pain	n/N (%)	n/N (%)
Visits for back or knee pain	n/N (%)	n/N (%)

NRS=numerical rating scale; RMDQ=Roland Morris Disability Questionnaire; WOMAC=Western Ontario and McMaster Universities Index; BMI=Body Mass Index; SF12.v2= Short Form Health Survey version 2; PCS=Physical Component Score; MCS=Mental Component Score; 21=Depression Anxiety Stress Scale; MVPA=Moderate-to-Vigorous Physical Activity; AUDIT=Alcohol Use Disorders Identification Test; SOPA=Survey of Pain Attitudes; FABQ=Fear Avoidance Beliefs Questionnaire.

- Self-reported weight (kg);
- Objective weight (kg) measured to the nearest 0.1kg by a trained research assistant using International Society for the Advancement of Kinanthropometry (ISAK) procedures[11];
- BMI calculated as weight /height squared (kg/m^2)[12];
- Waist circumference measured by a trained research assistant using ISAK procedures taken at the level of the narrowest point between the inferior rib border and the iliac crest using a flexible tape measure to the nearest 0.1 cm[11];
- Quality of life, measured using the physical and mental health component scores from the 12-item Short Form Health Survey version 2 (SF12.v2)[7];
- Global perceived change in symptoms, measured using the Global Perceived Effect (GPE) scale (-5 'vastly worse' to 5 'completely recovered')[13];
- Emotional distress, measured using the Depression Anxiety Stress Scale-21 (DASS-21) 0-63 scale[14];
- Sleep quality, measured using item 6 from the Pittsburgh Sleep Quality Index (response options: very bad, fairly bad, fairly good, very good)[15];
- Physical activity, measured using the Active Australia Survey[16], reported as the average minutes spent participating in moderate-to-vigorous physical activity (MVPA) per week;
- Diet, measured using a short food frequency questionnaire (FFQ)[17], reported as serves of fruit (0-1, 2 or more), serves of vegetables (0-2, 3-4, 5 or more), serves of discretionary foods including processed meats, salty snacks, takeaway meals, sweet or savoury snacks, confectionary and sugar sweetened beverages (more than once per week, once per week or less);
- Alcohol consumption measured using the Alcohol Use Disorders Identification Test (AUDIT) 0-12 scale[18];
- Smoking prevalence (have you smoked any tobacco in the last 4 weeks? (this can include cigarettes, roll your own, pipes, cigars or any other tobacco products))[19];
- Attitudes and beliefs, measured using the Survey of Pain Attitudes (SOPA)[20]; and the physical component of the Fear Avoidance Beliefs Questionnaire (FABQ) 0-24 scale[21]; and
- Health care utilisation for each trial respectively, including back or knee pain medication use (name), type of health service utilised for back or knee pain including number of sessions, and attended orthopaedic consultation or received surgery.

See Table 2 for data collection time points for secondary outcomes.

Process variables

Intervention fidelity

Delivery of the intervention is assessed by the GHS, data includes; commencement, the number, length, and timing of coaching calls and achievement of identified goals.

Concomitant treatments

Participants were asked to record separately all medication and health care services used for the back or knee pain, for each trial respectively, at baseline, and weeks 6 and 26 post-randomisation. Information for each additional treatment was provided as free text often using variable terminology. These will be aggregated using a common terminology. Medications will be coded using the Anatomical Therapeutic Chemical Classification System at the third level. Other health services will be coded according to common provider types, for example specialist, hospital or emergency department presentation or admission, physical therapy, chiropractic, massage therapy, other allied health, alternative medicine, and other.

Safety

Participants were monitored for adverse events throughout the intervention period. All adverse events (AE), that is, any new medical conditions or an exacerbation of another existing condition, were recorded at 6 and 26 weeks. All AEs will be described for each group.

Design issues

General design

These trials were parallel group RCTs, established as part of a cohort multiple RCT. Patients waiting for an outpatient orthopaedic consultation at a public tertiary referral hospital within NSW were sent an information letter to invite participation in the cohort (telephone survey) and again at 12-months follow-up. At 12-month follow-up patients consenting to the

Table 2. Secondary outcome measures.

Construct	Measurement	Time-point (weeks)
Disability and function	Trial one: Roland Morris Disability Questionnaire (RMDQ)[9]	0, 6, 26
	Trial two: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[10]	0, 6, 26
Subjective weight	Self-reported weight (kg)	0, 6, 26
Objective weight	Measured to the nearest 0.1kg[11]	0[a], 26
BMI	BMI calculated as weight/height squared (kg/m^2)[12]	0, 6, 26
Waist circumference	Measured to the nearest 0.1cm[11]	26
Quality of life	Short Form Health Survey version 2 (SF12.v2)[7]	0, 6, 26
Perceived change in condition	Global Perceived Effect scale (–5 to 5 scale)[13]	6, 26
Emotional distress	Depression Anxiety Stress Scale-21 (DASS-21)[14]	0, 26
Sleep quality	Item 6 from the Pittsburgh Sleep Quality Index[15]	0, 6, 26
Physical activity	The Active Australia Survey[16]	0, 6, 26
Diet	Short food frequency questionnaire[17]	0, 6, 26
Alcohol consumption	Alcohol Use Disorders Identification Test (AUDIT)[18]	0, 6, 26
Smoking prevalence	Self-reported current smoking status[19]	0, 6, 26
Pain Attitudes	Survey of Pain Attitudes (SOPA)[20]	0, 6, 26
Fear avoidance beliefs	Fear Avoidance Beliefs Questionnaire (FABQ)[21]	0, 26
Health care utilisation	Medication use for back (trial one) or knee pain (trial two)	0, 6, 26
	Visits for back (trial one) or knee pain (trial two) – type and number of sessions	0, 6, 26
	Attended orthopaedic consultation, received surgery	26

[a] Intervention group of low back pain patients (trial one) only. BMI: Body Mass Index.

telephone survey were screened for eligibility for the RCT by a trained interviewer and invited to participate if eligible for the study.

Treatment allocation

Eligible patients were randomised in a 1:1 allocation ratio, to either receive the weight management and healthy lifestyle intervention at that time (intervention group) or remain as part of the cohort and be told they will be offered clinical services in 6 months (control group). The randomisation schedule was generated a priori by an independent statistician using SAS 9.3 through the SURVEYSELECT procedure. To randomise patients, a trained interviewer opened a sealed opaque envelope containing group allocation. A staff member not involved in the study prepared the envelopes.

Sample size

The sample size for both trials was calculated using Stata sample size calculator.

For trial one a standard deviation of 2.3, a two-sided alpha of 0.025 (to account for two outcomes of interest, the primary outcome (pain) and the key secondary outcome (weight)[22] and allowing for 15% loss to follow-up was used. A sample size of 80 participants per group (n=160) has 90% power to detect a clinically meaningful difference of 1.5 points in pain intensity (pain NRS) between intervention and control groups[23]. This sample also provides power 80% to detect a 6% reduction in weight in the underlying sampling population, based on evidence from other musculoskeletal conditions this is hypothesised to lead to a clinically meaningful reduction in pain[23].

For trial two a standard deviation of 2.7, a two-sided alpha of 0.025 (to account for two outcomes of interest, the primary outcome (pain) and the key secondary outcome (weight)[22] and allowing for 15% loss to follow up, a sample of 60 participants per group will provide 90% power to detect a clinically meaningful difference of 2 points in pain intensity (pain NRS) scores between intervention and control groups at 26 weeks. This sample also provides 80% power to detect a 6% weight reduction which is hypothesised to be lead to a clinically meaningful reduction in pain[23].

In these calculations the increase in statistical power conferred by reducing error variance through repeated

outcome measures over time and the correlations among repeated measures have been conservatively ignored.

Data collection and follow up

The different stages of data collection and follow-up for secondary outcomes are summarised in table one. The primary outcome, pain intensity score, was collected at baseline, week 2, 6, 10, 14, 18, 22 and at 26 weeks. Baseline assessment was conducted prior to randomisation.

Interim analysis

No interim analysis was conducted.

Statistical analysis

Trial profile

Flow of the patients through the study will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram for each trial. We will report the number of screened patients who met study inclusion criteria, reasons for exclusion of non-included patients, the number of participants randomised per group, and the number who completed follow-up, as shown in Figures 1A and 1B.

Data integrity

Trial data integrity will be monitored by regularly scrutinising data files for data omissions and errors. Manually entered data (i.e. data not recorded directly by the participant) will be double entered and the source of any inconsistencies will be explored and resolved in consultation with the lead investigator (CW).

Analysis principles

Primary analyses will be conducted independently by an independent statistician who is blinded to group status.

Analyses will be conducted using SAS V9.4 (SAS Institute, Cary, North Carolina, USA). Intention-to-treat (ITT) (analysed as randomised) will be utilised. All statistical tests will be two-tailed. Treatment effect for the primary and secondary outcomes will be considered significant if $p \leq 0.025$ and $p \leq 0.01$, respectively.

Summaries of continuous variables that are symmetrically distributed will be presented as means and standard deviations (SD) or medians and inter-quartiles for skewed data, whereas categorical variables will be presented as frequencies and percentages. Large count variables will be reported as medians and interquartile

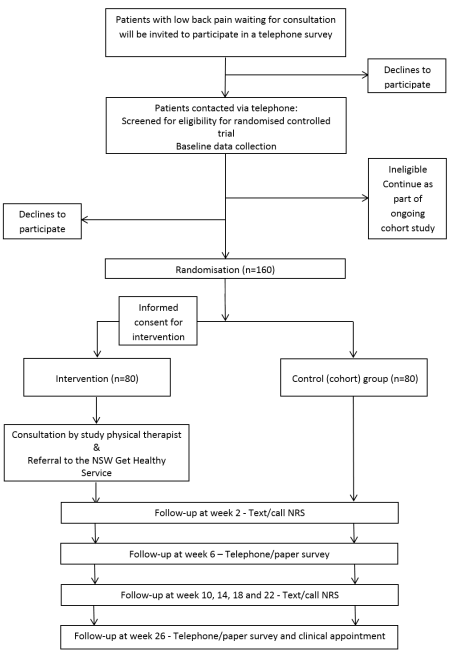

Figure 1A. Progress of participants through trial one (low back pain).

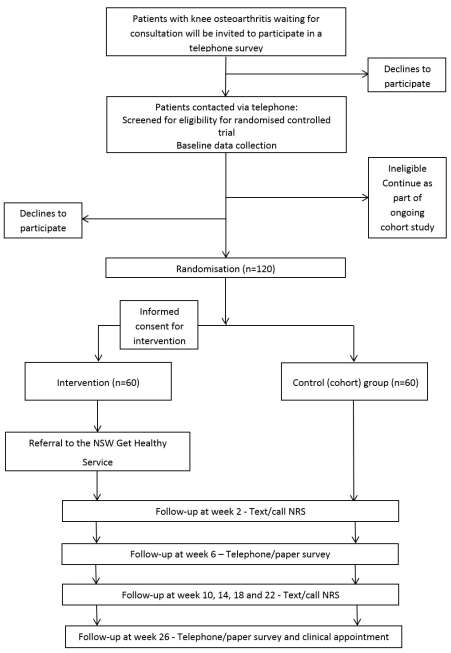

Figure 1B. Progress of participants through trial two (knee osteoarthritis).

ranges, low counts (max count <5) will be presented as frequencies and percentages.

Analysis population

The ITT population is defined as all randomised participants with a baseline measurement. Participants failing to record an outcome value at any follow-up period will be treated using the methods described below (see "Methods for handling missing data").

Methods for handling missing data

The number of participants with missing observations will be reported for each outcome variable. Patterns of missing data will be investigated and compared by demographic characteristics of the participants, t-tests will be used to compare continuous variables and chi-square tests will be used to compare categorical variables. For the primary outcome variable (average weekly pain intensity score) for participants with <10% missing pain intensity values, the missing pain intensity values will be interpolated using cubic spline interpolation. For participants with 10% or greater missing data an AUC will not be computed. The primary method of dealing with missing AUC data will be through multiple imputation (assuming missing at random), where missing AUC data will be imputed using the chained equations method of generating a number of complete data sets; the imputation model will include a range of covariates believed to be associated with either the missing outcome or the outcome itself (baseline pain and duration, waiting time, BMI). Sensitivity of analysis results will be assessed by comparing results obtained various imputation models. If there is reason to suggest the data may be missing not at random, pattern mixture models will be utilised[24].

Evaluation of demographics and baseline characteristics

The description of baseline characteristics listed below will be presented by treatment group. Categorical variables will be summarized by frequencies or denominators and percentages. Percentages will be calculated using the number of patients for whom data is available as the denominator. Denominators will be systematically reported (for example, nn/NN, %). Continuous variables will be summarised using standard measures of central tendency and dispersion, either mean and SD, or median and interquartile range.

- Age at randomisation
- Gender
- Aboriginal and/or Torres Strait Islander
- Employment status
- Country of origin
- Highest level of education
- Private health insurance
- Other co-existing medical conditions needing medication
- Length of time waiting for consultation (days)
- Triage classification
- Pain intensity and duration
- Disability and function
- Subjective weight
- BMI
- Quality of Life
- Emotional distress
- Sleep quality
- Physical activity
- Diet
- Alcohol consumption
- Smoking prevalence
- Pain attitudes
- Fear avoidance beliefs
- Health care utilisation

Process measures and concomitant treatments

When indicated, data will be summarised per group. Again continuous variables will be summarised by use of standard measures of central tendency and dispersion, either mean and SD, or median and interquartile range. Categorical variables will be summarised by frequencies or denominators and percentages.

Primary analysis

To examine between-group differences in the primary outcome (AUC – based on pain intensity score) we will use an independent sample Students

t-test. The primary analysis will not adjust for known prognostic variables as covariates, but results adjusting for these will be presented as a sensitivity analysis (see below). Separate models will be estimated for each imputed dataset and the means and standard errors will be combined using Rubin's method[25]. We will assess other model assumptions (homoscedasticity, normality) through inspecting appropriate residual plots, where serious violations are observed we will apply a rank-inverse normal transformation to the pain intensity score values. Dummy coded variables representing group allocation will be used to ensure blinding of the analyses. See Table 3 for details.

Secondary analysis

Between group differences in the trajectory of pain intensities over the follow-up period will be examined using growth curve modelling. Hierarchical linear models will be used, with fixed effects for treatment group, time, and the interaction between the two. The model will include random subject-level intercepts and slopes. A linear growth trend will initially be assumed, and if not appropriate different functional forms for the trend will be applied (for example the square root transformation). If an appropriate functional form cannot be determined a flexible piecewise linear model will be used[26]. We will also investigate treatment effect heterogeneity that may exist in latent subgroups of participants through growth mixture models[27]. In these models a number of latent classes are specified that model the potential for participants to have different trajectory types, the functional forms identified from the previous growth curve analyses will inform the functional forms for this analysis. The model will include the following random effects that are all conditional trajectory class membership: intercept linear slope and quadratic slope. The random effects are influenced by the treatment group, so there will potentially be 3 lots of treatment effects (for each random effect) for each latent class.

Longitudinal generalised linear mixed models will be used to assess treatment effect on post randomisation secondary outcome measurements with random intercepts for individuals to account for correlation of repeated measures and an appropriate link function dependent on the type and distribution of the data. We will compare the adjusted mean change (continuous variables) or relative risks (dichotomous variables) in outcome from baseline to each time point between the treatment and control groups. A binomial distribution family (with log link) will be used for dichotomous outcomes (sleep quality, smoking prevalence), and a Poisson or negative-binomial distribution family (with a log link function) will be used for count outcomes (health care utilisation) based on assessment of data dispersion. T-tests will be used to test between group differences in variables collected only at 26 weeks (objective weight, BMI, waist circumference). See Table 4 for details.

Sensitivity analyses

Adjusting for prognostic variables:

The following variables hypothesised to effect outcome will be assessed by their inclusion as covariates

Table 3. Analyses of primary outcome.

Analysis	Outcome	Intervention	Control	Difference
Primary (ITT Multiple Imputation)	Area under the pain intensity curve (AUC)	mean(95%CI)	mean(95%CI)	mean(95%CI)
Sensitivity	Adjusted AUC*	mean(95%CI)	mean(95%CI)	mean(95%CI)
Secondary	Pain intensity score			
	Baseline	mean(SD)	mean(SD)	
	Week 2,	mean(SD)	mean(SD)	
	Week 6	mean(SD)	mean(SD)	
	Week 10	mean(SD)	mean(SD)	
	Week 14	mean(SD)	mean(SD)	
	Week 18	mean(SD)	mean(SD)	
	Week 22	mean(SD)	mean(SD)	
	Week 26	mean(SD)	mean(SD)	
	Weekly trend	mean(95%CI)	mean(95%CI)	mean(95%CI)

* Adjusted for baseline pain and duration, waiting time, previous surgery; BMI: physical activity and dietary intake; ITT: Intention to treat.

Table 4. Secondary outcomes.

Outcome	Intervention	Control	Intervention - control
Disability and function (Trial 1: RMDQ / Trial 2: WOMAC)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Subjective weight			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Objective weight			
Baseline[a]	mean (SD)	N/A	N/A
Week 26	mean (SD)	mean (SD)	mean (95% CI)
BMI			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Waist circumference			
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Quality of life (SF12v2, PCS)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Quality of life (SF12v2, MCS)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Perceived change in condition (GPE)			
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Emotional distress (DASS-21)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)

[a] Intervention group of low back pain patients (trial one) only. RMDQ=Roland Morris Disability Questionnaire; WOMAC=Western Ontario and McMaster Universities Index; BMI=Body Mass Index; SF12.v2=Short Form Health Survey version 2; PCS=Physical Component Score; MCS=Mental Component Score; GPE=Global Perceived Effect; DASS-21=Depression Anxiety Stress Scale; MVPA=Moderate-to-Vigorous Physical Activity; AUDIT=Alcohol Use Disorders Identification Test; SOPA=Survey of Pain Attitudes; FABQ=Fear Avoidance Beliefs Questionnaire.

Table 4. Continued...

Outcome	Intervention	Control	Intervention - control
Poor sleep quality (item 6, Pittsburgh Sleep Quality Index)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Physical activity (mins MVPA/week)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Diet (Fruit, serves)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Diet (Vegetable, serves)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Diet (Discretionary foods, serves)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Alcohol consumption (AUDIT)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Smoking prevalence			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Pain Attitudes (SOPA)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 6	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)

[a] Intervention group of low back pain patients (trial one) only. RMDQ=Roland Morris Disability Questionnaire; WOMAC=Western Ontario and McMaster Universities Index; BMI=Body Mass Index; SF12.v2=Short Form Health Survey version 2; PCS=Physical Component Score; MCS=Mental Component Score; GPE=Global Perceived Effect; DASS-21=Depression Anxiety Stress Scale; MVPA=Moderate-to-Vigorous Physical Activity; AUDIT=Alcohol Use Disorders Identification Test; SOPA=Survey of Pain Attitudes; FABQ=Fear Avoidance Beliefs Questionnaire.

Table 4. Continued...

Outcome	Intervention	Control	Intervention - control
Fear avoidance beliefs (FABQ)			
Baseline	mean (SD)	mean (SD)	mean (95% CI)
Week 26	mean (SD)	mean (SD)	mean (95% CI)
Overall	mean (SD)	mean (SD)	mean (95% CI)
Health care utilisation (Medication use for back or knee pain)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Health care utilisation (Visits for back or knee pain)			
Baseline	n/N (%)	n/N (%)	OR (95% CI)
Week 6	n/N (%)	n/N (%)	OR (95% CI)
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Overall	n/N (%)	n/N (%)	OR (95% CI)
Health care utilisation (Attended orthopaedic consultation for back or knee)			
Week 26	n/N (%)	n/N (%)	OR (95% CI)
Health care utilisation (Received surgery for back or knee)			
Week 26	n/N (%)	n/N (%)	OR (95% CI)

[a] Intervention group of low back pain patients (trial one) only. RMDQ=Roland Morris Disability Questionnaire; WOMAC=Western Ontario and McMaster Universities Index; BMI=Body Mass Index; SF12.v2=Short Form Health Survey version 2; PCS=Physical Component Score; MCS=Mental Component Score; GPE=Global Perceived Effect; DASS-21=Depression Anxiety Stress Scale; MVPA=Moderate-to-Vigorous Physical Activity; AUDIT=Alcohol Use Disorders Identification Test; SOPA=Survey of Pain Attitudes; FABQ=Fear Avoidance Beliefs Questionnaire.

in a linear regression model for the analysis of the primary outcome (AUC): baseline pain intensity, time since onset of pain, waiting time, BMI.

Evaluation of adverse events

The Fisher exact test will be used to compare the incidence of any AEs between groups. This test will be used as the event rate of AEs is expected to be low.

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CHAPTER FOUR

Effectiveness of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial

Chapter Four is a published paper:

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CO-AUTHOR STATEMENT FOR CHAPTER FOUR

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: “Effectiveness of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial,” in the following ways:

- Conception and design of the research
- Data collection
- Analysis and interpretation
- Writing of the manuscript and critical appraisal of content

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Research Paper

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Effectiveness of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial

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Abstract

We assessed the effectiveness of a 6-month healthy lifestyle intervention, on pain intensity in patients with chronic low back pain who were overweight or obese. We conducted a pragmatic randomised controlled trial, embedded within a cohort multiple randomised controlled trial of patients on a waiting list for outpatient orthopaedic consultation at a tertiary hospital in NSW, Australia. Eligible patients with chronic low back pain (>3 months in duration) and body mass index ≥27 kg/m^2 and <40 kg/m^2 were randomly allocated, using a central concealed random allocation process, to receive advice and education and referral to a 6-month telephone-based healthy lifestyle coaching service, or usual care. The primary outcome was pain intensity measured using an 11-point numerical rating scale, at baseline, 2 weeks, and monthly for 6 months. Data analysis was by intention-to-treat according to a prepublished analysis plan. Between May 13, 2015, and October 27, 2015, 160 patients were randomly assigned in a 1:1 ratio to the intervention or usual care. We found no difference between groups for pain intensity over 6 months (area under the curve, mean difference = 6.5, 95% confidence interval −8.0 to 21.0; $P = 0.38$) or any secondary outcome. In the intervention group, 41% (n = 32) of participants reported an adverse event compared with 56% (n = 45) in the control group. Our findings show that providing education and advice and telephone-based healthy lifestyle coaching did not benefit patients with low back pain who were overweight or obese, compared with usual care. The intervention did not influence the targeted healthy lifestyle behaviours proposed to improve pain in this patient group.

Keywords: Low back pain, Lifestyle, Obesity, Randomised controlled trial

1. Background

Low back pain is the leading cause of disability worldwide and imposes considerable economic burden.[11,13] There is strong evidence that the development and persistence of low back pain is linked to "lifestyle risks," such as overweight and obesity.[34] Clinical practice guidelines recommend that patients with low back pain should be advised to engage in physical activity,[23,30] and there is widespread suggestion that managing lifestyle risks, such as weight, should be a key focus of care for patients with low back pain.[12,37]

Systematic review evidence suggests that targeting lifestyle risk factors reduces pain and disability in other musculoskeletal conditions such as knee osteoarthritis (OA).[10] A meta-analysis of randomised controlled trials (RCTs) showed that behavioural weight loss interventions lead to moderate improvements in pain and physical function for patients with knee OA who were overweight or obese.[10] Furthermore, patients who achieve at least a 5% weight loss experience a significant reduction in disability.[10] In contrast to knee OA, no RCTs have assessed the impact of lifestyle interventions on patient outcomes for low back pain.[37] This means that despite the known links between lifestyle risks and low back pain, there is currently no evidence about the effectiveness of lifestyle management to guide clinical practice recommendations for low back pain.

There are several theories for why targeting lifestyle risk factors could improve patient-reported outcomes such as pain and disability for people with low back pain. Weight loss may reduce mechanical load on the spine, reduce systemic inflammation,[12,32] or reduce mood or emotional distress which is believed to exacerbate the effect of weight on the experience of pain.[9] Furthermore, increased physical activity and a better diet (ie, less energy-dense, nutrient-poor foods) may influence these processes by contributing to weight loss.[12]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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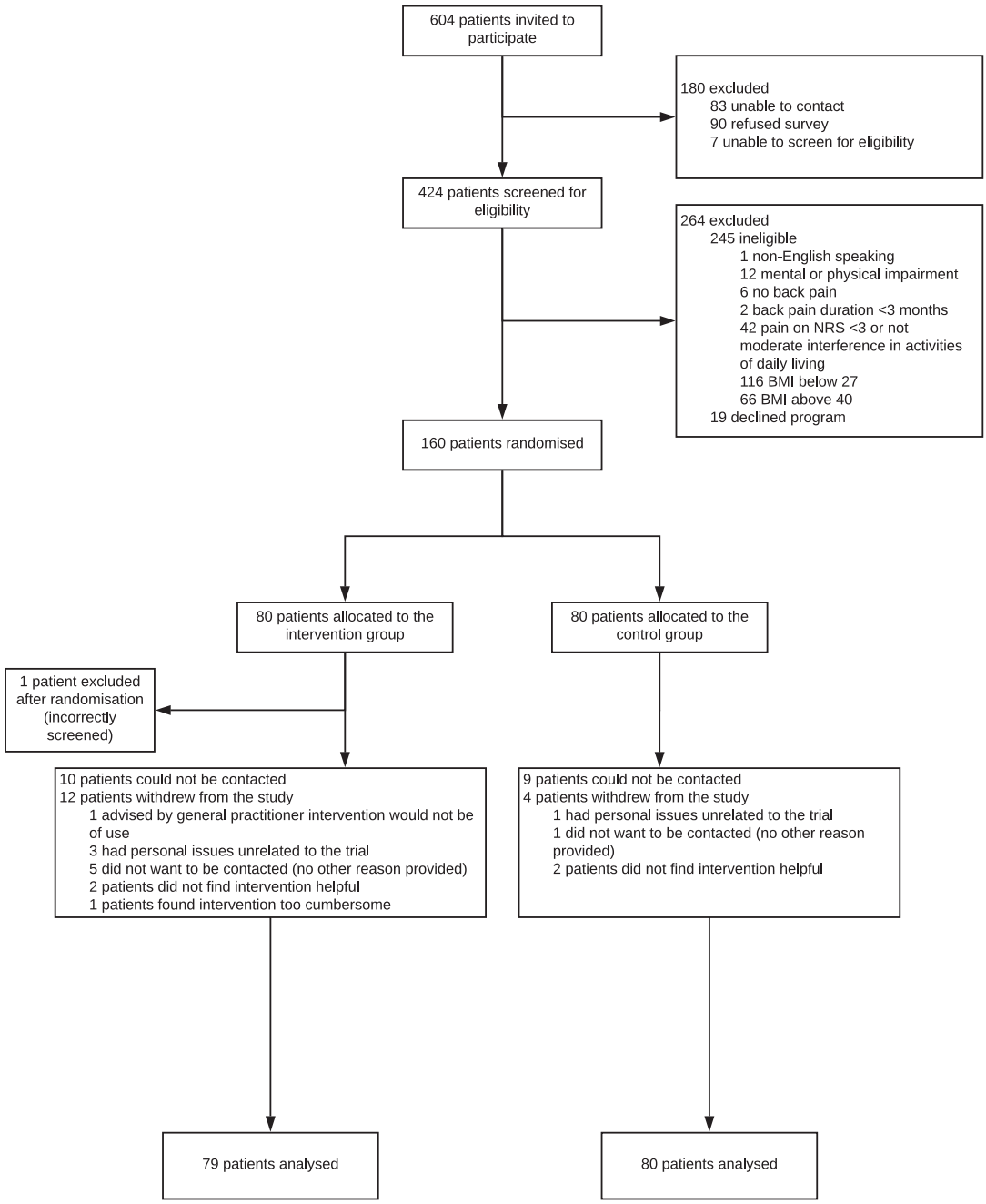

Figure 1. Trial profile. BMI, body mass index; NRS, numerical rating scale.

In view of this, we aimed to assess the effectiveness of a healthy lifestyle intervention, which targeted weight, physical activity, and diet behaviours, to reduce pain intensity for patients with chronic low back pain who were overweight or obese, compared with usual care. The trial also aimed to determine whether the intervention approach improved disability, weight, body mass index (BMI), physical activity, diet, sleep quality, global rating of symptom change, emotional distress, quality of life, and health care use, compared with usual care.

Table 1
Baseline characteristics.

	Intervention (n = 79)	Control (n = 80)
Demographic characteristics		
Age (y), mean (SD)	56.0 (13.3)	57.4 (13.6)
Sex (male), n (%)	31 (39.2)	34 (42.5)
Aboriginal and/or Torres Strait Islander status, n (%)	7 (8.9)	5 (6.3)
Employment status, n (%)		
Employed	17 (21.5)	17 (21.3)
Unemployed	15 (19.0)	9 (11.3)
Retired	27 (34.2)	29 (36.3)
Can not work (health reasons)	20 (25.3)	25 (31.3)
Country of origin (Australia), n (%)	69 (87.3)	68 (85.0)
Highest level of education, n (%)		
>High school	27 (34.2)	31 (38.8)
Private health insurance, n (%)	6 (7.6)	9 (11.3)
Other coexisting medical conditions needing medication, n (%)	67 (84.8)	68 (85.0)
Current time on the waiting list for consultation (d), median (IQR)	685 (255-1289)	525 (184-1185)
Triage classification, n (%)*		
Nonurgent	5 (6.3)	3 (3.8)
Semiurgent	64 (81.0)	66 (82.5)
Urgent	8 (10.1)	9 (11.3)
Clinical characteristics		
Pain intensity (NRS), mean (SD)	6.7 (1.8)	6.8 (1.6)
Pain duration (how long have you been troubled with your pain) (y), mean (SD)	13.0 (11.9)	18.5 (15.7)
Disability and function (RMDQ), mean (SD)	14.7 (5.2)	15.8 (5.1)
Self-reported weight, mean (SD)	91.9 (16.5)	90.8 (14.6)
Subjective BMI, mean (SD)	32.4 (3.5)	32.1 (3.6)
Quality of life (SF12.v2), mean (SD)		
PCS	31.3 (9.2)	29.2 (9.6)
MCS	46.7 (13.9)	46.1 (13.8)
Emotional distress (DASS-21), mean (SD)		
Depression subscale	11.3 (10.9)	9.9 (9.1)
Anxiety subscale	9.3 (7.7)	9.0 (7.8)
Stress subscale	13.3 (9.3)	13.6 (9.0)
Poor sleep quality (item 6, Pittsburgh Sleep Quality Index), n (%)†	11 (14)	24 (30)
Physical activity (mins MVPA/wk), mean (SD)	73.9 (219.3)	146.7 (504.0)
Diet, n (%)		
Daily fruit intake (<2 serves)	40 (51)	41 (51)
Daily vegetable intake (<5 serves)	64 (81)	67 (84)
Consumes discretionary foods more than once a wk	9 (11)	11 (14)
Alcohol consumption (AUDIT), mean (SD)	2.2 (2.5)	2.2 (2.6)
Smoking prevalence, n (%)	17 (22)	21 (26)
Pain attitudes (SOPA), mean (SD)	16.9 (4.7)	16.5 (4.7)
Fear avoidance beliefs (FABQ), mean (SD)	17.2 (5.5)	17.5 (6.0)
Health care utilisation, n (%)		
Medication use for back pain	66 (84)	63 (79)
Health care visits for back pain	37 (47)	47 (59)

* Note that these percentages do not add up to 100% because n = 4 participants had no triage classification recorded (intervention, n = 2; control, n = 2).
† Item 6 from the Pittsburgh Sleep Quality Index dichotomised as very bad and fairly bad vs very good and fairly good.
AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; DASS-21, Depression Anxiety Stress Scale; FABQ, Fear Avoidance Beliefs Questionnaire; IQR, interquartile range; MCS, Mental Component Score; MVPA, moderate-to-vigorous physical activity; NRS, numerical rating scale; PCS, Physical Component Score; RMDQ, Roland Morris Disability Questionnaire; SF12.v2, Short Form Health Survey Version 2; SOPA, survey of pain attitudes.

2. Methods

2.1. Study design and participants

The study was a 2-arm pragmatic parallel group RCT, part of a cohort multiple RCT.[31] Details of the study are reported in the study protocol and statistical analysis plan.[26,39] Protocol deviations are specified in Text S1 in the supplementary file (available online at http://links.lww.com/PAIN/A548). The study was conducted at the John Hunter Hospital, New South Wales (NSW), Australia. Patients with musculoskeletal conditions, who were on the waiting list for outpatient consultation with an orthopaedic specialist, were invited to participate in the cohort study involving telephone assessments. All patients in the cohort were informed that regular surveys were being conducted as part of hospital audit processes and to track patient health while waiting for consultation. During one of the telephone assessments, participants of the cohort study with chronic low back pain were assessed for eligibility for the RCT. Eligible consenting patients were randomised to study conditions: (1) offered the intervention (intervention group), or (2) remained in the cohort follow-up (usual care control group).

Participant inclusion criteria were: a primary complaint of chronic low back pain (defined as pain between the 12th rib and buttock crease with or without leg pain for longer than 3 months)[2]; with an average low back pain intensity ≥3 of 10 on a 0 to 10 numerical rating scale (NRS) over the past week, or moderate

Table 2

Analyses of primary outcome (pain intensity).

Analysis	Outcome	Intervention mean (95% CI) (n = 79)	Control mean (95% CI) (n = 80)	Mean difference* (95% CI)	P
Primary (ITT and MI)	Area under the pain intensity curve (AUC)	156.8 (146.2 to 167.5)	163.4 (153.6 to 173.1)	6.5 (−8.0 to 21.0)	0.38
Analysis	**Outcome**	**Intervention mean (SD) (n = 79)**	**Control mean (SD) (n = 80)**	**Mean difference* (95% CI)**	**P**
Secondary	Pain intensity score				
	Baseline	6.7 (1.8)	6.8 (1.6)		
	Week 2	6.4 (2.1)	6.4 (1.9)	0.0 (−0.6 to 0.6)	1.00
	Week 6	6.2 (2.1)	6.2 (2.1)	−0.1 (−0.8 to 0.5)	0.72
	Week 10	5.7 (2.4)	6.4 (2.0)	0.6 (0.0 to 1.3)	0.05
	Week 14	6.4 (2.3)	6.8 (1.8)	0.4 (−0.2 to 1.1)	0.20
	Week 18	5.6 (2.5)	6.5 (1.8)	0.8 (0.2 to 1.5)	0.01
	Week 22	5.7 (2.5)	6.2 (2.0)	0.4 (−0.3 to 1.1)	0.24
	Week 26	5.8 (2.7)	6.3 (2.4)	0.3 (−0.4 to 1.0)	0.36
	Monthly trend			0.08 (−0.04 to 0.21)	0.19

* Mean difference = control − intervention.
AUC, area under the curve; CI, confidence interval; ITT, intention to treat; MI, multiple imputation.

level of interference in activities of daily living (adaptation of item 8 on SF36); 18 years or older; overweight or obese (BMI ≥27 kg/m^2 and <40 kg/m^2) based on self-reported weight and height; and access to a telephone. Exclusion criteria were: known or suspected serious pathology as the cause of back pain as advised by their general practitioner (eg, fracture, cancer, infection, inflammatory arthritis, and cauda equina syndrome); previous obesity surgery; currently participating in any prescribed, medically supervised or commercial weight loss program; back surgery in the past 6 months or booked for surgery in the next 6 months; unable to comply with the study protocol that required adaption of meals or exercise due to nonindependent living arrangements; any medical or physical impairment precluding safe participation in exercise, such as uncontrolled hypertension; and unable to speak and read English sufficiently to complete the study procedures.

Ethical approval was obtained from the Hunter New England Human Research Ethics Committee (approval No. 13/12/11/5.18) and the University of Newcastle Human Research Ethics Committee (approval No. H-2015-0043). This study adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

2.2. Randomisation and masking

The randomisation schedule was prepared a priori by an independent investigator using SAS 9.3 through the SURVEYSELECT procedure. Patients were randomised into study conditions (offered the intervention, or usual care control) in a 1:1 ratio, using a central concealed random allocation process. Specifically, when a patient was deemed eligible, they were allocated the next available study identification number which corresponded with study identification numbers of the randomisation schedule. At this point, the patient was considered randomised to the study. After baseline assessment, interviewers opened a prepacked opaque envelope labelled with the corresponding study identification number and contained the participant's group status. The envelopes were arranged by a research assistant, who was not involved in the study. Outcome assessors conducting follow-up data collection telephone interviews, and trial statisticians were masked to group allocation. Because of the design of the study (ie, cohort multiple RCT),[31] participants were not aware of alternate study conditions.

2.3. Interventions

Participants randomised to the intervention group were offered a healthy lifestyle intervention involving brief telephone advice, offer of a clinical consultation followed by referral to a 6-month telephone-based healthy lifestyle coaching service. The approach was based on formative evaluation which identified telephone services as the most preferred method by patients to support lifestyle change and weight loss.[40] Participants in the intervention group remained on the waiting list for orthopaedic specialist consultation and could attend a consultation during the study period. Patients were free to access care outside the study, as they saw fit.

The brief telephone advice was provided by trained telephone interviewers after baseline assessment, immediately after randomisation. This advice included information that a broad range of factors contribute to the experience of low back pain, followed by description of the potential benefits of weight loss and physical activity for reducing low back pain.

The clinical consultation was a face-to-face consultation (up to 1 hour) conducted in a community health centre with the study physiotherapist, who was not involved in data collection. As detailed in our protocol,[39] the consultation was informed by Self Determination Theory and involved 2 broad approaches: (1) clinical assessment followed by low back pain education and advice and (2) behaviour change techniques.[1]

In brief, the patient education and advice aimed to improve understanding about low back pain, correct erroneous beliefs about the cause of back pain, (ie, provide information about the nature of the condition, that persistent low back pain is multifactorial with multiple influences and not usually the result of pathological tissue damage), reduce pain-related fear and distress that may hamper participation in the intervention, as well as describe the broader influences of back pain including lifestyle risks (overweight, inactivity, nutrition, smoking, alcohol, and poor sleep). The education and advice included information about the role of weight loss and physical activity in managing low back pain symptoms and introduced the telephone health coaching service as a way to support weight loss, physical activity, and diet. The behaviour change techniques were incorporated to facilitate intentions to change and adopt healthy lifestyle habits for back pain self-management, using the following techniques: intention formation[1] (by encouraging commitment from the participant to engage with the coaching service and confirming that monitoring of

Table 3

Analyses of secondary outcomes.

Outcome	Time point	Intervention	Control	Mean difference* (95% CI)
		Mean (SD)	Mean (SD)	
Disability score (RMDQ)	Baseline	14.7 (5.2); n = 79	15.8 (5.1); n = 80	
	Week 6	14.2 (5.6); n = 57	15.8 (5.1); n = 69	0.8 (−0.6 to 2.2)
	Week 26	13.9 (6.5); n = 38	14.7 (5.9); n = 55	−0.1 (−1.7 to 1.5)
Self-reported weight	Baseline	91.9 (16.5); n = 79	90.8 (14.6); n = 80	
	Week 6	93.9 (18.0); n = 62	90.2 (15.0); n = 72	−0.3 (−1.9 to 1.2)
	Week 26	93.5 (17.4); n = 54	93.3 (16.8); n = 63	1.8 (0.2 to 3.5)
Objective weight	Baseline†	98.5 (18.6); n = 25	—	
	Week 26	96.1 (15.7); n = 13	97.9 (20.3); n = 26	1.8 (−11.2 to 14.8)
Subjective BMI	Baseline	32.4 (3.5); n = 79	32.1 (3.6); n = 80	
	Week 6	32.8 (4.1); n = 62	32.0 (4.1); n = 72	−0.1 (−0.6 to 0.5)
	Week 26	32.7 (4.3); n = 54	32.5 (4.6); n = 63	0.6 (0.0 to 1.2)
Objective BMI	Week 26	33.3 (4.3); n = 12	35.2 (6.5); n = 26	1.8 (−2.3 to 6.0)
Objective waist circumference	Week 26	121.0 (21.9); n = 10	110.8 (17.7); n = 23	−10.1 (−24.8 to 4.6)
Quality of life PCS (SF12.v2)	Baseline	31.3 (9.2); n = 79	29.2 (9.6); n = 79	
	Week 6	31.8 (9.1); n = 57	30.3 (10.6); n = 69	−0.3 (−3.0 to 2.4)
	Week 26	32.1 (10.9); n = 43	30.5 (10.1); n = 61	−0.6 (−3.5 to 2.4)
Quality of life MCS (SF12.v2)	Baseline	46.7 (13.9); n = 79	46.1 (13.8); n = 79	
	Week 6	46.6 (11.0); n = 57	45.0 (11.6); n = 69	−0.9 (−4.3 to 2.4)
	Week 26	46.5 (13.8); n = 43	44.3 (13.3); n = 61	−1.7 (−5.4 to 2.0)
Global rating of symptom change (GPE)	Week 6	4.3 (1.8); n = 58	4.5 (1.8); n = 70	0.2 (−0.5 to 0.9)
	Week 26	4.9 (2.2); n = 41	4.2 (1.9); n = 58	−0.6 (−1.3 to 0.2)
DASS-21, depression	Baseline	11.3 (10.9); n = 79	9.9 (9.1); n = 79	
	Week 26	13.1 (11.2); n = 43	11.9 (11.1); n = 61	0.5 (−2.7 to 3.7)
DASS-21, anxiety	Baseline	9.3 (7.7); n = 79	9.0 (7.8); n = 79	
	Week 26	9.8 (8.3); n = 43	9.4 (9.0); n = 61	−0.3 (−3.2 to 2.7)
DASS-21, stress	Baseline	13.3 (9.3); n = 79	13.6 (9.0); n = 79	
	Week 26	14.3 (10.7); n = 43	13.8 (11.1); n = 61	−0.2 (−3.9 to 3.4)
Physical activity (MVPA/wk)	Baseline	73.9 (219.3); n = 79	146.7 (504.0); n = 80	
	Week 6	95.8 (208.3); n = 59	130.6 (382.1); n = 71	−7.1 (−150.0 to 135.8)
	Week 26	229.2 (755.1); n = 43	148.6 (400.0); n = 61	−99.3 (−260.2 to 61.5)
Alcohol consumption (AUDIT)	Baseline	2.2 (2.5); n = 79	2.2 (2.6); n = 80	
	Week 6	2.3 (2.8); n = 58	2.3 (2.6); n = 70	−0.1 (−0.5 to 0.4)
	Week 26	2.2 (2.6); n = 43	2.3 (2.7); n = 58	0.1 (−0.4 to 0.6)
Pain attitudes (SOPA)	Baseline	16.9 (4.7); n = 79	16.5 (4.7); n = 80	
	Week 6	16.2 (4.2); n = 59	16.1 (4.7); n = 71	0.3 (−1.3 to 1.8)
	Week 26	16.9 (5.5); n = 43	15.8 (5.3); n = 61	−0.5 (−2.3 to 1.2)
Fear avoidance beliefs scale (FABQ)	Baseline	17.2 (5.5); n = 79	17.5 (6.0); n = 79	
	Week 26	15.4 (7.4); n = 43	16.6 (6.4); n = 60	1.0 (−1.4 to 3.5)
Outcome	**Time point**	**Intervention, n/N (%)**	**Control, n/N (%)**	**OR (95% CI) ref = control**
Poor sleep quality‡	Baseline	11/79 (14)	24/80 (30)	
	Week 6	7/58 (12)	15/71 (21)	0.59 (0.23 to 1.51)
	Week 26	5/43 (12)	8/61 (13)	1.04 (0.37 to 2.96)
Diet—daily fruit intake (0-1 serves)§	Baseline	40/79 (51)	41/80 (51)	
	Week 6	24/59 (41)	37/71 (52)	0.63 (0.32 to 1.24)
	Week 26	16/43 (37)	25/61 (41)	0.79 (0.38 to 1.63)
Diet—daily vegetable intake (0-2 serves)	Baseline	35/79 (44)	37/80 (46)	
	Week 6	27/59 (46)	37/71 (52)	—
	Week 26	21/42 (50)	29/61 (48)	—
Diet—daily vegetable intake (3-4 serves)	Baseline	29/79 (37)	30/80 (38)	
	Week 6	27/59 (46)	22/71 (31)	—
	Week 26	17/42 (40)	20/61 (33)	—
Diet—daily vegetable intake‖	Week 6	—	—	0.96 (0.50 to 1.82)
	Week 26	—	—	1.30 (0.62 to 2.72)

(*continued on next page*)

Table 3 (*continued*)

Outcome	Time point	Intervention, n/N (%)	Control, n/N (%)	OR (95% CI) ref = control
Diet—consumes discretionary foods more than once a wk	Baseline	73/79 (92)	73/80 (91)	
	Week 6	51/58 (88)	60/71 (85)	1.17 (0.44 to 3.12)
	Week 26	37/43 (86)	52/61 (85)	1.11 (0.36 to 3.41)
Smoking prevalence	Baseline	17/79 (22)	21/80 (26)	
	Week 6	11/59 (19)	14/71 (20)	0.93 (0.43 to 2.00)
	Week 26	4/43 (9)	11/61 (18)	0.56 (0.24 to 1.27)
Participants using other health care for back pain	Baseline	37/79 (47)	47/80 (59)	
	Week 6	24/60 (40)	39/72 (54)	0.56 (0.28 to 1.12)
	Week 26	14/38 (37)	25/56 (45)	0.73 (0.33 to 1.65)
Attended orthopaedic consultation for back pain	Baseline	4/79 (5)	6/80 (8)	
	Week 6	3/60 (5)	4/72 (6)	—
	Week 26	0/38 (0)	2/56 (4)	—
Participants using medication for back pain	Baseline	66/79 (84)	63/80 (79)	
	Week 6	44/60 (73)	58/72 (81)	0.64 (0.29 to 1.44)
	Week 26	27/38 (71)	45/56 (80)	0.54 (0.20 to 1.44)

* Mean difference = control − intervention, adjusted for baseline values (where baseline value exists).
† Measured for intervention group only at the clinical consultation.
‡ Item 6 from the Pittsburgh Sleep Quality Index dichotomised as very bad and fairly bad vs very good and fairly good.
§ Reference = 2 or more serves.
‖ Vegetable intake categories = 0 to 2 serves, 3 to 4 serves, and 5 or more serves; OR is the proportional odds of reporting a lower category of vegetable intake for the intervention group.
AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index; CI, confidence interval; DASS-21, Depression Anxiety Stress Scale; FABQ, Fear Avoidance Beliefs Questionnaire; GPE, Global Perceived Effect Scale; MCS, Mental Component Score; MVPA, moderate-to-vigorous physical activity; OR, odds ratio; PCS, Physical Component Score; RMDQ, Roland Morris Disability Questionnaire; SF12.v2, Short Form Health Survey Version 2; SOPA, survey of pain attitudes.

participation and lifestyle behaviours would occur throughout the program); setting graded tasks and specific behaviour goals[1]; prompting barrier identification[1] (by discussing patient-specific potential barriers to behaviour change); and prompting self-monitoring of behaviour and outcomes.[1]

The telephone-based health coaching service was the NSW Get Healthy Service (GHS) (www.gethealthynsw.com.au).[27] The service involves 10 individually tailored coaching calls, based on national Healthy Eating and Physical Activity guidelines,[5,24] delivered over 6 months by qualified health professionals.[27] The GHS is a public health telephone-based service to support individuals to modify eating behaviours, increase physical activity, achieve and maintain a healthy weight, and where appropriate, referral to smoking cessation services. The GHS is funded by the NSW government and provided free to all residents of the state. A pre–post study showed the GHS to be effective for reducing weight, BMI, and waist circumference in the general population, for those adherent to the program.[27]

Participant referrals to the GHS were sent by the researchers through fax or email and indicated that referred participants were patients with low back pain. The GHS directly contacted the participants. All GHS health coaches were trained in evidence-based advice for low back pain by a study investigator (C.W.). This training involved a 2-hour interactive workshop and information resources to facilitate adaption of advice for study participants. The workshop and resources were based on information contained in international clinical practice guidelines for low back pain and included topics of diagnosis, prognosis, pain-related distress, evidence-based management strategies, and the role of a healthy lifestyle and weight loss.

Participants randomised to the control group continued on the usual care pathway (ie, remained on the waiting list to have an orthopaedic specialist consultation and could progress to consultation if scheduled) and took part in data collection during the study period. No other active intervention was provided as part of the study; however, no restrictions were placed on the use of other health services during the study period. Control participants were informed that a new clinical service would be available in approximately 6 months involving clinical assessment and support from other services for their back pain should they need it. No other details about the new service, or that other patients had started this service were disclosed.

2.4. Outcome measures

The primary outcome was average self-reported back pain intensity, over the 6-month follow-up. At baseline, and weeks 2, 6, 10, 14, 18, 22, and 26 participants were asked to report the "average pain intensity experienced in their back over the past week" on an NRS, where 0 was "no pain" and 10 was the "worst possible pain." The NRS is a widely used and validated measure.[15] Pain intensity was chosen as the primary outcome, as it is recommend as a core outcome for clinical trials in nonspecific low back pain and is a key priority for patients.[8]

Secondary outcomes were: self-reported weight (kg); low back pain disability, using the Roland Morris Disability Questionnaire (0-24 scale; high score indicates greater disability)[33]; quality of life, using the 12-item Short Form Health Survey (physical and mental health component scores [0-100 scale; high score indicates greater quality of life])[38]; sleep quality using item 6 from the Pittsburgh Sleep Quality Index (very bad, fairly bad, fairly good, and very good)[6]; physical activity, using the Active Australia Survey (average minutes spent participating in moderate-to-vigorous physical activity per week)[3]; diet, using a short food frequency questionnaire (serves of fruit [0-1, 2, or more]; serves of vegetables [0-2, 3-4, 5, or more]); serves of discretionary foods, for example, processed meats, salty snacks, confectionary, sugar-sweetened beverages (more than once per week, once per week, or less)[7]; alcohol consumption using the Alcohol Use Disorders Identification Test (0-12 scale; high score indicates greater risk of alcohol-related harm)[4]; smoking prevalence (have you smoked any tobacco in the past 4 weeks? [including cigarettes, roll your own, pipes, cigars, or any other tobacco products])[35]; back pain beliefs, using the 1-item Survey of Pain Attitudes (0-28 scale; a high score indicates worse pain attitude);[19] and health care utilisation over the past 6 weeks including

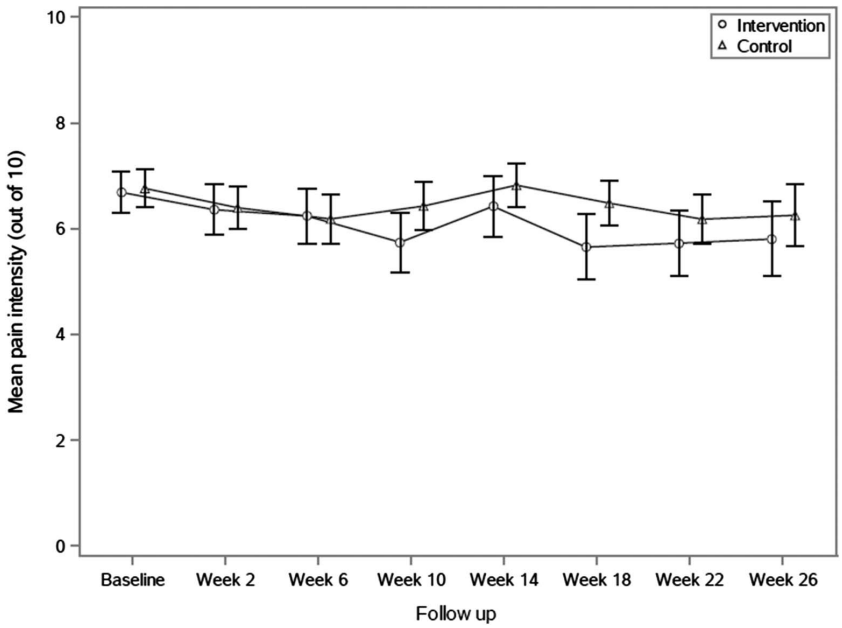

Figure 2. Mean pain intensity over the follow-up period.

medication use and type of health service for back pain, all measured at 0, 6, and 26 weeks.

Emotional distress, using the Depression Anxiety Stress Scale-21 (0-63 scale; high score indicates greater severity)[22] and the physical component of the Fear Avoidance Beliefs Questionnaire (0-24 scale; a high score indicates greater degree of fear-avoidance beliefs)[36] were measured at 0 and 26 weeks. Global rating of symptom change, using the Global Perceived Effect Scale (−5 "vastly worse" to 5 "completely recovered"),[21] was measured at 6 and 26 weeks.

Objective weight (kg) and waist circumference were measured by a trained research assistant using International Society for the Advancement of Kinanthropometry procedures[16] at 26 weeks only. Body mass index was calculated as weight/height squared (kg/m^2) using self-reported and objective measures of weight separately.

Commencement date and the number of health coaching calls received were reported directly by the GHS. Participants were asked to report any adverse events (any new medical conditions or an exacerbation of another condition) during the intervention period in the 6- and 26-week questionnaires.

2.5. Data collection

Participants were asked to complete questionnaires (primary and secondary outcomes); at baseline, 6 weeks, and 26 weeks after randomisation. Baseline data were collected during a telephone interview from eligible participants before random allocation. Week 6 and week 26 questionnaires were completed through telephone by telephone interviewers blind to group allocation or mailed in the post as per participant preference. Participants were also asked to provide self-reported primary outcome data at weeks 2, 10, 14, 18, and 22 through telephone or text message, as per participant preference. Participants were asked to attend a clinical appointment with a research assistant at 6 months at which time objective weight and waist circumference were measured. At baseline, current time on the waiting list for consultation (days) and triage classification was obtained from hospital records.

2.6. Statistical analysis

Sample size calculations estimated that a sample of 80 participants per group allowing for 15% loss to follow-up would provide 90% power to detect a clinically meaningful difference of 1.5 in pain intensity (NRS) (equivalent to a 39-point difference in the area under the curve [AUC]), with a SD of 2.3, and a 2-sided alpha of 0.025. Weight loss was the mechanism hypothesised to influence pain; therefore, we also powered for self-reported weight as a secondary outcome. Therefore, using the reduced alpha of 0.025 to account for multiplicity,[29] the sample provided 80% power to detect a 6% reduction in self-reported weight, which has been hypothesised to lead to a clinically meaningful reduction in symptoms for other musculoskeletal conditions.[10] In these calculations, the increase in statistical power conferred by reducing error variance through repeated outcome measures over time and the correlation among repeated measures have been conservatively ignored.

All outcomes were analysed under the intention-to-treat principle. The primary outcome was examined as the average self-reported pain intensity over 6 months defined as the AUC of all pain intensity scores. Area under the curve for pain intensity represents cumulative average pain intensity over time (ie, average pain intensity score at each time point multiplied by the time elapsed since the previous observation) in each treatment group. For interpretation, dividing the AUC result by the number of weeks of follow-up (ie, 26) will give the mean between-group differences in the NRS.

For participants with <10% missing pain intensity values, the missing values were interpolated and an AUC computed. For participants with 10% or greater missing data, an AUC was not computed. Multiple imputation using the chained equations method was used to impute missing AUC data. The imputation model included a range of covariates believed to be associated with missingness or the outcome itself (baseline back pain intensity, time since onset of pain, waiting time, and baseline BMI). The primary outcome analysis assessed the between-group differences in AUC using an independent sample Student *t* test. Statistical significance was defined as *P* values less than 0.025.

Continuous secondary outcomes were assessed using baseline-adjusted hierarchical linear models with fixed effects for treatment group, time, group × time interaction, baseline value of the outcome, and random subject-level intercepts. Continuous outcomes measured at baseline and week 26 were assessed using baseline-adjusted analysis of covariance at 26 weeks. Continuous outcomes measured at week 26 only were assessed using 2 sample *t*-tests. Categorical secondary outcomes were assessed using General Estimating Equations with fixed effects for treatment group, time, and group × time interaction. Dichotomous outcomes used the binomial distribution (with logit link), ordinal outcomes used the multinomial distribution (with cumulative logit link), and count outcomes used the negative-binomial distribution (with a log link function). Adverse events were classified according to the International Classification of Diseases version 10 by research personnel; the proportion of participants reporting an adverse event was compared between groups using the χ^2 test. A secondary analysis of the primary outcome used hierarchical linear models to assess between-group differences in the trajectory of pain intensities over the follow-up period, modelled using growth curve modelling. Sensitivity analysis for the primary outcome analysis (AUC) used linear regression models adjusting for baseline prognostic variables (back pain intensity, time since onset of pain, waiting time, and BMI). Statistical significance in these models was defined as *P* values less than 0.01 to account for multiple comparisons.[29]

The analysis plan was approved and published before analysis of data.[26] Independent statistician(s) who were blinded to allocation completed the statistical analyses as per the published protocol using SAS V9.4 (SAS Institute, Cary, NC). The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000478516).

3. Results

Patients were recruited and randomly assigned to study groups between May 13, 2015, and October 27, 2015. Of 521 patients screened, 179 were eligible, and 160 (89.4%) provided consent and were randomised to either the lifestyle intervention (n = 80) or usual care (n = 80) (**Fig. 1**). One participant was excluded after randomisation, as he was found to be ineligible. Participants had a mean age of 56.7 (SD 13.4) years and 94 (59.1%) were female. The mean baseline pain intensity was 6.7 (SD 1.7) and mean pain duration was 15.8 (SD 14.2) years. The mean self-reported weight at baseline was 91.4 (SD 15.6) kg. Participant characteristics at baseline were similar between groups (**Table 1**).

The completeness of the primary outcome data, back pain intensity, over the follow-up period was 87.7%. Missingness for primary outcome data was associated with a lower baseline weight (mean difference = −8.0 kg, 95% confidence interval [CI] −3.0 to −13.1; *P* = 0.002). At 26 weeks, 22 participants in the intervention group and 13 participants in the control group did not complete data collection (**Fig. 1**). There were no meaningful differences in baseline characteristics between participants lost to follow-up and participants who completed 26-week follow-up.

Pain intensity over the 6-month follow-up period was not significantly different between groups (AUC mean difference = 6.5 of total pain scores, 95% CI −8.0 to 21.0; *P* = 0.38; equivalent to a 0.25 point difference on the pain intensity NRS 95% CI −0.31 to 0.81) (**Table 2**). Similarly, there were no significant differences between groups for any secondary outcome during follow-up (**Table 3**).

Adverse events per group are reported in Table S1 in the supplementary file (available online at http://links.lww.com/PAIN/A548). The proportion of participants reporting an adverse event was not different between groups; 41% (n = 32) and 56% (n = 45) for the intervention and control group, respectively. The number and type of health services and medications used were similar across groups (Table S2 and S3 in the supplementary file, available online at http://links.lww.com/PAIN/A548).

In regard to intervention adherence, 37 (46.8%) participants from the intervention group attended the single consultation with the study physiotherapist. Get Healthy Service data showed that 76 participants (96.2%) in the intervention group commenced GHS coaching calls (received at least 1 call), 38 (48.1%) participants received at least 3 calls (median 3; interquartile range: 1-9), and 33 (41.8%) participants receiving 6 or more calls. The mean number calls conducted with participants was 5.1 (SD 4.5). Twenty-three participants (29.1%) attended the clinical consult and received 6 or more GHS calls.

Analysis of the pain intensity trajectory found no significant between-group difference in mean pain intensity over 6 months (−0.08, 95% CI −0.04 to 0.21; *P* = 0.19) (**Fig. 2** and **Table 2**). We also noted no between-group difference in the primary outcome when adjusted for prognostic variables (baseline pain intensity, time since onset of pain, waiting time, and baseline BMI), (AUC mean difference = 6.2, 95% CI −6.3 to 18.8; *P* = 0.32).

After consideration of the adherence results, we undertook a post hoc analysis to assess the effect of receiving the clinical consult and 6 or more GHS calls in the intervention group (ie, 29% of participants) compared with the control group. This analysis showed no between-group difference for pain intensity or self-reported weight (Table S4 and S5 in the supplementary file, available online at http://links.lww.com/PAIN/A548).

4. Discussion

We have shown that a healthy lifestyle intervention involving brief telephone advice, offer of a clinical consultation involving detailed education, and referral to a 6-month telephone-based healthy lifestyle coaching service targeting weight loss, physical activity, and diet did not improve pain intensity for patients with low back pain who were overweight or obese. The intervention did not reduce self-reported weight, the hypothesised mechanism to influence pain, nor did the intervention improve other secondary outcomes including physical activity, diet, disability, sleep quality, emotional distress, global rating of symptom change, quality of life, or health care use.

4.1. Strengths and limitations of this study

Several study features ensured low risk of bias including central randomisation and allocation concealment, blinding of outcome assessors and statisticians, and prepublication of a study protocol and statistical analysis plan.[26,39] The cohort multiple RCT design meant that patients were not aware of the alternate study

group. This mimics real-world heath care, reduces participant performance bias, and minimises sampling bias by reducing nonconsent.[31]

A potential limitation of the trial is that participants were recruited from 1 tertiary hospital. Although this hospital has a wide referral base of general practitioners (n > 1300), from a large health district (population size > 900,000), the single centre design may impact generalisability of the findings. Because of the pragmatic design of the study, it was not feasible to collect objective weight across the intervention period, so our measurement of weight relied on self-report. Measuring objective weight across all time points may have increased the validity of our assessment of weight outcomes.

Our intervention included several pragmatically delivered components. The overall adherence to these components was low. Around half (47%) of the intervention group attended the initial consult, and although 96% of patients commenced the GHS, just 42% received 6 or more (of 10) GHS calls. Only 29% attended the consult and received 6 or more calls. Poor engagement with the intervention may explain why the intervention failed to provide benefits to participants. However, in our post hoc analysis, we did not note any signal of an effect on pain intensity or weight loss for participants who received the clinical consultation and 6 or more GHS calls.

Although our approach was based on formative evaluation, which indicated telephone services as the most preferred method to support healthy lifestyle and weight loss,[40] for patients with low back pain who are overweight, it remains unclear how to encourage patient adherence and support patients to make lifestyle changes. In the general population, telephone services have been shown to be as effective as face-to-face services when addressing lifestyle risks.[14] In our study, we used a nondisease-specific healthy lifestyle intervention designed for the general population. Current best practice guidelines for weight loss and behaviour change recommend tailored support to cater for the needs of different patient groups and to provide support for at least 3 months.[25] Although our study aimed to provide up to 6 months of support, it is possible that patients with long-standing chronic low back pain require more intensive and disease-specific support to adequately manage their pain and facilitate lifestyle changes; for example, such as that offered in multidisciplinary pain management programs.[20] Certainly, patients with low back pain who are overweight may encounter additional challenges to engaging in positive behaviour changes. Combined with mobility restrictions, patients with chronic pain are often fearful that physical activity will make their condition worse.[28] There is also evidence that patients may use food to help cope with their pain, as eating certain foods can elicit a chemical response in the brain providing feelings of comfort.[17,18] In our study, it is unclear if these additional challenges contributed to poor adherence and led to no effect, or if a lack of benefit from participating in the service resulted in poor adherence or drop out over time. Future studies should appropriately identify how to optimise involvement of patients with low back pain in health behaviour change to elicit and assess any potential effect of lifestyle-focused care.

Lifestyle risks such as overweight and obesity have been shown to increase persistent low back pain and health care seeking for low back pain.[34] Accordingly, targeting lifestyle as part of the management of low back pain is widely recommended.[12,37] However, there is no direct evidence that addressing lifestyle and weight, in particular, benefits these patients.[37] Evidence from other musculoskeletal conditions indicates that clinically meaningful weight loss of 6% of body weight leads to reduced pain intensity.[10] As our intervention did not affect patients' weight, we cannot confirm whether targeting this, or other aspects of lifestyle, has a meaningful influence on patients with low back pain.

Given the link between lifestyle risks and chronic low back pain, it is surprising that no other trials in this area have been conducted.[37] Currently, there is no evidence to guide the clinical management of patients with these comorbid health issues. This is a significant oversight, as patients with low back pain who are also overweight and have other poor lifestyle behaviours are likely to face additional challenges, managing these coexisting health issues. As together they are likely to elicit a greater burden on the health of individuals and across the population, there is a need for research which aims to understand the interaction between lifestyle and back pain, and also develop integrative management approaches to guide the development of effective interventions.

5. Conclusions

Our study provides high-quality evidence that a healthy lifestyle intervention involving brief advice, clinical education and advice, and referral to a telephone-based health coaching service was not effective in reducing back pain intensity, weight, disability, and other outcomes in patients with low back pain who were overweight or obese. Clinical education and advice coupled with referral to nondisease-specific telephone-based healthy lifestyle coaching service is unlikely to provide benefits to this patient group.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A548.

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Supplementary file

Text S1: Summary of changes to the original study protocol and statistical analysis plan

Deviations from the original protocol:

1. In the original study protocol we stated that we would use linear mixed models to assess the primary outcome. Based on further statistical advice we changed the analysis to examine the between-group differences in the area under the curve (AUC). These changes were made prior to undertaking the analysis and are documented in the published statistical analysis plan
2. The protocol stated that we would report process data including the length and timing of the Get Healthy Service coaching calls and achievement of participant identified goals. We were unable to report this data as it was not available from the Get Healthy Service provider.
3. The original study protocol stated that we would report subjective body mass index (BMI) at baseline and 26 weeks only. However as detailed in our statistical analysis plan we reported subjective BMI at baseline, 6 weeks and 26 weeks. We reported data for BMI at baseline, 6 weeks and 26 weeks.

Deviations from statistical analysis plan:

1. The statistical analysis plan stated that we would analyse the number of adverse events between groups using a Fishers exact test. This test was chosen as the event rate of adverse events was expected to be low. As numbers were larger than expected a Chi-squared test was used.
2. In the statistical analysis plan a table was provided for the secondary outcomes. The table layout included an ‘overall’ row for each secondary outcome. This row was removed as it was irrelevant given the analyses we undertook.

3. After considering the results we conducted post hoc analyses to further explore intervention adherence. These analyses are explicitly identified as ‘post hoc’ in our manuscript.

Addendum

The Get Healthy Service was unable to provide certain data (i.e. duration of calls, patient goals) which would contribute to an assessment of intervention fidelity and assist in interpretation of the results. Future research of lifestyle interventions should consider inclusion of an audit assessing fidelity of the intervention.

Table S1: Details of adverse events by group

ICD-10 codes	Intervention (n=79)	Control (n=80)
Week 6		
C26 Malignant neoplasm of other and ill-defined digestive organs	0	1
E07 Other disorders of thyroid	0	1
F32 Depressive episode	0	1
G03 Meningitis due to other and unspecified causes	0	1
G47 Sleep disorders	0	2
H81 Disorders of vestibular function	1	1
H83 Other diseases of inner ear	0	1
I51 Complications and ill-defined descriptions of heart disease	0	1
J11 Influenza, virus not identified	2	0
J40 Bronchitis, not specified as acute or chronic	0	2
J45 Asthma	1	0
K57 Diverticular disease of intestine	0	1
K85 Acute pancreatitis	0	1
M06 Other rheumatoid arthritis	1	0
M25 Other joint disorders, not elsewhere classified	5	7
M54 Dorsalgia	5	3
M79 Other soft tissue disorders, not elsewhere classified	1	0
N28 Other disorders of kidney and ureter, not elsewhere classified	0	2
N30 Cystitis	1	0
N39 Other disorders of urinary system	3	0
R19 Other symptoms and signs involving the digestive system and abdomen	1	1
R20 Disturbances of skin sensation	2	2
R52 Pain, not elsewhere classified	1	2
S32 Fracture of lumbar spine and pelvis	0	1
S50 Superficial injury of forearm	0	1
T12 Fracture of lower limb, level unspecified	0	1
W19 Unspecified fall	0	1

Total week 6	24	34
Week 26		
E14 Unspecified diabetes mellitus	1	0
F32 Depressive episode	0	1
G71 Primary disorders of muscles	0	1
H54 Visual impairment including blindness (binocular or monocular)	1	0
I10 Essential (primary) hypertension	0	1
I51 Complications and ill-defined descriptions of heart disease	0	1
I61 Intracerebral haemorrhage	1	0
I80 Phlebitis and thrombophlebitis	1	0
I83 Varicose veins of lower extremities	0	1
J11 Influenza, virus not identified	0	1
K74 Fibrosis and cirrhosis of liver	0	1
M06 Other rheumatoid arthritis	0	2
M25 Other joint disorders, not elsewhere classified	1	7
M54 Dorsalgia	5	8
M79 Other soft tissue disorders, not elsewhere classified	0	3
M99 Biomechanical lesions, not elsewhere classified	0	1
N39 Urinary tract infection, site not specified	1	0
R01 Cardiac murmurs and other cardiac sounds	1	0
R19 Other symptoms and signs involving the digestive system and abdomen	1	1
R20 Disturbances of skin sensation	0	1
S39 Other and unspecified injuries of abdomen, lower back and pelvis	0	1
S86 Injury of muscle and tendon at lower leg level	0	1
Total week 26	13	32

Adverse event; any new medical condition or exacerbation of and old medical conditions during the defined reporting period

Table S2: Descriptions of concomitant healthcare services used for low back pain*

Service category	Time point	Intervention	Control
		n (%)	n (%)
General Practitioner	Baseline	28 (58)	35 (56)
	Week 6	19 (51)	21 (40)
	Week 26	13 (87)	19 (53)
Medical specialist	Baseline	0 (0)	1 (2)
	Week 6	0 (0)	1 (2)
	Week 26	0 (0)	1 (3)
Chiropractor	Baseline	1 (2)	6 (10)
	Week 6	1 (3)	6 (11)
	Week 26	0 (0)	2 (6)
Physiotherapy	Baseline	5 (10)	5 (8)
	Week 6	3 (8)	7 (13)
	Week 26	0 (0)	4 (11)
Dietitian	Baseline	0 (0)	0 (0)
	Week 6	1 (3)	0 (0)
	Week 26	1 (7)	0 (0)
Other allied health	Baseline	1 (2)	1 (2)
	Week 6	1 (3)	0 (0)
	Week 26	0 (0)	2 (6)
Massage therapy	Baseline	2 (4)	1 (2)
	Week 6	2 (5)	4 (8)
	Week 26	0 (0)	0 (0)
Alternative medicine	Baseline	0 (0)	2 (3)
	Week 6	1 (3)	1 (2)
	Week 26	0 (0)	2 (6)
Emergency	Baseline	1 (2)	4 (6)
	Week 6	1 (3)	2 (4)
	Week 26	0 (0)	2 (6)
Hospital admission	Baseline	1 (2)	0 (0)
	Week 6	0 (0)	1 (2)
	Week 26	0 (0)	0 (0)
Spinal injection	Baseline	2 (4)	0 (0)
	Week 6	2 (5)	1 (2)
	Week 26	0 (0)	0 (0)
Imaging	Baseline	3 (6)	1 (2)
	Week 6	2 (5)	0 (0)
	Week 26	0 (0)	0 (0)
Physical activity services	Baseline	0 (0)	0 (0)
	Week 6	1 (3)	2 (4)
	Week 26	1 (7)	1 (3)

Community services	Baseline	0 (0)	1 (2)
	Week 6	0 (0)	1 (2)
	Week 26	0 (0)	0 (0)
Orthopaedic surgeon consultation	Baseline	4 (8)	6 (10)
	Week 6	3 (8)	4 (8)
	Week 26	0 (0)	2 (6)
Pain clinic	Baseline	0 (0)	0 (0)
	Week 6	0 (0)	2 (4)
	Week 26	0 (0)	0 (0)
Other	Baseline	0 (0)	0 (0)
	Week 6	0 (0)	0 (0)
	Week 26	0 (0)	1 (3)

Data are the number of reported health services accessed by participants. Emergency refers to participants who presented to emergency department but were not admitted. Other allied health professional includes Back Fit, osteopath, psychologist, exercise physiologist and diabetes clinic. Alternative medicine refers to Bowen therapy, naturopath and acupuncture. Physical activity services refer to hydrotherapy and aqua aerobics. Community services refer to patient transport and home care. Other refers to Lite n' Easy.

*Sample size at baseline n=159 (79 intervention, 80 control), 6 weeks=132 (60 intervention, 72 control), 26 weeks n=94 (38 intervention, 56 control).

Table S3: Descriptions of concomitant medications used for low back pain*

Service category	Time point	Intervention	Control
		n (%)	n (%)
Paracetamol	Baseline	32 (28)	26 (24)
	Week 6	25 (28)	38 (33)
	Week 26	15 (30)	28 (29)
Paracetamol with opioid	Baseline	21 (18)	13 (12)
	Week 6	14 (16)	8 (7)
	Week 26	4 (8)	6 (6)
Paracetamol with other combinations	Baseline	2 (2)	2 (2)
	Week 6	2 (2)	1 (1)
	Week 26	2 (4)	1 (1)
Anticonvulsant	Baseline	13 (11)	13 (12)
	Week 6	8 (9)	12 (10)
	Week 26	7 (14)	14 (14)
Muscle relaxant	Baseline	1 (1)	5 (5)
	Week 6	0 (0)	2 (2)
	Week 26	0 (0)	2 (2)
NSAID	Baseline	17 (15)	5 (5)
	Week 6	16 (18)	9 (8)
	Week 26	9 (18)	10 (10)
NSAID with opioid	Baseline	6 (5)	7 (6)
	Week 6	8 (9)	8 (7)
	Week 26	1 (2)	4 (4)
Opioid	Baseline	19 (17)	33 (30)
	Week 6	15 (17)	35 (30)
	Week 26	12 (24)	24 (24)
Psychoactive	Baseline	3 (3)	3 (3)
	Week 6	0 (0)	2 (2)
	Week 26	0 (0)	3 (3)
Other	Baseline	1 (1)	2 (2)
	Week 6	0 (0)	1 (1)
	Week 26	0 (0)	6 (6)

Data are the number of reported medications used by participants. NSAID with opioid refers to any NSAID-opioid combination medicine. Paracetamol with opioid refers to any paracetamol-opioid combination. Other refers to Antihypertensive, cholesterol lowering, topical gels and creams, alternative medicines or supplements e.g. glucosamine, calcium channel blocker, herbal medicine (unspecified), folic acid, fish oil, and emu oil.
Abbreviations: NSAID=non-steroidal anti-inflammatory drug.
*Sample size at baseline n=159 (79 intervention, 80 control), 6 weeks=132 (60 intervention, 72 control), 26 weeks n=94 (38 intervention, 56 control).

Table S4: Post hoc analyses of pain intensity

Analysis	Outcome	Intervention mean (95%CI) (n=23)	Control mean (95%CI) (n=80)	Mean difference* (95%CI)	p value
Primary (ITT, MI)	Area under the pain intensity curve (AUC)	154·3 (137·9 to 170·7)	163·4 (153·9 to 172·8)	9·0 (-10·1 to 28·2)	0·35
Secondary	Pain intensity score	**Intervention mean (SD) (n=23)**	**Control mean (SD) (n=80)**	**Mean difference* (95%CI)**	**p value**
	Baseline	6·7 (1·4)	6·8 (1·6)		
	Week 2	6·4 (1·9)	6·4 (1·9)	-0·0 (-0·9 to 0·9)	0·92
	Week 6	6·3 (2·4)	6·2 (2·1)	-0·1 (-1·0 to 0·8)	0·79
	Week 10	5·8 (2·7)	6·4 (2·0)	0·6 (-0·3 to 1·5)	0·21
	Week 14	6·3 (2·2)	6·8 (1·8)	0·5 (-0·4 to 1·4)	0·31
	Week 18	5·9 (2·1)	6·5 (1·8)	0·6 (-0·4 to 1·5)	0·24
	Week 22	5·8 (2·7)	6·2 (2·0)	0·4 (-0·5 to 1·3)	0·44
	Week 26	5·2 (2·9)	6·3 (2·4)	0·9 (-0·0 to 1·9)	0·05
	Monthly trend			0·14 (-0·05 to 0·33)	0·16

Abbreviations: ITT=Intention to treat, MI= Multiple Imputation, AUC= Area under the curve
*Mean difference= control-intervention

Table S5: Post hoc analyses of subjective weight

Outcome	Time point	Intervention (n=23)	Control (n=80)	
		Mean(SD)	**Mean(SD)**	**Mean difference* (95% CI)**
Subjective weight	Baseline	97·7 (17·5)	90·8 (14·6)	
	Week 6	98·6 (17·7)	90·2 (15·0)	-0·9 (-3·1, 1·4)
	Week 26	99·2 (18·4)	93·3 (16·8)	1·1 (-1·4, 3·5)

*Mean difference= control-intervention, adjusted for baseline values

CHAPTER FIVE

Mechanism evaluation of a lifestyle intervention for patients with musculoskeletal pain who are overweight or obese: protocol for a causal mediation analysis

Chapter Five is a published paper:

Lee H, Wiggers J, Kamper SJ, **Williams A**, O'Brien KM, Hodder RK, Wolfenden L, Yoong SL, Campbell E, Haskins R, Robson EK, McAuley JH, Williams, CM: Mechanism evaluation of a lifestyle intervention for patients with musculoskeletal pain who are overweight or obese: protocol for a causal mediation analysis. *BMJ Open.* 2017; 7(6):e014652. doi: 10.1136/bmjopen-2016-014652.

CO-AUTHOR STATEMENT FOR CHAPTER FIVE

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: "Mechanism evaluation of a lifestyle intervention for patients with musculoskeletal pain who are overweight or obese: protocol for a causal mediation analysis," in the following ways:

• Conception and design of the research

• Writing of the manuscript and critical appraisal of content

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BMJ Open

Mechanism evaluation of a lifestyle intervention for patients with musculoskeletal pain who are overweight or obese: protocol for a causal mediation analysis

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ABSTRACT

Introduction Low back pain (LBP) and knee osteoarthritis (OA) are highly prevalent and disabling conditions that cause societal and economic impact worldwide. Two randomised controlled trials (RCTs) will evaluate the effectiveness of a multicomponent lifestyle intervention for patients with LBP and knee OA who are overweight or obese. The key targets of this intervention are to improve physical activity, modify diet and correct pain beliefs. These factors may explain how a lifestyle intervention exerts its effects on key patient-relevant outcomes: pain, disability and quality of life. The aim of this protocol is to describe a planned analysis of a mechanism evaluation for a lifestyle intervention for overweight or obese patients with LBP and knee OA.

Methods and analysis Causal mediation analyses of 2 two-armed RCTs. Both trials are part of a cohort-multiple RCT, embedded in routine health service delivery. In each respective trial, 160 patients with LBP and 120 patients with knee OA waiting for orthopaedic consultation will be randomised to a lifestyle intervention, or to remain part of the original cohort. The intervention consists of education and advice about the benefits of weight loss and physical activity, and the Australian New South Wales Get Healthy Service. All outcome measures including patient characteristics, primary and alternative mediators, outcomes, and potential confounders will be measured at baseline (T0). The primary mediator, weight, will be measured at 6 months post randomisation; alternative mediators including diet, physical activity and pain beliefs will be measured at 6 weeks post randomisation. All outcomes (pain, disability and quality of life) will be measured at 6 months post randomisation. Data will be analysed using causal mediation analysis with sensitivity analyses for sequential ignorability. All mediation models were specified a priori before completing data collection and without prior knowledge about the effectiveness of the intervention.

Ethics and dissemination The study is approved by the Hunter New England Health Human Research Ethics Committee (13/12/11/5.18) and the University of Newcastle Human Research Ethics Committee (H-2015–0043). The results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number ACTRN12615000490572 and ACTRN12615000478516; Pre-results.

Strengths and limitations of this study

- Understanding the underlying causal mechanisms of a lifestyle intervention will explain how the intervention works, or why the intervention failed. These findings will have important clinical and policy implications and could guide implementation strategies.
- We propose to use contemporary methods for causal mediation analysis with sensitivity analyses to evaluate the robustness of the estimated mediation effects to violation of sequential ignorability—a critical assumption required for causal inference in mechanism evaluations.
- The primary mediator (weight) and the outcomes will be captured at the same time point. Thus, it will be challenging to attest the possibility of reverse causation of the mediator–outcome effect.
- Putative mediators including diet and physical activity are measured using self-reported questionnaires.

BACKGROUND

Low back pain (LBP) and knee osteoarthritis (OA) are highly prevalent[1 2] and disabling musculoskeletal conditions[3 4] that cause societal[5–7] and economic[8 9] impact worldwide. The lifetime prevalence of LBP is 84%,[2] and 40%–47% for knee OA.[10] Of all health conditions, LBP is ranked first and OA ranked 11th as contributors to global disability.[4 11] Direct costs for the management of LBP are estimated at $A4.7 billion in Australia (2012),[7] £2.8 billion

in the UK (2013)[12] and US$90 billion in the USA (1998)[8]; and the cost of OA accounts for up to 2.5% of the gross national product in Australia, UK and USA.[9]

A range of risk factors contribute to the development and persistence of LBP and OA. A large proportion of patients with LBP or OA are physically inactive,[13 14] have poor diet[14 15] and are overweight or obese.[16–19] Targeting factors such as diet and physical activity as part of routine management is a plausible strategy to improve outcomes for these patients.[20–22] Two randomised controlled trials (RCTs) will test the effectiveness of a multicomponent lifestyle intervention for patients with LBP[23] and knee OA[24] who are overweight or obese. However, merely evaluating the effectiveness of these interventions is insufficient[25]; it is important to understand the underlying causal mechanisms that explain how the intervention works, or why the intervention doesn't work.[26 27]

Explaining underlying mechanisms

Complex interventions for patients with LBP and knee OA are usually evaluated by their effects on patient-relevant outcomes such as pain, disability and quality of life (QoL).[23 24 26 28 29] However, pragmatic interventions such as a lifestyle intervention do not directly target patient-related outcomes; they target *intermediate* factors (often called mediators), such as diet or physical activity, that are then hypothesised to have a causal effect on patient-relevant outcome(s).[26] Therefore, merely evaluating the effect of the intervention leaves a black-box that conceals the underlying mechanism(s) of the intervention. The aim of a mechanism evaluation is to unpack the black box by decomposing the entire intervention effect into indirect and direct effects. The indirect effect is the effect of the intervention on an outcome that is carried through a selected mediator, and the direct effect is the remaining effect of the intervention that is not explained via the selected mediator. For example, the entire effect of the lifestyle intervention on QoL could be decomposed into an effect carried through changes in diet (indirect effect) and remaining unexplained mechanisms (direct effect).

One way of quantifying causal mechanisms is by conducting causal mediation analysis.[25 27] This approach can produce important information about the underlying mechanisms of an intervention. If the intervention is effective, causal mediation analysis informs whether the hypothesised mechanisms actually occurred.[27] Conversely, if the intervention is ineffective, causal mediation analysis can identify where the hypothesised mechanism breaks down.[27] By using this information, interventions can be refined on the basis of empirical evidence about the underlying mechanism.[26 30] Elements of the intervention that aim to target proposed mediators that do not affect the outcome can be eliminated; and elements that influence a mediator that actually affects outcome can be retained and optimised.

Mechanisms of a lifestyle intervention

Causal mechanisms of lifestyle interventions are unknown. However, there is evidence suggesting that weight loss, inactivity and poor diet are important risk factors that should be considered treatment targets for patients with LBP and OA (ie, mediators). For knee OA, being overweight or obese is a modifiable risk factor.[18 19 31 32] Further, meta-analyses show that weight loss interventions result in moderate improvements in pain and function for overweight or obese patients with knee OA.[33] Similarly for LBP, meta-analyses show significant associations between overweight or obesity and a number of LBP outcomes.[16 34] This suggests that weight might be an appropriate treatment target for both of these conditions to improve patient-related outcomes. It is also apparent that physical activity and diet may play a role in this mechanism for both conditions because of their effects on weight.[14 35–37] Inaccurate beliefs about pain are also associated with poor LBP and OA outcomes.[38 39] Despite evidence for the relationship between weight, physical activity, and pain beliefs and patient-relevant outcomes, these risk factors have not been tested as underlying mechanisms of lifestyle interventions for patients with LBP and knee OA.

To test these underlying mechanisms, we have embedded a priori mechanism evaluations into two RCTs that will test the effectiveness of a lifestyle intervention for patients with LBP[23] and knee OA[24] who are overweight or obese. Our primary hypothesis is that in patients with either LBP or knee OA who are overweight or obese, a lifestyle intervention will have a causal effect on outcomes (pain, disability and QoL) via a primary mechanism through weight. Our secondary hypothesis is that the causal effect of a lifestyle intervention will also be explained via alternative mechanisms including changes in diet, physical activity and pain beliefs.

Objectives

The objective of this study is to test the underling mechanisms of a lifestyle intervention for patients with LBP or OA who are obese or overweight. The specific objectives of this study vary according to whether the lifestyle intervention is effective (unknown at the time of writing this protocol):

- If the intervention is effective, our primary objective is to estimate the extent to which weight mediates this effect. Our secondary objective will be to further refine this mechanism via three serial multiple mediator paths (changes in diet, physical activity and pain beliefs) that then cause changes in weight.
- If the intervention is ineffective, our primary objective is to determine where the causal path breaks down. All potential mediators (weight, diet, physical activity and pain beliefs) will be tested independently.

METHOD

Design

We will conduct a combined causal mediation analysis of 2 two-armed RCTs.[23 24] Both trials are part of a cohort multiple RCT,[40] embedded in routine health service delivery. In both trials, participants are recruited from an existing cohort of patients waiting for orthopaedic consultation; then randomised to receive a lifestyle intervention (intervention group), or to receive usual care by

remaining in the original cohort (control group). The key differences between Williams *et al*[23] and O'Brien *et al*[24] are the clinical populations (LBP[23] and knee OA),[24] and the additional physiotherapy consultations exclusively delivered in the LBP trial.[23] Thus, it is plausible that the two different clinical populations may respond differentially to their respective interventions. To accommodate this hypothesis, we will use moderated causal mediation analysis to estimate trial-specific effects, and averaged effects across both trials. If trial assignment (LBP trial vs OA trial) is a significant moderator, we will interpret trial-specific mediation effects in separation; however, if trial assignment is not a significant moderator, we will interpret the averaged mediation effects across both trials.

The trials began recruiting on 11 May 2015 and we expect to close the trial by June 2017. Data collection is still ongoing and all investigators were blind to group allocation at the time of planning and writing this study protocol. Further details of each trial have been outlined by Williams *et al*[23] (ACTRN12615000478516) and O'Brien *et al*[24] (ACTRN12615000490572).

Participants and recruitment

One RCT involves 120 patients with OA of the knee,[24] and the other, 160 patients with non-specific LBP.[23] Patients in both RCTs are those waiting for outpatient orthopaedic consultation at a tertiary referral public hospital in New South Wales (NSW), Australia.

Randomisation

In both trials, eligible patients from the cohort are randomised to an intervention or control group (1:1 ratio). The randomisation schedule was a priori generated by an independent statistician using the SURVEYSELECT procedure (SAS V.9.3). Allocation is concealed and all outcome assessors, patients and investigators are blind to group allocation. Patients are blind to group allocation by nature of the cohort multiple design. This design offers the intervention and control as part of a routine clinical service, where patients consent to routine data collection. Patients randomised to the intervention group are not aware of the offer of the control arm. Likewise, patients randomised to the control group are not aware of the offer of the intervention arm. Thus, patients are not able to discriminate whether the intervention or control are being offered as part of a clinical trial. This reduces the risk of performance bias (how well the participants engage with the intervention). Service providers delivering the intervention are blind to treatment status as they are not aware that patients were being referred from a clinical trial. The outcome assessors do not have access to the randomisation schedule, thus blind to group allocation. This reduces the risk of detection bias (differential outcome measurement between groups).

Intervention groups

Participants in both RCTs[23 24] will receive advice and education about the benefits of weight loss and physical activity for their conditions by trained interviewers. Participants are then referred to the NSW Get Healthy Information and Coaching Service (GHS; www.gethealthynsw.com.au).[41] The GHS is a free, population-wide, telephone-based health coaching service provided by the NSW Government to support adults in NSW to make sustained healthy lifestyle improvements including diet, physical activity and achieving or maintaining a healthy weight. This service consists of 10 individually tailored coaching calls delivered by university-qualified health coaches, including dieticians, exercise physiologists and psychologists, over a 26-week period. All coaches undergo standardised training before delivering the GHS, thus reducing the potential for differential between coach effects. Coaching is provided on a tapered schedule. Six calls are made in the first 12 weeks to guide, monitor and improve uptake; and four calls are dispersed over the remaining 12 weeks to maintain adherence and avoid relapse.[42] This tapered schedule will be kept consistent across all participants, reducing the potential for bias.

Participants with LBP[23] will receive an additional clinical consultation with the study physiotherapist before beginning the NSW GHS programme. The consultation aims to correct erroneous pain beliefs, highlight the consequences of unhealthy lifestyle factors, and to provide general encouragement and examples of how improving lifestyle factors can influence pain outcomes and QoL. The consultation also involves behaviour change techniques, informed by self-determination theory[43 44] that aims to develop autonomous motivation by increasing perceived competence and self-regulation.[44]

Control groups

Participants allocated to the control group will remain in usual care. The health service does not provide any active management for patients with knee OA or LBP during the orthopaedic consultation waiting period.

Assessment time points

Patient characteristics, outcome measures, primary and alternative mediators, and potential confounders are measured at baseline (T0) prior to randomisation. The primary putative mediator (weight) will be measured 6 months after randomisation. All putative alternative mediators (diet, physical activity and pain beliefs) will be measured 6 weeks after randomisation. Outcomes will be measured 6 months after randomisation. The intervention and assessment time points are outlined in table 1.

Primary outcome measures

Average pain intensity over 7 days will be measured using an 11-point pain Numeric Rating Scale (NRS; 0=no pain, 10=pain as bad as it could be).[45] We will measure self-perceived disability using the 24-item Roland-Morris Disability Questionnaire in patients with LBP[46]; and the Western Ontario and McMaster Universities Osteoarthritis Index[47] in patients with knee OA. We will measure QoL using the Short Form Health Survey V.2.[48]

Table 1 Timing of intervention, mediator and outcome assessments

Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26
Intervention	Initial consult* Six GHS calls							Four GHS calls						
Primary mediator	■													■
Alternative mediators	■			■										
Outcomes	■													■

Primary mediator: weight. Alternative mediators: diet, physical activity and pain beliefs. Outcomes: pain, disability and quality of life.
*Patients with low back pain only.
GHS, New South Wales Get Healthy Service.

Putative mediators

The primary mediator, weight, will be measured to the nearest 0.1 kg by a trained research assistant using the International Society for the Advancement of Kinanthropometry procedures.[49] Physical activity will be measured using the Active Australia Survey,[50] which has moderate reliability (Cohen's kappa=0.52)[51] and good face and criterion validity.[52] Dietary intake will be measured using a Short Food Frequency Questionnaire,[53] which has moderate reliability (weighted kappa range=0.37–0.85)[54 55] and criterion validity.[55] Pain-related attitudes and beliefs will be measured using the Survey of Pain Attitudes Questionnaire.[56] All putative mediators are measured in both control and intervention groups in both trials. These mediators are measured using self-reported questionnaires with known limitations.[57]

Potential confounders

We will control for the following pretreatment confounders: pain duration, baseline pain, disability and QoL. These variables were selected on the basis of their theorised causal relationships with the mediator and outcome variables. We will include baseline measures of the mediators and outcomes in the regression models

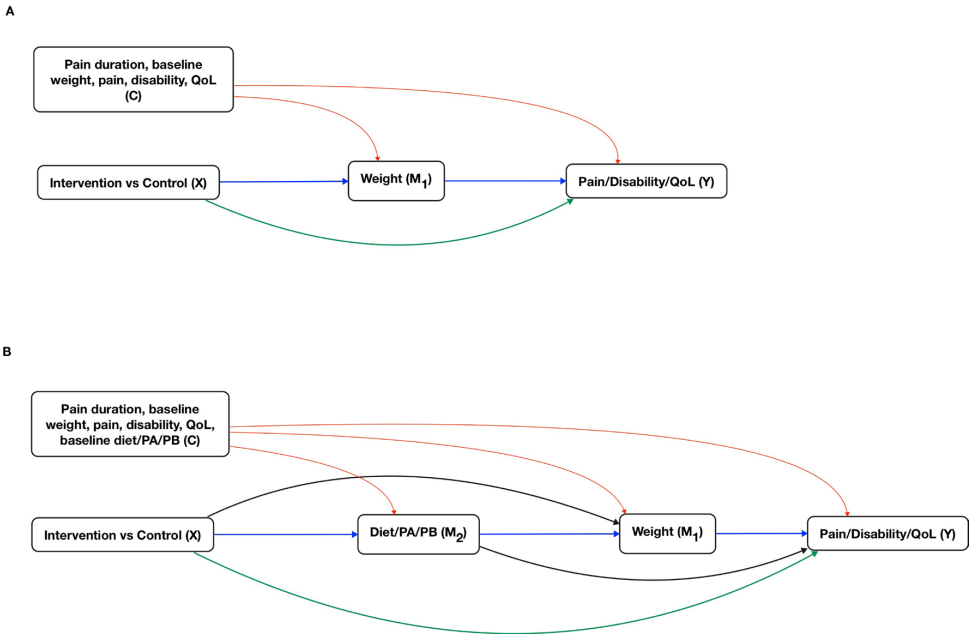

Figure 1 Directed acyclic graphs. Blue lines represent indirect effects (mechanisms) of interest. Green lines represent direct effects (direct effect of treatment on outcome plus all unspecified indirect effects). Red lines represent possible effects that could induce confounding for indirect and direct effects. (A) A single mediator model where the intervention (X) exerts its effect on the outcome(s) (Y), via an indirect path through the primary mediator (M_1), and via a direct path (X to Y). (B) A serial multiple mediator model where the intervention (X) exerts its effect on the outcome (Y), via an indirect path through two mediators—alternative mediator (M_2) and primary mediator (M_1), and via a direct path (X to Y). This model allows for the potential causal relationship from M_2 to M_1. PA, physical activity; PB, pain beliefs; QoL, quality of life.

Table 2 Overview of all mediation models

Model	Treatment (X)	Alternative mediator (M_2) at 6 weeks	Primary mediator (M_1) at 6 months	Outcome (Y) at 6 months
If the total effect of the intervention on the selected outcome is significant:				
1.0	Rx		Weight	Pain/Disability/QoL
If the indirect effect through weight is significant (from model 1.0):				
1.1*	Rx	Diet	Weight	Pain/Disability/QoL
1.2*	Rx	Physical activity	Weight	Pain/Disability/QoL
1.3*	Rx	Pain beliefs	Weight	Pain/Disability/QoL
If the indirect effect through weight is not significant (from model 1.0):				
1.4	Rx	Diet		Pain/Disability/QoL
1.5	Rx	Physical activity		Pain/Disability/QoL
1.6	Rx	Pain beliefs		Pain/Disability/QoL
If the total effect of the intervention on the selected outcome is not significant:				
2.0	Rx		Weight	Pain/Disability/QoL
2.1	Rx	Diet		Pain/Disability/QoL
2.2	Rx	Physical activity		Pain/Disability/QoL
2.3	Rx	Pain beliefs		Pain/Disability/QoL

*Multiple mediator models will only be tested if there is a significant relationship between M_1 and M_2. If the relationship is non-significant, then the alternative mediators will be tested in separate single mediator models with the mediator measured at week 6. Significance levels are set a priori at p<0.05.
QoL, quality of life.

as covariates.[58] Directed acyclic graphs specific to each model are presented in figure 1.

Causal mediation analysis

We plan to construct single and multiple mediator models based on current recommendations for causal mediation analysis.[59–61] The details of each model are illustrated in figure 1 and table 2; and the overall analysis plan is outlined in figure 2.

Justification for primary and alternative mechanisms

Our hypothesised mechanisms are based on theory and evidence. We selected weight at 6-month follow-up as our primary mediator because the key component of the lifestyle intervention was targeted to reduce weight, and because the target population was overweight or obese. Evidence suggests that weight might have direct causal effects on patient-related outcomes (pain, disability and QoL).[15–17 62] The primary mechanism via weight will be tested in a single mediator model (figure 1A).

If we find that the intervention does exert its effect via the primary mechanism (weight), we plan to refine this mechanism to understand how the intervention led to changes in weight (that then affects outcome). Because the intervention includes aspects of lifestyle management (NSW GHS) that aimed to modify diet and increase physical activity, we hypothesise that the intervention will exert its effect on the primary mediator (weight) and outcomes via initial changes in diet and physical activity levels during treatment (captured at week 6). Preliminary evidence supports this hypothesised causal mechanism.[63] Finally, we hypothesise that the intervention may also exert its effect through changes in pain beliefs.[39 64] This is because initial consultations in the LBP trial[23] aimed to reassure patients and reframe erroneous beliefs about pain. Although patients with OA did not receive a clinical consultation that directly targeted pain beliefs, the GHS may have inadvertently changed pain beliefs through the promotion of physical activity. The physical activity component could enable the patients to realise that pain does not need to be a barrier to keeping a physically active lifestyle. This theory is informed by Albert Bandura's techniques of verbal persuasion, modelling and mastery.[65] These refined mechanisms will be tested in serial multiple mediator models (figure 1B).

Sample size

Both trials are sufficiently powered (90%) to detect clinically meaningful between-group changes in pain (1.5-point reduction on NRS) and weight (6% reduction).[23 24] To gain a general appreciation for the required sample size to detect an indirect effect through the primary mediator (weight), we used the sample size estimator for joint indirect effects developed by Vittinghoff and Neilands.[66] With a two-sided alpha of 0.05, exposure-mediator error term correlation coefficient of 0, and mediator-outcome error term correlation coefficient of 0.2, a sample of 71 per group provides 80% power to detect a proportion mediated of 50%, with clinically meaningful treatment-mediator (r=0.5) and

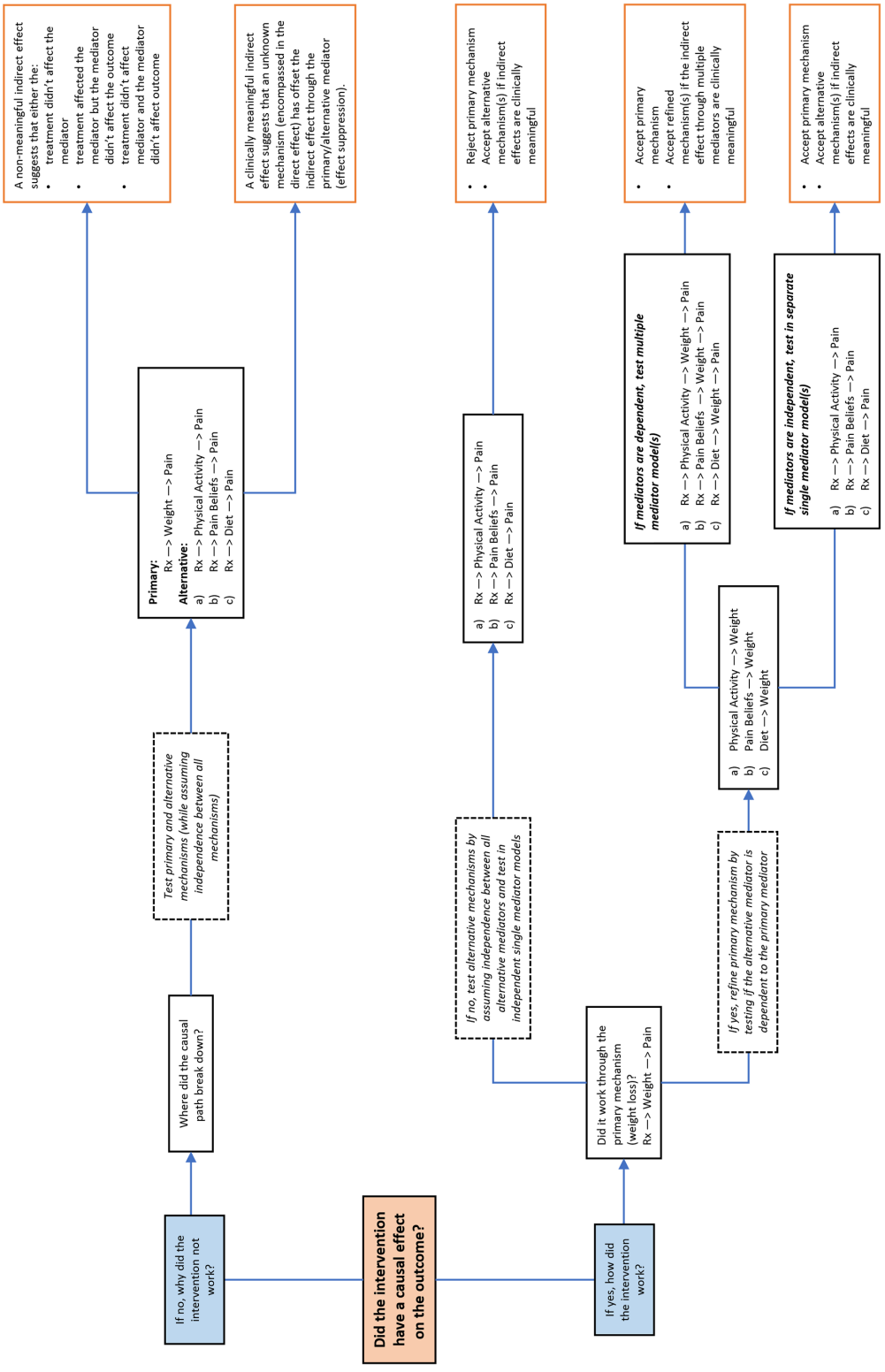

Figure 2 Overall analysis plan. Note: 'pain' is interchangeable with disability and QoL. PA, physical activity; PB, pain beliefs; QoL, quality of life.

mediator-outcome (r=0.3) effects. The sample sizes for both trials were primarily estimated to detect the main effect of the intervention on pain and weight. Therefore, this post hoc power calculation provides indication that both trials would be powered to detect an indirect effect that consists of moderate treatment-mediator and mediator-outcome effects. Moderate effects would be considered clinically meaningful effects based on previous work.[67 68] Sample size estimators for multiple mediator models are currently unavailable.[69] O'Rourke and Mackinnon provide evidence that multiple mediator models have more power than single mediator models.[70] Thus we expect this study to have sufficient power for multiple mediator models.

Methodological considerations

No-confounding assumption (sequential ignorability)

Estimating indirect effects that have causal meaning relies on satisfying the 'no-confounding' assumption, often termed 'sequential ignorability.'[60] It is critical that the treatment-mediator effect and the mediator-outcome effect are not confounded.[25] In mediation analyses of standard RCTs, this assumption only holds for the treatment-mediator and treatment-outcome effects (due to randomisation). However, since the mediators cannot be randomised, this assumption does not hold for the mediator-outcome relationship.[60] There may be unknown or unmeasured confounders that might induce a spurious relationship between the mediator and outcome. Recent advances in causal mediation analysis have developed sensitivity analysis techniques that can estimate the impact of violating this assumption, which we will employ in this study.[71] These methods are an extension of the traditional methods (Baron and Kenny)[72] and reflect contemporary advances in causal mediation analysis.[61]

Alternative mediator as a post-randomisation confounder in multiple mediator models

In mediation analyses, post-randomisation confounders are variables that are affected by the treatment that then simultaneously influence the mediator and outcome. The presence of a post-randomisation confounder effectively induces bias for indirect and direct effects.[73] By construction of the multiple mediator model, an alternative mediator (M_2) is a post-randomisation confounder for the primary mediator-outcome relationship (ie, the alternative mediator that is affected by the treatment might causally affect both the primary mediator and the outcome and induce a spurious relationship). For example, changes in diet caused by the treatment can subsequently have a causal effect on weight and QoL, thereby inducing a spurious relationship between weight and QoL. To overcome this problem, we will assess the dependence between the alternative mediators (diet, physical activity, pain beliefs) and the primary mediator (weight). If an alternative mediator and a primary mediator are significantly correlated, we will build serial multiple mediator models, as recommended by Imai *et al*.[59] If the alternative and primary mediators are not related, then we will not treat the alternative mediator as a post-randomisation confounder, and test the alternative mediators in independent single mediator models.

Data analysis

Analyses will be performed in R (The R Foundation for Statistical Computing) using the mediation package.[74]

Single mediator models

A model-based inference approach will be used to estimate the average causal mediation effect (ACME), average direct effect (ADE) and the average total effect.[74] First, we will fit two regression models: the mediator model and the outcome model. The mediator model is constructed with the treatment status as the independent variable and the mediator as the dependent variable. The outcome model is constructed with the treatment status and the mediator as independent variables, the outcome as the dependent variable, and the set of observed pretreatment confounders as covariates. Continuous mediators and outcomes that are normally distributed will be modelled using linear models (`lm`); but if skewed, they will be modelled using generalised linear models (`glm`) with appropriate family and link functions.[75] The ordinal mediator (diet) will be modelled using the proportional odds logistic model (`polr`).[74]

Because it is plausible that the indirect and direct effect sizes might depend on treatment allocation (treated and non-treated), we will include a treatment-mediator interaction term in the outcome model. We will calculate two separate ACMEs that are conditional on treatment status (x=1 and x=0) and their marginal effects. We will interpret both conditional effects to generalise to their respective treatment group (treated and non-treated) and the marginal effect to generalise to the overall population. Not accounting for small non-significant interaction effects can dramatically influence the indirect and direct effect estimates.[69]

The `mediates` function will use the mediator and outcome models to estimate the potential values of the mediator and outcome. The simulated potential values of the mediator and the outcome will be used to compute the ACME, ADE and average total effects. We will use 1000 bootstrap stimulations to generate 95% CIs. We will interpret the unstandardised point estimate of ACME and its 95% CIs.

Trial assignment (OA trial vs LBP trial) could moderate indirect and direct effects. Therefore, we will test the moderating effect of trial assignment by using the `test.modmed` function. This function directly tests the difference in the ACME and ADE between two levels of the hypothesised moderator (OA trial vs LBP trial). If the ACME and ADE are statistically different, we will analyse the two trials separately to estimate the ACME and ADE that are specific to each trial. However, if they are not different, we will estimate an averaged ACME and ADE across both trials.

A sensitivity analysis will be conducted to determine the robustness of the ACME to the influence of violating the no-confounding assumption (sequential ignorability). The level of confounding due to unknown confounders is represented by the correlation between the residuals (error terms) from the mediator and outcome models, denoted ρ (rho). If ρ=0 (ie, no correlation between residuals), then this can be hypothetically interpreted as no unmeasured confounding. We will use the `medsens` function to explore how varying levels of ρ (between the extremes of −1 and +1) influence the ACME. The output will provide the values of ρ at which the CIs for the ACME include 0 (a non-significant ACME). That is, how strong the effect of unmeasured confounding would need to be to invalidate the estimated ACME.

Multiple mediator models

For multiple mediator models, we will use an expanded mathematical framework.[59] Multiple mediator models will only be constructed if the alternative mediator (diet, physical activity and pain beliefs) and primary mediator (weight) are related.[59] We will use the `multimed` function from the `mediation` package to estimate the ACME and ADE, and the sensitivity parameters. We will use 1000 bootstrap stimulations to generate 95% CIs.

Conclusion

We present an analysis plan for a mechanism evaluation of a lifestyle intervention for patients with knee OA and LBP who are overweight or obese. In the event that the intervention is effective, this investigation will provide evidence for hypothesised causal mechanisms through changes in weight, diet, physical activity and pain beliefs. If the intervention is ineffective it will provide explanations for why the intervention did not work. These results will help refine the intervention and guide implementation strategies.

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CHAPTER SIX

Causal mechanisms of a healthy lifestyle intervention for patients with musculoskeletal pain who are overweight or obese

Chapter Six has been published as a preprint on the bioRxiv server:

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CO-AUTHOR STATEMENT FOR CHAPTER SIX

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: “Causal mechanisms of a healthy lifestyle intervention for patients with musculoskeletal pain who are overweight or obese,” in the following ways:

- Conception and design of the research
- Data collection
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Causal mechanisms of a healthy lifestyle intervention for patients with musculoskeletal pain who are overweight or obese

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Abstract

We assessed the causal mechanisms of a healthy lifestyle intervention for patients with chronic low back pain and knee osteoarthritis (OA), who are overweight or obese. We conducted causal mediation analyses of aggregated data from two RCTs; which included 160 patients with chronic low back pain, and 120 patients with knee OA. Participants were randomised via one central randomisation schedule, to the intervention, or usual care. The intervention consisted of brief advice and referral to a 6-month telephone-based healthy lifestyle coaching service. Participants in the back pain trial were also offered a single physiotherapy consultation. The hypothesised primary mediator was self-reported weight, and alternative mediators were diet, physical activity, and pain beliefs. Outcomes were pain intensity, disability, and quality of life (QoL). Data were analysed using causal mediation analyses with sensitivity analyses for sequential ignorability. All mediation models were specified *a priori*. The intervention had no effect on pain intensity, disability or physical QoL. The intervention significantly improved mental QoL, however, the intervention effect was not channelled via the selected mediators. The intervention did not reduce weight, or the alternative mediators (diet, physical activity, pain beliefs), and these mediators were not associated with the outcomes (with one exception; poor diet was associated with lower mental QoL). The sensitivity analyses showed that our estimates were stable across all possible levels of residual confounding. Our findings show that the intervention did not cause a meaningful change in the hypothesised mediators, and these mediators were not associated with patient outcomes.

Background

Low back pain and knee osteoarthritis (OA) are common musculoskeletal conditions responsible for a significant global burden.[1] In the latest Global Burden of Disease Study (2016), low back pain ranked 1st and OA, for which knee OA is the highest contributor, ranked 12th among all causes of years lived with disability.[1] Consequently, these conditions cause substantial economic strain. For example, the total annual cost to Australian society was estimated at $9.2 billion (2001)[2] for low back pain and $23.1 billion[3] (2008) for OA.

A number of factors potentially affect the course of low back pain and knee OA. Among those commonly reported are lifestyle risk factors and erroneous pain beliefs. For example, meta-analyses have shown that being overweight or obese is associated with the persistence of low back pain[4,5] and is an adverse prognostic factor for knee OA.[6,7] Given their influence on weight gain, lifestyle risk factors such as poor diet and physical inactivity are also likely to indirectly influence the course of low back pain and knee OA, via weight status.[8,9] Independently, physical inactivity is directly associated with the persistence of low back pain[10] and poorer physical function in people with knee OA.[11] In addition, erroneous pain beliefs are known to adversely influence outcomes from low back pain and knee OA resulting in delayed recovery and higher disability.[12,13]

Targeting lifestyle risk factors and erroneous pain beliefs are considered important aspects of treatment programs for managing chronic low back pain and knee OA.[14,15] We conducted two randomised controlled trials (RCTs) of complex interventions targeting weight, diet, physical activity and pain beliefs, aiming to reduce pain intensity in patients with chronic low back pain,[16] and patients with knee OA,[17] who are overweight or obese. Standard analyses of RCTs estimate whether an intervention is effective or not.[18,19] However, these analyses cannot provide explanations for how an intervention works, or why they do not.[20] To do so, causal mediation analysis of RCTs can be used to determine the extent to which a selected treatment target (mediator) channels the effect of the treatment

onto the primary outcome.[20] Such analyses are important to generate evidence to refine interventions, with the aim of improving their effectiveness. For example, treatment components that target effective mediators can be prioritised and strengthened in future iterations of that intervention. Conversely, mediation analyses can also explain why an intervention is ineffective. That is, by determining whether it was the intervention that failed to influence mediators, or whether the mediators were not associated with outcomes, or both.[18,21]

The underlying mechanisms of lifestyle interventions for patients with chronic low back pain and knee OA have rarely been tested.[18] To our knowledge, only one study of a lifestyle intervention in a similar population group has investigated treatment mechanisms. Foy et al. found that in adults with knee pain and diabetes, who were overweight or obese, a reduction in weight mediated the intervention effect on disability.[22] Given the paucity of research, the objective of this study was to test the underlying causal mechanisms of a healthy lifestyle intervention for patients with chronic low back pain or knee OA, who are overweight or obese.

Methods

Study design and participants

We conducted causal mediation analyses on aggregated data from two, two-arm RCTs, both part of a cohort multiple RCT.[23,24] Full details of the methods of each trial are outlined in Williams et al.[16,23] (ACTRN12615000478516) and O'Brien et al.[17,24] (ACTRN12615000490572). Briefly, all patients were recruited from a waiting list for outpatient consultation with an orthopaedic specialist at the John Hunter Hospital, New South Wales (NSW), Australia. One RCT involved 160 patients with chronic non-specific low back pain,[23] and the other, 120 patients with knee OA.[24] All patients across both trials had a body mass index of ≥27kg/m^2 and <40kg/m^2 based on self-reported weight and height. Participants were randomised to both trials via one central randomisation schedule, to receive a healthy lifestyle intervention (intervention group), or remain in the cohort follow up (usual care control group), in a 1:1 ratio. The randomisation schedule was generated *a priori* by an independent investigator using SAS 9.3 through the

SURVEYSELECT procedure. The pre-specified analysis plan for the current study is outlined in Lee et al. 2017.[25]

Intervention

In both trials, participants allocated to the intervention group received brief telephone advice provided by trained telephone interviewers immediately after baseline assessment and randomisation. This advice included information about the potential benefits of weight loss and physical activity for low back pain or knee OA. Participants were then referred to the NSW Get Healthy Service (GHS) (www.gethealthynsw.com.au).[26] The GHS is a free public health telephone-based service provided by the NSW Government to support adults to make sustained lifestyle improvements including diet, physical activity, and achieving or maintaining a healthy weight.[26] All GHS health coaches were trained in evidence-based advice for chronic low back pain and knee OA. This training involved a 2-hour interactive workshop and information resources to guide advice for study participants.

Participants in the chronic low back pain trial were also offered a clinical consultation with the study physiotherapist. The consultation involved a clinical assessment, patient education to correct erroneous pain beliefs and behaviour change techniques to facilitate healthy lifestyle habits and weight management, informed by Self Determination Theory.[27] Although pain beliefs were not directly targeted in the knee OA trial, we hypothesised that promotion of physical activity by the GHS service could change pain beliefs (e.g. that pain does not need to be a barrier to a physically active lifestyle).

Control

Participants allocated to the control group continued on the usual care pathway (i.e. remained on the waiting list to have an orthopaedic consultation and could progress to consultation if scheduled) and took part in data collection during the study period. No other active intervention was provided as part of the study, however; no restrictions were placed upon the use of other health services during the study period. Control participants were informed that a new clinical service would be available in approximately 6 months involving clinical assessment and

support from other services for their back pain or knee OA should they need it. No other details about the new service, or that other patients had started this service were disclosed.

Measures

Mediators

The selected primary mediator was self-reported weight, in kilograms. Alternative mediators were: physical activity measured using the Active Australia Survey,[28] which has moderate reliability (Cohen's Kappa = 0.52)[29] and good face and criterion validity;[30] dietary intake measured using a short food frequency questionnaire,[31] which has moderate reliability (Weighted Kappa range = 0.37 to 0.85)[32,33] and criterion validity;[33] and pain related attitudes and beliefs measured using the Survey of Pain Attitudes One-item Questionnaire, which is strongly associated with the parent questionnaire that has acceptable levels of reliability and validity.[34,35]

Outcomes

The primary outcomes were average self-reported pain intensity over the previous 7-days, measured using an 11-point pain Numeric Rating Scale (0=no pain, 10=worst possible pain);[36] self-reported disability measured using the 24-item Roland-Morris Disability Questionnaire (RMDQ) in participants with chronic low back pain,[37] and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[38] in participants with knee OA; and physical and mental quality of life (QoL) measured using the Short Form Health Survey 12 V.2.[39] All outcomes are widely used and validated measures for these populations.[36–40]

Potential confounders

We identified potential confounders of the mediator-outcome effects based on theorised causal effects on the mediator and outcome variables. The selected confounders were: duration of pain (years since onset), pain intensity, disability and QoL, all measured at baseline.

Data collection

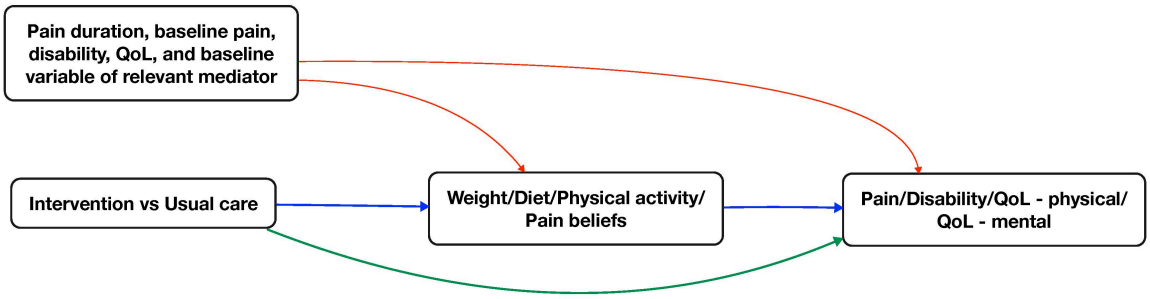
Participant characteristics, primary and alternative mediators, outcomes and potential confounders were measured at baseline prior to random allocation by telephone interview. The primary mediator (self-reported weight) was measured 6 months after randomisation. The alternative mediators (diet, physical activity, pain beliefs) were measured 6 weeks after randomisation. The different timing of the measurement of the primary and alternative mediators was planned *a priori* to facilitate analysis via multiple mediator models (if appropriate), as per the pre-specified analysis plan outlined in Lee et al. 2017.[25] The outcomes (pain intensity, disability, and QoL) were measured 6 months after randomisation. All mediators and outcomes were collected by a questionnaire completed via telephone by trained telephone interviewers blind to group allocation or mailed in the post as per participant preference.

Statistical analysis

We used causal mediation analyses to analyse the data following the pre-specified analysis plan outlined in Figure 2 of Lee et al. 2017.[25] We conducted all analyses in R (The R Foundation for Statistical Computing) using the “mediation” package.[41]

We constructed independent single mediator models for each hypothesised mediator (weight, diet, physical activity and pain beliefs) for each outcome (pain intensity, disability, physical QoL and mental QoL). Directed acyclic graphs for each model are shown in Figure 1.

Figure 1. Directed acyclic graph representing a single mediator model where the intervention exerts its effect on the outcome (i.e. pain intensity/disability/QoL – physical/QoL – mental), via an indirect path (blue lines) through the mediator (i.e. weight/diet/physical activity/pain beliefs) and via a direct path (green line). Red lines represent possible effects that could induce confounding for indirect and direct effects. We assumed independence between all four mediators. Abbreviations: QoL = Quality of Life



We assumed that the intervention-mediator and intervention-outcome paths were not confounded due to random allocation of patients to intervention and control groups. However, as the mediator cannot be randomised, the mediator-outcome path is likely to be confounded. Therefore, we included theorised potential confounders (duration of pain, baseline pain intensity, disability and QoL) in the outcome regression models as covariates.

For each model, we estimated the average total effect (ATE), average causal mediation effect (ACME), average direct effect (ADE), and the proportion mediated. The ACME is the intervention effect on the outcome via the mediator; ADE is the intervention effect that is not channelled via the selected mediator; and ATE is the sum of ACME and ADE (the entire intervention effect). The proportion mediated is the fraction of ATE that is explained by ACME.

For each single mediator model, we fit two regression models: the mediator model and the outcome model. The mediator model was constructed with treatment allocation as the independent variable, and the mediator as the dependent variable. The outcome model was constructed with treatment allocation and the mediator as independent variables, the outcome as the

dependent variable, and baseline measures of the mediator and the set of theorised potential confounders of the mediator-outcome path as covariates.[42] We also included an interaction term (treatment allocation X mediator) in the outcome model to allow for a treatment-mediator interaction effect on the outcome. We used the mediate function to compute ATE, ACME, and ADE.

We planned to present the aggregate data from both trials as per our pre-specified protocol.[25] However, given that there were some differences between the two trials, namely the clinical populations (chronic low back pain and knee OA) and the additional physiotherapy consultation exclusively delivered in the back pain trial, it seemed plausible that effects could have been moderated by trial assignment. To determine whether this was the case, we used moderated causal mediation analysis to estimate both trial-specific effects, and average effects across both trials. We decided to interpret trial-specific effects rather than averaged effects if the ACME and ADE were conditional on trial assignment.

Our mediation models were not protected against residual confounding (i.e. due to unmeasured confounders) of the mediator-outcome path. Therefore, we explored how much residual confounding would explain away the indirect effect, by using sensitivity analyses.[20] The level of residual confounding is represented by the correlation between the residuals (error terms) from the mediator and outcome models, denoted ρ (rho). We used the medsens function to explore how varying levels of ρ (between the extremes of −1 and +1) influenced the ACME. The output provides the value of ρ at which the point estimate and CIs of the ACME includes 0 (no mediating effect). From this, we determined how strong the effect of unmeasured confounding would need to be to invalidate the estimated ACME.

Deviations from the pre-specified analysis plan

We made three deviations from the pre-specified analysis plan. First, the primary mediator, weight, was self-reported rather than objectively measured, this decision was made due to the availability of data. Second, we transformed the diet measure and the physical activity measure, from an ordinal and continuous scale respectively, to a binary scale to benchmark the measures against Australian Guidelines.[43,44] A score of '1' indicates meeting the guidelines (i.e. diet:

2 or more serves of fruit and 5 or more serves of vegetables per day; physical activity: participation in ≥150 minutes of moderate to vigorous physical activity per week) and '0' indicates not meeting these guidelines. Third, we harmonised measures of disability (RMDQ in participants with chronic low back pain,[37] and the WOMAC[38] in participants with knee OA) to facilitate the interpretation of aggregate data from the two trials. We computed standardised scores for disability using the method of Van Cleave et al. 2011.[45] These procedures are described in Text S1 in the supplementary file.

Results

Trial assignment (chronic low back pain vs. knee OA trial) did not moderate the ACME nor ADE for all single mediator models. Thus, we present the aggregate ACME, ADE, and ATE from both trials.

Pain intensity

The intervention had no effect on pain intensity. The intervention did not reduce the primary mediator (weight) and did not improve the alternative mediators (diet, physical activity, and pain beliefs). None of the mediators were associated with pain intensity (Table 1).

Disability

The intervention had no effect on disability. The intervention did not reduce the primary mediator (weight) and did not improve the alternative mediators (diet, physical activity, pain beliefs), and none of the mediators were associated with disability.

Physical QoL

The intervention had no effect on physical QoL. The intervention did not reduce the primary mediator (weight) and did not improve the alternative mediators (diet, physical activity, and pain beliefs), and none of the mediators were associated with physical QoL.

Mental QoL

The intervention significantly improved mental QoL, however, the intervention effect was not channelled via the selected mediators (Table 1). The intervention did not reduce the primary mediator (weight), and weight was not associated with mental QoL. The intervention did not improve the alternative mediators (diet, physical activity, and pain beliefs); and physical activity and pain beliefs were not associated with mental QoL. Diet was negatively associated with mental QoL (i.e. meeting the dietary guidelines for serves of fruits and vegetables per day was associated with poorer mental QoL).

Sensitivity analyses

The sensitivity analyses showed that our estimated ACME's were stable across all possible levels of residual confounding. The sensitivity plots for each model are reported in Figure S1 in the supplementary file.

Multiple mediator models

As per the pre-specified analysis plan,[25] we did not conduct multiple mediator models because the intervention did not reduce weight (primary mediator).

Table 1. Effect decomposition for each single mediator model

Analysis	Intervention-mediator effect (path a)	Mediator-outcome effect (path b)	ATE	ADE	ACME	Proportion mediated (%)
Pain intensity						
Weight	1.50 (-2.82 to 5.81)	0.04 (-0.02 to 0.09)	0.14 (-0.53 to 0.84)	0.11 (-0.54 to 0.81)	0.03 (-0.12 to 0.23)	0.04 (-2.27 to 2.46)
Diet	0.79 (0.50 to 1.25)[a]	0.09 (-1.41 to 1.58)	0.11 (-0.64 to 0.82)	0.10 (-0.65 to 0.82)	0.01 (-0.06 to 0.08)	0.00 (-0.71 to 1.14)
Physical activity	1.11 (0.77 to 1.60)[a]	-0.33 (-1.62 to 0.95)	0.13 (-0.58 to 0.85)	0.12 (-0.58 to 0.84)	0.01 (-0.08 to 0.12)	0.00 (-1.20 to 1.31)
Pain beliefs	0.52 (-0.71 to 1.74)	0.05 (-0.05 to 0.14)	0.13 (-0.62 to 0.84)	0.12 (-0.65 to 0.82)	0.03 (-0.05 to 0.13)	0.01 (-1.30 to 2.18)
Disability						
Weight	1.50 (-2.82 to 5.81)	0.01 (-0.02 to 0.03)	0.12 (-0.14 to 0.37)	0.12 (-0.13 to 0.34)	0.00 (-0.08 to 0.10)	0.03 (-2.23 to 1.85)
Diet	0.79 (0.50 to 1.25)[a]	0.13 (-0.31 to 0.56)	0.13 (-0.10 to 0.37)	0.15 (-0.09 to 0.38)	-0.02 (-0.08 to 0.02)	-0.05 (-2.08 to 1.25)
Physical activity	1.11 (0.77 to 1.60)[a]	0.08 (-0.34 to 0.50)	0.14 (-0.10 to 0.38)	0.14 (-0.10 to 0.37)	0.00 (-0.02 to 0.03)	0.00 (-0.61 to 0.45)
Pain beliefs	0.52 (-0.71 to 1.74)	0.01 (-0.02 to 0.04)	0.13 (-0.10 to 0.35)	0.12 (-0.10 to 0.34)	0.01 (-0.02 to 0.05)	0.03 (-0.84 to 1.01)
QoL - Physical						
Weight	1.50 (-2.82 to 5.81)	-0.18 (-0.40 to 0.04)	-2.05 (-4.75 to 0.54)	-1.88 (-4.45 to 0.60)	-0.16 (-1.15 to 0.59)	0.05 (-0.99 to 0.96)
Diet	0.79 (0.50 to 1.25)[a]	1.45 (-2.99 to 5.90)	-1.24 (-3.78 to 1.30)	-1.22 (-3.79 to 1.35)	-0.02 (-3.79 to 1.35)	0.01 (-1.17 to 1.06)
Physical activity	1.11 (0.77 to 1.60)[a]	2.98 (-1.42 to 7.38)	-1.22 (-3.95 to 1.27)	-1.29 (-4.09 to 1.18)	0.07 (-0.32 to 0.55)	-0.01 (-1.63 to 1.62)
Pain beliefs	0.52 (-0.71 to 1.74)	0.06 (-0.25 to 0.38)	-1.21 (-4.12 to 1.53)	-1.10 (-3.85 to 1.52)	-0.11 (-0.60 to 0.20)	0.05 (-0.92 to 0.84)
QoL - Mental						
Weight	1.50 (-2.82 to 5.81)	-0.11 (-0.39 to 0.17)	3.80 (0.48 to 7.16)*	3.90 (0.70 to 7.02)*	-0.10 (-1.29 to 0.92)	-0.01 (-0.96 to 0.29)
Diet	0.79 (0.50 to 1.25)[a]	-6.40 (-12.06 to -0.74)*	4.73 (1.40 to 8.10)*	4.62 (1.32 to 7.97)*	0.10 (-0.53 to 0.93)	0.03 (-0.16 to 0.29)
Physical activity	1.11 (0.77 to 1.60)[a]	1.78 (-4.01 to 7.58)	4.70 (1.34 to 8.00)*	4.69 (1.31 to 7.96)*	0.01 (-0.37 to 0.40)	0.00 (-0.10 to 0.11)
Pain beliefs	0.52 (-0.71 to 1.74)	-0.23 (-0.64 to 0.18)	4.92 (1.61 to 8.30)*	5.04 (1.71 to 8.36)*	-0.12 (-0.77 to 0.30)	-0.02 (-0.20 to 0.06)

Abbreviations: ATE = average total effect, ADE = average direct effect, ACME = average causal mediation effect, QoL = Quality of Life
Adjusted coefficients (β) with their 95% confidence intervals unless otherwise stated.
[a]Binary model presented as an odds ratio
*p= <0.05

Discussion

Key findings

Our findings showed that the healthy lifestyle intervention did not improve pain intensity, disability or physical QoL in patients with chronic low back pain or knee OA. The intervention did improve mental QoL, however, the intervention effect was not channelled via the selected mediators. The intervention did not cause a meaningful change in the hypothesised primary and alternative mediators, and these mediators were not associated with the selected outcomes.

Previous studies demonstrate that interventions have successfully improved weight, diet, physical activity and pain beliefs in patients with low back pain and knee OA.[46–48] For example, Messier and colleagues report that a 6-month diet and exercise intervention led to a mean weight loss of 8.5kg in participants with knee OA.[48] However, most of these trials evaluated intensive face-to-face consultations and none were delivered using telephone health coaching. This difference in the mode of delivery might explain why our intervention did not exert an effect on the hypothesised mediators, whereas interventions in previous studies did. Although telephone interventions are effective in reducing weight and the behavioural determinants of weight (diet and physical activity) for the general population,[49,50] their effectiveness for patients with chronic low back pain and knee OA have not been established.[51,52] The telephone-based intervention used in our study was not effective in reducing self-reported weight, improving diet or physical activity, or changing erroneous pain beliefs in these patient groups.

Meta-analyses of observational cohort studies suggest that the hypothesised mediators are associated with patient outcomes.[4–6,10,13,53] Although these meta-analyses report adjusted estimates, they did not consider the effects of unmeasured or residual confounding.[54–56] Therefore, it is possible that these estimates were influenced by confounding bias. In our study, the ACME was stable across all possible levels of residual confounding, and we found no association between the majority of the hypothesised mediators and outcomes of pain intensity, disability, and QoL. It is important to note that the lack of association between these mediators and outcomes was not determined by the lack of treatment effect on the mediators. This is because we controlled for a

treatment-mediator interaction effect in the estimation of the mediator-outcome effect.

To our knowledge only one previous study of a lifestyle intervention in a similar population has undertaken causal mediation analyses. Foy et al. found that in adults with knee pain and diabetes who were overweight or obese, reduction in weight explained 98% of the intervention effect on disability.[22] Conversely, we did not detect a mediating effect through weight loss. The difference in results may be because Foy et al. included patients with concomitant diabetes, which could have moderated the indirect effect. Furthermore, Foy et al. used an objective measure of weight, which may have increased the reliability and/or validity, compared to our self-reported measure. Lastly, Foy et al. did not undertake a sensitivity analysis to determine the impact of residual confounding on the mediator-outcome path, thus their estimate of the indirect effect through weight could be confounded.

Other studies suggest that improving lifestyle risk factors or changing pain beliefs positively affects patient outcomes in these patient groups.[51,57,58] However, in the absence of causal mediation analyses, these studies can only assume that the intervention worked through hypothesised treatment targets. Without strong evidence for mediation through these targets, it remains possible that intervention acted via alternative mechanisms. Despite this uncertainty, trials without mediation analyses have informed clinical practice guidelines for chronic low back pain and knee OA. For example, for knee OA, weight loss is strongly recommended.[14] Likewise, for chronic low back pain advice and education to correct erroneous pain beliefs is advised.[15] Such guidelines should be better informed through robust evidence of treatment mechanisms. Collectively, the evidence to date does not convincingly demonstrate that overweight or obesity, poor diet, low levels of physical activity and erroneous pain beliefs are the appropriate mechanisms that should be targeted to improve pain intensity, disability, and QoL in patients with chronic low back pain or knee OA.

Limitations

The hypothesised mediators in this study were measured using self-reported questionnaires. Objective measures may increase the reliability and validity of

the measurement of the hypothesised mediators. The mediators, diet and physical activity, were transformed from an ordinal and continuous scale respectively, to a binary scale to allow interpretation against the existing national guidelines. This may have reduced the responsiveness of these measures. We made three deviations from the published protocol. Although we transparently disclosed these deviations, they could have introduced bias.

Implications for future research

Although clinical guidelines advocate focusing on lifestyle risk factors and erroneous pain beliefs in patients with chronic low back pain or knee OA, there is uncertainty about whether they are causes of pain intensity, disability, and poor QoL. Future RCTs targeting lifestyle risk factors or erroneous pain beliefs in patients with chronic low back pain and knee OA should undertake mediation analyses to understand if the intervention changed the intended targets and if the targets were causally associated with the selected outcomes. To provide more convincing evidence, objective measures should be used when possible and sensitivity analyses assessing the effects of residual confounding should be undertaken.

Clinical implications

Our study found that the healthy lifestyle intervention delivered primarily using the telephone did not change the intended targets of weight, diet, physical activity and pain beliefs. Other studies suggest that a more intensive lifestyle intervention delivered face-to-face might change these targets. Currently, we cannot recommend that a lifestyle intervention delivered by telephone is preferable over face-to-face for patients with chronic low back pain and knee OA. As it remains unclear whether the hypothesised mediators in this study are causes of pain, disability and poor QoL in patients with chronic low back pain or knee OA, it is difficult to provide clinical guidance regarding prioritisation of these mediators. However, targeting these mediators, in particular, the lifestyle risk factors, may offer other health benefits such as improved cardiovascular disease risk,[59] particularly for overweight or obese patients.

Conclusions

This study aimed to test the underlying causal mechanisms of a healthy lifestyle intervention for patients with chronic low back pain or knee OA who are overweight or obese. Our findings show that the intervention did not improve pain intensity, disability and physical QoL in participants with chronic low back pain and knee OA. The intervention did improve mental QoL, however, the intervention effect was not channelled via the selected mediators. The intervention did not cause a meaningful change in the hypothesised mediators, and these mediators were not associated with patient outcomes.

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Supplementary file

Text S1: Procedure for standardization of disability scores

The following steps were followed:

1. Transformation of raw scale scores to 0 – 100

Transformed score= $\frac{actual\ raw\ score - lowest\ possible\ raw\ score}{possible\ raw\ score\ range}\ x\ 100$

2. Calculating standard scores

Standard score= $\frac{X - \bar{X}}{standard\ deviation}$

Figure S1. Sensitivity analysis plots for each single mediator model with pain (1.1), disability (1.2), QoL-physical (1.3), QoL-mental (1.4) as the outcome and weight (A), diet (B), physical activity (C) or pain beliefs (D) as the mediator for the usual care control (left panel) and intervention (right panel), respectively. The correlation between the error terms in the mediator and outcome regression models (ρ) is plotted against the average causal mediation effect (ACME). The estimated ACME (assuming sequential ignorability) is the dashed line and the 95% confidence intervals are represented by the shaded regions.

Figure1.1A

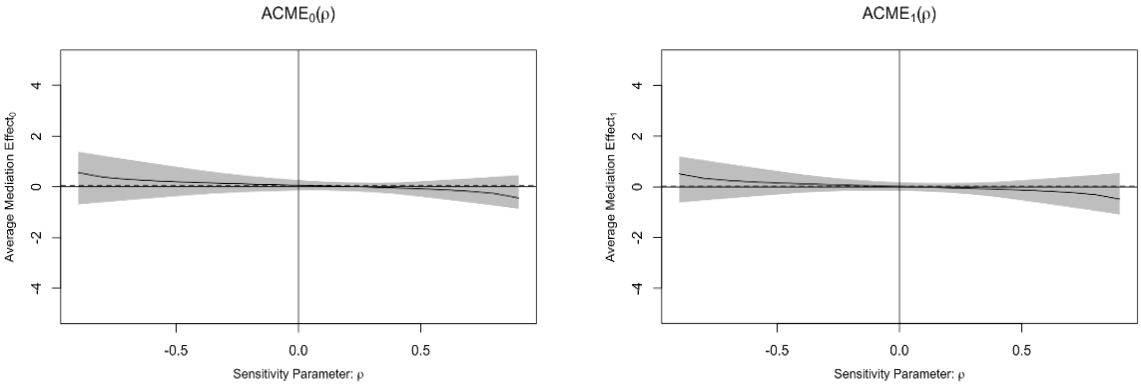


Figure 1.1B

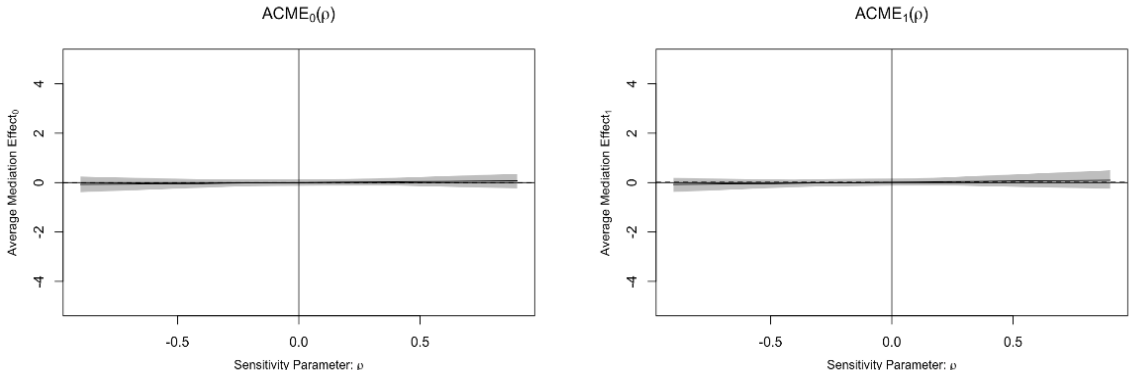


Figure 1.1C

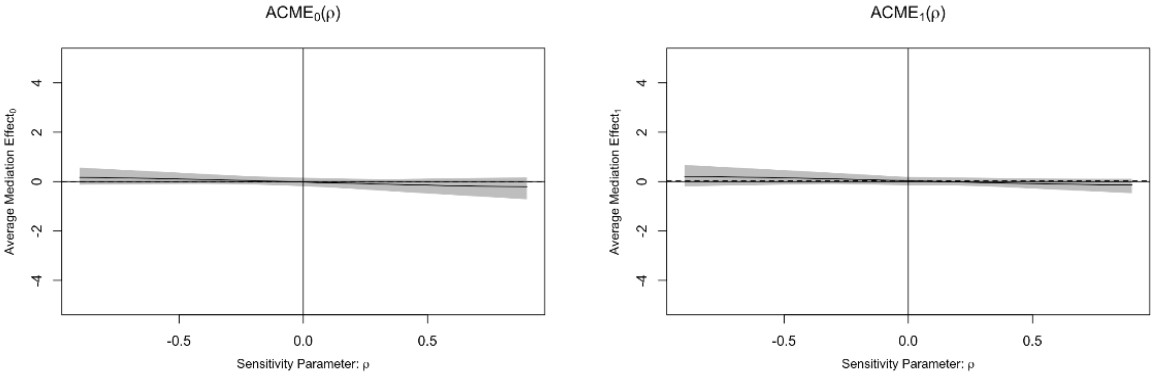


Figure 1.1D

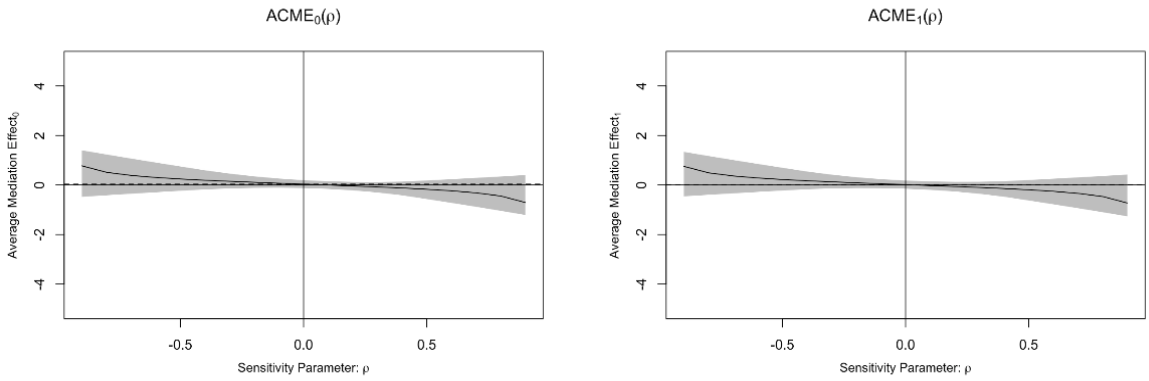


Figure 1.2A

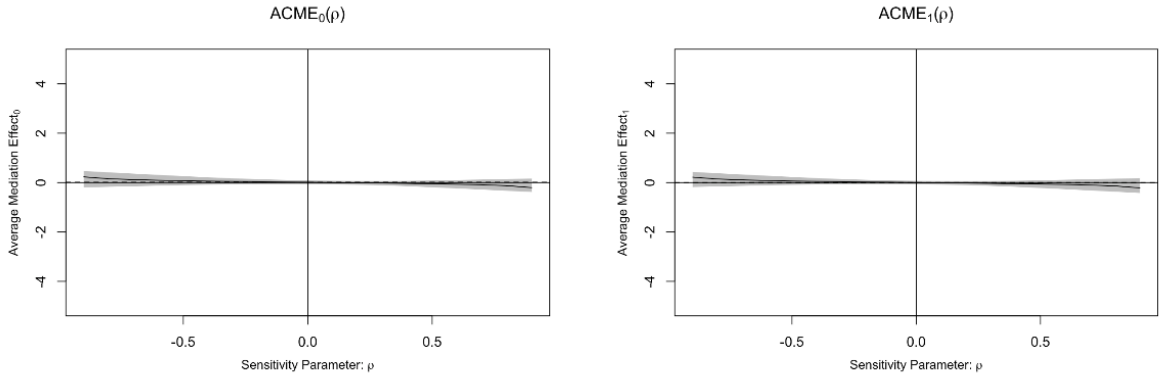
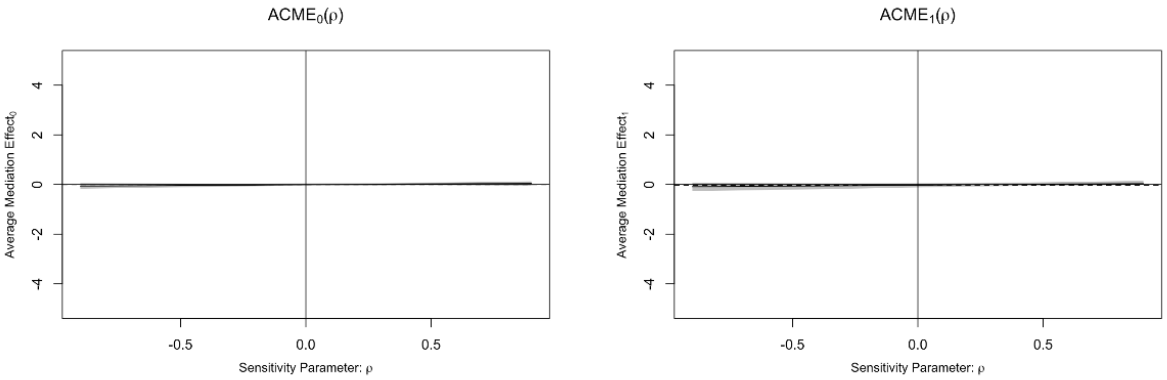


Figure 1.2B



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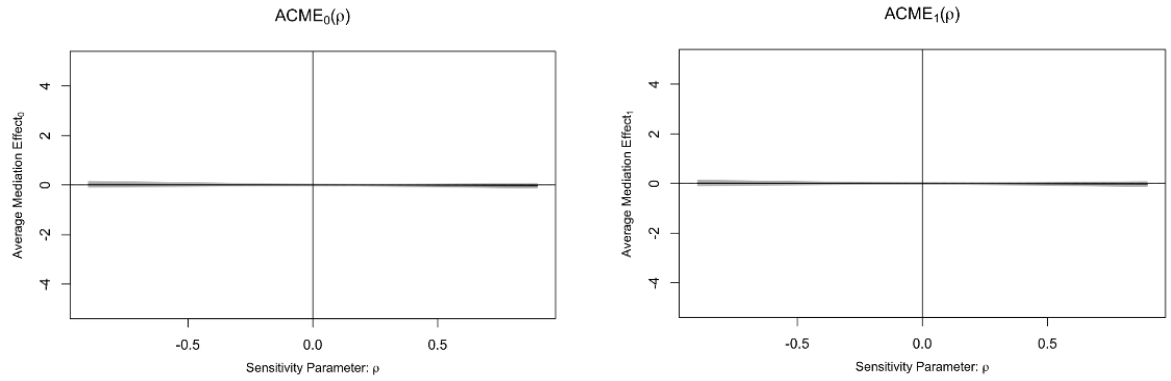

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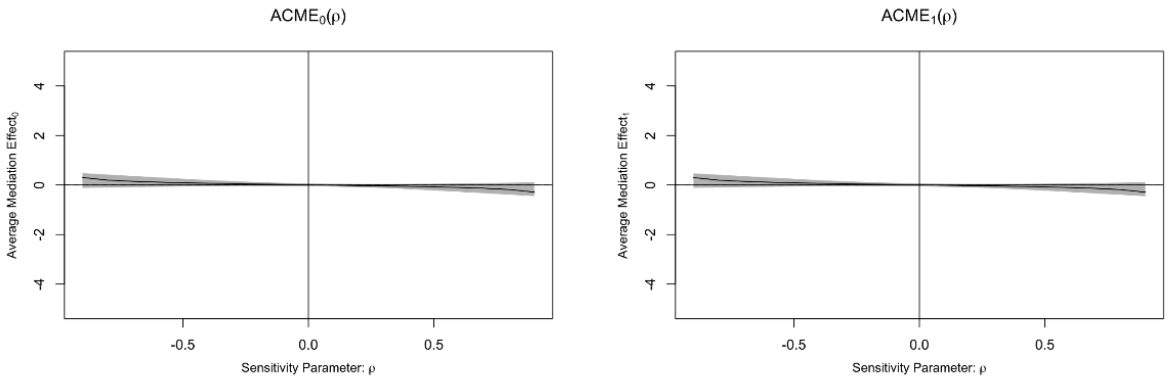

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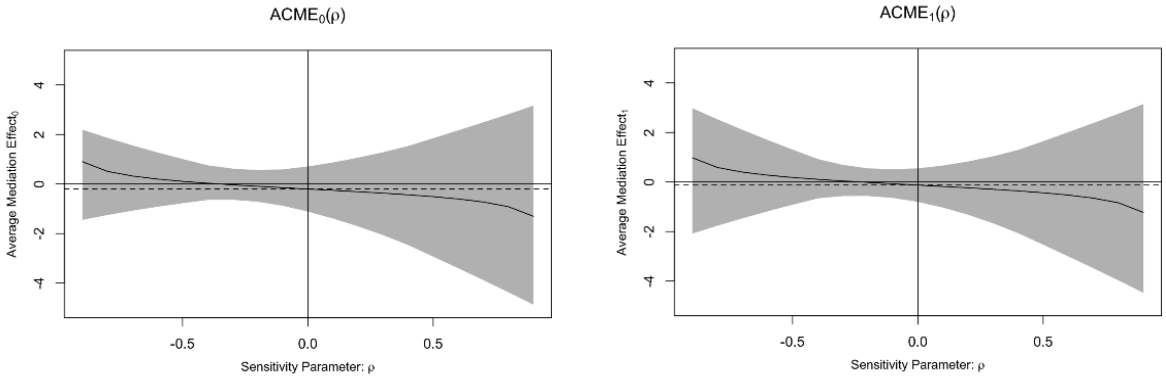

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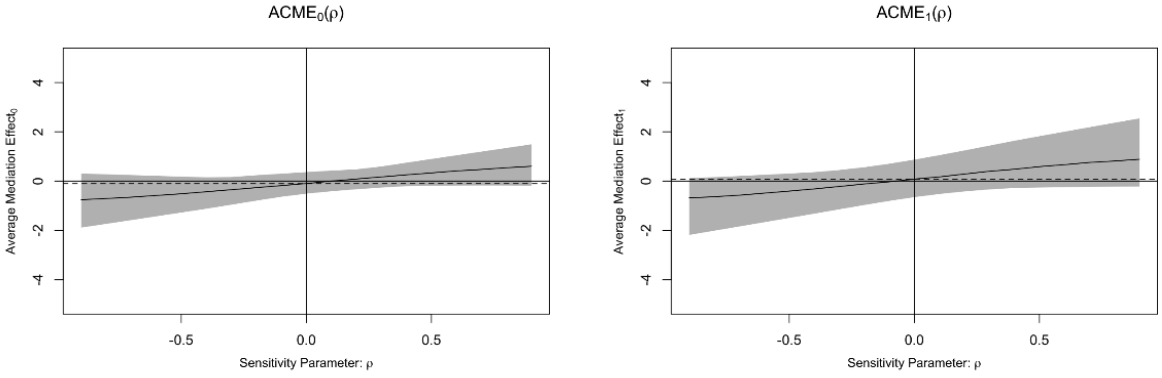

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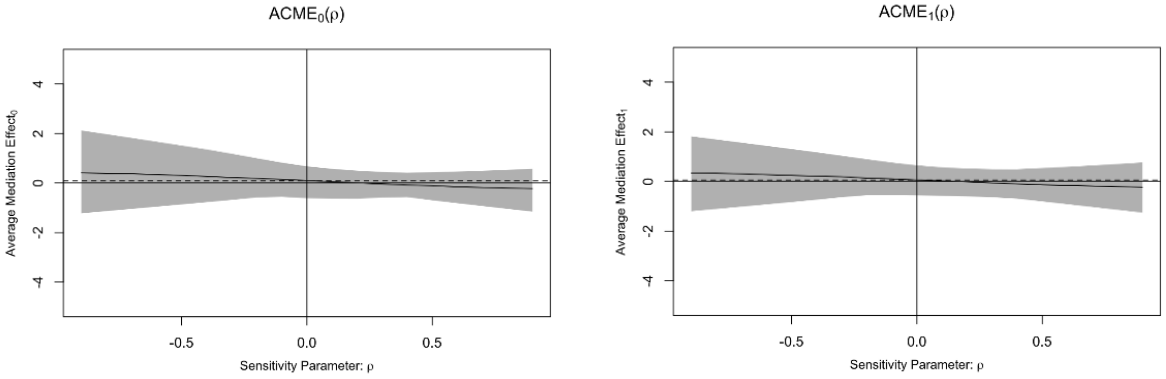

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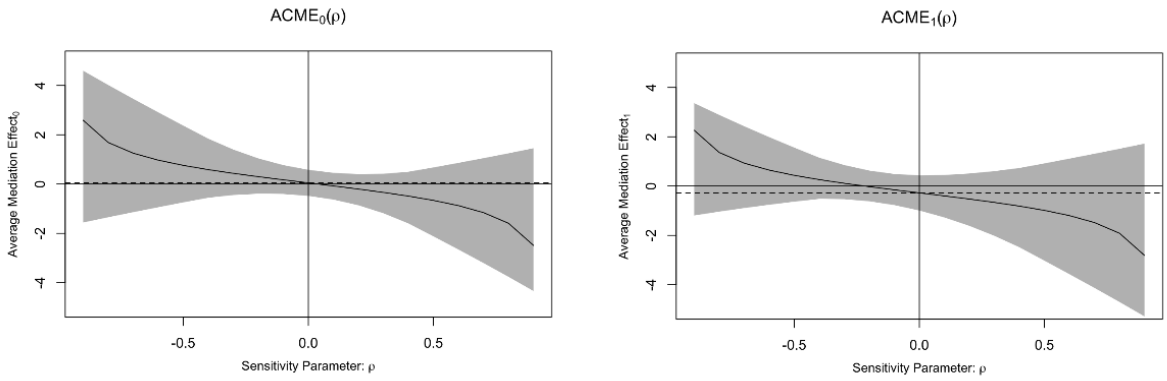

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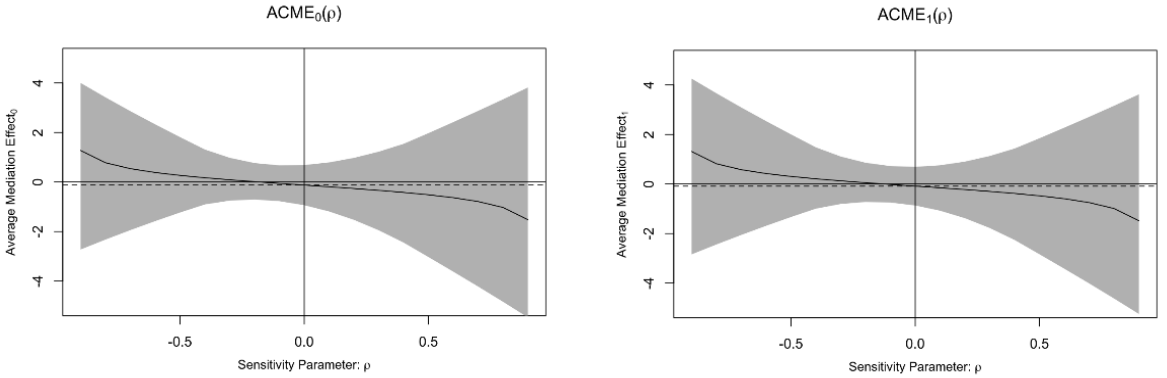

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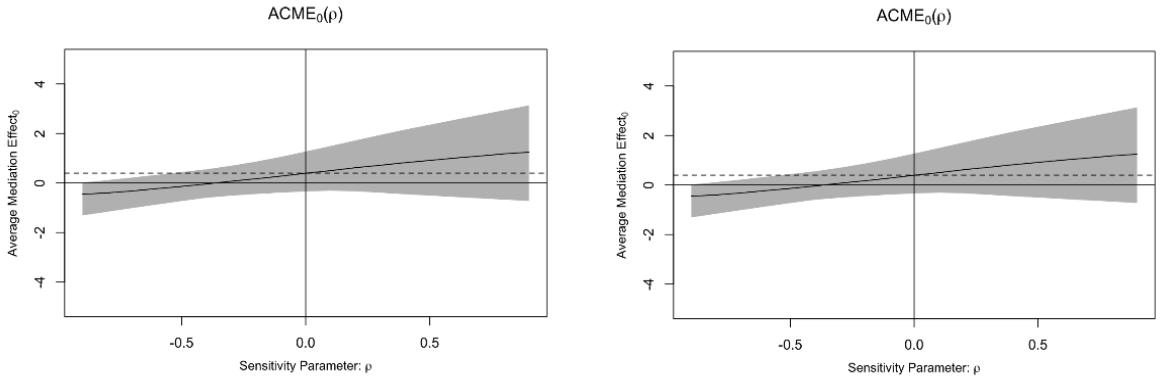

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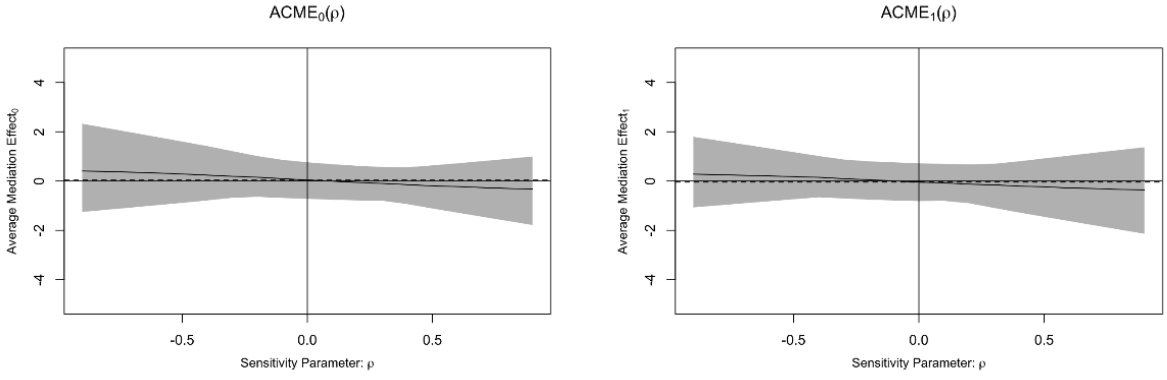

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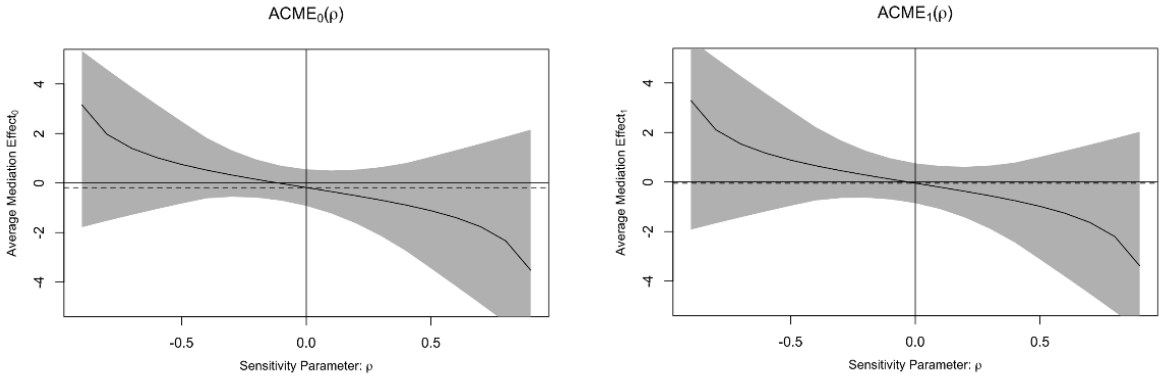
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ACME$_1$(ρ)
Average Mediation Effect$_1$
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2
0
-2
-4
-0.5
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Sensitivity Parameter: ρ

CHAPTER SEVEN

Economic evaluation of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial

Chapter Seven is published as a preprint on the bioRxiv server:
Williams A, van Dongen JM, Kamper SJ, O'Brien KM, Wolfenden L, Yoong SL, Hodder RK, Lee H, Robson EK, Haskins R, Rissel C, Wiggers J, Williams CM: Economic evaluation of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial. bioRxiv [Internet]. 2018. Available from: https://doi.org/10.1101/296285.

Chapter Seven has also been submitted to: *European Journal of Pain*.

CO-AUTHOR STATEMENT FOR CHAPTER SEVEN

I attest that Research Higher Degree candidate **Amanda Williams** contributed to the paper entitled: "Economic evaluation of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial," in the following ways:

- Conception and design of the research
- Data collection
- Analysis and interpretation
- Writing of the manuscript and critical appraisal of content

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Economic evaluation of a healthy lifestyle intervention for chronic low back pain: a randomised controlled trial

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Abstract

We performed an economic evaluation of a healthy lifestyle intervention targeting weight loss, physical activity and diet for patients with chronic low back pain, who are overweight or obese. Eligible patients with chronic low back pain (n=160) were randomised to an intervention or usual care control group. The intervention included brief advice, a clinical consultation and referral to a 6-month telephone-based healthy lifestyle coaching service. The primary outcome was quality-adjusted life years (QALYs). Secondary outcomes were pain intensity, disability, weight, and body mass index. Costs included intervention costs, healthcare utilisation costs and work absenteeism costs. An economic analysis was performed from the societal perspective. Mean total costs were lower in the intervention group than the control group (-$614; 95%CI: -3133 to 255). The intervention group had significantly lower healthcare costs (-$292; 95%CI: -872 to -33), medication costs (-$30; 95%CI: -65 to -4) and absenteeism costs (-$1000; 95%CI: -3573 to -210). For all outcomes, the intervention was on average less expensive and more effective than usual care, and the probability of the intervention being cost-effective compared to usual care was relatively high (i.e. 0.81) at a willingness-to-pay of $0/unit of effect. However, the probability of cost-effectiveness was not as favourable among sensitivity analyses. The healthy lifestyle intervention seems to be cost-effective from the societal perspective. However, variability in the sensitivity analyses indicates caution is needed when interpreting these findings.

Background

Low back pain places a substantial burden on society. Globally, low back pain is ranked first in terms of disability burden, and sixth in overall disease burden.[1] Low back pain is also very costly, total annual costs are estimated at $9.2 billion in Australia,[2] and £11 billion in the United Kingdom,[3] with the largest proportion of these costs attributed to healthcare service use and lost work productivity.[4] Given the economic burden of low back pain, undertaking economic evaluations of low back pain management approaches is important.

Systematic reviews show that the development and persistence of low back pain is linked to 'lifestyle risk factors', such as overweight and obesity.[5] Interventions targeting lifestyle changes including weight loss, increasing physical activity and improving diet, present a novel and promising strategy to improve outcomes (e.g. pain or disability) for patients with low back pain. In response to a lack of research in this area,[6,7] we conducted the first randomised controlled trial (RCT) of a healthy lifestyle intervention for patients with chronic low back pain who are overweight or obese.[8] The intervention involved brief telephone advice, a clinical consultation and referral to a 6-month telephone-based healthy lifestyle coaching service. The primary goal of the intervention was to reduce pain intensity, by reducing weight and improving physical activity and diet behaviours. The purpose of the current study is to undertake an economic evaluation of the healthy lifestyle intervention, compared with usual care.

Economic analyses can be performed from various perspectives including the societal, and healthcare perspectives.[9] The societal perspective includes all costs regardless of who pays. This frequently incorporates direct costs; intervention costs, plus costs of care unrelated to the intervention (i.e. healthcare services and medication costs), and the indirect costs; absence from work and impact on productivity.[9,10] In contrast, the healthcare perspective only includes direct costs i.e. intervention costs and the costs of other care.[9] In this study the primary analysis was conducted from a societal perspective and a secondary analysis was conducted from the healthcare perspective.

Methods

Design

We performed an economic evaluation alongside a two-arm pragmatic parallel group RCT, which was part of a cohort multiple RCT.[11] The study design is described in detail elsewhere.[8,12] The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000478516). Ethical approval was obtained from the Hunter New England Human Research Ethics Committee (approval No. 13/12/11/5.18) and the University of Newcastle Human Research Ethics Committee (approval No. H-2015-0043).

Participants

We invited all patients with chronic low back pain who were on a waiting list for outpatient orthopaedic consultation at the John Hunter Hospital, New South Wales (NSW), Australia, to participate in a cohort study involving telephone assessments. All patients in the cohort were informed that regular surveys were being conducted as part of hospital audit processes and to track patient health while waiting for consultation. During one of the telephone assessments, participants of the cohort study were assessed for eligibility for the RCT. Eligible consenting patients were then randomised to study conditions: i) offered the intervention (intervention group), or ii) remained in the cohort follow-up (usual care control group). Due to the design of the study (i.e. cohort multiple RCT)[11] participants were not aware of alternate study conditions. Participants from either group remained on the waiting list for orthopaedic specialist consultation and could attend a consultation during the study period if scheduled. Participants were also free to access care outside the study as they saw fit.

Participant inclusion criteria for the RCT were: primary complaint of chronic low back pain defined as: pain between the 12th rib and buttock crease with or without leg pain for longer than 3 months;[13] average low back pain intensity ≥3 out of 10 on a 0-10 numerical rating scale (NRS) over the past week, or moderate level of interference to activities of daily living (adaptation of item 8 on SF-36); 18 years or older; overweight or obese (body mass index (BMI) ≥27kg/m^2 and <40kg/m^2) based on self-reported weight and height; and access to a telephone. Exclusion criteria were: known or suspected serious pathology as the cause of back pain, as diagnosed by their general practitioner (e.g. fracture, cancer, infection,

inflammatory arthritis, cauda equina syndrome); previous obesity surgery; currently participating in any prescribed, medically supervised or commercial weight loss program; back surgery in the last 6 months or booked for surgery in the next 6 months; unable to comply with the study protocol that required adaption of meals or exercise due to non-independent living arrangements; any medical or physical impairment precluding safe participation in exercise, such as uncontrolled hypertension; unable to speak and read English sufficiently to complete the study procedures.

Intervention

Participants randomised to the intervention group were offered an intervention involving brief telephone advice, a clinical consultation with a physiotherapist, and referral to a 6-month telephone-based health coaching service.

Immediately after baseline assessment and randomisation, trained telephone interviewers provided the brief telephone advice. This advice included information that a broad range of factors, including lifestyle risk factors contribute to the experience of low back pain, and description of the potential benefits of weight loss and physical activity for reducing low back pain.

The clinical consultation was a face-to-face consultation (up to one hour) conducted in a community health centre with the study physiotherapist, who was not involved in data collection. As detailed in our protocol,[12] the consultation was informed by Self Determination Theory and involved two broad approaches; (i) clinical assessment followed by low back pain education and advice, and (ii) behaviour change techniques.[14]

The telephone-based health coaching service was the NSW Get Healthy Information and Coaching Service (GHS).[15] The service involves 10 individually tailored coaching calls, based on national Healthy Eating and Physical Activity guidelines,[16,17] delivered over 6 months by qualified health professionals.[15] The GHS is a telephone-based service to support individuals to modify eating behaviours, increase physical activity, achieve and maintain a healthy weight, and where appropriate includes referral to smoking cessation services.

Control

Participants randomised to the control group remained on the waiting list for orthopaedic consultation (usual care) and took part in data collection during the study period. No restrictions were placed upon their use of other health services during the study period. Control participants were not aware of the intervention group but were told they would be scheduled a clinical appointment for their back pain in 6 months (i.e. 26 weeks post baseline).

Measures

The primary outcome for this economic evaluation was quality-adjusted life years (QALYs). Secondary outcomes included pain intensity, disability, weight and BMI. We measured costs in terms of intervention costs, healthcare utilisation costs (healthcare service and medication use) and absenteeism costs due to low back pain. For the primary analysis conducted from the societal perspective, all of these cost categories were included. For the secondary analysis conducted from the healthcare perspective, absenteeism costs were excluded.

Outcomes

Health-related quality of life was assessed at baseline, 6 and 26 weeks using the 12-item Short Form Health Survey version 2 (SF-12.v2).[18] The patients' SF-6D health states were translated into utility scores using the British tariff.[19] QALYs were calculated by multiplying patients' utility scores by their time spent in a health state using linear interpolation between measurement points. Back pain intensity was assessed at baseline, 6 and 26 weeks using a 0-10 point NRS. Participants were asked to report the "average pain intensity experienced in their back over the past week", where 0 was 'no pain' and 10 was the 'worst possible pain'.[20] Disability was assessed at baseline, 6 and 26 weeks using the Roland Morris Disability Questionnaire (RMDQ).[21] The RMDQ score ranges from 0 to 24, with higher scores indicating higher disability levels. Self-reported weight (kg) was assessed at baseline, 6 and 26 weeks. BMI was calculated as weight / height squared (kg/m^2)[22] using self-reported weight at baseline, 6 and 26 weeks and self-reported height from baseline.

Cost measures

All costs were converted to Australian dollars 2016 using consumer price indices.[23] Discounting of costs was not necessary due to the 26-week follow-up.[9]

Intervention costs were micro-costed and included the cost to provide the brief advice, estimated from the development and operational costs of the call and the interviewer wages for the estimated average time (5 minutes) taken to provide the brief advice. Intervention costs also included the cost of a one hour clinical physiotherapy appointment, valued using Australian standard costs.[24] Lastly, intervention costs included the cost to provide a health coaching call from the GHS multiplied by the number of calls each patient received.[25] The number of health coaching calls received was reported directly by the GHS.

Healthcare utilisation costs included any healthcare services or medication used for low back pain (other than intervention costs). Healthcare utilisation costs were calculated from a patient reported healthcare utilisation inventory. Participants were asked to recall any health services (the type of services and number of sessions) and medications for their low back pain during the past 6 weeks, at 6 and 26 weeks follow-up. Healthcare services were valued using Australian standard costs and, if unavailable, prices according to professional organisations.[24,26,27] Medication use was valued using unit prices of the Australian Pharmaceutical Benefits Scheme (PBS)[28] and, if unavailable, prices were obtained from Australian online pharmacy websites. The average of the week 6 and week 26 costs per patient was extrapolated, assuming linearity, to estimate the cost over the entire 26-week period.

Absenteeism was assessed by asking patients to report the total number of sickness absence days due to low back pain during the past 6 weeks, at 6 and 26-week follow up. Absenteeism costs were estimated using the Human Capital Approach (HCA),[9] calculated per patient by multiplying their total number of days off by the national average hourly income for their gender and age according to the Australian Bureau of Statistics.[23] Absenteeism costs were extrapolated using the same method as described above for healthcare utilisation.

Statistical analysis

All outcomes and cost measures were analysed under the intention-to-treat principle (i.e. analyses were based on initial group assignment and missing data were imputed). Means and proportions of baseline characteristics were compared between the intervention and control group participants to assess comparability of the groups. Missing data for all outcomes and cost measures were imputed using

multiple imputation by chained equations (MICE), stratified by treatment group.[29] Data were assumed missing at random (MAR). Ten complete datasets needed to be created in order for the loss-of-efficiency to be below the recommended 5%.[29] We analysed each of the 10 imputed datasets separately as specified below. Following this, pooled estimates from all imputed datasets were calculated using Rubin's rules, incorporating both within-imputation variability (i.e., uncertainty about the results from one imputed data set) and between-imputation variability (i.e. uncertainty due to missing information).[29]

We calculated unadjusted mean costs and cost differences between groups for total and disaggregated costs (intervention costs, healthcare utilisation costs (healthcare services, medications used) and absenteeism costs). Seemingly unrelated regression (SUR) analyses were performed to estimate total cost differences (ΔC) and effect differences for all outcomes (ΔE), adjusted for the baseline value of the relevant outcome and potential prognostic factors (baseline pain intensity, time since onset of pain, waiting time for orthopaedic consultation and baseline BMI). An advantage of SUR is that two regression equations (one for ΔC and one ΔE) are modelled simultaneously so that the possible correlation between cost and outcome differences can be accounted for.[30]

We calculated incremental cost-effectiveness ratios (ICERs) for all outcomes by dividing the difference in total costs by the difference in outcomes (ΔC/ΔE). Uncertainty surrounding the ICERs and 95% confidence intervals (95%CIs) around cost differences were estimated using bias corrected and accelerated bootstrapping (5000 replications). Uncertainty of the ICERs were graphically illustrated by plotting bootstrapped incremental cost-effect pairs on cost-effectiveness planes.[9] We produced a summary measure of the joint uncertainty of costs and outcomes (i.e. cost-effectiveness acceptability curves [CEACs]) for all outcomes. CEACs express the probability of the intervention being cost-effective in comparison with usual care at different values of willingness-to-pay (i.e. the maximum amount of money decision-makers are willing to pay per unit of effect).[9] Data were analysed in STATA (v13, Stata Corp).

Sensitivity analyses

We tested the robustness of the primary analysis, through two sensitivity analyses. First, an analysis was performed excluding one patient with very high absenteeism costs (absenteeism costs > $15,000) (SA1). A second sensitivity analysis involved exclusion of intervention participants who did not have reasonable adherence, defined as not attending the clinical consultation and receiving less than 6 GHS health coaching calls (SA2).

Secondary analysis

A secondary analysis was performed from the healthcare perspective (i.e. excluding absenteeism costs).

Results

Participants

One hundred and sixty patients were randomised into the study (Figure 1). Participant characteristics at baseline are reported in Table 1. At 26 weeks, complete outcome data were available for between 65%-75% of participants, depending on the outcome measure, and 59% of participants had complete cost data at 26 weeks. Thus, 26%-35% of effect measure data and 41% of cost data were imputed (Figure 1).

Figure 1. Progress of participants through the study

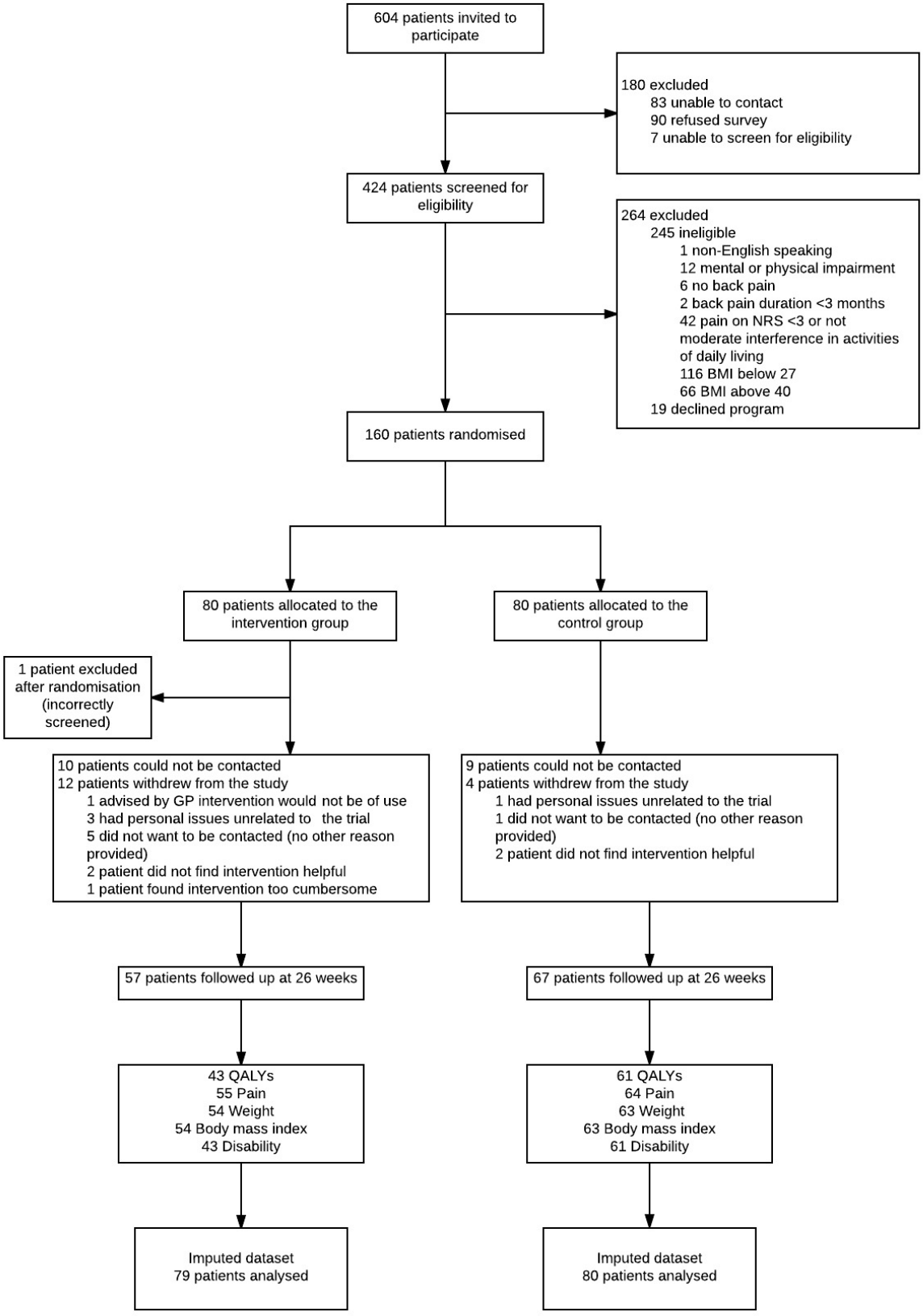


Table 1. Baseline characteristics

Baseline characteristics	Intervention (n=79)	Control (n=80)
Gender (male) (n,%)	31 (39.2)	34 (42.5)
Indigenous status (Aboriginal and/or Torres Strait Islander) (n,%)	7 (8.9)	5 (6.3)
Country of origin (Australia) (n,%)	69 (87.3)	68 (85.0)
Employment (n,%)		
Employed	17 (21.5)	17 (21.3)
Unemployed	15 (19.0)	9 (11.3)
Retired	27 (34.2)	29 (36.3)
Can't work (health reasons)	20 (25.3)	25 (31.3)
Highest level of education (> high school) (n,%)	27 (34.2)	31 (38.8)
Private health insurance (had private health insurance) (n,%)	6 (7.6)	9 (11.3)
Age (yrs) (mean [SD])	56.0 (13.3)	57.4 (13.6)
Height (m) (mean [SD])	1.7 (0.1)	1.7 (0.1)
Pain duration (how long have you been troubled with your pain) (yrs) (mean [SD])	13.0 (11.9)	18.5 (15.7)
Pain intensity (NRS) (mean [SD])	6.7 (1.8)	6.8 (1.6)
Disability score (mean [SD])	14.7 (5.2)	15.8 (5.1)
Weight (kg) (mean [SD])	91.9 (16.5)	90.8 (14.6)
BMI (mean [SD])	32.4 (3.5)	32.1 (3.6)
Utility score (mean [SD])	0.6 (0.1)	0.6 (0.1)

Abbreviations: *yrs* years, *m* metres, *NRS* Numerical Rating Scale, *kg* kilograms, *BMI* Body Mass Index

Outcomes

No differences were found between the intervention and control group participants in QALYs (MD 0.02; 95%CI: -0.00 to 0.04), pain (MD -0.35; 95%CI: -1.33 to 0.64), disability (MD -0.57; 95%CI: -10.41 to 9.27), weight (MD -2.04; 95%CI: -4.22 to 0.14) and BMI (MD -0.67; 95%CI: -1.44 to 0.09) (Table 2).

Table 2. Differences in pooled mean costs and effects (95% Confidence intervals), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes

Analysis	Sample size		Effects	∆C (95% CI)	∆E (95% CI)	ICER	Distribution CE-plane (%)			
	Int	Cont		AUD	Points	AUD/point^	NE[a]	SE[b]	SW[c]	NW[d]
Societal perspective – Primary analysis	79	80	QALYs	-614 (-3094 to 245)	0.02 (-0.00 to 0.04)	-31087	18.7	77.2	2.9	1.2
	79	80	Pain	-614 (-3124 to 243)	-0.35 (-1.33 to 0.64)	1765	15.1	61.2	18.8	4.8
	79	80	Disability	-614 (-3133 to 239)	-0.57 (-10.41 to 9.27)	1087	11.0	41.5	38.5	8.9
	79	80	Weight	-614 (-3132 to 246)	-2.04 (-4.22 to 0.14)	302	19.3	77.6	2.4	0.7
	79	80	BMI	-614 (-3110 to 251)	-0.67 (-1.44 to 0.09)	915	19.3	76.5	3.5	0.7
SA1 – Excluding high absenteeism costs (>$15,000)	79	79	QALYs	-8 (-830 to 499)	0.02 (-0.01 to 0.04)	-432	48.4	46.2	2.5	3.0
	79	79	Pain	-8 (-837 to 502)	-0.32 (-1.30 to 0.67)	25	38.7	35.4	13.1	12.8
	79	79	Disability	-8 (-839 to 504)	-0.32 (-10.23 to 9.59)	25	28.4	22.8	25.4	23.4
	79	79	Weight	-8 (-829 to 504)	-2.01 (-4.20 to 0.17)	4	49.8	47.0	1.6	1.5
	79	79	BMI	-8 (-830 to 500)	-0.67 (-1.43 to 0.10)	12	49.6	46.1	2.2	2.0
SA2 – Excluding non-adherent participants	23	80	QALYs	-74 (-2597 to 793)	0.02 (-0.01 to 0.05)	-3437	47.4	47.0	2.3	3.2
	23	80	Pain	-74 (-2496 to 800)	-0.83 (-2.09 to 0.42)	89	45.0	46.2	3.9	4.9
	23	80	Disability	-74 (-2530 to 787)	-2.92 (-14.24 to 8.39)	25	35.6	34.3	15.4	14.7
	23	80	Weight	-74 (-2561 to 793)	-1.33 (-4.19 to 1.52)	56	42.2	40.9	8.6	8.2
	23	80	BMI	-74 (-2533 to 794)	-0.43 (-1.38 to 0.52)	173	41.1	40.9	9.1	9.0
Healthcare perspective – Secondary analysis	79	80	QALYs	386 (-188 to 688)	0.02 (-0.00 to 0.05)	19036	91.8	4.3	0.2	3.7
	79	80	Pain	386 (-180 to 691)	-0.37 (-1.35 to 0.60)	-1031	74.3	3.7	0.8	21.2
	79	80	Disability	386 (-185 to 687)	-0.88 (-10.78 to 9.03)	-440	53.1	2.7	1.7	42.5
	79	80	Weight	386 (-183 to 690)	-2.10 (-4.23 to 0.10)	-187	92.8	4.3	0.1	2.8
	79	80	BMI	386 (-176 to 687)	-0.68 (-1.44 to 0.08)	-566	91.8	4.3	0.1	3.7

Abbreviations: *Int* Intervention, *Cont* Control, *CI* confidence interval, *C* costs, *E* effects, *ICER* incremental cost-effectiveness ratio, *SA* sensitivity analysis.
Note: costs are expressed in 2016 Australian Dollars
^All ICERs are for a one point increase in the respective effect measure
[a] The northeast quadrant of the CE plane, indicating that the intervention is more effective and more costly than control
[b] The southeast quadrant of the CE plane, indicating that the intervention is more effective and less costly than control
[c] The northwest quadrant of the CE plane, indicating that the intervention is less effective and more costly than control
[d] The southwest quadrant of the CE plane, indicating that the intervention is less effective and less costly than control

Resource use and costs

Of the intervention group patients, 47% (n=37) attended the initial consultation provided by the study physiotherapist and the average number of successful GHS calls was 5.1 (SD 4.5). The mean intervention cost was $708 (SEM 68) per patient. Intervention group participants had significantly lower healthcare costs (-$292; 95%CI: -872 to -33), medication costs (-$30; 95%CI: -65 to -4) and absenteeism costs (-$1000; 95%CI: -3573 to -210) than those of the control group (Table 3). From the societal perspective, the mean total costs were lower in the intervention group than in the control group, however, were not significant (-$614; 95%CI: -3133 to 255) (Table 3). From the healthcare perspective, the mean total costs were higher in the intervention group than in the control group, however, were not significant ($386; 95%CI: -188 to 688) (Table 2).

Table 3. Mean costs per participant in the intervention and control groups, and unadjusted mean cost differences between study groups during the 26-week follow-up period (based on the imputed dataset)

Cost category	Intervention group *n*=79; mean (SEM)	Control group *n*=80; mean (SEM)	Mean cost difference (95 % CI)
Intervention costs	708 (68)	0 (NA)	708 (581 to 850)
Healthcare utilisation			
Healthcare costs	355 (94)	648 (175)	-292 (-872 to -33)
Medication costs	119 (12)	149 (14)	-30 (-65 to -4)
Absenteeism costs	89 (68)	1089 (652)	-1000 (-3573 to -210)
Total	**1272 (135)**	**1886 (683)**	**-614 (-3133 to 255)**

Abbreviations: *n* number, *SEM* standard error of the mean, *CI* confidence interval.
Note: costs are expressed in 2016 Australian Dollars

Societal perspective: cost-utility

The incremental cost-effectiveness ratios (ICER) for QALYs was -31,087 indicating that one QALY gained was associated with a societal cost saving of $31,087 (Table 2), with 77.2% of the cost-effect pairs located in the south-east quadrant, demonstrating that the intervention was on average less costly and more effective than usual care. The cost-effectiveness acceptability curve (CEAC) for QALYs in

Figure 2 (2a) indicates that the probability of the intervention being cost-effective compared with usual care was 0.81 at a willingness-to-pay of $0/QALY, increasing to 0.90 at a willingness-to-pay of $17,000, and reached a maximum of 0.96 at $67,000.

Societal perspective: cost-effectiveness

The ICER for pain intensity was 1,765, indicating that a one point decrease in pain intensity was associated with a societal cost saving of $1,765. ICERs in the same direction were found for disability ($1,087 per one point decrease on the Roland Morris scale), weight ($302 per one kilogram weight loss) and BMI ($915 per one BMI point decrease) (Table 2). In all cases, the majority of incremental cost-effect pairs were located in the southeast quadrant (Table 2, Figure 2 [1b-1e]), indicating that the intervention was on average less expensive and more effective than usual care. CEACs for pain intensity, disability, weight, and BMI are presented in Figure 2 (2b-2e).

For all of these outcomes, the probability of cost-effectiveness was 0.81 at a willingness-to-pay of $0/unit of effect. For pain intensity, the probability of cost-effectiveness reached a maximum of 0.88 at a willingness-to-pay of $1000/unit of effect and after this it gradually decreased to 0.76. For disability, the probability of cost-effectiveness decreased with increasing values of willingness-to-pay. For weight and BMI, the probability of cost-effectiveness reached 0.90 at a willingness-to-pay of $1,000/unit of effect (i.e. -1kg or -1 unit of BMI), and remained above 0.90 irrespective of increasing values of willingness-to-pay.

Societal perspective: sensitivity analyses

The total cost difference between groups was -$8 when we removed one outlier (absenteeism costs > $15,000) from the analysis (SA1), and -$74 when we included only adherent participants (SA2); compared to -$614 in the primary analysis (Table 2).

For QALYs the probability of cost-effectiveness was 0.51 (SA1) and 0.54 (SA2) at a willingness-to-pay of $0/unit of effect. For SA1, the probability of cost-effectiveness increased to 0.90 at a willingness-to-pay of $47,000/QALY, and reached a maximum of 0.92 at a willingness-to-pay of $77,000/QALY. For SA2, the probability of cost-

effectiveness increased to 0.90 at a willingness-to-pay of $72,000/QALY, and reached a maximum of 0.91 at a willingness-to-pay of $86,000/QALY. These values are higher than that of the primary analysis (i.e. a probability of 0.90 at a willingness-to-pay of $17,000/QALY).

For pain intensity, the probability of cost-effectiveness was relatively low (i.e. <0.55) at a willingness-to-pay of $0/unit of effect, however, it did reach 0.90 at a willingness-to-pay of $3000/unit of effect in SA2. For disability, in contrast to the primary analysis, the probability of cost-effectiveness remained relatively low (i.e. 0.50 to 0.70) in both sensitivity analyses, regardless of willingness-to-pay. Conversely, for weight and BMI, similar to the primary analysis, the probability of cost-effectiveness reached 0.80-0.90 in both sensitivity analyses.

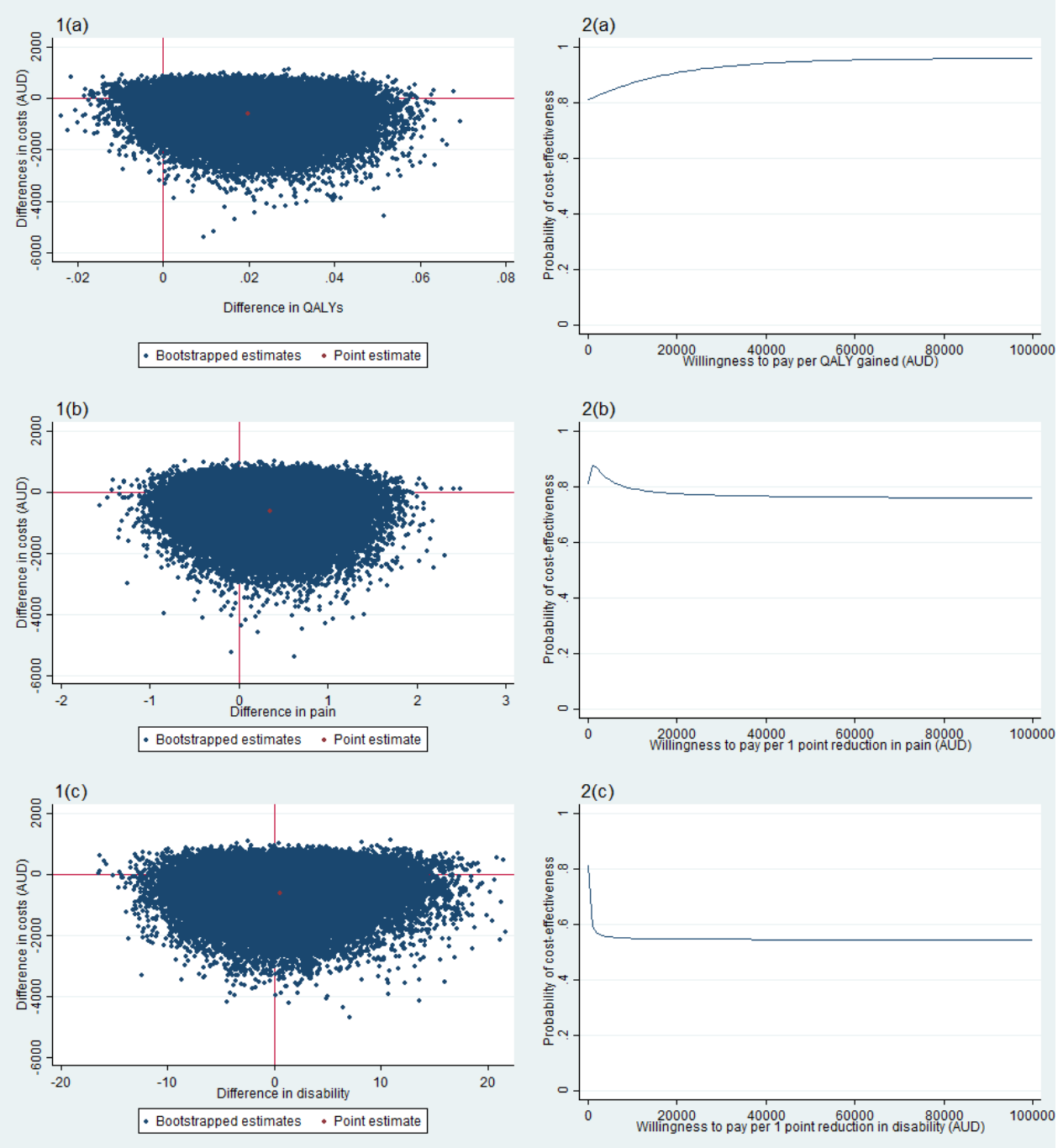
Healthcare perspective: cost-utility

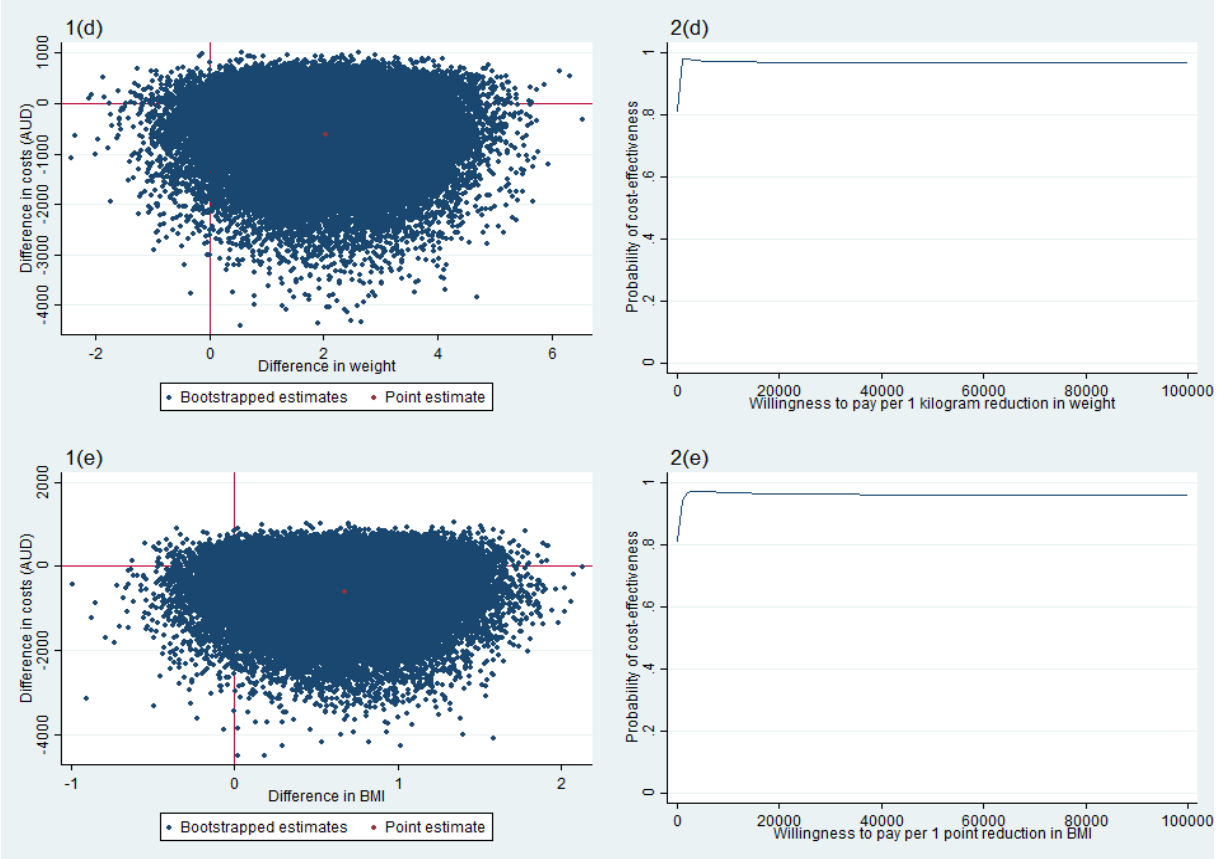
For QALYs the ICER was 19,036 indicating that one QALY gained was associated with a cost to the healthcare system of $19,036 (Table 2) and the probability of cost-effectiveness reached a maximum of 0.90 at a willingness-to-pay of $98,000/QALY.

Healthcare perspective: cost-effectiveness

For pain intensity, the ICER was -1,031, indicating that a one point decrease in pain was associated with a cost of $1,031. ICERs in the same direction were found for disability ($440 per one point decrease on the Roland Morris scale), weight ($187 per one kilogram weight loss) and BMI ($566 per one BMI point decrease) (Table 2). The probability of cost-effectiveness for pain intensity and disability did not reach 0.90 at any value of willingness-to-pay. For pain intensity and disability, the probability of cost effectiveness reached a maximum of 0.77 at $27,000/unit of effect and 0.57 at $8000/unit of effect, respectively. For weight and BMI, the probability of cost-effectiveness was similar to the primary analysis reaching 0.90 at $1000/unit of effect and $3000/unit of effect, respectively.

Figure 2. Cost-effectiveness planes indicating the uncertainty around the incremental cost-effectiveness ratios (1) and cost-effectiveness acceptability curves indicating the probability of the intervention being cost-effective at different values ($AUD) of willingness-to-pay per unit of effect gained (2) for QALYs (a), pain (b), disability (c), weight (d) and BMI (e) (based on the imputed dataset).





Discussion

Key findings

We found that a healthy lifestyle intervention involving brief telephone advice, offer of a clinical consultation involving detailed education, and referral to a 6-month telephone-based healthy lifestyle coaching service was on average less expensive and more effective than usual care from the societal perspective. For QALYs, the intervention had a high probability (0.81) of cost-effectiveness from the societal perspective at a willingness-to-pay of $0/unit of effect, and increased at higher willingness-to-pay thresholds. However, the probability of cost-effectiveness was not as favourable among sensitivity analyses nor from the healthcare perspective.

Interpretation of findings

Results of the cost-utility analysis from the societal perspective suggest that the intervention can be considered cost-effective compared with usual care for QALYs.

From a probability of cost-effectiveness of 0.81 at a willingness-to-pay of $0/QALY, the probability increased to 0.90 at a willingness-to-pay of $17,000/QALY and reached a maximum of 0.96 at $67,000. The intervention had a high probability (>0.93) of cost-effectiveness at the published Australian ($64,000/QALY) and UK willingness-to-pay thresholds ($34,000-51,000/QALY).[31]

Results of the cost-effectiveness analysis from the societal perspective for pain intensity, disability, weight, and BMI appear favourable. However, because society's willingness-to-pay per unit of effect gained has not been reported/determined for these outcomes, decisions regarding cost-effectiveness would depend on the willingness-to-pay of decision-makers and the probability of cost-effectiveness that they perceive acceptable. Nonetheless, for all of these outcomes there were relatively high probabilities of cost-effectiveness (i.e. 0.81) at a willingness-to-pay of $0/unit of effect and for all outcomes excluding disability, the probability of cost-effectiveness increased to 0.88 or 0.90 at a willingness-to-pay of $1000/unit of effect.

The two sensitivity analyses indicate that the findings from the societal perspective should be interpreted with caution for QALYs, pain intensity and disability. For QALYs, the results of SA1 are consistent with the primary analysis as the probability of cost-effectiveness is relatively high (0.90) at a willingness-to-pay of $47,000/QALY, which is considered acceptable according to the Australian and UK willingness-to-pay thresholds. However, for SA2 (i.e. excluding patients without reasonable adherence), the intervention may not be considered cost-effective. The probability of cost-effectiveness was relatively low (<0.55) at a willingness-to-pay of $0/QALY and only reached 0.90 at $72,000/QALY, which is above both the Australian and UK willingness-to-pay thresholds.[31] For pain intensity in SA2 and for disability in both sensitivity analyses, in contrast to the primary analysis the probability of cost-effectiveness was relatively low (i.e. 0.50 to 0.70), regardless of willingness-to-pay.

We also undertook a secondary analysis from the healthcare perspective, this involved considering intervention, healthcare utilisation and medication costs, but not absenteeism costs. From the healthcare perspective, the intervention may be considered cost-effective for QALYs, weight, and BMI depending on the probability of cost-effectiveness that decision-makers perceive as acceptable. However, the

intervention seems not to be cost-effective for pain intensity or disability due to relatively low maximum probabilities of cost-effectiveness (i.e. <0.77).

Comparison with the literature

This study is the first economic evaluation of a healthy lifestyle intervention for patients with chronic low back pain. As such, direct comparisons to similar interventions are limited. Nonetheless, similar to our findings, other conservative approaches appear to be cost-effective relative to usual general practitioner (GP) care.[32,33] Specifically, exercise alone or exercise plus GP care and/or spinal manipulation is cost-effective compared to GP care alone; and cognitive behavioural therapy plus physiotherapy is cost-effective compared to GP care alone.[32,34] However, systematic reviews in this area indicate these results warrant some caution based on overall methodological quality.[32–34] Our study utilises recommended contemporary methods of economic evaluation and provides comprehensive data to guide decisions about healthcare for this patient group.

Strengths

A strength of this study is the pragmatic RCT design, meaning the study was completed under 'real world' conditions. The design is advantageous for decision-makers to use the study's findings to guide decisions about real world healthcare services. Another strength of this study is the use of contemporary methods for cost-effectiveness analyses including SUR and bootstrapping. SUR was used to account for potential correlation between cost and effect data and bootstrapping allowed for estimation of uncertainty around the right skewed cost-effectiveness estimates.

Limitations and directions for future research

A limitation of this study is the amount of incomplete data. The amount of missing outcome data varied between the effect measures however, was at least 25% in all cases. Cost data was missing for 41% of participants after 26-weeks. These levels of missing data are common in economic evaluations of interventions delivered in real-world settings.[35] We used multiple imputation to account for the missing data, which is recommended over complete case analyses, despite this, results from this study should be treated with caution. A further limitation is that costs were self-reported and based on participant recall. This may have introduced recall bias,

although the period over which participants were required to report their resource use was reasonably short (6 weeks). This study was completed over a relatively short follow-up period of 6 months. It is unknown whether the cost-effectiveness estimates from this study would be similar over a longer follow-up period. Assessing the cost-effectiveness of lifestyle interventions for chronic low back patients over the longer term could possibly produce more meaningful insight. Lastly, the study did not include measures of presenteeism, i.e. reduced productivity while at work. As presenteeism is a potentially significant cost of chronic low back pain,[4] further research in this area should include such a measure.[36]

Implications for policy

We found that the intervention group had significantly lower absenteeism and healthcare utilisation costs. These findings suggest that targeting lifestyle risk factors, as part of chronic low back pain management, could result in cost savings from less time off work and reduced healthcare use. Currently, clinical practice guidelines focus on reducing pain and disability, and lifestyle is largely overlooked. Given the global economic burden of chronic low back pain, further recognition of lifestyle as a priority in the treatment of chronic low back pain is warranted. Despite this, inconsistencies among the sensitivity analyses results mean that this interpretation should be treated with caution.

The decision to utilise this healthy lifestyle intervention on the basis of cost-effectiveness, would depend on the priorities of the decision-maker. Such priorities may include the perspective they are interested in (i.e. societal vs. healthcare). To illustrate, for this economic evaluation, analysis from the societal perspective appeared more promising than from the healthcare perspective. Additionally, decision makers would need to determine what they value as an outcome and what they are willing to pay per unit of improvement. Currently, we only know how much society is willing to pay per QALY gained, but this remains unclear for pain intensity, disability, weight, or BMI. Moreover, decision makers would need to consider if they were interested in cost-effectiveness alone or if clinical effectiveness should be considered concurrently and what value is given to each analysis. Once a decision-maker determines what they value as an outcome, the methodological limitations and variability found in the sensitivity analyses should be considered in the decision

to utilise this intervention. Nonetheless, considering the high prevalence of chronic low back pain globally, and limited resources available to support such patients, this study provides decision-makers with valuable information to guide decisions about the utility of available interventions.

Conclusions

We conducted an economic evaluation of a healthy lifestyle intervention involving brief telephone advice, offer of a clinical consultation involving detailed education, and referral to a 6-month telephone-based healthy lifestyle coaching service for patients with chronic low back pain, who are overweight or obese. The intervention seems to be cost-effective for QALYs from the societal perspective but not from the healthcare perspective. Variability found in the sensitivity analyses findings should be considered in the decision to utilise this intervention.

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CHAPTER EIGHT

Thesis implications and future directions

8.1 Overview of findings

In this thesis, I have addressed several evidence gaps regarding the relationship between musculoskeletal conditions and non-communicable chronic diseases, as well as the management of lifestyle risk factors in patients with common musculoskeletal conditions, including chronic low back pain and knee osteoarthritis (OA). Each of the thesis chapters addressed one of these identified evidence gaps. Chapter Two reported a systematic review of the relationship between musculoskeletal conditions and development of non-communicable chronic diseases. The review found that having a musculoskeletal condition may increase the risk of subsequent chronic disease. Chapters Three and Four presented the first high quality randomised controlled trial (RCT) testing whether targeting lifestyle risk factors could improve pain outcomes for patients with chronic low back pain. Chapter Three included an a priori study protocol (Part A) and statistical analysis plan (Part B) for the trial, both important procedures to ensure research transparency and trial quality. Chapter Four presented the results of the trial, which showed that the healthy lifestyle intervention did not reduce pain or disability. Chapter Five detailed an a priori protocol for a mediation analysis of aggregate data from two trials of a healthy lifestyle intervention for patients with chronic low back pain or knee OA, who are overweight or obese. The findings of this analysis (reported in Chapter Six) revealed that, the healthy lifestyle intervention did not change the hypothesised targets (i.e. weight, physical activity, diet and pain beliefs) and those targets were not associated with the outcomes (i.e. pain, disability and quality of life). Chapter Seven reported an economic evaluation of a lifestyle intervention for patients with chronic low back pain which found that the intervention may be cost-effective relative to usual care, from a societal perspective.

The findings of these studies have advanced the evidence-base regarding the links between musculoskeletal conditions and chronic diseases, and the management of lifestyle risk factors in patients with common musculoskeletal conditions. There are several important implications and future directions from these studies.

8.2 Implications of findings

8.2.1 Consideration of people with musculoskeletal conditions in the prevention of chronic diseases

The study in Chapter Two suggested that people with musculoskeletal conditions, as a population group, should be considered in strategies to prevent chronic disease. Specifically, because people with musculoskeletal conditions have a higher risk of developing chronic disease, addressing chronic disease risks in people with musculoskeletal conditions has the potential to support population level chronic disease prevention goals. Despite this, people with musculoskeletal conditions are overlooked as a priority population in chronic disease prevention policies and programs.[1] A better understanding of the relationships between musculoskeletal conditions and chronic diseases is required to assist inclusion of musculoskeletal conditions in the current chronic disease prevention agenda.

To support chronic disease prevention in patients with musculoskeletal conditions, their clinical care should consider an individual's broader health. Although the primary priorities of musculoskeletal treatment are to reduce pain and improve function, the findings of Chapter Two and other studies[2–4] suggest that clinicians managing patients with musculoskeletal conditions should also consider concomitant chronic disease health risks such as excess weight, physical inactivity, smoking and excess alcohol consumption. Implementing strategies to screen for and address these risk factors, for example by referral to relevant services, is a widely practised and accepted preventative care strategy for other conditions and in other settings.[5–7] There is evidence however, that this does not routinely occur as part of current musculoskeletal care.[8] By extending the focus of musculoskeletal care to address these issues, clinicians will increase the likelihood of providing patients with the best possible chance to improve musculoskeletal specific outcomes and their overall health. Further research is warranted to identify effective ways to deliver or integrate risk factor minimisation strategies in the care of patients with musculoskeletal conditions.

8.2.2 Effectiveness and value of lifestyle-focused care for patients with musculoskeletal conditions

One possible barrier to the inclusion of lifestyle risk factor care in the treatment of musculoskeletal conditions is that it is unknown if improving lifestyle risk factors in patients with chronic low back pain improves their musculoskeletal symptoms. The study in Chapter Four showed that a telephone-based model of addressing lifestyle risk factors did not lead to improved patient pain symptoms nor facilitate lifestyle changes. While this study is the first to evaluate the effects of a healthy lifestyle intervention on chronic low back pain, the results are inconsistent with evidence from other pain conditions (e.g. knee OA), which show that lifestyle interventions are effective in improving patient pain and disability.[9] A point of difference is that our trial utilised a generic, non-disease specific population health prevention-focused intervention. It is possible that patients with chronic low back pain may require more intensive and disease specific support to facilitate lifestyle changes. This is because patients with chronic low back pain likely face additional challenges beyond that of the general population that hinder behaviour change.[10] For example, these patients are often fearful that physical activity will make their condition worse.[11] There is also evidence that patients use food to help cope with their pain, as eating certain foods can elicit a chemical response in the brain providing feelings of comfort.[10,12] To understand the true value of lifestyle-focused care for patients with chronic low back pain, and optimise patient engagement in modifying lifestyle risk factors, further research is required to identify how to effectively support patients with chronic low back pain to make lifestyle changes. In particular, research is needed to identify what barriers these patients face to engage in lifestyle services and change their health-related behaviours.

Although clinical practice guidelines recommend that lifestyle risk factors be addressed in the management of musculoskeletal conditions, and there is evidence that doing so for patients with knee OA improves patient symptoms, it remains unclear if lifestyle risk factors are appropriate intervention targets. In previous studies, implicit assumptions have been made - that lifestyle interventions work via improving lifestyle targets (indirect effects). However, without evidence from causal mediation analyses it remains possible that the interventions acted via some other mechanism(s). The mediation study in Chapter Five showed that the proposed mediators (lifestyle risk factors) were not

associated with the intended outcomes (pain, disability and quality of life) in patients with chronic low back pain or knee OA who were overweight or obese. These findings suggest that addressing lifestyle risk factors may not be appropriate targets to improve pain, disability and quality of life in these patients. However, this is based on a single study, further research is needed to support this statement. Only by analysing the mediator – outcome effect can we understand whether (or not) the hypothesised mediators are important targets. To provide accurate recommendations about treatment targets for patients with musculoskeletal conditions, routine use of causal mediation analyses is required.

The study in Chapter Seven showed that a healthy lifestyle intervention for patients with chronic low back pain who are overweight or obese may be cost-effective from the societal perspective, compared to usual care. For QALYs, the cost-utility analysis results revealed that the intervention had a high probability of cost-effectiveness (>0.93) at the published Australian ($64,000/QALY) and UK willingness-to-pay thresholds ($34,000-$51,000/QALY).[13] The results of the cost-effectiveness analyses from the societal perspective for pain intensity, disability, weight, and BMI also were favourable. However, variability in the sensitivity analyses indicates caution is needed when interpreting these findings. The results align with suggestions by others that the clinical effectiveness of a treatment is not a prerequisite for a treatment to be cost-effective.[14] The decision maker will consider clinical and economic evidence concurrently to inform the prioritisation of available healthcare interventions and allocation of resources.[15] In certain situations, decision makers may value cost-effectiveness over that of clinical effectiveness based on the perceived societal gain. For example, an intervention that has large clinical benefits for a specific patient outcome but is costly to implement may be considered less valuable than an intervention that has little clinical benefit for that same outcome, but is cost-effective for QALYs.[15] For these reasons, and others discussed in section 8.3.3, economic evaluations of treatments should be routinely planned and conducted in trials of health interventions.

8.3 Proposed future directions

8.3.1 Relationships between musculoskeletal conditions and other health risks

To improve understanding about the causal relationships between musculoskeletal conditions and other health risks, better use of longitudinal data is needed. Understanding causal links requires assessment of temporal sequencing and adjustment of other possible causes of the outcome (confounding). Much of the current literature in this area uses cross-sectional research designs,[16–19] which do not provide indication about direction of the causal relationships between musculoskeletal conditions and other health risks. For understanding the cause of disease (i.e. onset) RCTs are neither useful because many exposures of interest cannot be randomly allocated. However, the reported longitudinal studies in this area, as reported in Chapter Two, have used analytical methods that do not adequately account for confounding.[19–22] Applying more contemporary analytical methods (e.g. a structural identification approach for selection of confounding variables, instrumental variables) to the analysis of existing longitudinal data sets will enhance understanding of causal relationships. Because existing data sets are likely to contain a limited set of potential confounding variables, primary studies designed to answer specific causal hypotheses would be ideal, but arguably less feasible.

An important step to facilitate better use of longitudinal data is routine use of methods that allow for robust identification and assessment of confounders. Historically, it has been common to select potential confounding variables for such analyses based on statistical criteria or a combination of statistical associations and some background understanding of the causal network.[23] However, as Hernán and colleagues argue, these approaches may lead to bias, resulting in inappropriate adjustment for variables that are not confounders (i.e. mediators) as well as the exclusion of variables that are in fact confounders.[23] Instead, researchers are recommended to use methods that provide more confidence of accurate identification of confounding variables.[23] For example, a structural identification approach uses causal diagrams and subject-matter knowledge to identify confounders of a hypothesised causal relationship.[23] Researchers using this approach explore the impact of various causal structures by performing multiple analyses, and undertake sensitivity analyses to assess the effects of residual and unmeasured confounding.[23] Although these and other contemporary analytical methods (i.e. instrumental variable analysis)[24] can

provide more accurate information about causal questions, understanding how to increase their use is an important next step.

One way to improve the use of contemporary analytical methods in the assessment of longitudinal data, is to revise the existing Strengthening the reporting of observational studies in epidemiology (STROBE) Statement for longitudinal studies. Specifically, guidelines are required to outline methods for studies aiming to answer causal questions versus those aiming to estimate associations for the purpose of prediction, because as Hernán argues these approaches are explicitly different.[25,26] However, researchers often refrain from making this distinction because observational studies cannot unquestionably prove causation.[26] Such a distinction is arguably necessary to improve clarity of casual research questions and reduce errors in data analysis.[26]

Beyond revising the STROBE statement to provide such guidance, monitoring its use and assessing methodological quality of observational research is required. Although research to examine the methodological quality of RCTs is common, observational studies have not been subject to such monitoring and critique. Such actions are essential to improve the quality of observational research by ensuring questions of prediction or cause use appropriate methods and to facilitate appropriate interpretation of the results.

8.3.2 Integrating population health services with clinical care of patients with musculoskeletal conditions

Although there is existing infrastructure of population health services, which provide a scalable model to support clinicians to provide lifestyle-focused care for patients with musculoskeletal conditions, the research described in this thesis found that the provision of a telephone-based chronic disease prevention service, while potentially cost-effective did not improve clinical outcomes. Given the continued investment in these existing population health services, adapting them to better support patients with musculoskeletal conditions, is a more logical next step, than developing new dedicated services. Adaptation is acknowledged within the implementation science framework and could be used to optimise existing services.[27] Adaptation involves: identifying differences between the population that the original service was designed for and the new target population,

determining what changes are required, and testing those changes.[27] Given the high prevalence of musculoskeletal conditions, a dedicated line of research is warranted to support adaptation of existing services to increase their likelihood of benefit for patients with musculoskeletal conditions and concomitant health risks. Two important research directions to support such adaptation are: i) understanding the barriers patients with musculoskeletal conditions may face in making lifestyle changes; and ii) improving the processes to link population health and clinical services.

To date, research to understand the barriers that patients with musculoskeletal conditions face in making lifestyle changes is scarce. Janke and colleagues however, have explored how comorbid chronic pain and obesity can negatively influence weight loss outcomes.[10] They identified several themes including, depression that exacerbates physical symptoms and impedes treatment; hunger prompted by pain, depression and shame; emotional eating and choice of less healthy foods when in pain; and reduced engagement and low self-efficacy for physical activity.[10] Although this research provides some valuable insight, further research is warranted to comprehensively identify barriers to behaviour change specific to patients with musculoskeletal conditions and importantly, how to address them. In addition to identifying barriers before planning a new intervention, the conduct of patient exit interviews following completion of lifestyle interventions is one strategy that could be used to understand the extent to which the intervention met the patients' needs and what barriers were or were not overcome. This information could then be used by existing services to tailor care and optimise support for patients with musculoskeletal conditions.

Establishing better processes to link clinical services to population health services is likely to improve the integration and utility of these services for patients with musculoskeletal conditions. One strategy to improve links between these service sectors is to improve the communication mechanisms between the involved parties, at the time of referral and throughout a program. Electronic referrals and automated processes to guide more efficient referrals are a promising approach.[28,29] However, more is needed to improve both clinician and patient engagement. Notably, the failure of self-management orientated

programs such as population health telephone-based lifestyle coaching services has been attributed to ineffective communication by health care professionals to patients regarding their benefits and function.[30] At a functional level, strategies such as a joint call between the clinician, telephone support coach and the patient, to discuss the patient's condition, concepts of care, and lifestyle-related goals could be used to support information transfer and conceptual change towards a lifestyle focus. Other approaches would be to investigate ways for easier sharing of data about patient progress, barriers and changes to management plans. Technological advances across a range of IT platforms make dedicated research in this area a future direction with huge opportunity. However, navigating ethical and confidentiality concerns with automation or routine data access are an important consideration.

8.3.3 Routinely planning and using available methods beyond standard analyses of treatment effectiveness

Planning and undertaking a RCT to test a particular treatment requires significant resources. Unfortunately, researchers often expend these resources and only plan analyses of treatment effectiveness. To maximise knowledge gained from investment in RCTs, clinical trialists are recommended to routinely undertake additional analyses that can inform future research, clinical policy and practice, such as causal mediation analyses and economic evaluation. These additional analyses can extend knowledge gained from RCTs by informing intervention refinement, appropriate resource allocation and implementation by clinical or policy decision-makers.[14,31,32] However, planning for these analyses should ideally happen at the trial design stage.

Causal mediation analysis can be used to determine how an intervention worked or why it did not work.[31] That is, did the intervention work as hypothesised (i.e. through the intended treatment targets), or did the intervention fail to change the intended treatment targets. Understanding how a complex treatment achieves its outcomes has important implications. Such information enables the prioritisation of intervention components contributing to mediating pathways.[31] In addition, where several treatments produce similar effects on an outcome of interest, through a common set of mediators, decision makers can choose treatments that

are less resource intensive.[31] Finally, in clinical practice, knowledge of treatment targets allows clinicians to tailor their treatments to include multiple strategies that are known to act on those targets. Overall, the information gained from routine use of causal mediation analysis provides a valuable evidence-base to support policy and practice.

The routine conduct of economic evaluations of RCTs is recommended to occur irrespective of the trial findings.[14] However, economic evaluations are often overlooked, particularly if a treatment is not effective. This limitation of existing research practice has two main implications. First, as demonstrated in this thesis, a treatment that is not clinically effective can be cost-effective. Second, because systematic reviews of economic evaluations are used by decision makers to guide their choice between various treatments, when economic evaluations are not conducted for all treatments those reviews are subject to publication bias.

A key future direction is to understand how to influence the conduct of routine mechanism and economic evaluations. Strategies to facilitate this may include understanding clinical trialists' motivation and barriers to undertaking these analyses, and increased guidance and research training regarding methods and interpretation. However, mandatory reporting is most likely to have the greatest influence, for example, inclusion of their requirement in reporting guidelines for journals,[33] mandating their listing in trial registrations and their necessity from governments. An example of the latter is demonstrated by the Australian Government's Health Technology Assessment (HTA) framework. Under this framework, decisions regarding subsidy of health-related services are based on HTAs, which involves assessment of the scientific evidence supporting a particular service including the quality, safety, efficacy, effectiveness and cost-effectiveness. As such, the Australian Government is encouraging comprehensive evaluation of health services to ensure that the health care system is safe, effective and efficient. Mechanism and economic evaluations are important tools that can be used to support such an assessment and facilitate translation of a particular health service in the Australian context.

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