



THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

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

Amanda Jayne Williams

Bachelor of Nutrition and Dietetics (Hons)

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School of Medicine and Public Health

Faculty of Health and Medicine

University of Newcastle

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DECLARATIONS

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Amanda Williams reports no conflict of interest.

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PUBLICATIONS

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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.