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Complete List of Authors:	Lee, Hopin; Hunter Medical Research Institute; University of Newcastle, School of Medicine and Public Health Wiggers, John; Hunter New England Population Health; University of Newcastle, School of Medicine and Public Health Kamper, Steve; The George Institute for Global Health, University of Sydney, Musculoskeletal Division Williams, Amanda; Hunter New England Population Health; University of Newcastle, School of Medicine and Public Health O'Brien, Kate; Hunter New England Population Health; University of Newcastle, School of Medicine and Public Health Hodder, Rebecca; Hunter New England Population Health; University of Newcastle, School of Medicine and Public Health Wolfenden, Luke; Hunter New England Population Health; Hunter Medical Research Institute Yoong, Sze Lin; Hunter New England Population Health; University of Newcastle, School of Medicine and Public Health Campbell, Elizabeth; Hunter New England Population Health Haskins, Robin; John Hunter Hospital, Ambulatory Care Centre McAuley, James; Neuroscience Research Australia, University of New South Wales Williams, Christopher; Hunter Medical Research Institute; University of Newcastle, School of Medicine and Public Health
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Mechanism evaluation of a lifestyle behavioural intervention for patients with musculoskeletal pain who are overweight or obese. Protocol for a Causal Mediation Analysis

Hopin Lee[1,2], John Wiggers[2,3], Steven J. Kamper[4], Amanda Williams[2,3], Kate M. O'Brien[2,3], Rebecca K. Hodder[2,3], Luke Wolfenden[1,3], Sze Lin Yoong[2,3], Elizabeth Campbell[3], Robin Haskins[5], James H. McAuley[6], Christopher, M. Williams[1,2]

1. Hunter Medical Research Institute, Newcastle, NSW, Australia
2. School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia
3. Hunter New England Population Health, Wallsend, NSW, Australia
4. The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia
5. Ambulatory Care Centre, John Hunter Hospital, Hunter New England Local Health District, Newcastle, NSW, Australia.
6. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia

Corresponding Author: Hopin Lee, Hunter Medical Research Institute, Newcastle, NSW, Australia. Email: hopinlee@gmail.com

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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 multi-component lifestyle behavioural intervention for patients with LBP and knee OA who are overweight or obese. The key targets of the behavioural lifestyle intervention are to improve physical activity, modify diet, and correct pain beliefs. These factors may explain how a lifestyle behavioural 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 for a mechanism evaluation for a lifestyle behavioural intervention for patients with LBP and knee OA.

Methods and analysis: Causal mediation analyses of two, two-arm 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 behavioural 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 Information and Coaching Service. All outcome measures including patient characteristics, primary and alternative mediators, outcomes, and potential confounders will be measured at baseline (T0) prior to randomisation. The primary mediator: weight, will be measured at 6 months' post-randomisation; alternative mediators including diet, physical activity, and pain beliefs will be measured 6 weeks' post-randomisation. All outcomes will be measured 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 & ACTRN12615000478516

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This protocol describes a mechanism evaluation of a lifestyle behavioural intervention for patients with knee osteoarthritis and low back pain who are waiting for orthopaedic consultation.

- Understanding the underlying causal mechanisms of a complex lifestyle behavioural 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 used 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 mechanism (weight) and the outcomes will be captured at the same timepoint. Thus, it will be challenging to reject the possibility of reverse causation of the mediator-outcome effect.

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 to 47% for knee OA.[10] Of all health conditions, LBP is ranked first and OA ranked eleventh as contributors to global disability.[4,11] Direct costs for the management of LBP is estimated at $AU4.7 billion in Australia (2012),[7] £2.8 billion in the United Kingdom (2013),[12] and $US90 billion in the United States (1998);[8] and the cost of OA accounts for up to 2.5% of the gross national product in Australia, UK and US.[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 RCTs will test the effectiveness of a multi-component lifestyle behavioural 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 worked, or why the intervention failed.[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, complex interventions such as a lifestyle behavioural 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 on outcome(s) 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 proposed mediator, and the direct effect is the remaining effect of the intervention that is not explained via the proposed mediator. For example, the entire effect of the lifestyle behavioural 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 indirect path 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 or optimised.

Mechanisms of a lifestyle behavioural intervention that aimed to address weight, diet, physical activity and pain beliefs

Causal mechanisms of lifestyle behavioural interventions aimed to reduce pain, disability, and QoL 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 behavioural interventions for patients with LBP and knee OA.

To test these underlying mechanisms, we have embedded a priori planned mechanism evaluations into two RCTs that will test the effectiveness of a lifestyle behavioural 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 behavioural 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 behavioural 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 or not (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

Combined Causal Mediation Analyses of two, two-arm RCTs.[23,24] Both trials are part of a cohort multiple RCT,[40] embedded in routine health service delivery. In both trials, participants were recruited from an existing cohort of patients waiting for orthopaedic consultation; then were randomised to a lifestyle behavioural intervention (intervention group), or remained part of 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 estimate averaged effects across both trials. If trial assignment is a significant moderator, we will interpret the mediation effects in separation; however, if trial assignment is not a significant moderator, we will interpret averaged mediation effects across both trials.

The trials began recruiting on the 11th of January 2016 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 were waiting for outpatient orthopaedic consultation at a tertiary referral public hospital in New South Wales (NSW), Australia.

Randomisation

For both trials, eligible patients from the cohort were randomised to an intervention or control group (1:1 ratio). The randomisation schedule was generated a priori by an independent statistician using the SURVEYSELECT procedure (SAS V.9.3). Allocation was concealed and all outcome assessors, patients, and investigators are blind to group allocation.

Intervention groups

Participants in both RCTs[23,24] received advice and education about the benefits of weight loss and physical activity for their conditions by trained interviewers. Participants were 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. Coaching was provided on a tapered schedule. Six calls were made in the first 12 weeks to guide, monitor and improve uptake; and 4 calls were dispersed over the remaining 12 weeks to maintain adherence and avoid relapse.[42]

Participants with LBP[23] received an additional clinical consultation with the study Physiotherapist before beginning the NSW Get Healthy Service program. The consultation aimed 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 involved behaviour change techniques, informed by Self Determination Theory[43,44] that aimed to develop autonomous motivation by increasing perceived competence and self-regulation.[44]

Control groups

Participants allocated to the control group remained on the usual care pathway. The health service did not provide any active management for knee OA or LBP patients during the orthopaedic consultation waiting period.

Assessment timepoints

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 and 6 months after randomisation. Outcomes will be measured 6 months after randomisation. The intervention and assessment time points are outlined in **Table 1**.

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* 6 GHS Calls							4 GHS Calls						
Primary Mediator	■			■										■
Alternative Mediators	■			■										■
Outcomes	■													■

*Legend: Primary mediator = weight; Alternative mediators = diet, physical activity, and pain beliefs; Outcomes = Pain, Disability, and Quality of Life; GHS = NSW Get Healthy Service; *LBP patients only*

Primary outcome measures

Average pain intensity over 7-days will be measured using an 11-point pain Numeric Rating Scale (0=no pain, 10=pain as bad as 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 (WOMAC)[47] in patients with knee OA. We will measure QoL using the Short Form Health Survey V.2.[48]

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] Dietary intake will be measured using a short food frequency questionnaire.[51] Pain related attitudes and beliefs will be measured using the Survey of Pain Attitudes Questionnaire.[52]

Potential confounders

We will control for the following pre-treatment 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 as covariates.[53] Directed acyclic graphs (DAGs) 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.[54,55] 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 behavioural intervention was targeted to reduce weight, and because the target population were overweight or obese. Evidence suggests that weight might have direct causal effects on patient-related outcomes (pain, disability, and QoL).[15–17,56] 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 Get Healthy Service) 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.[57] Finally, we hypothesise that the intervention may also exert its effect through changes in pain beliefs.[39,58] This is because initial consultations in the LBP trial[23] aimed to reassure patients and re-frame erroneous beliefs about pain. These refined mechanisms will be tested in serial multiple mediator models (Figure 1b).

(a)

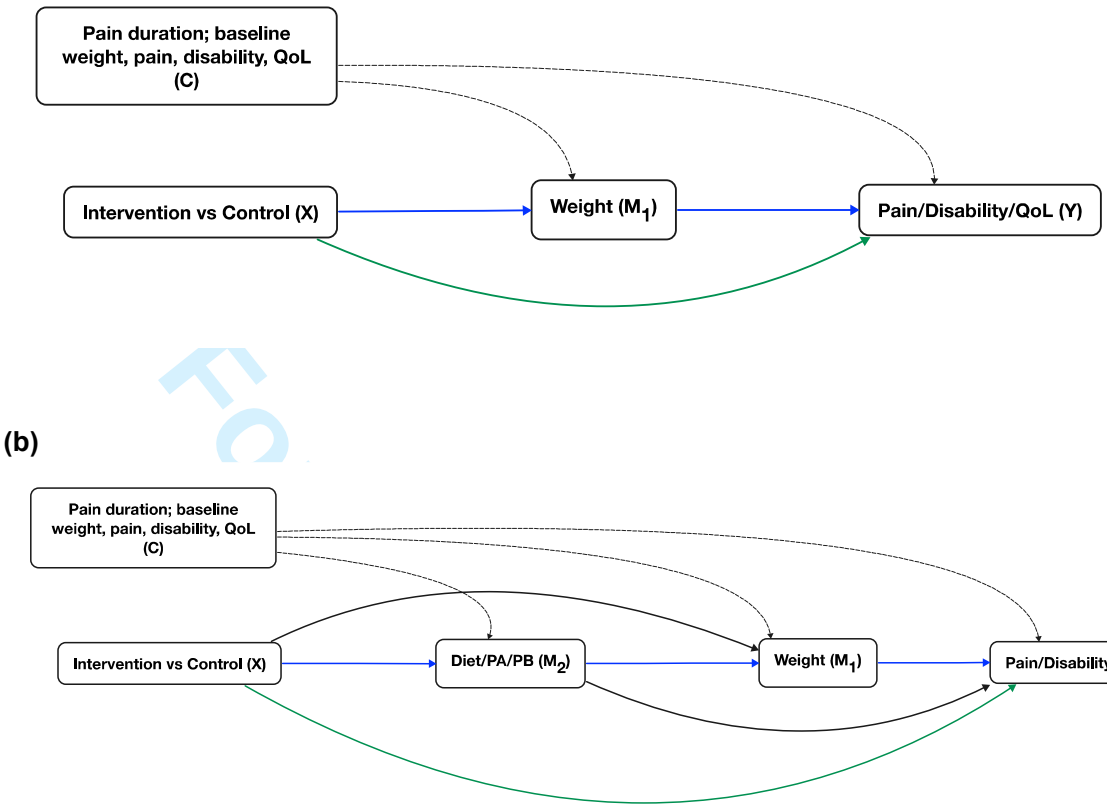

Figure 1. Directed Acyclic Graphs. Blue lines represent indirect effects (mechanisms) of interest. Green lines represent direct effects (direct effect of treatment on outcome plus all unexplained indirect effects). Dotted lines represent possible effects that could induce confounding for indirect and direct effects. PA = Physical Activity; PB = Pain Beliefs; QoL = Quality of Life. **(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.

Table 2. Overview of all mediation models

Model	X	M_2 at 6 weeks	M_1 at 6 months	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

M_1 = primary mediator; M_2 = alternative mediator; Rx = Intervention vs Control; X = exposure; Y = outcomes. *= 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 ($P<0.05$).

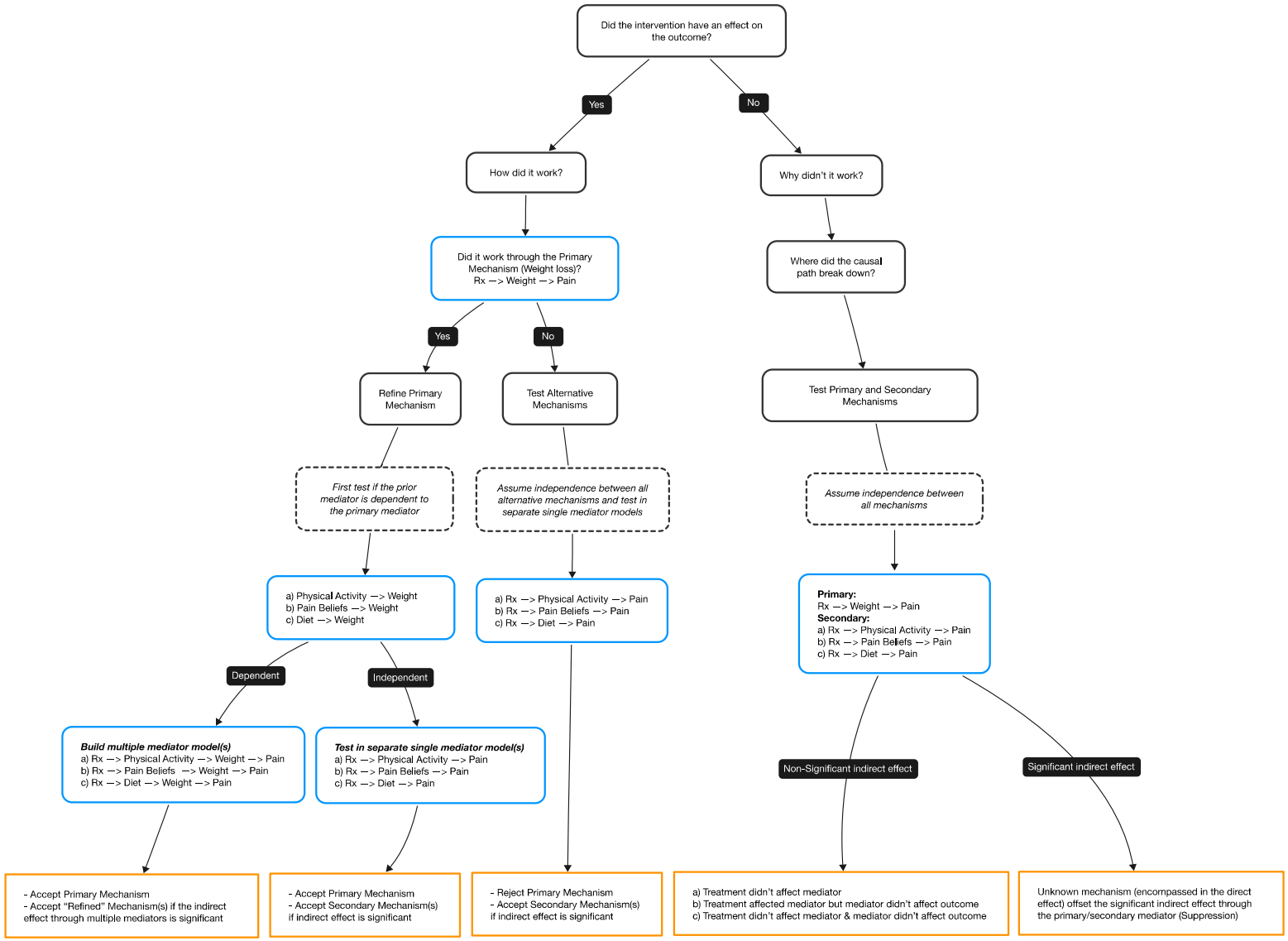

Figure 2. Overall Analysis Plan. Note: "Pain" is interchangeable with disability and QoL.

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 (2014).[59] With a two-sided alpha of 0.05, exposure-mediator error term correlation coefficient of 0, 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 mediator-outcome (r=0.3) effects. Sample size estimators for multiple mediator models are currently unavailable.[60] O'Rourke and Mackinnon (2014) provide evidence that multiple mediator models have more power than single mediator models.[61] 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".[55] One needs to be certain 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. However, since the mediators cannot be randomised, this assumption does not hold for the mediator-outcome relationship.[55] 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.[62]

Alternative Mediator as a Post-Treatment Confounder in Multiple Mediator Models

In mediation analyses, post-treatment confounders are variables that are affected by the treatment that then simultaneously influence the mediator and outcome. The presence of a post-treatment confounder effectively induces bias for indirect and direct effects.[63] By construction of the multiple mediator model, an alternative mediator (M_2) is a post-treatment 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 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 and primary mediator is significantly correlated,

we will build serial multiple mediator models, as recommended by Imai et al.[54] If the alternative and primary mediators are not related, then we will not treat the alternative mediator as a post-treatment 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.[64]

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.[64] 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, the mediator as the dependent variable, and the set of observed pre-treatment confounders as covariates. The outcome model is constructed with the treatment status and the mediator as the independent variables, the outcome as the dependent variable, and the set of observed pre-treatment confounders as covariates.

Because it is possible that the ACME is dependent on treatment status, the outcome model will also include an interaction term between the treatment status and the mediator of interest. Not accounting for even small non-significant interaction effects can dramatically influence the indirect and direct effect estimates.[60]

The "mediates" function will use the mediator and outcome models to estimate 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% confidence intervals. We will interpret the unstandardised point estimate of ACME and its 95% confidence intervals.

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 (i.e. no correlation between residuals), then this can be hypothetically interpreted as no unmeasured confounding. We will use the "medsens" function to estimate ρ and vary ρ between the extremes of -1 and +1 to examine how the ACME changes. The output will provide the values of ρ at which the confidence intervals 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.[54] Multiple mediator models will only be constructed if the alternative mediator (diet, physical activity, and pain beliefs) and primary mediator (weight) are related.[54] 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% confidence intervals.

Conclusion

We present an analysis plan for a mechanism evaluation of a lifestyle behavioural 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 clues as to why the intervention did not work. These results will help refine the intervention and guide implementation strategies.

REFERENCES

1. Croft P, Blyth F, van der Windt D. *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press; 2010.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012;379(9814):482-491.
3. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
4. Vos T, Barber RRM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800.
5. Borghouts JAJ, Koes BW, Vondeling H, Bouter LM. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*. 1999;80(1999):629-636.
6. Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013;27(5):575-589.
7. Arthritis and Osteoporosis Victoria. *A Problem Worth Solving - The Rising Cost of Musculoskeletal Conditions in Australia*.; 2013.
8. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. 2008;8(1):8-20.
9. March LM, Bachmeier CJM. Economics of osteoarthritis: A global perspective. *Baillieres Clin Rheumatol*. 1997;11(4):817-834.
10. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15.
11. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330.
12. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine (Phila Pa 1976)*. 2013;38(1):75-82.
13. Verbunt JA, Westerterp KR, van der Heijden GJ, Seelen HA, Vlaeyen JW, Knottnerus JA. Physical activity in daily life in patients with chronic low back pain. *Arch Phys Med Rehabil*. 2001;82(6):726-730.
14. Messier SP, Loeser RF, Miller GD, et al. Exercise and Dietary Weight Loss in Overweight and Obese Older Adults with Knee Osteoarthritis: The Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510.
15. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA - J Am Med Assoc*. 2013;310(12):1263-1273.
16. Leboeuf-Yde C. Body weight and low back pain: A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976)*. 2000;25(2):226-237.
17. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: A meta-analysis. *Am J Epidemiol*. 2010;171(2):135-154.
18. Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. *Int J Obes*. 2008;32(2):211-222.

19. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthr Cartil*. 2010;18(1):24-33.
20. Wai EK, Rodriguez S, Dagenais S, Hall H. Evidence-informed management of chronic low back pain with physical activity, smoking cessation, and weight loss. *Spine J*. 2008;8(1):195-202.
21. Roffey DM, Budiansky A, Coyle MJ, Wai EK. Obesity and Low Back Pain: Is There a Weight of Evidence to Support a Positive Relationship? *Curr Obes Rep*. 2013;2:241-250.
22. Graves N, Barnett AG, Halton K a, et al. Cost-effectiveness of a telephone-delivered intervention for physical activity and diet. *PLoS One*. 2009;4(9):e7135.
23. Williams A, Wiggers J, O'Brien KM, et al. A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol. *BMC Musculoskelet Disord*. 2016;17(1):70.
24. O'Brien KM, Wiggers J, Williams A, et al. Randomised controlled trial of referral to a telephone-based weight management and healthy lifestyle programme for patients with knee osteoarthritis who are overweight or obese: a study protocol. *BMJ Open*. 2016;6(3):e010203.
25. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res*. 2010;19(3):237-270.
26. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *Bmj*. 2015;350:h1258-h1258.
27. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the Black Box of Causality: Learning about Causal Mechanisms from Experimental and Observational Studies. *Am Polit Sci Rev*. 2011;105(4):765-789.
28. Eriksson MK, Hagberg L, Lindholm L, Malmgren-Olsson E-B, Österlind J, Eliasson M. Quality of Life and Cost-effectiveness of a 3-Year Trial of Lifestyle Intervention in Primary Health Care. *Arch Intern Med*. 2010;170(16):1470-1479.
29. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: A meta-analysis. *Am J Med*. 2004;117(10):762-774.
30. Lange T, Starkopf L. Mediation analyses in the real world. *Epidemiology*. 2016;27(5):1.
31. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41(8):1343-1355.
32. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol*. 2010;22(5):533-537.
33. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: A systematic review and meta-analysis. *Ann Rheum Dis*. 2007;66(4):433-439.
34. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between smoking and low back pain: a meta-analysis. *Am J Med*. 2010;123(1):87.e7-35.
35. Curioni CC, Lourenço PM. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes*. 2005;29(10):1168-1174.
36. Goodpaster BH, Delany JP, Otto AD, et al. Clinician's corner: Effects of Diet and Physical Activity Interventions on Weight Loss and Cardiometabolic Risk Factors in Severely Obese Adults. 2010;304(16):1795-1802.
37. Wu T, Gao X, Chen M, Van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: A meta-analysis: Obesity

Management. *Obes Rev*. 2009;10(3):313-323.

38. Turner AP, Barlow JH, Buszewicz M, Atkinson A, Rait G. Beliefs about the causes of osteoarthritis among primary care patients. *Arthritis Care Res*. 2007;57(2):267-271.
39. Buchbinder R, Jolley D, Wyatt M. Population based intervention to change back pain beliefs and disability: three part evaluation. *BMJ*. 2001;322(7301):1516-1520.
40. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. *BMJ*. 2010;340(7753):963-967.
41. O'Hara BJ, Phongsavan P, Venugopal K, et al. Effectiveness of Australia's Get Healthy Information and Coaching Service: translational research with population wide impact. *Prev Med (Baltim)*. 2012;55(4):292-298.
42. Larimer ME, Palmer RS, Marlatt GA. Relapse prevention: An overview of Marlatt's cognitive-behavioral model. *Alcohol Res Heal*. 1999;23(2):151-160.
43. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol*. 2000;55(1):68-78.
44. Silva MN, Markland D, Minderico CS, et al. A randomized controlled trial to evaluate self-determination theory for exercise adherence and weight control: Rationale and intervention description. *BMC Public Health*. 2008;8.
45. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133-149.
46. Roland M, Morris R. A study of the natural history of back pain: part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976)*. 1983;8(2):141-144.
47. Bellamy N. *WOMAC® User Guide IX*.; 2009.
48. Maruish ME. User's manual for the SF-12v2 Health Survey. *Lincoln, RI Qual*. 2012.
49. *International Standards for Anthropometric Assessment*. Underdale, SA; 2001.
50. *The Active Australia Survey: A Guide and Manual for Implementation, Analysis and Reporting*.; 2003.
51. *Centre for Epidemiology and Research NSW Population Health Survey*. Sydney; 2014.
52. Jensen MP, Karoly P, Huger R. The development and preliminary validation of an instrument to assess patients' attitudes toward pain. *J Psychosom Res*. 1987;31(3):393-400.
53. Landau S, Emsley R, Dunn G. Beyond total treatment effects in RCTs: why we need to measure outcomes at baseline when investigating mediation. *Trials*. 2015;16(Suppl 2):O42.
54. Imai K, Yamamoto T. Identification and Sensitivity Analysis for Multiple Causal Mechanisms: Revisiting Evidence from Framing Experiments. *Polit Anal*. 2013;21(2):141-171.
55. Imai K, Keele L, Yamamoto T. Identification, Inference and Sensitivity Analysis for Causal Mediation Effects. *Stat Sci*. 2010;25(1):51-71.
56. Cicuttini FM, Wluka AE. Not just loading and age: The dynamics of osteoarthritis, obesity and inflammation. *Med J Aust*. 2016;204(2):47-47.e1.
57. O'Hara BJ, Bauman AE, Eakin EG, et al. Evaluation Framework for Translational Research: Case Study of Australia's Get Healthy Information and Coaching Service®. *Health Promot Pract*. 2013;14(3):380-389.
58. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(8):1153-1159.

59. Vittinghoff E, Neilands TB. Sample Size for Joint Testing of Indirect Effects. *Prev Sci*. 2014;16(8):1128-1135.

60. VanderWeele T. *Explanation in Causal Inference: Methods for Mediation and Interaction*. Oxford University Press; 2015.

61. O'Rourke HP, Mackinnon DP. When the test of mediation is more powerful than the test of the total effect. *Behav Res*. 2014:424-442.

62. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4):309-334.

63. Manson J, Shufelt C, Robins J. The Potential for Postrandomization Confounding in Randomized Clinical Trials. *Jama*. 2016;315(21):2273-2274.

64. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R Package for Causal Mediation Analysis. *J Stat Softw*. 2014;59(5):1-38.

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

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

Hopin Lee[1,2,6], John Wiggers[2,3], Steven J. Kamper[4], Amanda Williams[2,3], Kate M. O'Brien[2,3], Rebecca K. Hodder[2,3], Luke Wolfenden[1,3], Sze Lin Yoong[2,3], Elizabeth Campbell[3], Robin Haskins[5], James H. McAuley[6], Christopher, M. Williams[1,2]

1. Hunter Medical Research Institute, Newcastle, NSW, Australia
2. School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia
3. Hunter New England Population Health, Wallsend, NSW, Australia
4. The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia
5. Ambulatory Care Centre, John Hunter Hospital, Hunter New England Local Health District, Newcastle, NSW, Australia.
6. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia

Corresponding Author: Hopin Lee, Hunter Medical Research Institute, Newcastle, NSW, Australia. Email: hopinlee@gmail.com

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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 multi-component lifestyle behavioural 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 behavioural 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 for a mechanism evaluation for a lifestyle behavioural intervention for overweight or obese patients with LBP and knee OA.

Methods and analysis: Causal mediation analyses of two, two-arm 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 behavioural 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 6 weeks' post-randomisation. All outcomes: pain, disability, and quality of life, will be measured 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 & ACTRN12615000478516

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

- Understanding the underlying causal mechanisms of a complex lifestyle behavioural 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.

Limitations:

- The primary mechanism (weight) and the outcomes will be captured at the same time-point. Thus, it will be challenging to test 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 to 47% for knee OA.[10] Of all health conditions, LBP is ranked first and OA ranked eleventh as contributors to global disability.[4,11] Direct costs for the management of LBP is estimated at $AU4.7 billion in Australia (2012),[7] £2.8 billion in the United Kingdom (2013),[12] and $US90 billion in the United States (1998);[8] and the cost of OA accounts for up to 2.5% of the gross national product in Australia, UK and US.[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 RCTs will test the effectiveness of a multi-component lifestyle behavioural 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 worked, or why the intervention failed.[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, complex interventions such as a lifestyle behavioural 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 on outcome(s) 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 proposed mediator, and the direct effect is the remaining effect of the intervention that is not explained via the proposed mediator. For example, the entire effect of the lifestyle behavioural 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 indirect path 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 or optimised.

Mechanisms of a lifestyle behavioural intervention that aimed to address weight, diet, physical activity and pain beliefs

Causal mechanisms of lifestyle behavioural interventions aimed to reduce pain, disability, and QoL 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 behavioural interventions for patients with LBP and knee OA.

To test these underlying mechanisms, we have embedded a priori planned mechanism evaluations into two RCTs that will test the effectiveness of a lifestyle behavioural 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 behavioural 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 behavioural 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 or not (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 Analyses of two, two-arm RCTs.[23,24] Both trials are part of a cohort multiple RCT,[40] embedded in routine health service delivery. In both trials, participants were recruited from an existing cohort of patients waiting for orthopaedic consultation; then were randomised to a lifestyle behavioural intervention (intervention group), or remained part of 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 the 11th of January 2016 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 were waiting for outpatient orthopaedic consultation at a tertiary referral public hospital in New South Wales (NSW), Australia.

Randomisation

For both trials, eligible patients from the cohort were randomised to an intervention or control group (1:1 ratio). The randomisation schedule was generated a priori by an independent statistician using the SURVEYSELECT procedure (SAS V.9.3). Allocation was concealed and all outcome assessors, patients, and investigators were blind to group allocation. *Patients were 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 were not aware of the control arm. Likewise, patients randomised to the control group were not aware of the intervention arm. Thus, the patients were not able to discriminate whether the intervention or control was 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 were blind to treatment status as they were not aware that patients were being referred from a clinical trial. The outcome assessors did not have access to the randomisation schedule, thus were blind to group allocation. This reduces the risk of detection bias (differential outcome measurement between groups).*

Intervention groups

Participants in both RCTs[23,24] received advice and education about the benefits of weight loss and physical activity for their conditions by trained interviewers. Participants were 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 bias introduced through between coach effects. Coaching was provided on a tapered schedule. Six calls were made in the first 12 weeks to guide, monitor and improve uptake; and 4 calls were dispersed over the remaining

12 weeks to maintain adherence and avoid relapse.[42] This tapered schedule was kept consistent across all participants, reducing the potential for bias.

Participants with LBP[23] received an additional clinical consultation with the study Physiotherapist before beginning the NSW Get Healthy Service program. The consultation aimed 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 involved behaviour change techniques, informed by Self Determination Theory[43,44] that aimed to develop autonomous motivation by increasing perceived competence and self-regulation.[44]

Control groups

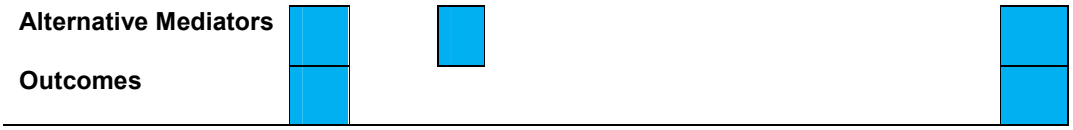
Participants allocated to the control group remained on the usual care pathway. The health service did not provide any active management for knee OA or LBP patients during the orthopaedic consultation waiting period.

Assessment timepoints

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 and 6 months after randomisation. Outcomes will be measured 6 months after randomisation. The intervention and assessment time points are outlined in **Table 1**.

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* 6 GHS Calls							4 GHS Calls						
Primary Mediator														



*Legend: Primary mediator = weight; Alternative mediators = diet, physical activity, and pain beliefs; Outcomes = Pain, Disability, and Quality of Life; GHS = NSW Get Healthy Service; *LBP patients only*

Primary outcome measures

Average pain intensity over 7-days will be measured using an 11-point pain Numeric Rating Scale (0=no pain, 10=pain as bad as 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 (WOMAC)[47] in patients with knee OA. We will measure QoL using the Short Form Health Survey V.2.[48]

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 to 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. Putative mediators are measured using self-reported questionnaires with known limitations.[57]

Potential confounders

We will control for the following pre-treatment 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 as covariates.[58] Directed acyclic graphs (DAGs) 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 behavioural intervention was targeted to reduce weight, and because the target population were 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 Get Healthy Service) 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 re-frame erroneous beliefs about pain. Although patients with OA did not receive a clinical consultation that directly targeted pain beliefs, the Get Healthy Information and Coaching Service 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).

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 ($P<0.05$).

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 (2014).[66] With a two-sided alpha of 0.05, exposure-mediator error term correlation coefficient of 0, 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 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 (2014) 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. 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 reflects 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 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 and primary mediator is 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, the mediator as the dependent variable, and the set of observed pre-treatment confounders as covariates. The outcome model is constructed with the treatment status and the mediator as the independent variables, the outcome as the dependent variable, and the set of observed pre-treatment 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 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% confidence intervals. We will interpret the unstandardised point estimate of ACME and its 95% confidence intervals.

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 or 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 (i.e. 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 confidence intervals 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% confidence intervals.

Conclusion

We present an analysis plan for a mechanism evaluation of a lifestyle behavioural 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 clues as to why the intervention did not work. These results will help refine the intervention and guide implementation strategies.

REFERENCES

1. Croft P, Blyth F, van der Windt D. *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press; 2010.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012;379(9814):482-491.
3. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
4. Vos T, Barber RRM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800.
5. Borghouts JAJ, Koes BW, Vondeling H, Bouter LM. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*. 1999;80(1999):629-636.
6. Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013;27(5):575-589.
7. Arthritis and Osteoporosis Victoria. *A Problem Worth Solving - The Rising Cost of Musculoskeletal Conditions in Australia*.; 2013.
8. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. 2008;8(1):8-20.
9. March LM, Bachmeier CJM. Economics of osteoarthritis: A global perspective. *Baillieres Clin Rheumatol*. 1997;11(4):817-834.
10. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15.
11. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330.
12. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine (Phila Pa 1976)*. 2013;38(1):75-82.
13. Verbunt JA, Westerterp KR, van der Heijden GJ, Seelen HA, Vlaeyen JW, Knottnerus JA. Physical activity in daily life in patients with chronic low back pain. *Arch Phys Med Rehabil*. 2001;82(6):726-730.
14. Messier SP, Loeser RF, Miller GD, et al. Exercise and Dietary Weight Loss in Overweight and Obese Older Adults with Knee Osteoarthritis: The Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510.
15. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA - J Am Med Assoc*. 2013;310(12):1263-1273.
16. Leboeuf-Yde C. Body weight and low back pain: A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976)*. 2000;25(2):226-237.
17. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: A meta-analysis. *Am J Epidemiol*. 2010;171(2):135-154.
18. Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. *Int J Obes*. 2008;32(2):211-222.
19. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of

the knee in older adults: a systematic review and meta-analysis. *Osteoarthr Cartil*. 2010;18(1):24-33.

20. Wai EK, Rodriguez S, Dagenais S, Hall H. Evidence-informed management of chronic low back pain with physical activity, smoking cessation, and weight loss. *Spine J*. 2008;8(1):195-202.
21. Roffey DM, Budiansky A, Coyle MJ, Wai EK. Obesity and Low Back Pain: Is There a Weight of Evidence to Support a Positive Relationship? *Curr Obes Rep*. 2013;2:241-250.
22. Graves N, Barnett AG, Halton K a, et al. Cost-effectiveness of a telephone-delivered intervention for physical activity and diet. *PLoS One*. 2009;4(9):e7135.
23. Williams A, Wiggers J, O'Brien KM, et al. A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol. *BMC Musculoskelet Disord*. 2016;17(1):70.
24. O'Brien KM, Wiggers J, Williams A, et al. Randomised controlled trial of referral to a telephone-based weight management and healthy lifestyle programme for patients with knee osteoarthritis who are overweight or obese: a study protocol. *BMJ Open*. 2016;6(3):e010203.
25. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res*. 2010;19(3):237-270.
26. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*. 2015;350:h1258-h1258.
27. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the Black Box of Causality: Learning about Causal Mechanisms from Experimental and Observational Studies. *Am Polit Sci Rev*. 2011;105(4):765-789.
28. Eriksson MK, Hagberg L, Lindholm L, Malmgren-Olsson E-B, Österlind J, Eliasson M. Quality of Life and Cost-effectiveness of a 3-Year Trial of Lifestyle Intervention in Primary Health Care. *Arch Intern Med*. 2010;170(16):1470-1479.
29. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: A meta-analysis. *Am J Med*. 2004;117(10):762-774.
30. Lange T, Starkopf L. Mediation analyses in the real world. *Epidemiology*. 2016;27(5):1.
31. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41(8):1343-1355.
32. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol*. 2010;22(5):533-537.
33. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: A systematic review and meta-analysis. *Ann Rheum Dis*. 2007;66(4):433-439.
34. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between smoking and low back pain: a meta-analysis. *Am J Med*. 2010;123(1):87.e7-35.
35. Curioni CC, Lourenço PM. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes*. 2005;29(10):1168-1174.
36. Goodpaster BH, Delany JP, Otto AD, et al. Clinician's corner: Effects of Diet and Physical Activity Interventions on Weight Loss and Cardiometabolic Risk Factors in Severely Obese Adults. 2010;304(16):1795-1802.
37. Wu T, Gao X, Chen M, Van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: A meta-analysis: Obesity Management. *Obes Rev*. 2009;10(3):313-323.

38. Turner AP, Barlow JH, Buszewicz M, Atkinson A, Rait G. Beliefs about the causes of osteoarthritis among primary care patients. *Arthritis Care Res*. 2007;57(2):267-271.
39. Buchbinder R, Jolley D, Wyatt M. Population based intervention to change back pain beliefs and disability: three part evaluation. *BMJ*. 2001;322(7301):1516-1520.
40. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. *BMJ*. 2010;340(7753):963-967.
41. O'Hara BJ, Phongsavan P, Venugopal K, et al. Effectiveness of Australia's Get Healthy Information and Coaching Service: translational research with population wide impact. *Prev Med (Baltim)*. 2012;55(4):292-298.
42. Larimer ME, Palmer RS, Marlatt GA. Relapse prevention: An overview of Marlatt's cognitive-behavioral model. *Alcohol Res Heal*. 1999;23(2):151-160.
43. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol*. 2000;55(1):68-78.
44. Silva MN, Markland D, Minderico CS, et al. A randomized controlled trial to evaluate self-determination theory for exercise adherence and weight control: Rationale and intervention description. *BMC Public Health*. 2008;8.
45. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133-149.
46. Roland M, Morris R. A study of the natural history of back pain: part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976)*. 1983;8(2):141-144.
47. Bellamy N. *WOMAC® User Guide IX*.; 2009.
48. Maruish ME. User's manual for the SF-12v2 Health Survey. *Lincoln, RI Qual*. 2012.
49. *International Standards for Anthropometric Assessment*. Underdale, SA; 2001.
50. *The Active Australia Survey: A Guide and Manual for Implementation, Analysis and Reporting*.; 2003.
51. Brown W, Trost S, Bauman A, Mummery K, Owen N. Test-retest reliability of four physical activity measures used in population surveys. *J Sci Med Sport*. 2004;7(2):205-215.
52. Booth M, Bauman AE, Timperio A, Salmon J, Trost S. *Measurement of Adult Physical Activity: Reliability, Comparison and Validity of Self-Report Surveys for Population Surveillance. Summary and Recommendations*.; 2002.
53. *Centre for Epidemiology and Research NSW Population Health Survey*. Sydney; 2014.
54. CATI Technical Reference Group. *Population Health Monitoring and Surveillance: Question Development Field Testing*.; 2004.
55. Flood VM, Wen LM, Hardy LL, Rissel C, Simpson JM, Baur LA. Reliability and validity of a short FFQ for assessing the dietary habits of 2-5-year-old children, Sydney, Australia. *Public Health Nutr*. 2014;17(3):498-509.
56. Jensen MP, Karoly P, Huger R. The development and preliminary validation of an instrument to assess patients' attitudes toward pain. *J Psychosom Res*. 1987;31(3):393-400.
57. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*. 2003;37(3):197-206.
58. Landau S, Emsley R, Dunn G. Beyond total treatment effects in RCTs: why we need to measure outcomes at baseline when investigating mediation. *Trials*. 2015;16(Suppl 2):O42.
59. Imai K, Yamamoto T. Identification and Sensitivity Analysis for Multiple Causal Mechanisms: Revisiting Evidence from Framing Experiments. *Polit Anal*.

2013;21(2):141-171.

60. Imai K, Keele L, Yamamoto T. Identification, Inference and Sensitivity Analysis for Causal Mediation Effects. *Stat Sci*. 2010;25(1):51-71.

61. Dunn G, Emsley R, Liu H, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health. *NIHR Rep*. 2015;19(93).

62. Cicuttini FM, Wluka AE. Not just loading and age: The dynamics of osteoarthritis, obesity and inflammation. *Med J Aust*. 2016;204(2):47-47.e1.

63. O'Hara BJ, Bauman AE, Eakin EG, et al. Evaluation Framework for Translational Research: Case Study of Australia's Get Healthy Information and Coaching Service®. *Health Promot Pract*. 2013;14(3):380-389.

64. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(8):1153-1159.

65. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84(2):191.

66. Vittinghoff E, Neilands TB. Sample Size for Joint Testing of Indirect Effects. *Prev Sci*. 2014;16(8):1128-1135.

67. Warkentin LM, Majumdar SR, Johnson JA, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. *BMC Med*. 2014;12:175.

68. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004;8(4):283-291.

69. VanderWeele T. *Explanation in Causal Inference: Methods for Mediation and Interaction*. Oxford University Press; 2015.

70. O'Rourke HP, Mackinnon DP. When the test of mediation is more powerful than the test of the total effect. *Behav Res*. 2014:424-442.

71. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4):309-334.

72. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-1182.

73. Manson J, Shufelt C, Robins J. The Potential for Postrandomization Confounding in Randomized Clinical Trials. *Jama*. 2016;315(21):2273-2274.

74. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R Package for Causal Mediation Analysis. *J Stat Softw*. 2014;59(5):1-38.

75. Ng VKY, Cribbie RA. Using the Gamma Generalized Linear Model for Modeling Continuous, Skewed and Heteroscedastic Outcomes in Psychology. *Curr Psychol*. 2016:1-11.

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 unexplained indirect effects). Red lines represent possible effects that could induce confounding for indirect and direct effects. PA = Physical Activity; PB = Pain Beliefs; QoL = Quality of Life. **(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.

Figure 2. Overall Analysis Plan. Note: “Pain” is interchangeable with disability and QoL.

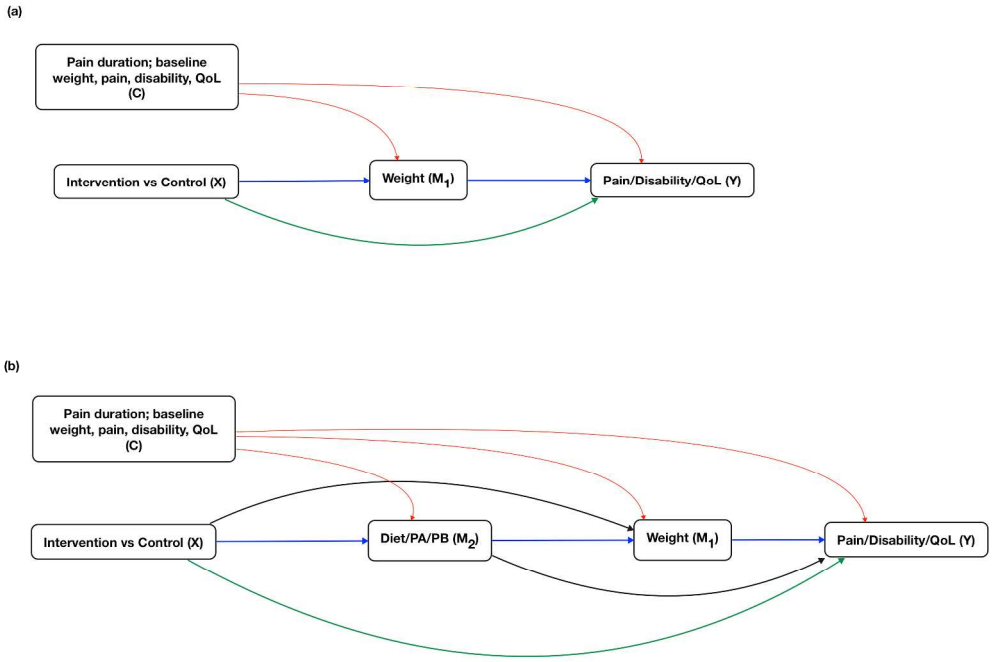


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Figure 1
369x249mm (300 x 300 DPI)

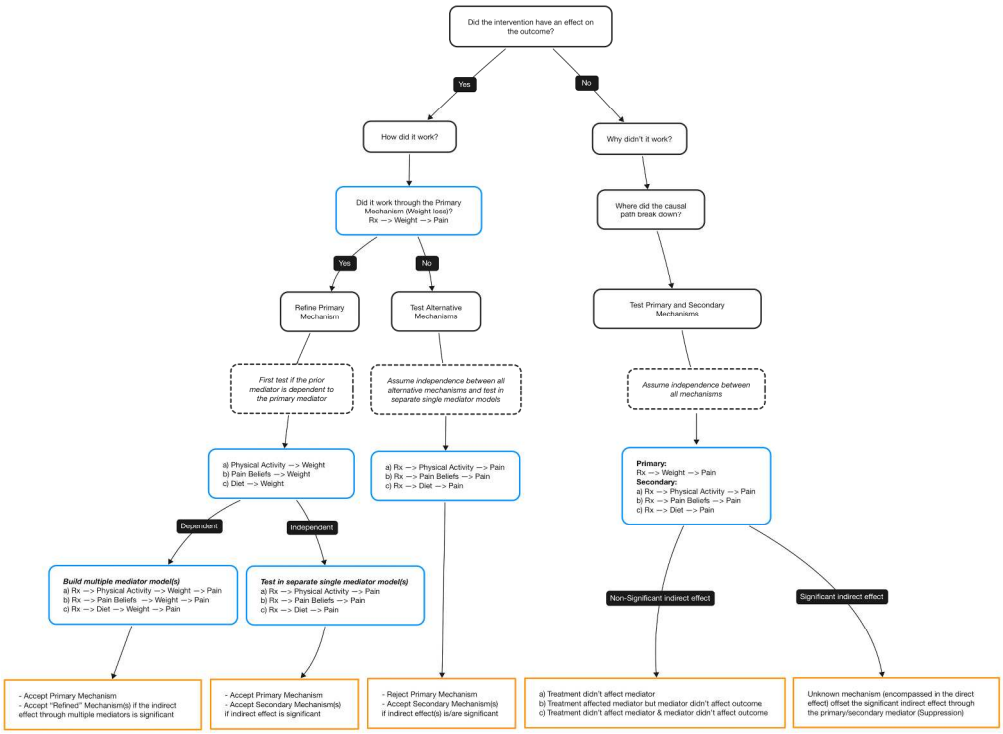

Figure 2. Overall Analysis Plan. Note: "Pain" is interchangeable with disability and QoL.

Figure 2
342x249mm (300 x 300 DPI)

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

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

Hopin Lee[1,2,6], John Wiggers[2,3], Steven J. Kamper[4], Amanda Williams[2,3], Kate M. O'Brien[2,3], Rebecca K. Hodder[2,3], Luke Wolfenden[1,3], Sze Lin Yoong[2,3], Elizabeth Campbell[3], Robin Haskins[5], Emma K Robson[2,3], James H. McAuley[6], Christopher, M. Williams[1,2]

1. Hunter Medical Research Institute, Newcastle, NSW, Australia
2. School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia
3. Hunter New England Population Health, Wallsend, NSW, Australia
4. The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia
5. Ambulatory Care Centre, John Hunter Hospital, Hunter New England Local Health District, Newcastle, NSW, Australia.
6. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia

Corresponding Author: Hopin Lee, Hunter Medical Research Institute, Newcastle, NSW, Australia. Email: hopinlee@gmail.com

Authors' contributions: HL, JW, SK, AW, KO, RKH, LW, SY, EC, RH, ER, JM, CW 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. HL drafted the manuscript, and all authors subsequently contributed to the manuscript. All authors have read and approved the final manuscript.

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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 multi-component lifestyle behavioural 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 behavioural 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 for a mechanism evaluation for a lifestyle behavioural intervention for overweight or obese patients with LBP and knee OA.

Methods and analysis: Causal mediation analyses of two, two-arm 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 behavioural 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 6 weeks' post-randomisation. All outcomes: pain, disability, and quality of life, will be measured 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 & ACTRN12615000478516

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

- Understanding the underlying causal mechanisms of a complex lifestyle behavioural 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.

Limitations:

- The primary mediator (weight) and the outcomes will be captured at the same time-point. Thus, it will be challenging to test 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 to 47% for knee OA.[10] Of all health conditions, LBP is ranked first and OA ranked eleventh as contributors to global disability.[4,11] Direct costs for the management of LBP is estimated at $AU4.7 billion in Australia (2012),[7] £2.8 billion in the United Kingdom (2013),[12] and $US90 billion in the United States (1998);[8] and the cost of OA accounts for up to 2.5% of the gross national product in Australia, UK and US.[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 RCTs will test the effectiveness of a multi-component lifestyle behavioural 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 worked, or why the intervention failed.[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, complex interventions such as a lifestyle behavioural 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 on outcome(s) 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 behavioural 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 indirect path 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 behavioural intervention that aimed to address weight, diet, physical activity and pain beliefs

Causal mechanisms of lifestyle behavioural interventions aimed to reduce pain, disability, and QoL 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 behavioural 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 behavioural 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 behavioural 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 behavioural 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 or not (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 analyses of two, two-arm 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 behavioural 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 the 11th of January 2016 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 was 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] 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 4 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 Get Healthy Service program. 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

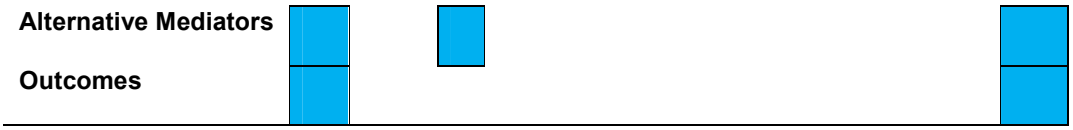
Participants allocated to the control group will remain on the usual care pathway. The health service does not provide any active management for knee OA or LBP patients during the orthopaedic consultation waiting period.

Assessment timepoints

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 and 6 months after randomisation. Outcomes will be measured 6 months after randomisation. The intervention and assessment time points are outlined in **Table 1**.

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* 6 GHS Calls							4 GHS Calls						
Primary Mediator														



*Legend: Primary mediator = weight; Alternative mediators = diet, physical activity, and pain beliefs; Outcomes = Pain, Disability, and Quality of Life; GHS = NSW Get Healthy Service; *LBP patients only*

Primary outcome measures

Average pain intensity over 7-days will be measured using an 11-point pain Numeric Rating Scale (0=no pain, 10=pain as bad as 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 (WOMAC)[47] in patients with knee OA. We will measure QoL using the Short Form Health Survey V.2.[48]

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 to 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. Putative mediators are measured using self-reported questionnaires with known limitations.[57]

Potential confounders

We will control for the following pre-treatment 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 as covariates.[58] Directed acyclic graphs (DAGs) 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 behavioural intervention was targeted to reduce weight, and because the target population were 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 Get Healthy Service) 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 re-frame erroneous beliefs about pain. Although patients with OA did not receive a clinical consultation that directly targeted pain beliefs, the Get Healthy Information and Coaching Service 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).

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 ($P<0.05$).

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 (2014).[66] With a two-sided alpha of 0.05, exposure-mediator error term correlation coefficient of 0, 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 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 (2014) 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 reflects 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 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 and primary mediator is 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 pre-treatment 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 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% confidence intervals. We will interpret the unstandardised point estimate of ACME and its 95% confidence intervals.

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 or 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 (i.e. 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 confidence intervals 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% confidence intervals.

Conclusion

We present an analysis plan for a mechanism evaluation of a lifestyle behavioural 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 clues as to why the intervention did not work. These results will help refine the intervention and guide implementation strategies.

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.

REFERENCES

1. Croft P, Blyth F, van der Windt D. *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press; 2010.
2. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012;379(9814):482-491.
3. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
4. Vos T, Barber RRM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800.
5. Borghouts JAJ, Koes BW, Vondeling H, Bouter LM. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain*. 1999;80(1999):629-636.
6. Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013;27(5):575-589.
7. Arthritis and Osteoporosis Victoria. *A Problem Worth Solving - The Rising Cost of Musculoskeletal Conditions in Australia*.; 2013.
8. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J*. 2008;8(1):8-20.
9. March LM, Bachmeier CJM. Economics of osteoarthritis: A global perspective. *Baillieres Clin Rheumatol*. 1997;11(4):817-834.
10. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol*. 2014;28(1):5-15.
11. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014;73(7):1323-1330.
12. Hong J, Reed C, Novick D, Happich M. Costs associated with treatment of chronic low back pain: an analysis of the UK General Practice Research Database. *Spine (Phila Pa 1976)*. 2013;38(1):75-82.
13. Verbunt JA, Westerterp KR, van der Heijden GJ, Seelen HA, Vlaeyen JW, Knottnerus JA. Physical activity in daily life in patients with chronic low back pain. *Arch Phys Med Rehabil*. 2001;82(6):726-730.
14. Messier SP, Loeser RF, Miller GD, et al. Exercise and Dietary Weight Loss in Overweight and Obese Older Adults with Knee Osteoarthritis: The Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum*. 2004;50(5):1501-1510.
15. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: The IDEA randomized clinical trial. *JAMA - J Am Med Assoc*. 2013;310(12):1263-1273.
16. Leboeuf-Yde C. Body weight and low back pain: A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976)*. 2000;25(2):226-237.
17. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: A meta-analysis. *Am J Epidemiol*. 2010;171(2):135-154.
18. Anandacoomarasamy A, Caterson I, Sambrook P, Fransen M, March L. The impact of obesity on the musculoskeletal system. *Int J Obes*. 2008;32(2):211-222.
19. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of

the knee in older adults: a systematic review and meta-analysis. *Osteoarthr Cartil*. 2010;18(1):24-33.

20. Wai EK, Rodriguez S, Dagenais S, Hall H. Evidence-informed management of chronic low back pain with physical activity, smoking cessation, and weight loss. *Spine J*. 2008;8(1):195-202.
21. Roffey DM, Budiansky A, Coyle MJ, Wai EK. Obesity and Low Back Pain: Is There a Weight of Evidence to Support a Positive Relationship? *Curr Obes Rep*. 2013;2:241-250.
22. Graves N, Barnett AG, Halton K a, et al. Cost-effectiveness of a telephone-delivered intervention for physical activity and diet. *PLoS One*. 2009;4(9):e7135.
23. Williams A, Wiggers J, O'Brien KM, et al. A randomised controlled trial of a lifestyle behavioural intervention for patients with low back pain, who are overweight or obese: study protocol. *BMC Musculoskelet Disord*. 2016;17(1):70.
24. O'Brien KM, Wiggers J, Williams A, et al. Randomised controlled trial of referral to a telephone-based weight management and healthy lifestyle programme for patients with knee osteoarthritis who are overweight or obese: a study protocol. *BMJ Open*. 2016;6(3):e010203.
25. Emsley R, Dunn G, White IR. Mediation and moderation of treatment effects in randomised controlled trials of complex interventions. *Stat Methods Med Res*. 2010;19(3):237-270.
26. Moore GF, Audrey S, Barker M, et al. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ*. 2015;350:h1258-h1258.
27. Imai K, Keele L, Tingley D, Yamamoto T. Unpacking the Black Box of Causality: Learning about Causal Mechanisms from Experimental and Observational Studies. *Am Polit Sci Rev*. 2011;105(4):765-789.
28. Eriksson MK, Hagberg L, Lindholm L, Malmgren-Olsson E-B, Österlind J, Eliasson M. Quality of Life and Cost-effectiveness of a 3-Year Trial of Lifestyle Intervention in Primary Health Care. *Arch Intern Med*. 2010;170(16):1470-1479.
29. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with type 2 diabetes: A meta-analysis. *Am J Med*. 2004;117(10):762-774.
30. Lange T, Starkopf L. Mediation analyses in the real world. *Epidemiology*. 2016;27(5):1.
31. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41(8):1343-1355.
32. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. *Curr Opin Rheumatol*. 2010;22(5):533-537.
33. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: A systematic review and meta-analysis. *Ann Rheum Dis*. 2007;66(4):433-439.
34. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between smoking and low back pain: a meta-analysis. *Am J Med*. 2010;123(1):87.e7-35.
35. Curioni CC, Lourenço PM. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes*. 2005;29(10):1168-1174.
36. Goodpaster BH, Delany JP, Otto AD, et al. Clinician's corner: Effects of Diet and Physical Activity Interventions on Weight Loss and Cardiometabolic Risk Factors in Severely Obese Adults. 2010;304(16):1795-1802.
37. Wu T, Gao X, Chen M, Van Dam RM. Long-term effectiveness of diet-plus-exercise interventions vs. diet-only interventions for weight loss: A meta-analysis: Obesity Management. *Obes Rev*. 2009;10(3):313-323.

38. Turner AP, Barlow JH, Buszewicz M, Atkinson A, Rait G. Beliefs about the causes of osteoarthritis among primary care patients. *Arthritis Care Res*. 2007;57(2):267-271.
39. Buchbinder R, Jolley D, Wyatt M. Population based intervention to change back pain beliefs and disability: three part evaluation. *BMJ*. 2001;322(7301):1516-1520.
40. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the "cohort multiple randomised controlled trial" design. *BMJ*. 2010;340(7753):963-967.
41. O'Hara BJ, Phongsavan P, Venugopal K, et al. Effectiveness of Australia's Get Healthy Information and Coaching Service: translational research with population wide impact. *Prev Med (Baltim)*. 2012;55(4):292-298.
42. Larimer ME, Palmer RS, Marlatt GA. Relapse prevention: An overview of Marlatt's cognitive-behavioral model. *Alcohol Res Heal*. 1999;23(2):151-160.
43. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol*. 2000;55(1):68-78.
44. Silva MN, Markland D, Minderico CS, et al. A randomized controlled trial to evaluate self-determination theory for exercise adherence and weight control: Rationale and intervention description. *BMC Public Health*. 2008;8.
45. Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. *Pain*. 1992;50(2):133-149.
46. Roland M, Morris R. A study of the natural history of back pain: part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976)*. 1983;8(2):141-144.
47. Bellamy N. *WOMAC® User Guide IX*.; 2009.
48. Maruish ME. User's manual for the SF-12v2 Health Survey. *Lincoln, RI Qual*. 2012.
49. *International Standards for Anthropometric Assessment*. Underdale, SA; 2001.
50. *The Active Australia Survey: A Guide and Manual for Implementation, Analysis and Reporting*.; 2003.
51. Brown W, Trost S, Bauman A, Mummery K, Owen N. Test-retest reliability of four physical activity measures used in population surveys. *J Sci Med Sport*. 2004;7(2):205-215.
52. Booth M, Bauman AE, Timperio A, Salmon J, Trost S. *Measurement of Adult Physical Activity: Reliability, Comparison and Validity of Self-Report Surveys for Population Surveillance. Summary and Recommendations*.; 2002.
53. *Centre for Epidemiology and Research NSW Population Health Survey*. Sydney; 2014.
54. CATI Technical Reference Group. *Population Health Monitoring and Surveillance: Question Development Field Testing*.; 2004.
55. Flood VM, Wen LM, Hardy LL, Rissel C, Simpson JM, Baur LA. Reliability and validity of a short FFQ for assessing the dietary habits of 2-5-year-old children, Sydney, Australia. *Public Health Nutr*. 2014;17(3):498-509.
56. Jensen MP, Karoly P, Huger R. The development and preliminary validation of an instrument to assess patients' attitudes toward pain. *J Psychosom Res*. 1987;31(3):393-400.
57. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*. 2003;37(3):197-206.
58. Landau S, Emsley R, Dunn G. Beyond total treatment effects in RCTs: why we need to measure outcomes at baseline when investigating mediation. *Trials*. 2015;16(Suppl 2):O42.
59. Imai K, Yamamoto T. Identification and Sensitivity Analysis for Multiple Causal Mechanisms: Revisiting Evidence from Framing Experiments. *Polit Anal*.

2013;21(2):141-171.

60. Imai K, Keele L, Yamamoto T. Identification, Inference and Sensitivity Analysis for Causal Mediation Effects. *Stat Sci*. 2010;25(1):51-71.

61. Dunn G, Emsley R, Liu H, et al. Evaluation and validation of social and psychological markers in randomised trials of complex interventions in mental health. *NIHR Rep*. 2015;19(93).

62. Cicuttini FM, Wluka AE. Not just loading and age: The dynamics of osteoarthritis, obesity and inflammation. *Med J Aust*. 2016;204(2):47-47.e1.

63. O'Hara BJ, Bauman AE, Eakin EG, et al. Evaluation Framework for Translational Research: Case Study of Australia's Get Healthy Information and Coaching Service®. *Health Promot Pract*. 2013;14(3):380-389.

64. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(8):1153-1159.

65. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84(2):191.

66. Vittinghoff E, Neilands TB. Sample Size for Joint Testing of Indirect Effects. *Prev Sci*. 2014;16(8):1128-1135.

67. Warkentin LM, Majumdar SR, Johnson JA, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. *BMC Med*. 2014;12:175.

68. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *Eur J Pain*. 2004;8(4):283-291.

69. VanderWeele T. *Explanation in Causal Inference: Methods for Mediation and Interaction*. Oxford University Press; 2015.

70. O'Rourke HP, Mackinnon DP. When the test of mediation is more powerful than the test of the total effect. *Behav Res*. 2014:424-442.

71. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods*. 2010;15(4):309-334.

72. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-1182.

73. Manson J, Shufelt C, Robins J. The Potential for Postrandomization Confounding in Randomized Clinical Trials. *Jama*. 2016;315(21):2273-2274.

74. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. mediation: R Package for Causal Mediation Analysis. *J Stat Softw*. 2014;59(5):1-38.

75. Ng VKY, Cribbie RA. Using the Gamma Generalized Linear Model for Modeling Continuous, Skewed and Heteroscedastic Outcomes in Psychology. *Curr Psychol*. 2016:1-11.

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 unexplained indirect effects). Red lines represent possible effects that could induce confounding for indirect and direct effects. PA = Physical Activity; PB = Pain Beliefs; QoL = Quality of Life. **(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.

Figure 2. Overall Analysis Plan. Note: “Pain” is interchangeable with disability and QoL.

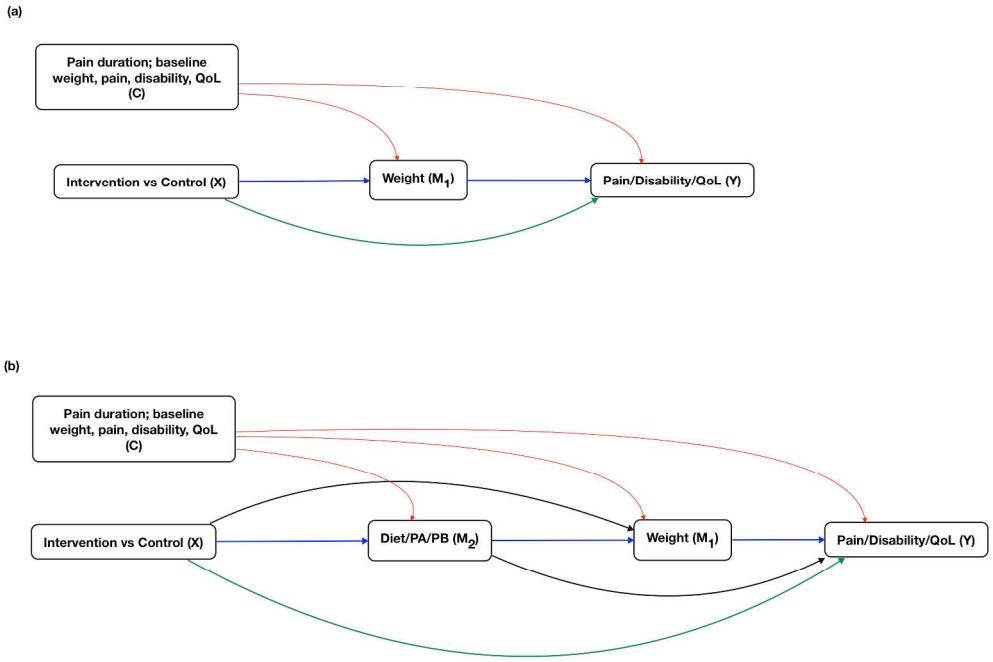


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Figure 1
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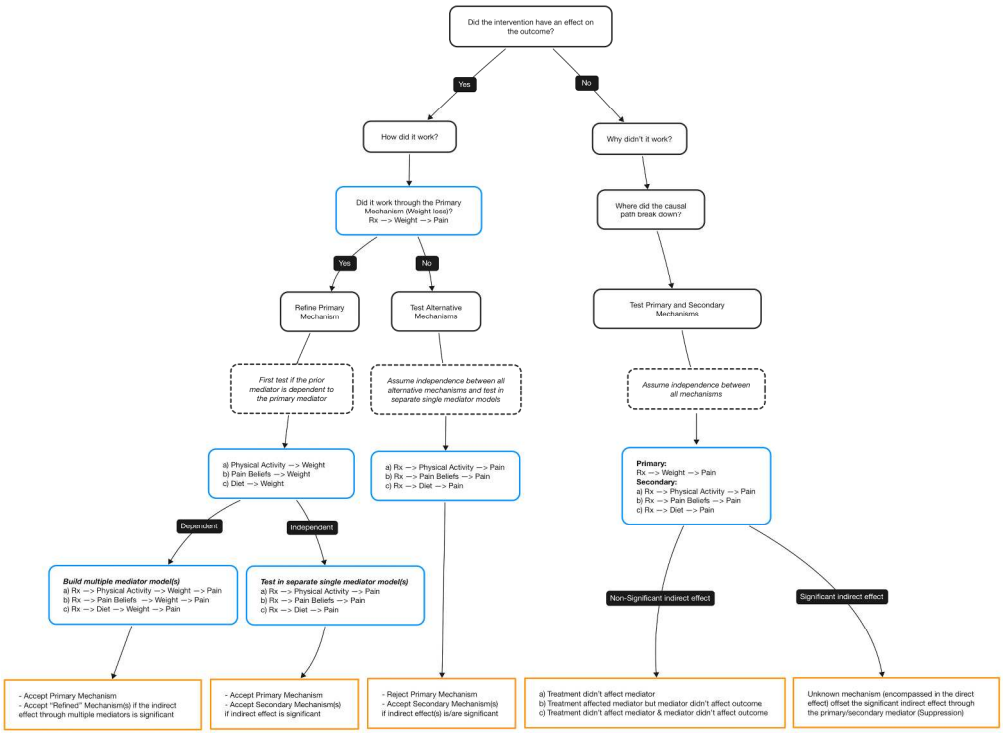

Figure 2. Overall Analysis Plan. Note: "Pain" is interchangeable with disability and QoL.

Figure 2
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