VERITY 2021 Methodology Core Course on Causal Inference and Mediation Analysis in Rheumatic and Musculoskeletal Diseases

Applications of mediation analysis.

Prof Rana Hinman

@HinmanRana

Disclosures

- I am currently supported by a Senior Research Fellowship from NHMRC
- My research is currently funded by grants from NHMRC, ARC, Medibank.
- I am a physiotherapist, not a biostatistician

medibank
For Better Health
Medibank Better Health Foundation

Australian Government
National Health and Medical Research Council
NHMRC

Australian Government
Australian Research Council

Acknowledgements- CHESM Team

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MELBOURNE

Goals & objectives

Understand the practical application of mediation analysis:

1. Provide examples of mediation including direct and indirect effect of treatment strategies on outcomes

2. Recommend practical implementations of mediation analysis in rheumatology and musculoskeletal conditions

Research context

Knee osteoarthritis……

High-burden chronic condition…

Pain & physical disability major problems…..

Focus on non-pharmacological management

How does mediation analysis help our research team?

- Helps us understand how/why treatments do and don’t work
  - Confirm hypothesized mechanism underlying intervention

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- Helps us understand our clinical trial findings
  - Examine why an intervention was not successful

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- Helps us understand our clinical trial findings
  - Examine why an intervention was not successful
- Helps us improve our treatments to improve patient outcomes
  - Boost treatment “potency” by focus on the mechanism of action
  - Help identify possible improvements to interventions for evaluation in future research

Biomechanics….null RCTs are common in knee OA!

Claims/assumptions about mediation made from indirect evidence, small, uncontrolled studies and/or correlational analyses without controlling for confounders

Annals of Internal Medicine ORIGINAL RESEARCH

Unloading Shoes for Self-Management of Knee Osteoarthritis

A Randomized Trial

Rana S. Hinman, BPhysio(Hons), PhD; Tim V. Wrigley, BSc(Hons), MSc; Ben R. Metcalf, BSc(Hons); Penny K. Campbell, BAppSci(FoodSci&Nutr); Kade L. Paterson, BAppSci(Hons), BPod, PhD; David J. Hunter, MBBS, PhD; Jessica Kasza, BSc(Hons), PhD; Andrew Forbes, BSc(Hons), MS, PhD; and Kim L. Bennell, BAppSci(Physio), PhD

Background: Appropriate footwear is recommended for self-management of knee osteoarthritis. Shoes that reduce harmful knee loads are available, but symptomatic effects are uncertain.

Objective: To evaluate the efficacy of unloading shoes in alleviating knee osteoarthritis symptoms.

Design: Participant- and assessor-blinded comparative effectiveness randomized, controlled trial. (Australian New Zealand Clinical Trials Registry: ACTRN12613000851763)

Setting: Community.

Participants: 164 persons with medial knee osteoarthritis.

Intervention: Walking shoes with triple-density, variable-stiffness midsoles and mild lateral-wedge insoles designed to unload the medial knee and worn daily (intervention) versus conventional walking shoes (comparator).

Measurements: Primary outcomes were pain with walking (assessed on a numerical rating scale [NRS]) and physical function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) at 6 months. Secondary outcomes were knee pain and stiffness (WOMAC), average pain (NRS), intermittent and constant knee pain (Intermittent and Constant Osteoarthritis Pain questionnaire), quality of life (Assessment of Quality of Life instrument), physical activity (Physical Activity Scale for the Elderly), and global change in pain and function (Likert scales).

Results: A total of 160 participants (98%) completed primary outcome measures at 6 months. Changes in pain (mean difference, 0.0 units [95% CI, −0.9 to 0.8 unit]) and function (mean difference, 0.3 unit [CI, −3.2 to 3.7 units]) did not differ between groups at 6 months, with both groups showing clinically relevant improvements in function and the intervention group showing clinically relevant improvements in pain. There were no differences in secondary outcomes. Pain was globally improved in 54% of participants, and function was globally improved in 44% to 48%. Unloading shoes were not associated with increased probability of improvement (odds ratios, 0.99 [CI, 0.53 to 1.86] for pain and 0.85 [CI, 0.45 to 1.61] for function).

Limitation: Effects on joint structure were not evaluated.

Conclusion: Shoes with modified midsoles to unload the medial knee conferred no additional benefit over conventional walking shoes. Both improved pain and function by clinically relevant amounts.

Primary Funding Source: Australian National Health and Medical Research Council.

Ann Intern Med. doi:10.7326/M16-0453 **www.annals.org**
For author affiliations, see end of text.

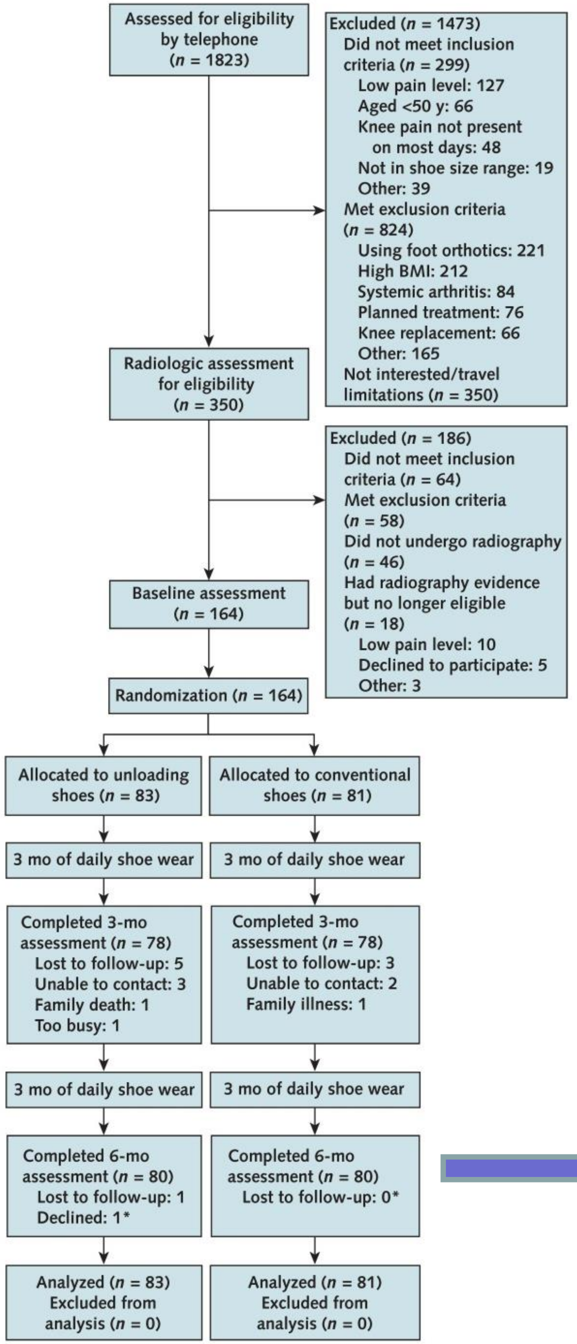
SHARK Trial

- **Design:** 2-arm parallel RCT, prospectively registered & protocol published in 2014

- **Participants:** 164 people with knee OA from community

- **Primary outcomes:** 6 months
  - Average pain on walking (NRS)
  - Self-reported physical function (WOMAC)

Figure. Study flow diagram.



Assessed for eligibility by telephone (*n* = 1823)

Excluded (*n* = 1473)
- Did not meet inclusion criteria (*n* = 299)
  - Low pain level: 127
  - Aged <50 y: 66
  - Knee pain not present on most days: 48
  - Not in shoe size range: 19
  - Other: 39
- Met exclusion criteria (*n* = 824)
  - Using foot orthotics: 221
  - High BMI: 212
  - Systemic arthritis: 84
  - Planned treatment: 76
  - Knee replacement: 66
  - Other: 165
- Not interested/travel limitations (*n* = 350)

Radiologic assessment for eligibility (*n* = 350)

Excluded (*n* = 186)
- Did not meet inclusion criteria (*n* = 64)
- Met exclusion criteria (*n* = 58)
- Did not undergo radiography (*n* = 46)
- Had radiography evidence but no longer eligible (*n* = 18)
  - Low pain level: 10
  - Declined to participate: 5
  - Other: 3

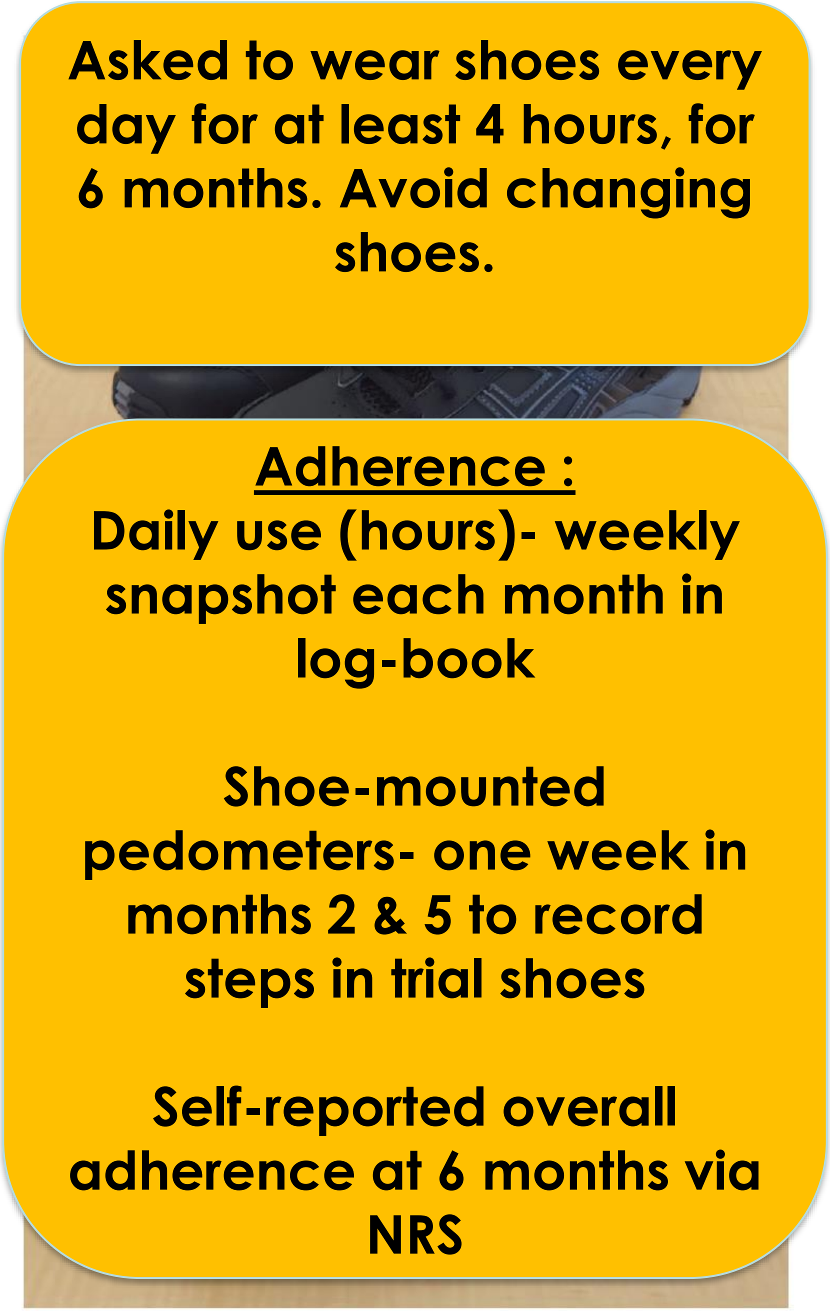
Baseline assessment (*n* = 164)

Randomization (*n* = 164)

Allocated to unloading shoes (*n* = 83)	Allocated to conventional shoes (*n* = 81)
3 mo of daily shoe wear	3 mo of daily shoe wear
Completed 3-mo assessment (*n* = 78) Lost to follow-up: 5 Unable to contact: 3 Family death: 1 Too busy: 1	Completed 3-mo assessment (*n* = 78) Lost to follow-up: 3 Unable to contact: 2 Family illness: 1
3 mo of daily shoe wear	3 mo of daily shoe wear
Completed 6-mo assessment (*n* = 80) Lost to follow-up: 1 Declined: 1*	Completed 6-mo assessment (*n* = 80) Lost to follow-up: 0*
Analyzed (*n* = 83) Excluded from analysis (*n* = 0)	Analyzed (*n* = 81) Excluded from analysis (*n* = 0)

98% of people completed primary outcome measures at 6 months

Appendix Figure. Intervention (unloading) shoes (*top*) and comparator (conventional) shoes (*bottom*).



Asked to wear shoes every day for at least 4 hours, for 6 months. Avoid changing shoes.

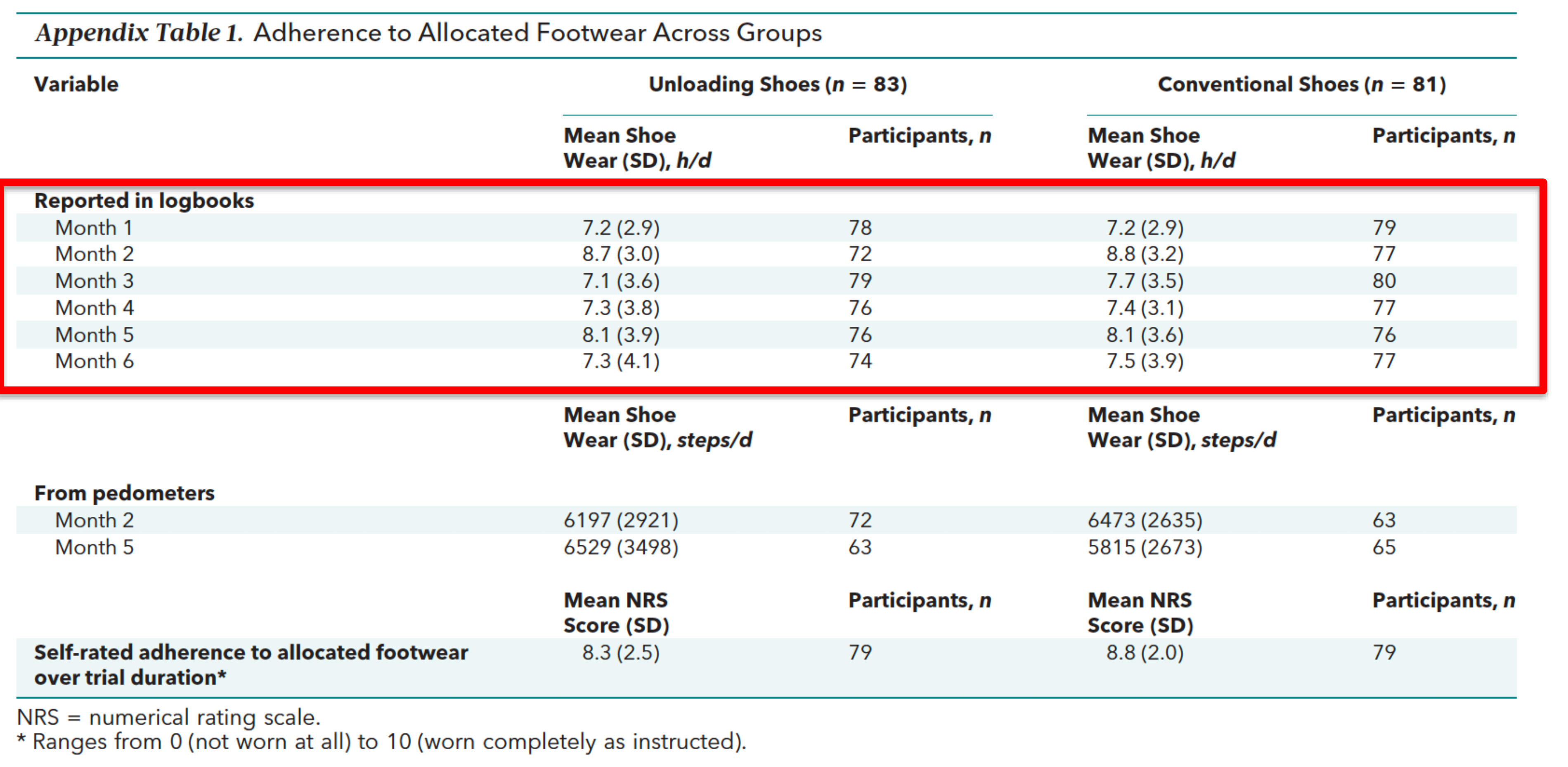
Adherence :

Daily use (hours)- weekly snapshot each month in log-book

Shoe-mounted pedometers- one week in months 2 & 5 to record steps in trial shoes

Self-reported overall adherence at 6 months via NRS

Adherence was excellent



Appendix Table 1. Adherence to Allocated Footwear Across Groups

Variable	**Unloading Shoes (*n* = 83)**		**Conventional Shoes (*n* = 81)**	
	Mean Shoe Wear (SD), *h/d*	**Participants, *n***	**Mean Shoe Wear (SD), *h/d***	**Participants, *n***
Reported in logbooks				
Month 1	7.2 (2.9)	78	7.2 (2.9)	79
Month 2	8.7 (3.0)	72	8.8 (3.2)	77
Month 3	7.1 (3.6)	79	7.7 (3.5)	80
Month 4	7.3 (3.8)	76	7.4 (3.1)	77
Month 5	8.1 (3.9)	76	8.1 (3.6)	76
Month 6	7.3 (4.1)	74	7.5 (3.9)	77
	Mean Shoe Wear (SD), *steps/d*	**Participants, *n***	**Mean Shoe Wear (SD), *steps/d***	**Participants, *n***
From pedometers				
Month 2	6197 (2921)	72	6473 (2635)	63
Month 5	6529 (3498)	63	5815 (2673)	65
	Mean NRS Score (SD)	**Participants, *n***	**Mean NRS Score (SD)**	**Participants, *n***
Self-rated adherence to allocated footwear over trial duration*	8.3 (2.5)	79	8.8 (2.0)	79

NRS = numerical rating scale.
* Ranges from 0 (not worn at all) to 10 (worn completely as instructed).

Main findings

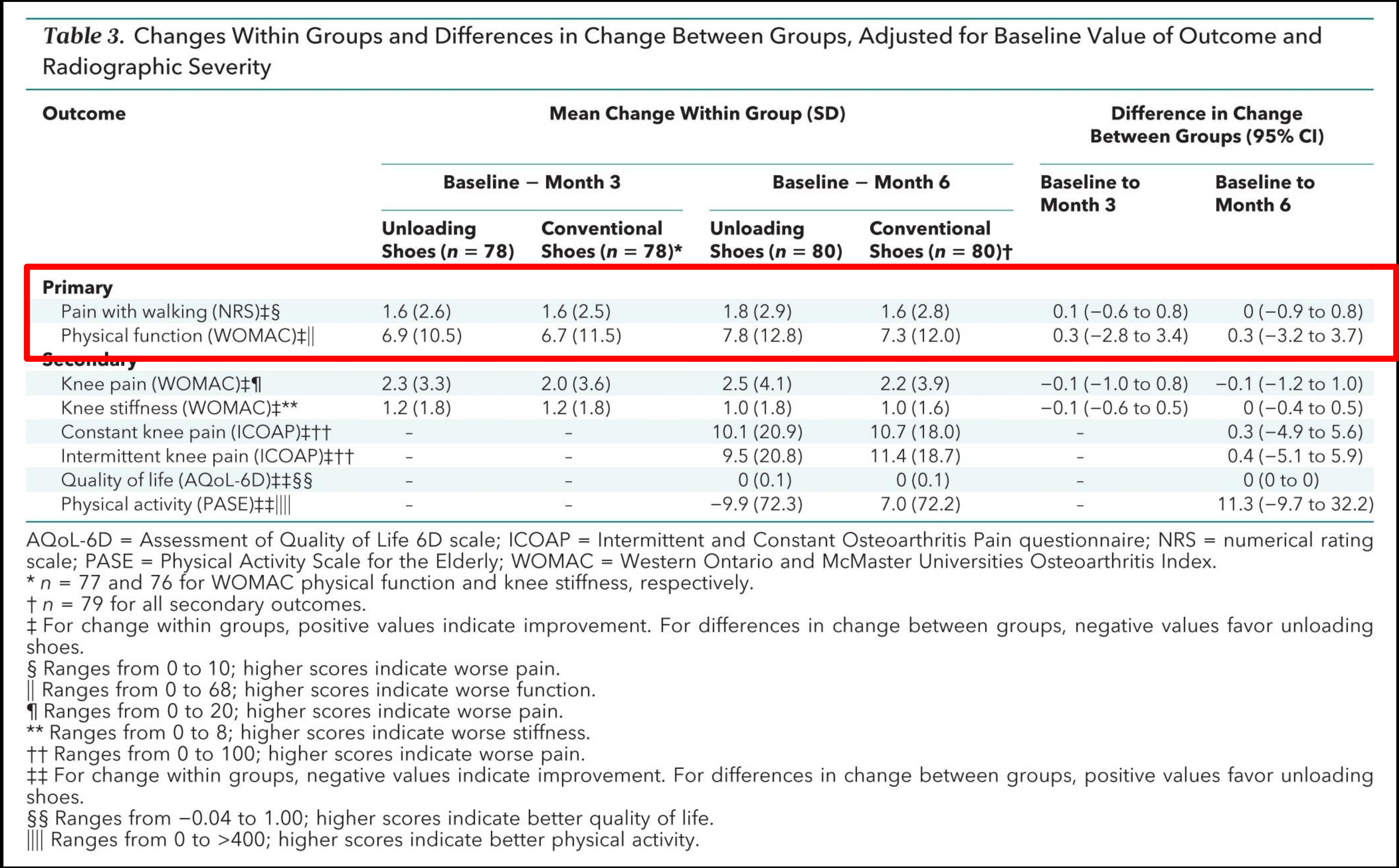


Table 3. Changes Within Groups and Differences in Change Between Groups, Adjusted for Baseline Value of Outcome and Radiographic Severity

Outcome	Mean Change Within Group (SD)				Difference in Change Between Groups (95% CI)	
	Baseline – Month 3		Baseline – Month 6		Baseline to Month 3	Baseline to Month 6
	Unloading Shoes (*n* = 78)	Conventional Shoes (*n* = 78)*	Unloading Shoes (*n* = 80)	Conventional Shoes (*n* = 80)†		
Primary						
Pain with walking (NRS)‡§	1.6 (2.6)	1.6 (2.5)	1.8 (2.9)	1.6 (2.8)	0.1 (−0.6 to 0.8)	0 (−0.9 to 0.8)
Physical function (WOMAC)‡‖	6.9 (10.5)	6.7 (11.5)	7.8 (12.8)	7.3 (12.0)	0.3 (−2.8 to 3.4)	0.3 (−3.2 to 3.7)
Secondary						
Knee pain (WOMAC)‡¶	2.3 (3.3)	2.0 (3.6)	2.5 (4.1)	2.2 (3.9)	−0.1 (−1.0 to 0.8)	−0.1 (−1.2 to 1.0)
Knee stiffness (WOMAC)‡**	1.2 (1.8)	1.2 (1.8)	1.0 (1.8)	1.0 (1.6)	−0.1 (−0.6 to 0.5)	0 (−0.4 to 0.5)
Constant knee pain (ICOAP)‡††	–	–	10.1 (20.9)	10.7 (18.0)	–	0.3 (−4.9 to 5.6)
Intermittent knee pain (ICOAP)‡††	–	–	9.5 (20.8)	11.4 (18.7)	–	0.4 (−5.1 to 5.9)
Quality of life (AQoL-6D)‡‡§§	–	–	0 (0.1)	0 (0.1)	–	0 (0 to 0)
Physical activity (PASE)‡‡‖‖	–	–	−9.9 (72.3)	7.0 (72.2)	–	11.3 (−9.7 to 32.2)

AQoL-6D = Assessment of Quality of Life 6D scale; ICOAP = Intermittent and Constant Osteoarthritis Pain questionnaire; NRS = numerical rating scale; PASE = Physical Activity Scale for the Elderly; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

* *n* = 77 and 76 for WOMAC physical function and knee stiffness, respectively.

† *n* = 79 for all secondary outcomes.

‡ For change within groups, positive values indicate improvement. For differences in change between groups, negative values favor unloading shoes.

§ Ranges from 0 to 10; higher scores indicate worse pain.

‖ Ranges from 0 to 68; higher scores indicate worse function.

¶ Ranges from 0 to 20; higher scores indicate worse pain.

** Ranges from 0 to 8; higher scores indicate worse stiffness.

†† Ranges from 0 to 100; higher scores indicate worse pain.

‡‡ For change within groups, negative values indicate improvement. For differences in change between groups, positive values favor unloading shoes.

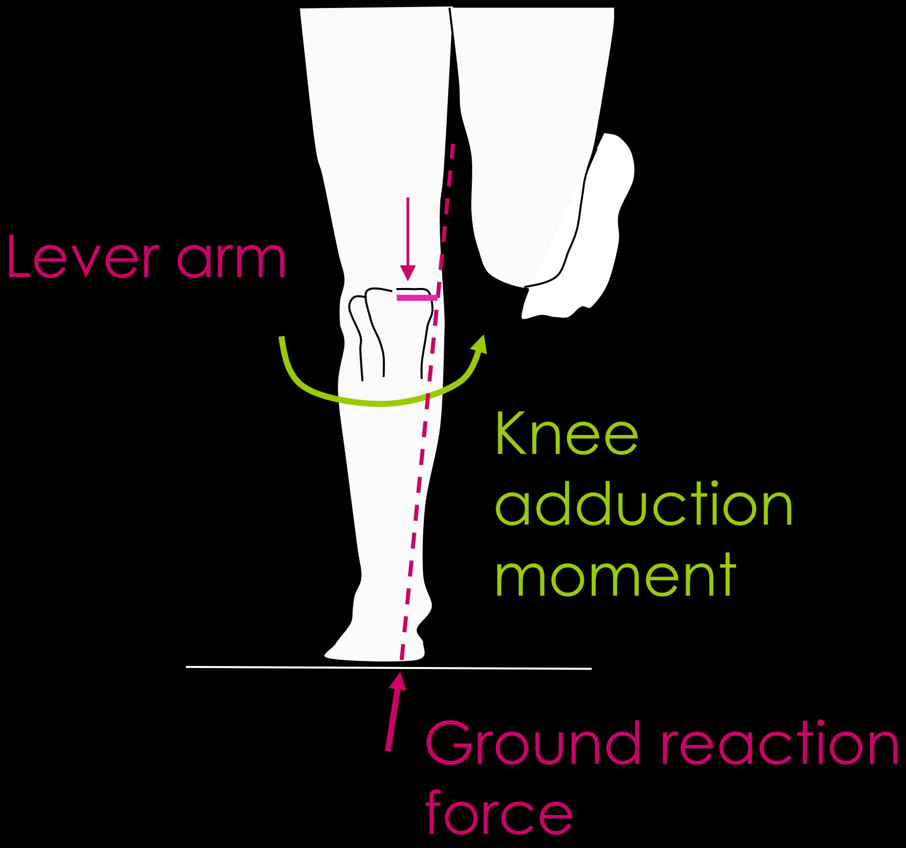
§§ Ranges from −0.04 to 1.00; higher scores indicate better quality of life.

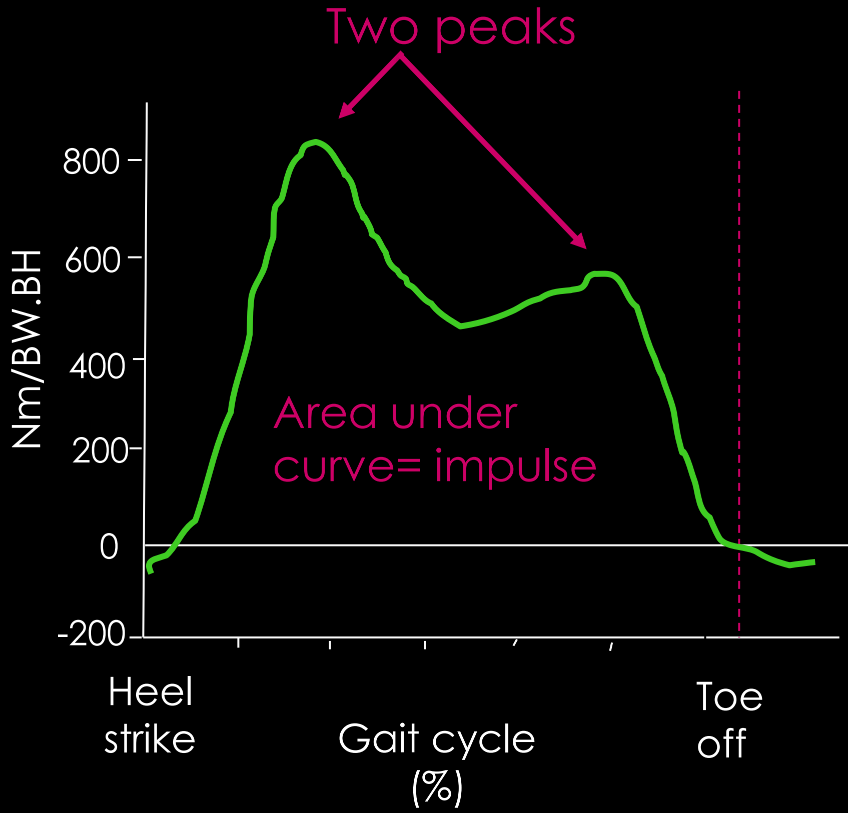
‖‖ Ranges from 0 to >400; higher scores indicate better physical activity.

Why were unloading shoes ineffective?

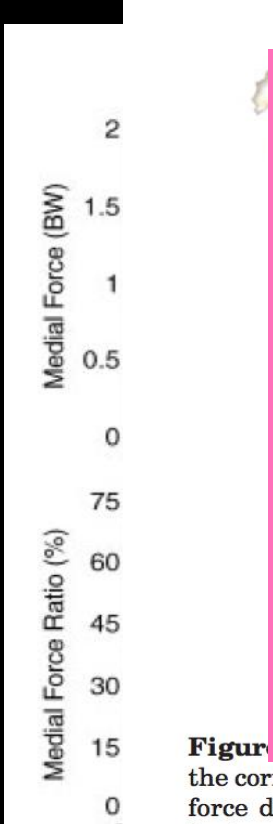
- Knee OA symptoms not as strongly linked to altered biomechanics as we previously thought?
- Modest reductions in knee load with unloading shoes not big enough to shift symptoms?
- Variability in biomechanical response to footwear?
- Causes of pain multi-factorial- perhaps only subgroups have biomechanically-driven pain?

Hypothesised mechanism of unloading shoes



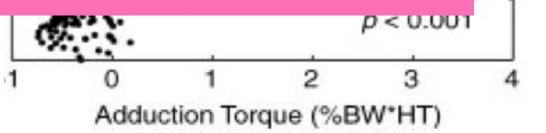


Knee load and osteoarthritis



Increased knee load:

- Increased prevalence of structural abnormalities (bone & cartilage)
- Increased risk of structural progression over time
- Increased risk of knee arthroplasty
- Development of knee pain



Figur the correlation between the external knee adduction torque and internal medial contact force during gait. Gait analysis was used to make adduction torque measurements. Instrumented implant load cell measurements and fluoroscopic motion measurements were used in a dynamic contact model to develop a linear regression model for calculating medial contact force directly from the four load cell measurements. [Color scheme can be viewed in the online issue, which is available at http://www.interscience.wiley.com]

Gel Melbourne OA shoes

Design features:

- Triple-density midsole, that is stiffer laterally compared to medially
- 5 degree lateral wedge insole attached to sock-liner

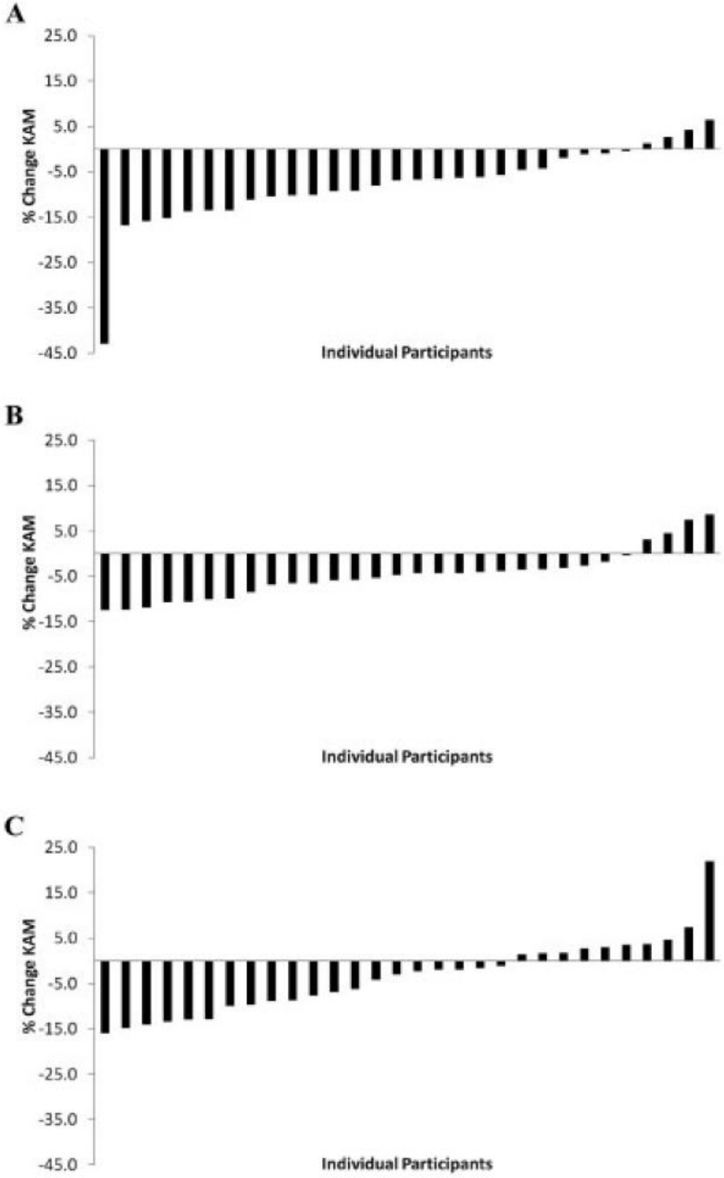


Figure 2. Individual changes in the first peak knee adduction moment (KAM) when walking in the modified shoe, reported as the percentage change from the control shoe condition. **A,** Osteoarthritis group. **B,** Overweight group. **C,** Healthy weight group.

8-9% mean reduction in the external knee adduction moment in people with knee OA

Bennell et al *Arthritis Rheum* (2013)

Osteoarthritis and Cartilage 26 (2018) 227–235

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Moderators and mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis: an exploratory analysis of the SHARK randomised controlled trial

K.L. Paterson [†] [*], J. Kasza [‡], K.L. Bennell [†], T.V. Wrigley [†], B.R. Metcalf [†], P.K. Campbell [†], D.J. Hunter [§], R.S. Hinman [†]

[†] *Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Melbourne, Australia*
[‡] *Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*
[§] *Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Rheumatology Department, Royal North Shore Hospital Australia, Sydney, Australia*

ARTICLE INFO

Article history:
Received 24 July 2017
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Keywords:
Osteoarthritis
Pain
Moderators
Mediators
Knee adduction moment
Phenotype

SUMMARY

Objective: To investigate moderators and biomechanical mediators of effects of unloading shoes on knee pain in people with knee osteoarthritis (OA).
Methods: Exploratory analysis from 164 participants in a clinical trial comparing unloading (ASICS GEL-Melbourne OA) to conventional walking shoes. The primary outcome was 6-month change in knee pain (11-point numerical rating scale (NRS)). Moderators included baseline peak knee adduction moment (KAM), radiographic severity (Kellgren & Lawrence (KL) scale), body mass, foot posture, neuropathic pain and diffuse knee pain. Mediators included change in peak KAM and KAM impulse.
Results: Radiographic severity was the only moderator to interact with footwear group ($P = 0.02$). Participants with KL = 2 experienced greater pain reductions with conventional compared to unloading shoes (mean difference in change in pain −1.64 units, 95% CI −3.07, −0.21), while unloading shoes tended to result in greater pain reductions than conventional shoes in KL = 3 (0.98, 95% CI −0.44, 2.39) and KL = 4 (0.64, 95% CI −0.64, 1.93). No variable showed any significant mediating effect in the entire cohort. However, there was some evidence that unloading shoes may reduce pain through reductions in peak KAM (indirect effect −0.31, 95% CIs −0.65, 0.03; $P = 0.07$) in people with KL ≥ 3, compared to conventional shoes.

Osteoarthritis and Cartilage 26 (2018) 227–235

Osteoarthritis and Cartilage

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[†] *Centre for Health, Exercise and Sports Medicine, The University of Melbourne, Melbourne, Australia*
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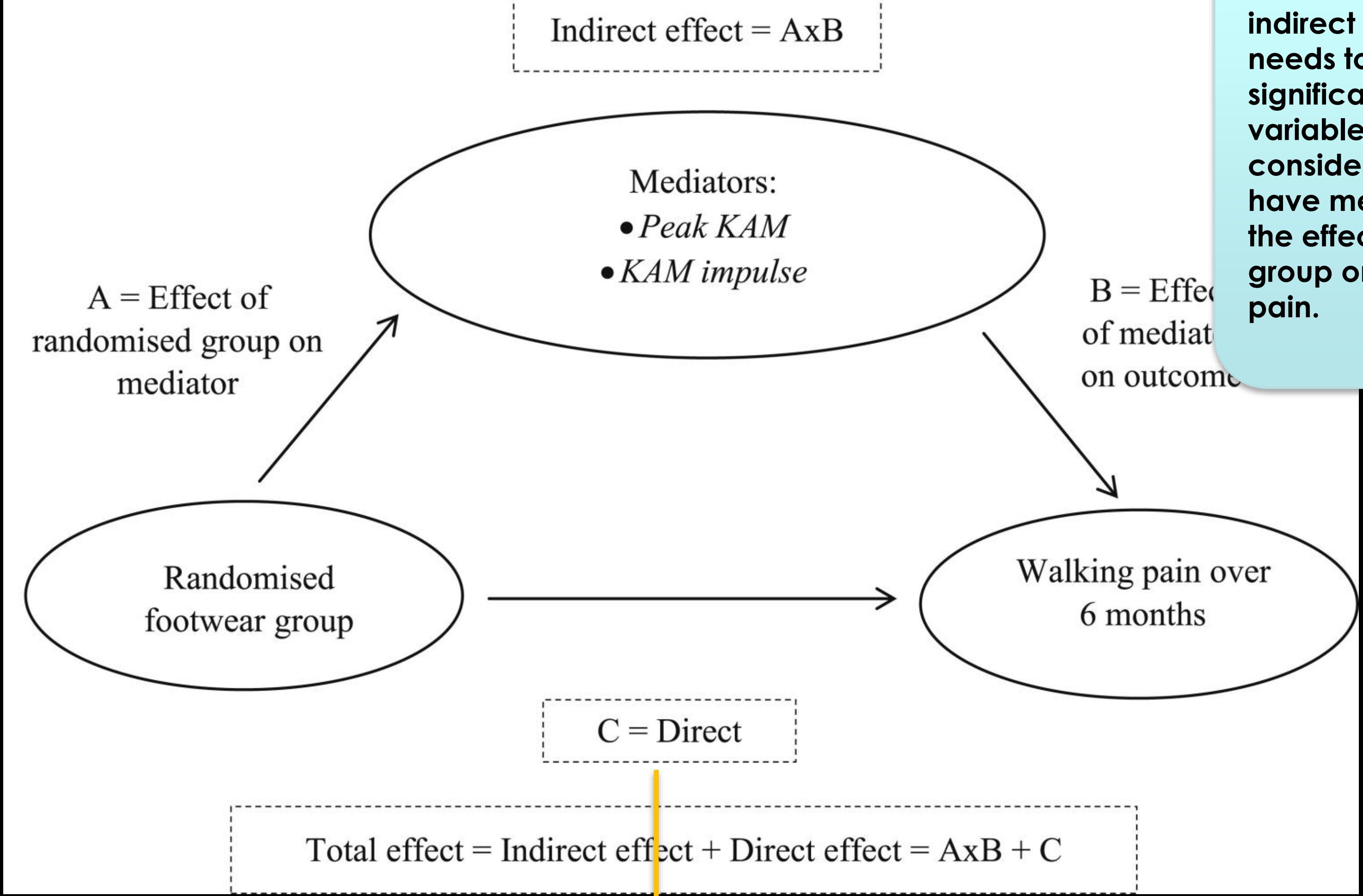
Biostatistician, Dr Jess Kasza
Monash University

The effect of the treatment on the outcome that acts through the mediator)



P value for the indirect pathway needs to be significant for the variable to be considered to have mediated the effect of group on walking pain.

The effect of the treatment on the outcome that does NOT act through the mediator)

Effect estimates (95% confidence intervals) of the total, direct, and indirect effects of randomised footwear group on walking pain at 6 months, by radiographic severity

Potential Mediator	Total effect Effect (95% CI), p value	Direct effect Effect (95% CI), p value	Indirect effect Effect (95% CI), p value
Peak KAM (Nm/BW*H%)			
KL Grade 2	-1.38 (-2.81, 0.06) 0.06	-1.26 (-2.71, 0.20) 0.09	-0.12 (-0.44, 0.20) 0.47
KL Grades 3 & 4	0.70 (-0.31, 1.70) 0.18	1.01 (0.01, 2.01) 0.05	-0.31 (-0.65, 0.03) 0.07
KAM impulse (Nm.s/BW*H%)			
KL Grade 2	-1.40 (-2.74, -0.06) 0.04	-1.32 (-2.70, 0.07) 0.06	-0.09 (-0.41, 0.24) 0.60
KL Grades 3 & 4	0.63 (-0.40, 1.66) 0.23	0.74 (-0.36, 1.85) 0.19	-0.11 (-0.46, 0.24) 0.54

May be some evidence that unloading shoes reduce walking pain by acting through reductions in peak KAM for KL grades 3 & 4, but not in people with KL grade 2???

Implications?

- Therapeut derated by radiog
  - Reductio n in walking p 4, but not KL grade
- Data sugg duction in KAM was n NRS walking p
  - mean ac conventi units (possibly
  - unloading y meaningful

Need to redesign unloading shoes to dramatically boost their unloading effects

- **-Adverse effects at foot ankle?**
- **Adherence & comfort?**

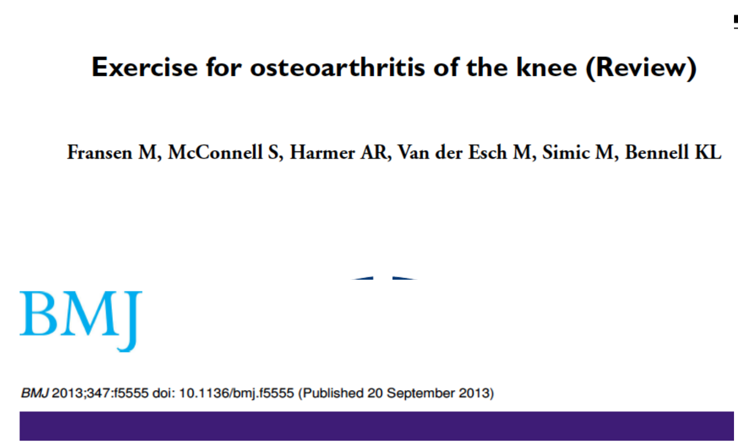
Or do we combine unloading shoes with another biomechanical treatment?

- **Knee brace?**
- **Gait retraining?**

Are there more fruitful interventions to explore?

Think carefully about the subgroup of patients we recruit for RCTs that test biomechanical interventions

How does strengthening exercise improve knee OA symptoms?



Exercise for osteoarthritis of the knee (Review)

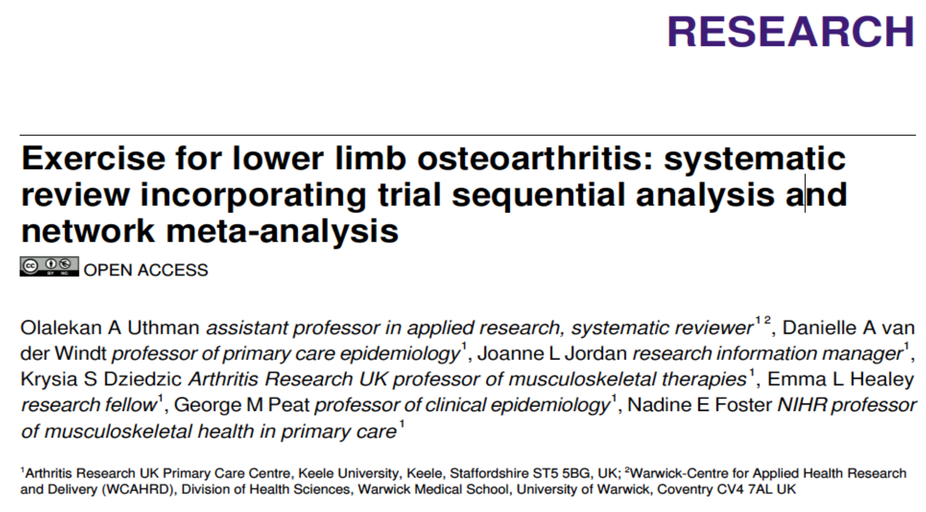
Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 3, March 2014, pp 622–636
DOI 10.1002/art.38290
© 2014, American College of Rheumatology

Impact of Exercise Type and Dose on Pain and Disability in Knee Osteoarthritis

A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials

C. Juhl,[1] R. Christensen,[2] E. M. Roos,[3] W. Zhang,[4] and H. Lund[3]



BMJ

BMJ 2013;347:f5555 doi: 10.1136/bmj.f5555 (Published 20 September 2013)

RESEARCH

Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis

OPEN ACCESS

Olalekan A Uthman *assistant professor in applied research, systematic reviewer*[1 2], Danielle A van der Windt *professor of primary care epidemiology*[1], Joanne L Jordan *research information manager*[1], Krysia S Dziedzic *Arthritis Research UK professor of musculoskeletal therapies*[1], Emma L Healey *research fellow*[1], George M Peat *professor of clinical epidemiology*[1], Nadine E Foster *NIHR professor of musculoskeletal health in primary care*[1]

[1]Arthritis Research UK Primary Care Centre, Keele University, Keele, Staffordshire ST5 5BG, UK; [2]Warwick-Centre for Applied Health Research and Delivery (WCAHRD), Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry CV4 7AL UK

THE COCHRANE COLLABORATION®

Potential mediators?

Inflammation

Cartilage/OA properties

Muscle strength

Muscle properties

ROM/flexibility

Gait properties

Biomechanics

ne

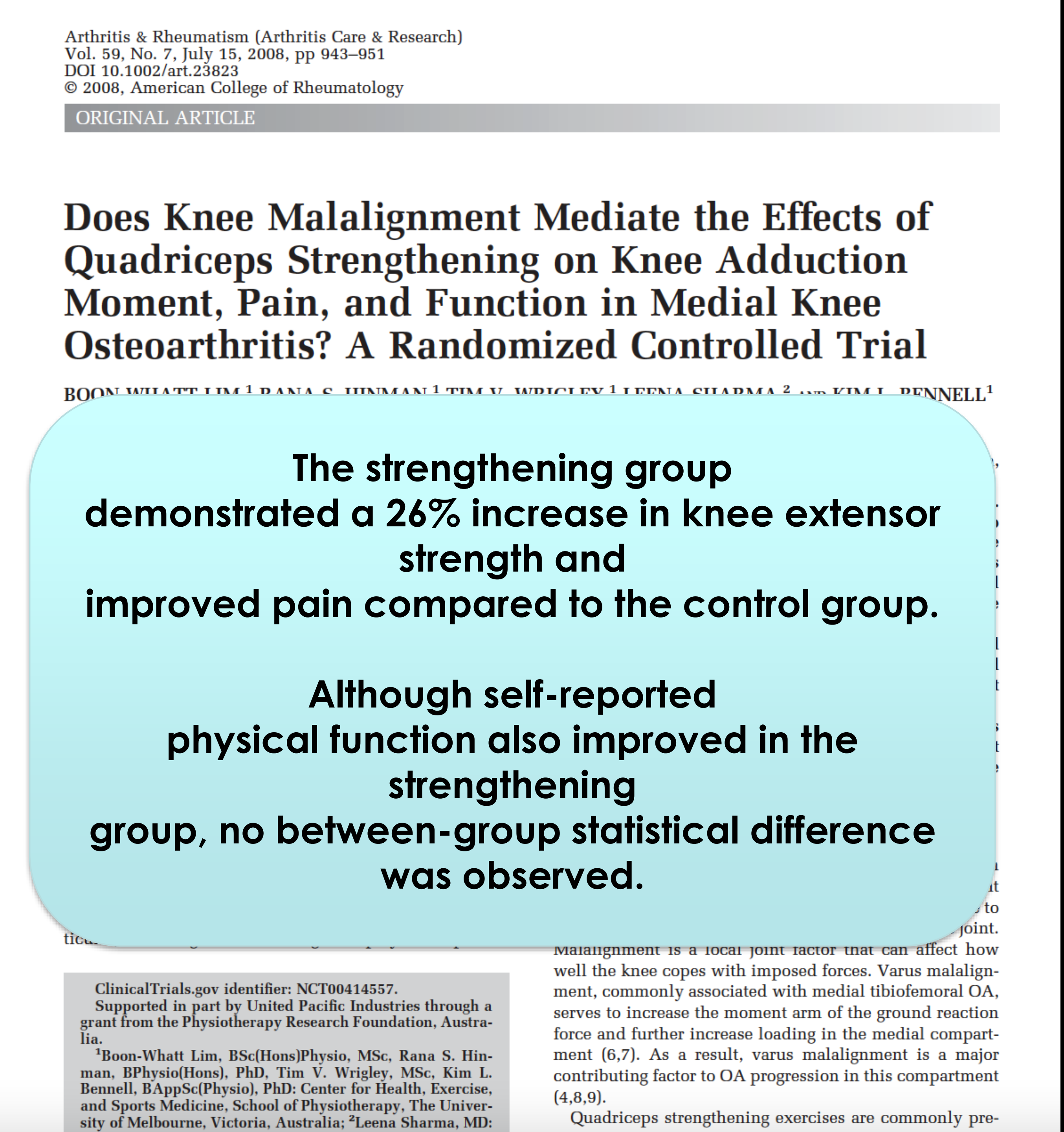
ce

60% (31 out of 52) of the studies showed a significant increase in knee extensor muscle strength
&
71% (22 out of 31) in knee flexor muscle strength

with exercise

No study performed a mediation analysis!

Runhaar et al, Osteoarthritis & Cartilage 2015



Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 7, July 15, 2008, pp 943–951
DOI 10.1002/art.23823

ORIGINAL ARTICLE

Does Knee Malalignment Mediate the Effects of Quadriceps Strengthening on Knee Adduction Moment, Pain, and Function in Medial Knee Osteoarthritis? A Randomized Controlled Trial

BOON-WHATT LIM,[1] RANA S. HINMAN,[1] TIM V. WRIGLEY,[1] LEENA SHARMA,[2] AND KIM L. BENNELL[1]

The strengthening group demonstrated a 26% increase in knee extensor strength and improved pain compared to the control group.

Although self-reported physical function also improved in the strengthening group, no between-group statistical difference was observed.

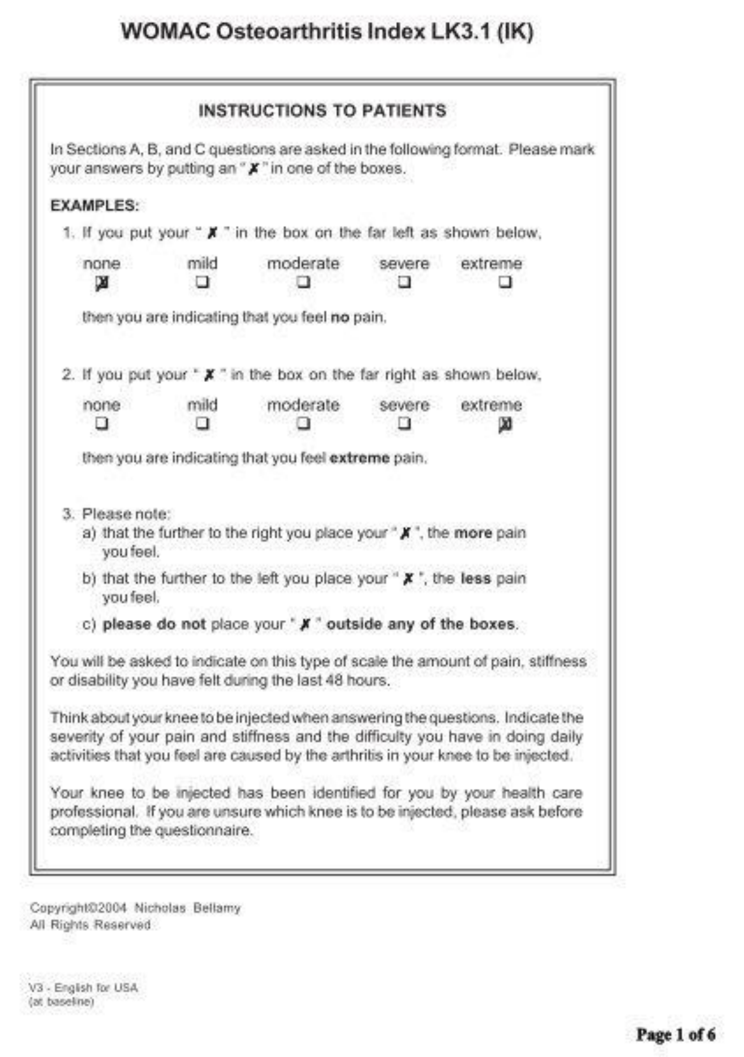
Malalignment is a local joint factor that can affect how well the knee copes with imposed forces. Varus malalignment, commonly associated with medial tibiofemoral OA, serves to increase the moment arm of the ground reaction force and further increase loading in the medial compartment (6,7). As a result, varus malalignment is a major contributing factor to OA progression in this compartment (4,8,9).

Quadriceps strengthening exercises are commonly pre-

ClinicalTrials.gov identifier: NCT00414557.
Supported in part by United Pacific Industries through a grant from the Physiotherapy Research Foundation, Australia.

[1] Boon-Whatt Lim, BSc(Hons)Physio, MSc, Rana S. Hinman, BPhysio(Hons), PhD, Tim V. Wrigley, MSc, Kim L. Bennell, BAppSc(Physio), PhD: Center for Health, Exercise, and Sports Medicine, School of Physiotherapy, The University of Melbourne, Victoria, Australia; [2] Leena Sharma, MD:

Clinical outcomes: pain and physical function



WOMAC Osteoarthritis Index LK3.1 (IK)

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an " ✗ " in one of the boxes.

EXAMPLES:

1. If you put your " ✗ " in the box on the far left as shown below,

none	mild	moderate	severe	extreme
☒	☐	☐	☐	☐

then you are indicating that you feel **no** pain.

2. If you put your " ✗ " in the box on the far right as shown below,

none	mild	moderate	severe	extreme
☐	☐	☐	☐	☒

then you are indicating that you feel **extreme** pain.

3. Please note:
   a) that the further to the right you place your " ✗ ", the **more** pain you feel.
   b) that the further to the left you place your " ✗ ", the **less** pain you feel.
   c) **please do not** place your " ✗ " **outside any of the boxes.**

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your knee to be injected when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your knee to be injected.

Your knee to be injected has been identified for you by your health care professional. If you are unsure which knee is to be injected, please ask before completing the questionnaire.

V3 - English for USA
(at baseline)

Page 1 of 6

Mediator: Knee extension strength

The effect of the treatment on the outcome that acts through the mediator)

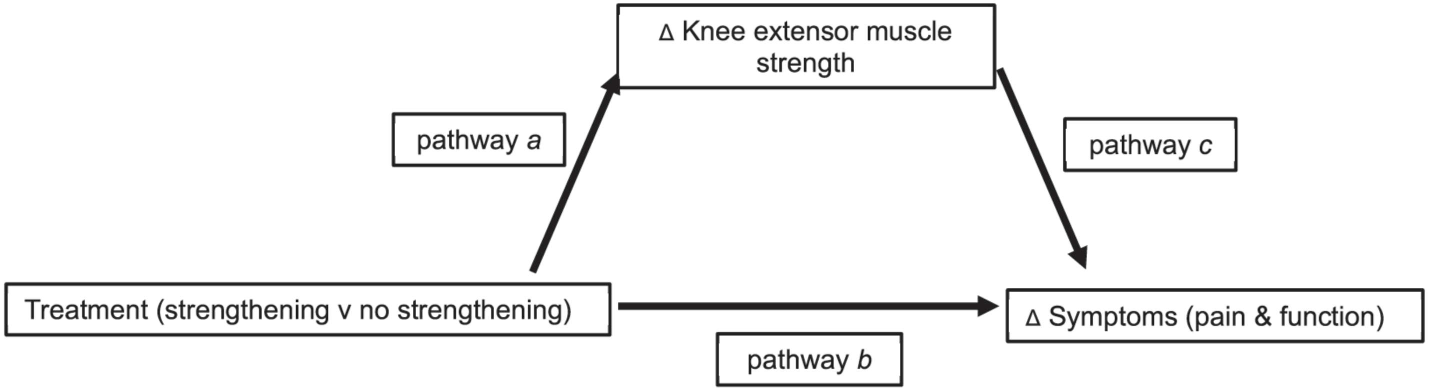


Fig. 1. Twelve-week change in knee extensor strength as a mediator of the effect of a 12-week knee extensor strengthening program (treatment) and symptoms (12-week change in pain and physical function). Pathway *a* is the effect of strengthening on knee extensor strength, pathway *b* is the direct effect of treatment on symptoms and pathway *c* is the effect of change in knee extensor strength on symptoms. Total effect is the sum of direct effect (pathway *b*) and indirect effect (pathway *a* multiplied by pathway *c*).

The effect of the treatment on the outcome that does NOT act through the mediator)

Effect estimates (95% confidence intervals) of the total, direct, and indirect effects of randomised group on pain & function

Potential Mediator	Total effect Effect (95% CI), p value	Direct effect Effect (95% CI), p value	Indirect effect Effect (95% CI), p value
Change in knee extensor strength (Nm/kg)			
Pain	1.8 (0.8, 2.8), 0.001	1.1 (0.0, 2.2), 0.064	0.7 (0.1, 1.3), 0.03
Function	2.9 (-0.2, 5.8), 0.052	1.0 (-2.3, 4.3), 0.536	1.9 (0.1, 3.6), 0.04

Increased knee extensor strength accounted for:
38% (24%, 98%) of the improvement in pain
60% (-192%, 356%) of the improvement in function

Implications?

- Increased … e effect of
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  - Data sug … tensor
    strength … t reduction
    (95% CI - …
  - 1-unit inc … ne was
    associate … -0.6) in
    physical …
- Our progr … rength
  between g …

Change in strength is one mediator, but what are the other unknown mediators??

Are we exercising patients hard enough?? Aim for greater strength increases??

Training/dosage parameters are often suboptimal in most research studies…… greater intensity, less frequency needed (in line with ACSM recommendations)

Recommendations for future research

Clinical trialists should design RCTs where possible to permit mediation analyses:

- WHY?
  - Take advantage of the robust design- utility of RCT extends beyond the estimation of intervention effects on health outcomes.
  - Increase knowledge- how to adapt interventions to improve the effectiveness of health interventions and guide implementation
  - Complex interventions with many treatment ‘ingredients” and potential mechanisms of action……
  - Non-pharma OA research has scant robust mediational analyses

EDUCATION

STRENGTHENING
EXERCISE

PHYSICAL ACTIVITY
ADVICE

DIET TO LOSE
WEIGHT

CLINICAL
OUTCOMES

Change in self-efficacy?
Change in pain beliefs?
Change in strength?
Change in physical activity?
Change in weight?

EDUCATION

STRENGTHENING EXERCISE

PHYSICAL ACTIVITY ADVICE

DIET TO LOSE WEIGHT

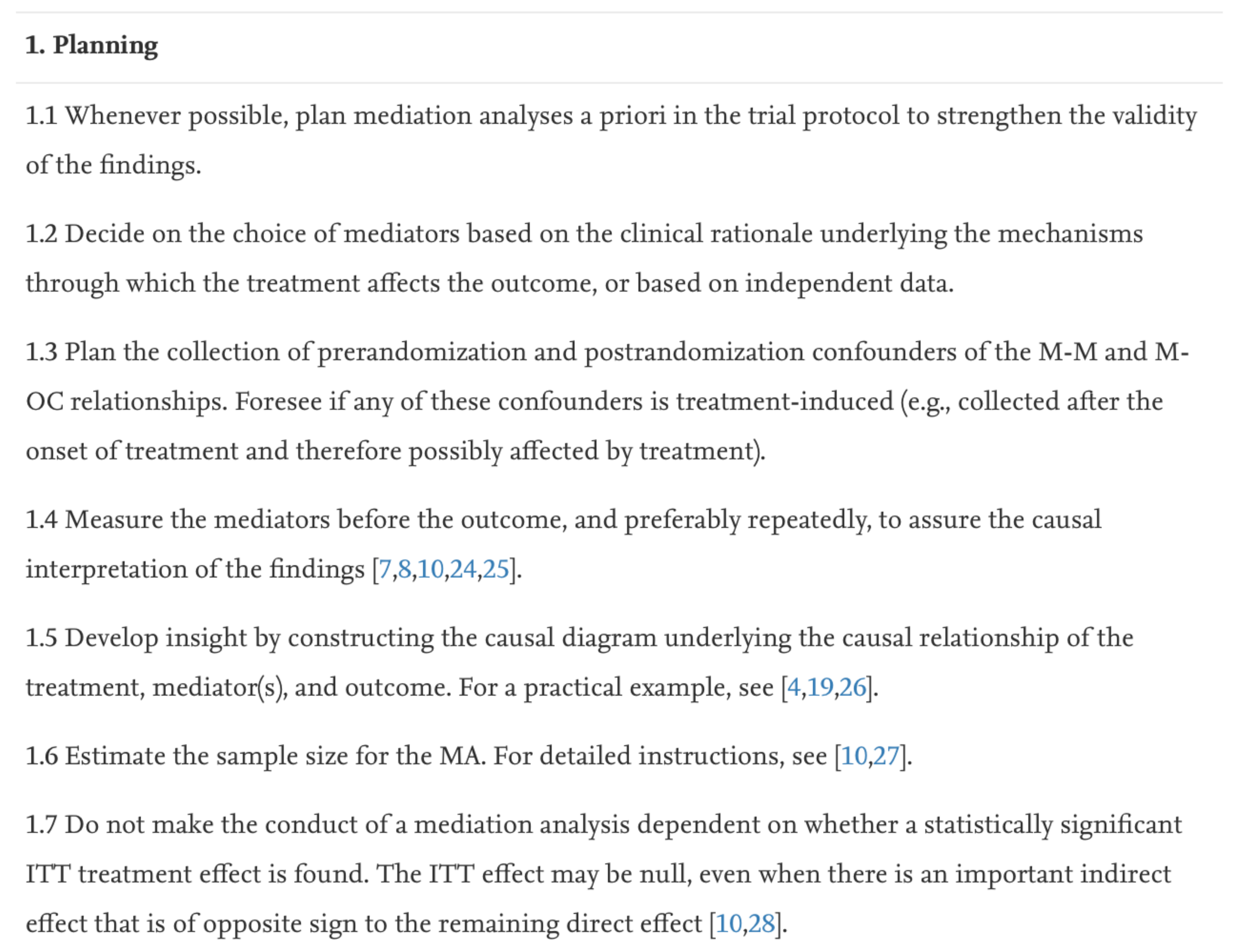
CLINICAL OUTCOMES

Change in self-efficacy?
Change in pain beliefs?
Change in strength?
Change in physical activity?
Change in weight?

Recommendations for future research

- HOW?
  - Work closely with a biostatistician!
  - *A priori* selection of mediators based on theoretical and/or empirical rationale, with pre-defined hypotheses
    - The variable must be expected to change because of the intervention, and therefore, must be measured before and after the intervention is administered.
  - Consider sample size/power issues
    - Often exploratory analyses that are hypothesis-generating rather than conclusive
    - Consider collecting data for pooling in future individual patient data meta-analysis

Recommendations on the conduct and reporting of mediation analysis in clinical research



1. Planning

1.1 Whenever possible, plan mediation analyses a priori in the trial protocol to strengthen the validity of the findings.

1.2 Decide on the choice of mediators based on the clinical rationale underlying the mechanisms through which the treatment affects the outcome, or based on independent data.

1.3 Plan the collection of prerandomization and postrandomization confounders of the M-M and M-OC relationships. Foresee if any of these confounders is treatment-induced (e.g., collected after the onset of treatment and therefore possibly affected by treatment).

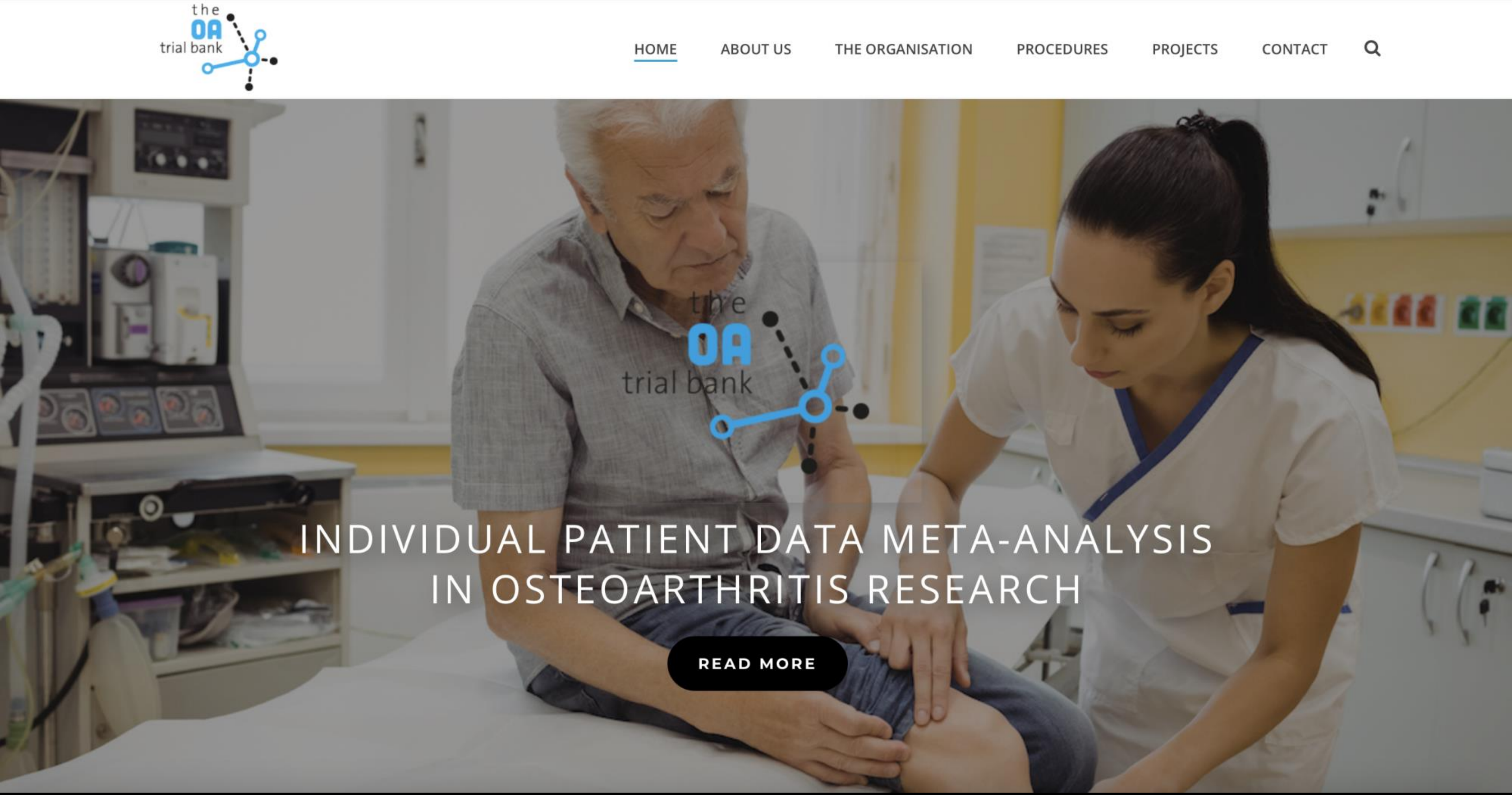
1.4 Measure the mediators before the outcome, and preferably repeatedly, to assure the causal interpretation of the findings [7,8,10,24,25].

1.5 Develop insight by constructing the causal diagram underlying the causal relationship of the treatment, mediator(s), and outcome. For a practical example, see [4,19,26].

1.6 Estimate the sample size for the MA. For detailed instructions, see [10,27].

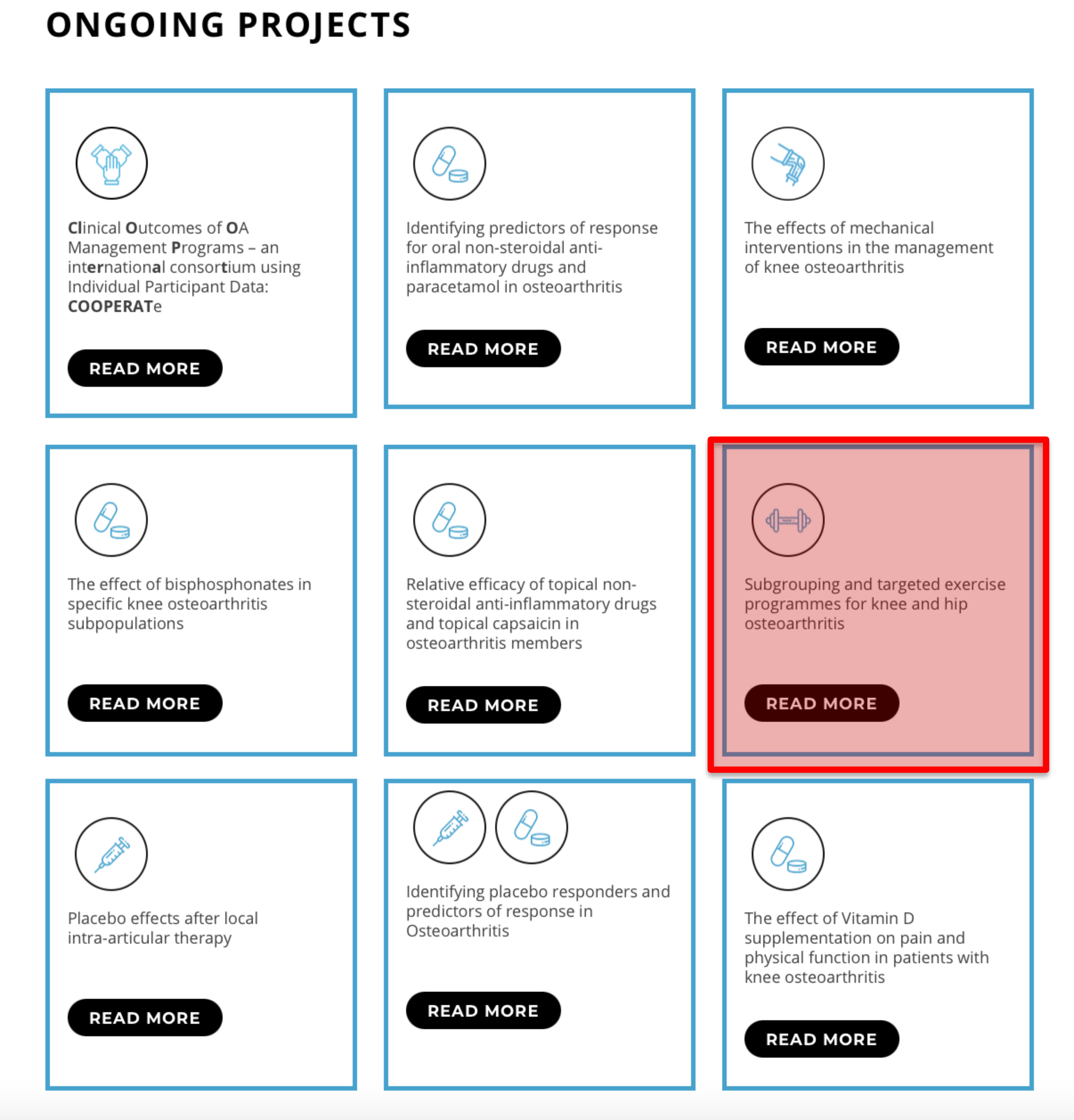
1.7 Do not make the conduct of a mediation analysis dependent on whether a statistically significant ITT treatment effect is found. The ITT effect may be null, even when there is an important indirect effect that is of opposite sign to the remaining direct effect [10,28].

Vo et al, J Clin Epi 2020



INDIVIDUAL PATIENT DATA META-ANALYSIS IN OSTEOARTHRITIS RESEARCH

https://www.oatrialbank.com



ONGOING PROJECTS

Clinical **O**utcomes of **OA** Management **P**rograms – an int**er**nation**a**l consor**t**ium using Individual Participant Data: **COOPERAT**e

Identifying predictors of response for oral non-steroidal anti-inflammatory drugs and paracetamol in osteoarthritis

The effects of mechanical interventions in the management of knee osteoarthritis

The effect of bisphosphonates in specific knee osteoarthritis subpopulations

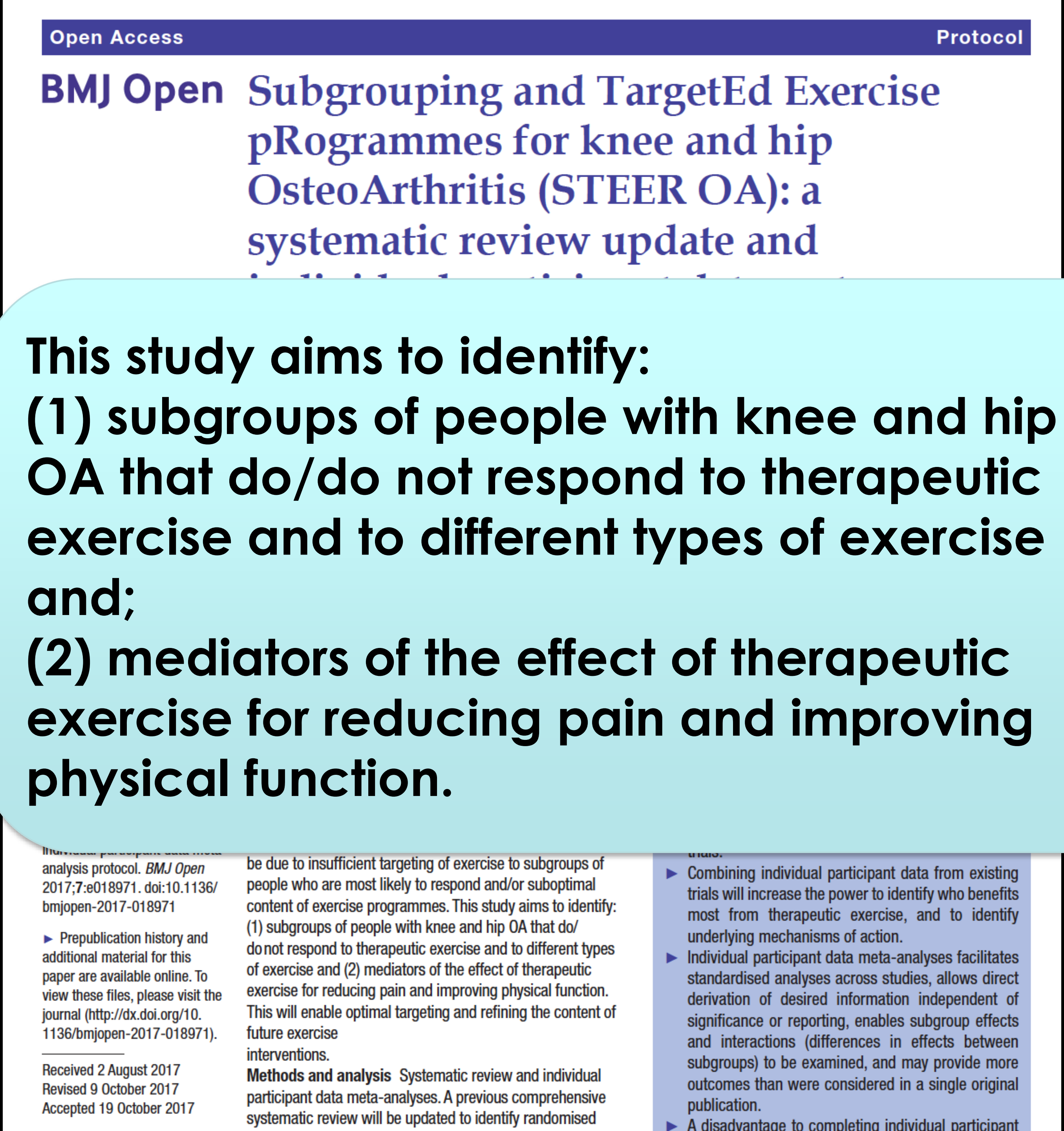
Relative efficacy of topical non-steroidal anti-inflammatory drugs and topical capsaicin in osteoarthritis members

Subgrouping and targeted exercise programmes for knee and hip osteoarthritis

Placebo effects after local intra-articular therapy

Identifying placebo responders and predictors of response in Osteoarthritis

The effect of Vitamin D supplementation on pain and physical function in patients with knee osteoarthritis



Open Access — Protocol

BMJ Open

Subgrouping and TargetEd Exercise pRogrammes for knee and hip OsteoArthritis (STEER OA): a systematic review update and

This study aims to identify:
(1) subgroups of people with knee and hip OA that do/do not respond to therapeutic exercise and to different types of exercise and;
(2) mediators of the effect of therapeutic exercise for reducing pain and improving physical function.

analysis protocol. *BMJ Open* 2017;**7**:e018971. doi:10.1136/bmjopen-2017-018971

- Prepublication history and additional material for this paper are available online. To view these files, please visit the journal (http://dx.doi.org/10.1136/bmjopen-2017-018971).

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Accepted 19 October 2017

be due to insufficient targeting of exercise to subgroups of people who are most likely to respond and/or suboptimal content of exercise programmes. This study aims to identify: (1) subgroups of people with knee and hip OA that do/do not respond to therapeutic exercise and to different types of exercise and (2) mediators of the effect of therapeutic exercise for reducing pain and improving physical function. This will enable optimal targeting and refining the content of future exercise interventions.

Methods and analysis Systematic review and individual participant data meta-analyses. A previous comprehensive systematic review will be updated to identify randomised

- Combining individual participant data from existing trials will increase the power to identify who benefits most from therapeutic exercise, and to identify underlying mechanisms of action.
- Individual participant data meta-analyses facilitates standardised analyses across studies, allows direct derivation of desired information independent of significance or reporting, enables subgroup effects and interactions (differences in effects between subgroups) to be examined, and may provide more outcomes than were considered in a single original publication.
- A disadvantage to completing individual participant

Unpacking why……

- Observed effect sizes from exercise RCTs are small to moderate at best
- Exercise benefits decline over time
- Only 50% of participants achieve a clinically important treatment response with exercise

Mediation analysis

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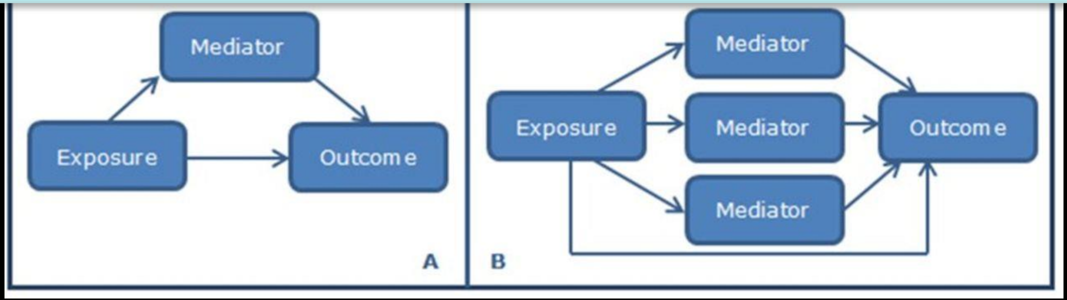
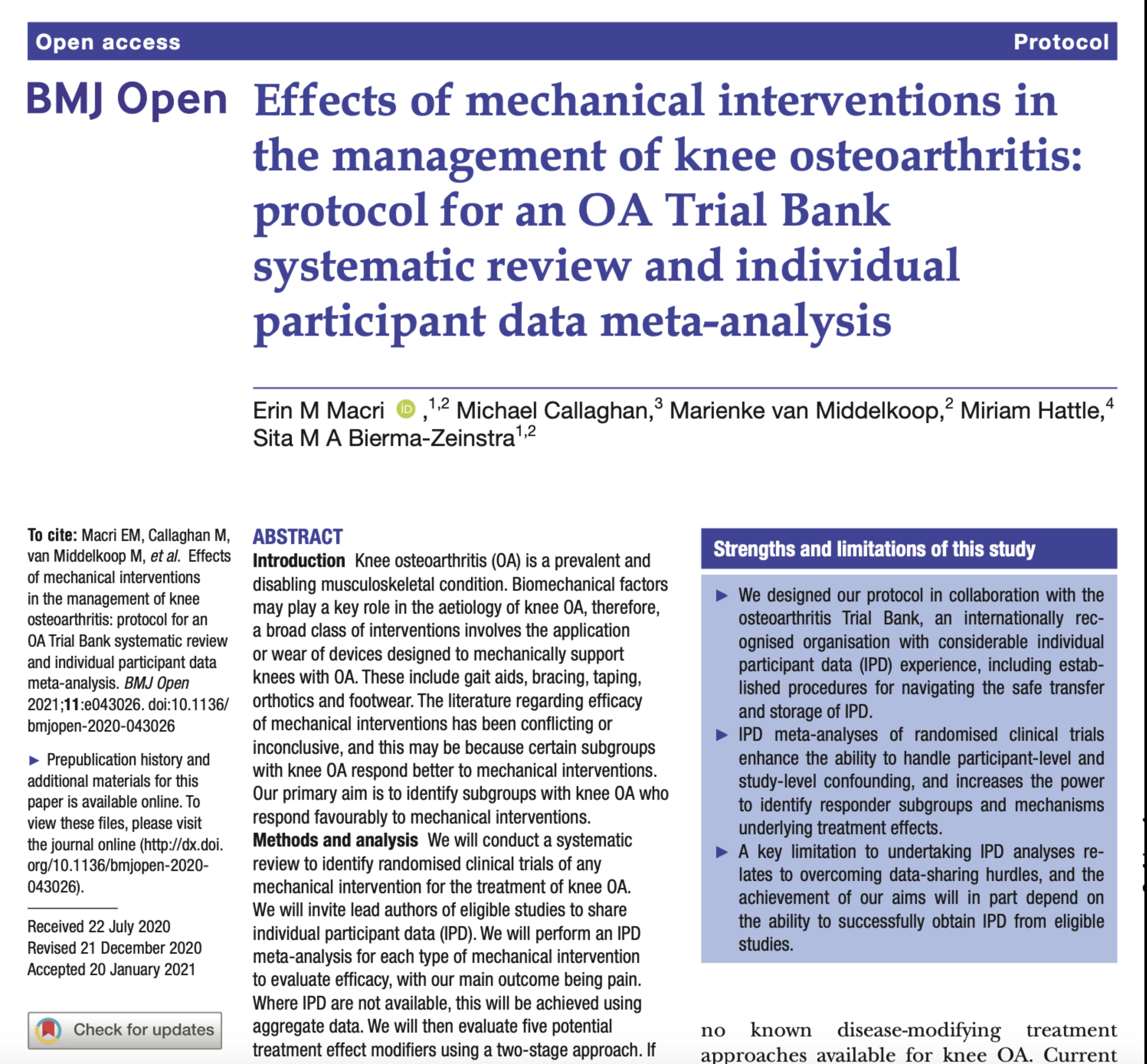
In total, 114 RCTs met our criteria and are included in the review.

To date, 61 have agreed, in principle, to share IPD (approximately 8500 participants in total).





Open access Protocol

BMJ Open

Effects of mechanical interventions in the management of knee osteoarthritis: protocol for an OA Trial Bank systematic review and individual participant data meta-analysis

Erin M Macri ,[1,2] Michael Callaghan,[3] Marienke van Middelkoop,[2] Miriam Hattle,[4] Sita M A Bierma-Zeinstra[1,2]

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- Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-043026).

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Check for updates

ABSTRACT

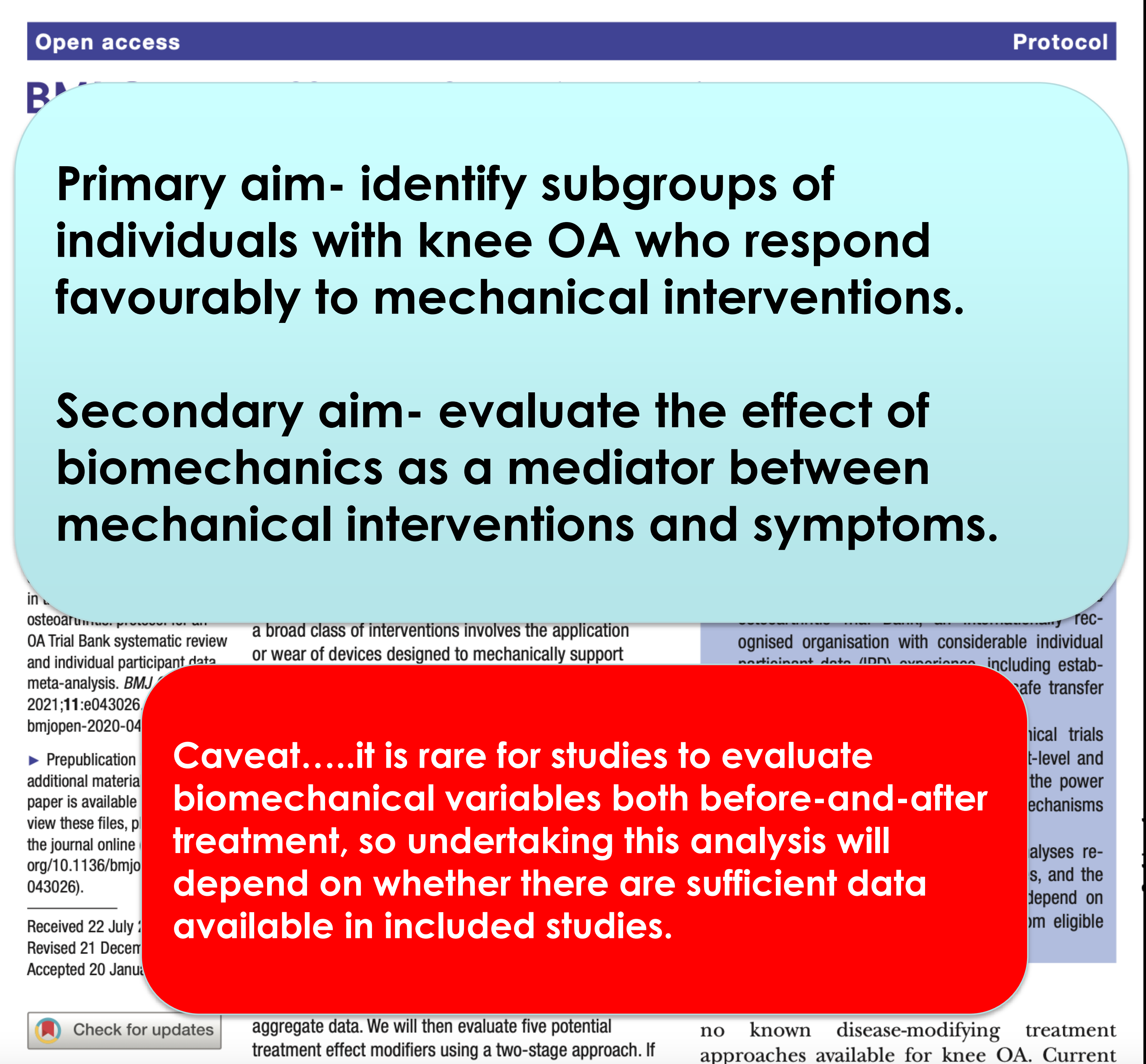
Introduction Knee osteoarthritis (OA) is a prevalent and disabling musculoskeletal condition. Biomechanical factors may play a key role in the aetiology of knee OA, therefore, a broad class of interventions involves the application or wear of devices designed to mechanically support knees with OA. These include gait aids, bracing, taping, orthotics and footwear. The literature regarding efficacy of mechanical interventions has been conflicting or inconclusive, and this may be because certain subgroups with knee OA respond better to mechanical interventions. Our primary aim is to identify subgroups with knee OA who respond favourably to mechanical interventions.

Methods and analysis We will conduct a systematic review to identify randomised clinical trials of any mechanical intervention for the treatment of knee OA. We will invite lead authors of eligible studies to share individual participant data (IPD). We will perform an IPD meta-analysis for each type of mechanical intervention to evaluate efficacy, with our main outcome being pain. Where IPD are not available, this will be achieved using aggregate data. We will then evaluate five potential treatment effect modifiers using a two-stage approach. If

Strengths and limitations of this study

- We designed our protocol in collaboration with the osteoarthritis Trial Bank, an internationally recognised organisation with considerable individual participant data (IPD) experience, including established procedures for navigating the safe transfer and storage of IPD.
- IPD meta-analyses of randomised clinical trials enhance the ability to handle participant-level and study-level confounding, and increases the power to identify responder subgroups and mechanisms underlying treatment effects.
- A key limitation to undertaking IPD analyses relates to overcoming data-sharing hurdles, and the achievement of our aims will in part depend on the ability to successfully obtain IPD from eligible studies.

no known disease-modifying treatment approaches available for knee OA. Current



Primary aim- identify subgroups of individuals with knee OA who respond favourably to mechanical interventions.

Secondary aim- evaluate the effect of biomechanics as a mediator between mechanical interventions and symptoms.

Caveat…..it is rare for studies to evaluate biomechanical variables both before-and-after treatment, so undertaking this analysis will depend on whether there are sufficient data available in included studies.

Open access Protocol

BM

in
osteoarthritis: protocol for an
OA Trial Bank systematic review
and individual participant data
meta-analysis. *BMJ*
2021;**11**:e043026.
bmjopen-2020-04

► Prepublication
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approaches available for knee OA. Current

Centre for Health, Exercise & Sports Medicine

https://healthsciences.unimelb.edu.au/departments/physiotherapy/chesm#home

A range of patient & clinician resources all freely available

Questions???