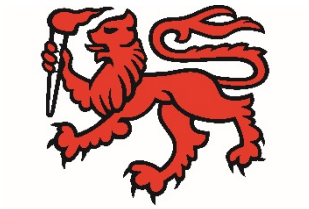

Determinants and management of the progression of osteoarthritis in older adults

By

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Declaration of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by any other person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

Ishanka Praneeth Munugoda

Date: 10-12-2019

Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Tasmanian Older Adult Cohort (TASOAC) study

The Southern Tasmanian Health and Medical Research Ethics Committee approved the TASOAC study, and written informed consent was obtained from all participants who attended the data collection sessions. In order to obtain the data on joint replacements for those who did not attend the 10-year follow-up, ethics approval was obtained for waiver of consent.

Approval reference numbers:

Initial ethics approval - H6488; 10-year follow-up ethics approval - H12938

Intensive Diet and Exercise for Arthritis (IDEA) trial

The Human Subjects Committee of Wake Forest University Health Sciences approved the IDEA study, and written informed consent was obtained from all the participants.

Approval reference numbers: IRB00000602,

ClinicalTrials.gov identifier: NCT00381290;

Protocol: Messier, SP., Legault, C., Mihalko, S., et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. *BMC Musculoskelet Disord.* 2009; 10:93.

Ishanka Praneeth Munugoda

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Ishanka Praneeth Munugoda

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Statement of co-authorship

This thesis includes publications for which Ishanka Praneeth Munugoda (IPM) was not the sole author. Ishanka was the first author in the research of each manuscript; however, he was assisted by the co-authors whose contributions are detailed below.

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Paper 1: Located in Chapter 4

Munugoda, IP., Brennan-Olsen, SL., Wills, K., Cai, G., Graves, SE., Lorimer, M., Cicuttini, FM., Callisaya, ML., Aitken, D., Jones, G. (2019). 'The association between socioeconomic status and joint replacement of the hip and knee: A population-based cohort study of older adults in Tasmania.' *Internal Medicine Journal* (under review).

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Project management of study during implementation: Author 3

Acquisition of data: Candidate, Author 1, Author 6, Author 7, Author 13

Design of data analysis plan: Candidate, Author 3, Author 4, Author 13

Analysis and interpretation of data: Candidate, Author 13, Author 3, Author 4, Author 9, Author 1, Author 5, Author 2

Drafting the manuscript: Candidate

Critically review and final approval of manuscript: Candidate, Author 13, Author 3, Author 4, Author 9, Author 1, Author 2, Author 5, Author 6, Author 7

Paper 2: Located in Chapter 5,

Munugoda, I., Wills, K., Cicuttini, F., Graves, S., Lorimer, M., Jones, G., Callisaya, M., Aitken, D. (2018). The association between ambulatory activity, body composition and hip or knee joint replacement due to osteoarthritis: a prospective cohort study. *Osteoarthritis Cartilage, 26*(5), 671-9. DOI: 10.1016/j/joca.2018.02.895.

Author contributions:

Study conception and design: Author 1, Author 3, Author 2

Project management of study during implementation: Author 1, Author 2

Acquisition of data: Candidate, Author 1, Author 6, Author 7

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Paper 3: Located in Chapter 6

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Author contributions:

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Acquisition of data: Candidate, Author 10, Author 1, Author 6, Author 7, Author 8, Author 11, Author 12

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Analysis and interpretation of data: Candidate, Author 10, Author 1, Author 2, Author 3, Author 4, Author 11

Drafting the manuscript: Candidate

Critically review and final approval of manuscript: Candidate, Author 10, Author 1, Author 2, Author 3, Author 4, Author 5, Author 6, Author 7, Author 8, Author 11, Author 12

Paper 4: Located in Chapter 7

Munugoda, IP., Beavers, DP., Wirth, W., Aitken, D., Loeser, RF., Miller, GD., Lyles, M., Carr, JJ., Guermazi, A., Hunter, DJ., Messier, SP., Eckstein, F. (2020). 'The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: A post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial.' *Osteoarthritis Cartilage*, 28(4): 410-7. DOI: 10.1016/j.joca.2020.01.006.

Author contributions:

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Project management of study during implementation: Author 16, Author 15

Acquisition of data: Candidate, Author 16, Author 15, Author 21

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We the undersigned, endorse the above stated contribution of work undertaken for each of the above published (or submitted) peer-reviewed manuscripts contributing to this thesis:

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University of Tasmania	*University of Tasmania*	*University of Tasmania*
Date: 10-12-2019	Date: 10-12-2019	Date: 10-12-2019

Abstract

Osteoarthritis (OA) is one of the most common musculoskeletal disorders, of which knee and hip OA account for the biggest burden of disease. It is a multifactorial disease with many risk factors and determinants such as age, sex and lifestyle factors including obesity, physical activity and diet being associated with both the onset and progression of the disease. Owing to the complex nature of the disease, no definitive treatment is available for OA. In order to better manage and treat this condition, it is important to improve the understanding of the lifestyle and structural factors related to the progression of the disease as well as the management of these factors. Therefore, the overall aims of this thesis were to identify determinants, risk factors and potential management strategies for the progression of OA in older adults.

In this thesis, data from two studies were utilised. The first study was a prospective population-based cohort study of older adults who were between 50 and 80 years of age named the Tasmanian Older Adults Cohort Study (TASOAC). The participants for the study were selected from sex-stratified random sampling from the electoral role in Southern Tasmania (population 229,000). Data was collected at baseline and at 2.5, 5 and 10 years after the initial clinic assessment. At baseline, information on objective measures of body composition using body mass index (BMI) obtained by weight and height measures and fat and lean mass using dual-energy x-ray absorptiometry (DXA) were obtained. Pedometer measured ambulatory activity (AA) was recorded at baseline and socioeconomic status (SES) of the participants was collected by matching each participant's residential address to the corresponding Australian Bureau of Statistics (ABS) Census Collection District to determine the Socio-Economic Indexes for Areas (SEIFA) value from the 2001 census. Knee pain of the participants at baseline and the 10-year follow-up was collected using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). In addition, various imaging modalities such as

radiography of the knee and hip at baseline and Magnetic Resonance Imaging (MRI) of the knee at baseline and the 10-year follow-up were conducted. Based on the radiographs, the status of radiographic OA (ROA) was defined. Utilising the knee MRI of the participants, several structural features such as Tibial cartilage volume and bone-marrow lesions (BMLs) were measured. The incidence of primary (first-time) total knee replacements (TKR) and total hip replacements (THR) were determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR).

The second study was a single-blind, single-center, 18-month, randomized controlled trial of older adults aged over 55 years named the Intensive Diet and Exercise for Arthritis trial (IDEA). The study was designed to evaluate the effects of weight loss obtained by diet and/or exercise on OA outcomes of the knee. Participants were eligible for the study if they had Kellgren-Lawrence grade (KLG) 2-3 tibiofemoral or tibiofemoral with patellofemoral OA of at least one knee, pain on most days due to knee OA, a BMI between 27 and 41 kg/m^2 and a sedentary lifestyle, i.e. <30 min/week of formal exercise over the past 6 months. The participants were randomized to one of three 18-month interventions: exercise only, diet only or diet+exercise. MRI was obtained in a random subsample (n=105) of the IDEA participants at baseline and the 18-month follow-up. Using these MRIs, the medial and lateral menisci were segmented, and position and size parameters were measured quantitatively, along with semiquantitative extrusion measures.

In the first study of this thesis, we assessed the association between SES and time to THR and TKR due to OA in older adults. The results showed that less disadvantaged participants were less likely to have a THR (i.e. less disadvantaged participants had a longer time to THR) in comparison to the most disadvantaged participants; however, this association was attenuated

after adjustments for hip pain and hip ROA. This suggests that time to joint replacements is determined according to the symptoms/need of the participants rather than their SES, indicating reductions in expected disparity between SES and time to joint replacement. This further confirms the usefulness of using joint replacement as a marker of end-stage OA in the knee and hip.

The second study evaluated the association between AA and body composition measures such as BMI, fat mass, lean mass and waist circumference with the risk of TKR and THR due to OA in a population of community-dwelling older adults. The results showed that AA was related to a higher risk of TKR and a lower risk of THR. BMI, total fat, trunk fat mass and waist circumference were associated with a higher risk of TKR although body composition measures were not related to THR. These finding suggest that habitual activity and obesity may have different causal pathways for OA progression in knee and hip joints.

In the third study, we investigated the prospective associations between baseline hip morphology defined as hip shape modes using Statistical Shape Modelling (SSM) and the progression of several clinical and MRI-based knee OA outcomes in older adults. The results showed that longer, wider femoral neck and larger femoral head (mode 1) was associated with increased risk of worsening knee pain, whereas wider femoral neck (mode 9) was related to reduced risk of worsening knee pain. Larger greater trochanter (mode 7) and greater acetabular coverage (mode 10) were linked to lower cartilage volume loss, while shorter, wider femoral neck (mode 9) was associated with increased cartilage volume loss. Smaller femoral head (mode 4) was related to increased risk of worsening BMLs. Greater acetabular coverage (mode 10) was associated with a reduced risk of TKR. Overall these findings may imply that hip shape variations are important in the long-term progression of knee OA in older adults.

The fourth study assessed whether weight loss achieved by diet and/or exercise is related to meniscus extrusion parameters in the medial and lateral meniscus over 18 months. The results showed that weight loss was related to less progression of medial meniscus extrusion as measured by the maximum and mean extrusion distances. Weight loss was not associated with lateral meniscus position, medial or lateral meniscus size or with semiquantitative measures. These findings suggest that weight loss is related to beneficial modifications of medial meniscus extrusion in older adults.

In conclusion, this sequence of studies first established the importance of TKR and THR as a marker of end-stage OA and showed that habitual activity and obesity act differently on end-stage OA of the hip and knee joints. Additionally, variations in hip shape may be an important structural feature that is associated with the progression of knee OA. Lastly, weight loss was related to less progression of meniscus extrusion in older adults with knee OA. Overall, the findings of this thesis suggest the importance of certain lifestyle factors. Better management of these factors may help to reduce OA progression in older adults.

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List of publications

Publications Arising from the Thesis

Chapter 4: **Munugoda, IP.,** Brennan-Olsen, SL., Wills, K., Cai, G., Graves, SE., Lorimer, M., Cicuttini, FM., Callisaya, ML., Aitken, D., Jones, G. (2019). 'The association between socioeconomic status and joint replacement of the hip and knee: A population-based cohort study of older adults in Tasmania.' *Internal Medicine Journal* (under review).

Chapter 5: **Munugoda, IP.,** Wills, K., Cicuttini, F., Graves, SE., Lorimer, M., Jones, G., Callisaya, ML., Aitken, D. (2018). 'The association between ambulatory activity, body composition and hip or knee joint replacement due to osteoarthritis: a prospective cohort study'. *Osteoarthritis and Cartilage*, 26(5): 671-9. DOI: 10.1016/j.joca.2018.02.895.

Chapter 6: **Munugoda, IP.,** Ahedi, HG., Aspden, RM., Mattap, SM., Wills, K., Graves, SE., Lorimer, M., Cicuttini, F., Gregory, JS., Jones, G., Callisaya, ML., Aitken, D. (2019). 'Longitudinal associations of hip shape with knee osteoarthritis outcomes over 12 years in older adults: A population-based cohort study'. *Rheumatology* (under review).

Chapter 7: **Munugoda, IP.,** Beavers, DP., Wirth, W., Aitken, D., Loeser, RF., Miller, GD., Lyles, M., Carr, JJ., Guermazi, A., Hunter, DJ., Messier, SP., Eckstein, F. (2020). 'The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: A post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial.' *Osteoarthritis and Cartilage*, 28(4): 410-7. DOI: 10.1016/j.joca.2020.01.006.

Manuscripts published during the candidature, but external to the thesis material

Munugoda, IP., Pan, F., Wills, K., Mattap, SM., Cicuttini, F., Graves, SE., Lorimer, M., Jones, G., Callisaya, ML., Aitken, D. (2019). 'Identifying subgroups of community-dwelling older-adults and their prospective associations with long-term knee osteoarthritis outcomes'. *Clinical Rheumatology.* DOI: 10.1007/s10067-019-04920-8.

Cai, G., Otahal, P., Cicuttini, F., Wu, F., **Munugoda, IP**., Jones, G., Aitken, D. (2020). 'The association of subchondral and systemic bone mineral density with osteoarthritis-related joint replacements in older adults.' *Osteoarthritis and Cartilage,* 28(4): 438-45. DOI: 10.1016/j.joca.2020.02.832.

Pan, F., Tian, J., **Munugoda, IP**., Graves, S., Lorimer, M., Cicuttini, F., Jones, G. (2020). 'Do knee pain phenotypes have different risk of total knee replacement?' *Journal of Clinical Medicine,* 2020; 9 (3): 632. DOI: 10.3390/jcm9030632.

Mattap, SM., Aitken, D., Wills, K., Halliday, A., Ding, C., Han, W., **Munugoda, I.,** Grave, SE., Lorimer, M., Cicuttini, F., Jones., Laslett, LL. (2019). 'Patellar tendon enthesis abnormalities and their association with knee pain and structural abnormalities in older adults.' *Osteoarthritis and Cartilage*, 27(3): 449-58. DOI: 10.1016/j.joca.2018.11.009.

Gunathunga, W., Jayakody, O., Bartlett, L., **Munugoda, I.,** Gunathunga, CK. (2019). 'Comparative study on the mental wellbeing among regularly meditating and non-meditating health care personnel in Sri Lanka.' *Journal of the College of Community Physicians of Sri Lanka*, 25(3): 112-20. DOI: 10.4038/jccpsl.v25i3.8206.

Senarath, U., Senanayake, S., Pathirana, S., Karunaweera, N., Weerasinghe, MC., Gunawardena, NS., **Munugoda, IP.**, Jayasinghe, S., Amarathunga, P., Corea, E., De Silva, V., Fernando, D., Fernando, R., Gnanathasan, A., Gunatilake, M., Gunawardena, S., Katulanda, P., Rajapakse, S., Samaranayake, N. and Siriwardana, Y. (2019). 'Health in rural Sri Lanka: A cross-sectional survey of three rural districts.' *Ceylon Medical Journal*, 64(3): 103–10. DOI: 10.4038/cmj.v64i3.8957.

Manuscripts submitted during candidature, external to this thesis material and currently under review

Mezhov, V., Laslett, LL., Ahedi, H., Blizzard, CL., Aspden, RM., Gregory, JS., Saunders, FR., Graves, SE., Lorimer, M., **Munugoda, IP**., Cai, G., Cicuttini, F., Jones, G. (2019). 'Predictors of total hip replacement in community based older adults: a cohort study.' *Arthritis Care and Research* (under review).

Scientific Presentations during the PhD

May 2019

Osteoarthritis Research Society International (OARSI) World Congress, Toronto, Canada.

'The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: A post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial.' (Plenary oral presentation).

'Associations of hip shape with knee osteoarthritis outcomes in older adults.' (Poster presentation).

'Do body mass index and knee osteoarthritis status affect meniscal extrusion and size?' (Poster presentation).

July 2018

International Workshop on Osteoarthritis Imaging (IWOAI), Menton, France.

'Hip shape predicts knee osteoarthritis outcomes over a decade in older adults.' (Poster presentation).

Identification of sub-groups of participants based on physical activity, knee pain, body mass index and socioeconomic status for knee osteoarthritis: A population-based cohort study.' (Poster presentation).

June 2018

European League Against Rheumatism (EULAR), Amsterdam, The Netherlands.

'Increasing a person's own physical activity and strength can minimize cartilage volume loss in older-adults: A between- and within- person analysis on a population-based prospective cohort.' (Poster presentation).

'Identification and validation of physical activity phenotypes for knee osteoarthritis: A population-based cohort study.' (Poster presentation).

'Hip shape predicts knee osteoarthritis outcomes over a decade in older adults.' (Poster presentation).

April 2018

Osteoarthritis Research Society International (OARSI) World Congress, Liverpool, United Kingdom.

'Identifying physical activity phenotypes and their association with osteoarthritis outcomes over 10.7 years.' (Poster presentation).

'A novel analysis method to examine the relationship between physical activity and leg strength with knee cartilage volume loss over 10.7 years.' (Poster presentation).

World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal diseases (WCO-IOF-ESCEO), Krakow, Poland.

‘Physical activity phenotypes are associated with cartilage volume loss and knee replacement, but not with incident bone-marrow lesions over 10.7 years.’ (Plenary oral presentation).

‘Associations of hip shapes with knee osteoarthritis outcomes over 10.7 years, in older adults.’ (Poster presentation).

‘Between-person & within-person associations of physical activity and leg strength with knee cartilage volume loss over 10.7 years, in older adults.’ (Poster presentation).

‘Association of statin therapy with 10-year change in intra-muscular fat percentage, muscle cross-sectional area and muscle strength.’ (Poster presentation).

June 2017

Joint meeting of Australian and New Zealand Bone and Mineral Society (ANZBMS) & International Federation of Musculoskeletal Research Societies, Brisbane, Australia.

‘The effect of ambulatory activity and body composition on the risk of joint replacement for knee and hip osteoarthritis.’ (Plenary Poster presentation).

Awards resulting from the thesis

2019 Young Investigator Award & Highest rated abstract with travel award, Osteoarthritis Research Society International (OARSI) World Congress.

2018 Young Investigator Award, Osteoarthritis Research Society International (OARSI) World Congress.

2018 ESCEO-Eli Lilly top rated abstract travel grant, World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal diseases (WCO-IOF-ESCEO).

2018 Osteoarthritis Research Society International (OARSI) Collaborative Scholarship.

2018 Travel Award, University of Tasmania Conference and Research Travel Funding.

2015 Ashdown Family Elite Scholarship in Medical Research for the PhD.

List of Abbreviations

3MSE	Modified Mini-Mental State Exam
AA	Ambulatory Activity
AASK	Ambulation Adjusted Score for Knee pain
ABS	Australian Bureau of Statistics
ACdAB.Cov	Tibial coverage area (by the meniscus)
ACR	American College of Rheumatology
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Covariance
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ASM	Active Shape Modelling
BLOKS	Boston–Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
BMLs	Bone-Marrow Lesions
CES-D	Center for Epidemiological Studies Depression
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disorder
CV	Coefficient of Variation
D	Diet only
D+E	Diet with Exercise
DXA	Dual-energy X-ray Absorptiometry
E	Exercise only
FSE	Fast Spin-Echo

GXT	Graded Exercise Test
HOAMS	Hip osteoarthritis MRI scoring system
HR	Hip Replacements
ICC	Intraclass Correlation Coefficient
IDEA	Intensive Diet and Exercise for Arthritis
IEO	Index of Education and Occupation
IER	Index of Economic Resources
IRSAD	Index of Relative Socioeconomic Advantage and Disadvantage
IRSD	Index of Relative Socio-Economic Disadvantage
JR	Joint Replacement
JSN	Joint Space Narrowing
JSW	Joint Space Width
KLG	Kellgren-Lawrence Grade
KOOS	Knee injury and Osteoarthritis Outcome Score
KR	Knee Replacements
LSC	Least Significant Criterion
MICE	Multiple Imputation by Chained Equations
MOAKS	MRI Osteoarthritis Knee Score
MOST	Multicentre Osteoarthritis
MRI	Magnetic Resonance Imaging
NC	North Carolina
NHANES-I	First National Health and Nutrition Examination Survey
NIH	National Institute of Health
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis

OARSI	Osteoarthritis Research Society International
OvD	Mean overlap distance between the meniscus and tibial plateau
PA	Physical Activity
PASE	Physical Activity Scale for the Elderly
PDw	Proton-Density-weighted
PROOF	Prevention of knee Osteoarthritis in Overweight Females
RCT	Randomised Controlled Trials
RMS SD	Root Mean Square Standard Deviation
ROA	Radiographic Osteoarthritis
RR	Relative Risk
SD	Standard Deviation
SEIFA	Socio-Economic Indexes for Areas
SES	Socioeconomic Status
SHOMRI	Scoring Hip Osteoarthritis with MRI
SPGR	Spoiled Gradient-echo
SSM	Statistical Shape Modelling
STIR	Short Tau Inversion Recovery
TASOAC	Tasmanian Older Adult Cohort
TA.Uncov	Area of the meniscus not covering (i.e. extruding) the tibial plateau
THR	Total Hip Replacement
TJR	Total Joint Replacement
TKR	Total Knee Replacement
UK	United Kingdom
US	United States
USA	United States of America

WOMAC	Western Ontario and McMaster University Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging score
YLDs	Years Lived with Disability
β-coef	Beta coefficient

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Chapter 1: Introduction

1.1 Overview of osteoarthritis

Osteoarthritis (OA) is one of the most prevalent musculoskeletal conditions, of which knee and hip OA account for the most significant burden of disease[1]. It is defined as a disorder involving movable joints characterized by cell stress and extracellular matrix degradation. These processes may be initiated by micro- and macro- injury that activates maladaptive repair and responses, which includes proinflammatory pathways of innate immunity. The disease may manifest as a molecular derangement (abnormal joint tissue metabolism) at first, which is followed by anatomic, and/or physiologic derangements[2].

OA is considered a progressive disease affecting a range of joint structures such as cartilage, subchondral bone, meniscus, peri-articular muscles, synovium, ligaments and peri-articular fat[3]. The pathological changes in these structures are manifested mainly as pain, stiffness, tenderness, crepitus and movement restriction[4].

1.2 Epidemiology of OA

Globally, it is estimated that approximately 9.6% of men and 18.0% of women, 60 years or older are suffering from the symptomatic problems related to OA[5, 6]. In Australia, nearly 2.1 million (or 9%) of people were suffering from OA in 2014-15 which is projected to increase up to 3.1 million (or 10.7%) by 2030[7, 8]. In the United States (US), over 30 million adults were estimated to have OA[9]. It is the 10th largest contributor to the years lived with disability (YLDs) worldwide, accounting for up to 2.4% of all YLDs[10]. As the risk of OA increases with age, the incidence of OA is expected to increase in the future with longer life expectancy.

Estimates suggest that it will be one of the four leading causes of disability by the year 2034[11].

The prevalence of knee OA is reported to be higher than that of hip OA, as data suggests a prevalence of 4.15% for knee and 1.91% for hip in North America, in 2010[12]. Furthermore, the lifetime risk of symptomatic knee OA was estimated to be 40% in men, and 47% in women[13], while for hip OA, it was estimated to be 18.5% for men and 28.6% for women[14].

Owing to this, OA has a considerably high economic and societal burden on the community. In Australia, the total OA related healthcare cost was about $3.75 billion in 2012[15, 16], with the majority being due to hospitalisation[17]. This cost is projected to increase up to $5.3 billion by 2030[15]. In the US, it was estimated that the direct and indirect cost due to OA was $486.4 billion on average between 2008 – 2014[18]. Indeed, the indirect costs of OA due to job-specific costs such as productivity loss also accounts for up to about $3.4 – $13.2 billion per year[19].

1.3 Clinical symptoms of OA

Pain is the most common symptom of OA. It is a subjective and complex phenomenon and is the primary driver of healthcare-seeking behaviour in patients[20]. Previous reports showed that the prevalence of knee pain in older adults was nearly 25%[21, 22] and that it has been increasing over the past 20 years[23].

Joint stiffness with inactivity, typically seen in the mornings for a short period of time, is another common symptom in OA[24]. Additionally, crepitus, which is a cracking sound of the

joint with the movement, is also seen in patients with OA[25]. Furthermore, growing evidence suggests that systemic, low-grade inflammation is associated with OA[26]. Altogether, these symptoms lead to functional difficulties.

1.4 Risk factors for OA

OA is a multifactorial disease with many determinants and risk factors being associated with the condition. These factors could be classified as person-level and/or joint-level factors which may be specific to each joint, as well as to the stage of the disease, i.e. development, progression or end-stage of the disease, making it a challenging condition to mitigate[27].

Common person-level risk factors for OA include age, gender, genetics and obesity[27]. Increasing age is a key risk factor for development, progression and end-stage OA, most likely due to the changes of the adaptability of the tissues to mechanical stimuli[27]. Women have a higher prevalence of OA and a higher risk of severe disease compared to men[28]. This is suggested to be due to the effects of sex hormones; however, several studies have reported variable findings on the relationship between sex hormones and OA[27, 29]. Genetics may also play an essential role in the pathogenesis of OA especially in the hand and hip, while weaker associations have been observed for the knee, with an estimated heritability component of 40-65%, depending on the joint[27, 30].

Obesity is well-recognised as a risk factor for OA[31]. While it has been strongly associated with knee OA, the relationship has been weaker for hip[32] and hand OA[33]. Reports show that being overweight or obese increases the risk of developing knee OA by 2.96 times, compared to being normal weight[34], while this was 1.9 times for developing hand OA[35].

The mechanisms underlying these associations have been attributed to increased joint loads and metabolic factors[33]. The association between obesity and OA is discussed in detail in a later section.

Physical activity (PA) is commonly performed by older people and has beneficial effects on overall health and in many diseases[36]. It is suggested that PA may have beneficial effects on joint health because the dynamic loading exerted by PA may improve the integrity of the structures such as joint cartilage[37]. However, it is also suggested that the excessive or repetitive loading exerted by PA on joint structures and joint injury caused during PA may have detrimental effects on joint health[38], owing to the higher prevalence of knee and hip OA and joint replacements (JR) seen in elite athletes[39]. Hence, PA may act as a potential risk factor for OA, especially in weight-bearing joints. Among different types of PA, ambulatory activity (AA) is one of the most common forms performed by older adults[40]. An in-depth discussion on the relationship between PA and OA is given later in this chapter.

Several joint-level factors have also been identified as potential risk factors for OA. Joint injury has been known to increase the risk of OA, especially in the knee[34, 41]. Anterior cruciate ligament (ACL) injuries increase the risk of radiographic OA by 4 times[27]. Meniscal injuries also increase the risk of symptomatic and structural knee OA[42]. Furthermore, joint shape has been recognised as a critical structural risk factor. Prior studies have reported that hip shapes are associated with hip OA[43-45]. For instance, hip dysplasia and femoroacetabular impingement are suggested to increase the risk of hip OA[30], potentially strengthening the findings that hip shapes may be associated with hip OA. Similarly, knee shapes are related to knee OA[46, 47]. Muscle strength around the joint is also a significant risk factor. Quadriceps muscle weakness has also been linked to an increased risk of knee OA[48]. Nevertheless, there

has been contradictory evidence for the relationship between grip strength and hand OA[27]. Joint malalignment is another potential risk factor, especially for knee OA. Several reports have shown that varus alignment increases the risk of progressive OA in the medial compartment, while valgus alignment increases the risk of progressive OA in the lateral compartment[49, 50].

1.5 Diagnosis of OA

The diagnosis of OA can be made based on symptoms and a physical examination alone in clinical settings[51]. However, imaging is also commonly used when diagnosing OA[51]. Diagnosis of OA for research purposes also closely follow these criteria used in clinical settings. However, depending on the objectives of the particular research, certain specific criteria such as radiography or magnetic resonance imaging may be used.

1.5.1 Clinical Diagnosis of OA

The American College of Rheumatology (ACR) criteria is the most widely used method for clinical diagnosis of OA in the knee[52] and hip[24]. In the knee, this includes criteria such as; 1) age > 50 years, 2) morning stiffness lasting < 30 minutes, 3) crepitus on active motion, 4) bony tenderness, 5) bony enlargement, and 6) no detectable warmth[52]. In the hip, this criteria include pain and the presence of a combination of either, 1) hip internal rotation ≥ 15°, pain on internal rotation of the hip, morning stiffness of the hip for ≤ 60 minutes, and age > 50 years, or 2) hip internal rotation <15° and an erythrocyte sedimentation rate (ESR) ≤ 45 mm/hour; if no ESR was obtained, then hip flexion ≤ 115° is substituted[24].

For the assessment of symptoms in epidemiological and clinical research, several tools have been developed such as Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC)[53], Knee injury and Osteoarthritis Outcome Score (KOOS)[54] and Ambulation Adjusted Score for Knee pain (AASK)[55].

1.5.2 Radiographical Diagnosis of OA

Several features viewed on plain film radiographs can be used in the radiographical diagnosis of OA, including the presence of osteophytes and bony cysts[56]. In addition, joint space narrowing (JSN) and joint space width (JSW) can also be measured using radiographs, which are largely used for the radiographic diagnosis[56].

Diagnosis criteria for radiographic OA were first defined by Kellgren and Lawrence in 1957[57] and since has been widely used in clinical practice and research. The defined grading system includes a semi-quantitative scoring method with five ordinal grades, based mainly on JSN and the presence of osteophytes[57] (Table 1.1).

Subsequently, several other criteria were also defined, addressing the limitations in the Kellgren and Lawrence grading system. Osteoarthritis Research Society International (OARSI)[58, 59] radiographic atlas is one such widely used grading system. According to the OARSI atlas, JSN and osteophytes are scored separately (grades 0 – 3; 0 – normal, 1 – mild, 2 – moderate, 3 - severe) in different sites of the knee and hip joints (Table 1.2 & 1.3).

Table 1.1: Kellgren and Lawrence grading system for knee

Grade	Description
0 - None	No changes
1 - Doubtful	Doubtful narrowing of joint space and possible osteophyte lipping
2 - Mild	Definite osteophytes, definite narrowing of joint space
3 - Moderate	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour
4 - Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis and possible deformity of bone contours

Table 1.2: OARSI grading system for knee

Feature & site	Grade
Osteophytes	
Medial femoral	0 - 3
Medial tibial	0 - 3
Lateral femoral	0 - 3
Lateral tibial	0 - 3
Joint space narrowing	
Medial compartment	0 - 3
Lateral compartment	0 - 3
Other	
Medial tibial attrition	0 (absent) – 1 (present)
Medial tibial sclerosis	0 (absent) – 1 (present)

Lateral femoral sclerosis	0 (absent) – 1 (present)

OARSI - Osteoarthritis Research Society International

Table 1.3: OARSI grading system for hip

Feature & site	Grade
Osteophytes	
Superior femoral	0-3
Superior acetabular	0-3
Joint space narrowing	
Axial	0-3
Superior	0-3

OARSI - Osteoarthritis Research Society International

Although radiography is widely used, there are several limitations that include lack of visualisation of soft tissues around the joints including cartilage, meniscus, adipose tissue or muscles, less sensitivity to change over time and to early pathological changes[60]. Additionally, the visualisation of structures in radiographs depends on the joint positioning and the anatomical alignment[61]. Hence, alternative imaging tools that are more sensitive to change are often considered when confirming the diagnosing or evaluating OA in both clinical and research settings.

1.5.3 Magnetic Resonance Imaging for diagnosis of OA

Magnetic Resonance Imaging (MRI) has been shown to be a useful imaging tool, owing to its high spatial resolution and increased tissue contrast that allows the assessment of the whole joint including the soft tissues such as cartilage, meniscus, adipose tissue, ligaments and muscle[62]. MRI also provides accurate visualisation of the structural features and abnormalities in knee and hip joints such as cartilage defects[63], bone marrow lesions (BMLs)[64], meniscal tear[65] and extrusions[66], infra-patella fat pad abnormalities[67], effusion/synovitis[68], labral tears[69] and geometric shapes in hip[45] and knee[46]. Therefore, MRI is extensively used in both clinical and epidemiological studies in order to assess these structures that will help to understand the disease process better and to define effective treatment strategies.

Broadly, two methods are used to evaluate MRI structures in joints; semi-quantitative and quantitative methods. Various semi-quantitative methods have been developed to evaluate structural abnormalities in the knee, such as Whole-Organ Magnetic Resonance Imaging Score (WORMS)[70], Boston–Leeds Osteoarthritis Knee Score (BLOKS)[71], MRI Osteoarthritis Knee Score (MOAKS)[72], Knee Osteoarthritis Scoring System (KOSS)[73] and in the hip, including Hip osteoarthritis MRI scoring system (HOAMS)[69] and Scoring Hip Osteoarthritis with MRI (SHOMRI)[74]. While there are advantages in semi-quantitative analyses such as ease of use in large scale studies[75] and high reliability[76], they are less sensitive to change over time compared to quantitative methods[75] needing longer follow-up periods in studies that are expensive. Therefore, novel quantitative methods are used in studies that are more sensitive to change over a short period of time[75] in order to evaluate cartilage volume[77, 78], BML size[64], meniscus extrusion and size[79] and infra-patella[80] and supra-patella[81] fat pad.

1.6 Management & treatments

Given that OA has both symptomatic and structural consequences, defining treatments that can mitigate both these aspects are essential. Unfortunately, due to the complex nature of the disease, there is currently no definitive treatment that can alleviate both symptoms and modify the structure. However, several management/treatment strategies are being used that include non-surgical and surgical treatments. Additionally, several evidence-based guidelines have been developed by professional/scientific organisations for the management of OA to aid the decision making such as The Royal Australian College of General Practitioners (RACGP)[51] and OARSI[82, 83].

1.6.1 Non-surgical treatments

Non-surgical treatments include both non-pharmacological and pharmacological treatments.

1.6.1.1 Non-pharmacological treatments

Currently, a wide range of non-pharmacological management strategies are used. Land-based exercises are considered front-line management strategies for improving pain and function in patients with lower-limb OA of any age, disease status and pain severity[51]. The recommended exercises include a combination of aerobic, active range of motion and strengthening exercises[83]. In addition, aquatic exercises are also used in alleviating symptoms, despite the weaker evidence compared to land-based exercises[51]. Yet, aquatic exercises may be useful for certain patients with lower-limb OA who may be challenged in full weight-bearing conditions, due to the buoyant effects of water[51].

Weight management/loss is also strongly recommended as a management strategy for overweight or obese people with OA[83]. The RACGP guidelines recommend a minimum weight loss of 5 – 7.5% of body weight[51]. Weight loss as a treatment is discussed in detail in later sections.

Furthermore, several guidelines suggest that patient education and cognitive behavioural therapy (CBT) may be beneficial in managing chronic pain in OA patients. In addition, massage and manual therapy, localised heat therapy, devices such as assistive walking devices (e.g. cane), splints for base-of-thumb OA, and transcutaneous electrical nerve stimulation (TENS) are also recommended mainly as adjunctive therapy that may assist in alleviating pain in patients with OA[30, 51, 83].

1.6.1.2 Pharmacological treatments

Specific pharmacological treatments are also used for patients with OA. These can be orally or topically administered or injected to the site. Nevertheless, these are only moderately effective in alleviating pain, and most people may experience continuing pain. These medications may also be related to various adverse effects[30, 51].

Oral Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[84], paracetamol and cyclooxygenase-2 (COX-2) inhibitors are considered first-line treatments, although paracetamol may be less effective for symptom relief in OA. Yet, NSAIDs and COX-2 inhibitors are associated with gastrointestinal, renal and cardiovascular adverse events [30, 51]. Additionally, Duloxetine which is a serotonin and noradrenaline reuptake inhibitor, is also

recommended for multiple-joint OA[82]. Although nutraceutical treatments, such as Chondroitin sulfate and Glucosamine have been used as analgesics and disease-modifying drugs previously, recent evidence has shown mixed results; hence, the recent guidelines including the RACGP recommends that these are not appropriate for treatments[51]. Similarly, opioids have also been used previously for patients who are contraindicated for other medications; however, current guidelines recommend against their use[51, 82].

Topical NSAIDs are also recommended for pain relief in knee OA and have been shown to be comparable to oral NSAIDs in efficacy. These are related to a lower risk of gastrointestinal adverse events but a higher risk of dermatological adverse events[30]. Additionally, topical Capsaicin which is a chilli pepper extract that contributes to reduced transmission of pain impulses from the joints is also recommended for alleviating pain in OA[83], especially for knee and hand OA[30]. However, these are associated with an increased risk of local adverse events[30].

Intra-articular corticosteroids have also been recommended as adjust therapy by several guidelines for short-term pain relief potentially due to their anti-inflammatory actions[30, 51, 82]. Yet, repeated use of corticosteroids needs to be done with caution due to potential harms. In addition, viscosupplementation injections such as hyaluronate have also been used previously; however, recent guidelines recommend against these, especially for hip OA[51].

1.6.2 Surgical treatments

1.6.2.1 Joint replacements

JR are effective procedures for people with end-stage OA in both hip[85] and knee[15] when all the other non-pharmacological and pharmacological treatments have failed. It has been shown to be beneficial in reducing pain and improving function in people with OA and hence, is considered a definitive treatment option for patients with severe OA[86, 87]. The incidence rates of JR have been steadily increasing with the ageing of the populations and the incidence of more severe disease status[88-90]. In Australia, 47,972 hip replacements (HR) were reported in 2017, demonstrating an increase of 1.1% compared to 2016[91]. The Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), reports that this is an increase of 99.5% for HR compared to 2003. Additionally, 63,854 knee replacements (KR) were reported in 2017, which is a 5% increase compared to 2016[91] and a 151.6% increase for KR in comparison to 2003. Similar trends in the increase in JR are observed globally, with over 700,000 KR and 450,000 HR being reported in the United States of America in 2011 [92]. These rates are expected to increase in the future with the ageing of the populations[93]. Besides, the rates of revision JR has also seen an increase over the years. The AOANJRR report reveals that in 2017, the rate of revision KR's increased by 4.1% compared to 2016, and this was an increase of 103.3% compared to 2003[91]. Interestingly, the rate of revision HR has declined from 12.9% in 2003 to 8.9% in 2017, potentially due to the development of advanced prosthesis[91].

JRs are cost-effective procedures[94]. The increase in the incidence of JRs has a major impact on healthcare budgets[85, 95]. In 2012, the cost of JR due to OA was estimated to be over $2.3 billion in Australia[15], and this is projected to increase up to $5.3 billion by 2030[15]. In the United States, these costs related to JR were estimated to be nearly $28.5 billion for KR and $13.7 billion for HR in 2009[96]. With the projected increase in incidence, the cost is also expected to rise[97].

1.6.2.2 Arthroscopic surgery

While arthroscopic surgeries such as arthroscopic lavage and debridement, meniscectomy and cartilage repair, have been used previously, current guidelines strongly recommend against these unless there is clear evidence of mechanical locking. These have been shown to be associated with various side effects and harms[30, 51].

1.7 Disease progression

Disease progression in OA is commonly classified using markers of symptomatic and structural progression as well as markers of end-stage OA. This section explains widely used markers for clinical and research purposes.

1.7.1 Symptomatic progression

1.7.1.1 Pain

Pain in the most critical symptom which directly relates to reduced function and decreased quality of life in patients with OA[98]. Hence, it is the hallmark of OA disease progression. While pain may be intermittent during the early stages of OA and may be alleviated with rest or pain medication, it becomes constant as the disease progresses and more difficult to mitigate with currently available treatments[98]. Pharmacological agents such as paracetamol and NSAIDs as well as non-pharmacological treatments, including exercise, are widely used in the

treatment of pain[83]. However, pain management still remains inadequate in those with advanced disease[20].

1.7.2 Structural progression

Identification of accurate and reproducible structural progression markers is important in both clinical and research settings. These are particularly useful for the development of treatments that modify structural progression. Structural disease progression is determined mainly by radiographic and MRI markers.

1.7.2.1 Radiographic progression

Radiographic progression of the disease is often determined by the criteria based on Kellgren and Lawrence grading system[57] or OARSI radiographic atlas[58, 59] as explained above. It is largely used for research purposes to determine the increasing structural severity of the disease to identify risk factors for progression and to assess the response to treatments. Traditionally, radiographic progression was often interpreted as cartilage loss[99]; however, the development of more sensitive imaging tools has shown this interpretation to be inaccurate[99].

Although radiography has been widely used due to the lower cost and ease of use in clinical practice and large research studies[56], there are limitations in using radiography for the assessment of disease progression. Increasing evidence suggests that radiographs may be less sensitive to changes over time, especially when compared to MRI[60, 100], challenging its use, especially for research purposes. Due to its lower sensitivity to change, studies with longer

follow-up times are required[101]. Furthermore, studies show that JSW is strongly related to meniscal pathology[61], suggesting that it may be not optimal for the evaluation of cartilage loss. Additionally, the sensitivity to change may mainly depend on achieving proper medial tibial plateau alignment, which may be challenging. As an alternative, recent evidence suggests that using multiple radiographic views can increase sensitivity[102].

Given the limitations of radiography, MRI is increasingly used, especially in research to assess the progression of the disease due to its higher sensitivity to change over time.

1.7.2.2 Structural progression on MRI markers

1.7.2.2.1 Cartilage volume

Articular cartilage is an avascular and aneural soft tissue made of fibrocartilage, that rests on the joint surfaces. It reduces friction between the surfaces and facilitates relative movement[103] and is also capable of load-bearing and load-transmission[104, 105]. Cartilage loss determined by the reduced volume or thickness is considered the leading indicator of structural disease progression in OA; thus, it is commonly measured in epidemiological and clinical studies on OA progression. Although the cartilage is aneural, previous studies have reported mixed evidence with regard to the relationships between cartilage volume loss and symptoms[106, 107]. Furthermore, cartilage has been a common therapeutic target, yet no definitive treatments for reversal of cartilage loss have been clearly defined[105]. Measurement of cartilage is conducted using high-resolution MRIs, on which manual segmentation of cartilage contours are done, and the volume/thickness is then calculated.

1.7.2.2.2 Bone Marrow Lesions

Abnormalities in the subchondral bone play a vital role in the pathogenesis of OA[108]. Of these, BMLs are shown to be important features related to knee OA[109]. BMLs are defined as ill-defined areas of hyper- or hypo- signal intensity in fat-saturated T2-weighted MR images or short tau inversion recovery (STIR) sequences[110]. BMLs have previously been associated with symptomatic (i.e. knee pain)[111] and other structural markers (i.e. cartilage volume loss[112] and cartilage defects[113]) of OA progression. Therefore, BMLs are recognized as salient components that signify the progression of the disease and widely considered as targets for potential treatments owing to its role in knee OA[114]. Various semi-quantitative grading systems have been developed to assess BMLs, e.g. WORMS[70], BLOKS[71], MOAKS[72] and KOSS[73]. However, with the recent development of new software, the quantitative measurement of BML size[64] is becoming increasingly popular in OA research.

1.7.2.2.3 Meniscus position and size

The meniscus is a crescent-shaped fibrocartilaginous structure located on the tibial plateau in the joint space between the tibia and femur of the knee[115]. There are two menisci in the knee, each in medial and lateral compartments. These are wedge-shaped cross-sectionally and consist of two horns, anteriorly and posteriorly. Nearly 10% to 30% of the thick periphery of the meniscus is supplied by nerves and blood capillaries[116]. The menisci help in load transmission across the joint, shock absorption between the femur and tibia and distribution of loads over a larger surface area on the articular cartilage surfaces[115], while facilitating joint stability, proprioception and lubrication[117, 118]. Hence, changes in the meniscus position (e.g. meniscus extrusion) may result in altered load distribution and load-bearing capacities in

the knee. Meniscus extrusion, also known as subluxation, has been shown to be related to knee pain[119], cartilage volume loss[120] and BMLs[121], demonstrating the vital role of the meniscus in disease progression.

Meniscal extrusion is common in people with and without knee OA, especially in the medial meniscus than the lateral meniscus[122]. Crema et. al., 2012 reported a 44.2% prevalence of medial meniscal extrusion as opposed to a 9.4% of lateral meniscal extrusion, in a prospective cohort study that included participants with or at high risk of developing knee OA[122]. In another study of non-OA, overweight and obese women, Landsmeer et al., 2018, reported a prevalent medial meniscus extrusion in 54% and a prevalent lateral meniscus extrusion in 6% of the sample[123]. Several semi-quantitative scoring methods have been defined for the assessment of extrusion, namely; WORMS, BLOKS[71], MOAKS[72] and KOSS[73]. Additionally, quantitative measurement of meniscus position with improved precision has been developed and is being currently used in clinical and epidemiological research[79]. Both semi-quantitative and quantitative methods on MRI have been widely utilized for static rather than dynamic extrusion measurement of the meniscus. Interestingly, ultrasound can be effectively used in measuring load-dependent changes of the meniscus[124] even though MRI assessment is the gold standard for meniscus investigations. At present, no definitive treatment is available for meniscal extrusion, while weight loss is hypothesized to be effective due to the suggested reduction in loading forces on the knee structures.

1.7.3 Markers of end-stage OA

1.7.3.1 Joint replacements

JR is a major surgical procedure performed on people with conditions in which the joint structures are severely affected. While the majority of JR are due to OA[125, 126], the procedures are also commonly done for other joint-related conditions such as rheumatoid arthritis, inflammatory arthritis, tumour, developmental dysplasia, osteonecrosis and fractured neck of the femur[91]. There are mainly two categories of JR, namely; primary (or first-time) and revision JR. Primary JR is an initial JR that is done either partly (partial) or as a whole (total). Revision JR is the procedure in which a previous JR is replaced, or a new component is added to an existing JR[91]. The primary JR procedure involves the removal of damaged articular cartilage and bone and the replacement of these structures with prosthetics. These prosthetics are made of metal, ceramic or plastic and bears the shape of a natural joint to facilitate the movements.

Furthermore, in order to study the pathogenesis of OA, JR is considered as the ultimate point of the progression of OA of the joint, or the end-stage of OA of the joint, that signifies the overall joint failure. Hence it is considered a clinically relevant marker of end-stage OA[127]. The main indications for JR are pain and radiographic osteoarthritis (ROA)[126, 128]. Yet, the decision to undergo a JR may also depend on many other factors. These can be broadly categorised into personal-level and physician-level factors. The personal-level factors include those that may determine the socioeconomic status of the patients, such as the financial resources, health insurance, educational status, occupation, health literacy, area of residence, social support, functional motivation as well as other factors such as willingness/health-seeking behaviour and perception on JR[129-133]. The physician-level factors include physicians' perception on the patients and referral patterns[129, 130].

Hence, there may be challenges in considering JR as a marker of end-stage OA. However, the universal health-care system in Australia arguably attempts to make sure that the patients are given the necessary treatments including JR based on the disease severity, and regardless of the socioeconomic status and other factors.

1.8 Determinants/risk factors and management strategies for OA progression

OA is a multifactorial disease with many determinants and risk factors being associated with the condition. These factors can be largely categorised to person-level and/or joint-level factors which may be specific to each joint, as well as to the stage of the disease, i.e. development, progression or end-stage of the disease[27]. As explained earlier, common risk factors for OA are age, gender, and obesity[27]. In addition, factors such as joint injury and genetics may also play an important role as potential risk factors[27, 28].

Given the personal, societal and economic burden of OA, it is imperative to understand better the risk factors associated with each stage of the condition at different joints. Identification of determinants and risk factors may further help to define better preventative strategies and developing novel and effective treatments. This thesis focuses on determinants such as socioeconomic status and risk factors including PA, body composition measures and joint morphology and their association with OA progression as explained below.

1.8.1 Socioeconomic status and OA in knee and hip

It is reported that there is a socioeconomic gradient to the prevalence of OA among populations[134-136]. One such study based on the Johnston County Osteoarthritis Project that

examined the prevalence of symptomatic and radiographic knee OA found that lower socioeconomic status (SES), especially lower educational attainment was related to higher prevalence of symptomatic knee OA for men and women, while it was associated with radiographic knee OA only for women[137]. Another study on the First National Health and Nutrition Examination Survey (NHANES-I; 1971–1975), found that low educational levels were associated with symptomatic knee OA independent of potential confounding factors for both men and women[138].

Similar relationships have been reported for hip OA, in which residing in a high poverty area was related to higher odds of having radiographic hip OA, while low educational attainment was associated with higher odds of having symptomatic hip OA[135].

1.8.1.1 Socioeconomic status and joint replacement in knee and hip

JR is an effective, yet expensive procedure with various direct and indirect costs being associated with it. Despite low SES populations having a higher risk of symptomatic OA, evidence suggests that they do not experience more JR in the hip and knee, which may also indicate that there may be access disparities.

1.8.1.1.1 Socioeconomic status and total hip replacement due to OA

A US-based study previously reported that those in the lowest income group had a reduced likelihood of having a total hip replacement (THR) compared to the people in the highest income group[139, 140]. A similar trend was observed in a few studies conducted from Italy and Canada highlighting that people living in the lowest income areas had a reduced likelihood

of having a THR compared to those living in highest income areas[141]. In a study conducted in Sweden, researchers found a lower rate of THR for OA in people working in professions that are mostly related to lower SES[142].

A similar trend of association between SES and OA has been reported in Australia as well, but with mixed results. People in the most disadvantaged groups have demonstrated lower rates of THR in comparison to the least disadvantaged groups[143]. Whereas another study found that those in the most socioeconomically advantaged groups had a higher likelihood of undergoing a THR compared to the most socioeconomically disadvantaged group[144]. In contrast, no significant differences across SES strata in THR utilization was observed in another Australian study, yet, a non-significant U-shaped pattern in which higher rates was noticed for both the most disadvantaged and the least disadvantaged groups[145].

1.8.1.1.2 Socioeconomic status and total knee replacement due to OA

Similar to THR, studies looking at SES and total knee replacement (TKR) have also shown conflicting evidence both in international and Australian contexts.

A few US-based studies reported that people in the highest income group had a higher rate of TKR, in comparison to the lowest income group[146], and those living in low-income areas had a lower likelihood of having a TKR compared to people living in high-income areas[140]. Similarly, in a study in Sweden, researchers found a lower rate of TKR for OA in people working in professions that are mostly related to lower SES[142].

Correspondingly, reports in the Australian context showed that people in the most socioeconomically advantaged groups had a higher likelihood of undergoing a TKR compared to the most socioeconomically disadvantaged group[144] and that lower SES was related with a decrease in the incidence of TKR[147]. Interestingly, a sex difference was also observed where the men in the most disadvantaged group were less likely to undergo TKR in comparison to the men in the less disadvantaged groups, while no relationships were evident for women across SES groups[132]. In contrast, some Australian studies have reported otherwise. A few studies have shown that increased SES levels are related to a decrease in TKR utilization[131, 143].

This contradictory nature of evidence highlights the need for further explorations. Most of these studies have used registry verified or administrative data to conduct cross-sectional analyses[144, 145]. Interestingly, to date, only one study has evaluated the longitudinal relations between SES and time to JR in a community-based sample[129]. Therefore, **Chapter 4,** in this thesis describes the longitudinal associations between SES and time to THR and TKR in a population-based cohort.

1.8.2 Physical activity and OA in knee and hip

The association between PA and OA has been conflicting. Previous studies have shown that PA is not associated with the risk of developing symptomatic OA[148]. Interestingly, PA may be beneficial for symptomatic relief, resulting in reduced pain and improved function in both knee and hip OA[83]. Therefore, PA is widely recommended for the conservative management of the condition[83]. However, the effects of PA on the structural pathology in the knee and hip OA remain controversial[149-151]. A recent report revealed that PA defined using the

Physical Activity Scale for the Elderly (PASE) questionnaire was not linked with cartilage thickness loss, yet suggested differential effects for women, in which moderate PA was associated with a lower rate of cartilage thickness loss but not for men[152]. In contrast, another study showed that persistent vigorous PA was associated with adverse cartilage changes defined by cartilage defects and volume and further suggested that these may be dependent on other prevalent structural features of the joint[153]. In addition, Lin et al., 2013 revealed threshold effects in which both very low and very high PA levels measured using the PASE questionnaire, were related to worse biochemical changes in the knee cartilage matrix[154].

One key limitation in most of the prior studies is the use of self-reported questionnaires in evaluating PA levels. These questionnaires, although useful and commonly used, are less reliable because of over-reporting and moderate reproducibility while demonstrating a modest correlation with the actual level of activity performed[155-157]. This highlights the importance of objective measures of PA, such as ambulatory activity (AA) based on pedometers and accelerometers. However, only a few studies have used such objective measures yet have reported inconclusive evidence on associations between PA and OA.

In a previous report based on the Tasmanian Older Adults Cohort (TASOAC) study, Doré et al., 2013 revealed that pedometer-measured AA defined as steps per day was deleteriously related to knee structural changes over 2.7 years in older adults. They further reported that AA showed a protective effect against cartilage volume loss in participants with more cartilage volume at baseline, while it had detrimental effects in those with less cartilage volume at baseline[151]. In contrast, one report on the Multicentre Osteoarthritis (MOST) study by Øiestad et al., 2015 found that accelerometer-measured steps per day were not related to structural changes in the knee[158]. This inconsistency in findings across these two studies

could be attributed to the differences in population characteristics, especially different prevalence of ROA, in which the study by Doré et al., 2013 was based on a cohort of older adults with a prevalence of ROA of 57%, while the study by Øiestad et al., 2015 was conducted on a population with 28% of ROA[158].

Little is known about the association between PA and structural features in the hip. A report based on the TASOAC study demonstrated that AA was related to a lower prevalence of cartilage defects in hip cross-sectionally[150] with a graded effect of lower of cartilage defects among those who did >10,000 steps per day compared to those who did <5000 steps per day[150].

These inconsistent findings may also be due to the fact that PA may have heterogeneous effects on various structures in the joints[152]. Therefore, studying the association between PA and clinically relevant outcomes such as JR which characterizes the end-stage of OA may prove beneficial.

1.8.2.1 Physical activity and joint replacement in knee and hip

1.8.2.1.1 Physical activity and knee replacement due to OA

Similar to the nature of the evidence for structural factors, prior research assessing the relationship between PA and TKR have been inconclusive[159-162]. Most studies have assessed PA with self-reported questionnaires and reported differential effects. A study by Wang et al., 2011 found that increased PA levels were associated with increased risk of TKR while walking was not associated with the risk of TKR[159]. Interestingly, a sex difference

was also reported in which higher levels of PA were linked with increased risk of TKR for women, while no associations were observed for men[160], while Ageberg et al., 2012 showed no association between total PA and TKR[161]. A systematic review that assessed the relationship between running and TKR concluded that higher PA was associated with lower odds, yet these findings were mainly based on case-control studies that used retrospective data[149]. By contrast, a study that looked at participants who conducted intensive PA such as elite athletes has suggested that participation in these high-intensity activities may increase the risk of TKR[163].

1.8.2.1.2 Physical activity and hip replacement due to OA

Research assessing the relations between PA and THR have also shown mixed evidence. While self-reported walking and running have been associated with reduced risk of THR[164] especially in women[161], some studies oppose this argument by showing that higher PA was linked with increased risk of THR in a population-based cohort [160] and elite athletes[163]. On the contrary, a few studies have reported no associations between PA and the risk of THR[159, 165].

There could be several reasons that may explain the inconsistency in prior research, mostly linked to the differences in methodological approaches such as the use of questionnaire-based PA data[159-162], and different study designs including prospective[159-161] or case-control[162] designs.

Owing to the inconclusive nature of evidence, further prospective studies with long-term follow-up times that utilize objective measures of PA are necessary to untangle these

associations. Improving the understanding of these associations will help in defining better preventative and management programs for people with or at risk of knee and hip OA. Therefore, a longitudinal study that assessed the associations between objectively-measured PA defined as AA and the risk of TKR and THR over 13 years is discussed in **Chapter 5** in this thesis.

1.8.3 Body composition measures and OA in knee and hip

Obesity has been long known as a factor affecting the health and wellbeing of the people. While it is a complex disease, its pathogenesis is only partly understood and is associated with many other diseases[166]. But, it is a mostly modifiable and preventable disease[166]. Obesity is often determined using body mass index (BMI)[167]. Yet, there are other potentially more sensitive measures of body composition that include total fat mass, lean mass and distribution of fat mass (trunk fat, waist circumference). These measures may be useful in identifying potential mechanisms of pathogenesis.

The association between obesity/high BMI and knee OA has been well recognized[34, 168, 169] with several reports showing that obesity is related to both symptomatic and structural markers of OA progression[112, 170, 171].

Interestingly, more sensitive markers of body composition such as fat mass and lean mass have also been positively related to radiographic[172, 173] and symptomatic knee OA[174], although there is some evidence showing differential effects for lean mass[175]. With regard to structural markers, several reports have shown that while fat mass may have detrimental

effects on cartilage properties, cartilage defects and BMLs, fat-free mass or skeletal mass may have beneficial effects on cartilage properties[176], and cartilage volume[177].

The relationship between obesity/BMI with hip OA, however, is inconclusive. An early systematic review showed moderate evidence for a positive relationship between BMI and hip OA[178], whereas a few recent studies have reported that BMI was not associated with incidence or progression of hip OA[179, 180]. There is a lack of evidence for the associations between different body composition measures and hip OA, yet, a few reports have shown that participants with hip OA may have lower lean mass[181, 182], despite some evidence suggesting otherwise[183].

1.8.3.1 Body composition measures and joint replacements in knee and hip

1.8.3.1.1 Body composition measures and knee replacements due to OA

Similarly, prior studies examining the relationship between BMI and JR in the knee have consistently shown an increased risk of TKR with higher BMI[184-187]. Leyland et al., 2016 found that overweight and obese participants had a 40% - 100% increased risk of TKR compared to the participants with a normal BMI[186]. Nevertheless, limited prospective studies have examined the relations of different body composition measures with TKR focusing on measures of adiposity and fat distribution. Studies by Wang et al., 2009 and Lohmander et al., 2009 revealed that adiposity measures and measures of fat distribution are linked to increased risk of TKR[187, 188]. Albeit, no studies have evaluated the relationship of lean mass and TKR, especially in the same study with other body composition measures.

1.8.3.1.2 Body composition measures and hip replacements due to OA

A greater risk of THR with higher BMI have been reported[189, 190], although some studies have demonstrated sex differences where higher odds of THR were observed only for men cross-sectionally[191]. Limited research has investigated the effects of obesity using different body composition measures with only two prior studies reporting that body composition measures were predictive of the risk of THR[187, 188]. Interestingly, no study has evaluated the relations of lean muscle on THR in the same study with other body composition measures.

Therefore, further longitudinal studies are warranted to clearly identify the associations between body composition measures and JR in the knee and hip. **Chapter 5** in this thesis describes a 13-year prospective study that examined these associations in a population-based cohort.

1.8.4 Joint morphology and OA

Joint morphology, especially bone morphology, is an important factor for the incidence and progression of OA, as shown in hip and knee[43, 45, 192]. In the hip, which is challenging to characterise, various measurements, including geometric measures such as centre-edge angle or Wiberg angle, triangular index, hip-axis-length and femoral-neck-width, have been used in prior studies to assess the morphology[192-195]. These measures have limitations as these may depend on the body size of the participant, may be highly correlated with each measurement and may lack important information on subtle shape variations[196]. Additionally, these do not provide a global measurement of the joint morphology as these only focus on specific

components of the morphology[197] and has a higher liability of measurement error. Therefore, it is essential to utilise accurate methods to assess joint morphology.

Joint morphology determined as the variation of bone shape may thus be beneficial in assessing their relationship with OA. These can be measured using imaging software such as Active Shape Modelling (ASM) that can be used to assess the variations in joint shapes[194] on radiographs, MRI or dual-energy x-ray absorptiometry (DXA). Using ASM, Statistical Shape Models (SSM) can be defined based on the points on the bones of the images. These then identify different shape modes. These shape modes quantify the global bone shape[197], thus, helps to assess joint morphology accurately.

1.8.4.1 Relationship between hip and knee joints

Literature suggests that there could be interrelationships between hip and knee joints. A previous report from the TASOAC study found that there is a correlation between hip and knee cartilage volume[78]. Another study conducted on the Johnston County Osteoarthritis Project showed that people with OA in one of the hip or knee joints had 40-80% greater odds of developing OA in another hip or a knee joint[198].

Additionally, studies have further shown that alterations in the hip joint may have differential effects on the knee joint. A study showed that knee OA progression on the THR leg was less likely when compared to the non-THR leg[199]. Similar findings were reported in several studies that showed a relationship between the first THR side and the successive TKR side[200, 201]. This was suggested to be due to the changes in the knee biomechanical factors such as changes in dynamic joint loads, that occur following the alterations in the hip joint[202-205].

Furthermore, people with developmental dysplasia of the hip are more likely to undergo both THR and TKR[206]. Taken together; these suggest that alterations of the hip joint may have implications for knee health. Interestingly, a strong correlation has also been reported between certain morphological features of the proximal femur and the morphology of the distal femoral trochlea, further strengthening the theory that the hip and knee joints are inter-related[207].

In light of this, a previous report showed that the geometry of the pelvis and hip were related to the severity of OA in the knee[208]. A cross-sectional study further reported that people with symptomatic knee OA with malalignment (varus alignment) had a higher prevalence of CAM morphology of the hip[209] which is a deformity with a reduced concavity at the femoral head-neck junction[210]. Several case-control reports have also shown that certain anatomical variations of the hip and pelvis were associated with compartment-specific knee OA[192, 193]. However, as explained earlier, these geometric measurements have limitations that challenge the interpretation of these findings, as these only focus on specific components of the morphology of hip. Therefore, it is essential to identify the associations between hip morphology and knee OA using independent shape variants of the hip[211].

Chapter 6 in this thesis describes the longitudinal associations of hip shape variations with the progression of knee pain, cartilage volume loss, worsening of BMLs and incidence of primary TKR in a population-based cohort.

1.8.5 Management strategies for OA

1.8.5.1 Weight loss and knee OA

Given the well-documented evidence suggesting an increased risk of onset and progression of OA due to obesity[33], weight loss is considered an important management strategy for OA in people with obesity[83].

Weight loss is effective in reducing symptoms such as pain[212], with a possible dose-response relationship[213] especially in knee OA[214, 215] and reduces the risk of development of symptomatic OA[216]. In addition, weight loss has beneficial effects on functional improvements[217] and reduction of disability[218] in overweight and obese older adults with knee OA, with studies reporting functional improvements by 28% with a 10% loss of body weight[219]. Hence, several guidelines on the symptomatic management of OA released by the OARSI[82, 83] and ACR[84] recommend weight loss as a management strategy for symptomatic OA in overweight and obese people. Possible mechanisms via which weight loss promotes symptomatic relief, and improved function could be, 1) reducing the widespread inflammation[220] and, 2) knee joint loads[221].

Diet interventions are central to achieve weight loss. However, several studies have suggested that weight loss attained by a combination of diet and exercises may have more significant improvements in symptoms related to knee OA than either of the interventions alone[217, 222]. Similarly, the Intensive Diet and Exercise for Arthritis trial (IDEA), which is a single-blind, randomised clinical trial conducted over 18 months showed that the group with a combination of diet and exercise had greater improvements not only in pain and function but also in inflammatory markers. This study also reported that knee compressive forces were lower in the group who had diet intervention alone compared to the participants who only had an exercise intervention[223].

Although weight loss has been shown to be effective for symptom reduction, whether it has structure modifying effects has not been clearly elucidated[224]. There is a lack of evidence on structure modification by weight loss on radiography[225]. While no significant effects on the incidence of knee OA was reported in the first preventive trial in knee OA, the 'Prevention of knee osteoarthritis in overweight females (PROOF)' study, conducted on middle-aged female participants who were at a higher risk of developing knee OA[226], in a follow up exploratory analysis from the same study showed that participants who achieved 5kg or 5% of weight reduction over 30 months had a reduced risk of incident knee OA on radiography[227].

Interestingly, there is increasing evidence on structure modifying effects of weight loss from studies using MRI[228]. A study looking at knee cartilage morphology reported that weight loss was associated with both the quality and quantity of cartilage of the medial compartment, but not on the lateral compartment[229]. Another observational study in obese participants looking at the effects of massive weight loss achieved by gastric surgery showed significant improvements in cartilage quality determined by several biomarkers[230].

In contrast to these findings, a study conducted on the radiographical and MRI outcomes in the knee of the IDEA trial which included quantitative cartilage morphometry, semiquantitative BMLs and Hoffa-synovitis measures reported no significant between-group differences among the exercise only, diet only and diet + exercise groups[225]. This is also in line with a recent report from the PROOF study which did not identify any associations between MRI based structural features and weight loss group, compared to a stable weight group[123].

The meniscus is an important knee structure that plays a key role in load distribution (as explained above); however, the effects of weight loss on meniscus position in participants who

have developed knee OA has not yet been clearly identified. Hence, **Chapter 7** in this thesis describes the relationships between weight loss and quantitative measures of meniscus position in older adults with knee OA.

1.9 Summary

OA affects nearly 9.6% of men and 18.0% of women who are 60 years or older globally, and its incidence is suggested to increase with the ageing population and the increasing prevalence of risk factors. It is a major cause of disability around the world and has an enormous impact on healthcare costs.

OA progression is associated with many determinants and risk factors. Given that there are no definitive treatments for OA, an improved understanding of the person- and joint-level factors that may be related to OA progression would be helpful to improve preventive and treatment strategies. Additionally, there is an urgent need to identify effective treatments for certain joint-level factors. Therefore, the following chapters of this thesis describe the relationships between determinants, risk factors and potential management strategies for progressive OA in older adults.

Chapter 2: Research Questions

2.1 Research questions

Research questions 1, 2 and 3 focus on identifying determinants and risk factors for progressive OA in a population-based cohort of older adults aged between 50 – 80 years,

Research question 1.

1.1 Is socioeconomic status of the participant associated with time to THR and TKR due to OA?

Research question 2.

2.1. Is ambulatory activity measured as steps per day associated with the risk of TKR and THR due to OA?

2.2. Are different body composition measures associated with the risk of TKR and THR due to OA?

Research question 3.

3.1. Are hip shape variations associated with worsening pain, cartilage volume loss, worsening BMLs in the knee and the risk of TKR due to OA?

Research question 4 focuses on identifying a potential management strategy for OA progression in overweight and obese older adults over the age of 55 years,

Research question 4.

4.1. Is interventional weight loss associated with less meniscal damage progression (assessed using quantitative measures of meniscus extrusion and size, and semiquantitative meniscus scores) over time?

4.2. Is a diet-induced weight loss program, with or without exercise, more effective in modifying meniscus extrusion and size compared to exercise alone?

2.2 Key hypothesis

1. Determinants such as socioeconomic status of the participants and the risk factors such as ambulatory activity, body composition measures and hip shape variations are associated with knee OA progression determined by worsening pain, cartilage volume loss, worsening BMLs and the incidence of TKR.

2. Determinants such as socioeconomic status of the participants and the risk factors such as ambulatory activity and body composition measures are associated with hip OA progression determined by the incidence of THR.

3. In overweight and obese participants,

   3.1. 18-month interventional weight loss is associated with less progression in quantitative measures of meniscus extrusion and size, and in semiquantitative meniscus scores, over time; and,

   3.2. A diet-induced weight loss program, with or without exercise, is more efficient in modifying meniscus extrusion and size than exercise alone.

Chapter 3: Methodology

3.1 Prelude

This chapter describes the designs, study populations, protocols of exposure and outcome measures of the TASOAC and the IDEA trial. The chapters 4,5,6 in this thesis utilized data from the TASOAC study while chapter 7 was based on the data from the IDEA trial. The chapters 4 to 7 are presented in a way that they were accepted by, or submitted to peer-reviewed journals, and therefore, there may be some differences and repetition in the descriptions of the methods due to the requirements or requests from the journals in each chapter. Additionally, the sample sizes of each chapter may vary as it depends on the availability of the data for the particular research question.

3.2 Tasmanian Older Adult Cohort Study

3.2.1 Study population and design

The TASOAC was a prospective, population-based study that was mainly aimed at identifying the environmental, genetic and biochemical factors related to the onset and progression of OA in the hand, knee, hip and spine. Participants between 50 and 80 years were selected using computer-generated random numbers from the electoral roll in Southern Tasmania (population 229,000). Electoral rolls contain the most comprehensive listing of community-based Australian residents. A sex-stratified sampling method was used to allow the recruitment of equal numbers of men and women. Participants who had a contraindication to MRI and who were institutionalised were excluded from the cohort. Eligible participants (n=1099; response rate 57%) attended a baseline clinic (phase 1) between March 2002 and September 2004. Three

follow-up phases were then conducted 2.5 (phase 2), 5 (phase 3) and 10 (phase 4) years after the baseline assessment. Figure 3.1 shows the participant flow at each phase.

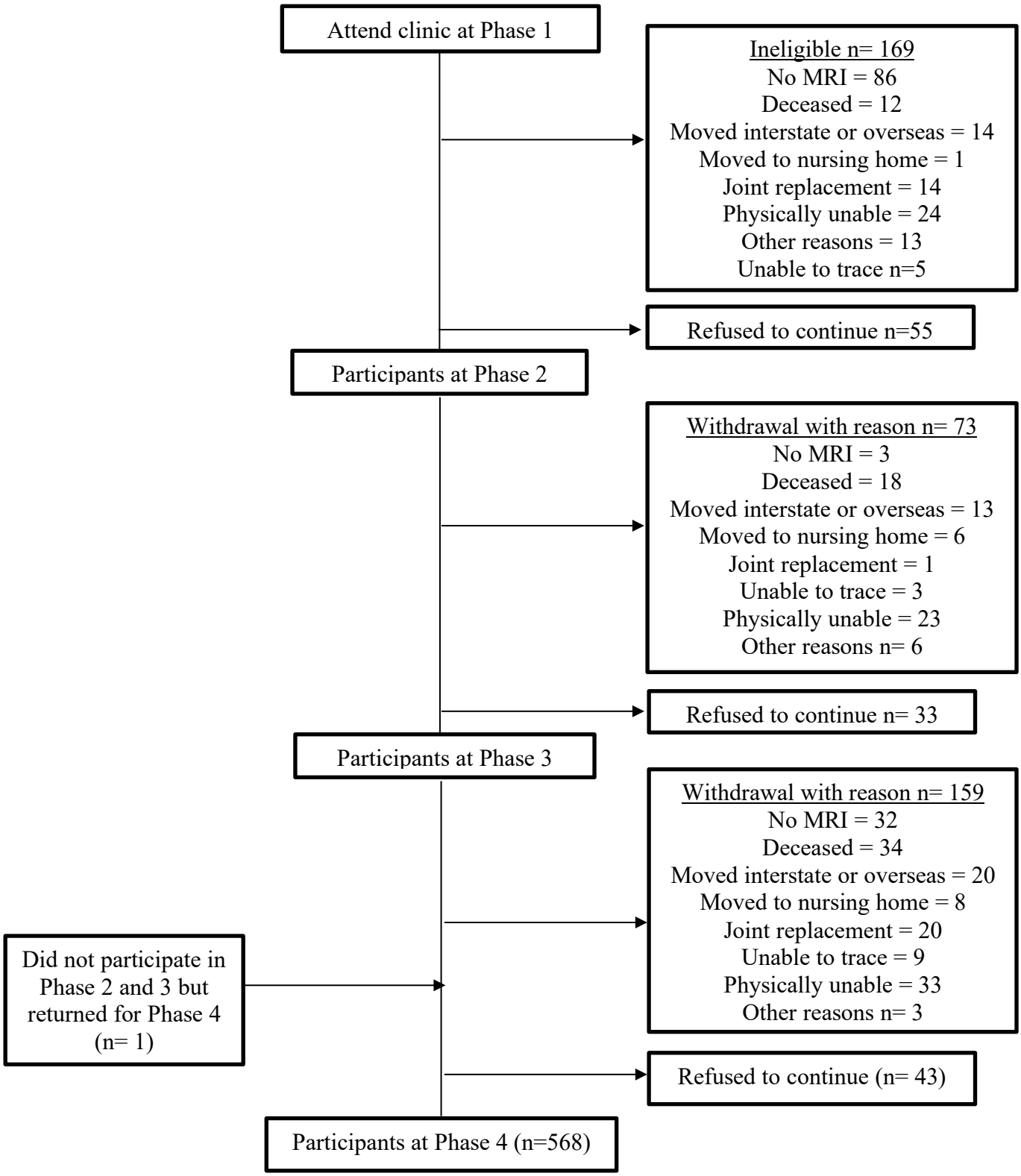


Figure 3.1: Flowchart of TASOAC participants

3.2.2 Ethical approval

Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee (Approval Number: H6488) and written informed consent was obtained from all the participants. In order to link the cohort data to national registries, an amendment of ethics was approved for a waiver of consent for the participants who were lost to follow-up at the 4th phase (Amendment Approval Number: H12938).

3.2.3 Measurements

3.2.3.1 Demographic and anthropometric measures

At baseline, age, sex, ethnicity, education level, occupation, smoking status, medical history and other lifestyle factors were collected using a questionnaire. Weight of the participants was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using electronic scales (Heine, Dover, New Hampshire, USA). Height was measured to the nearest 0.1 cm (with shoes, socks and headwear removed) using a Leicester stadiometer (Invicta, Leicester, UK). BMI (kg/m^2) was then calculated as weight/height^2.

3.2.3.2 Exposure measures

3.2.3.2.1 Body composition measures

Waist circumference of the participants was measured to the nearest 0.1 cm. Total fat mass, trunk fat mass and total lean mass (g) was measured by a dual-energy x-ray absorptiometry

(DXA) scanner (Hologic Delphi, Waltham, Massachusetts, USA) at baseline. Lean mass percentage was calculated as a percentage of total body mass.

3.2.3.2.2 Physical activity

Ambulatory physical activity at baseline was determined as steps/day using a pedometer (Omron HJ–003 & HJ-102, Omron Healthcare, Kyoto, Japan). Pedometers were first calibrated with the presence of the participant at the clinic, utilising a 100-pace walking test. Participants were given instructions (both verbal and written) about using the pedometer and keeping a pedometer log (diary). They were required to wear the pedometer on the dominant side for seven consecutive days while conducting their normal day-to-day activities except during bathing, water activities and sleeping. They were also advised to maintain a log of the step count per day and the time duration during which the pedometers were worn. This was repeated after six months in order to account for habitual changes in different seasons. Hence, there were two sets of pedometer logs for each participant. Readings were excluded if there was evidence for artificial pedometer readings such as work done on heavy machinery. Then, pedometer wear time was determined for each day using the pedometer logs. A 'valid wear day' was defined as a day on which the pedometer was worn for at least 8 hours. For the analyses, steps/day was calculated as the mean of the two pedometer logs, with a minimum of five valid wear days. An ICC of 0.71 to 0.84 was reported in a prior study for a record of 2-days and an ICC higher than 0.90 was reported for a record of 4, 5 and 6 days[231, 232].

3.2.3.2.3 Socioeconomic Status

The SES of the participants was ascertained by matching each participant's residential address at baseline to the corresponding Australian Bureau of Statistics (ABS) Census Collection District. The ABS software was then utilized to determine the Socio-Economic Indexes for Areas (SEIFA) value from the 2001 census. SEIFA constitutes of four separate indices, obtained using different variables which summarize the characteristics of residents within an area (~ 250 households), thereby providing a single measure to rank the level of advantage and/or disadvantage at the area-level, not of the individual person. These indices are Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD), Index of Relative Socio-Economic Disadvantage (IRSD), Index of Economic Resources (IER) and Index of Education and Occupation (IEO). The IRSAD is a measure that incorporates variables such as household income, car ownership, number of one-parent families and educational attainment[233]. The IRSD is based on low income, low educational attainment, high unemployment, jobs in relatively unskilled occupations and measures that show disadvantage (e.g., Indigenous and Separated/Divorced). The IER is derived from the income and expenditure of families, such as income and rent, while the IEO is a measure of the educational and occupational levels of communities.

3.2.3.2.4 Hip morphology/shape

Hip shapes were measured using dual-energy x-ray absorptiometry images of the left hip at baseline. There were 264 participants with no DXA images, and a further four images were excluded due to low quality.

SSM was used to assess the hip shape of the proximal femoral head, acetabulum and femoral neck using two software; ASM toolkit[194, 234] (Manchester University, Manchester UK) and

SHAPE (University of Aberdeen, UK) software. An SSM, which is a set of landmark points that define the shape to be identified, was constructed of the femoral head, acetabulum, femoral neck, greater and lesser trochanters and proximal part of the shaft with 85-points. The placement of points is done on the same feature of the outline of the bone, in order to facilitate comparison between images. First, the main points are placed at anatomical landmarks such as the beginning of greater trochanter, the highest point of the greater trochanter, higher and lower points of the lesser trochanter and the rest of the points are placed evenly among the main points. These points are then used to define coordinates of each point for each participant and are transferred to SHAPE software as a 'point file'. Using Procrustes Analysis, the coordinates are aligned into a common coordinate frame that allows translating, rotating and scaling each shape in order to minimize the sum of squared distances from the mean of the set[234]. Then the SSM model is compared with the DXA image, and the alignment of the points was checked with the anatomical feature. Using a two-dimensional point cloud, the data distribution for the participants is additionally checked for discrepant values. Following this, the principal components of the data, which are also called as shape modes, are derived as independent sets of orthogonal mode scores for each image. The mode scores were then normalized to zero as mean and a unit standard deviation so that the scores assigned to each image are in units of standard deviations. Hence, the reference to a 'lower' score, therefore, implies a position towards the more negative end of the distribution rather than smaller in absolute terms. A scree plot was generated to visualize the variance described by each mode[45]. Further, 10 images were randomly selected, and two independent assessors did the point placement on these images in order to evaluate the point-to-point variability which is the variability of the distance between equivalent points placed by each assessor. The variability was not normally distributed, and the median was 1.6 pixels[45].

The first 10 shape modes explained 78% of the total shape variance of the cohort and were numbered in descending order of shape variance from mode 01 (31% variance) to mode 10 (1.82% variance). The 10 shape modes were selected as each of these modes explained at least 1.5% of the total variance of the cohort, based on expert opinion (R. Aspden & J. Gregory) and the scree plot developed as the line describing the variance of each mode flattens after the first 10 modes[235]. These modes are further explained in Chapter 6.

3.2.3.3 Outcome measures

3.2.3.3.1 Pain

Self-reported knee pain was assessed using the WOMAC[53] at all four time-points. This index constitutes of five subscales (walking on flat surface, going up/down stairs, at night in the bed, sitting/lying and standing upright), which are marked on 10-point scales ranging from 0 (no pain) to 9 (most severe pain). A total WOMAC pain score was calculated by summing the five subscales (range; 0-45). The pain change was calculated as follow-up pain – baseline pain. An increase in the pain was determined by calculating the smallest detectable difference. For our cohort, this was calculated to be 0.6[236]; hence an increase in the WOMAC score of 1 or more was defined as a worsening of knee pain[237].

3.2.3.3.2 Magnetic Resonance Imaging

A 1.5T MRI scan of the right knee was performed at baseline and 10 years. At baseline, participants were scanned in the sagittal plane on a Picker, Cleveland, Ohio, USA unit using a commercial transmit-receive extremity coil. The image sequences obtained are: (1) a T1-

weighted fat saturation three–dimensional gradient-recalled acquisition in the steady-state, echo time 6.71 ms, 512×512–pixel matrix, flip angle 30°, repetition time 31 ms, 60 partitions, field of view 16 cm, slice thickness of 1.5 mm without an inter-slice gap; (2) a T2-weighted fat saturation two-dimensional fast spin echo, flip angle 90°, repetition time 3,067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 × 256-pixel matrix, slice thickness of 4 mm with a between-slice gap of 0.5 to 1.0 mm[64]. At the 10-year visit, the MRIs were obtained in the sagittal plane on a Siemens, Espree, Pennsylvania, USA unit using the same sequences as above.

3.2.3.3.2.1 Tibial and patella cartilage volume (mm^3)

Tibial and patella cartilage volume was assessed by a single trained reader on T1-weighted MR images using OsiriX software (University of Geneva, Geneva, Switzerland). The MRIs were paired and read, with the chronological order known to the reader using baseline and 10-year scans, which were only performed for participants who had an MRI at both baseline and 10-year follow-up (n=496). The reader manually drew disarticulation contours around the cartilage boundaries and isolated the cartilage volume of individual cartilage plate (medial tibial, lateral tibial, patella & trochlear) from the total volume. Then a final three-dimensional rendering was done reassembling the data utilizing bilinear and cubic interpolation (area of 312 × 312 mm and 1.5 mm thickness, continuous sections). The tibial and patella cartilage volumes were determined by summing the pertinent cartilage plates within compartments. Medial and lateral tibial cartilage volumes were summed to calculate total tibial cartilage volume and the cartilage volume change over the 10 years was then calculated as follow-up volume – baseline volume. The coefficient of variation for intra-observer repeatability ranged from 2.1–2.2%[238].

3.2.3.3.2.2 Bone-Marrow Lesions (mm^2)

Subchondral BMLs were assessed on T2-weighted fat saturation images using OsiriX software at medial and lateral sites of tibia and femur, and patella. BMLs were defined as areas of increased signal intensity on T2-weighted images, located immediately under the articular cartilage. One trained observer read the BMLs with the images paired and the chronological order known, by measuring the maximum area of the lesion at each site in mm^2 using the computer cursor at baseline and the 10-year follow-up. The largest BML was considered if there were more than one lesion at the same site. Intra-observer reliability was evaluated in 40 randomly selected participants with a 2-week interval between the readings, and the intra-class correlation coefficient (ICC) was excellent (0.98 (95% CI; 0.96, 0.99)) for BMLs at baseline and 10-years[239].

3.2.3.3.3 Primary (first-time) knee and hip replacement

The incidence of primary (first-time) KR and HR between 1 March 2002 and 21 September 2016 were determined by data linkage to the AOANJRR. AOANJRR started data collection in Tasmania in September 2000 and collects data from both public and private hospitals. Data validation against State and Territory Health Department data is done using a sequential multi-level matching process[240]. Matched data were then obtained which included the date, side of JR, primary or revision JR and the reason for the procedure (e.g. OA, fracture of neck of femur, osteonecrosis, inflammatory arthritis, tumour). In this study, we only considered JR's that were due to OA.

3.2.3.4 Other covariates

3.2.3.4.1 Knee radiographs

A standing, anteroposterior, semi-flexed view of the right knee with 15° of fixed knee flexion was obtained in all the participants at baseline. The radiographs were scored based on the Altman atlas[59] on a scale of 0–3 (0 – normal, 3 – severe) by two readers simultaneously. The features scored were medial joint space narrowing (JSN), lateral JSN, medial femoral and tibial osteophytes and lateral femoral and tibial osteophytes. Each score was determined by consensus of two readers. Intra-observer repeatability was evaluated in 40 participants with a one-week interval between the two measurements. ICCs ranged from 0.65–0.85. The presence of ROA was defined as a score ≥1 for JSN or osteophytes.

3.2.3.4.2 Hip radiographs

Antero-posterior radiographs of the right hip were obtained in all the participants at baseline. The radiographs were assessed based on the OARSI grading system[59] on a scale of 0-3 (0 – no disease, 3 – severe) by two readers simultaneously. The features assessed were superior acetabular or superior femoral osteophytes and axial or superior JSN. Intra-observer repeatability was evaluated in 40 participants, and the ICCs ranged from 0.60-0.87. The presence of ROA was defined as a score ≥1 for JSN or osteophytes.

3.2.3.4.3 Self-reported covariates

Hip pain was recorded as presence or absence by asking whether the participants had hip pain at baseline. History of knee surgery was obtained from questionnaires. History of knee injury was not assessed at baseline but was asked at a 2.7-year follow-up: 'Have you had a previous knee injury requiring non-weight-bearing treatment for more than 24 h or surgery?'.

3.3 Intensive Diet and Exercise for Arthritis trial

3.3.1 Study design

The IDEA trial was a single-blind, single-center, 18-month, randomized controlled trial that aimed at identifying the effects of interventional weight loss on knee symptoms and structural changes in participants with knee OA. The trial was conducted from July 2006 to June 2011 at Wake Forest School of Medicine and Wake Forest University, Winston-Salem, NC, USA[223, 241]. The inclusion and exclusion criteria of the study are as follows:

3.3.1.1 Inclusion criteria

1) Age 55 years or older
2) Kellgren-Lawrence grade (KLG) 2-3 (mild to moderate) radiographic tibiofemoral or tibiofemoral with patellofemoral OA of at least one knee;
3) pain on most days due to knee OA;
4) a BMI between 27 and 41 kg/m^2
5) a sedentary lifestyle (<30 min/week of formal exercise over the past 6 months).

3.3.1.2 Exclusion criteria

1) Significant co-morbid disease that would pose a safety threat or impair the ability to participate,
    - Symptomatic or severe coronary artery disease, severe hypertension, active cancer other than skin cancer, anemia, dementia, liver disease, Chronic Obstructive Pulmonary Disorder (COPD), peripheral vascular disease, inability to walk without an assistive device, blindness, osteoporosis, type 1 diabetes, type 2 diabetes on thiazolidinediones agents;
2) Previous acute knee injury (ligament or cartilage damage from the acute event),
3) Patellofemoral OA in the absence of tibiofemoral OA,
4) Unwillingness or inability to change eating and physical activity habits due to environment,
5) Inability to speak and read English,
6) Excess alcohol use (≥ 21 drinks per week),
7) Inability to finish an 18-month study or unlikely to be compliant (Lives > 50 miles from the site or planning to leave area ≥ 3 months over the study period of 18 months),
8) Contraindications to knee MRI,
    - Pacemaker, severe claustrophobia, defibrillator, implanted metal objects in the leg, neurostimulator, magnetic aneurysm clip, any kind of metal implant or foreign metal objects in the body, such as bullets, shrapnel, metal slivers
9) Significant cognitive impairment or depression,
    - Diagnosis of dementia or a Modified Mini-Mental State Exam (3MSE) score < 70, Center for Epidemiological Studies Depression (CES-D) score > 17.

3.3.2 Ethics

The study was approved by the Human Subjects Institutional Review Board of Wake Forest Health Sciences, and conducted in compliance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all the participants.

3.3.3 Study population

The participants were recruited over 37 months from November 2006 to December 2009 from the community[223, 241]. Various methods were used for recruitment such as mass mailings, newspaper advertisements, presentations at local ageing service networks, senior centres, and churches and via selected physicians in geriatrics, orthopaedics and rheumatology areas. Sample size calculations were performed prior to participant recruitment, and a total sample of 450 participants with 150 per group was calculated to provide 80% statistical power to detect 20% and 15% differences in the primary outcomes of the trial (IL-6 and knee joint loads). A total of 3035 participants were prescreened, and following 2 screening sessions, 454 ambulatory, community-dwelling older adults were randomized (Figure 3.2). Additionally, a random sub-sample of 105 participants were selected for the MRI sub-cohort[223, 241].

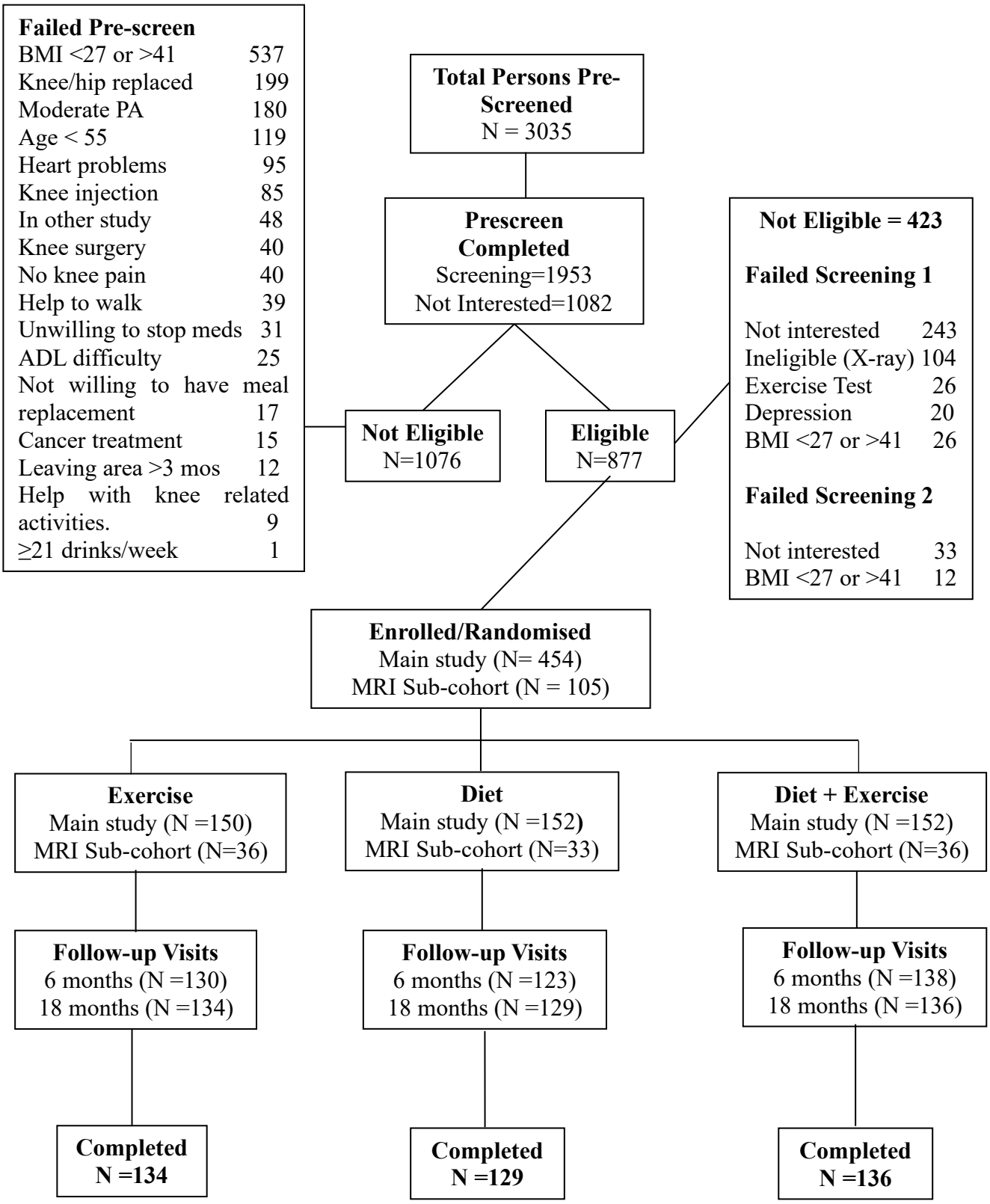


Figure 3.2: Flowchart of IDEA participants

3.3.4 Interventions

Stratified-block randomization was used to assign all the eligible participants to one of the three intervention groups, stratified by BMI and sex: exercise-only (E), diet-only (D) and diet with exercise (D+E). The exercise group received an exercise-only intervention; the diet-only group received a diet-induced weight-loss intervention while the diet with exercise group received both[223, 241].

3.3.4.1 Diet-induced weight loss intervention

This intervention was aimed at achieving a minimum weight loss of 10% of baseline body weight, and the intervention was based on partial meal replacements that included up to 2 meal-replacement shakes per day (Lean Shake; General Nutrition Centers) and the 3rd meal of 500 – 750 kcal which was low in fat and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits.

The initial diet plan was designed to provide an energy-intake deficit of 800 to 1000 kcal/day as calculated by energy expenditure (estimated resting metabolism × 1.2 activity factor). The minimum level of calorie intake was 1100 kcal for women and 1200 kcal for men. The goal of calorie distribution was 15% - 20% from protein, > 30% from fat, and 45% - 60% from carbohydrates based on the Dietary Reference Intakes for Energy and Macronutrients[241].

During the intervention, weight was monitored weekly or biweekly. In order to facilitate the adherence and the success of the intervention, behavioural sessions and nutrition education sessions were conducted. During the first six months, 1 individual session and 3 group sessions

per month were carried out while biweekly group sessions and an individual session every 2 months, from the 7th to 18th months[223, 241].

3.3.4.2 Exercise intervention

The exercise intervention was comprised of an aerobic walking phase (15 minutes), strength training phase (20 minutes), a second aerobic phase (15 minutes) and a cool-down phase (10 minutes). This was carried out as 1-hour sessions on 3 days per week over the study period of 18 months. The intervention was centre-based over the first 6 months and after the 6-month follow-up testing and a transition phase of 2 weeks, the participants were allowed to remain in the centre-based program, choose a home-based program or to combine both.

The aerobic training was done using walking and participants who were unable to practice walking over the defined time period were suggested to` use stationary bicycles. The intensity of the training ranged between 50-75% of the heart-rate reserve based on symptom-limited maximum heart rate defined using a graded exercise test (GXT). The strength training was mainly focused on lower limb muscles and to a lesser extent on upper extremity muscles. The session was comprised of 1–2 sets of 10–12 repetitions on leg extension, leg press, seated leg curl, seated calf raises, compound row and vertical chest or incline press.

The participants who opted to conduct the home-based training were contacted over the phone, and monthly exercise and attendance logs were collected to monitor the progress. The home-based strengthening program was done using Thera-Bands[223, 241].

3.3.5 Techniques to Improve Adherence

Behavioural techniques based on social cognitive theory and group dynamics were conducted by the interventionists (diet and exercise), and the data on adherence were regularly reviewed. All the participants were requested to monitor their participation using daily logs. The participants who had difficulty in reaching the weight-loss goals in the diet groups were provided with additional individual and group counselling, social support and incentives[223, 241].

3.3.6 Magnetic Resonance Imaging acquisition

MRI of the most symptomatic knee was obtained in a random sub-sample of 105 participants at both baseline and 18-month follow-up. The sample sizes per group were as follows: E: n=36; D: n=33; D+E: n=36. MRIs were obtained using a 1.5T (SIGNA HDx, General Electric Medical Systems, Milwaukee, WI, USA) scanner with an extremity coil. The MRI sequences acquired included; (1) Double oblique coronal three-dimensional spoiled gradient-echo (SPGR) with fat suppression; (2) Axial T1-weighted spin-echo (SE); (3) Double oblique coronal T1-weighted SE; (4) Sagittal T1-weighted SE; (5) Sagittal T2-weighted fast spin-echo (FSE) with fat suppression; (6) Double oblique coronal T2-weighted FSE with fat suppression[225].

3.3.6.1 Quantitative meniscus position and size measures

The coronal SPGR sequence with fat suppression (1.5 mm slice thickness; interpolated in-plane resolution 0.31 mm × 0.3 mm) was utilised to quantitatively measure the meniscus in the

central 5 slices (determined by the anatomical location)[242]. The images were first checked to ensure sufficient quality to support segmentation by an expert reader, and 7 MRIs were excluded due to poor image quality[225]. Further, 8 medial and 3 lateral menisci needed to be excluded as they were severely macerated and could therefore not be analysed quantitatively, leaving 90 medial and 95 lateral menisci at each time-point for segmentation. Manual segmentation of the medial and lateral menisci was then performed using specialised software (Chondrometrics GmbH, Ainring, Germany)[79]. The tibial cartilage surface including the denuded areas of subchondral bone and the surfaces of the meniscus (tibial, femoral and external area) were segmented on the SPGR images; this was assisted by the concurrent display of the proton-density-weighted (PDw) spin-echo images that are commonly used for radiological evaluation of the menisci[243]. Baseline and follow-up images were segmented as pairs by one reader with blinding to the intervention, acquisition order, and OA (KLG) status. All segmentations were quality controlled by an expert reader with > 10 years of experience in quantitative joint tissue analysis; adjustments were made by consensus. Test-retest reliability of the readings was conducted on 10% of the participants (n=10), 1 month apart. The intra-rater variability determined as root mean square standard deviation (RMS SD) and intraclass correlation (ICC) for maximum extrusion distance at baseline was RMS SD, 0.50, ICC, 0.98 (0.94, 1.00) and at follow-up was RMS SD, 0.65, ICC, 0.97 (0.89, 0.99). The RMS SD and ICC for mean extrusion distance at baseline was RMS SD, 0.48, ICC, 0.99 (0.94, 1.00) and at follow-up was RMS SD, 0.58, ICC, 0.97 (0.90, 0.99). Performance of the quantitative data was in the excellent range for all the other measures (ICC range 0.92 – 0.99) (Supplementary Table 3). Furthermore, the precision of this methodology has been presented previously[244] that shows that the sensitivity-to-change of the 3D meniscus parameters are correlated with the changes in joint space width (JSW), suggesting that the precision is high.

Following the segmentation, the measures of meniscus position and size[244] were calculated using the Chondrometrics software[79]. Meniscus position measures included maximum and mean extrusion distances (mm), area of the meniscus not covering (i.e. extruding) the tibial plateau (mm^2), tibial coverage (by the meniscus) (mm^2) and overlap distance between the meniscus and tibial plateau (mm). The size measures included meniscus width (mm) and height (mm). Additionally, previous studies have shown that this measurement methodology on MRI with similar resolutions (i.e. resolution 0.31 mm × 0.3 mm) is capable of detecting changes that are smaller than the resolution for the meniscus parameters[244-247].

3.3.6.2 Semiquantitative meniscus measures

3.3.6.2.1 Meniscus extrusion

An expert musculoskeletal radiologist read T2-weighted MRIs paired but unblinded to the acquisition order, using the BLOKS method[71]. Extrusions in medial and lateral menisci were graded in two sub-regions (medially or laterally and anteriorly) as grade 0, normal; grade 1, < 2 mm; grade 2, 2 – 5 mm; grade 3, > 5 mm, at both baseline and 18-month follow-up. In the statistical analysis, a maximum scoring approach which focuses on the maximum extrusion score for a meniscus was used. The intra-rater agreement measured using kappa statistic was excellent[248] for semi-quantitative meniscus extrusion measurements[72]; medial meniscus extrusion – 0.82 (95% CI; 0.66, 0.98), and lateral meniscus extrusion – 0.89 (0.75, 1.00).

3.3.6.2.2 Meniscal tears

Meniscal tears in medial and lateral menisci were recorded considering three sub-regions (anterior, body and posterior) as absent or present (signal abnormality, horizontal tear, vertical tear, complex tear, posterior horn root tear and maceration) at both baseline and 18-month follow-up. The intra-rater agreement measured using kappa statistic was excellent[248] for semi-quantitative meniscal tear measurements[72]; medial meniscus tears – 1.00 (95% CI; 1.00, 1.00), and lateral meniscus tears – 0.91 (0.77, 1.00).

3.3.7 Radiographic OA

Bilateral, posteroanterior, weight-bearing, semi-flexed, knee X-rays were obtained at baseline[225, 249]. The knees were flexed for 15º with the help of a SynaFlexerpositioning device (Synarc, San Francisco, CA). The X-ray beams were centred on the joint space and were perpendicularly directed to the cassette to pass between the femoral condyles and the patella surfaces. The focus-to-film distance was held constant. This method was used to standardize the positioning in order to optimize the reproducibility. Following the acquisition of X-rays, the status of tibiofemoral radiographic OA was determined using the KLG grade. The intra-rater reliability was excellent (ICC - 0.994).

3.3.7.1 Mechanical alignment

A full-length, anteroposterior radiograph was obtained for each participant using the Agfa ADC system (Quantum Q-Rad based imaging) approach. With feet positioned 15 cm apart, the participant stood upright in such a way that both the tibial tubercles were faced directly forward and the weight equally distributed on both feet[50, 249], and both the lower limbs were imaged. The mechanical alignment was then measured as the angle formed by the intersection of the

lines connecting the centres of the femoral head and the intercondylar notch and the centres of the ankle talus and tibial spines[225]. A varus knee was defined as a knee with an angle >2º in the varus direction (a bowlegged appearance), and a valgus knee was defined as a knee with an angle <-2º in the valgus direction (a knock-kneed appearance). A neutral knee was a knee with an angle between -2º and 2º in the varus direction. All of the measurements were conducted by a single reader using the National Institute of Health (NIH) ImageJ program. Inter-rater reliability was excellent (ICC - 0.994).

Table 3.1: Summary of the outcome, exposure variables and covariates used in this thesis

Chapter	Outcome variables	Exposure variables	Covariates
4	Total knee replacements, Total hip replacements	Index of Relative Socio-Economic Advantage and Disadvantage (SEIFA)	Age, sex, body mass index, WOMAC pain, knee ROA, hip pain, hip ROA
5	Total knee replacements, Total hip replacements	Ambulatory activity, body mass index, total fat mass, trunk fat mass, total lean mass, lean mass percentage, waist circumference	Age, sex, WOMAC pain, knee ROA, hip pain, hip ROA
6	WOMAC pain, BMLs, Tibial cartilage volume, Total knee replacements	Hip shape modes	Age, sex, body mass index, WOMAC pain, knee ROA

7	Maximum & mean extrusion distance, TA.Uncov, ACdAB.Cov, OvD, width, height	Weight change	Age, sex

WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index, ROA – radiographic osteoarthritis, SEIFA - Socio-Economic Indexes for Areas, BML – bone-marrow lesions, TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.

3.4 Statistical analysis

T-tests and chi-square tests were used to compare the differences in means and percentages where appropriate. A *P-value* of less than 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Intercooled Stata V.12.1 and V.14.1 for Mac (StataCorp LP, Texas, USA). Each following chapter extensively describes the statistical analysis methods employed in each study.

Chapter 4: The association between socioeconomic status and joint replacement of the hip and knee: A population-based cohort study of older adults in Tasmania

4.1 Prelude

A socioeconomic gradient is reported for total joint replacement (TJR) utilisation for hip and knee OA. However, the association between SES and time to TJR is not clearly known. Hence, in this chapter we aimed to describe the relationships between SES and time to hip and knee TJR due to OA in a cohort of community-dwelling older adults. This chapter is presented in a way that it was submitted to the peer-reviewed journal.

4.2 Introduction

Total joint replacement (TJR) is a common and cost-effective procedure performed predominantly for severe, end-stage osteoarthritis (OA) and has been shown to be highly effective in alleviating pain and dysfunction[132, 145]. In Australia, 47,972 total hip replacements (THR) and 63,854 total knee replacements (TKR) were performed in 2017, and these numbers are predicted to increase[91] with the ageing of the population[93].

Owing to the direct and indirect costs associated with TJR and the availability and use of private health insurance, it is possible that utilization/rates and time to these procedures may differ by socioeconomic variation in populations[131]. Yet, several Australian and international studies have shown mixed evidence on the associations between socioeconomic status (SES) and TJR[93, 129-133, 140-146]. The majority of these studies are cross-sectional analyses of registry or administrative data for participants who underwent TJR[144, 145]. They mostly assess the utilization/rates of TJR, which may be primarily driven by risk factors rather than SES. In contrast, time to TJR may be mostly dependent on SES over and above the known

risk factors. Interestingly, only one study conducted in Canada has examined the time to TJR in a population-based cohort[129].

It is known from prior studies that conducting surgery earlier is associated with better postoperative clinical outcomes[250]. Hence, it is important to identify whether SES is associated with time to TJR in prospective studies, particularly in Australia. Therefore, this study aimed to describe the relationships between SES and time to THR and TKR due to OA in community-dwelling older adults.

4.3 Materials and methods

4.3.1 Study population

This study was conducted as a part of the Tasmanian Older Adult Cohort Study (TASOAC), which is a prospective, population-based study primarily aimed at examining the causes and progression of OA. Participants aged between 50-80 years were selected using sex-stratified random sampling from the electoral roll in Southern Tasmania (population 229,000). Participants were excluded if they had any contraindication to Magnetic Resonance Imaging (MRI) or were living in a nursing home. Data collection was undertaken at baseline (n=1,099) between March 2002 and September 2004 (response rate 58%, 1099/1904). Ethical approval was obtained from the Southern Tasmanian Health and Medical Human Research Ethics Committee. The study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki of 1975, as revised in 2000 and written informed consent was obtained from all participants.

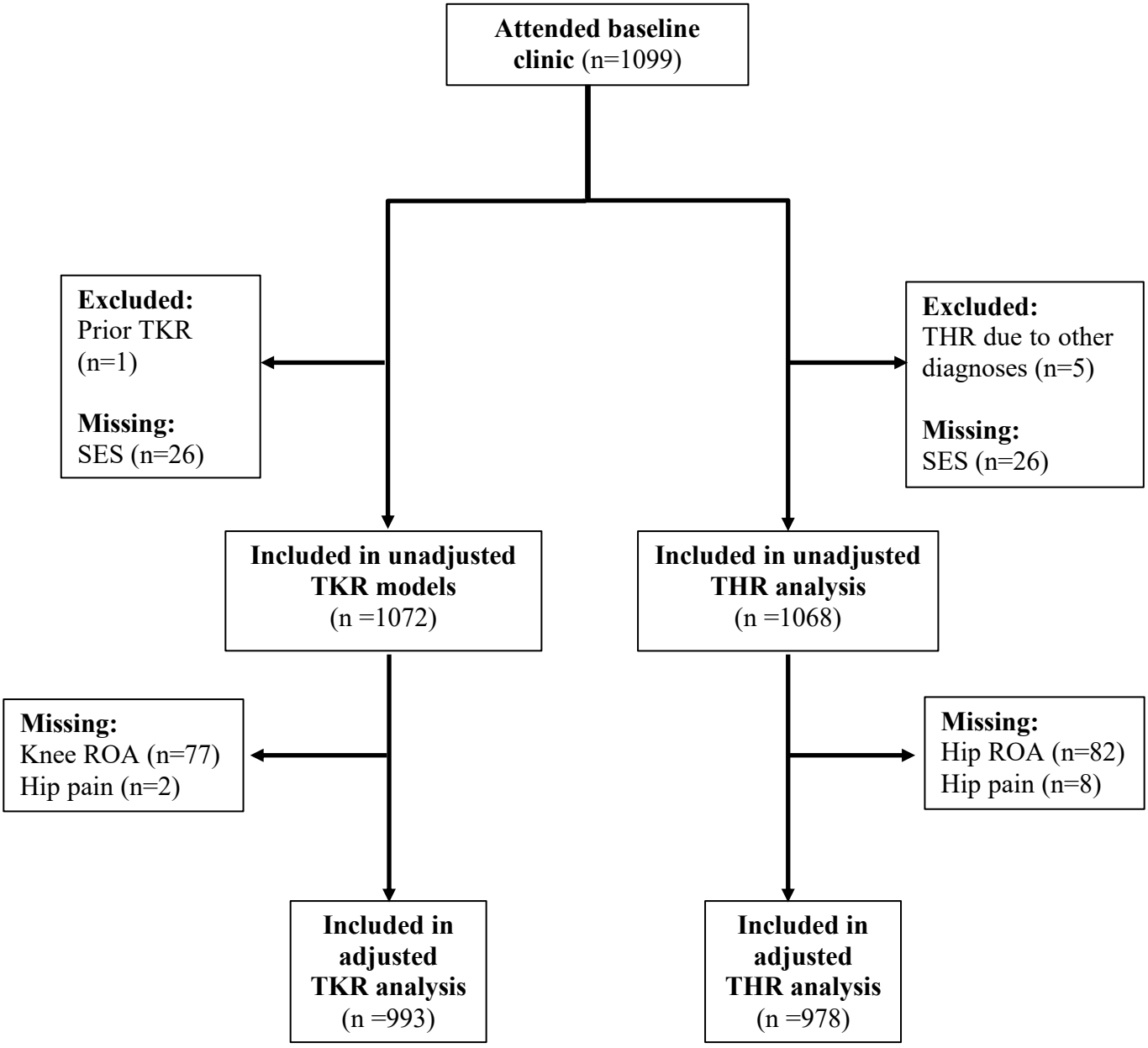
4.3.2 Primary (first-time) total hip and knee replacement

Incident primary THR and TKR were determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), between 1 March 2002 and 21 September 2016. The data collection for AOANJRR in Tasmania started in September 2000 and is collected from both public and private hospitals; data validation is performed using a sequential multi-level matching process with State and Territory Health Department data[91]. Matched data included the type (primary or revision), date, side (left/right) and the reason for the procedure (e.g. OA, fracture, osteonecrosis, inflammatory arthritis, tumour)[251]. In this study, only primary TJR due to OA were included, and there were 3 uni-compartmental knee replacements. Of 1099 participants, 1068 were included in the THR models due to the exclusion of THR due to prior THR and missing data while 1072 participants were included in the TKR models due to the exclusion of prior TKR and missing data (Figure 4.1).

4.3.3 Socioeconomic Status

Area-level SES was ascertained by matching each participant's residential address at baseline to the corresponding Australian Bureau of Statistics (ABS) Census Collection District. The ABS software was then utilized to determine the Socio-Economic Indexes for Areas (SEIFA) values from the 2001 census. SEIFA constitutes of four separate indices, obtained using different variables which summarizes the characteristics of residents within an area (~250 households), thereby providing a single measure to rank the level of advantage and/or disadvantage at the area-level, not of the person. In this study, we employed the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD), which is a measure that incorporates variables such as household income, car ownership, number of one-parent

families and educational attainment[233]. The IRSAD scores were analysed in two ways; 1) categorised into quartiles, with quartile 1 representing the most socioeconomically disadvantaged group, 2) dichotomized the cohort at the lowest quartile to compare the most disadvantaged group with the rest of the participants.



TKR – total knee replacement, SES- socioeconomic status, ROA – radiographic osteoarthritis, THR – total hip replacement

Figure 4.1: Participant Flowchart

4.3.4 Potential confounders

Body mass index (BMI) was measured using objective weight and height measures and steps/day using pedometers[251]. Knee and hip x-rays were performed at baseline and individually scored for osteophytes and joint space narrowing. Prevalence of radiographic OA (ROA) was then defined as 0 or 1[251]. Knee pain was assessed using the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)[53]. Age, sex, presence of hip pain, number of comorbidities, smoking, and history of knee surgery (other than TJR) were self-reported[251].

4.3.5 Statistical analysis

Baseline characteristics of the population by SES quartiles were described using means and standard deviations or percentages where appropriate.

The association between baseline SES groups and the time to THR and TKR was estimated using Cox proportional hazards models. All the multivariable models were adjusted for baseline age, sex and BMI. Since pain and ROA are the main indications for TJR[126], further mediation analyses were conducted adjusting for presence of hip pain and hip ROA at baseline for the THR models and WOMAC pain and presence of knee ROA for the TKR models in order to assess if the relationships between SES and TJR were independent of pain and ROA[251]. Other potential confounders considered were smoking, comorbidities and history of knee surgery; however, these were excluded from the final models as they did not change the hazard ratio by at least 10%. The assumptions for proportional hazards for all the models

were assessed using Schoenfeld residuals. Additionally, linear trends were assessed across SES quartiles.

Further analyses were conducted comparing the participants in the most disadvantaged SES quartile with those in the less disadvantaged SES quartiles (quartiles 2,3 & 4) with and without adjustments for the variables mentioned above.

To address any potential bias due to missing data, we conducted further sensitivity analyses using multiple imputation by chained equations (MICE), assuming that the data were missing at random (MAR). 197 participants had missing data (knee ROA, n=80; WOMAC pain, n=3; hip pain, n=10; hip ROA, n=160; IRSAD scores, n=26). Participants with missing data were older, compared to those without missing data. A total of 20 imputed datasets were created, and the results from the analysis of imputed datasets were combined to obtain a single estimate.

A p-value of < 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Stata/SE V.15.1 for Mac (StataCorp LP, Texas, USA).

4.4 Results

The median follow-up period of the cohort was 12.9 years (interquartile range; 12.2, 13.9). There were 56/1069 participants (5%) who had a THR and 79/1072 participants (7%) who had a TKR (Table 4.1). Nearly 51% of the participants were women. Baseline age, BMI, the prevalence of knee ROA, the prevalence of hip pain, WOMAC pain and prevalence of comorbidities were different between SES quartiles, in which the most disadvantaged group demonstrated consistently greater values.

Table 4.1: Baseline characteristics of the participants by SES quartiles

	Quartile 1† (n = 269)	Quartile 2 (n = 267)	Quartile 3 (n = 268)	Quartile 4 (n = 268)	P value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	63.7 (7.7)	63.3 (7.7)	62.4 (7.3)	62.8 (7.4)	**0.047**
Sex (Women: %)	56	50	52	47	0.19
BMI (kg/m^2)	28.8 (4.9)	27.4 (4.6)	28.0 (4.5)	27.3 (4.7)	**<0.001**
Incidence of THR (%)	6	4	5	5	0.19
Incidence of TKR (%)	8	6	7	7	0.22
Time to THR (years) (median, IQR)	12.6 (12.1–13.8)	13.0 (12.3-14.1)	12.9 (12.2-13.9)	12.9 (12.3-13.9)	0.45
Time to TKR (years) (median, IQR)	12.6 (12.1–13.8)	12.9 (12.2-14.0)	12.9 (12.2-13.9)	12.9 (12.3-13.9)	0.61
Hospital performed THR, (Private: %)	**67**	**92**	**93**	**100**	**0.03**
Hospital performed TKR, (Private: %)	82	79	91	85	0.659
Prevalence of Hip ROA (%)	47	45	42	45	0.948
Prevalence of Knee ROA (%)	70	68	67	67	**0.04**

Prevalence of Hip pain (%)	53	44	33	37	**<0.001**
WOMAC knee pain‡	5.6 (8.0)	3.7 (6.7)	3.2 (5.2)	2.5 (4.6)	**<0.001**
Prevalence of comorbidities	82	74	70	69	**0.02**

Student's T-test or X^2 test (proportions) used. BMI – body mass index, THR – total hip replacements, TKR – total knee replacements, IQR – inter-quartile range, ROA – radiographic osteoarthritis, WOMAC - Western Ontario McMaster Osteoarthritis Index; † Quartile 1 represents the most disadvantaged group, ‡ Range: 0-45. Significant differences between groups shown in Bold.

For THR and TKR, no statistically significant associations between SES quartiles were observed in unadjusted or adjusted analyses, nor were any trends detected (Tables 4.2 and 4.3).

Table 4.2: Associations between socioeconomic status quartiles with the time to total hip replacements over 12 years

	Unadjusted (n=1068)		†Adjusted (n=1068)		††Adjusted (n=978)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Quartile 1*	Ref		Ref		Ref	
Quartile 2	0.45	(0.20, 1.05)	0.46	(0.20, 1.05)	0.45	(0.19, 1.06)
Quartile 3	0.54	(0.26, 1.12)	0.55	(0.26, 1.14)	0.59	(0.27, 1.31)
Quartile 4	0.65	(0.31, 1.36)	0.68	(0.32, 1.43)	0.74	(0.33, 1.65)
P for trend		0.316		0.367		0.537

* Quartile 1 represents the most socioeconomically disadvantaged group.

†Adjusted for age, sex, BMI. ††Further adjusted for presence of hip pain and hip radiographic osteoarthritis. HR = Hazard Ratio.

Table 4.3: Associations between socioeconomic status quartiles with the time to total knee replacements over 12 years

	Unadjusted (n=1072)		†Adjusted (n=1072)		††Adjusted (n=993)	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Quartile 1*	Ref		Ref		Ref	
Quartile 2	0.63	(0.33, 1.21)	0.75	(0.20, 1.05)	0.80	(0.38, 1.68)
Quartile 3	0.75	(0.39, 1.47)	0.85	(0.26, 1.14)	0.91	(0.43, 1.94)
Quartile 4	0.91	(0.49, 1.66)	1.13	(0.32, 1.43)	1.48	(0.75, 2.93)
P for trend		0.877		0.704		0.315

* Quartile 1 represents the most socioeconomically disadvantaged group.

†Adjusted for age, sex, BMI. ††Further adjusted for Western Ontario McMaster Universities Osteoarthritis Index pain and knee radiographic osteoarthritis. HR = Hazard Ratio.

Further analyses showed that, compared with participants in the most disadvantaged SES quartile, those in less disadvantaged SES quartiles (quartiles 2, 3 and 4) were less likely to have a THR in the unadjusted model and the model adjusted for age, sex and BMI (all $p \leq 0.05$). These associations were attenuated when further adjusted for hip pain and hip ROA (Table 4.4). However, no associations were observed for the time to TKR with SES in the unadjusted or adjusted models in these further analyses (Table 4.5).

Table 4.4: Associations between socioeconomic status quartiles with the time to total hip replacements over 12 years (Sensitivity analysis)

	Unadjusted (n=1068)	†Adjusted (n=1068)	††Adjusted (n=978)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Quartile 1*	Ref	Ref	Ref
Quartile 2,3 & 4	**0.55 (0.31, 0.98)**	*0.56 (0.32, 1.00)*	0.59 (0.32, 1.09)

* Quartile 1 represents the most socioeconomically disadvantaged group. †Adjusted for age, sex, BMI. ††Further adjusted for presence of hip pain and hip radiographic osteoarthritis. Statistical significance ($p<0.05$) shown in Bold. P value = 0.05, shown in *Italics*. HR = Hazard Ratio.

Table 4.5: Associations between socioeconomic status quartiles with the time to total knee replacements over 12 years (Sensitivity analysis)

	Unadjusted (n=1072)	†Adjusted (n=1072)	††Adjusted (n=993)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Quartile 1*	Ref	Ref	Ref
Quartile 2,3 & 4	0.76 (0.46, 1.27)	0.90 (0.53, 1.54)	1.01 (0.57, 1.82)

* Quartile 1 represents the most socioeconomically disadvantaged group. †Adjusted for age, sex, BMI. ††Further adjusted for Western Ontario McMaster Universities. Osteoarthritis Index pain and knee radiographic osteoarthritis. HR = Hazard Ratio.

Examination of Schoenfeld residuals showed that the proportional hazards assumptions were reasonable (Data not shown). The results of the sensitivity analyses that used MICE to account for missing data were similar with no changes to the inference when compared to the complete case analysis (Data not shown).

4.5 Discussion

This prospective cohort study describes the relationships between SES and time to THR and TKR in community-dwelling older adults, over an average follow-up of 12 years in Tasmania, Australia. The results show that less disadvantaged participants were less likely to have a THR compared to the most disadvantaged participants (i.e. less disadvantaged participants had a longer time to THR compared to the most disadvantaged participants). However, this association was attenuated after further adjusting for hip pain and hip ROA, suggesting that the observed association was mediated by these factors. Taken together, these suggest that in fact, participants are treated according to their symptoms or need rather than their SES, potentially indicating reductions in expected disparity between SES and time to TJR in hip and knee.

Given that the most disadvantaged group had a greater prevalence of pain, and that the association observed in the further analyses between less disadvantaged participants and time to THR attenuated after adjustments for hip pain and ROA, it appears that participants have been treated based on their symptoms or need, irrespective of their SES. While no studies have been conducted on time to THR in Australia, previous cross-sectional studies focusing on the utilization/rates of THR across SES categories also reported no significant differences[145]. However, the authors reported a non-significant U-shaped pattern of THR across the SES

groups, where both the most disadvantaged and least disadvantaged groups appeared to have a higher utilisation of THR[145]. In contrast, another Australian study found that people living in most disadvantaged areas were less likely to have a THR[143], and a recent study showed higher rates of THR for most advantaged group[144]. Differences in SEIFA indexes in various time periods[131] may contribute to these divergent findings in the literature. Furthermore, several reports from Sweden[142], Canada[130], United States[140] and Italy[141] have shown considerable discrepancy in the utilisation of THR across the SES gradient[133]. Indeed, the associations of SES with THR between different countries may be dissimilar, owing to the differences in healthcare systems[145].

We did not observe any association between SES categories and time to TKR. Although no reports exist on time to TKR with regard to SES in Australia, a prior Australian study assessing the utilisation of TKR showed no relationship for women, however, found that men in the most disadvantaged group were less likely to undergo TKR, in comparison to less disadvantaged men[132]. A few other Australian studies also showed lower[131, 143], or higher rates[144] of TKR for the most socioeconomically advantaged group. These differences in rates of TKR could be attributed to slight differences in the characteristics included within SEIFA indexes across different time periods[131]. Similar to Australian studies, conflicting evidence has been reported in several international studies[140, 146] potentially because of the differences in the structure of the healthcare systems[145].

Both public and private healthcare providers deliver services in Australia[131]. Access to private healthcare is dependent on having greater financial resources, such as private health insurance and higher income. Hence, most socioeconomically disadvantaged groups usually would utilise public health services[145]. It is likely that the waiting times are much longer in

public healthcare facilities than in private facilities[145]. However, the finding that there may be no disparity between SES and time to TJR in this study could be due to several reasons.

The Department of Health and Human Services (DHHS) in Tasmania has implemented several policies such as 'Tasmania's Elective Surgery Access Policy'[252] and 'Tasmania's Elective Surgery Improvement Plan'[253] to manage waiting lists and to improve the equity of access to elective surgeries (e.g. TJR) by ensuring the timeliness of surgeries based on the clinical urgency/need. In instances where the public hospitals may not have the capacity to cater to the higher demand of these surgeries, the DHHS considers redirecting patients to private hospitals appropriately, in order to ensure the timeliness of surgeries for patients in the waiting lists[252]. The treatment costs related to the surgeries are covered by the DHHS[252]. These policies may ensure that the patients are treated according to the need rather than their SES.

Additionally, in Australia, health insurance reforms were instigated in 1999-2000, with government rebates, which had led to an increase of private health insurance utilization from 38% in 1998, to 51% in 2001[254]. Furthermore, AOANJRR reports that the rates of TJR have increased over the years in private healthcare facilities[255]. Similarly, Hanchate et al., 2015 also showed increased utilization of TJR following the introduction of health reforms in specific subpopulations in the state of Massachusetts, United States[256]. Hence, it is possible that the waiting times in public healthcare facilities were reduced, resulting in reduced time to TJR, as more people who obtained private insurance may be attracted to private healthcare facilities.

Furthermore, people with higher SES have higher choice to undertake TJR due to having higher health literacy, financial as well as personal resources with greater supportive networks which

may facilitate accessing conservative management strategies such as physiotherapy[257]. They may also have better coping mechanisms and the ability to bring about lifestyle changes with flexible work-related activities and early retirement[131, 133]. These may strikingly delay the need for TJR. Diversely, the limited health literacy, personal resources and weaker coping strategies observed in people with lower SES may facilitate the health-seeking behaviour and accessing healthcare for surgical treatments reducing the time to TJR[131, 133]. Altogether, these may explain the lack of disparity between SES and time to TJR.

There are several strengths to this study. First, this is a prospective study of population-based older adults randomly selected from the community, which makes it generalisable to the Southern Tasmanian population. Second, incident TJRs were ascertained from a comprehensive national registry over the study period from 2002 to 2016, which has the most complete data on TJR in Australia. However, there are a few limitations to this study. These results may not be directly applicable to other regions of Australia or the country as a whole, due to the use of area-specific socioeconomic indexes. Additionally, the SES was obtained on an area-level index, and not on an individual level, hence, there may be slight variations in the true SES of the participants. Yet, this area-level index is a validated index which is an aggregate of several parameters of SES obtained from the Australian census. We did not have information on personal-level factors such as willingness/perception on TJR or physician-level factors including physicians' perception on the patients and referral patterns, which may play a role in the time to TJR. Furthermore, information on insurance usage was not available. Additionally, the TASOAC cohort is predominantly comprised of Caucasians; hence we were unable to assess any ethnic/cultural differences that may affect the time to TJR.

4.6 Conclusion

The findings of this study suggest that the time to TJR is determined according to the need or symptoms of the participants rather than their SES, indicating reductions in the expected disparity between SES and time to TJR in hip and knee.

Chapter 5: The association between ambulatory activity, body composition and hip or knee joint replacement due to osteoarthritis: a prospective cohort study

5.1 Prelude

Having established the importance of TJR as a marker of end-stage OA in the hip and knee, we first proceeded to address a gap in literature on how person-level life-style factors are associated with end-stage OA. As AA and obesity are considered to be important life-style factors and because of the conflicting nature of evidence, this chapter evaluated the association between AA and body composition measures and the risk of TJR in hip and knee due to OA. This chapter is presented in a way that it was published by the peer-reviewed journal.

5.2 Introduction

Joint replacement (JR) is an effective treatment for severe osteoarthritis (OA)[187]. The rates of JR are rising with the increase in incidence of OA and have a significant impact on health budgets[85, 95]. A better understanding of the risk factors for JR will assist in designing better conservative treatments which would in-turn help reduce the health burden.

Ambulatory activity (AA) is one of the most common forms of physical activity (PA) performed by older people, and has beneficial effects on overall health and in certain diseases[40]. However, there is some concern that excessive or repetitive loading exerted on joint structures could be detrimental to joint health[38]. Hence AA may be a potential risk factor for OA in weight bearing joints. Alternatively, AA may be beneficial for joint health because dynamic loading may improve the integrity of the structures; especially joint cartilage[37]. Furthermore, AA may have differential effects on different joints. There is evidence suggesting AA has detrimental effects on the knee[151] but protective effects[164]

or no effects[159] on the hip. No studies have utilised objectively measured AA in order to examine its association with the risk of JR.

Measures of body composition may also be important in predicting risk of JR. Body mass index (BMI) is a known risk factor for KR[184, 186] and HR due to OA[187, 258], most likely due to increased joint loading and metabolic factors[187]. However, there are potentially more sensitive measures of body composition including total fat mass, lean mass and distribution of fat mass (trunk fat, waist circumference). Studies evaluating the associations between different body composition measures and JR are limited[187, 188].

In this study, we examine the association between AA, body composition measures and the risk of JR due to OA using a 13-year population-based prospective cohort study.

5.3 Methods

5.3.1 Study population

Data used for this study are from the Tasmanian Older Adult Cohort (TASOAC), which is a prospective, population-based study[151]. Participants (n=1099) between 50 and 80 years were selected using computer generated random numbers from the electoral roll in Southern Tasmania, between March 2002 and September 2004, with an equal number of men and women (response rate 57%, 1099/1904). Participants who had contraindication to magnetic resonance imaging (MRI) were excluded from the cohort. Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants. In this study, participants who had a JR prior to

their baseline visit and those who had a JR due to diagnoses other than OA were excluded (Figure 5.1). Therefore, 1082 participants were included in the KR models and 1066 were included in the HR models.

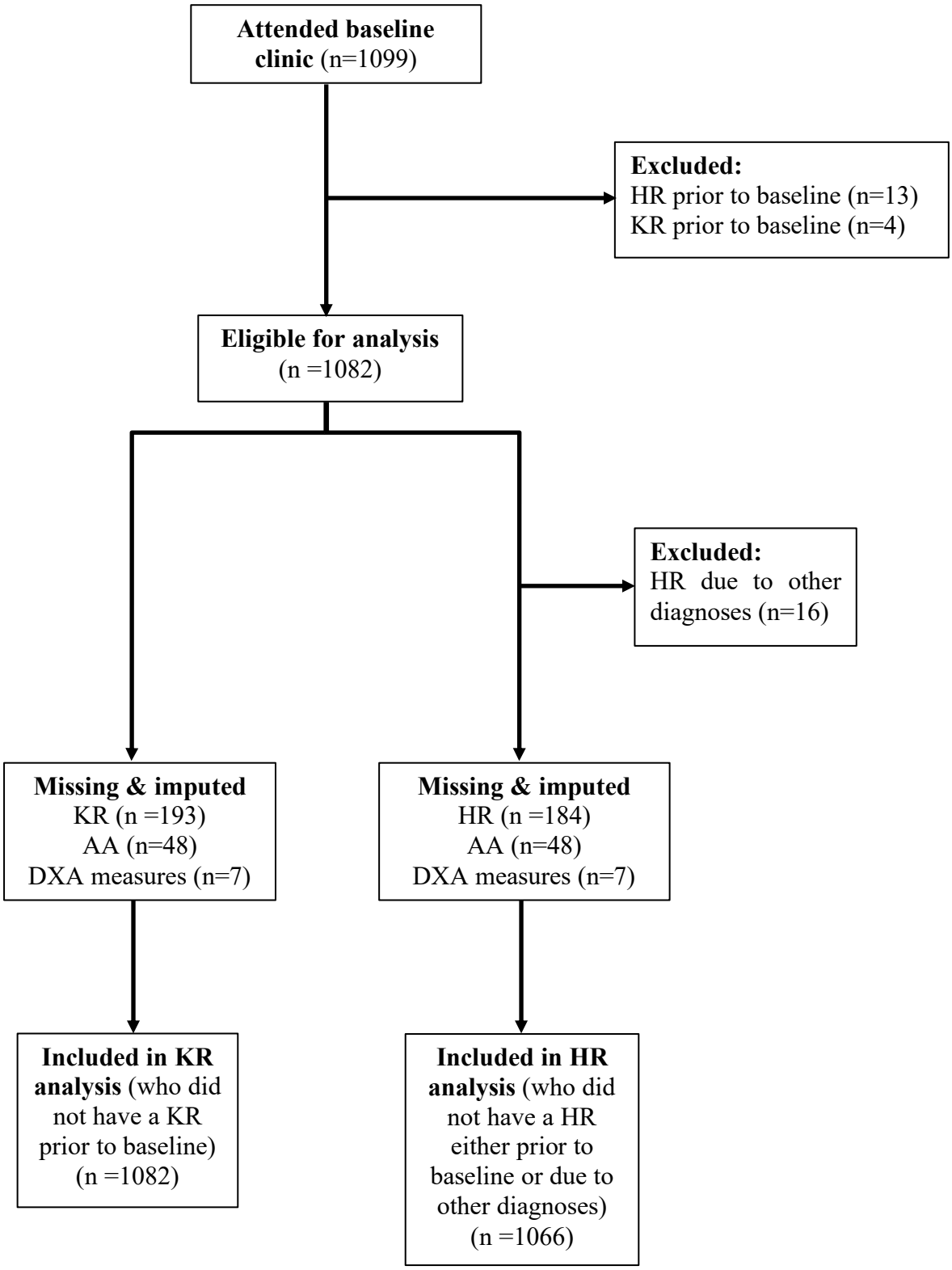
5.3.2 Identification of primary (first-time) joint replacement

The incidence of primary (first-time) KR and HR between 1 March 2002 and 21 September 2016 were determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). AOANJRR started data collection in Tasmania in September 2000 and collects data from both public and private hospitals. Data validation against State and Territory Health Department data is done using a sequential multi-level matching process[240]. Matched data were then obtained which included the date, side of JR, primary or revision JR and the reason for the procedure (e.g. OA, fracture of neck of femur, osteonecrosis, inflammatory arthritis, tumour). In this study, we only considered JR's that were due to OA.

5.3.3 Ambulatory activity

AA at baseline was determined as steps/day using a pedometer (Omron HJ–003 & HJ-102, Omron Healthcare, Kyoto, Japan). Pedometers were first calibrated with the presence of the participant at the clinic, utilising a 100-pace walking test. Participants were given instructions (both verbal and written) about using the pedometer and keeping a pedometer log (diary). They were required to wear the pedometer on the dominant side for seven consecutive days while conducting their normal day-to-day activities except during bathing, water activities and sleeping. They were also advised to maintain a log of the step count per day and the time

duration during which the pedometers were worn. This was repeated after six months in order to account for habitual changes in different seasons. Hence, there were 2 sets of pedometer logs for each participant. Readings were excluded if there was evidence for artificial pedometer readings such as work done on heavy machinery. Then, pedometer wear time was determined for each day using the pedometer logs. A 'valid wear day' was defined as a day on which the pedometer was worn for at least 8 hours. For the analyses, steps/day was calculated as the mean of the two pedometer logs, with a minimum of five valid wear days[151]. In this study, AA was treated as a continuous measure and a categorical measure, grouped into tertiles according to the distribution of the study population, in order to check for dose-response relationships or threshold effects; tertile 1 (≤6,266 steps/day); tertile 2 (6,267 – 9,051 steps/day); tertile 3 (≥9,052 steps/day).



HR – Hip replacement, KR – knee replacement, AA – ambulatory activity, DXA - dual-energy x-ray absorptiometry

Figure 5.1: Study flowchart

5.3.4 Body composition measures

Weight of the participants was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using electronic scales (Heine, Dover, New Hampshire, USA). Height was measured to the nearest 0.1 cm (with shoes, socks and headwear removed) using a Leicester stadiometer (Invicta, Leicester, UK). *BMI* (kg/m^2) was calculated as weight/height^2. In addition to the continuous measure, BMI was analyzed in predefined categories; underweight/normal (<25 kg/m^2), overweight (≥25 to <30 kg/m^2) & obese (≥30 kg/m^2)[259]. As the number of participants in the underweight BMI group was low (n=4/1082), they were grouped with the normal BMI participants. *Waist circumference* of the participants was measured to the nearest 0.1 cm[260]. *Total fat mass, trunk fat mass* and *total lean mass* (g) was measured by a dual-energy x-ray absorptiometry (DXA) scanner (Hologic, Waltham, Massachusetts, USA) at baseline[260]. *Lean mass percentage* was calculated as a percentage of total body mass.

5.3.5 Other covariates

Knee and hip x-rays were performed at baseline in all participants and scored individually for osteophytes and joint space narrowing as previously described[261]. Presence or absence of radiographic osteoarthritis (ROA) was defined as a score of 0 or 1 respectively. Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline[53]. Hip pain was recorded as presence or absence by asking whether the participants had hip pain at baseline. At baseline, questions were asked about age, comorbidities, smoking habits, and history of knee surgery. History of knee injury was not assessed at baseline but was asked at a 2.7-year follow-up: ‘Have you had a previous knee injury requiring non-weight-bearing treatment for more than 24 h or surgery?’. The

socioeconomic status of the participants were determined by the Socio-Economic Indexes for Areas (SEIFA) defined by Australian Bureau of Statistics. The indexes that were used as covariates include Index of Relative Socio-Economic Disadvantage, Index of Relative Socio-Economic Advantage/Disadvantage, Index of Economic Resources and Index of Education and Occupation.

5.3.6 Statistical analysis

Characteristics of the sample were described by AA tertiles as means and standard deviations or as percentages as appropriate. Differences in characteristics between AA tertiles were compared using ANOVA for continuous and chi squared test for categorical variables.

Log-binomial regression using a generalized estimating equation with log link and binomial family, was used to estimate the association between baseline measures of AA and body composition measures and risk of knee and hip JR. Correlation between observations on the same individual (right and left leg) were taken into account by adjusting standard errors using the sandwich (robust) estimator of variance[262] and an exchangeable correlation structure. Separate univariable and multivariable models were fitted for knee and hip replacement.

Multivariable models for KR were adjusted for age, sex, presence of knee ROA and WOMAC pain while models for HR were adjusted for age, sex, presence of hip ROA and hip pain. Additionally, AA models were adjusted for BMI while body composition models were adjusted for AA. Other potential confounders were considered including smoking, presence or absence of comorbidities, socio economic status and history of knee surgery or knee injury. These were

excluded from the final models as they did not change the relative risk (RR) by at least 10%[263].

Possible effect modification of the association between AA and BMI/body composition with JR were explored using interaction terms with age and sex. In order to check if the associations between AA and JR were modified by BMI/body composition and if the associations between BMI/body composition and JR were modified by AA, interaction terms between AA and BMI/body composition were also examined. Using Baron and Kenny method[264], further analysis was done to test if there was evidence for mediation of the association between AA and JR by BMI.

Missing data were handled using multiple imputation by chained equations (MICE) based on 'missing at random' assumption. 229 participants had missing data (DXA measures n=7; AA n=48; JR n=201 (due to leaving Australia n=7, or being deceased n=194, preventing them from having a JR if required)). Participants with missing data were older, with lower steps/day, socio-economic status, and higher waist circumference, WOMAC pain, and were more likely to be male (Appendix 1, Supplementary Table 1). In addition to the variables in the analysis models, alcohol use, smoking, knee surgery, knee injury, comorbidities and socio-economic status were included in the imputation model. A total of 50 imputed datasets were created and the results from the analysis of imputed datasets were combined to obtain a single estimate and are presented.

A priori analyses were performed to examine the nature of the relationship between AA and JR (e.g. whether the relationship was linear, quadratic, dose-response based on AA tertiles or whether threshold effects existed).

A p value less than 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Intercooled Stata V.12.1 for Mac (StataCorp LP, Texas, USA).

5.4 Results

The average follow-up period of the cohort was 13.3 years (SD 0.8; range 11.1, 14.6). There were 74/1082 participants (6.8%) who had a KR and 50/1066 participants (4.7%) who had a HR over the follow-up period.

Table 5.1 shows the characteristics of participants at baseline stratified by AA tertiles. Overall, the mean level of AA of the participants was 8,646.2 steps/day (±3,356.2) and mean BMI was 27.9 kg/m^2 (±4.7). The average total fat mass, trunk fat mass, lean mass % and waist circumference of the participants were 28.2 kg (± 8.7); 12.7 kg (±4.7); 63.0 (±7.8) and 94.0 cm (±13.1) respectively. In comparison to participants in AA tertile one, those in the second and third tertiles were younger, had lower BMI, total fat mass, trunk fat mass, waist circumference, WOMAC pain and higher lean mass %. Participants in tertile three were younger, had lower BMI, total fat mass, trunk fat mass, waist circumference and higher lean %, compared to participants in tertile two. Furthermore, prevalence of hip replacements and knee ROA were lower for tertile three, when compared to tertiles one and two.

Table 5.1: Baseline characteristics of the participants

	Steps/day tertile 1 (n = 346)	Steps/day tertile 2 (n = 344)	Steps/day tertile 3 (n = 344)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	66.3 (7.8)	62.1 (6.8)	60.1 (6.2)
Sex (Female: %)	54	53	48
BMI (kg/m^2)	29.2 (5.4)	27.7 (4.6)	26.6 (3.6)
BMI categories			
Underweight/Normal (%)	25	34	41
Overweight (%)	31	32	37
Obese (%)	47	34	19
Total fat mass (kg)	31.0 (9.3)	28.0 (8.7)	25.4 (7.0)
Trunk fat mass (kg)	14.3 (4.9)	12.5 (4.6)	11.2 (3.8)
Lean mass (%)	60.8 (7.5)	63.2 (7.8)	65.3 (7.4)
Waist circumference (cm)	97.6 (13.9)	93.0 (13.0)	90.9 (11.6)
Knee replacement (%)	9	8	8
Hip replacement (%)	7	6	4
Knee ROA (%)	66	62	59
WOMAC knee pain*	4.5 (6.8)	3.2 (5.3)	3.1 (5.9)
History of knee surgery (%)	12	12	13
History of knee injury (%)	10	12	14
Hip ROA (%)	38	38	38
Hip pain (%)	41	43	37

ANOVA & X^2 test (proportions) used. BMI – body mass index, ROA - radiographic osteoarthritis, WOMAC - Western Ontario McMaster Osteoarthritis Index; *Range: 0-39.

5.4.1 Risk of knee replacement

Table 5.2 shows the unadjusted and adjusted relative risks of KR for AA and body composition measures as continuous variables. In the adjusted model, every 1000 steps/day increase at baseline was associated with a 9% greater risk of KR (RR 1.09/1000 steps/day, 95% CI 1.01, 1.16). In the categorical analysis, while the risk of KR increases with increasing step/day tertiles, this was not statistically significant (p=0.10) (Figure 5.2 A).

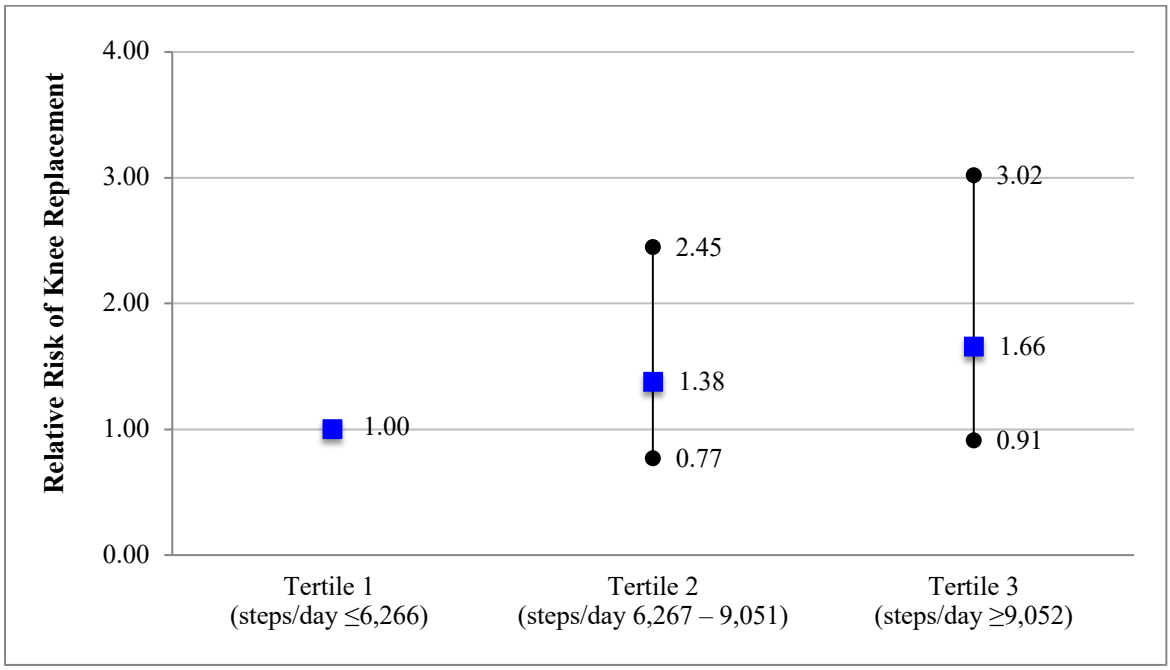
Greater BMI (continuous variable) was associated with an increased risk of KR (RR 1.07/kg/m^2, 95% CI 1.03, 1.12). Those with a BMI in the obese range had a 2-fold higher risk of KR (RR 2.05, 95% CI 1.16, 3.65) compared to underweight / normal participants (Figure 5.2 B). Higher baseline total fat mass (RR 1.03/kg, 95% CI 1.01, 1.06), trunk fat mass (RR 1.05/kg, 95% CI 1.00, 1.09), and waist circumference (RR 1.02/cm, 95% CI 1.00, 1.04) all significantly increased the risk of KR.

Table 5.2: Relative risk of knee replacement for ambulatory activity and body composition measures

Variable	Unadjusted (n=1082) RR (95% CI)	†Adjusted model (n=1082) RR (95% CI)
Steps/day (In 1000s)	0.98 (0.92, 1.05)	**1.09 (1.01, 1.16)**
BMI (kg/m^2)	**1.08 (1.04, 1.12)**	**1.07 (1.03, 1.12)**
Total fat mass (kg)	**1.04 (1.02, 1.07)**	**1.03 (1.01, 1.06)**
Trunk fat mass (kg)	**1.07 (1.03, 1.12)**	**1.05 (1.00, 1.09)**
Lean mass (%)	**0.96 (0.93, 0.99)**	0.97 (0.93, 1.02)
Waist circumference (cm)	**1.03 (1.01, 1.05)**	**1.02 (1.00, 1.04)**

†Adjusted for age, sex, Western Ontario McMaster Universities Osteoarthritis Index pain, knee radiographic osteoarthritis. Steps/day model adjusted for BMI. BMI model adjusted for steps/day. Significant results shown in bold. BMI – body mass index.

A



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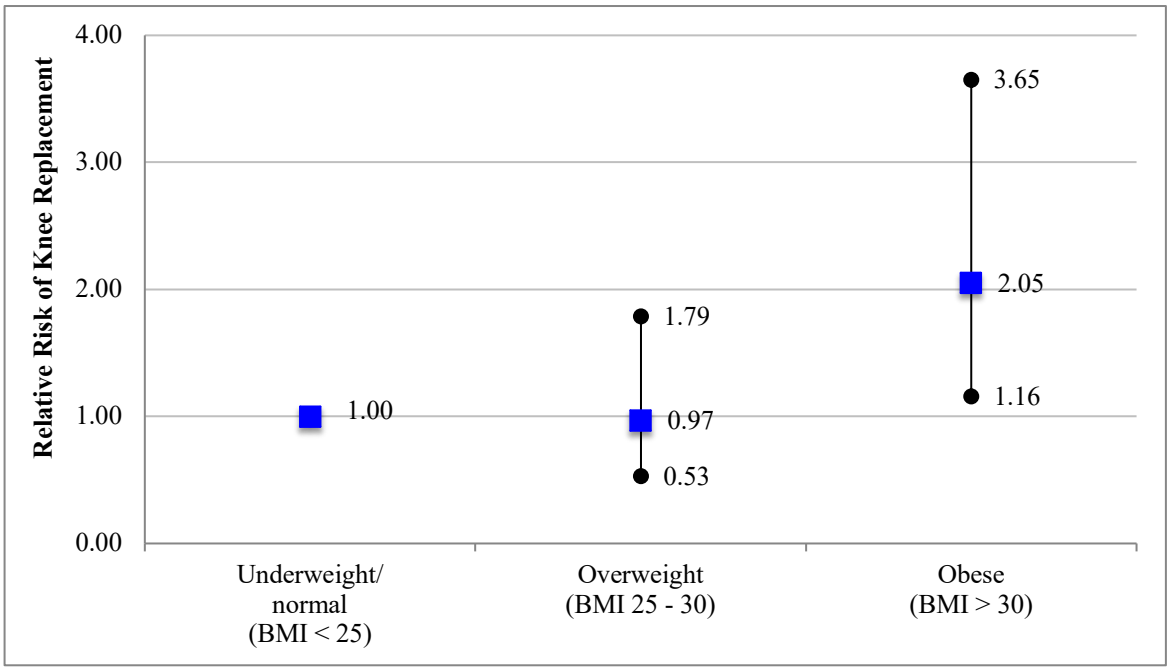


Figure 5.2: A. Association between steps/day tertiles & knee replacements, B. Association between BMI categories & knee replacements.

All models adjusted for age, sex, Western Ontario McMaster Universities Osteoarthritis Index pain, knee radiographic osteoarthritis. Steps/day tertiles model adjusted for BMI. BMI categories model adjusted for steps/day. BMI – body mass index.

5.4.2 Risk of hip replacement

Table 5.3 shows the unadjusted and adjusted RRs of HR for AA and body composition measures. In the multivariable analyses, every 1000 steps/day increase at baseline was associated with a 10% reduced risk of HR (RR 0.90/1000 steps/day, 95% CI 0.81, 0.99). In the categorical analysis, while the risk of HR decreases with increasing step/day tertiles, this was not statistically significant (p=0.25) (Figure 5.3 A).

BMI as a continuous (RR 0.96/kg/m^2, 95% CI 0.90, 1.02) or categorical measure (Overweight – RR 0.80, 95% CI 0.43, 1.49; Obese – RR 0.66, 95% CI 0.33, 1.35, vs underweight/normal) was not associated with HR (Table 5.3, Figure 5.3 B). There was no evidence for a relationship between other body composition measures and risk of HR.

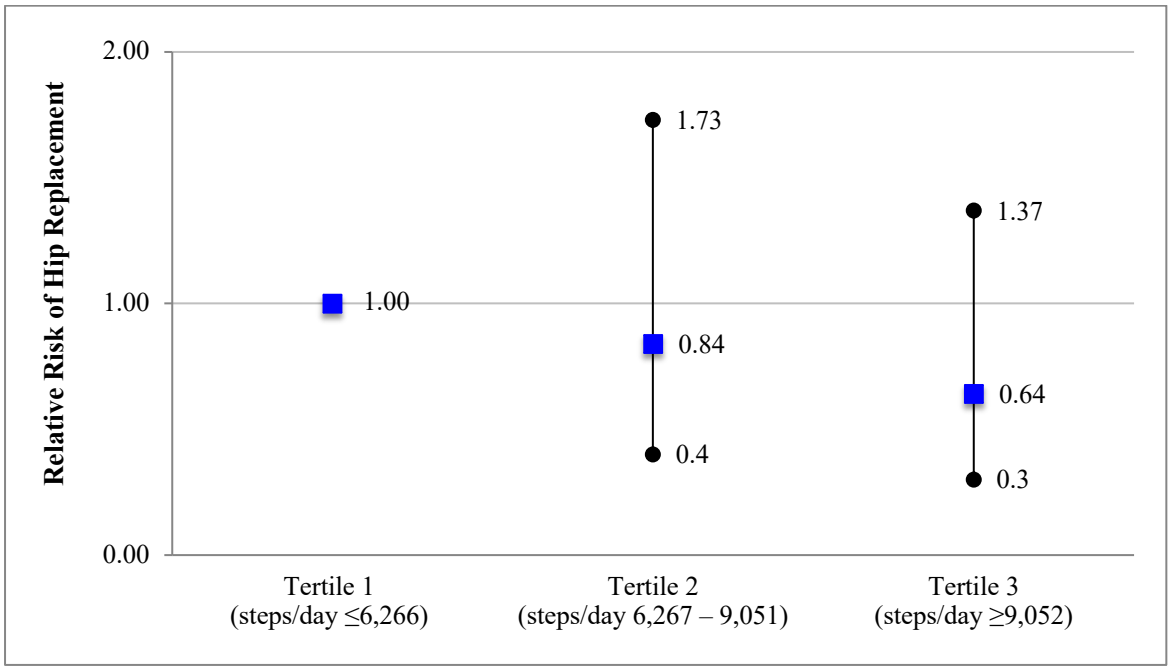
In the results presented above, there was no evidence for interaction by age and sex. The association between AA and JR was not modified by BMI/body composition. Similarly, the association between BMI/body composition and JR was not modified by AA. Furthermore, no statistical evidence was found for mediation of the association between AA and JR by BMI. Additionally, there was no evidence in the KR or HR models for confounding by smoking, education, current occupation, presence or absence of comorbidities, socio-economic status and history of knee injury or surgery or time to follow-up. Our analysis indicates that the relationship between AA, KR, and HR is linear. There was no statistical evidence for a quadratic, a dose-response relationship or threshold effect for AA and the risk of JR.

Table 5.3: Relative risk of hip replacement for AA and body composition measures

Variable	Unadjusted (n=1066) RR (95% CI)	†Adjusted model (n=1066) RR (95% CI)
Steps/day (In 1000s)	**0.89 (0.81, 0.98)**	**0.90 (0.81, 0.99)**
BMI (kg/m^2)	0.99 (0.93, 1.05)	0.96 (0.90, 1.02)
Total fat mass (kg)	1.00 (0.97, 1.03)	0.98 (0.95, 1.01)
Trunk fat mass (kg)	0.99 (0.94, 1.05)	0.97 (0.91, 1.03)
Lean mass (%)	1.00 (0.96, 1.03)	1.03 (0.98, 1.08)
Waist circumference (cm)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)

†Adjusted for age, sex, hip pain, hip radiographic osteoarthritis. Steps/day model adjusted for BMI. BMI model adjusted for steps/day. Significant results shown in bold. BMI – body mass index.

A



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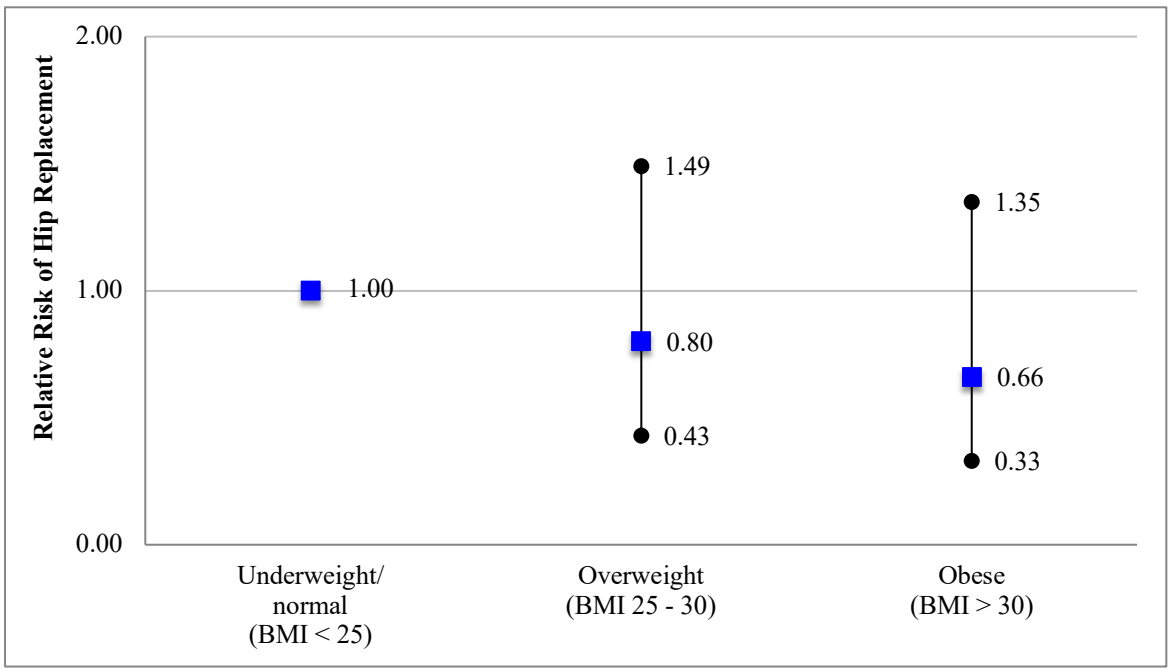


Figure 5.3: A. Association between steps/day tertiles & hip replacements, B. Association between BMI categories & hip replacements.

All models adjusted for age, sex, hip pain, hip radiographic osteoarthritis. Steps/day tertiles model adjusted for BMI. BMI categories model adjusted for steps/day. BMI – body mass index.

5.5 Discussion

This longitudinal prospective cohort study describes the relationship between objectively measured AA, body composition measures at baseline and risk of JR over 13 years in older adults. Higher levels of AA were associated with a 9% increased risk of KR but a 10% reduced risk of HR due to OA. Higher BMI, total fat mass, trunk fat mass and waist circumference were also associated with an increased risk of KR.

5.5.1 Ambulatory activity and joint replacement

To our knowledge, this is the first study to evaluate the longitudinal association between objectively measured AA and the risk of KR and HR. We found that for every 1000 steps/day increase at baseline, the risk of KR increased by 9%. There was a non-significant trend for a dose-response association between steps/day tertiles and risk of KR. Previous studies examining PA and KR have shown inconsistent findings[159-162]. A prospective cohort study which used self-reported PA measures, reported that frequency of walking was not associated with the risk of KR, while higher frequency of total PA including both ambulatory and non-ambulatory activity, was associated with an increased risk of KR[159]. Interestingly, a recent systematic review examining running suggested that higher AA was associated with lower odds of KR. However, this study only evaluated case-control studies which used retrospective PA data[149]. Studies using MRI and x-ray measures have also shown mixed findings with detrimental effects[151, 265], no effects[158, 266] or beneficial effects[267, 268] on structural pathology. We previously showed that doing greater than 10,000 steps/day was detrimental for MRI-assessed structural changes over 2.7 years, mostly in those with pre-existing structural

abnormalities[151]. In contrast, another report showed that objectively measured AA was not associated with MRI-determined structural changes in knee over 10 years[158].

Our analyses demonstrated that every 1000 steps/day increase at baseline resulted in a 10% reduced risk of HR. This is consistent with previous studies reporting that self-reported AA significantly reduced the risk of HR[164] and that leisure-time PA was protective against HR in women[161]. In addition, a recent cross-sectional study using our same cohort showed that higher levels of AA was associated with a lower prevalence of hip cartilage damage measured by MRI[150]. In contrast, a few earlier reports suggested that PA was associated with an increased risk of HR[39, 160, 163] or no association with HR[159, 165].

As outlined above, there is heterogeneity of effects between AA and JR which may be due to a number of factors including: 1) heterogeneity of tools used to measure PA[159-162, 165]; 2) use of self-reported surveys to measure PA[160, 161, 164] which is less reliable because of over-reporting and moderate reproducibility[157]; 3) diversity of study designs including case-control[162] and prospective[159-161] studies with varying follow-up times; 4) different study populations (e.g.: differences in age, gender, disease severity)[39, 159-164].

Interestingly, our analysis showed that the association between AA and JR was different for the knee and hip joints. This could be due to different morphological characteristics of the joints[159]. Studies have shown that biomechanical factors such as knee alignment[49, 269] and knee adduction moment[270] are associated with incident and progressive knee OA. Therefore, one possibility is that the deleterious effect of AA on the risk of KR may be mediated or modified by these factors[157]. We did not have measures of joint alignment in our cohort to examine this in the current study. Moreover, reduced muscle strength is suggested

to be a risk factor for OA progression[271]. Hip muscle strength declines at a greater rate than knee muscle strength with increasing age[272] and this difference may affect the relationships seen between AA, KR and HR.

5.5.2 Body composition measures and joint replacement

Our results show that body composition measures have differential effects on knee and hip joints. We found that higher BMI was associated with increased risk of KR over 13 years, which corresponds with previous longitudinal studies[184-187]. Furthermore, obese participants had a 2 times higher risk of KR compared to underweight and normal participants. This suggests that the effect of high BMI in this cohort is more pronounced in the obese category. This is in line with a population based study which found that overweight and obese participants had a 40 – 100% greater risk of KR in comparison to those with normal BMI over 2.6 years[186]. We have also demonstrated that sensitive measures of body fat, including total fat mass, trunk fat mass are associated with an increased risk of KR. Earlier studies published by Wang et al., 2009, and Lohmander et al., 2009, found similar associations[188, 273]. Higher body mass may increase joint loading and biomechanical aspects that leads to severe OA requiring KR[184]. In addition, the detrimental associations between proxy measures of central adiposity (trunk fat mass and waist circumference) also suggest that there may be inflammatory and metabolic mechanisms[188, 260], as there is increasing evidence to suggest that adipokines and cytokines released by adipose tissue are associated with disease progression in OA[33].

In the current analysis, BMI was not associated with an increased risk of HR, which is contradictory to previous longitudinal reports showing overweight participants have a higher risk of HR[189, 190]. Yet, a case-control study found that higher BMI was weakly associated

with higher odds of HR only for men, but the effect was negligible for women[191]. Similarly, there was no relationship between any body composition measures and the risk of HR in this cohort. This again contrasts the findings of two earlier studies which found that fat mass predicted HR[187, 188]. These variations in findings on the relationship between body composition measures and HR in our study and with previous studies could be due to the differences in the age and anthropometrics of the study sample, or the relatively small number of HRs in this cohort. We observed that there was a discrepancy in the association between body composition measures and knee and hip JR. The knee and hip joints may have different capacity with regard to enduring different levels of mechanical loading exerted by body mass, owing to the variations in morphology, underlying anatomical structures[273] and alignment[274]. Furthermore, metabolic factors released by adipose tissue may affect joints differently[273, 275]. However, further studies can be recommended to define this dissimilarity.

5.5.3 Strengths and limitations

The strengths of our study include the prospective design, utilising objectively measured AA which comprises both habitual and leisure-time AA and using National Joint Replacement Registry verified outcome data on JR. However, there are a few limitations to the study. First, in the current analysis, temporal changes in AA were not considered. We also did not have information on the intensity or nature of the activity (e.g. kneeling, climbing, squatting, running, twisting, manual labour and workload). The biomechanical aspects of different types of activities including the effects of joint loading is likely to have different effects on the risk of JR[276]. Therefore, our study results may not be generalizable to broader types of physical activity. Second, we considered JR as a surrogate measure of severe ‘end-stage’ OA. We

acknowledge that there are limitations in using JR as an outcome measure when assessing potential causal pathways for OA, as undergoing JR due to OA depends on many factors including disease severity, physician bias, patient-specific and socioeconomic factors (e.g.: access to health care)[277]. Hence these results should be interpreted with caution. However, the publicly-funded universal health system (Medicare) in Australia ensures that all the people without private health insurance have access to JR facilities. Furthermore, there are many important facets to OA such as progression of symptoms and progression of joint damage. JR encompasses both of these, but they could also be considered separately in evaluating the relationship between AA, body composition and OA. Our results need to be interpreted considering these issues. Third, JRs were performed only on a small proportion of participants (KR was 6.8% and HR was 4.7%). Therefore, it is possible that our study was underpowered. Despite the low incidence of JR (particularly HRs), we were able to detect statistically significant associations between AA, body composition and JR. Studies with larger sample sizes are needed to confirm these findings. Fourth, our measure of knee injury was recorded at the 2.7-year follow-up instead of baseline. Further adjustment for history of knee surgery (assessed at baseline) and history of knee injury (assessed at 2.7 years) did not alter our study findings. Fifth, since an Omron pedometer was used, which displays steps/day completed, it is possible that the participants were influenced by the readings of the pedometer while they were wearing them.

To conclude, an objective measure of AA was associated with a small increased risk of KR and a small reduced risk of HR. Worse body composition profiles were associated with knee, but not hip replacement. Altogether this may suggest different causal pathways for each site with regard to habitual activity and obesity.

Chapter 6: Longitudinal associations of hip shape with knee osteoarthritis outcomes over 12 years in older adults: A population-based cohort study

6.1 Prelude

Following the assessment of person-level factors, we further set out to identify joint-level factors that may be associated with the progression of the disease. Given that existing literature suggests that hip-related factors such as hip morphology may be associated with knee OA, in this chapter we evaluated the prospective relationships between hip shapes and clinical, structural and end-stage markers of knee OA. This chapter is presented in a way that it was submitted to the peer-reviewed journal.

6.2 Introduction

Osteoarthritis (OA) is a chronic condition manifested mainly by symptomatic and structural changes in a joint[98, 278]. Being a multifactorial condition[279], OA is a significant healthcare challenge and affects nearly 5% of the world's population[12] and its prevalence increases with ageing.

Joint morphology is an important structural feature for the development and progression of OA[43, 45, 192]. While several methods have been used to assess joint morphology, statistical shape modelling (SSM) is widely utilized to quantify joint shape, based on radiographs[280] or dual-energy x-ray absorptiometry (DXA) images[45]. SSM uses principal components analysis to describe each image in terms of a set of mode scores[45]. Previous studies using SSM have shown that hip shapes are associated with clinical, radiographical and structural factors in hip OA[43-45], while knee shapes are related to the onset of knee radiographic OA (ROA)[46, 47]. Yet, little is known about the relationship between the morphologies of adjoining joints such as hip and knee OA. The hip and the knee are biomechanically linked.

Hence, the variations in hip morphology, especially defined by shape modes, may be associated with the progression of knee OA[211, 281].

A few studies have described the relationship between hip shapes and the progression of knee OA. Nelson et al. found that while hip shapes were related to prevalent radiographic knee OA, they were not associated with incidence or progression of radiographic knee OA[211]. Additionally, Wise et al. reported that the prevalence of radiographic knee OA in lateral and medial compartments were related to different proximal femur shapes in a case-control study[281]. The lack of associations between hip shapes and progression of knee OA in those prior studies could, however, be due to the lower sensitivity of radiographs to changes over time, especially compared with Magnetic Resonance Imaging (MRI)[60, 100], and the shorter follow-up periods. Moreover, no studies have evaluated the relationship between hip shapes and long-term progression of knee OA using clinical[211] and MRI-based outcomes. Therefore, in this study, we investigate whether hip shape variations are associated with worsening pain, cartilage volume loss, worsening bone-marrow lesions (BML) in knee and risk of total knee replacements (TKR) in a cohort of community-dwelling older adults over a follow-up period of 10 - 12 years.

6.3 Methods

6.3.1 Study population

This research utilizes data from the Tasmanian Older Adult Cohort Study (TASOAC), which is a prospective, population-based study primarily aimed at examining the causes and progression of OA. The study recruited participants who were between 50-80 years, using a

sex-stratified random sampling technique from the electoral roll in Southern Tasmania (population 229,000). Participants were excluded if they had any contraindications to MRI or were living in a nursing home. Data was collected at baseline (n=1,099) between March 2002 and September 2004 (response rate 57%, 1099/1904) and at 2.5 (n=875), 5 (n=769) and 10 (n=568) years after the initial clinic assessment. Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee and conducted in compliance with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all participants.

6.3.2 Dual-energy x-ray absorptiometry (DXA)

DXA images of the left hip were obtained at baseline. There were 264 participants with no DXA images, and further four images were excluded due to low quality. The DXA images were obtained using a Hologic Delphi scanner (Hologic, Waltham, Massachusetts, USA). Left leg positioning was done by keeping the foot positioner (provided by Hologic) in between the participant's feet and aligning the center of the positioner with the participant's midline. The left leg was then internally rotated for 25^0 and the foot was strapped to the positioner to be held in position[282].

6.3.2.1 Hip shape

Hip shapes were measured using SSM on DXA images. An SSM with 85-points was constructed of the femoral head, acetabulum, femoral neck, greater and lesser trochanters and proximal part of the shaft using the Active Shape Modelling toolkit (University of Manchester, Manchester, UK), as described elsewhere[45]. Once the model was built, the coordinates of

the points were transferred to SHAPE software (University of Aberdeen, UK). Principal component analysis was then run on these coordinates to create an independent set of orthogonal mode scores for each image[45, 283]. The mode scores were then normalized with zero as the mean and a unit standard deviation so that the scores assigned to each image were in units of standard deviations. Hence, a reference to a 'lower' score implies a position towards the more negative end of the distribution rather than smaller in absolute terms. A scree plot was generated to visualize the variance described by each mode[45].

6.3.3 Knee pain

Knee pain of both legs was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[53] at baseline and 10-year follow-up. This index consists of five subscales (walking on a flat surface, going up or downstairs, at night in the bed, sitting/lying and standing upright), which are marked on 10-point scales ranging from 0 (no pain) to 9 (most severe pain). A total WOMAC pain score was calculated by summing the five subscales (range; 0-45).

6.3.4 Magnetic Resonance Imaging

A 1.5T MRI of the right knee was performed at baseline and 10 years, in the sagittal plane on a Picker apparatus (Cleveland, Ohio, USA) and a Siemens apparatus (Espree, Pennsylvania, USA). The image sequence is explained elsewhere[64], in brief: (1) a T1-weighted fat saturation three–dimensional gradient-recalled acquisition in the steady-state, echo time 6.71 ms, 512×512–pixel matrix, flip angle 30°, repetition time 31 ms, 60 partitions, field of view 16 cm, slice thickness of 1.5 mm without an inter-slice gap; (2) a T2-weighted fat saturation two-

dimensional fast spin echo, flip angle 90°, repetition time 3,067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 × 256-pixel matrix, slice thickness of 4 mm with a between-slice gap of 0.5 to 1.0 mm[64].

6.3.4.1 Tibial cartilage volume (mm^3)

Tibial cartilage volume was assessed an expert musculoskeletal reader with >20 years of experience on T1-weighted MR images using OsiriX software (University of Geneva, Geneva, Switzerland). The coefficient of variation for intra-observer repeatability ranged from 2.1–2.2%[238]. Medial and lateral tibial cartilage volumes were measured, and were summed to calculate total tibial cartilage volume.

The MR images were paired and read, with the chronological order known to the reader, for participants who had MRI scans at both baseline and 10-year follow-up (n=496).

6.3.4.2 Bone-Marrow Lesions (mm^2)

Subchondral BMLs were assessed on T2-weighted fat saturation images using OsiriX software at medial and lateral sites of tibia and femur, and patella. BMLs were defined as areas of increased signal intensity on T2-weighted images, located immediately under the articular cartilage. One trained observer read the BMLs with the images paired and the chronological order known, by measuring the maximum area of the lesion at each site in mm^2 at the baseline and the 10-year follow-up. The measurements were quality controlled by an expert reader with >12 years of experience in BML measurements and adjustments were done by consensus. Intra-

observer reliability was excellent (0.98 (95% CI; 0.96, 0.99)) for BML at baseline and 10-year follow-up[239].

6.3.5 Primary (first-time) total knee replacement

Primary incident TKR between 1 March 2002 and 21 September 2016 were determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). The data collection for AOANJRR in Tasmania started in September 2000 and is collected from both public and private hospitals. Data validation against State and Territory Health Department data was done using a sequential multi-level matching process[91]. Matched data were then obtained from AOANJRR, which included the date of procedure, side of TKR, primary or revision TKR and the reason for the procedure (e.g. OA)[251]. In this study, only primary TKR due to OA were included, and there were three uni-compartmental knee replacements.

6.3.6 Anthropometrics

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using electronic scales (Heine, Dover, New Hampshire, USA). Height was measured to the nearest 0.1 cm (with shoes, socks and headwear removed) using a Leicester stadiometer (Invicta, Leicester, UK). Body mass index (BMI) was calculated from weight divided by $(\text{height})^2$ (kg/m^2).

6.3.7 Other variables

Information on age, sex, comorbidities and smoking status were collected at baseline. The socioeconomic status of the participants was determined by the Socio-Economic Indexes for Areas (SEIFA) scores defined by the Australian Bureau of Statistics. Knee and hip radiographs were performed at baseline in all participants and scored individually for osteophytes and joint space narrowing as previously described[261]. Presence or absence of ROA was defined as a score of 0 or 1, respectively. Baseline physical activity (ambulatory activity) was measured using pedometers (Omron HJ–003 & HJ-102, Omron Healthcare, Kyoto, Japan)[151].

6.3.8 Statistical analysis

Characteristics of the population at baseline were described as means and standard deviations or as percentages.

The smallest detectable difference for WOMAC pain in the cohort was calculated to be 0.6[236]; hence, an increase in the WOMAC score of 1 or more was defined as a worsening of knee pain[237]. The relationship between the hip shape scores and the risk of worsening pain was assessed using log-binomial regression with log link and binomial family.

The association between hip shape scores and 10-year change in cartilage volume was estimated using linear mixed-effects models with participants as random effects. An unstructured covariance matrix was used to model the correlation between the repeated measures. Variables included in the univariable model were the outcome (cartilage volume), time (in years), hip shape scores and a hip shape scores by time interaction. The estimate for the hip shape scores × time interaction was considered of primary interest; it represents the

annual change in cartilage volume for one SD increase in hip shape score, additional to the average change estimated by the coefficient for time.

The risk of a deleterious change in BMLs (worsening BMLs) associated with hip shape scores was estimated using log-binomial regression, modelled using the binomial family with a log link. A deleterious change in BMLs was defined as an increase of BMLs size larger than the least significant criterion[284] ($52mm^2$); this considers the measurement error and the correlation between the BMLs measurements at both baseline and 10-year follow-up and represents a genuine change of BMLs over the 10-year period[64, 284].

The association between hip shape scores and the risk of TKR was assessed using generalized estimating equations with log link and binomial family. Correlation between observations on the same individual (right and left leg) was taken into account by adjusting standard errors using the sandwich (robust) estimator of variance[262] and an exchangeable correlation structure.

All the models were adjusted for age, sex and BMI and further adjusted for the presence of hip and knee ROA to check if the associations were mediated by these factors. Since knee pain is one of the primary indications for TKR[126], we additionally adjusted the TKR model for baseline WOMAC pain in order to assess if the relationship between the hip shapes and TKR were independent of these factors.

In order to assess if the estimates were biased due to missing data (flowchart shown in Figure 6.1), sensitivity analyses were performed using inverse probability weighting, assuming that the data were missing at random[285, 286]. A two-steps process was used in which, first, the

probability of a participant being present at the 10-year visit was estimated by fitting logistic regression models using baseline variables (age, sex, BMI, comorbidities, SEIFA scores, physical activity and smoking status). Second, the models estimating the associations between the hip shape scores and the outcomes were weighted using the inverse of the estimated probabilities of being present at the 10-year follow-up visit.

An a priori decision was taken to not adjust for multiple testing owing to the exploratory nature in these analyses[287]. A *P*-value of less than 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Intercooled Stata V.15.1 for Mac (StataCorp LP, Texas, USA).

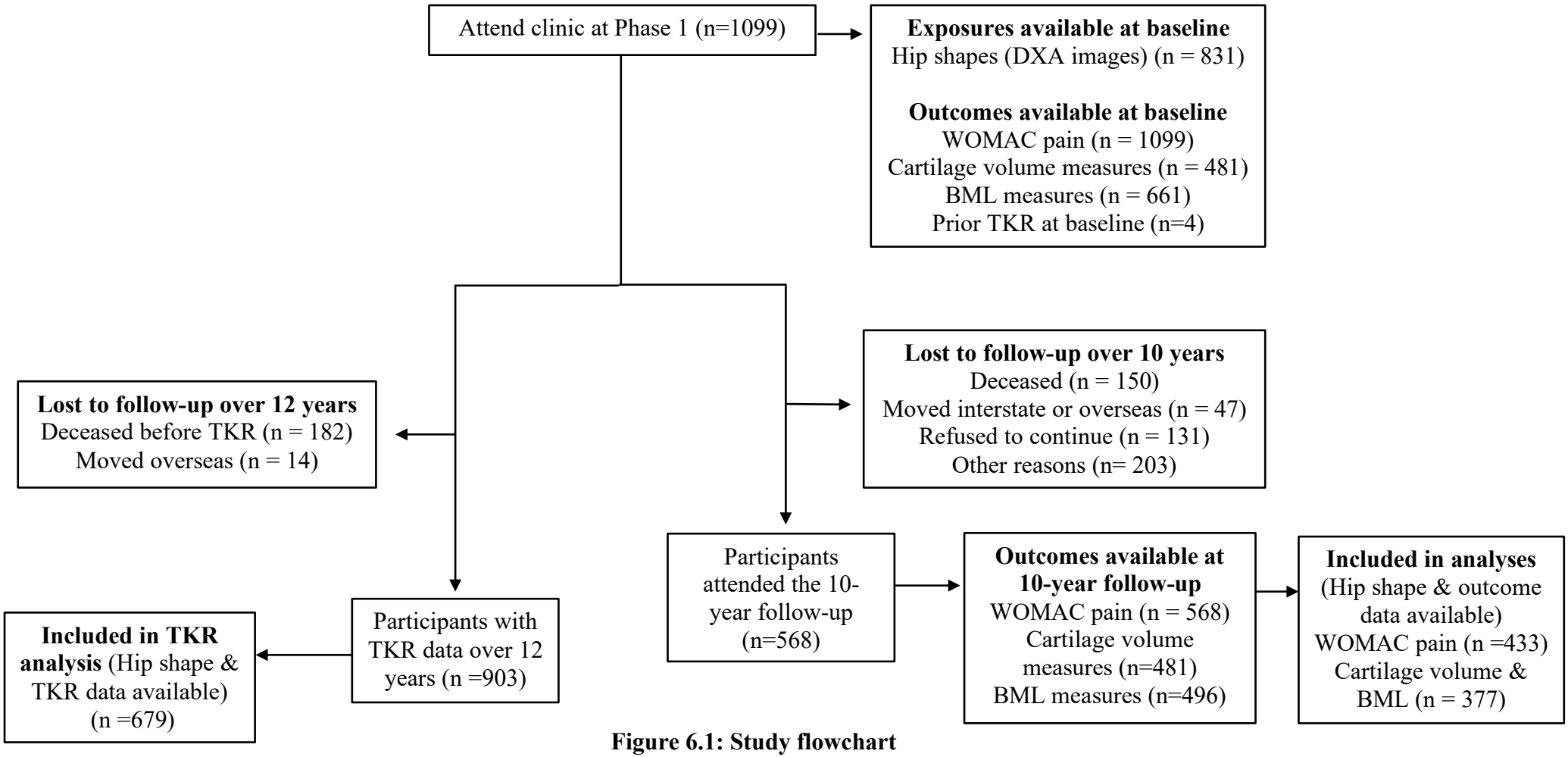


Figure 6.1: Study flowchart

DXA – Duel-energy x-ray absorptiometry, WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index, BML - bone-marrow lesions, TKR - total knee replacements.

6.4 Results

The average follow-up of the cohort was 10.7 (SD 0.7) years for pain and MRI measures, whereas it was 12.1 (SD 2.8) years for TKR. The mean age of the sample was 63.2 (SD 7.5) years, and the average BMI was 27.7 (SD 4.6) kg/m^2, while 52% were females (Table 6.1). There were 99 (23%) participants with worsening pain, 165 (43%) participants with worsening of BML and 58 (5%) participants underwent a TKR. Average cartilage volume loss over the follow-up period was 465.7 (SD 219.9) mm^3.

Table 6.1: Baseline characteristics of the participants (n = 831)

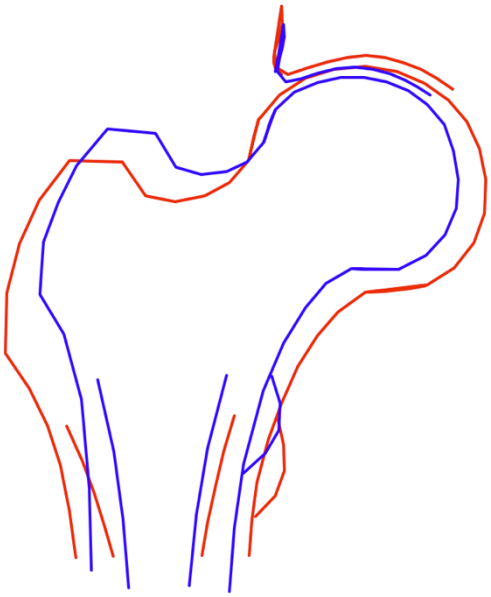
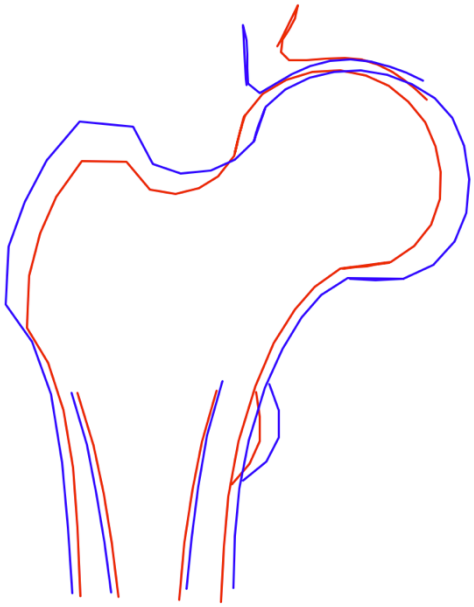
	Mean (SD)
Age (years)	63.2 (7.5)
Sex (Female: %)	52
BMI (kg/m^2)	27.7 (4.6)
Physical activity (steps/day)	8,677 (3,309)
WOMAC pain	3.7 (6.3)
Cartilage volume (mm^3)	3558 (913)
BML size (mm^2)	43.8 (91.8)
Comorbidities (%)	70
Knee ROA (%)	62
Hip ROA (%)	41

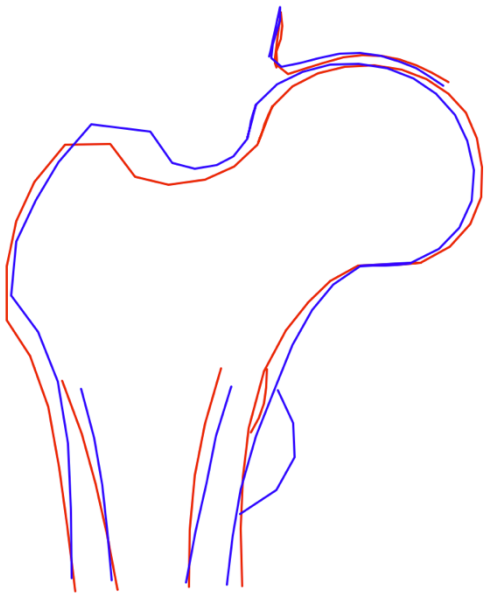
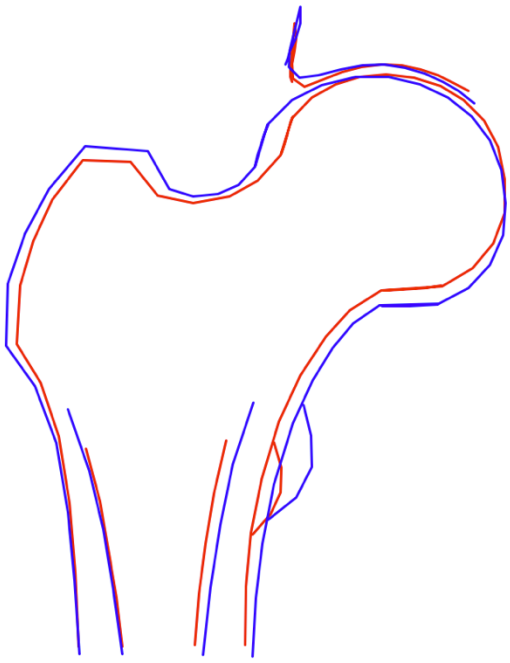
BMI – body mass index, WOMAC - Western Ontario McMaster Osteoarthritis Index, BML – bone-marrow lesions, ROA – Radiographic osteoarthritis

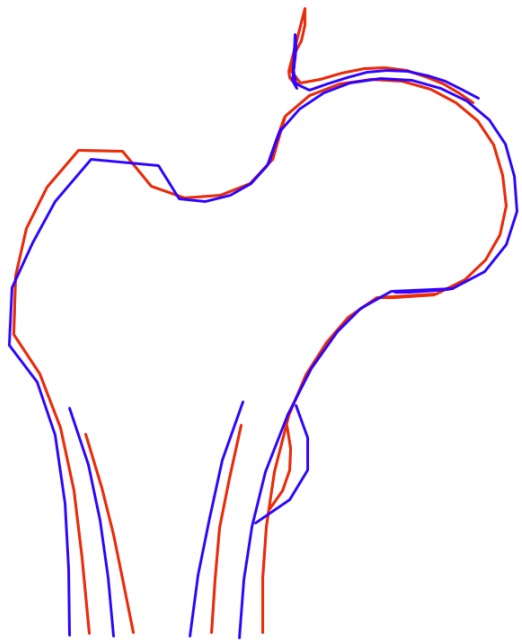
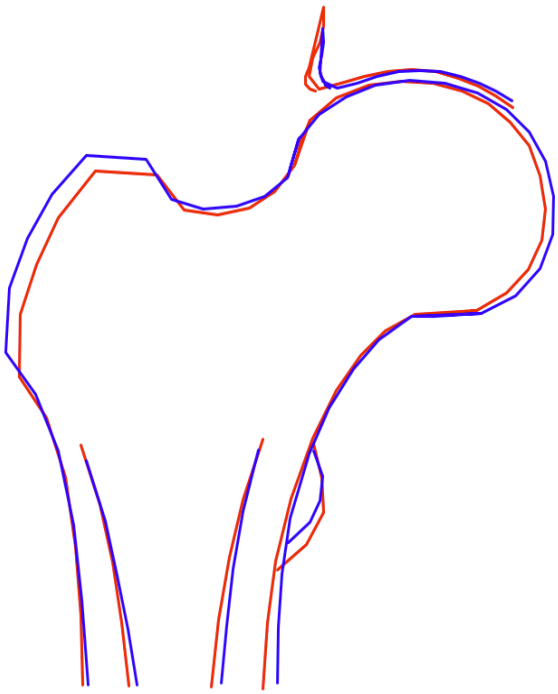
6.4.1 Identification of hip shape modes

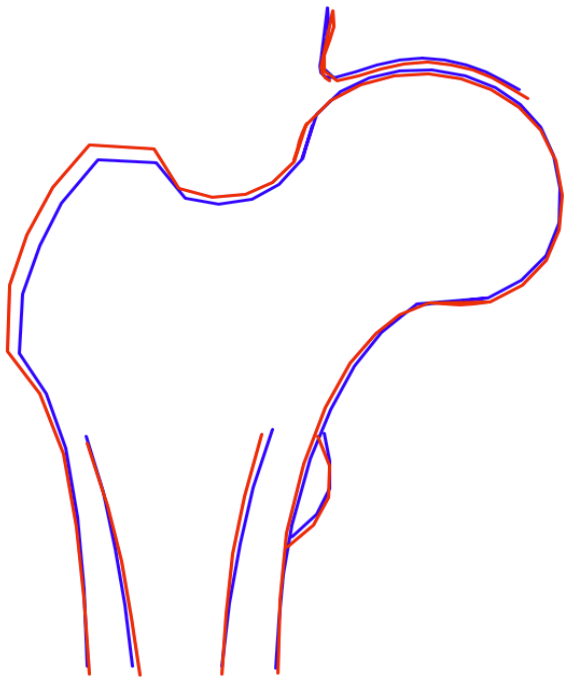
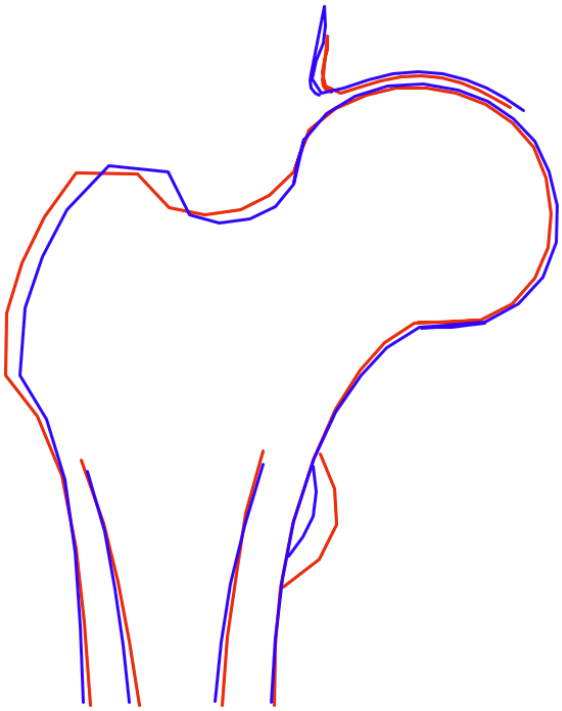
Ten hip shape modes were selected based on the scree plot (data not shown), which explained 78% of the total shape variance in the sample. The modes were numbered in descending order of shape variance from mode 1 (31% variance) to mode 10 (1.82% variance). Each shape mode variation ranged from -2 SD to +2SD.

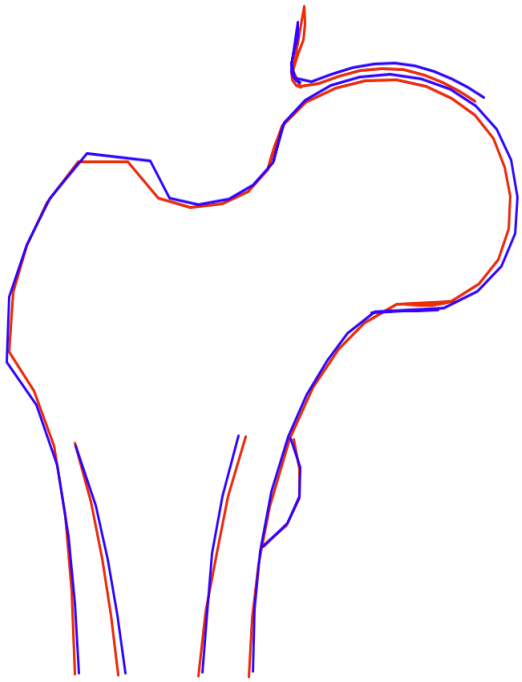
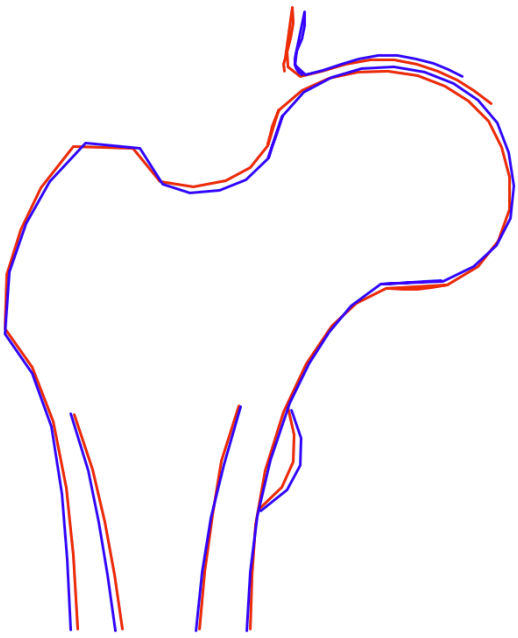
Table 6.2: Descriptions of the main features in each hip shape mode

Mode 1 (31% variance) **Increasing positive scores** • Longer femoral neck • Wider femoral neck • Larger femoral head **Increasing negative scores** • Shorter femoral neck • Narrower femoral neck • Smaller femoral head	
Mode 2 (14% variance) **Increasing positive scores** • Greater neck-shaft angle • Narrower femoral neck • Smaller, flatter femoral head • Less acetabular coverage of femoral head **Increasing negative scores** • Smaller neck-shaft angle • Wider femoral neck • Larger femoral head • Greater acetabular coverage of femoral head possibly indicating impingement	

Mode 3 (8.42% variance) **Increasing positive scores** • Longer femoral neck • Narrower neck • Possible increasing external rotation, shown by lesser trochanter inside femoral shaft **Increasing negative scores** • Shorter femoral neck • Wider femoral neck • Possibly internally rotated	
Mode 4 (6.00% variance) **Increasing positive scores** • Narrower femoral neck • Smaller femoral head more deeply seated in the acetabulum • Smaller joint space width • Distinct transition from superior neck to head **Increasing negative scores** • Wider femoral neck • Larger femoral head • Larger joint space width • Loss of sphericity at transition from superior neck to head – Pistol grip deformity	

Mode 5 (5.03% variance) **Increasing positive scores** • Smaller neck-shaft angle • More compacted femoral head **Increasing negative scores** • Larger neck-shaft angle	
Mode 6 (3.60% variance) **Increasing positive scores** • Greater acetabular lip • Smaller greater trochanter • Slightly compacted femoral head **Increasing negative scores** • Bigger greater trochanter	

Mode 7 (3.42% variance) **Increasing positive scores** • Larger greater trochanter **Increasing negative scores** • Smaller greater trochanter	
Mode 8 (2.40% variance) **Increasing positive scores** • Larger greater trochanter. • Longer and wider upper femoral neck • Larger lesser trochanter **Increasing negative scores** • Smaller greater trochanter • Shorter and narrower upper femoral neck • Smaller lesser trochanter	

Mode 9 (2.13% variance) **Increasing positive scores** • Smooth, and long upper femoral neck • Smaller femoral head • Wider femoral neck **Increasing negative scores** • Shorter upper femoral neck • Larger femoral head • Narrower femoral neck • sharper transition from the femoral head to the lower part of the neck	
Mode 10 (1.82% variance) **Increasing positive scores** • Greater acetabular coverage **Increasing negative scores** • Smaller acetabular coverage	

6.4.2 Association between hip shape modes and the risk of worsening knee pain

Table 6.3 shows the relationship between hip shape modes and worsening knee pain over 10 years. Increasing mode 1 scores were related to an increased risk of worsening knee pain, whereas increasing mode 9 scores were associated with a lower risk of worsening knee pain.

Table 6.3: Association between hip shape mode scores and worsening knee pain over 10 years

	Unadjusted (n=433)			†Adjusted (n=433)			††Adjusted (n=370)		
	RR	(95% CI)		RR	(95% CI)		RR	(95% CI)	
Mode 1	**1.21**	**(1.01,**	**1.44)**	**1.26**	**(1.08,**	**1.48)**	**1.31**	**(1.09,**	**1.59)**
Mode 2	0.95	(0.80,	1.12)	0.97	(0.82,	1.15)	0.98	(0.82,	1.18)
Mode 3	0.99	(0.83,	1.17)	1.00	(0.84,	1.20)	0.93	(0.76,	1.14)
Mode 4	1.10	(0.92,	1.30)	1.15	(0.97,	1.38)	1.10	(0.90,	1.33)
Mode 5	1.01	(0.86,	1.19)	1.07	(0.92,	1.25)	1.05	(0.88,	1.26)
Mode 6	0.89	(0.74,	1.06)	0.85	(0.70,	1.03)	0.85	(0.69,	1.04)
Mode 7	0.89	(0.75,	1.05)	0.94	(0.79,	1.11)	0.92	(0.77,	1.12)
Mode 8	0.96	(0.81,	1.14)	0.96	(0.81,	1.14)	1.05	(0.87,	1.26)
Mode 9	0.85	(0.72,	1.00)	**0.85**	**(0.72,**	**1.00)**	**0.79**	**(0.66,**	**0.95)**
Mode 10	1.06	(0.89,	1.27)	1.03	(0.87,	1.22)	1.15	(0.94,	1.40)

† Adjusted age, sex & body mass index. ††Further adjusted for knee and hip radiographic osteoarthritis. Significant results shown in bold.

6.4.3 Association between hip shape modes and total tibial cartilage volume loss

Table 6.4 shows the association between hip shape modes and total tibial cartilage volume loss over 10 years. Increasing mode 7 and mode 10 scores were associated with a lower knee cartilage volume loss while the increasing mode 9 scores were related to an increased cartilage volume loss.

Table 6.4: Association between hip shape mode scores and total tibial cartilage volume loss of the knee over 10 years

	Unadjusted (n=377)		†Adjusted (n=377)		††Adjusted (n=324)	
	β*	(95% CI)	β*	(95% CI)	β*	(95% CI)
Mode 1	-15.28	(-36.45, 5.88)	-15.89	(-37.08, 5.31)	-15.78	(-39.29, 7.73)
Mode 2	2.42	(-18.27, 23.11)	1.69	(-19.04, 22.41)	4.08	(-18.61, 26.76)
Mode 3	-1.44	(-22.39, 19.50)	-0.73	(-21.73, 20.27)	1.24	(-21.56, 24.05)
Mode 4	2.37	(-18.45, 23.20)	2.16	(-18.68, 23.00)	2.63	(-20.22, 25.47)
Mode 5	9.98	(-9.94, 29.91)	9.74	(-10.19, 29.68)	10.57	(-11.55, 32.69)
Mode 6	9.95	(-11.58, 31.49)	11.02	(-10.60, 32.64)	10.41	(-13.72, 34.55)
Mode 7	**23.80**	(**4.57, 43.04**)	**24.38**	(**5.12, 43.64**)	**22.21**	(**1.18, 43.25**)
Mode 8	2.14	(-18.46, 22.74)	2.73	(-17.90, 23.36)	-1.07	(-24.21, 22.08)
Mode 9	**-27.49**	(**-48.77, -6.22**)	**-28.08**	(**-49.39, -6.77**)	**-32.70**	(**-56.28, -9.13**)
Mode 10	**25.44**	(**4.29, 46.59**)	**25.15**	(**3.99, 46.31**)	**24.72**	(**0.96, 48.47**)

† Adjusted age, sex & body mass index. ††Further adjusted for knee and hip radiographic osteoarthritis. Significant results shown in bold, *β-coefficient represents the change in cartilage volume per 10 years.

6.4.4 Relationship between hip shape modes and the risk of worsening BML

Table 6.5 shows the relationship between hip shape modes and the risk of worsening BML over the 10 years. Increasing mode 4 scores were associated with an increased risk of worsening knee BML.

Table 6.5: Association between hip shape mode scores and worsening of bone-marrow lesions of the knee over 10 years

	Unadjusted (n=377)		†Adjusted (n=377)		††Adjusted (n=327)	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Mode 1	1.08	(0.95, 1.23)	1.07	(0.95, 1.22)	1.03	(0.89, 1.19)
Mode 2	0.98	(0.87, 1.09)	0.98	(0.88, 1.10)	1.01	(0.90, 1.13)
Mode 3	0.94	(0.83, 1.07)	0.96	(0.85, 1.10)	0.96	(0.84, 1.10)
Mode 4	**1.18**	**(1.07, 1.31)**	**1.21**	**(1.09, 1.35)**	**1.19**	**(1.06, 1.33)**
Mode 5	0.98	(0.88, 1.10)	0.99	(0.89, 1.12)	1.02	(0.90, 1.15)
Mode 6	1.01	(0.88, 1.14)	1.01	(0.88, 1.15)	0.98	(0.86, 1.12)
Mode 7	0.99	(0.88, 1.11)	0.99	(0.88, 1.11)	1.00	(0.88, 1.12)
Mode 8	1.01	(0.91, 1.13)	1.02	(0.91, 1.14)	1.02	(0.90, 1.15)
Mode 9	1.00	(0.88, 1.13)	1.00	(0.89, 1.13)	0.96	(0.84, 1.09)
Mode 10	0.98	(0.87, 1.11)	0.99	(0.88, 1.13)	1.00	(0.88, 1.14)

† Adjusted age, sex & body mass index. ††Further adjusted for knee and hip radiographic osteoarthritis. Significant results shown in bold.

6.4.5 Association between hip shape modes and the risk of TKR

Table 6.5 shows the association between hip shape modes and the risk of TKR over 12.1 years. Increasing mode 10 scores were associated with a lower risk of TKR.

Table 6.6: Association between hip shape mode scores and risk of total knee replacement over 12 years

	Unadjusted (n=679)		†Adjusted (n=631)		††Adjusted (n=629)	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Mode 1	0.89	(0.71, 1.13)	0.98	(0.75, 1.28)	1.01	(0.76, 1.33)
Mode 2	0.89	(0.71, 1.11)	1.06	(0.82, 1.37)	1.04	(0.78, 1.39)
Mode 3	0.84	(0.63, 1.11)	1.01	(0.81, 1.27)	1.04	(0.80, 1.37)
Mode 4	0.97	(0.74, 1.26)	0.90	(0.65, 1.25)	0.92	(0.69, 1.23)
Mode 5	1.05	(0.80, 1.38)	0.92	(0.76, 1.12)	0.94	(0.72, 1.22)
Mode 6	0.99	(0.69, 1.42)	0.86	(0.56, 1.32)	0.88	(0.67, 1.17)
Mode 7	1.05	(0.81, 1.36)	1.15	(0.90, 1.47)	1.16	(0.89, 1.52)
Mode 8	1.26	(0.97, 1.63)	1.24	(0.92, 1.67)	1.19	(0.91, 1.56)
Mode 9	1.00	(0.71, 1.40)	0.91	(0.62, 1.34)	0.90	(0.68, 1.18)
Mode 10	**0.69**	(**0.53**, **0.90**)	0.77	(0.55, 1.08)	**0.74**	(**0.56**, **0.97**)

† Adjusted age, sex, body mass index, Western Ontario McMaster Osteoarthritis Index knee pain & knee radiographic osteoarthritis. ††Further adjusted for hip radiographic osteoarthritis. Significant results shown in bold.

The estimates of the presented complete case analyses were similar with no changes to the inference although the effect sizes changed slightly, when compared to the sensitivity analyses in which inverse probability weighting was used to account for missing data (Data not shown).

6.5 Discussion

To the best of our knowledge, this is the first study to assess the longitudinal associations of baseline hip shape variations with the progression of clinical and MRI-based outcomes of the knee in community-dwelling older adults. The results show that certain hip shape variations are associated with the progression of different clinical and MRI-based knee OA outcomes over a follow-up of 10 - 12 years.

We found that the combination of features with a longer, wider femoral neck and larger femoral head was related to an increased risk of worsening knee pain (mode 1). In a previous study on this cohort, we showed that increasing mode 1 scores were associated with a greater prevalence of hip pain after 5 years[45]. Taken together, these findings suggest that there may be common factors underlying both hip and knee pain due to OA and that these factors, in both joints, separately associate with a larger proximal femur. Furthermore, the characteristics that signify smooth, long upper femoral neck, wider femoral neck and smaller femoral head was associated with a reduced risk of worsening knee pain (mode 9).

Additionally, the hip shapes with larger greater trochanter (mode 7) and the mode with greater acetabular coverage (mode 10) were related to lower cartilage volume loss, while the combined features of smooth, long upper femoral neck, wider femoral neck and smaller femoral head (mode 9) were associated with increased cartilage volume loss. Furthermore, the shape mode

with narrower femoral neck, smaller femoral head that is more deeply seated in acetabulum and smaller joint space width (mode 4) was linked with increased risk of worsening knee BML. Previously we showed that increasing mode 4 scores were related to lower prevalence of hip BML after 5 years in this cohort[45]. This may suggest that hip shape variations with smaller femoral head and smaller joint space width may have differential effects on hip and knee BML. In addition, it should be noted that except mode 4, other hip shapes that were associated with structural hip OA outcomes were not associated with knee structural outcomes. Moreover, hip shapes with greater acetabular coverage were linked with reduced risk of TKR (mode 10).

To date, only a few studies assessed the associations between hip shape variations and knee OA outcomes. Previously Nelson et al. reported that hip shapes reflecting differences in the width of the femoral neck, size of the trochanters and the width of the greater trochanter and femoral neck length were associated with increased prevalence of knee ROA, while no relationships were observed for the incident or progressive knee ROA[211]. The authors argued that hip shapes may, therefore, be associated with early onset of knee ROA but may not be related to the later incident or progressive ROA[211]. The lack of findings in that study on the progression of knee OA could be due to the use of radiographs, which are less sensitive to changes over time in comparison to MRI[60, 100], and a shorter follow-up time of 6 years. In this study, we utilized clinical, and MRI defined knee structural outcomes over a longer follow-up of 10 years. Additionally, Wise et al. also showed an association between ROA in medial and lateral compartments of the knee and hip shape variations in a case-control design[281].

Each SSM is unique to the set of images on which it is based. Accordingly, it is difficult to compare different studies directly because: 1) the number of participants/hips used in the model varies, 2) different numbers of points are used to define the models and 3) actual differences

in the study populations[43, 44]. While different shape modes are associated with various outcomes, these may be dependent on the cumulative effects of these shape modes rather than the single shape mode[281]. Yet, our findings further extend the predictive ability of hip shape variations defined by SSM on knee OA outcomes. Since it is not possible to compare hip shapes of different studies with each other, there is currently an international effort underway called the Worldwide COllaborative initiative on OA and morphological data of the Hip (WorldCOACH) consortium, in order to define hip shapes using more universal SSM applied to several worldwide OA cohorts.

Mechanisms underlying the associations between hip shape variations and progression of knee OA are largely unclear. Yet, the hip and knee are the adjacent joints in the kinematic chain and are linked biomechanically[288]. Hence, it is possible that the variations in hip shapes/geometry may result in altered hip[192] and knee biomechanics[193]. Altered knee alignment is related to the incidence and progression of knee OA[49, 289], potentially due to changes in loading patterns on the knee compartments and structures[49]. A possible explanation for the associations between hip shape variations and knee OA progression is that these could be mediated through the changes in knee biomechanics such as knee alignment[281] or alterations in gait. However, studies that evaluate biomechanical aspects comprehensively are warranted in order to confirm this hypothesis. Additionally, genetic or lifestyle factors such as physical activity may also contribute to the relations between hip shape and knee OA progression, and further studies are necessary to evaluate the effects of these common factors.

The findings of this study are clinically important as these suggest that hip shape variations could be a crucial imaging biomarker that may be used to identify participants who are at a

higher risk of progressing knee OA. However, given the fact that generalizability of the hip shape modes is limited in the existing studies, it is also essential to establish if there are common hip shape modes among different populations and to assess their associations with knee OA outcomes. Preventive strategies may then be implemented in those with higher risk, such as treatments that focus on altering abnormal knee biomechanics[290, 291].

This study has several strengths including the prospective population-based design of the cohort, the long-term follow-up of 10 - 12 years, use of an advanced, standardized method to quantify hip shape variations and the use of clinical, MRI-based and registry verified outcome data. However, as in any study, there are a few limitations. The hip shapes were measured on the left hip, while the MRI measures were taken on the right knee and the knee pain and incident TKR were obtained considering both knees. However, it is reported that OA in one joint is strongly related to OA in the contralateral joint[198]. Similar results have been found in studies that used SSM[45]. Additionally, genetic factors have been shown to be related to hip shapes[292, 293]. Therefore, it is likely that the shapes are modelled genetically and/or embryonically[292, 293] and hence, both right and left hip shapes may be highly correlated within a person, except in pathological conditions such as OA[292, 293]. The hip shapes only explained 78% of the shape variance of the cohort, however, each selected shape mode explained at least 1.5% of the variance of the cohort. Although standardized protocols are used, variations in the positioning of the lower limb may occur, affecting the shape measurements on DXA. Yet, the SSM is designed to identify these changes when the model is developed[280, 283]. The two-dimensional DXA images may lack important shape variations that could be identified in three-dimensional models. Although DXA may have lower resolution than x-rays, it provides a better illustration of the ‘true’ femur as DXA captures both form and density of the bones[294].

In conclusion, hip shape variations were associated with significant MRI-based and clinical outcomes in the knee over 10 - 12 years, possibly due to biomechanical, lifestyle, genetic or other factors related to both joints. These results suggest that hip shape may play a hitherto unrecognized role in the pathogenesis/progression of knee osteoarthritis over time.

Chapter 7: The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: A post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial

7.1 Prelude

Having shown previously that obesity is a significant risk factor for knee OA and given the favourable effects of weight loss on symptomatic outcomes, we hypothesized that weight loss may lead to structural modifications in the knee. Hence, we proceeded to investigate the associations between weight loss and meniscus extrusion in older adults as explained in this chapter. This chapter is presented in a way that it was submitted to the peer-reviewed journal.

7.2 Introduction

Obesity is a major modifiable risk factor for osteoarthritis (OA) that has been linked to increased risk of incidence and progression of the disease[33, 251]. Previous reports suggest that weight loss has beneficial effects on clinical outcomes in patients with knee OA[214, 215, 223]. Yet, the effects of weight loss on joint structures have been unclear, with evidence suggesting either beneficial[229, 230] or no effects[295]. Clinical improvement may be conveyed by endocrine/inflammatory[223, 296] and mechanical pathways[297, 298], however, the mechanism (or mechanisms) by which weight loss translates into clinical benefits has not been clearly elucidated.

The menisci are pivotal in distributing mechanical loads between the distal femoral and proximal tibial cartilage surfaces[299]. Meniscus pathology, such as meniscal lesions (tears) and extrusion have been reported to be associated with incidence[247, 300] and progression[301, 302] of knee OA and knee symptom status[119, 302]. Modification of meniscus pathology may thus entail potential benefits on knee symptoms. While studies suggest that a higher body mass index (BMI) is related to meniscal lesions[302], findings on

whether a higher BMI is related to meniscus extrusion are controversial[122, 124]. Interestingly, a recent report showed that participants who lost weight had less progression of meniscal lesions compared to the participants with stable weight[303]. However, no interventional study has yet confirmed the effect of weight loss on the quantitative measures of meniscus extrusion.

The Intensive Diet and Exercise for Arthritis (IDEA) trial showed that weight loss achieved by a combination of diet and exercise significantly reduced knee OA symptoms and improved function, compared to an exercise only intervention[223]. A secondary analysis in a subpopulation of the IDEA trial did not identify differences in radiographic joint space width loss (JSW), cartilage thickness loss (by Magnetic Resonance Imaging (MRI)), bone marrow lesion scores, or synovitis/effusion scores between the three intervention groups[295]. Yet, whether weight loss is associated with beneficial effects on the meniscus, and whether this represents a potential mechanism by which weight loss translates into clinical improvement has not yet been studied.

The objective of the current study therefore, was to test the hypotheses that, in overweight and obese participants of the IDEA trial, (1) 18-month interventional weight loss is associated with less progression in quantitative measures of meniscus extrusion and size, and in semiquantitative meniscus scores, over time; and that, (2) a diet-induced weight loss program, with or without exercise, is more efficient in modifying meniscus extrusion and size than exercise alone.

7.3 Methods

7.3.1 Study design

Intensive Diet and Exercise for Arthritis trial was a single-blind, single-center, 18-month, randomized controlled trial. The trial was conducted from July 2006 to June 2011 at Wake Forest School of Medicine and Wake Forest University, Winston-Salem, NC, USA[223, 241]. The study was approved by the Human Subjects Institutional Review Board of Wake Forest Health Sciences, and conducted in compliance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all the participants.

7.3.2 Study population

The study population consisted of 454 ambulatory, community-dwelling older adults, aged ≥ 55 years. The inclusion criteria were: (1) Kellgren-Lawrence grade (KLG) 2-3 (mild to moderate) radiographic tibiofemoral or tibiofemoral with patellofemoral OA of at least one knee; (2) pain on most days due to knee OA; (3) a BMI between 27 and 41 kg/m^2 and (4) a sedentary lifestyle (<30 min/week of formal exercise over the past 6 months). The participants were recruited over 37 months (November 2006 to December 2009) from the community[223, 241].

Stratified-block randomization was used to assign all the eligible participants to one of the three intervention groups, stratified by BMI and sex: exercise-only (E), diet-only (D) and diet with exercise (D+E). A comprehensive description of the trial design, rationale, and the exercise and diet interventions and primary outcomes has been provided elsewhere[223, 241]. In brief: the exercise intervention, conducted for 3 sessions/week (each 1 hour) over the 18-month period, comprised of aerobic walking (15 mins), strength training (20 mins), another

aerobic phase (15 mins) and a cool-down (10 mins). The diet intervention was based on partial meal replacements with 2 meal replacement shakes per day (Lean Shake; General Nutrition Centers) and the third meal with recipes that were low in fat and high in vegetables and were 500-750 kcal.

7.3.3 Magnetic Resonance Imaging acquisition

MRI of the most symptomatic knee was obtained in a random sub-sample of 105 participants at both baseline and 18-month follow-up. The sample sizes per group are as follows: E: n=36; D: n=33; D+E: n=36. MRIs were obtained using a 1.5T (SIGNA HDx, General Electric Medical Systems, Milwaukee, WI, USA) scanner with an extremity coil. The MRI sequences acquired included; (1) Double oblique coronal three-dimensional spoiled gradient-echo (SPGR) with fat suppression; (2) Axial T1-weighted spin-echo (SE); (3) Double oblique coronal T1-weighted SE; (4) Sagittal T1-weighted SE; (5) Sagittal T2-weighted fast spin-echo (FSE) with fat suppression; (6) Double oblique coronal T2-weighted FSE with fat suppression[225].

7.3.3.1 Quantitative meniscus position and size measures

The coronal SPGR sequence with fat suppression (1.5 mm slice thickness; interpolated in-plane resolution 0.31 mm × 0.3 mm) was utilised to quantitatively measure the meniscus in the central 5 slices (determined by the anatomical location)[242]. The images were first checked to ensure sufficient quality to support segmentation by an expert reader and 7 MRIs were excluded due to poor image quality[225]. Further, 8 medial and 3 lateral menisci needed to be excluded as they were severely macerated and could therefore not be analysed quantitatively,

leaving 90 medial and 95 lateral menisci at each time-point for segmentation. Manual segmentation of the medial and lateral menisci was then performed using specialised software (Chondrometrics GmbH, Ainring, Germany)[79]. The tibial cartilage surface including the denuded areas of subchondral bone and the surfaces of the meniscus (tibial, femoral and external area) were segmented on the SPGR images; this was assisted by the concurrent display of the proton-density-weighted (PDw) spin-echo images that are commonly used for radiological evaluation of the menisci[243]. Baseline and follow-up images were segmented as pairs by one reader (IPM) with blinding to the intervention, acquisition order, and OA (KLG) status. All segmentations were quality controlled by an expert reader with > 10 years of experience in quantitative joint tissue analysis; adjustments were done by consensus. Test-retest reliability of the readings was conducted on 10% of the participants (n=10), 1 month apart. The intra-rater variability determined as root mean square standard deviation (RMS SD) and intraclass correlation (ICC) for maximum extrusion distance at baseline was RMS SD, 0.50, ICC, 0.98 (0.94, 1.00) and at follow-up was RMS SD, 0.65, ICC, 0.97 (0.89, 0.99). The RMS SD and ICC for mean extrusion distance at baseline was RMS SD, 0.48, ICC, 0.99 (0.94, 1.00) and at follow-up was RMS SD, 0.58, ICC, 0.97 (0.90, 0.99). Performance of the quantitative data was in the excellent range for all the other measures (ICC range 0.92 – 0.99) (Supplementary Table 3).

Following the segmentation, the measures of meniscus position and size[244] were calculated using the Chondrometrics software[79]. Meniscus position measures included maximum and mean extrusion distances (mm), area of the meniscus not covering (i.e. extruding) the tibial plateau (mm^2), tibial coverage (by the meniscus) (mm^2) and overlap distance between the meniscus and tibial plateau (mm). The size measures included meniscus width (mm) and height (mm).

7.3.3.2 Semiquantitative meniscus measures

7.3.3.2.1 Meniscus extrusion

An expert musculoskeletal radiologist (AG) read T2-weighted MRIs paired and unblinded to the acquisition order, using the BLOKS method[71]. Extrusions in medial and lateral menisci were graded in two sub-regions (medially or laterally and anteriorly) as grade 0, normal; grade 1, < 2 mm; grade 2, 2 – 5 mm; grade 3, > 5 mm, at both baseline and 18-month follow-up. In the statistical analysis, a maximum scoring approach which focuses on the maximum extrusion score for a meniscus was used. The intra-rater agreement measured using kappa statistic was excellent[248] for semiquantitative meniscus extrusion measurements[72]; medial meniscus extrusion – 0.82 (95% CI; 0.66, 0.98), and lateral meniscus extrusion – 0.89 (0.75, 1.00).

7.3.3.2.2 Meniscal tears

Meniscal tears in medial and lateral menisci were recorded considering three sub-regions (anterior, body and posterior) as absent or present (signal abnormality, horizontal tear, vertical tear, complex tear, posterior horn root tear and maceration) at both baseline and 18-month follow-up. The intra-rater agreement measured using kappa statistic was excellent[248] for semiquantitative meniscal tear measurements[72]; medial meniscus tears – 1.00 (95% CI; 1.00, 1.00), and lateral meniscus tears – 0.91 (0.77, 1.00).

7.3.3.2.3 Radiographic OA (KLG status)

Bilateral, posteroanterior, weight-bearing, semi-flexed, knee X-rays were obtained at baseline[225, 249]. The status of tibiofemoral radiographic OA was determined using the KLG (grades 0 – 4; 0 – normal, 1 – doubtful, 2 – mild, 3 – moderate, 4 - severe) that utilizes information on the osteophytes, joint space narrowing, subchondral bone sclerosis and deformities of bone contours[57].

7.3.3.2.4 Mechanical alignment

A full-length, anteroposterior radiograph was obtained for each participant. With feet positioned 15 cm apart, the participant stood upright in such a way that both the tibial tubercles were faced directly forward and the weight equally distributed to both feet[50, 249]. The mechanical alignment was then measured as the angle formed by the intersection of the lines connecting the centers of the femoral head and the intercondylar notch and the centers of the ankle talus and tibial spines[225]. The alignment was then defined as normal (alignment angle $\geq -2° \ \& \leq 2°$), varus (alignment angle $> 2°$) or valgus (alignment angle $<-2°$) as previously described[225].

7.3.4 Statistical analysis

Baseline characteristics of the sample were described as means and standard deviations or frequencies and percentages.

Linear regression was used to determine the association between absolute change in weight (in kg) and change in position and size parameters of both the medial and lateral menisci over 18 months. Separate univariable and multivariable models were fitted for medial and lateral

menisci; in the multivariable models, adjustments were made for age, sex, baseline value of the respective parameter, baseline radiographic OA status (KLG status), baseline mechanical alignment (normal, varus or valgus) and presence/absence of meniscal tears.

Only a few participants had a change in semiquantitative scores of meniscus extrusion by at most one grade (medial meniscus - n=11; lateral meniscus n=1). Hence, log-binomial regression with log link and binomial family was used to assess the associations between absolute change in weight (in kg) and change in semiquantitative scores of meniscus extrusion of the medial and lateral menisci. The models for medial and lateral menisci were adjusted for age, sex and the baseline semiquantitative extrusion score.

Between-group comparisons of changes in meniscus position and size over time were evaluated using analysis of covariance (ANCOVA) with adjustments for age, baseline BMI and the respective meniscus parameter.

In order to assess whether the observed change in the quantitative measurements was larger than a minimal detectable significant change, the least significant criterion (LSC)[284] was calculated that takes into account the measurement error and the correlation between the measurements at both baseline and follow-up. Model assumptions for linear regression were tested in all the models. A p-value less than 0.05 (two-tailed) was regarded as statistically significant. In addition, adjustment for multiple comparisons was performed for the fully adjusted models based on the Benjamini-Hochberg method[304]. All statistical analyses were performed on Intercooled Stata V.15.1 for Mac (StataCorp LP, Texas, USA).

7.4 Results

7.4.1 Participant characteristics

Of the 105 participants who had MRIs in the IDEA trial, 98 were included in the quantitative analyses and 101 were included in the semiquantitative analyses in this study. The mean age was 65 years (SD ± 6.0), the mean BMI was 33.8 kg/m^2 (SD ± 3.8), and 73% were women at baseline (Table 7.1). No baseline differences were observed for age, sex, weight/BMI, mechanical alignment, KLG and meniscus position and size parameters between the three intervention groups. Semiquantitative measures of extrusion showed that 89% of the participants had a medial meniscus extrusion and 9% had a lateral meniscus extrusion, and again, no differences were detected between the intervention groups at baseline. The mean weight change of the participants was -5.28 kg (SD ± 8.6). The participant characteristics at the 18-month follow up are shown in (Appendix 1, Supplementary Table 3).

Table 7.1: Baseline characteristics of the 3 intervention groups

	Total sample (n=98) Mean (SD)	Exercise only (n=35) Mean (SD)	Diet only (n=30) Mean (SD)	Diet + Exercise (n=33) Mean (SD)
Age (years)	65.1 (6.0)	65.6 (6.0)	63.9 (6.0)	65.7 (6.1)
Sex (Female: n (%))	72 (73)	27 (77)	20 (67)	25 (76)
Weight (kg)	90.1 (13.2)	88.5 (12.3)	93.4 (14.7)	89.0 (12.7)
BMI (kg/m^2)	33.8 (3.8)	33.7 (3.7)	34.0 (4.1)	33.6 (3.8)
Mechanical alignment (degrees)	-0.21 (4.0)	-0.37 (4.0)	0.14 (4.0)	-0.37 (4.0)
Kellgren & Lawrence grade (% grade 2)	43	40	47	42
Meniscus parameters (Medial) (n=90)				
Max. extrusion distance (mm)	4.6 (2.3)	4.5 (2.3)	4.3 (2.2)	5.0 (2.6)
Mean extrusion distance (mm)	3.7 (2.3)	3.7 (2.3)	3.4 (2.2)	4.0 (2.5)
TA.Uncov (mm^2)	23.5 (11.5)	23.3 (11.7)	22.5 (10.5)	24.5 (12.4)
ACdAB.Cov (mm^2)	15.1 (14.5)	16.5 (16.2)	15.3 (11.6)	13.4 (15.4)

OvD (mm)	2.8 (1.9)	3.1 (2.1)	2.6 (1.5)	2.5 (2.0)
Width (mm)	6.0 (1.2)	6.1 (1.4)	5.9 (1.0)	6.1 (1.2)
Height (mm)	2.3 (0.4)	2.2 (0.4)	2.2 (0.4)	2.4 (0.3)
Meniscus parameters (Lateral) (n=95)				
Max. extrusion distance (mm)	0.6 (1.3)	0.8 (1.6)	0.2 (1.1)	0.7 (1.1)
Mean extrusion distance (mm)	-0.6 (1.2)	-0.4 (1.5)	-0.9 (1.1)	-0.5 (1.1)
TA.Uncov (mm^2)	3.5 (6.3)	4.8 (8.2)	2.1 (4.4)	3.3 (5.1)
ACdAB.Cov (mm^2)	50.5 (11.9)	49.6 (11.8)	48.9 (11.5)	52.9 (12.2)
OvD (mm)	8.3 (2.1)	8.0 (2.0)	8.2 (1.9)	8.6 (2.3)
Width (mm)	8.5 (1.6)	8.5 (1.6)	8.1 (1.5)	8.9 (1.7)
Height (mm)	2.5 (0.4)	2.6 (0.5)	2.5 (0.3)	2.5 (0.3)
Semiquantitative medial meniscus extrusion (%)	89	85	93	91
Semiquantitative lateral meniscus extrusion (%)	9	12	3	12
Presence of medial meniscal tears (%)	65	66	63	67
Presence of medial lateral tears (%)	14	11	20	12

BMI – body mass index, TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.

7.4.2 Association of weight change with quantitative meniscus parameters across groups

In the medial meniscus, a 1 kg loss of body weight between baseline and 18-month follow-up was associated with a 24.59 μm (β: -24.59 μm, 95% CI: -41.86, -7.33) reduction of progression in maximum extrusion distance and a 19.08 μm (β: -19.08 μm, 95% CI: -36.47, -1.70) reduction of progression in mean extrusion distance (Table 7.2). Other position markers, such as the tibial meniscal surface area not covering the tibial plateau, and tibial coverage (by the meniscus), also showed trends towards beneficial effects with weight loss, but the relationship failed to reach statistical significance ($p = 0.13$ and 0.12, respectively). The mean overlap distance between the tibial plateau and meniscus, and size parameters (width and height) were not significantly associated with weight change. In the lateral meniscus, none of the changes in position or size parameters over time was significantly associated with the weight change (Data not shown).

Table 7.2: Association between change in weight and change in measures of position and size in the medial meniscus

	Model 1 -Unadjusted (n=90) β-coef (95% CI)	Model 2 - Adjusted* (n=90) β-coef (95% CI)	Model 3 - Adjusted** (n=88) β-coef (95% CI)
Position parameters			
Maximum extrusion distance (μm)	**-24.27 (-41.21, -7.33)**	**-25.61 (-42.70, -8.51)**	**-24.59 (-41.86, -7.33)**
Mean extrusion distance (μm)	**-18.68 (-35.72, -1.64)**	**-20.24 (-37.43, -3.05)**	**-19.08 (-36.47, -1.70)**
TA.Uncov (mm^2)	-0.08 (-0.17, 0.02)	-0.08 (-0.18, 0.01)	-0.07 (-0.16, 0.02)
ACdAB.Cov (mm^2)	0.07 (-0.04, 0.17)	0.09 (-0.01, 0.20)	0.08 (-0.01, 0.20)
OvD. (μm)	2.75 (-13.86, 19.35)	6.62 (-10.38, 23.62)	5.12 (-11.92, 22.16)
Size parameters			
Width (μm)	0.88 (-10.53, 12.29)	4.06 (-7.91, 16.04)	2.40 (-9.77, 14.57)
Height (μm)	2.01 (-1.72, 5.74)	2.80 (-0.86, 6.50)	2.83 (-0.96, 6.62)

β-coefficient represents the effect per 1 kg loss of body weight. TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau. Linear regression, *- Adjusted for baseline age, sex and baseline values of the outcome; **- Further adjusted for radiographic OA status, baseline mechanical alignment and presence/absence of meniscal tears (n=88). Statistically significant results shown in bold.

7.4.3 Association of weight change with semiquantitative meniscus extrusion parameters across groups

No significant association was observed between weight change and worsening of semiquantitative measures of extrusion of the medial or lateral meniscus (Table 7.3).

Table 7.3: Association between change in weight and change in measures of position in menisci using semiquantitative measures

	Change / no change in meniscus extrusion	Model 1 – Unadjusted (n=101) RR (95% CI)	Model 2 - Adjusted* (n=101) RR (95% CI)	Model 3 - Adjusted** (n=101) RR (95% CI)
Medial meniscus extrusion	11 / 101	0.98 (0.92, 1.05)	0.99 (0.92, 1.05)	0.98 (0.92, 1.05)
Lateral meniscus extrusion	1 / 101	0.95 (0.76, 1.18)	0.95 (0.77, 1.18)	0.96 (0.74, 1.25)

RR represents the effect per 1 kg loss of body weight. *Model 2 - For medial meniscus - adjusted for baseline age and sex, for lateral meniscus - adjusted for baseline age; **Model 3 - Further adjusted for baseline values of the outcome.

7.4.4 Differences in the change in quantitative meniscus parameters between intervention groups

No significant between-group differences were observed for the meniscus position or size parameters in the medial (Tables 7.4) or lateral meniscus (Data not shown), among the 3

intervention groups. However, there was a significant between-group difference in the weight change.

The minimal detectable significant change was smaller than the effects observed in the medial compartment (data not shown). The associations remained unchanged when adjustment for multiple comparisons was conducted. Additionally, model assumptions for linear regression were satisfied in all the models.

Table 7.4: Change in extrusion and size parameters in the medial meniscus and weight change across 3 intervention groups

	Intervention Group			P-value for
	E (95% CI) (n=32)	D (95% CI) (n=28)	D + E (95% CI) (n=30)	between-group difference
Position parameters				
Maximum Extrusion Distance (mm)*	0.14 (-0.11, 0.40)	0.34 (0.06, 0.61)	0.04 (-0.22, 0.31)	0.197
Mean Extrusion Distance (mm)*	0.04 (-0.21, 0.30)	0.30 (0.03, 0.57)	0.05 (-0.21, 0.31)	0.164
TA.Uncov (mm^2)*	0.12 (-1.21, 1.46)	1.26 (-0.17, 2.69)	0.55 (-0.83, 1.92)	0.074
ACdAB.Cov (mm^2)*	0.58 (-0.95, 2.11)	-1.77 (-3.41, -0.13)	-0.27 (-1.85, 1.31)	0.177
OvD (mm)*	0.10 (-0.14, 0.34)	-0.22 (-0.47, 0.04)	-0.14 (-0.38, 0.11)	0.143
Size parameters				
Width (mm)*	0.13 (-0.04, 0.30)	0.01 (-0.17 0.19)	0.05 (-0.12, 0.22)	0.512
Height (mm)*	0.01 (-0.04, 0.07)	0.01 (-0.05, 0.07)	0.04 (-0.02, 0.09)	0.079
Weight change (kg)	**-1.39 (-4.28, 1.50)**	**-6.19 (-9.28, -3.09)**	**-9.37 (-12.36, -6.38)**	**0.001**

TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau. *ANCOVA models adjusted for baseline

value of the outcome, baseline BMI and sex. Boldface shows a statistically significant change of parameters in the particular group compared to its baseline value ($p<0.05$).

7.5 Discussion

This is the first study to investigate the associations of weight loss, achieved by diet and/or exercise interventions, on quantitative measures of meniscus extrusion and size in overweight or obese participants with knee pain and radiographic OA over time. We found that weight loss was associated with less progression in maximum and mean extrusion distances of the medial meniscus over 18 months; however, no between-group differences by intervention type were detected.

A limitation of this study was that the analysis was done only on a subsample of the larger IDEA cohort, due to the limited availability of the MRI[225]. Yet, this MRI subsample was randomly selected from the cohort and was shown to be representative of the characteristics of the participants of the main study[67]. Another limitation is that the meniscus extrusion was assessed on non-weight bearing knees and therefore, these results are only valid for meniscus extrusion in non-weight bearing position, as evidence suggest that the extrusion may vary with loading[305, 306]. Yet, work by Frobell et al., 2009[307] has shown that quantitative parameters of meniscus extrusion are highly correlated between weight-bearing and non-weight-bearing imaging. Another limitation is that the confidence intervals are somewhat large in the effects observed suggesting that these results should be interpreted with caution, however, the minimal detectable significant change was smaller than the effects observed. A strength of our study is that we assessed meniscal position and size on MRI[308] using state-of-the-art quantitative measurements and semiquantitative scoring systems.

In the medial meniscus, a significant association between weight loss and less progression for maximum and mean extrusion distances was observed over time. Weight loss reduces knee

compressive forces[223]; therefore, one possible mechanism for this association is that the reduced compressive forces may have led to less progression of maximum and mean extrusion distances. Although we did not detect any significant associations between weight change and other position parameters, the observed trends for these parameters suggest that weight loss was favorable. These trends may further indicate that less extrusion may translate to increased mechanical protection[246], with improved load distribution over a larger area on the tibial plateau[115] and reduced knee joint contact stress[299, 309, 310].

There were no significant associations between weight loss and the parameters of the lateral meniscus. This finding is not totally unexpected, as biomechanical studies have shown that a lower amount of compressive forces are transferred through the lateral compartment compared to the medial compartment[311], even in the knees with normal alignment[312], and the effects of higher BMI were observed mostly on the medial compartment rather than on the lateral compartment[313].

We did not detect a significant association between weight loss and change in semiquantitative scores of meniscus extrusion. Similarly, a recent report based on the PROOF study, evaluating the association of weight change subgroups (loss and gain) compared to a stable weight subgroup over 2.5 years in overweight and obese females without OA, did not find a relationship between weight change subgroups and meniscal extrusion using a semiquantitative scoring system[123]. Since we found associations between quantitative measures of extrusion, the lack of association with semiquantitative measures could be due to its attenuated sensitivity to change, as larger changes are required to detect a change in semiquantitative grades[75]. Additionally, a change in semiquantitative scores of meniscus extrusion by at most one grade

was only seen in a very few participants in this study and this may also suggest that a larger sample is needed to detect frequent changes in semiquantitative scores.

The IDEA trial confirmed that weight loss in the diet + exercise group significantly improved pain and reduced knee compressive forces, compared to the exercise-only group[223]. However, Hunter et al., 2015, found no significant between-group differences for radiographical and MRI outcomes in the knee which included quantitative cartilage morphometry, semiquantitative bone-marrow lesions and Hoffa-synovitis measures[225]. Similarly, we were unable to identify any significant between-group differences in quantitative meniscus position and size parameters, likely due to the relatively large variability of weight change within each intervention group, the lack of a no-intervention group and a potential limited statistical power in this subsample of IDEA cohort[225]. The PROOF study, conducted on overweight and obese women without clinical signs of OA, found beneficial effects on semiquantitative measures of meniscus extrusion in the diet + exercise group compared with a non-treated control group[314]. The control group in the PROOF study did not receive any active intervention, which may be a reason for the enhanced beneficial effects.

In the current study, a higher proportion of participants had medial meniscus extrusion at baseline (89%) than observed previously by Crema et. al., 2012 (44.2%), and Landsmeer et al., 2018 (54%), whereas the prevalence of lateral meniscus extrusion was 9% at baseline which was approximately similar to the previous reports (Crema et. al., 2012 (9.4%), Landsmeer et al., 2018 (6%))[122, 123]. The high prevalence of medial meniscus extrusion in our study is potentially due to the demographics of our participants with prevalent ROA (KLG 2-3) and obesity.

The observed association between weight loss and maximum and mean extrusion distance of the medial meniscus was relatively small in magnitude. For example, as per the regression equation (Regression equation (Unadjusted): $y = 0.304 + -0.024X$, $R^2 = 8.4\%$, $p = 0.005$), if an average participant in this study (i.e. bodyweight – 90.1 kg, baseline maximum extrusion distance of medial meniscus – 4.6 mm) lost 12.7 kg, no further progression of the maximum extrusion distance of medial meniscus may be seen. If a weight loss of > 12.7 kg is achieved, this may lead to an actual decrease in maximum extrusion distance of medial meniscus. Additionally, the clinical significance of this association with regard to symptoms and the rate of structural progression is unclear. However, a previous study has shown that meniscus extrusion, when measured quantitatively, is associated with knee pain[119], potentially because the extruded meniscus may generate mechanical stress on the pain-sensitive structures such as external aspects of the meniscus as well as the joint capsule. Hence, it is plausible that the beneficial effects of weight loss on knee pain may be at least partly mediated by the less progression of medial meniscal extrusion. Additionally, the progression of meniscus extrusion has been related with incident radiographic knee OA[247] and increased risk of knee replacements[315]. Therefore, further studies are needed to confirm whether the clinical benefits of weight loss are mediated through less progression of medial meniscal extrusion.

In conclusion, the current study found that weight loss was associated with less progression and an actual decrease in maximum and mean extrusion distances of the medial meniscus over 18 months in overweight or obese men and women with knee pain and radiographic knee OA. Given the relationship between quantitative measures of meniscus extrusion and knee symptoms shown previously, the current data may indicate that meniscus extrusion could be one of the mechanisms by which weight loss translates into a clinical benefit.

Chapter 8: Summary and Future directions

8.1 Summary

OA is one of the most common conditions of the musculoskeletal system and knee and hip osteoarthritis account for the biggest burden of disease[1]. Nearly 9.6% of men and 18.0% of women who are 60 years or older are affected by symptomatic OA, and this is expected to increase as the population ages[5, 6]. The pathogenesis and the risk factors of the disease remain uncertain, and there is no definitive cure for OA. Hence, identifying risk factors of OA is a significant global challenge, to look for potential avenues of better preventive strategies and treatments[316]. While prior studies have explored risk factors for OA, this thesis aimed to identify the longitudinal associations between determinants and risk factors with long-term clinical and structural knee and hip OA outcomes in older adults.

TJR for end-stage OA is a successful procedure, resulting in improved symptoms and function. Although TJR is cost-effective, there are significant direct and indirect costs associated with it[131]. Consequently, the uptake of these procedures may be dependent on an individual's SES, potentially leading to a disparity in utilization[131]. Previous research in both Australian and international contexts has mainly focused on identifying the relations between SES and utilization rates of TJR, which may depend more heavily on the SES. To extend this knowledge, **Chapter 4** investigated the longitudinal associations of SES with time to THR and TKR in a prospective cohort of community-dwelling older adults in Tasmania, Australia, over an average follow-up of 12 years. The results showed that less disadvantaged participants were less likely to have a THR (i.e. less disadvantaged participants had a longer time to THR) compared to the most disadvantaged participants independent of age, sex and BMI. However, this association was attenuated after controlling for symptomatic and structural mediating factors (e.g. hip pain and hip ROA). This suggests that time to TJR is more likely to be

determined according to the symptoms and joint structure rather than their SES. One potential reason for this could be the policies implemented by governments in Australia, e.g., policies to manage waiting lists for surgeries to ensure the equity of access to these procedures, and the health insurance reforms. Additionally, 1) the structure of Australian healthcare system (i.e. both public and private healthcare providers delivering services)[131], 2) the characteristics of people in different SES levels (i.e. health literacy, health-seeking behaviour, coping strategies), and 3) financial and personal resources, may also have contributed to these findings. The findings of this study also confirm the usefulness of TJR as a marker of end-stage OA in the knee and hip.

Prior studies have shown contradictory and limited findings on the association between person-level, lifestyle factors such as PA and body composition measures with knee and hip TJR due to OA. Hence, **Chapter 5** evaluated the longitudinal associations between PA (assessed as AA) and body composition measures such as BMI, total fat mass, trunk fat mass, lean mass percentage and waist circumference with the risk of knee and hip TJR using a 13-year population-based prospective cohort. This study was the first to use objectively-measured AA determined by pedometers to examine the relationships with TJR. The results showed that every 1000 steps/day increase at baseline was associated with a 9% greater risk of TKR while every 1000 steps/day increase at baseline was associated with a 10% reduced risk of THR. Additionally, a unit increase in BMI at baseline was associated with a 7% increased risk of TKR. Similarly, higher total fat mass, trunk fat mass and waist circumference were related to increased risk of TKR. BMI and other body composition measures were not associated with risk of THR. These findings highlight that AA and body composition measures may have differential effects on the hip and knee joints and warrants further investigations.

Joint morphology is a crucial joint-level factor for the incidence and progression of OA. Previous studies have suggested that hip morphology may have implications on the knee joint, potentially due to probable biomechanical links between the two joints. However, there is a lack of knowledge on the association between hip morphology and knee OA progression. **Chapter 6** investigated the longitudinal relationships between hip shapes and clinical, structural and end-stage markers of OA in the knee. Ten hip shapes were identified using statistical shape modelling. The results showed that hip shapes with longer, wider femoral neck and with larger femoral head were related to an increased risk of worsening knee pain, while shapes with wider femoral neck were associated with reduced risk of worsening knee pain. Larger greater trochanter and greater acetabular coverage were linked to lower cartilage volume loss, while shorter, wider femoral neck was associated with increased cartilage volume loss. Hip shapes with smaller femoral head were related to increased risk of worsening BMLs. Greater acetabular coverage was associated with a reduced risk of TKR. Taken together, these findings suggest that hip shape variations may play a key role in the long-term progression of knee OA in older adults.

In **Chapter 5,** we showed that obesity is a major modifiable risk factor for knee OA. Accordingly, weight loss could be beneficial in alleviating clinical outcomes concerning knee OA[214, 215, 223]. However, current evidence on the effects of weight loss on knee structure is debatable[229, 230, 295]. Similarly, the association between weight loss and meniscal extrusion has not been clearly described, although meniscal extrusion is linked to incident[247] and progressive[301] knee OA and knee symptom status[119]. Therefore, **Chapter 7** studied the relationship between weight loss achieved by diet, exercise and a combination of diet and exercise and meniscus extrusion and size. This study further examined whether a diet-induced weight loss program, with or without exercise, is more effective in modifying meniscus

extrusion and size than exercise alone. The results revealed that weight loss was related to less progression of the medial meniscus extrusion as measured by the maximum (β: -24.59 μm, 95%CI: -41.86, -7.33) and mean (β: -19.08 μm, 95%CI: -36.47, -1.70) extrusion distances. This finding was irrespective of the type of intervention, as the change in meniscus position and size parameters did not differ significantly between the interventional groups. These findings suggest that less progression of meniscus extrusion could be one mechanism that mediates the effects of weight loss for improving knee symptoms.

8.2 Future directions

This thesis presents a number of novel findings on the pathogenesis and management of progressive knee and hip OA in older adults, based on a distinct population-based cohort study and a randomised controlled clinical trial. These findings, while advancing the understanding of OA, warrant further studies to continue to build our overall understanding of OA progression and improve management strategies.

Chapter 4 showed that the SES levels were not related to time to knee and hip TJR independent of symptomatic and structural mediating factors. Early surgery is associated with better postoperative clinical outcomes[250]. We found that the SES is not a barrier for early surgery in Tasmania, possibly due to policy implications. However, as reported in the annual elective surgery waiting times of the public hospitals, published by the Australian Institute of Health and Welfare, the waiting times for TKR and THR are higher for Tasmania, compared to other Australian states[317]. Taken altogether, this suggests that SES is not impacting on time to joint replacement in Tasmania, but access to joint replacement may be relatively poor and need to be improved.

TJR is considered as a marker of the end-stage of OA, an outcome that signifies the failure of the natural joint. However, this concept is not without limitations. The decision to perform TJR as a treatment may depend on patient-specific behavioural factors (i.e. health-seeking behaviour, willingness to undergo TJR) and physician-related factors[277]. These factors challenge the use of TJR as an end-stage outcome. Future studies need to explore the associations between such factors and TJR and thereby validate the use of TJR as an end-stage OA marker.

While TJR is an effective procedure, it is costly[15]. Nearly 7% to 23% of people who receive a THR and 10% to 34% of people who receive a TKR will have long-term persistent pain even after the procedures[318]. This highlights the importance of identifying and providing access to better conservative management strategies (i.e. weight loss, exercise and education) to delay the progression of OA and need for TJR.

Chapter 5 highlighted that there are different effects of AA and body composition on TJR in hip and knee. PA, mainly walking, is considered a first-line treatment for knee and hip OA[51]. We observed that higher AA was associated with a small increased risk of KR and, a small reduced risk of HR. These findings need to be interpreted with caution and call for future studies on potential mediating factors. For example, knee alignment[49, 269] and knee adduction moment[270] are associated with the incidence and progression of knee OA and potentially could mediate or modify the effects of AA on knee OA[157]. Biomechanical factors of the adjacent joints (hip and ankle) that are associated with knee OA progression could be other potential candidates for mediators[319]. Therefore, future observational studies need to investigate the mediating effects of lower limb joint biomechanical factors on the associations

between AA with knee and hip OA. Findings from these will assist refining PA guidelines and treatment strategies. The differential associations between body composition measures and knee/hip TJR highlight the need for studies to assess the mediating factors on the associations between OA and body composition measures.

Chapter 5 used pedometer-determined AA, a quantitative measurement of the number of steps per day. However, accelerometry defined AA gives an additional measure, the intensity of AA, which has been associated with the risk of hip/knee TJR[159, 160]. The intensity of AA is self-reported in most existing studies. Objective measures, as provided by accelerometry data, may reduce bias associated with self-reported intensity data[151]. Therefore, we suggest that future research should focus on identifying the associations between objectively-measured AA intensity and joint health in the knee and hip, rather than self-reported measures.

Different types of PA may affect joint health differently. Activities such as kneeling, squatting, heavy lifting and climbing more than 10 flights of stairs per day are associated with higher risks[320-322], possibly due to biomechanical factors like joint loading. For example, kneeling/squatting requires a higher degree of knee flexion and result in increased contact forces[323]. Thereby, repetitive kneeling/squatting may lead to knee injuries and increased risk of knee OA[321]. Therefore, specific effects of different activity types on end-stage OA rather than considering PA as a homogenous entity should be conducted, following this work.

While the relationship between AA and OA in knee and hip have been of interest, the evidence has been contradictory[149-151] and has mostly been from observational studies. This has highlighted the need for rigorous studies that assess these associations. Hence, our group is currently conducting an RCT, examining the effects of walking compared to usual care on

symptomatic and structural markers of knee OA. Similar work should focus on evaluating the effects of walking or other PA on symptomatic and structural markers of hip OA.

Chapter 5 of this thesis emphasises that obesity is a significant risk factor for end-stage knee OA. The total fat mass, trunk fat mass and waist circumference can be more sensitive measures of body fat and fat distribution; however, BMI also showed consistent associations. This supports the use of BMI as a simple, inexpensive marker of obesity which could be particularly helpful at a population level and in the primary care.

Chapter 6 showed that specific hip shape modes were associated with several longitudinally measured knee OA outcomes. Yet, the mechanisms of these associations are unclear and warrant exploratory studies to determine how biomechanical, morphological and lifestyle factors may mediate the observed associations. Our results suggest that there may be inter-relationships between the morphology of the adjacent joints (i.e. hip, knee and ankle joints) of the lower limb kinematic chain that could affect OA in another joint[288]. This underlines that in clinical practice, a detailed evaluation of the morphological and biomechanical factors of the adjacent joints (i.e. hip, knee and ankle joints) of the lower limb needs to be done as a part of the assessment of lower limb OA.

The findings of **Chapter 6** can also be used to identify people with a higher risk of progressing OA. Treatments for OA should move from a 'one-size-fits-all' approach to a 'tailor-made' approach, where the patients are treated based on their specific phenotypic characteristics. For this, first OA phenotypes should be clearly defined using structural, psychological and lifestyle factors. We suggest that hip shapes modes could be considered in such phenotypic studies in the future.

Obesity is associated with end-stage OA in the knee and a significant risk factor for symptomatic and structural OA in the knee[33]. Obesity is modifiable, and weight loss is associated with improved pain and function[230]. In **Chapter 7,** we revealed for the first time, that weight loss was associated with less progression of medial meniscus extrusion in people with knee OA. This would strengthen the current evidence on using weight loss programs for overweight and obese people with knee OA. Weight loss could be an attractive prevention strategy given that no disease-modifying treatments (modifying both symptoms and structures) are available for OA. We found that if a weight loss of > 12.7 kg was achieved, this might lead to an actual decrease in maximum extrusion distance of medial meniscus, a beneficial structure modifying effect, in addition to symptomatic relief in knee OA. This amounts to a weight loss of around 14%. Recently, the RACGP guidelines recommended that a weight loss of 5 – 7.5% of body weight is required to obtain symptomatic benefit[51]. As per our data, a 5 – 7.5% loss of body weight may not be sufficient to gain *structural benefits* in knee OA. Similar findings have been reported for cartilage biomarkers in a study that assessed the effects of massive weight loss (20%) after gastric surgery[230]. However, massive weight loss via surgery is only recommended for people with a BMI > 35 kg/m^2[324]. For those who do not qualify for surgical interventions for weight loss, a combination of diet and exercise would be beneficial for symptomatic improvement[223]. However, the effects of diet and exercise-induced weight loss on structure modification remain understudied[225] and warrant further investigations.

Following our finding in **Chapter 7**, it would be interesting to test whether less meniscal extrusion progression seen with weight loss, is associated with improvements in knee pain. This is important as the symptoms, and structural outcomes in OA do not always align[111]. For instance, knee pain prevalence is approximately 15 – 81% in people with knee ROA[325],

while hip pain prevalence is only 15.6% among those with hip ROA[326]. One potential reason for this disagreement between pain and structure could be that radiographs are less sensitive in detecting structural features[56]. In contrast, MRI provides better visualisation of structures, including soft tissues[56]. MRI detected structures might correlate better with structural features such as BMLs[327], infra-patella fat pad (IPFP)[328] and synovitis[329], although particular MRI-detected structures such as cartilage volume show low correlation with pain[329]. MRI detected structures explain nearly 20 – 35% of the variations in pain[330]. Hence, more advanced imaging techniques, such as those employed in **Chapter 7** as well as advanced modalities, are necessary to have improved correlations between joint structures and symptoms. Recently, several compositional MRI techniques have been adopted in research to assess the biochemical properties of the articular and periarticular tissue. These include delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), relaxometry measurements (T2, T1-rho mapping and T1), glycosaminoglycan specific Chemical Exchange Saturation Transfer (gagCEST), Diffusion Weighted Imaging (DWI), and Diffusion Tensor Imaging (DTI)[329]. In addition to this, hybrid techniques, including Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) are also currently being used in research[331]. These novel modalities are only used to assess limited structures such as cartilage in current research. Future work should focus on increased use of these modalities to examine correlations between structures and symptoms of OA.

We also suggest the use of MRI detected structures in trails for structure modifying drugs. Currently, radiography is the only Food and Drug Administration (FDA) approved imaging modality to assess the efficacy of such drugs for OA. However, as highlighted, radiographs demonstrate a weak correlation with pain and are less sensitive to change over time[30, 51, 325]. This may challenge identifying the efficacy of structure modifying treatments and further

substantiates the need for more sensitive imaging tools such as MRI, to be approved as imaging modalities to assess the efficacy of treatments. **Chapter 7's** findings that weight loss may modify menisci, further strengthens the utility of using MRI in studies to detect structure modification.

In conclusion, the findings from this thesis based on a population-based cohort study and a randomised controlled clinical trial, first established that hip and knee TJR is an acceptable marker of end-stage OA of the respective joint and that person-level factors such as habitual activity, and obesity/body composition markers may have differential effects on OA progression. This data identified that joint-level factors, (i.e. variations in hip shape), might be a crucial structural feature that is associated with the progression of knee OA and detailed the importance of weight loss as a management strategy for knee OA progression. Overall, this thesis emphasised the importance of certain lifestyle factors and showed that better management of these factors might help to reduce OA progression in older adults.

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Chapter 10: Appendices

Appendix 1

Supplementary Table 1: Baseline characteristics of participants with and without missing data

	KR model		HR model	
	Missing (n = 193)	Non-missing (n = 889)	Missing (n = 184)	Non-missing (n = 882)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	68.2 (7.6)	61.7 (6.9)	68.2 (7.5)	61.7 (6.9)
Sex (Female: %)	38	54	38	54
Steps/day (In 1000s)	6.88 (3.12)	9.00 (3.29)	6.89 (3.15)	9.02 (3.27)
Steps/day categories				
Tertile 1 (%)	58.0	28.5	58.3	28.4
Tertile 2 (%)	26.4	34.6	26.2	34.7
Tertile 3 (%)	15.6	36.9	15.5	36.9
BMI (kg/m^2)	27.9 (4.7)	27.8 (5.0)	28.1 (4.9)	27.8 (4.7)
BMI categories				
Underweight/Normal (%)	30.6	22.8	27.7	29.3
Overweight (%)	41.9	30.4	43.5	43.4
Obese (%)	27.5	46.8	28.8	27.3
Total fat mass (kg)	27.3 (9.3)	28.4 (8.6)	27.7 (9.6)	28.3 (8.5)
Trunk fat mass (kg)	12.6 (4.9)	12.7 (4.9)	12.8 (5.0)	12.7 (4.6)
Lean mass (%)	64.1 (8.2)	62.8 (7.7)	63.9 (8.4)	62.9 (7.6)
Waist circumference (cm)	96.7 (13.7)	93.5 (12.9)	97.3 (13.5)	93.4 (12.9)
Knee ROA (%)	59	62	62	60

WOMAC knee pain*	4.4 (7.2)	3.6 (6.1)	4.5 (7.2)	3.6 (6.2)
History of knee surgery (%)	11	11	12	10
History of knee injury (%)	7	11	8	13
Hip ROA (%)	18	17	18	11
Hip pain (%)	16	19	15	19

KR – knee replacement, HR – hip replacement, BMI – body mass index, ROA – radiographic osteoarthritis, WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; *Range: 0-39.

Supplementary Table 2: Characteristics of the 3 intervention groups at the 18-month follow-up

	Total sample (n=98) Mean (SD)	Exercise only (n=35) Mean (SD)	Diet only (n=30) Mean (SD)	Diet + Exercise (n=33) Mean (SD)	P-value for between-group difference
Weight (kg)	84.9 (14.2)	**87.2 (13.2)**	**87.6 (13.7)**	**79.9 (14.7)**	**0.0426**
BMI (kg/m^2)	31.4 (4.6)	**33.3 (4.5)**	**31.1 (4.1)**	**29.6 (4.4)**	**0.0036**
Meniscus parameters (Medial) (n=90)					
Max. extrusion distance (mm)	4.8 (2.3)	4.7 (2.3)	4.7 (2.2)	5.0 (2.2)	0.8254
Mean extrusion distance (mm)	3.8 (2.3)	3.7 (2.3)	3.7 (2.1)	4.1 (2.5)	0.7908
TA.Uncov (mm^2)	24.1 (11.3)	23.4 (11.2)	23.9 (10.1)	25.0 (12.7)	0.8501
ACdAB.Cov (mm^2)	14.7 (14.6)	17.0 (15.9)	13.5 (11.7)	13.2 (15.8)	0.5285
OvD (mm)	2.7 (1.9)	3.2 (2.0)	2.4 (1.5)	2.4 (2.2)	0.2097
Width (mm)	6.1 (1.2)	6.2 (1.4)	5.9 (1.0)	6.1 (1.3)	0.6985
Height (mm)	2.3 (0.4)	2.2 (0.4)	2.2 (0.4)	2.4 (0.3)	0.2242
Meniscus parameters (Lateral) (n=95)					
Max. extrusion distance (mm)	0.5 (1.4)	0.7 (1.8)	0.2 (1.1)	0.5 (1.3)	0.4506

Mean extrusion distance (mm)	-0.7 (1.4)	-0.6 (1.6)	-1.0 (1.2)	-0.7 (1.2)	0.5286
TA.Uncov (mm^2)	3.5 (6.9)	4.6 (9.2)	2.3 (5.3)	3.3 (5.4)	0.4450
ACdAB.Cov (mm^2)	50.6 (12.4)	49.1 (11.9)	49.3 (11.6)	53.3 (13.4)	0.3094
OvD (mm)	8.4 (2.2)	8.2 (2.1)	8.2 (1.9)	8.8 (2.4)	0.4834
Width (mm)	8.4 (1.6)	8.3 (1.4)	8.1 (1.4)	8.9 (1.8)	0.1328
Height (mm)	2.6 (0.4)	2.6 (0.5)	2.5 (0.3)	2.5 (0.3)	0.6429
Semiquantitative medial meniscus extrusion (%)	89	85	93	91	0.541
Semiquantitative lateral meniscus extrusion (%)	9	12	3	12	0.413
Presence of medial meniscal tears (%)	65	66	63	67	
Presence of medial lateral tears (%)	14	11	20	12	

BMI – body mass index, TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.

Supplementary Table 3. Root mean square standard deviation of each variable of the medial meniscus

Variable	Original readings (mean (SD))	Root mean square standard deviation	Intra-Class Correlations (mean (95% CI))
Max. extrusion distance (mm)			
Baseline	4.6 (2.3)	0.498	0.98 (0.94, 1.00)
Follow-up	4.8 (2.3)	0.652	0.97 (0.89, 0.99)
Mean extrusion distance (mm)			
Baseline	3.7 (2.3)	0.484	0.99 (0.94, 1.00)
Follow-up	3.8 (2.3)	0.579	0.97 (0.90, 0.99)
TA.Uncov (mm^2)			
Baseline	23.5 (11.5)	1.816	0.99 (0.95, 1.00)
Follow-up	24.1 (11.3)	1.672	0.99 (0.98, 0.99)
ACdAB.Cov (mm^2)			
Baseline	15.1 (14.5)	2.978	0.97 (0.96 0.99)
Follow-up	14.7 (14.6)	2.993	0.97 (0.95, 0.99)
OvD (mm)			
Baseline	2.8 (1.9)	0.606	0.95 (0.80, 0.98)
Follow-up	2.7 (1.9)	0.599	0.94 (0.78, 0.98)
Width (mm)			
Baseline	6.0 (1.2)	0.156	0.98 (0.93, 0.99)

Follow-up	6.1 (1.2)	0.181	0.98 (0.93, 0.99)
Height (mm)			
Baseline	2.3 (0.4)	0.091	0.96 (0.85, 0.99)
Follow-up	2.3 (0.4)	0.095	0.96 (0.87, 0.99)

TA.Uncov – the area of the meniscus not covering (i.e. extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.

Appendix 2

The association between ambulatory activity, body composition and hip or knee joint replacement due to osteoarthritis: a prospective cohort study

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The association between ambulatory activity, body composition and hip or knee joint replacement due to osteoarthritis: a prospective cohort study

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SUMMARY

Objective: To examine the association between ambulatory activity (AA), body composition measures and hip or knee joint replacement (JR) due to osteoarthritis.
Design: At baseline, 1082 community-dwelling older-adults aged 50–80 years were studied. AA was measured objectively using pedometer and body composition by dual-energy X-ray absorptiometry. The incidence of primary (first-time) JR was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). Log binomial regression with generalized estimating equations were used to estimate the risk of JR associated with baseline AA and body composition measures, adjusting for age, sex, X-ray disease severity, and pain.
Results: Over 13 years of follow-up, 74 (6.8%) participants had a knee replacement (KR) and 50 (4.7%) a hip replacement (HR). AA was associated with a higher risk of KR (RR 1.09/1000 steps/day, 95% CI 1.01, 1.16) and a lower risk of HR (RR 0.90/1000 steps/day, 95% CI 0.81, 0.99). Body mass index (BMI) (RR 1.07/kg/m^2, 95% CI 1.03, 1.12), total fat mass (RR 1.03/kg, 95% CI 1.01, 1.06), trunk fat mass (RR 1.05/kg, 95% CI 1.00, 1.09), and waist circumference (RR 1.02/cm, 95% CI 1.00, 1.04) were associated with a higher risk of KR. Body composition measures were not associated with HR.
Conclusions: An objective measure of AA was associated with a small increased risk of KR and a small reduced risk of HR. Worse body composition profiles were associated with KR, but not HR. Altogether this may suggest different causal pathways for each site with regard to habitual activity and obesity.

Introduction

Joint replacement (JR) is an effective treatment for severe osteoarthritis (OA)[1]. The rates of JR are rising with the increase in incidence of OA and have a significant impact on health budgets[2,3]. A better understanding of the risk factors for JR will assist in designing better conservative treatments which would in-turn help reduce the health burden.

Ambulatory activity (AA) is one of the most common forms of physical activity (PA) performed by older people, and has beneficial effects on overall health and in certain diseases[4]. However, there is some concern that excessive or repetitive loading exerted on joint structures could be detrimental to joint health[5]. Hence AA may be a potential risk factor for OA in weight bearing joints. Alternatively, AA may be beneficial for joint health because dynamic loading may improve the integrity of the structures; especially joint cartilage[6]. Furthermore, AA may have differential effects on different joints. There is evidence suggesting AA has detrimental effects on the

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knee[7] but protective effects[8] or no effects[9] on the hip. No studies have utilised objectively measured AA in order to examine its association with the risk of JR.

Measures of body composition may also be important in predicting risk of JR. Body mass index (BMI) is a known risk factor for knee replacement (KR)[10,11] and hip replacement (HR) due to OA[1,12], most likely due to increased joint loading and metabolic factors[1]. However, there are potentially more sensitive measures of body composition including total fat mass, lean mass and distribution of fat mass (trunk fat, waist circumference). Studies evaluating the associations between different body composition measures and JR are limited[1,13].

In this study, we examine the association between AA, body composition measures and the risk of JR due to OA using a 13-year population-based prospective cohort study.

Methods

Study population

Data used for this study are from the Tasmanian Older Adult Cohort (TASOAC), which is a prospective, population-based study[7]. Participants (n = 1099) between 50 and 80 years were selected using computer generated random numbers from the electoral roll in Southern Tasmania, between March 2002 and September 2004, with an equal number of men and women (response rate 57%, 1099/1904). Participants who had contraindication to magnetic resonance imaging (MRI) were excluded from the cohort. Ethical approval was granted by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and written informed consent was obtained from all participants. In this study, participants who had a JR prior to their baseline visit and those who had a JR due to diagnoses other than OA were excluded (Fig. 1). Therefore, 1082 participants were included in the KR models and 1066 were included in the HR models.

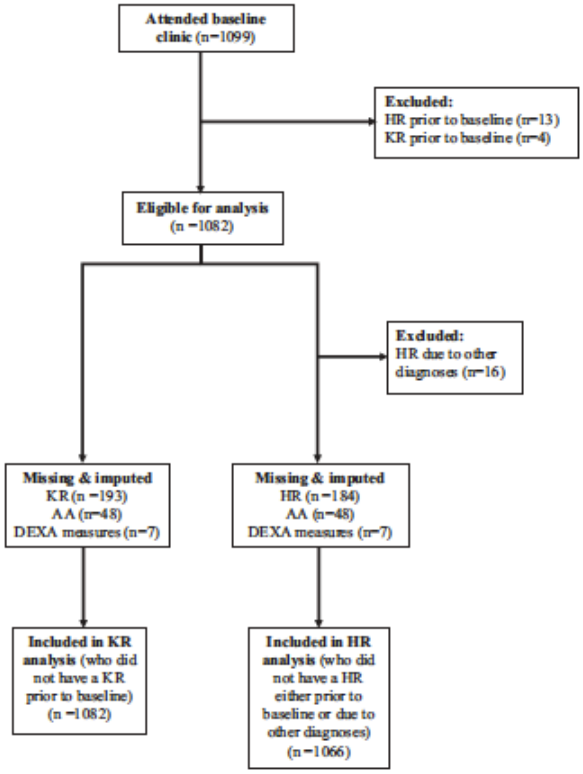

Fig. 1. Study flow chart.

Identification of primary (first-time) joint replacement

The incidence of primary (first-time) KR and HR between 1 March 2002 and 21 September 2016 were determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR). AOANJRR started data collection in Tasmania in September 2000 and collects data from both public and private hospitals. Data validation against State and Territory Health Department data is done using a sequential multi-level matching process[14]. Matched data were then obtained which included the date, side of JR, primary or revision JR and the reason for the procedure (e.g., OA, fracture of neck of femur, osteonecrosis, inflammatory arthritis, tumour). In this study, we only considered JR's that were due to OA.

Ambulatory activity

AA at baseline was determined as steps/day using a pedometer (Omron HJ–003 & HJ-102, Omron Healthcare, Kyoto, Japan). Pedometers were first calibrated with the presence of the participant at the clinic, utilising a 100-pace walking test. Participants were given instructions (both verbal and written) about using the pedometer and keeping a pedometer log (diary). They were required to wear the pedometer on the dominant side for seven consecutive days while conducting their normal day-to-day activities except during bathing, water activities and sleeping. They were also advised to maintain a log of the step count per day and the time duration during which the pedometers were worn. This was repeated after six months in order to account for habitual changes in different seasons. Hence, there were two sets of pedometer logs for each participant. Readings were excluded if there was evidence for artificial pedometer readings such as work done on heavy machinery. Then, pedometer wear time was determined for each day using the pedometer logs. A 'valid wear day' was defined as a day on which the pedometer was worn for at least 8 hours. For the analyses, steps/day was calculated as the mean of the two pedometer logs, with a minimum of five valid wear days[7]. In this study, AA was treated as a continuous measure and a categorical measure, grouped into tertiles according to the distribution of the study population, in order to check for dose–response relationships or threshold effects; tertile 1 (≤6,266 steps/day); tertile 2 (6,267–9,051 steps/day); tertile 3 (≥9,052 steps/day).

Body composition measures

Weight of the participants was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using electronic scales (Heine, Dover, New Hampshire, USA). Height was measured to the nearest 0.1 cm (with shoes, socks and headwear removed) using a Leicester stadiometer (Invicta, Leicester, UK). *BMI* (kg/m^2) was calculated as weight/height^2. In addition to the continuous measure, BMI was analyzed in predefined categories; underweight/normal (<25 kg/m^2), overweight (≥25 to <30 kg/m^2) & obese (≥30 kg/m^2)[15]. As the number of participants in the underweight

BMI group was low (n = 4/1082), they were grouped with the normal BMI participants. *Waist circumference* of the participants was measured to the nearest 0.1 cm[16]. *Total fat mass, trunk fat mass* and *total lean mass* (g) was measured by a dual-energy X-ray absorptiometry (DXA) scanner (Hologic, Waltham, Massachusetts, USA) at baseline[16]. *Lean mass percentage* was calculated as a percentage of total body mass.

Other covariates

Knee and hip x-rays were performed at baseline in all participants and scored individually for osteophytes and joint space narrowing as previously described[17]. Presence or absence of radiographic osteoarthritis (ROA) was defined as a score of 0 or 1 respectively. Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline[18]. Hip pain was recorded as presence or absence by asking whether the participants had hip pain at baseline. At baseline, questions were asked about age, comorbidities, smoking habits, and history of knee surgery. History of knee injury was not assessed at baseline, but was asked at a 2.7-year follow-up: 'Have you had a previous knee injury requiring non-weight-bearing treatment for more than 24 hours or surgery?'. The socio-economic status of the participants were determined by the Socio-Economic Indexes for Areas (SEIFA) defined by Australian Bureau of Statistics. The indexes that were used as covariates include Index of Relative Socio-Economic Disadvantage, Index of Relative Socio-Economic Advantage/Disadvantage, Index of Economic Resources and Index of Education and Occupation.

Statistical analysis

Characteristics of the sample were described by AA tertiles as means and standard deviations or as percentages as appropriate. Differences in characteristics between AA tertiles were compared using ANOVA for continuous and chi squared test for categorical variables.

Log-binomial regression using a generalized estimating equation with log link and binomial family, was used to estimate the association between baseline measures of AA and body composition measures and risk of knee and hip JR. Correlation between observations on the same individual (right and left leg) were taken into account by adjusting standard errors using the sandwich (robust) estimator of variance[19] and an exchangeable correlation structure. Separate univariable and multivariable models were fitted for knee and hip replacement.

Multivariable models for KR were adjusted for age, sex, presence of knee ROA and WOMAC pain while models for HR were adjusted for age, sex, presence of hip ROA and hip pain. Additionally, AA models were adjusted for BMI while body composition models were adjusted for AA. Other potential confounders were considered including smoking, presence or absence of comorbidities, socio economic status and history of knee surgery or knee injury. These were excluded from the final models as they did not change the relative risk (RR) by at least 10%[20].

Possible effect modification of the association between AA and BMI/body composition with JR were explored using interaction terms with age and sex. In order to check if the associations between AA and JR were modified by BMI/body composition and if the associations between BMI/body composition and JR were modified by AA, interaction terms between AA and BMI/body composition were also examined. Using Baron and Kenny method[21], further analysis was done to test if there was evidence for mediation of the association between AA and JR by BMI.

Missing data were handled using multiple imputation by chained equations (MICE) based on 'missing at random' assumption. 229 participants had missing data (DXA measures n = 7; AA n = 48; JR n = 201 (due to leaving Australia n = 7, or being deceased n = 194, preventing them from having a JR if required)). Participants with missing data were older, with lower steps/day, socio-economic status, and higher waist circumference, WOMAC pain, and were more likely to be male (Supplementary table 01). In addition to the variables in the analysis models, alcohol use, smoking, knee surgery, knee injury, comorbidities and socio-economic status were included in the imputation model. A total of 50 imputed datasets were created and the results from the analysis of imputed datasets were combined to obtain a single estimate and are presented.

A priori analyses were performed to examine the nature of the relationship between AA and JR (e.g., whether the relationship was linear, quadratic, dose–response based on AA tertiles or whether threshold effects existed).

A p value less than 0.05 (two-tailed) was regarded as statistically significant. All statistical analyses were performed on Intercooled Stata V.12.1 for Mac (StataCorp LP, Texas, USA).

Results

The average follow-up period of the cohort was 13.3 years (SD 0.8; range 11.1, 14.6). There were 74/1082 participants (6.8%) who had a KR and 50/1066 participants (4.7%) who had a HR over the follow-up period.

Table I shows the characteristics of participants at baseline stratified by AA tertiles. Overall, the mean level of AA of the participants was 8,646.2 steps/day (±3,356.2) and mean BMI was 27.9 kg/m^2 (±4.7). The average total fat mass, trunk fat mass, lean mass % and waist circumference of the participants were 28.2 kg

Table I
Baseline characteristics of the participants

	Steps/day tertile 1 (n = 346)	Steps/day tertile 2 (n = 344)	Steps/day tertile 3 (n = 344)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	66.3 (7.8)	62.1 (6.8)	60.1 (6.2)
Sex (Female: %)	54	53	48
BMI (kg/m^2)	29.2 (5.4)	27.7 (4.6)	26.6 (3.6)
BMI categories			
Underweight/ Normal (%)	25	34	41
Overweight (%)	31	32	37
Obese (%)	47	34	19
Total fat mass (kg)	31.0 (9.3)	28.0 (8.7)	25.4 (7.0)
Trunk fat mass (kg)	14.3 (4.9)	12.5 (4.6)	11.2 (3.8)
Lean mass (%)	60.8 (7.5)	63.2 (7.8)	65.3 (7.4)
Waist circumference (cm)	97.6 (13.9)	93.0 (13.0)	90.9 (11.6)
Knee replacement (%)	9	8	8
Hip replacement (%)	7	6	4
Knee ROA (%)	66	62	59
WOMAC knee pain*	4.5 (6.8)	3.2 (5.3)	3.1 (5.9)
History of knee surgery (%)	12	12	13
History of knee injury (%)	10	12	14
Hip ROA (%)	38	38	38
Hip pain (%)	41	43	37

ANOVA & X^2 test (proportions) used. BMI – body mass index, ROA - radiographic osteoarthritis, WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index; *Range: 0–39.

(±8.7); 12.7 kg (±4.7); 63.0 (±7.8) and 94.0 cm (±13.1) respectively. In comparison to participants in AA tertile one, those in the second and third tertiles were younger, had lower BMI, total fat mass, trunk fat mass, waist circumference, WOMAC pain and higher lean mass %. Participants in tertile three were younger, had lower BMI, total fat mass, trunk fat mass, waist circumference and higher lean %, compared to participants in tertile two. Furthermore, prevalence of HRs and knee ROA were lower for tertile three, when compared to tertiles one and two.

Table II
Relative risk of knee replacement (KR) for ambulatory activity (AA) and body composition measures

Variable	Unadjusted ($n = 1082$)	*Adjusted model ($n = 1082$)
	RR (95% CI)	RR (95% CI)
Steps/day (In 1000s)	0.98 (0.92, 1.05)	**1.09 (1.01, 1.16)**
BMI (kg/m^2)	**1.08 (1.04, 1.12)**	**1.07 (1.03, 1.12)**
Total fat mass (kg)	**1.04 (1.02, 1.07)**	**1.03 (1.01, 1.06)**
Trunk fat mass (kg)	**1.07 (1.03, 1.12)**	**1.05 (1.00, 1.09)**
Lean mass (%)	**0.96 (0.93, 0.99)**	0.97 (0.93, 1.02)
Waist circumference (cm)	**1.03 (1.01, 1.05)**	**1.02 (1.00, 1.04)**

* Adjusted for age, sex, WOMAC pain, knee ROA. Steps/day model adjusted for BMI. BMI model adjusted for steps/day. Significant results shown in bold.

Risk of knee replacement

Table II shows the unadjusted and adjusted RRs of KR for AA and body composition measures as continuous variables. In the adjusted model, every 1000 steps/day increase at baseline was associated with a 9% greater risk of KR (RR 1.09/1000 steps/day, 95% CI 1.01, 1.16). In the categorical analysis, while the risk of KR increases with increasing step/day tertiles, this was not statistically significant ($p = 0.10$) [Fig. 2 (A)].

Greater BMI (continuous variable) was associated with an increased risk of KR (RR 1.07/kg/m^2, 95% CI 1.03, 1.12). Those with a BMI in the obese range had a 2-fold higher risk of KR (RR 2.05, 95% CI 1.16, 3.65) compared to underweight/normal participants [Fig. 2 (B)]. Higher baseline total fat mass (RR 1.03/kg, 95% CI 1.01, 1.06), trunk fat mass (RR 1.05/kg, 95% CI 1.00, 1.09), and waist circumference (RR 1.02/cm, 95% CI 1.00, 1.04) all significantly increased the risk of KR.

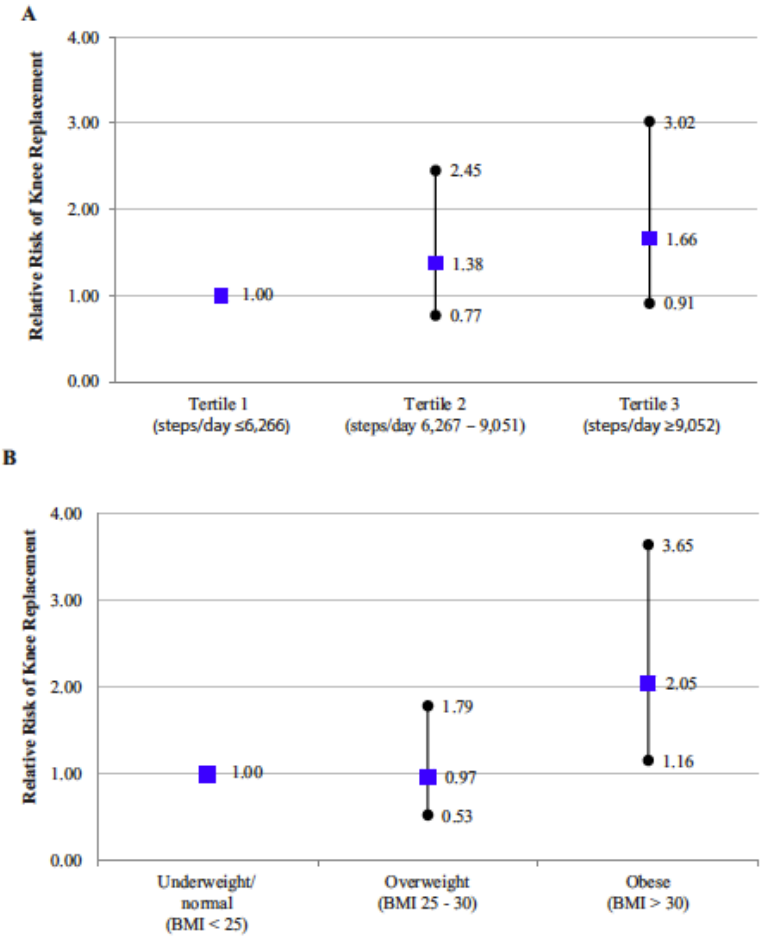

Fig. 2. A. Association between steps/day tertiles & knee replacements, B. Association between Body mass index (BMI) categories & knee replacements. All models adjusted for age, sex, WOMAC pain, knee radiographic osteoarthritis (ROA). Steps/day tertiles model adjusted for BMI. BMI categories model adjusted for steps/day.

Table III
Relative risk of hip replacement (HR) for ambulatory activity (AA) and body composition measures

Variable	Unadjusted ($n = 1066$)	*Adjusted model ($n = 1066$)
	RR (95% CI)	RR (95% CI)
Steps/day (ln 1000s)	**0.89 (0.81, 0.98)**	**0.90 (0.81, 0.99)**
BMI (kg/m^2)	0.99 (0.93, 1.05)	0.96 (0.90, 1.02)
Total fat mass (kg)	1.00 (0.97, 1.03)	0.98 (0.95, 1.01)
Trunk fat mass (kg)	0.99 (0.94, 1.05)	0.97 (0.91, 1.03)
Lean mass (%)	1.00 (0.96, 1.03)	1.03 (0.98, 1.08)
Waist circumference (cm)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)

* Adjusted for age, sex, hip pain, hip ROA. Steps/day model adjusted for BMI. BMI model adjusted for steps/day. Significant results shown in bold.

Risk of hip replacement

Table III shows the unadjusted and adjusted RRs of HR for AA and body composition measures. In the multivariable analyses, every 1000 steps/day increase at baseline was associated with a 10% reduced risk of HR (RR 0.90/1000 steps/day, 95% CI 0.81, 0.99). In the categorical analysis, while the risk of HR decreases with increasing steps/day tertiles, this was not statistically significant ($p = 0.25$) [Fig. 3 (A)].

BMI as a continuous (RR 0.96/kg/m^2, 95% CI 0.90, 1.02) or categorical measure (Overweight – RR 0.80, 95% CI 0.43, 1.49; Obese – RR 0.66, 95% CI 0.33, 1.35, vs underweight/normal) was not associated with HR [Table III, Fig. 3 (B)]. There was no evidence for a relationship between other body composition measures and risk of HR.

In the results presented above, there was no evidence for interaction by age and sex. The association between AA and JR was not modified by BMI/body composition. Similarly, the association between BMI/body composition and JR was not modified by AA. Furthermore, no statistical evidence was found for mediation of the association between AA and JR by BMI. Additionally, there was no evidence in the KR or HR models for confounding by smoking, education, current occupation, presence or absence of comorbidities, socio-economic status and history of knee injury or surgery or time to follow-up. Our analysis indicates that the relationship between AA, KR, and HR is linear. There was no statistical evidence for a quadratic, a dose-response relationship or threshold effect for AA and the risk of JR.

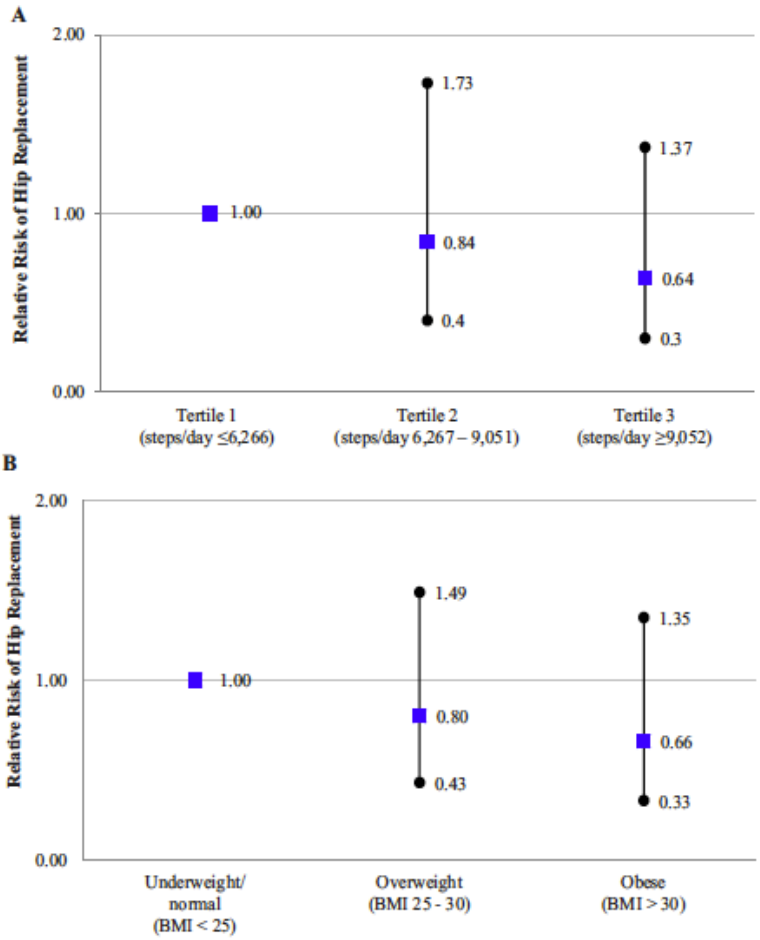

Fig. 3. A. Association between steps/day tertiles & hip replacements, B. Association between BMI categories & hip replacements. All models adjusted for age, sex, hip pain, hip ROA. Steps/day tertiles model adjusted for BMI. BMI categories model adjusted for steps/day.

Discussion

This longitudinal prospective cohort study describes the relationship between objectively measured AA, body composition measures at baseline and risk of JR over 13 years in older adults. Higher levels of AA were associated with a 9% increased risk of KR but a 10% reduced risk of HR due to OA. Higher BMI, total fat mass, trunk fat mass and waist circumference were also associated with an increased risk of KR.

Ambulatory activity and joint replacement

To our knowledge, this is the first study to evaluate the longitudinal association between objectively measured AA and the risk of KR and HR. We found that for every 1000 steps/day increase at baseline, the risk of KR increased by 9%. There was a non-significant trend for a dose–response association between steps/day tertiles and risk of KR. Previous studies examining PA and KR have shown inconsistent findings[9,22–24]. A prospective cohort study which used self-reported PA measures, reported that frequency of walking was not associated with the risk of KR, while higher frequency of total PA including both ambulatory and non-ambulatory activity, was associated with an increased risk of KR[9]. Interestingly, a recent systematic review examining running suggested that higher AA was associated with lower odds of KR. However, this study only evaluated case–control studies which used retrospective PA data[25]. Studies using MRI and X-ray measures have also shown mixed findings with detrimental effects[7,26], no effects[27,28] or beneficial effects[29,30] on structural pathology. We previously showed that doing greater than 10,000 steps/day was detrimental for MRI-assessed structural changes over 2.7 years, mostly in those with pre-existing structural abnormalities[7]. In contrast, another report showed that objectively measured AA was not associated with MRI-determined structural changes in knee over 10 years[27].

Our analyses demonstrated that every 1000 steps/day increase at baseline resulted in a 10% reduced risk of HR. This is consistent with previous studies reporting that self-reported AA significantly reduced the risk of HR[8] and that leisure-time PA was protective against HR in women[23]. In addition, a recent cross-sectional study using our same cohort showed that higher levels of AA was associated with a lower prevalence of hip cartilage damage measured by MRI[31]. In contrast, a few earlier reports suggested that PA was associated with an increased risk of HR[22,32,33] or no association with HR[9,34].

As outlined above, there is heterogeneity of effects between AA and JR which may be due to a number of factors including: 1) heterogeneity of tools used to measure PA[9,22–24,34]; 2) use of self-reported surveys to measure PA[8,22,23] which is less reliable because of over-reporting and moderate reproducibility[35]; 3) diversity of study designs including case–control[24] and prospective[9,22,23] studies with varying follow-up times; 4) different study populations (e.g.,: differences in age, gender, disease severity)[8,9,22–24,32,33].

Interestingly, our analysis showed that the association between AA and JR was different for the knee and hip joints. This could be due to different morphological characteristics of the joints[9]. Studies have shown that biomechanical factors such as knee alignment[36,37] and knee adduction moment[38] are associated with incident and progressive knee OA. Therefore, one possibility is that the deleterious effect of AA on the risk of KR may be mediated or modified by these factors[35]. We did not have measures of joint alignment in our cohort to examine this in the current study. Moreover, reduced muscle strength is suggested to be a risk factor for OA progression[39]. Hip muscle strength declines at a greater rate than knee muscle strength with increasing age[40] and this difference may affect the relationships seen between AA and JR in knee and hip.

Body composition measures and joint replacement

Our results show that body composition measures have differential effects on knee and hip joints. We found that higher BMI was associated with increased risk of KR over 13 years, which corresponds with previous longitudinal studies[1,10,11,41]. Furthermore, obese participants had a two times higher risk of KR compared to underweight and normal participants. This suggests that the effect of high BMI in this cohort is more pronounced in the obese category. This is in line with a population based study which found that overweight and obese participants had a 40–100% greater risk of KR in comparison to those with normal BMI over 2.6 years[10]. We have also demonstrated that sensitive measures of body fat, including total fat mass and trunk fat mass, are associated with an increased risk of KR. Earlier studies published by Wang *et al.*, 2009, and Lohmander *et al.*, 2009, found similar associations[13,42]. Higher body mass may increase joint loading and biomechanical aspects that leads to severe OA requiring KR[11]. In addition, the detrimental associations between proxy measures of central adiposity (trunk fat mass and waist circumference) also suggest that there may be inflammatory and metabolic mechanisms[13,16], as there is increasing evidence to suggest that adipokines and cytokines released by adipose tissue are associated with disease progression in OA[43].

In the current analysis, BMI was not associated with an increased risk of HR, which is contradictory to previous longitudinal reports showing overweight participants have a higher risk of HR[44,45]. Yet, a case–control study found that higher BMI was weakly associated with higher odds of HR only for men, but the effect was negligible for women[46]. Similarly, there was no relationship between any body composition measures and the risk of HR in this cohort. This again contrasts the findings of two earlier studies which found that fat mass predicted HR[1,13]. These variations in findings on the relationship between body composition measures and HR in our study and with previous studies could be due to the differences in the age and anthropometrics of the study sample, or the relatively small number of HRs in this cohort. We observed that there was a discrepancy in the association between body composition measures and knee and hip JR. The knee and hip joints may have different capacity with regard to enduring different levels of mechanical loading exerted by body mass, owing to the variations in morphology, underlying anatomical structures[42] and alignment[47]. Furthermore, metabolic factors released by adipose tissue may affect joints differently[42,48]. However, further studies can be recommended to define this dissimilarity.

Strengths and limitations

The strengths of our study include the prospective design, utilising objectively measured AA which comprises both habitual and leisure-time AA and using National Joint Replacement Registry verified outcome data on JR. However, there are a few limitations to the study. First, in the current analysis, temporal changes in AA were not considered. We also did not have information on the intensity or nature of the activity (e.g., kneeling, climbing, squatting, running, twisting, manual labour and workload). The biomechanical aspects of different types of activities including the effects of joint loading is likely to have different effects on the risk of JR[49]. Therefore, our study results may not be generalizable to broader types of PA. Second, we considered JR as a surrogate measure of severe 'end-stage' OA. We acknowledge that there are limitations in using JR as an outcome

measure when assessing potential causal pathways for OA, as undergoing JR due to OA depends on many factors including disease severity, physician bias, patient-specific and socioeconomic factors (e.g.,: access to health care)[50]. However, the publicly-funded universal health system (Medicare) in Australia ensures that all the people without private health insurance have access to JR facilities. Furthermore, there are many important facets to OA such as progression of symptoms and progression of joint damage. JR encompasses both of these, but they could also be considered separately in evaluating the relationship between AA, body composition and OA. Our results need to be interpreted considering these issues. Third, JRs were performed only on a small proportion of participants (KR was 6.8% and HR was 4.7%). Therefore, it is possible that our study was underpowered. Despite the low incidence of JR (particularly HRs), we were able to detect statistically significant associations between AA, body composition and JR. Studies with larger sample sizes are needed to confirm these findings. Fourth, our measure of knee injury was recorded at the 2.7-year follow-up instead of baseline. Further adjustment for history of knee surgery (assessed at baseline) and history of knee injury (assessed at 2.7 years) did not alter our study findings. Fifth, since an Omron pedometer was used, which displays steps/day completed, it is possible that the participants were influenced by the readings of the pedometer while they were wearing them.

To conclude, an objective measure of AA was associated with a small increased risk of KR and a small reduced risk of HR. Worse body composition profiles were associated with KR, but not HR. Altogether this may suggest different causal pathways for each site with regard to habitual activity and obesity.

Authors roles/contributors

IPM was responsible for data management and cleaning, carried out analysis and interpretation of data, prepared the initial manuscript draft and completed manuscript revisions. KW participated in analysis and interpretation of the data, and critically revised the manuscript. FC designed and carried out the study planning, participated in analysis and interpretation of the data, and critically revised the manuscript. SEG helped in data collection, participated in interpretation of the data, and critically revised the manuscript. ML participated in data collection, participated in interpretation of the data, and critically revised the manuscript.

GJ designed and carried out the study planning, participated in analysis and interpretation of the data, and critically revised the manuscript. MLC designed and carried out the study planning, participated in analysis and interpretation of the data, assisted with the initial manuscript draft, and critically revised the manuscript. DA designed and carried out the study planning, helped in data management, participated in analysis and interpretation of the data, assisted with the initial manuscript draft, and critically revised the manuscript. All authors have approved the final manuscript. IP Munugoda (Ishanka.Munugoda@utas.edu.au), ML Callisaya (michele.callisaya@utas.edu.au) and D Aitken (dawn.aitken@utas.edu.au) takes responsibility for the integrity of the work as a whole, from inception to finished article.

Conflict of interests

No conflicts of interest to declare.

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Provenance and peer review

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Patient consent

Obtained.

Ethics approval

Southern Tasmanian Health and Medical Human Research Ethics Committee.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.joca.2018.02.895.

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The effect of weight loss on the progression of meniscal extrusion and size in knee osteoarthritis: a post-hoc analysis of the Intensive Diet and Exercise for Arthritis (IDEA) trial

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SUMMARY

Objective: Weight loss has beneficial effects on clinical outcomes in knee osteoarthritis (OA), but the mechanism is still unclear. Since meniscus extrusion is associated with knee pain, this study assessed whether weight loss by diet and/or exercise is associated with less progression in meniscus extrusion measures over time.

Design: The Intensive Diet and Exercise for Arthritis trial (IDEA) was a prospective, single-blind, randomized-controlled trial including overweight and obese older adults with knee pain and radiographic OA. Participants were randomized to 18-month interventions: exercise only, diet only or diet + exercise. In a random subsample of 105 participants, MRIs were obtained at baseline and follow-up. The medial and lateral menisci were segmented and quantitative position and size measures were obtained, along with semiquantitative extrusion measures. Linear and log-binomial regression were used to examine the association between change in weight and change in meniscus measures. Between-group differences were analyzed using an analysis of covariance.

Results: Weight loss was associated with less progression over time of medial meniscus extrusion as measured by the maximum (β: −24.59 μm, 95%CI: −41.86, −7.33) and mean (β: −19.08 μm, 95% CI: −36.47, −1.70) extrusion distances. No relationships with weight loss were observed for lateral meniscus position, medial or lateral meniscus size or semiquantitative measures. Change in meniscus position and size did not differ significantly between groups.

Conclusions: Weight loss was associated with beneficial modifications of medial meniscus extrusion over 18 months. This may be one of the mechanisms by which weight loss translates into a clinical benefit.

Clinical trial registration: NCT00381290.

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Introduction

Obesity is a major modifiable risk factor for osteoarthritis (OA) that has been linked to increased risk of incidence and progression of the disease[1,2]. Previous reports suggest that weight loss has beneficial effects on clinical outcomes in patients with knee OA[3–5]. Yet, the effects of weight loss on joint structures have been unclear, with evidence suggesting either beneficial[6,7], or no effects[8]. Clinical improvement may be conveyed by endocrine/inflammatory[4,9] and mechanical pathways[10,11], however, the mechanism (or mechanisms) by which weight loss translates into clinical benefits has not been clearly elucidated.

The menisci are pivotal in distributing mechanical loads between the distal femoral and proximal tibial cartilage surfaces[12]. Meniscus pathology, such as meniscal lesions (tears) and extrusion have been reported to be associated with incidence[13,14] and progression[15,16] of knee OA and knee symptom status[16,17]. Modification of meniscus pathology may thus entail potential benefits on knee symptoms. While studies suggest that a higher body mass index (BMI) is related to meniscal lesions[16], findings on whether a higher BMI is related to meniscus extrusion are controversial[18,19]. Interestingly, a recent report showed that participants who lost weight had less progression of meniscal lesions compared to the participants with stable weight[20]. However, no interventional study has yet confirmed the effect of weight loss on the quantitative measures of meniscus extrusion.

The Intensive Diet and Exercise for Arthritis (IDEA) trial showed that weight loss achieved by a combination of diet and exercise significantly reduced knee OA symptoms and improved function, compared to an exercise only intervention[4]. A secondary analysis in a subpopulation of the IDEA trial did not identify differences in radiographic joint space width loss (JSW), cartilage thickness loss (by Magnetic Resonance Imaging (MRI)), bone marrow lesion scores, or synovitis/effusion scores between the three intervention groups[8]. Yet, whether weight loss is associated with beneficial effects on the meniscus, and whether this represents a potential mechanism by which weight loss translates into clinical improvement has not yet been studied.

The objective of the current study therefore, was to test the hypotheses that, in overweight and obese participants of the IDEA trial, (1) 18-month interventional weight loss is associated with less progression in quantitative measures of meniscus extrusion and size, and in semiquantitative meniscus scores, over time; and that, (2) a diet-induced weight loss program, with or without exercise, is more efficient in modifying meniscus extrusion and size than exercise alone.

Methods

Study design

IDEA trial was a single-blind, single-center, 18-month, randomized controlled trial. The trial was conducted from July 2006 to June 2011 at Wake Forest School of Medicine and Wake Forest University, Winston–Salem, NC, USA[4,21]. The study was approved by the Human Subjects Institutional Review Board of Wake Forest Health Sciences, and conducted in compliance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all the participants.

Study population

The study population consisted of 454 ambulatory, community-dwelling older adults, aged ≥55 years. The inclusion criteria were: (1) Kellgren–Lawrence grade (KLG) 2–3 (mild to moderate) radiographic tibiofemoral or tibiofemoral with patellofemoral OA of at least one knee; (2) pain on most days due to knee OA; (3) a BMI between 27 and 41 kg/m^2 and (4) a sedentary lifestyle (<30 min/week of formal exercise over the past 6 months). The participants were recruited over 37 months (November 2006 to December 2009) from the community[4,21].

Stratified-block randomization was used to assign all the eligible participants to one of the three intervention groups, stratified by BMI and sex: exercise-only (E), diet-only (D) and diet with exercise (D + E). A comprehensive description of the trial design, rationale, the exercise and diet interventions and primary outcomes has been provided elsewhere[4,21]. In brief: the exercise intervention, conducted for three sessions/week (each 1 h) over the 18-month period, comprised of aerobic walking (15 min), strength training (20 min), another aerobic phase (15 min) and a cool-down (10 min). The diet intervention was based on partial meal replacements with two meal replacement shakes per day (Lean Shake; General Nutrition Centers) and the third meal with recipes that were low in fat and high in vegetables and were 500–750 kcal.

Magnetic Resonance Imaging acquisition

MRI of the most symptomatic knee was obtained in a random sub-sample of 105 participants at both baseline and 18-month follow-up. The sample sizes per group are as follows: E: $n = 36$; D: $n = 33$; D + E: $n = 36$. MRIs were obtained using a 1.5 T (SIGNA HDx, General Electric Medical Systems, Milwaukee, WI, USA) scanner with an extremity coil. The MRI sequences acquired included; (1) Double oblique coronal three-dimensional spoiled gradient-echo (SPGR) with fat suppression; (2) Axial T1-weighted spin-echo (SE); (3) Double oblique coronal T1-weighted SE; (4) Sagittal T1-weighted SE; (5) Sagittal T2-weighted fast spin-echo (FSE) with fat suppression; (6) Double oblique coronal T2-weighted FSE with fat suppression[8].

Quantitative meniscus position and size measures

The coronal SPGR sequence with fat suppression (1.5 mm slice thickness; interpolated in-plane resolution 0.31 mm × 0.3 mm) was utilised to quantitatively measure the meniscus in the central five slices (determined by the anatomical location)[22]. The images were first checked to ensure sufficient quality to support segmentation by an expert reader and seven MRIs were excluded due to poor image quality[8]. Further, eight medial and three lateral menisci needed to be excluded as they were severely macerated and could therefore not be analysed quantitatively, leaving 90 medial and 95 lateral menisci at each time-point for segmentation. Manual segmentation of the medial and lateral menisci was then performed using specialised software (Chondrometrics GmbH, Ainring, Germany)[23]. The tibial cartilage surface including the denuded areas of subchondral bone and the surfaces of the meniscus (tibial, femoral and external area) were segmented on the SPGR images; this was assisted by the concurrent display of the proton-density-weighted (PDw) spin-echo images that are commonly used for radiological evaluation of the menisci[24]. Baseline and follow-up images were segmented as pairs by one reader (IPM) with blinding to the intervention, acquisition order, and OA (KLG) status. All segmentations were quality controlled by an expert reader with >10 years of experience in quantitative joint tissue analysis; adjustments were done by consensus. Test-retest reliability of the readings was conducted on 10% of the participants ($n = 10$), 1 month apart. The intra-rater variability determined as root mean square standard deviation (RMS SD) and intraclass correlation (ICC) for maximum extrusion distance at baseline was RMS SD, 0.50, ICC, 0.98 (0.94, 1.00) and at follow-up was RMS SD, 0.65, ICC, 0.97 (0.89, 0.99). The RMS SD and ICC for mean extrusion distance at baseline was RMS

SD, 0.48, ICC, 0.99 (0.94, 1.00) and at follow-up was RMS SD, 0.58, ICC, 0.97 (0.90, 0.99). Performance of the quantitative data was in the excellent range for all the other measures (ICC range 0.92–0.99).

Following the segmentation, the measures of meniscus position and size[25] were calculated using the Chondrometrics software[23]. Meniscus position measures included maximum and mean extrusion distances (mm), area of the meniscus not covering (i.e., extruding) the tibial plateau (mm^2), tibial coverage (by the meniscus) (mm^2), and overlap distance between the meniscus and tibial plateau (mm). The size measures included meniscus width (mm) and height (mm).

Semiquantitative meniscus measures

Meniscus extrusion. An expert musculoskeletal radiologist (AG) read T2-weighted MRIs paired and unblinded to the acquisition order, using the BLOKS method[26]. Extrusions in medial and lateral menisci were graded in two sub-regions (medially or laterally and anteriorly) as grade 0, normal; grade 1, <2 mm; grade 2, 2–5 mm; grade 3, >5 mm, at both baseline and 18-month follow-up. In the statistical analysis, a maximum scoring approach which focuses on the maximum extrusion score for a meniscus was used. The intra-rater agreement measured using kappa statistic was excellent[27] for semiquantitative meniscus extrusion measurements[28]; medial meniscus extrusion – 0.82 (95% CI; 0.66, 0.98), and lateral meniscus extrusion – 0.89 (0.75, 1.00).

Meniscal tears. Meniscal tears in medial and lateral menisci were recorded considering three sub-regions (anterior, body and posterior) as absent or present (signal abnormality, horizontal tear, vertical tear, complex tear, posterior horn root tear and maceration) at both baseline and 18-month follow-up. The intra-rater agreement measured using kappa statistic was excellent[27] for semiquantitative meniscal tear measurements[28]; medial meniscus tears – 1.00 (95% CI; 1.00, 1.00), and lateral meniscus tears – 0.91 (0.77, 1.00).

Radiographic OA (KLG status). Bilateral, posteroanterior, weight-bearing, semi-flexed, knee X-rays were obtained at baseline[8,29]. The status of tibiofemoral radiographic OA was determined using the KLG (grades 0–4; 0 – normal, 1 – doubtful, 2 – mild, 3 – moderate, 4 - severe) that utilizes information on the osteophytes, joint space narrowing, subchondral bone sclerosis and deformities of bone contours[30].

Mechanical alignment. A full-length, anteroposterior radiograph was obtained for each participant. With feet positioned 15 cm apart, the participant stood upright in such a way that both the tibial tubercles were faced directly forward and the weight equally distributed to both feet[29,31]. The mechanical alignment was then measured as the angle formed by the intersection of the lines connecting the centers of the femoral head and the intercondylar notch and the centers of the ankle talus and tibial spines[8]. The alignment was then defined as normal (alignment angle $\geq -2°$ & $\leq 2°$), varus (alignment angle $> 2°$) or valgus (alignment angle $< -2°$) as previously described[8].

Statistical analysis

Baseline characteristics of the sample were described as means and standard deviations or frequencies and percentages.

Linear regression was used to determine the association between absolute change in weight (in kg) and change in position and size parameters of both the medial and lateral menisci over 18 months. Separate univariable and multivariable models were fitted for medial and lateral menisci; in the multivariable models, adjustments were made for age, sex, baseline value of the respective parameter, baseline radiographic OA status (KLG status), baseline mechanical alignment (normal, varus or valgus) and presence/absence of meniscal tears.

Only a few participants had a change in semiquantitative scores of meniscus extrusion by at most one grade (medial meniscus - $n = 11$; lateral meniscus $n = 1$). Hence, log-binomial regression with log link and binomial family was used to assess the associations between absolute change in weight (in kg), and change in semiquantitative scores of meniscus extrusion of the medial and lateral menisci. The models for medial and lateral menisci were adjusted for age, sex and the baseline semiquantitative extrusion score.

Between-group comparisons of changes in meniscus position and size over time were evaluated using analysis of covariance (ANCOVA) with adjustments for age, baseline BMI and the respective meniscus parameter.

In order to assess whether the observed change in the quantitative measurements was larger than a minimal detectable significant change, the least significant criterion (LSC)[32] was calculated that takes into account the measurement error and the correlation between the measurements at both baseline and follow-up. Model assumptions for linear regression were tested in all the models. A *P*-value less than 0.05 (two-tailed) was regarded as statistically significant. In addition, adjustment for multiple comparisons was performed for the fully adjusted models based on the Benjamini-Hochberg method[33]. All statistical analyses were performed on Intercooled Stata V.15.1 for Mac (StataCorp LP, Texas, USA).

Results

Participant characteristics

Of the 105 participants who had MRIs in the IDEA trial, 98 were included in the quantitative analyses and 101 were included in the semiquantitative analyses in this study. The mean age was 65 years (SD ± 6.0), the mean BMI was 33.8 kg/m^2 (SD ± 3.8), and 73% were women at baseline (Table I). No baseline differences were observed for age, sex, weight/BMI, mechanical alignment, KLG and meniscus position and size parameters between the three intervention groups. Semiquantitative measures of extrusion showed that 89% of the participants had a medial meniscus extrusion and 9% had a lateral meniscus extrusion, and again, no differences were detected between the intervention groups at baseline. The mean weight change of the participants was −5.28 kg (SD ± 8.6). The participant characteristics at the 18-month follow up are shown in Supplementary Table 1.

Association of weight change with quantitative meniscus parameters across groups

In the medial meniscus, a 1 kg loss of body weight between baseline and 18-month follow-up was associated with a 24.59 μm (β: −24.59 μm, 95% CI: −41.86, −7.33) reduction of progression in maximum extrusion distance and a 19.08 μm (β: − 19.08 μm, 95% CI: −36.47, −1.70) reduction of progression in mean extrusion distance (Table II). Other position markers, such as the tibial meniscal surface area not covering the tibial plateau, and tibial coverage (by the meniscus), also showed trends towards beneficial effects with weight loss, but the relationship failed to reach statistical significance ($p = 0.13$ and 0.12, respectively). The mean overlap distance between the tibial plateau and meniscus, and size parameters (width and height) were not significantly associated with weight change. In the lateral meniscus, none of the changes in

position or size parameters over time was significantly associated with the weight change (Data not shown).

Association of weight change with semiquantitative meniscus extrusion parameters across groups

No significant association was observed between weight change and worsening of semiquantitative measures of extrusion of the medial or lateral meniscus (Table III).

Differences in the change in quantitative meniscus parameters between intervention groups

No significant between-group differences were observed for the meniscus position or size parameters in the medial (Table IV) or lateral meniscus (Data not shown), among the three intervention groups. However, there was a significant between-group difference for the weight change.

The minimal detectable significant change was smaller than the effects observed in the medial compartment (data not shown). The associations remained unchanged when adjustments for multiple comparisons were conducted. Additionally, model assumptions for linear regression were satisfied in all the models.

Discussion

This is the first study to investigate the associations of weight loss, achieved by diet and/or exercise interventions, on quantitative measures of meniscus extrusion and size in overweight or obese participants with knee pain and radiographic OA over time. We found that weight loss was associated with less progression in maximum and mean extrusion distances of the medial meniscus over 18 months; however, no between-group differences by intervention type were detected.

A limitation of this study was that the analysis was done only on a subsample of the larger IDEA cohort, due to the limited availability of the MRI[8]. Yet, this MRI subsample was randomly selected from the cohort and was shown to be representative of the characteristics of the participants of the main study[34]. Another limitation is that the meniscus extrusion was assessed on non-weight bearing knees and therefore, these results are only valid for meniscus extrusion in non-weight bearing position, as evidence suggest that the extrusion may vary with loading[35,36]. Yet, work by Frobell *et al.*, 2009[37] has shown that quantitative parameters of meniscus extrusion are highly correlated between weight-bearing and non-weight-bearing imaging. A strength of our study is that we assessed meniscal position and size on MRI[38] using state-of-the-art quantitative measurements and semiquantitative scoring systems.

In the medial meniscus, a significant association between weight loss and less progression for maximum and mean extrusion distances was observed over time. Weight loss reduces knee compressive forces[4]; therefore, one possible mechanism for this association is that the reduced compressive forces may have led to less progression of maximum and mean extrusion distances. Although we did not detect any significant associations between weight change and other position parameters, the observed trends

	Total sample ($n = 98$)		Exercise only ($n = 35$)		Diet only ($n = 30$)		Diet + Exercise ($n = 33$)	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	65.1	(6.0)	65.6	(6.0)	63.9	(6.0)	65.7	(6.1)
Sex (Female: n (%))	72	(73)	27	(77)	20	(67)	25	(76)
Weight (kg)	90.1	(13.2)	88.5	(12.3)	93.4	(14.7)	89.0	(12.7)
BMI (kg/m^2)	33.8	(3.8)	33.7	(3.7)	34.0	(4.1)	33.6	(3.8)
Mechanical alignment (degrees)	−0.21	(4.0)	−0.37	(4.0)	0.14	(4.0)	−0.37	(4.0)
Kellgren & Lawrence grade (% grade 2)	43		40		47		42	
Meniscus parameters (Medial) ($n = 90$)								
Max. extrusion distance (mm)	4.6	(2.3)	4.5	(2.3)	4.3	(2.2)	5.0	(2.6)
Mean extrusion distance (mm)	3.7	(2.3)	3.7	(2.3)	3.4	(2.2)	4.0	(2.5)
TA.Uncov (mm^2)	23.5	(11.5)	23.3	(11.7)	22.5	(10.5)	24.5	(12.4)
ACdAB.Cov (mm^2)	15.1	(14.5)	16.5	(16.2)	15.3	(11.6)	13.4	(15.4)
OvD (mm)	2.8	(1.9)	3.1	(2.1)	2.6	(1.5)	2.5	(2.0)
Width (mm)	6.0	(1.2)	6.1	(1.4)	5.9	(1.0)	6.1	(1.2)
Height (mm)	2.3	(0.4)	2.2	(0.4)	2.2	(0.4)	2.4	(0.3)
Meniscus parameters (Lateral) ($n = 95$)								
Max. extrusion distance (mm)	0.6	(1.3)	0.8	(1.6)	0.2	(1.1)	0.7	(1.1)
Mean extrusion distance (mm)	−0.6	(1.2)	−0.4	(1.5)	−0.9	(1.1)	−0.5	(1.1)
TA.Uncov (mm^2)	3.5	(6.3)	4.8	(8.2)	2.1	(4.4)	3.3	(5.1)
ACdAB.Cov (mm^2)	50.5	(11.9)	49.6	(11.8)	48.9	(11.5)	52.9	(12.2)
OvD (mm)	8.3	(2.1)	8.0	(2.0)	8.2	(1.9)	8.6	(2.3)
Width (mm)	8.5	(1.6)	8.5	(1.6)	8.1	(1.5)	8.9	(1.7)
Height (mm)	2.5	(0.4)	2.6	(0.5)	2.5	(0.3)	2.5	(0.3)
Semiquantitative medial meniscus extrusion (%)	89		85		93		91	
Semiquantitative lateral meniscus extrusion (%)	9		12		3		12	
Presence of medial meniscal tears (%)	65		66		63		67	
Presence of medial lateral tears (%)	14		11		20		12	

BMI – body mass index, TA.Uncov – the area of the meniscus not covering (i.e., extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.

Table I Baseline characteristics of the three intervention groups

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	Model 1 -Unadjusted ($n = 90$)	Model 2 - Adjusted* ($n = 90$)	Model 3 - Adjusted† ($n = 88$)
	β-coef (95% CI)	β-coef (95% CI)	β-coef (95% CI)
Position parameters			
Maximum extrusion distance (μm)	**−24.27 (-41.21, -7.33)**	**−25.61 (-42.70, -8.51)**	**−24.59 (-41.86, -7.33)**
Mean extrusion distance (μm)	**−18.68 (-35.72, -1.64)**	**−20.24 (-37.43, -3.05)**	**−19.08 (-36.47, -1.70)**
TA.Uncov (mm^2)	−0.08 (−0.17, 0.02)	−0.08 (−0.18, 0.01)	−0.07 (−0.16, 0.02)
ACdAB.Cov (mm^2)	0.07 (−0.04, 0.17)	0.09 (−0.01, 0.20)	0.08 (−0.01, 0.20)
OvD. (μm)	2.75 (−13.86, 19.35)	6.62 (−10.38, 23.62)	5.12 (−11.92, 22.16)
Size parameters			
Width (μm)	0.88 (−10.53, 12.29)	4.06 (−7.91, 16.04)	2.40 (−9.77, 14.57)
Height (μm)	2.01 (−1.72, 5.74)	2.80 (−0.86, 6.50)	2.83 (−0.96, 6.62)

β-coefficient represents the effect per 1 kg loss of body weight. TA.Uncov – the area of the meniscus not covering (i.e., extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau. Linear regression.

* Adjusted for baseline age, sex and baseline values of the outcome.

† Further adjusted for radiographic OA status, baseline mechanical alignment and presence/absence of meniscal tears ($n = 88$). Statistically significant results shown in bold.

Table II Association between change in weight and change in measures of position and size in the medial meniscus

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for these parameters suggest that weight loss was favorable. These trends may further indicate that less extrusion may translate to increased mechanical protection[39], with improved load distribution over a larger area on the tibial plateau[40] and reduced knee joint contact stress[12,41,42].

There were no significant associations between weight loss and the parameters of the lateral meniscus. This finding is not totally unexpected, as biomechanical studies have shown that a lower amount of compressive forces are transferred through the lateral compartment compared to the medial compartment[43], even in the knees with normal alignment[44], and the effects of higher BMI were observed mostly on the medial compartment rather than on the lateral compartment[45].

We did not detect a significant association between weight loss and change in semiquantitative scores of meniscus extrusion. Similarly, a recent report based on the PROOF study, evaluating the association of weight change subgroups (loss and gain) compared to a stable weight subgroup over 2.5 years in overweight and obese females without OA, did not find a relationship between weight change subgroups and meniscal extrusion using a semiquantitative scoring system[46]. Since we found associations between quantitative measures of extrusion, the lack of association with semiquantitative measures could be due to its attenuated sensitivity to change, as larger changes are required to detect a change in semiquantitative grades[47]. Additionally, a change in semiquantitative scores of meniscus extrusion by at most one grade was only seen in a very few participants in this study and this may also suggest that a larger sample is needed to detect frequent changes in semiquantitative scores.

The IDEA trial confirmed that weight loss in the diet + exercise group significantly improved pain and reduced knee compressive forces, compared to the exercise-only group[4]. However, Hunter *et al.*, 2015, found no significant between-group differences for radiographical and MRI outcomes in the knee which included quantitative cartilage morphometry, semiquantitative bone-marrow lesions and Hoffa-synovitis measures[8]. Similarly, we were unable to identify any significant between-group differences in quantitative meniscus position and size parameters, likely due to the relatively large variability of weight change within each intervention group, the lack of a no-intervention group and a potential limited statistical power in this subsample of IDEA cohort[8]. The PROOF study, conducted on overweight and obese women without clinical signs of OA, found beneficial effects on semiquantitative measures of meniscus extrusion in the diet + exercise group compared with a non-treated control group[48]. The control group in the PROOF study did not receive any active intervention, which may be a reason for the enhanced beneficial effects.

In the current study, a higher proportion of participants had medial meniscus extrusion at baseline (89%) than observed previously by Crema *et al.*, 2012 (44.2%), and Landsmeer *et al.*, 2018 (54%), whereas the prevalence of lateral meniscus extrusion was 9% at baseline which was approximately similar to the previous reports (Crema *et al.*, 2012 (9.4%), Landsmeer *et al.*, 2018 (6%))[19,46]. The high prevalence of medial meniscus extrusion in our study is potentially due to the demographics of our participants with prevalent ROA (KLG 2–3) and obesity.

The observed association between weight loss and maximum and mean extrusion distance of the medial meniscus was relatively small in magnitude. For example, as per the regression equation (Supplementary document), if an average participant in this study (i.e., bodyweight – 90.1 kg, baseline maximum extrusion distance of medial meniscus – 4.6 mm) lost 12.7 kg, no further progression of the maximum extrusion distance of medial meniscus may be seen. If a weight loss of >12.7 kg is achieved, this may lead to an actual decrease in maximum extrusion distance of medial meniscus. Additionally, the clinical significance of this association with regard to symptoms and the rate of structural progression is unclear. However, a previous study has shown that meniscus extrusion, when measured quantitatively, is associated with knee pain[17], potentially because the extruded meniscus may generate mechanical stress on the pain-sensitive structures such as external aspects of the meniscus as well as the joint capsule. Hence, it is plausible that the beneficial effects of weight loss on knee pain may be at least partly mediated by the less progression of medial meniscal extrusion. Additionally, the progression of meniscus extrusion is associated with incident radiographic knee OA[13] and increased risk of knee replacements[49]. Therefore, further studies are needed to confirm whether the clinical benefits of weight loss

Change/no change in meniscus extrusion	Model 1 – Unadjusted ($n = 101$)	Model 2 - Adjusted* ($n = 101$)	Model 3 - Adjusted† ($n = 101$)
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Medial meniscus extrusion 11/101	0.98 (0.92, 1.05)	0.99 (0.92, 1.05)	0.98 (0.92, 1.05)
Lateral meniscus extrusion 1/101	0.95 (0.76, 1.18)	0.95 (0.77, 1.18)	0.96 (0.74, 1.25)

RR represents the effect per 1 kg loss of body weight.
* Model 2 - For medial meniscus - adjusted for baseline age and sex, for lateral meniscus - adjusted for baseline age.
† Model 3 - Further adjusted for baseline values of the outcome.

Table III Association between change in weight and change in measures of position in menisci using semi-quantitative measures

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	Intervention Group			*P*-value for between-group difference
	E (95% CI) ($n = 32$)	D (95% CI) ($n = 28$)	D + E (95% CI) ($n = 30$)	
Position parameters				
Maximum Extrusion Distance (mm)*	0.14 (−0.11, 0.40)	0.34 (0.06, 0.61)	0.04 (−0.22, 0.31)	0.197
Mean Extrusion Distance (mm)*	0.04 (−0.21, 0.30)	0.30 (0.03, 0.57)	0.05 (−0.21, 0.31)	0.164
TA.Uncov (mm^2)*	0.12 (−1.21, 1.46)	1.26 (−0.17, 2.69)	0.55 (−0.83, 1.92)	0.074
ACdAB.Cov (mm^2)*	0.58 (−0.95, 2.11)	−1.77 (−3.41, −0.13)	−0.27 (−1.85, 1.31)	0.177
OvD (mm)*	0.10 (−0.14, 0.34)	−0.22 (−0.47, 0.04)	−0.14 (−0.38, 0.11)	0.143
Size parameters				
Width (mm)*	0.13 (−0.04, 0.30)	0.01 (−0.17, 0.19)	0.05 (−0.12, 0.22)	0.512
Height (mm)*	0.01 (−0.04, 0.07)	0.01 (−0.05, 0.07)	0.04 (−0.02, 0.09)	0.079
Weight change (kg)	**−1.39 (-4.28, 1.50)**	**−6.19 (-9.28, -3.09)**	**−9.37 (-12.36, -6.38)**	**0.001**

TA.Uncov – the area of the meniscus not covering (i.e., extruding) the tibial plateau; ACdAB.Cov - tibial coverage area (by the meniscus); OvD - mean overlap distance between the meniscus and tibial plateau.
* ANCOVA models adjusted for baseline value of the outcome, baseline BMI and sex. Boldface shows a statistically significant between-group difference ($p < 0.05$).

Table IV Change in extrusion and size parameters in the medial meniscus and weight change across three intervention groups

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are mediated through less progression of medial meniscal extrusion.

In conclusion, the current study found that weight loss was associated with less progression and an actual decrease in maximum and mean extrusion distances of the medial meniscus over 18 months in overweight or obese men and women with knee pain and radiographic knee OA. Given the relationship between quantitative measures of meniscus extrusion and knee symptoms shown previously, the current data may indicate that meniscus extrusion could be one of the mechanisms by which weight loss translates into a clinical benefit.

Author contributions

Study design: FE, WW and IPM. Acquisition of data: IPM, FE, WW and AG. Statistical analysis: IPM, FE, WW and DB. Interpretation of data, manuscript preparation and final approval of the manuscript: IPM, FE, WW, DB, DA, RL, GM, ML, JJC, AG, DJH, SPM. IP Munugoda (Ishanka.Munugoda@utas.edu.au), F Eckstein (felix.eckstein@pmu.ac.at) and W Wirth (wolfgang.wirth@pmu.ac.at) take the responsibility for the integrity of the work as a whole, from inception to the finished article.

Conflict of interest

FE is CEO of Chondrometrics GmbH, a company providing MR image analysis services to academic researchers and to the industry. He has provided consulting services to EMD Serono, Bioclinica/Synarc, Samumed, Servier, KolonTissuegene, Roche and Galapagos, has prepared educational sessions for Medtronic and has received research support from Pfizer, Eli Lilly, Merck Serono, Novartis, Stryker, Abbvie, Kolon, Synarc, Ampio, BICL, Orthotrophix, Kolon-Tissue Gene, Servier and Galapagos. WW has a part-time employment with Chondrometrics GmbH and is a co-owner of Chondrometrics GmbH. He has provided consulting services to Galapagos NV. DJH provides consulting advice for Pfizer, Merck Serono, TLCBio and Zynerba. AG is a consultant to Pfizer, Merck Serono, Galapagos, Roche, TissueGene and AstraZeneca. He is a shareholder of BICL, LLC

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Supplementary data

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