**Longitudinal Associations between Adiposity and Change in Knee Pain: Tasmanian Older Adult Cohort Study**

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# KEYWORDS

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# TRANSPARENCY DECLARATION

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**ABSTRACT**

## Objective

The aim of this study was to describe the longitudinal relationship between adiposity and change in knee pain.

## Methods

1099 participants aged 50 to 79 were randomly selected from the local community in Southern Tasmania, of which 767 were followed up on average 5.1 years later. Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at each time point. Consistent knee pain was defined as knee pain at all three time-points. Five pain subscales were grouped into weight-bearing pain and non-weight bearing pain according to the nature of pain. Body fat and lean mass were assessed using dual energy x-ray absorptiometry (DXA).

## Results

Baseline body mass index (BMI) and body fat mass were deleteriously associated with consistent knee pain over follow-up. BMI was consistently associated with increases in weight-bearing and non-weight-bearing pain. Fat mass was associated with an increase in non-weight-bearing pain. In mixed-model analyses, WOMAC total pain score was associated with BMI (beta=1.27) and body fat mass (beta=1.17).The association of lean mass was not significant after adjustment for fat mass. .

## Conclusion

BMI is the most consistent correlate of knee pain in older adults. Fat mass is associated with non-weight-bearing knee pain suggesting systemic mechanisms are involved. .

**INTRODUCTION**

Obesity is a well-established risk factor for knee osteoarthritis (OA) and the worldwide obesity epidemic is expected to increase the burden of knee OA[1]. Knee OA commonly presents with knee pain and knee pain is a major musculoskeletal complaint in the elderly[2], thus it is important to understand the precise role of obesity in knee pain.

There is limited understanding of the mechanism how obesity is associated with knee pain[3]. Knee pain may be caused by both mechanical-structural factors[3] and metabolic-inflammatory factors[4]. There are a number of cross-sectional studies[5,6] and longitudinal studies[7,8] showing that obesity, as defined by increased body mass index (BMI), is associated with knee pain. Unfortunately, the use of BMI alone does not provide adequate information about the metabolic environment that may contribute to the obesity-OA-pain association, because BMI does not discriminate the relative contribution of body fat mass and muscle mass. By using dual energy x-ray absorptiometry (DXA), the amount of fat mass was found to be greater in people with knee pain than in those without[9]. Assessment of body fat in addition to BMI may help to further elucidate the complex mechanisms in which excess adipose tissue may impact knee pain, though a cross-sectional study suggests that precise measurements of body composition and measures of fat distribution may offer no advantage over the more simple measures of BMI or weight in assessment of risk of radiographic knee OA[10]. There are no longitudinal studies that incorporate body composition assessment using DXA to characterise the association between obesity and knee pain.

We hypothesized that fat mass was associated with increased knee pain over time. Therefore, this study aims to describe the longitudinal association between adiposity assessed in a number of ways and change in knee pain over an average of 5.1 years in older community living subjects.

# SUBJECTS AND METHODS

## Study design, setting and participants

The Tasmanian Older Adult Cohort Study (TasOAC) is an ongoing, prospective, population-based study, which aims to identify the environmental, genetic, and biochemical factors associated with the development and progression of OA at multiple sites (hand, knee, hip, and spine). Men and women between aged between 50 and 79 years in 2002 were selected from the electoral roll in Southern Tasmania (population 229,000) using sex-stratified random sampling (response rate 57%). Participants were excluded if they were institutionalised or had contraindications to MRI. The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants. Baseline (phase 1) data were collected from 1099 participants between February 2002 and September 2004. Participants who did not have an MRI at phase 1 (n=105) were excluded from follow-up as the primary aim of TasOAC study was to investigate progression of osteoarthritis assessed by MRI. Follow-up data (phase 2 and phase 3) were available in 875 and 767 participants, on average 2.6 years (range 1.4-4.9) and 5.1 years (range 3.6-7.0), respectively.

## Knee pain

Knee pain was assessed on the right knee using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a self-administered questionnaire[11]. Five categories of pain (walking on flat surface, going up/down stairs, standing upright, in bed when at night, and sitting/lying,) were rated on a 10-point numeric scale from 0 (no pain) to 9 (most severe pain). The five pain subscores were grouped into weight-bearing pain (walking on flat surface, going up/down stairs and standing) and non-weight bearing pain (in bed when at night, and sitting/lying) according to the nature of pain[12]. A total pain score (0-45) was created by summing up all five pain items. Knee pain was defined as a WOMAC total pain score ≥ 1 and was assessed at baseline, phase 2 and 3. Change in WOMAC pain score was calculated by subtracting baseline value from follow-up value. Increasing knee pain was defined as a change in pain score of ≥ 1 according to baseline knee pain status. This outcome definition was used in our previously published paper in which the minimal clinically important difference (MCID) for WOMAC knee pain score was calculated to be 0.9 for the population[13]. Frequency of knee pain was calculated from the number of time points when WOMAC total pain score was ≥ 1. Three levels of frequency were defined as following: 1) consistent knee pain, presence of knee pain at all three time-points (phase 1, 2 and 3); 2) fluctuating knee pain, presence of knee pain in any one or two time-points; 3) no knee pain, WOMAC total pain score = 0 at all time-points.

## Anthropometry

Height was measured to the nearest 0.1 cm (with shoes, socks, and headgear removed) using a stadiometer. Weight was measured to the nearest 0.1 kg (with shoes, socks, and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707, Bradford, MA) that were calibrated using a known weight at the beginning of each clinic. Body mass index (BMI) was calculated as weight/height2 (kg/m2). Waist circumference measurement (cm) was taken at the level of the mid-point between the inferior margin of the last rib and the crest of the ilium in the mid-auxiliary plane. Hip circumference measurement (cm) was taken at the level of the greatest posterior protuberance of the buttocks and the symphysis pubis.

## Body composition

Fat mass was measured using a DXA scanner (Hologic Corp, Waltham, Massachusetts, USA). Percentages of total body fat mass and trunk fat mass were calculated as the ratio of total body or trunk fat mass or lean mass by total body or trunk mass (the sum of fat mass, lean mass and bone mass).

## Radiographic OA

Participants had x-ray examinations of the knees in the standing anteroposterior position at baseline. X-ray pictures were taken of right knees with 15° of fixed kneeflexion using purpose made goniometer to for flexion angle. Films werescored individually by two rheumatologists (with over 10 years’ clinical experience) for osteophytes and joint space narrowing (JSN) each on a scale of 0-3 (0=normal, 3=severe) according to the Osteoarthritis Research Society International atlas[14]. Inter-observer repeatability (weighted k) was 0.61 for osteophyte and 0.64 for JSN. Disagreement was solved by consensus after discussion. Radiographic OA was defined as the presence of either JSN/osteophytes or both[15].

## Data analysis

Unpaired student t-test or x2 tests were used for comparison of means as appropriate. Propensity score weighting method was utilized to address missing data in subjects who were lost to follow-up. A weighting score was obtained by the estimation of response propensity based on the baseline characteristics of the participant. The score was used as sample weights in subsequent statistical analyses. Partial correlation analyses were performed to measure the relationship between BMI and body composition after adjustment for age and sex. Standardization of the coefficients was carried out in order to compare the effects between different measures of obesity.

Statistical analyses were performed to evaluate the association of baseline BMI, waist circumference, waist/hip ratio, body fat mass and lean mass with frequency of knee pain and increase in WOMAC pain scores over follow-up period. Log multinomial regression was used to analyse the frequency of knee pain (consistent or fluctuating knee pain vs no knee pain) and log binomial regression was used to analyse the increase in WOMAC pain scores (increase vs no increase). Multivariable analyses were adjusted for age, sex, height (not for BMI) and radiographic OA. Sensitivity analyses were performed to examine if the results were the same using different cut-offs for the increase in knee pain (≥2, 3, 4 and 5).

To fully utilize the longitudinal data of multiple obesity measures and knee pain scores, a linear mixed-effect model with subjects as a random effect was employed to analyse the association between change in obesity indicators and change in WOMAC total pain score. The number of years between the baseline and the follow-up visit was used as a time variable. All statistical analyses were performed on Stata V.12.0 (Stata Corp., College Station, Texas, USA). Statistical significance was set as a p value ≤ 0.05 (two-tailed).

# RESULTS

## Descriptive analyses

A total of 767 participants (69.8%) had complete knee pain data. 49 of them did not have knee X-ray at baseline. Compared to those lost to follow-up, study participants were younger, less obese as assessed by BMI, had less body fat mass and more lean mass, and had lower WOMAC total pain scores at baseline. The prevalence of knee pain was comparable between the two groups (*Table S1*).

The partial correlations are 0.48 (p<0.01) and 0.65 (p<0.01) for BMI with total body fat percentage and trunk fat percentage, respectively. Over the average follow-up period of 5.1 years, the mean change in WOMAC total pain score was -0.5 (standard deviation 5.1, range -36 to 24). 175 subjects (23%) had increased pain score from baseline to follow-up. *Table 1* presents the comparison of baseline characteristics between study participants with and without any increase in knee pain score. Compared to those without increased knee pain, participants with increased knee pain score had higher BMI, weight, waist circumference, body fat percentage and trunk fat mass. There were no significant differences in age, sex and baseline pain score between the two groups.

## Association between baseline obesity measures and increasing knee pain

The relative risk of increase in knee pain (developing knee pain and having worsening knee pain) associated with adiposity is presented in *Table 2*. There were no significant interactions between sex and obesity measures on knee pain (data not shown), therefore data from females and males were combined for analyses. Except for waist-to-hip ratio, all baseline obesity indicators were significantly associated with increasing knee pain in both univariable and multivariable analyses with the association for total fat mass being marginally stronger than the other obesity indicators. Lean mass was associated with increase in pain, however, the association became non-significant after adjustment for fat mass (data not shown). The results were very similar if different cut-offs were used to defined an increase in knee pain.

*Figure 1* shows the association between different adiposity measures and increasing knee pain in each WOMAC subscale after adjustment for covariates. The relative risks for weight-bearing pains are present in *Figure 1a* and the relative risks for non-weight-bearing pains are present in *Figure 1b*. BMI was the strongest and most consistent predictor for increased pain scores in both weight-bearing and non-weight-bearing pain. The associations between body fat mass, trunk fat mass and increasing weight-bearing knee pain subscales were not statistically significant (*Figure 1a*), but surprisingly, was for non-weight-bearing knee pain subscales (*Figure 1b*). Waist-to-hip ratio was significantly associated with weight-bearing knee pain going up/down stairs and non-weight-bearing knee pain sitting.

## Association between baseline obesity measures and consistency of knee pain

*Figure 2* describes the association between obesity measures at baseline and consistency of knee pain in a multinomial logistic regression model. Participants who were pain free for the entire course of the study were used as the reference group. Higher BMI, heavier weight, larger waist circumference and more fat mass were associated with both consistent and fluctuating knee pain over follow-up. A larger waist-to-hip ratio was significantly associated with fluctuating knee pain but not with consistent knee pain. Among all adiposity measures, total fat mass percentage was the strongest predictor for both consistent and fluctuating knee pain.

## Mixed modelling for longitudinal association between obesity measures and knee pain

The results of the analyses are presented in *Table 3*. In order to compare the strength of associations across different obesity measures, standardized coefficients were calculated. All fat measures were significantly and positively associated with WOMAC total pain score. After adjustment for common covariates, one standard deviation increase in BMI was associated with 1.27 (p<0.01) unit increase in WOMAC total pain score. Similarly, one standard deviation increase in total body fat resulted in 1.17 (p<0.01) higher in WOMAC total pain score. The results remained largely unchanged when radiographic OA was not included in the statistical models as an adjusting covariate (data not shown).

# DISCUSSION

Our study adds to previous cross-sectional studies by examining the longitudinal association between adiposity measures and change in knee pain over an average of 5.1 years. Our results suggest that adiposity measures at baseline are significant predictors of consistent and increasing knee pain over time. In addition, the change in adiposity measures corresponds to the change in WOMAC total pain score in time series analyses. Obesity measures, including BMI, waist circumference, waist-to-hip ratio, and percentage body fat, are deleteriously associated with knee pain in older adults. This study also suggests that body fat mass is more consistently associated with non-weight-bearing than weight-bearing knee pain, suggesting metabolic and inflammatory mechanisms may underlie knee pain.

Obesity-specific mechanisms associated with knee pain include mechanical stress, systemic inflammation and relative loss of muscle mass and strength[16]. As reported in a systematic review[17], being overweight and obese is associated with incident OA and this may be a result of increased loading, which affects the knee joint structure and biomechanical properties of the joint. Apart from mechanical causes, increased adipose tissues may exert a pro-inflammatory and metabolically active effect, by producing cytokines and adipokines, such as interleukin (IL)-6, tumour necrosis factor (TNF)-α, and leptin[18]. Our previous studies have shown that the serum levels of these cytokines and adipokines are independently associated with cartilage loss and may play an important role in the diseases process of OA[13,15,19]. Adiposity might also have a role in the perception of pain. Pro-inflammatory cytokines IL-6 and TNF-α secreted by adipose tissue can act as pain modulators to induce production of histamine and substance P[20], which contribute to the more musculoskeletal complaints seen in obese people[21]. Epidemiologic data have shown that the levels of TNF-α, IL-6 and high sensitivity C-reactive protein (CRP) are associated with increased knee pain[13]. Although previous research has not examined adipose tissue in relation to knee pain, a number of studies have reported that increased fat mass and central obesity are associated with the severity of pain from other body regions[22,23]. The results of current study support the hypothesis that obesity, reflected by increased BMI and body fat mass, is associated with knee pain through multiple mechanisms. BMI, as an obesity measure, may reflect both metabolic effects of adiposity and increased loading on the knee joint. Indeed, BMI was highly correlated with total body fat and trunk fat, and was consistently associated with total knee pain, weight-bearing and non-weight-bearing knee pain, suggesting both mechanic and metabolic mechanisms are involved in the pathogenesis. Compared to BMI, the results for body fat mass percentage and non-weight-bearing pain suggest a potential systemic effect.

Our results showed that one standard deviation (4.6kg/m2) increase in BMI at baseline would result in 34% more risk or one standard deviation (8.7kg) increase in total body fat mass at baseline would result in 36% more risk of having an increase in knee pain over average 5.1 years. Although these differences over 1 year would be modest, the clinical significance is high at a population level given the high prevalence of overweight. Although males and females are known to differ their adiposity deposition, we did not find significant interactions between adiposity measures and gender. This suggests that the effects of adiposity on pain could be the same in both genders. In general, females have more fat mass than males and adiposity may account for the higher prevalence of knee pain in women[1].

The major limitation of our study is potential selection bias resulting from loss to follow-up. The retention rate after follow-up was 69.7%. Those who remained in the study were younger (61.6 versus 64.7 years) and less obese (26% versus 32%) than those lost to follow-up. However, sensitivity analyses using inverse propensity weighting did not significantly differ from the results of the original analyses. Thus our results are generalizable to this population. In addition, such bias may have underestimated our findings given that age and obesity are associated with increased risk of knee pain.

Although the present study has identified significant associations between adiposity and knee pain, the exact underlying mechanisms for the relationship between adiposity and knee pain are beyond the scope of this study. More studies are needed to explore the causal pathways between obesity and knee pain in the future.

# CONCLUSIONS

BMI is the most consistent correlate of knee pain in older adults suggesting simple measures may provide the most information. Fat mass is only associated with non-weight-bearing knee pain suggesting mechanisms other than mechanical load are important.

# CONFLICT OF INTEREST

All authors have completed the Unified Competing Interest form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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# AUTHORS CONTRIBUTIONS

GJ designed and obtained funding for the original TasOAC study. Analyses were designed by XJ, CD and GJ. Analyses were conducted by XJ and XW with advice from CD, LB and LL. XJ, CD, BA and LB contributed to data interpretation. XJ and CD drafted the article. All authors critically revised it for important intellectual content, and approve the final version the article.

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**Figure 1.**

Association between baseline adiposity and increase in both weight-bearing and non-weight bearing knee pain.

BMI, body mass index; W/H ratio, waist-to-hip ratio; RR, relative risk; SD, standard deviation.

**Figure 2.**

Association between baseline obesity measures, body composition and consistency of knee pain (compared to no pain).

BMI, body mass index; WC, waist circumference; W/H ratio, waist-to-hip ratio; RR, relative risk; SD, standard deviation.