**Effects of body weight and fat mass on back pain – direct mechanical or indirect through inflammatory and metabolic parameters?**

Romain S Perera a,b; Lingxiao Chen c; Deborah J Hart d; Tim D Spector d; Nigel K Arden e,f; Manuela L Ferreira c; Maja R Radojčićb,e,\*

*a Department of Allied Health Sciences, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka*

*b Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom*

*c Institute of Bone and Joint Research, The Kolling Institute, Faculty of Medicine and Health, University of Sydney, Sydney, Australia*

*d Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom*

*e Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis, University of Oxford, Oxford, United Kingdom*

*f MRC Environmental Epidemiology Unit, University of Southampton, Southampton, United Kingdom*

\*Correspondence: Dr Maja R Radojčić – Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, The Botnar Research Centre, Windmill Road, OX3 7LD, Oxford, United Kingdom; Email: maja.radojcic@ndorms.ox.ac.uk.

**Abstract**

**Background** While reports indicate the association between obesity and back pain, its mechanism is still unclear. Thus, we aimed to investigate the effects of weight and its components on back pain in middle-aged women while considering direct mechanical and indirect effects via inflammatory and metabolic parameters.

**Methods** We used data from the Chingford 1000 Women Study, two follow-ups seven years apart. We assessed effects of weight, body mass index (BMI), total fat mass (TFM), total lean mass (TLM) and total bone mineral density (TBMD), measured by dual-energy X-ray absorptiometry, on back pain episode. We used inflammatory (C-reactive protein, interleukin-6, and tumour necrosis factor-alpha) and metabolic parameters (systolic and diastolic blood pressure, triglyceride, high-density lipoprotein cholesterol, and fasting blood glucose) as mediators of indirect effects. We investigated associations of interest cross-sectionally and longitudinally using binary logistic regression and parallel mediation model.

**Results** We included826 Chingford middle-aged women (mean age=60.7, SD=5.9) from the first used follow-up in cross-sectional and mediation analyses and 645 women that attended the follow-up seven years later, in longitudinal analyses. We found that increased weight was directly associated with increased odds of having back pain episode (OR=1.02; 95% CI 1.01-1.03), similarly as BMI (OR=1.05; 95% CI 1.02-1.08) and TFM (OR=1.03; 95% CI 1.01-1.04) consistently across the cross-sectional and longitudinal models, but not TLM or TBMD. However, we did not find consistent indirect effects of weight or its components through measured inflammatory or metabolic parameters on back pain.

**Conclusions** Our results show that in middle-aged women, weight, BMI and TFM are directly related to back pain, indicating prominence of mechanical loading effect.

*Keywords:* body weight, body mass index, body fat mass, back pain, mediation analysis.

**1. Introduction**

Back pain is the leading cause of disability worldwide and dominant musculoskeletal problem in general practitioner consultations1 2. It is prevalent in all age groups, with its maximum between the age of 40 and 69 years3. Women report back pain and seek care for it more often than men of all ages 3. Similarly, obesity has a comparable pattern of disability and prevalence4 5. Taken together, back pain and obesity have a colossal impact on health care systems worldwide due to direct costs and loss of productivity4 6.

There has been evidence about the association between obesity and back pain, but a little about its mechanism7 8. While obesity assumes increased body weight commonly assessed via body mass index (BMI), it is the amount of adipose/fat tissue that defines it. The primary assumption is that the effects of body weight and fat mass are mechanical, i.e., excessive or cumulative loading damages the spine and surrounding structures or makes them more susceptible to damage by everyday activities9 10. The recent systematic evidence about these associations found that the effects of different body composition components on back pain, particularly in the long-term, are sparse11. Nevertheless, obesity has been associated with pain in non-weight bearing joints such as hand12; thus, excessive mechanical loading may not be the only mechanism behind this association. Two studies found that BMI was directly and indirectly via hormone leptin associated with hand and knee osteoarthritis13 14. The adipose tissue has essential metabolic functions with significant effects on the cardiovascular system and the release of pro-inflammatory mediators15. Thus, another assumption can be that atherosclerotic changes in regional blood vessels can lead to ischemia. The ischemia reduces tissue healing properties and creates necrolytic cells that can initiate inflammation. Additionally, adipocytes synthesise pro-inflammatory mediators, further contributing to the maintenance of inflammation. However, whether atherosclerotic changes or low-grade inflammation contribute to back pain, i.e. whether body weight is indirectly related to back pain via inflammatory and metabolic parameters, is still unclear16.

Therefore, we hypothesised that the overall effect of body weight on back pain included direct loading effect and indirect effects via inflammatory and metabolic parameters. Given the epidemiology of obesity and back pain, we used a population-based study of middle-aged women. We used absolute measures - body weight, fat mass and lean mass, to assess direct loading effects and relative measures – BMI and bone mineral density due to their wide use. We investigated metabolic syndrome components as metabolic parameters and selected the most reported inflammatory parameters in back pain17 18. We aimed to examine the relationship between body composition components and back pain episode, cross-sectionally and longitudinally. Also, to cross-sectionally explore whether inflammatory and metabolic parameters play a mediating role in these associations.

**2. Methods**

**2.1. Study sample**

This study was embedded in the Chingford 1000 women study, a prospective population-based cohort of middle-aged women designed to understand medical conditions in mid-life. It started in 1989 in Chingford (North East London, United Kingdom). All women aged 45-64 from the register of the large general practice were contacted, and 1003 women (78% response rate) participated at baseline19 20. Women were followed up for 22 years and subjected to different assessments21-23. Here, we included data from two assessments, years 8 and 15, when both whole-body dual-energy X-ray absorptiometry (DEXA) (exposure) and back pain (outcome) data were collected.

The cohort has been accepted as a representative sample of middle-aged women in the United Kingdom19 24. The Waltham Forest and Redbridge local research ethics committee has approved the study. All participants have given written informed consent for participation.

**2.2. Exposures**

Bodyweight was measured in kilograms using an electronic scale, and the height was measured in centimetres using a wall-mount stadiometer (Seca Leicester Height Measure, Birmingham, UK). The measures were taken in a standing position with indoor clothing barefoot to the nearest 0.1 kg and 0.1 cm19 22. Here, we reported body height in metres and calculated body mass index (BMI) using weight (kg) and height (m).

A single operator used a standardised protocol of Delphi DEXA scanner (Hologic Corp., Waltham, Massachusetts, United States) to assess the body composition parameters25. Phantom was used to assess the reliability of the densitometry during regular quality control assessment. Participants were in a supine position with arms held against the side of the body during the scan. Standard regional analyses assessed the total fat mass (TFM), total lean mass (TLM), limb lean mass (LLM) in kilograms (to the nearest 0.1 kg), and total bone mineral density (TBMD) and spine (thoracic and lumbar) bone mineral density (SBMD). TFM refers to the total amount of body fat in the head, arms, legs, trunk, and pelvic region. TLM is the total body amount of fat-free mass, i.e., muscle, skin, bone, body fluids and viscera, while LLM means fat-free mass in arms and legs.

Additionally, we calculated relative measures, total fat mass index (TFMI) and total lean mass index (TLMI) as TFM and TLM in kilograms divided by the squared height in meters, respectively. These relative measures were used only for descriptive purposes.

**2.3. Mediators**

Blood levels of inflammatory and metabolic parameters were measured at follow-up year 8 and used for cross-sectional mediation analysis. Blood samples were obtained from the participants by venepuncture following overnight fasting, and serum levels of inflammatory biomarkers – high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNFα) were assessed. We used a high-sensitivity nephelometry for hsCRP (Beckman Instruments, Fullerton, California), an ultrasensitive enzyme-linked immunosorbent assay (ELISA) for IL-6 (BioSource, Nivelles, Belgium), and a high sensitivity ELISA with an alkaline phosphatase signal amplification for TNFα quantification (R&D Systems, Minneapolis, Minnesota). All measurements were carried out per the manufacturers' instructions26.

Metabolic parameters included here were systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL) and fasting blood glucose (FBG). A research nurse measured SBP and DBP with a calibrated sphygmomanometer. TG, HDL and FBG were measured in fasting serum samples using previously described protocol27.

**2.4. Outcomes**

The primary outcome in this study was the presence of back pain episode in the last year. This binary outcome was self-reported in the questionnaire administered by a nurse and included upper or lower back pain of any duration.

The secondary outcome was self-reported duration of back pain episode – less or equal to 14 days or more than 14 days in the past year. With this outcome, we aimed to provide additional information due to the possible difference in a relationship given the duration of the back pain episode as an indicator toward chronicity. It was available only in the follow-up year 8.

***2.5.* Covariates**

We included self-reported age, and current binary smoking habits, menopause status, hormone replacement therapy (HRT) use, and medication use as confounding variables in our analyses. Physical activity was only assessed in year 15 and used as a confounding variable in year 15 sensitivity analyses. Menopause and HRT use were assumed as biologically important confounding in middle-aged women. Women were defined as menopaused if they did not have periods in the last two years. HRT use reflected the ongoing treatment at the assessment with oestrogens-only, combined hormones or tibolone. We utilised women’s self-reports about any used medication, over the counter or prescribed, to create variable current medication use. We also provided details on a few medication classes – non-steroid anti-inflammatory drugs, opioids, steroids, antihypertensive, antilipemic, antidiabetic and bisphosphonates in our samples. However, as a confounding variable in the analyses, we included any medication use. We did not aim to investigate medication effects, only to control the associations of interest for the proxy of comorbidities and direct attenuations by different medication classes. Women reported physical activity as a frequency of walking and sport per week and job-related activity. They were assumed active if reported at least three days per week walking, the same for light, moderate, strenuous sport or muscle-strengthening or job involving standing/walking, heavy housework, and gardening. We reported the percentage of women meeting criteria for each activity type and used binary overall physical activity as a confounding variable.22

**2.6. Statistical analysis**

Firstly, we provided descriptive statistics of our study samples. Secondly, we explored correlations between exposure and mediator variables using Spearman’s correlation. For our main analyses, we used binary logistic regression to investigate the association of body weight and its components with the presence of back pain episode (Model 1) and while controlling for the influence of confounding variables (Model 2) cross-sectionally and longitudinally. The cross-sectional models included all variables from the same assessment, either year 8 or year 15, while in longitudinal models, exposure and confounding variables were from year 8, and the outcome was from year 15. The models were built similarly and included the same confounding to ensure complementary inference. Further, we employed multinomial logistic regression to investigate the association of the same exposure variables with the duration of back pain episode when referenced to no back pain, in the same step-by-step manner. Finally, we used mediation analyses to complement the cross-sectional main analysis and assess whether the effects of weight and its components on back pain episode were direct, i.e., loading, or there were also indirect effects via inflammatory and metabolic parameters28-33. We used a parallel mediation model that allows the inclusion of up to ten mediators in the model while controlling for confounding34-36. Mediation is based on quantifying the indirect effect as a product of effects of the exposure to mediator and mediator to the outcome, not on hypotheses testing34 37. Figure 1 shows the conceptualisation of the statistical model. Ordinary least squares regression models with a binary outcome38 39 and continuous exposures and mediators were used to produce direct and indirect effect estimates with 95% percentile bootstrap confidence intervals based on 5000 bootstrap iterations36 40. The effect is significant if its 95% CI does not include zero.

*[Insert Figure 1]*

**Figure 1** Schematic presentation of the mediation analysis models. a1-8 shows effects of the exposure on mediators; b1-8 presents effects of mediators to the outcome; a1-8 x b1-8 indicates indirect effects of exposures on the outcome via mediators; c – shows direct effects of exposures to the outcome; BMI – body mass index; hsCRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6; TNFα – tumour necrosis factor-alpha; HDL cholesterol – high-density lipoprotein cholesterol.

We also performed sensitivity analyses. We treated body height as a separate body constitution parameter to improve understanding of bodyweight and BMI findings as their link. We conducted the same cross-sectional and longitudinal analyses with height as the exposure. Given that physical activity can be an important confounding variable between body composition and back pain, and its assessment in year 15 only, we controlled for its influence in cross-sectional year 15 analyses (Model 2a). The inflammatory and metabolic parameters were not available for the whole sample, and the analyses with mediators were restricted to a subsample. To rule out selection bias in the subsample, we performed non-response analyses comparing available information between subsample and excluded women at year 8. Also, fewer women attended later follow-up. So, we did another non-response analysis to exclude bias due to loss to follow-up. We compared available information of subsample of women who attended both follow-ups with women who attended year 8 but not year 15. We used independent samples t-test for continuous and χ2-test for categorical variables. Furthermore, inflammatory and metabolic parameters often have skewed distribution with outlier values41. Given the population-based character of this study, outliers could indicate cases pathophysiologically related to the question of interest. However, these also could be measurement errors and introduce bias. To deal with it, we performed analyses with and without outliers. We interpreted findings as positive if they were consistent in both analyses.

To avoid the bias of complete cases, we accounted for missing information in covariates by using the fully conditional specification method of multiple imputations. We did not impute independent or dependant variables. For imputed covariates, we reported pooled estimates of 10 imputed datasets. These were used for main analyses. However, mediation analyses currently cannot deal with the multiple-imputed datasets, so these analyses were performed on complete cases.

We analysed data using IBM SPSS® Statistics 25.0 (IBM, Chicago, Illinois, United States) and macro PROCESS, model 436 42.

**3. Results**

**3.1. Study samples and descriptive statistics**

At the first follow-up used here (year 8), 844 women (84.1%) participated in the Chingford study. Of these, 18 (2.1%) did not attend the DEXA assessment or complete the back pain questionnaire. Thus, Main sample 1 included 826 women. Inflammatory and metabolic parameters were not measured in 379 (45.9%) women, and Subsample 1 comprised 447 women. The second follow-up of interest, year 15, attended 655 women (65.3%). Of these, 10 women (1.5%) did not have DEXA or back pain data. Therefore, Main sample 2 included 645 women (98.5%). Subsample 2 consisted of 621 women who attended both follow-ups; thus, were part of both main samples. Twenty-four women from the Main sample 2 missed year 8 but attended year 15 follow-up. Figure 2 shows the study flowchart. We used the main samples for the main cross-sectional analyses (in year 8 and year 15) and Subsample 2 for the main longitudinal analyses (prediction from year 8 to year 15), while Subsample 1 for cross-sectional mediation analyses (year 8). The percentage of missing values in covariates in Main sample 1 was: smoking 2.2%, HRT 2.5% and menopause 2.3%; and in Main sample 2: HRT 1.1%; these were imputed.

*[Insert Figure 2]*

**Figure 2** The study flowchart.

Descriptive statistics of the study samples are shown in Table 1. At the first follow-up, women were on average 61 years old, 16% of them were smoking, less than a third using HRT, and the great majority (81%) being menopaused. Further, 53% of them used some type of medication, with antihypertensive (24%) being the most common class. In the previous year, 39% experienced any back pain episode, and 10% an episode that lasted longer than two weeks. Average weight was 69kg and BMI 27 kg/m2.Seven years later, at the second follow-up, the percentage of women smoking and using HRT decreased to 7% and 6%, respectively. However, the percentage of women using any type of medication increased to 81%, with an overall increase in all medication classes, and antihypertensives the dominant class (36%). Further, 48% of women reported any episode of back pain. There were 174 (28%) women who reported back pain episodes on both follow-ups. Weight and body composition parameters were mainly the same as at the first follow-up.

*[Insert Table 1]*

Results of a non-response analysis comparing Subsample 1 and excluded women are in Appendix. We did not find any statistically significant results between the two groups. The second non-response analysis results, comparing Subsample 2 and women who attended year 8 but not year 15 follow-up, are in Appendix, too. Based on year 8 data, women lost to follow-up compared to those who attended both follow-ups were on average three years older, and consequently more often menopaused and used medications; but fewer used HRT. They reported smoking habits more often, too. Importantly, there was no difference between the two groups in back pain reports, body weight, BMI, or fat mass.

**3.2. Correlation analyses**

Spearman’s correlations are shown in Appendix. Weight and BMI were positively and strongly correlated with TFM (rs≥0.90, p<0.001). Weight was moderately correlated with TLM (rs=0.66, p<0.001) and weakly with TBMD (rs=0.27, p<0.001). Similar results were observed between BMI and TFM with TLM and TBMD with slightly weaker correlations. TLM and TBMD were moderately correlated (rs=0.38, p<0.001). We observed these results on both follow-ups with slight changes in the correlation coefficients. Further, inflammatory parameters, hsCRP and IL-6 were weakly to moderately correlated with weight, BMI and TFM but not with TLM or TBMD. These two mediators were moderately correlated with each other (rs=0.39, p<0.001), and both were weakly correlated with metabolic parameters. However, TNFα was only weakly correlated with IL-6 (rs=0.28, p = <0.001), TG (rs=0.15, p=0.002) and HDL (rs=-0.15, p=0.002), but none of the body composition variables. Finally, all metabolic parameters were weakly correlated with weight, BMI and TFM. TLM and LLM were weakly correlated with DBP, TG and HDL, while TBMD and SBMD were not correlated with any metabolic parameter. Correlations of metabolic parameters between each other were weak or non-significant, except moderate correlations between SBP and DBP (rs=0.73, p<0.001) and TG and HDL (rs=-0.53, p<0.001).

**3.3. Associations of body weight and its components with back pain**

We investigated associations of bodyweight and its components with back pain episode cross-sectionally and longitudinally (Table 2). We found that increased body weight (OR=1.02; 95% CI 1.01, 1.03), BMI (OR=1.05; 95% CI 1.01, 1.09) and TFM (OR=1.02; 95% CI 1.01, 1.04) were positively associated with increased odds of having back pain episode. The same magnitude of the effect was observed at both time points – cross-sectionally and longitudinally. We did not find any association between TLM, LLM, TBMD or SBMD with back pain episode.

Further, we examined the associations of weight and its components with the duration of the back pain episode. We found that increased body weight was associated with increased odds of back pain episode up to two weeks (OR=1.01; 95% CI 1.01, 1.03) and more with back pain episode longer than two weeks (OR=1.02; 95% CI 1.01, 1.04) when compared to no back pain. We found similar observations with TFM but not with other body composition parameters.

*[Insert Table 2]*

Finally, there was no association between body height and back pain episode cross-sectionally (adjusted OR=3.38; 95% CI 0.31, 37.23) or longitudinally (adjusted OR=1.29; 95% CI 0.09, 18.78). Physical activity did not attenuate any cross-sectional association between body composition and back pain in Main sample 2. The estimates from Model 2a were: body weight OR=1.02 (95% CI 1.01, 1.03); BMI OR=1.04 (95% CI 1.01, 1.08); TFM OR=1.03 (95% CI 1.01, 1.05); TLM OR=1.03 (95% CI 0.99, 1.06); LLM OR=1.04 (95% CI 0.98, 1.11); TBMD OR=1.60 (95% CI 0.38, 6.80); SBMD OR=3.04 (95% CI 0.90, 10.21); and height OR=1.01 (95% CI 0.07, 13.73).

**3.4. Mediation analyses**

We examined cross-sectionally whether the effects of weight and its components with the back pain episode were mediated via inflammatory and metabolic parameters (Table 3). We found the same associations showing direct effects of weight, BMI and TFM as in the main analyses described above. Additionally, in Subsample 1, we found direct effect of TLM (OR=1.06; 95% CI 1.01, 1.14), LLM (OR=1.16; 95% CI 1.02, 1.32) and TBMD (OR=23.57; 95% CI 1.42, 390.41) with back pain episode. We did not find any indirect effect of weight or its components via inflammatory parameters on back pain episode. However, we did observe some indirect effects mediated by metabolic parameters. We found that in addition to positive direct effects, weight, BMI, TFM, TLM and LLM showed positive indirect effects via TG to back pain episode. We observed a negative indirect effect mediated via FBG between weight, BMI, TFM and TLM with back pain episode. Nevertheless, in the sensitivity analyses without mediators’ outliers (Model 3), and after adjusting for the influence of confounding variables (Model 4), only direct effects remained.

*[Insert Table 3]*

**4. Discussion**

In this population-based study of women, we found that the overall effect of body weight on back pain episode included only a direct effect. We found that body weight, BMI and TFM were associated with back pain episode cross-sectionally and seven years later. However, we did not find that common inflammatory or metabolic parameters consistently mediated any indirect effects of body weight or its components on back pain episode.

While there are advantages of this study like a large population-representative sample, longitudinal character, reliable measures of body composition, assessment of indirect effects, inevitably, there are some limitations. Firstly, the study included only women. Although obesity and back pain have been reported more commonly in women, the question is equally important for men. We cannot make direct extrapolations to men due to differences in body constitution. However, in our recent report using another English population-based study, we showed that BMI effect on back pain was consistent in middle-aged and older, women and men43. Secondly, we investigated any duration upper or lower back pain episode, not chronic back pain; thus, findings might be different when processes become chronic. Thirdly, we studied the most commonly investigated inflammatory17 and metabolic parameters31 44 45. Yet, there might be other mediators that we did not investigate. The mediators limited our analyses to the subsample and cross-sectional analysis. However, we showed that the subsample was representative of the main sample. Further, in population-based settings, only a minority has pathological values. Here, distributions of inflammatory and metabolic parameters were skewed with outlier values. We performed sensitivity analyses without outliers and interpreted findings as positive only if consistent across the main and sensitivity analyses. Finally, we accounted for the influence of common confounding variables, but residual confounding cannot be excluded.

Bodyweight is directly related to back pain episodes, likely due to the mechanical loading of the spine. The direct effects we found in this study, we interpreted as the loading. We investigated absolute measures (amount) of body weight and fat mass and treated these as continuous, i.e., each kilogram increases the load linearly. These measures can be height- and obesity-related. However, the same weight produces the same load irrespective of other dimensions, as supported by the lack of height effect. In other words, while height per se does not increase the odds for having a back pain episode, absolute bodyweight, either height- or obesity-related, does increase it. It highlights that height-related weight should not be neglected, and more importantly, identifies women with a higher risk that prevention should be focused on. The weight puts a mechanical strain on the spinal discs, surrounding joints and skeletal muscles10 and increases the frequency of wear and tear due to repetitive stresses from daily activities and unsupported posture46. We found that each kilogram of weight and fat mass, and each BMI unit, increased the odds of back pain episode by 2, 2 and 5%, respectively. Systematised evidence of previous studies has shown similar effects of weight and BMI with back pain like ours7 8 47 48. The magnitude of the bodyweight effect should be interpreted keeping in mind the unit (kg), the range (number of units) of weight in women and the likelihood of unit increase. When this effect is expressed per 10kg, it means that woman’s chance of experiencing back pain increases by 20% per each 10kg weight gain. To illustrate the height- and obesity-related weight effects, in Figure 3, we provided examples of four women and comparisons of their chances to experience back pain episodes while keeping the height or BMI constant.

*[Insert Figure 3]*

**Figure 3** Illustration of the study findings with four women examples. (A) Four women of the same age, smoking habits, hormone replacement therapy use, menopause and medication use differ in height (short=1.60m and tall=1.85m) and body mass index (BMI) (fit=23kg/m2 and overweight=28kg/m2) as indicated by their initials – short fit (SF), tall fit (TF), short overweight (SO) and tall overweight (TO). Weight was calculated for each woman. (B) Comparison of the odds of back pain episode of fit women (weight due to height), fit vs overweight (weight due to obesity), and overweight women (weight due to height and obesity) based on estimates from Table 2 (for each unit increase of body weight the odds of back pain episode increases by 2%). Attribution for vector images to [www.vecteezy.com](http://www.vecteezy.com).

Importantly, we explored the duration of back pain episode as the indicator toward chronicity and found a small dose-response effect. Bodyweight, TFM and BMI were related to short-term pain and bodyweight with an increased effect size to the episode lasting more than two weeks. We did not have further evaluation to confirm chronic back pain, but the results indicate that body weight is associated with back pain irrespective of its duration. Even if all women reporting back pain “more than 15 days” had a chronic condition, the findings are the same as in women with acute back pain (less than 15 days). Further, if “more than 15 days” was a mixture of acute and chronic, and the true association was driven by either, it would be reflected in non-confident estimates (diluted intervals). As shown in Table 2, although that group included only 10% of the sample, the confidence interval was rather narrow, indicating the confident finding. Thus, bodyweight is likely of importance to chronic back pain.

The body composition parameter with the highest variability and most strongly correlated to bodyweight was fat mass. As shown in Table 1, lean mass and BMD had lower variability indicating that in this age group, it is the fat mass that describes differences between women, and the one consistently associated with back pain episode. In our mediation analyses, we did observe direct effects of TLM, LLM and BMD. While these findings support the absolute load findings, the estimates should be interpreted more carefully given the wider confidence intervals. Also, the only previous longitudinal report found a positive association between fat mass and back pain49. An interesting Japanese study investigating body composition and back pain cross-sectionally reported negative findings. Their participants, women and men, were on average normal weighted with the amount of body fat approximately half of the average found here50. Our study builds on these findings, and with a detailed report on all parameters and analyses, provides strong evidence and improves understanding of the bodyweight effects on back pain.

Previous studies investigating body composition speculated about indirect effects on back pain. To our knowledge, this is the first study that investigated indirect effects mediated via inflammatory and metabolic parameters. We assumed that part of the effect of body weight and its components is due to these parameters. We did not investigate the direct effects of these parameters on back pain or the contribution of other tissues such as inflamed/damaged tissue or immune cells to the systemic levels of these parameters. We did not find that inflammatory biomarkers mediated any indirect effect of body weight and its components. We found inconsistent mediation, i.e., suppressing effects of FBG in the associations of body weight, BMI, TFM and TLM with back pain episode, but these associations were driven by outliers. Also, we found that TG mediated several effects. Unlike the indirect effects of FBG that were explained by outliers, the TG effects were attenuated by the confounding variables. Overall, our study demonstrated the lack of consistent indirect effects of body weight and its components on back pain episode in women. It could be due to study samples being on average overweight but not obese, and low-grade inflammation and atherosclerotic changes if present not significantly contributing to back pain episode. Also, our outcome back pain episode, although of great importance for public health, was not chronic back pain, and chronic processes might additionally stimulate adipose tissue to release mediators that would add significant indirect effects.

**5. Conclusions**

Our study showed that in women representative of the UK population, the effects of body weight and fat mass on back pain episode were direct, presumably mechanical loading, not indirect through inflammatory or metabolic parameters. These suggest that weight reduction could decrease in short- and long-term obesity-related effects on back pain episode. However, the height-related body weight effects should be kept in mind when developing and delivering prevention programs. Our results indicate that further exploration should consider mediation analyses focusing on other mediators and chronic back pain. The indirect effects might be part of the overall effect in the chronic pain, and consequently, guide treatment approaches toward further improvement.

**Abbreviations**

BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; DEXA: dual-energy X-ray absorptiometry; ELISA: enzyme-linked immunosorbent assay; FBG: fasting blood glucose; HDL: high-density lipoprotein cholesterol; HRT: hormone replacement therapy; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin 6; LLM: limb lean mass; OR: odds ratio; rs: Spearmen’s correlation coefficient; SBMD: spine bone mineral density; SBP: systolic blood pressure; SF: short fit; SO: short overweight; TBMD: total bone mineral density; TG: triglycerides; TF: tall fit; TFM: total fat mass; TFMI: total fat mass index; TLM: total lean mass; TLMI: total lean mass index; TNFα: tumour necrosis factor-alpha; TO: tall overweight.

**Declaration of interest**

TDS reported serving as a scientific consultant for Zoe Global Ltd. NKA reported receiving personal fees from Pfizer/Lilly and Bristows LLP and grants from Merck outside the submitted work. No other disclosures were reported.

**Funding**

This work was supported by Versus Arthritis through Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis Grant Number 21595.

**Role of the Funder**

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Author contributions**

**Romain S Perera**: *Conceptualisation, Methodology, Formal analysis, Data curation, Writing - Original Draft;* **Lingxiao Chen:** *Conceptualisation, Data curation, Writing - Review & Editing;* **Deborah J Hart:** *Resources, Data curation, Writing – Review and Editing, Funding acquisition;* **Tim D Spector:** *Resources, Writing – Review and Editing, Funding acquisition;* **Nigel K Arden**: *Conceptualisation, Resources, Writing - Review & Editing, Funding acquisition;* **Manuela L Ferreira**: *Conceptualisation, Writing - Review & Editing;* **Maja R Radojčić**: *Conceptualisation, Methodology, Data curation, Visualisation, Writing - Review & Editing, Project administration.*

**Acknowledgement**

We would like to thank all the participants of the Chingford 1000 Women Study, Dr Alan Hakim, Ms Maxine Daniels and Ms Alison Turner for their time and dedication and Arthritis Research UK (now Versus Arthritis) for their funding support to the study and the Oxford NIHR Musculoskeletal Biomedical Research Unit for funding contributions. We would like to thank Dr Lyndsey Goulston for her contribution to data cleaning, and Ms Julie Damnjanović for her valued support to the team and the study data management.

**References**

1. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390(10100):1211-59. doi: 10.1016/S0140-6736(17)32154-2 [published Online First: 2017/09/19]

2. Jordan KP, Kadam UT, Hayward R, et al. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010;11:144. doi: 10.1186/1471-2474-11-144 [published Online First: 2010/07/06]

3. Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;64(6):2028-37. doi: 10.1002/art.34347 [published Online First: 2012/01/11]

4. Scheelbeek PFD, Cornelsen L, Marteau TM, et al. Potential impact on prevalence of obesity in the UK of a 20% price increase in high sugar snacks: modelling study. *Bmj* 2019;366:l4786. doi: 10.1136/bmj.l4786 [published Online First: 2019/09/06]

5. WHO. Prevalence of obesity among adults, BMI ≥ 30, age-standardized, estimates per WHO region 2016 [updated 22/09/2017. Available from: <https://apps.who.int/gho/data/node.main.A900A?lang=en2021>.

6. Hartvigsen J, Hancock MJ, Kongsted A, et al. What low back pain is and why we need to pay attention. *Lancet* 2018;391(10137):2356-67. doi: 10.1016/s0140-6736(18)30480-x [published Online First: 2018/03/27]

7. Shiri R, Karppinen J, Leino-Arjas P, et al. The association between obesity and low back pain: a meta-analysis. *Am J Epidemiol* 2010;171(2):135-54. doi: 10.1093/aje/kwp356 [published Online First: 2009/12/17]

8. Zhang TT, Liu Z, Liu YL, et al. Obesity as a Risk Factor for Low Back Pain: A Meta-Analysis. *Clin Spine Surg* 2018;31(1):22-27. doi: 10.1097/bsd.0000000000000468 [published Online First: 2016/11/23]

9. Coenen P, Kingma I, Boot CR, et al. Cumulative mechanical low-back load at work is a determinant of low-back pain. *Occup Environ Med* 2014;71(5):332-7. doi: 10.1136/oemed-2013-101862 [published Online First: 2014/03/29]

10. Singh D, Park W, Hwang D, et al. Severe obesity effect on low back biomechanical stress of manual load lifting. *Work* 2015;51(2):337-48. doi: 10.3233/wor-141945 [published Online First: 2014/09/25]

11. Walsh TP, Arnold JB, Evans AM, et al. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. *BMC Musculoskelet Disord* 2018;19(1):233. doi: 10.1186/s12891-018-2137-0 [published Online First: 2018/07/20]

12. Jiang L, Xie X, Wang Y, et al. Body mass index and hand osteoarthritis susceptibility: an updated meta-analysis. *Int J Rheum Dis* 2016;19(12):1244-54. doi: 10.1111/1756-185x.12895 [published Online First: 2017/04/04]

13. Kroon FPB, Veenbrink AI, de Mutsert R, et al. The role of leptin and adiponectin as mediators in the relationship between adiposity and hand and knee osteoarthritis. *Osteoarthritis Cartilage* 2019;27(12):1761-67. doi: 10.1016/j.joca.2019.08.003 [published Online First: 2019/08/27]

14. Fowler-Brown A, Kim DH, Shi L, et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. *Arthritis Rheumatol* 2015;67(1):169-75. doi: 10.1002/art.38913 [published Online First: 2014/10/11]

15. Ferrante AW, Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *J Intern Med* 2007;262(4):408-14. doi: 10.1111/j.1365-2796.2007.01852.x [published Online First: 2007/09/19]

16. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. *Clin Endocrinol (Oxf)* 2006;64(4):355-65. doi: 10.1111/j.1365-2265.2006.02474.x [published Online First: 2006/04/06]

17. Lim YZ, Wang Y, Cicuttini FM, et al. Association Between Inflammatory Biomarkers and Nonspecific Low Back Pain: A Systematic Review. *Clin J Pain* 2020;36(5):379-89. doi: 10.1097/ajp.0000000000000810 [published Online First: 2020/01/29]

18. Morris P, Ali K, Merritt M, et al. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. *BMC Musculoskelet Disord* 2020;21(1):142. doi: 10.1186/s12891-020-3154-3 [published Online First: 2020/03/05]

19. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *J Rheumatol* 1993;20(2):331-5. [published Online First: 1993/02/01]

20. Hart DJ, Spector TD. Cigarette smoking and risk of osteoarthritis in women in the general population: the Chingford study. *Ann Rheum Dis* 1993;52(2):93-6. doi: 10.1136/ard.52.2.93 [published Online First: 1993/02/01]

21. Kluzek S, Sanchez-Santos MT, Leyland KM, et al. Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women. *Ann Rheum Dis* 2016;75(10):1749-56. doi: 10.1136/annrheumdis-2015-208056 [published Online First: 2015/11/05]

22. Radojčić MR, Perera RS, Chen L, et al. Specific body mass index trajectories were related to musculoskeletal pain and mortality: 19-year follow-up cohort. *J Clin Epidemiol* 2021 doi: 10.1016/j.jclinepi.2021.09.020 [published Online First: 2021/09/20]

23. Chen L, Perera RS, Radojcic MR, et al. Association of Lumbar Spine Radiographic Changes With Severity of Back Pain-Related Disability Among Middle-aged, Community-Dwelling Women. *JAMA Netw Open* 2021;4(5):e2110715. doi: 10.1001/jamanetworkopen.2021.10715 [published Online First: 2021/05/21]

24. Spector TD, Hart DJ, Byrne J, et al. Definition of osteoarthritis of the knee for epidemiological studies. *Ann Rheum Dis* 1993;52(11):790-4. doi: 10.1136/ard.52.11.790 [published Online First: 1993/11/01]

25. Blumenfeld O, Williams FM, Hart DJ, et al. Lower limbs composition and radiographic knee osteoarthritis (RKOA) in Chingford sample--a longitudinal study. *Arch Gerontol Geriatr* 2013;56(1):148-54. doi: 10.1016/j.archger.2012.09.006 [published Online First: 2012/10/23]

26. Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: The Chingford Study. *Arthritis Rheum* 2009;60(7):2037-45. doi: 10.1002/art.24598 [published Online First: 2009/07/01]

27. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford Study. *J Rheumatol* 1995;22(6):1118-23. [published Online First: 1995/06/01]

28. Hashem LE, Roffey DM, Alfasi AM, et al. Exploration of the Inter-Relationships Between Obesity, Physical Inactivity, Inflammation, and Low Back Pain. *Spine (Phila Pa 1976)* 2018;43(17):1218-24. doi: 10.1097/brs.0000000000002582 [published Online First: 2018/02/09]

29. Heuch I, Hagen K, Zwart JA. Does high blood pressure reduce the risk of chronic low back pain? The Nord-Trondelag Health Study. *Eur J Pain* 2014;18(4):590-8. doi: 10.1002/j.1532-2149.2013.00398.x [published Online First: 2013/09/11]

30. Leino-Arjas P, Kaila-Kangas L, Solovieva S, et al. Serum lipids and low back pain: an association? A follow-up study of a working population sample. *Spine (Phila Pa 1976)* 2006;31(9):1032-7. doi: 10.1097/01.brs.0000214889.31505.08 [published Online First: 2006/04/28]

31. Pozzobon D, Ferreira PH, Dario AB, et al. Is there an association between diabetes and neck and back pain? A systematic review with meta-analyses. *PLoS One* 2019;14(2):e0212030. doi: 10.1371/journal.pone.0212030 [published Online First: 2019/02/23]

32. van den Berg R, Jongbloed EM, de Schepper EIT, et al. The association between pro-inflammatory biomarkers and nonspecific low back pain: a systematic review. *Spine J* 2018;18(11):2140-51. doi: 10.1016/j.spinee.2018.06.349 [published Online First: 2018/07/01]

33. Yoshimoto T, Ochiai H, Shirasawa T, et al. Association between serum lipids and low back pain among a middle-aged Japanese population: a large-scale cross-sectional study. *Lipids Health Dis* 2018;17(1):266. doi: 10.1186/s12944-018-0907-1 [published Online First: 2018/11/27]

34. Charalambous A, Giannakopoulou M, Bozas E, et al. Parallel and serial mediation analysis between pain, anxiety, depression, fatigue and nausea, vomiting and retching within a randomised controlled trial in patients with breast and prostate cancer. *BMJ Open* 2019;9(1):e026809. doi: 10.1136/bmjopen-2018-026809 [published Online First: 2019/01/27]

35. Fernandez I, Igartua JJ, Moral F, et al. Language use depending on news frame and immigrant origin. *Int J Psychol* 2013;48(5):772-84. doi: 10.1080/00207594.2012.723803 [published Online First: 2012/11/02]

36. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach . 2nd edition ed. New York: The Guilford Press 2018.

37. Cao-Lei L, Dancause KN, Elgbeili G, et al. DNA methylation mediates the effect of maternal cognitive appraisal of a disaster in pregnancy on the child's C-peptide secretion in adolescence: Project Ice Storm. *PLoS One* 2018;13(2):e0192199. doi: 10.1371/journal.pone.0192199 [published Online First: 2018/02/06]

38. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol* 2010;172(12):1339-48. doi: 10.1093/aje/kwq332 [published Online First: 2010/11/03]

39. Feingold A, MacKinnon DP, Capaldi DM. Mediation analysis with binary outcomes: Direct and indirect effects of pro-alcohol influences on alcohol use disorders. *Addict Behav* 2019;94:26-35. doi: 10.1016/j.addbeh.2018.12.018 [published Online First: 2019/01/15]

40. Hayes AF, Scharkow M. The relative trustworthiness of inferential tests of the indirect effect in statistical mediation analysis: does method really matter? *Psychol Sci* 2013;24(10):1918-27. doi: 10.1177/0956797613480187 [published Online First: 2013/08/21]

41. Radojčić MR, Thudium CS, Henriksen K, et al. Biomarker of extracellular matrix remodelling C1M and proinflammatory cytokine interleukin 6 are related to synovitis and pain in end-stage knee osteoarthritis patients. *Pain* 2017;158(7):1254-63. doi: 10.1097/j.pain.0000000000000908

42. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behav Res Ther* 2017;98:39-57. doi: 10.1016/j.brat.2016.11.001 [published Online First: 2016/11/21]

43. Perera RS, Chen C, Ferreira ML, et al. Age- and sex-specific obesity and metabolic syndrome effects on back pain: The English Longitudinal Study of Ageing. under review

44. Kauppila LI. Atherosclerosis and disc degeneration/low-back pain--a systematic review. *Eur J Vasc Endovasc Surg* 2009;37(6):661-70. doi: 10.1016/j.ejvs.2009.02.006 [published Online First: 2009/03/31]

45. Tsuboi Y, Ueda Y, Sugimoto T, et al. Association between metabolic syndrome and disability due to low back pain among care workers. *Int J Occup Med Environ Health* 2018;31(2):165-72. doi: 10.13075/ijomeh.1896.01004 [published Online First: 2017/10/03]

46. Chin SH, Huang WL, Akter S, et al. Obesity and pain: a systematic review. *Int J Obes (Lond)* 2020;44(5):969-79. doi: 10.1038/s41366-019-0505-y [published Online First: 2019/12/19]

47. Heuch I, Heuch I, Hagen K, et al. Body mass index as a risk factor for developing chronic low back pain: a follow-up in the Nord-Trøndelag Health Study. *Spine (Phila Pa 1976)* 2013;38(2):133-9. doi: 10.1097/BRS.0b013e3182647af2 [published Online First: 2012/06/22]

48. Leboeuf-Yde C. Body weight and low back pain. A systematic literature review of 56 journal articles reporting on 65 epidemiologic studies. *Spine (Phila Pa 1976)* 2000;25(2):226-37. doi: 10.1097/00007632-200001150-00015 [published Online First: 2000/02/24]

49. Hussain SM, Urquhart DM, Wang Y, et al. Fat mass and fat distribution are associated with low back pain intensity and disability: results from a cohort study. *Arthritis Res Ther* 2017;19(1):26. doi: 10.1186/s13075-017-1242-z [published Online First: 2017/02/12]

50. Iizuka Y, Iizuka H, Mieda T, et al. Association between neck and shoulder pain, back pain, low back pain and body composition parameters among the Japanese general population. *BMC Musculoskelet Disord* 2015;16:333. doi: 10.1186/s12891-015-0759-z [published Online First: 2015/11/06]

**Appendix**

**Table A1** Non-response analyses due to unavailable inflammatory and metabolic parameters (Follow-up Year 8)

**Table A2** Non-response analyses due to attendance of Year 15 follow-up

**Table A3** Spearman’s correlation between variables of interest in Main sample 1 and Subsample 1 (Follow-up Year 8)

**Table A4** Spearman’s correlation between variables of interest in Main sample 2 (Follow-up Year 15)