

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

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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 included 826 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 consultations^{1 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 ages³. Similarly, obesity has a comparable pattern of disability and prevalence⁴⁵. Taken together, back pain and obesity have a colossal impact on health care systems worldwide due to direct costs and loss of productivity^{4 6}.

There has been evidence about the association between obesity and back pain, but a little about its mechanism^{7 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 activities^{9 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 osteoarthritis^{13 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 pain^{17 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 baseline^{19 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 Kingdom^{19 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 cm^{19 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 (TNF α) 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 TNF α 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 menopausal 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 testing^{34 37}. Figure 1 shows the conceptualisation of the statistical model. Ordinary least squares regression models with a binary outcome^{38 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 iterations^{36 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. a_{1-8} shows effects of the exposure on mediators; b_{1-8} presents effects of mediators to the outcome; $a_{1-8} \times b_{1-8}$ 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; TNF α – 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 χ^2 -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 4^{36 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 menopausal. 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 menopausal 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 ($r_s \geq 0.90$, $p < 0.001$). Weight was moderately correlated with TLM ($r_s = 0.66$, $p < 0.001$) and weakly with TBMD ($r_s = 0.27$, $p < 0.001$). Similar results were observed between

BMI and TFM with TLM and TBMD with slightly weaker correlations. TLM and TBMD were moderately correlated ($r_s=0.38$, $p<0.001$). 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 ($r_s=0.39$, $p<0.001$), and both were weakly correlated with metabolic parameters. However, $TNF\alpha$ was only weakly correlated with IL-6 ($r_s=0.28$, $p = <0.001$), TG ($r_s=0.15$, $p=0.002$) and HDL ($r_s=-0.15$, $p=0.002$), 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 ($r_s=0.73$, $p<0.001$) and TG and HDL ($r_s=-0.53$, $p<0.001$).

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 parameters^{31 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 ours^{7 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.

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; r_s : Spearman'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; $TNF\alpha$: 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.

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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.

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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)

Table 1 Descriptive statistics of the study samples

| <i>Variable</i> | <i>Follow-up Year 8</i> | | <i>Follow-up Year 15</i> | |
|---|----------------------------------|---|----------------------------------|--------------------------------|
| | <i>Main sample 1 (n=826)</i> | <i>Subsample 1 ^a (n=447)</i> | <i>Main sample 2 (n=645)</i> | <i>Subsample 2 (n=621)</i> |
| Age (years), mean (SD) | 60.65 (5.89) | 60.70 (6.20) | 67.19 (5.81) | 67.11 (5.79) |
| Smoking habits, % | | | | |
| Currently smoking | 16.2 | 14.8 | 7.0 | 7.1 |
| Hormone Replacement Therapy, % | | | | |
| Current use | 30.1 | 31.6 | 5.8 | 5.8 |
| Menopause, % | | | | |
| Yes | 81.5 | 81.0 | N/A | N/A |
| Physical activity, % | | | | |
| Active | N/A | N/A | 97.5 | 97.4 |
| Walking | | | 78.8 | 78.9 |
| Sport | | | 14.6 | 14.7 |
| Job | | | 93.2 | 93.1 |
| Medication use, % | | | | |
| Any type | 53.1 | 53.0 | 81.2 | 84.4 |
| NSAIDs | 5.0 | 5.4 | 20.3 | 21.1 |
| Opioids | 5.6 | 6.5 | 8.8 | 9.2 |
| Antihypertensive | 24.2 | 22.4 | 36.3 | 37.7 |
| Antilipemic | 4.0 | 3.6 | 21.2 | 22.1 |
| Antidiabetic | 1.3 | 1.6 | 3.7 | 3.9 |
| Bisphosphonate | 1.8 | 1.1 | 9.0 | 9.3 |
| Steroids | 1.1 | 1.3 | 0.5 | 0.5 |
| Back pain, % | | | | |
| Any episode in the last year | 38.9 | 36.9 | 48.4 | 48.5 |
| Duration of the episode ^b | | | | |
| No episode | 61.2 | 63.1 | | |
| Less than or 2 weeks | 29.2 | 27.5 | N/A | N/A |
| More than 2 weeks | 9.6 | 9.4 | | |
| Weight (kg), mean (SD) | 68.86 (12.70) | 68.81 (12.24) | 69.44 (12.82) | 69.41 (12.82) |
| Height (m), mean (SD) | 1.61 (0.06) | 1.61 (0.06) | 1.59 (0.06) | 1.60 (0.06) |
| Body mass index (kg/m ²), mean (SD) | 26.67 (4.67) | 26.60 (4.49) | 27.25 (4.83) | 27.26 (4.85) |
| Body composition parameters, mean (SD) | | | | |

| | | | | |
|---|------------------------|------------------------|------------------------|------------------------|
| Total fat mass (kg) | 29.75 (10.03) | 29.88 (9.77) | 29.47 (8.67) | 29.45 (8.67) |
| Total fat mass index (kg/m ²) | 11.54 (3.87) | 11.57 (3.79) | 11.57 (3.39) | 11.57 (3.40) |
| Total lean mass (kg) | 38.34 (4.57) | 38.15 (4.40) | 39.27 (5.23) | 39.25 (5.25) |
| Total lean mass index (kg/m ²) | 14.83 (1.40) | 14.73 (1.32) | 15.40 (1.81) | 15.40 (1.82) |
| Limb lean mass (kg) | 15.13 (2.28) | 15.09 (2.16) | 16.30 (2.59) | 16.29 (2.60) |
| Total bone mineral density (g/cm ²) | 1.02 (0.10) | 1.02 (0.10) | 1.05 (0.11) | 1.06 (0.11) |
| Spine bone mineral density (g/cm ²) | 0.84 (0.11) | 0.84 (0.12) | 0.88 (0.13) | 0.88 (0.14) |
| Inflammatory parameters, median (IQR) | N/A | | N/A | N/A |
| hsCRP (mg/L) | | 0.14 (0.06-0.27) | | |
| IL-6 (pg/mL) | | 1.60 (0.95-2.99) | | |
| TNFα (pg/mL) | | 1.86 (1.38-3.29) | | |
| Metabolic parameters, median (IQR) ^c | | | | |
| Systolic blood pressure (mmHg) | 130.00 (120.00-140.00) | 130.00 (120.00-145.00) | 132.00 (120.33-143.33) | 132.17 (120.33-143.58) |
| Diastolic blood pressure (mmHg) | 80.00 (70.00-90.00) | 80.00 (70.00-90.00) | 78.83 (72.00-85.33) | 79.00 (72.33-85.33) |
| Triglycerides (mmol/L) | | 1.60 (1.20-2.12) | | |
| HDL cholesterol (mmol/L) | N/A | 0.85 (0.64-1.05) | N/A | N/A |
| Fasting blood glucose (mmol/L) | | 4.04 (3.74-4.42) | | |

SD – standard deviation; IQR – interquartile range; N/A – information not available; NSAID – non-steroid anti-inflammatory drug; hsCRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6; TNFα – Tumour necrosis factor alpha; HDL – High-density lipoprotein.

^a The subsample 1 was not subjected to multiple imputations, and there were 9, 13 and 11 participants with missing values in the covariates smoking habits, hormone replacement therapy and menopause, respectively.

^b One participant in the Main sample 1 did not have the information on the duration of the back pain episode in the last year.

^c Reported systolic and diastolic blood pressure were not available for six participants of the Main sample 1, and one participant of the Main sample 2 and Subsample 2.

Table 2 Weight, body mass index and body composition parameters in association with back pain episode

| | | <i>Main sample 1</i> | | | <i>Main sample 2</i> | <i>Subsample 2</i> |
|-----------------|--------------|--------------------------|-------------------------------------|-------------------------------------|--------------------------|--------------------------|
| | | Back pain episode | Duration of the episode ≤2 weeks | Duration of the episode >2 weeks | Back pain episode | Back pain episode |
| <i>Variable</i> | <i>Model</i> | <i>OR (95% CI)</i> | <i>OR (95% CI)</i> | <i>OR (95% CI)</i> | <i>OR (95% CI)</i> | <i>OR (95% CI)</i> |
| Weight | 1 | 1.02 (1.01, 1.03) | 1.01 (1.01, 1.03) | 1.02 (1.01, 1.04) | 1.02 (1.01, 1.03) | 1.02 (1.01, 1.03) |
| | 2 | 1.02 (1.01, 1.03) | 1.01 (1.01, 1.03) | 1.02 (1.01, 1.04) | 1.02 (1.01, 1.03) | 1.02 (1.01, 1.03) |
| BMI | 1 | 1.04 (1.01, 1.08) | 1.04 (1.01, 1.07) | 1.06 (1.01, 1.11) | 1.04 (1.01, 1.08) | 1.05 (1.01, 1.09) |
| | 2 | 1.04 (1.01, 1.07) | 1.04 (1.01, 1.07) | 1.05 (0.99, 1.10) | 1.05 (1.01, 1.08) | 1.05 (1.01, 1.09) |
| Total fat mass | 1 | 1.02 (1.01, 1.03) | 1.02 (1.01, 1.03) | 1.03 (1.01, 1.05) | 1.03 (1.01, 1.05) | 1.02 (1.01, 1.04) |
| | 2 | 1.02 (1.01, 1.04) | 1.02 (1.01, 1.03) | 1.02 (1.00, 1.05) | 1.03 (1.01, 1.05) | 1.02 (1.01, 1.04) |
| Total lean mass | 1 | 1.03 (0.99, 1.06) | 1.02 (0.99, 1.06) | 1.04 (0.99, 1.09) | 1.02 (0.99, 1.05) | 1.02 (0.98, 1.06) |
| | 2 | 1.03 (1.00, 1.06) | 1.02 (0.99, 1.06) | 1.04 (0.99, 1.10) | 1.02 (0.99, 1.06) | 1.02 (0.99, 1.06) |
| Limb lean mass | 1 | 1.05 (0.98, 1.11) | 1.03 (0.97, 1.11) | 1.07 (0.96, 1.18) | 1.03 (0.97, 1.10) | 1.02 (0.95, 1.10) |
| | 2 | 1.05 (0.98, 1.11) | 1.03 (0.96, 1.11) | 1.07 (0.96, 1.19) | 1.04 (0.98, 1.10) | 1.02 (0.95, 1.10) |
| Total BMD | 1 | 2.61 (0.63, 10.79) | 3.47 (0.74, 16.42) | 1.04 (0.09, 11.59) | 1.34 (0.34, 5.24) | 0.40 (0.08, 2.01) |
| | 2 | 3.86 (0.78, 19.06) | 4.49 (0.78, 25.76) | 2.38 (0.16, 34.54) | 1.50 (0.54, 4.21) | 0.47 (0.08, 2.97) |
| Spine BMD | 1 | 2.43 (0.72, 8.23) | 2.73 (0.72, 10.32) | 1.64 (0.21, 12.99) | 2.55 (0.79, 8.29) | 1.46 (0.36, 5.96) |
| | 2 | 2.81 (0.78, 10.18) | 2.87 (0.70, 11.67) | 2.56 (0.29, 19.69) | 2.72 (1.47, 5.02) | 1.95 (0.44, 8.74) |

OR – odds ratio; CI – confidence interval; BMI – body mass index; BMD – bone mineral density.

Analyses considering Main sample 1 (follow-up 8) and Main sample 2 (follow-up 15) were cross-sectional, while analyses considering Subsample 2 were longitudinal, i.e., exposures from follow-up year 8 related to the outcome at follow-up year 15. Models were constructed using binary logistic regression (back pain episode referenced to no pain) or multinomial logistic regression (duration of the episode more than two weeks and less or equal to two weeks referenced to no pain). Odds ratio shows the increased odds of back pain episode for every unit increase of the exposure variable. Bold results were statistically significant.

Model 1 was unadjusted.

Model 2 was adjusted for age, smoking habits, hormone replacement therapy use, menopause and medication use in analyses considering Main sample 1 and Subsample 2, or adjusted for age, smoking habits, hormone replacement therapy use, and medication use in analyses considering Main sample 2.

Table 3 Mediation analyses – effects of weight, body mass index and body composition parameters direct and indirect via inflammatory or metabolic parameters on back pain episode (Year 8 cross-sectional analyses)

| <i>Exposure</i> | <i>Mediator</i> | Model 1 | Model 2 | Model 3 | Model 4 |
|-----------------|-----------------|--|--|--|--|
| | | <i>Direct/Indirect effect OR [B (95% boot CI)]</i> | <i>Direct/Indirect effect OR [B (95% boot CI)]</i> | <i>Direct/Indirect effect OR [B (95% boot CI)]</i> | <i>Direct/Indirect effect OR [B (95% boot CI)]</i> |
| Weight | | 1.03 [0.0250 (0.0072, 0.0429)] | 1.03 [0.0268 (0.0074, 0.0463)] | 1.04 [0.0342 (0.0118, 0.0566)] | 1.04 [0.0349 (0.0110, 0.0587)] |
| | hsCRP | 0.99 [-0.0005 (-0.0035, 0.0040)] | 0.99 [-0.0014 (-0.0070, 0.0018)] | 0.99 [-0.0021 (-0.0115, 0.0053)] | 0.99 [-0.0041 (-0.0153, 0.0044)] |
| | IL-6 | 1.00 [0.0008 (-0.0005, 0.0028)] | 1.00 [0.0007 (-0.0007, 0.0029)] | 1.00 [0.0006 (-0.0043, 0.0060)] | 1.00 [0.0004 (-0.0056, 0.0070)] |
| | TNF α | 1.00 [0.0002 (-0.0009, 0.0017)] | 1.00 [0.0004 (-0.0011, 0.0024)] | 0.99 [-0.0013 (-0.0051, 0.0010)] | 0.99 [-0.0007 (-0.0036, 0.0019)] |
| | TG | 1.01 [0.0051 (0.0009, 0.0137)] | 1.00 [0.0038 (-0.0004, 0.0125)] | 1.01 [0.0081 (0.0015, 0.0175)] | 1.00 [0.0054 (-0.0021, 0.0156)] |
| | HDL | 0.99 [-0.0040 (-0.0101, 0.0004)] | 0.99 [-0.0040 (-0.0100, 0.0006)] | 0.99 [-0.0039 (-0.0108, 0.0011)] | 0.99 [-0.0032 (-0.0108, 0.0020)] |
| | SBP | 1.00 [0.0002 (-0.0057, 0.0061)] | 0.99 [-0.0012 (-0.0079, 0.0053)] | 1.00 [0.0010 (-0.0065, 0.0081)] | 1.00 [0.0001 (-0.0079, 0.0079)] |
| | DBP | 0.99 [-0.0037 (-0.0114, 0.0030)] | 0.99 [-0.0034 (-0.0116, 0.0033)] | 0.99 [-0.0040 (-0.0124, 0.0035)] | 0.99 [-0.0040 (-0.0135, 0.0034)] |
| BMI | FBG | 0.99 [-0.0042 (-0.0121, -0.0004)] | 0.99 [-0.0046 (-0.0125, -0.0003)] | 0.99 [-0.0002 (-0.0041, 0.0030)] | 1.00 [0.0006 (-0.0033, 0.0047)] |
| | | 1.07 [0.0668 (0.0184, 0.1153)] | 1.07 [0.0710 (0.0185, 0.1235)] | 1.09 [0.0839 (0.0232, 0.1447)] | 1.08 [0.0805 (0.0169, 0.1441)] |
| | hsCRP | 0.99 [-0.0006 (-0.0087, 0.0125)] | 0.99 [-0.0018 (-0.0185, 0.0124)] | 0.99 [-0.0059 (-0.0308, 0.0152)] | 0.99 [-0.0111 (-0.0411, 0.0134)] |
| | IL-6 | 1.00 [0.0019 (-0.0018, 0.0072)] | 1.00 [0.0015 (-0.0024, 0.0068)] | 1.00 [0.0019 (-0.0124, 0.0169)] | 1.00 [0.0014 (-0.0146, 0.0174)] |
| | TNF α | 1.00 [0.0004 (-0.0027, 0.0039)] | 1.00 [0.0012 (-0.0031, 0.0063)] | 0.99 [-0.0027 (-0.0116, 0.0033)] | 0.99 [-0.0015 (-0.0091, 0.0050)] |
| | TG | 1.01 [0.0141 (0.0023, 0.0384)] | 1.01 [0.0101 (-0.0011, 0.0329)] | 1.02 [0.0229 (0.0040, 0.0493)] | 1.02 [0.0147 (-0.0036, 0.0414)] |
| | HDL | 0.99 [-0.0085 (-0.0221, 0.0011)] | 0.99 [-0.0081 (-0.0218, 0.0017)] | 0.99 [-0.0098 (-0.0272, 0.0029)] | 0.99 [-0.0079 (-0.0270, 0.0050)] |
| | SBP | 0.99 [-0.0006 (-0.0202, 0.0188)] | 0.99 [-0.0045 (-0.0246, 0.0148)] | 1.00 [0.0010 (-0.0244, 0.0247)] | 0.99 [-0.0009 (-0.0253, 0.0219)] |
| TFM | DBP | 0.99 [-0.0099 (-0.0323, 0.0087)] | 0.99 [-0.0080 (-0.0295, 0.0103)] | 0.99 [-0.0093 (-0.0336, 0.0110)] | 0.99 [-0.0081 (-0.0318, 0.0107)] |
| | FBG | 0.99 [-0.0108 (-0.0313, -0.0009)] | 0.99 [-0.0112 (-0.0317, -0.006)] | 0.99 [-0.0009 (-0.0127, 0.0100)] | 1.00 [0.0018 (-0.0100, 0.0151)] |
| | | 1.03 [0.0314 (0.0092, 0.0536)] | 1.04 [0.0356 (0.0110, 0.0602)] | 1.04 [0.0416 (0.0132, 0.0700)] | 1.04 [0.0434 (0.0130, 0.0738)] |
| | hsCRP | 0.99 [-0.0004 (-0.0048, 0.0051)] | 0.99 [-0.0013 (-0.0096, 0.0035)] | 0.99 [-0.0032 (-0.0154, 0.0071)] | 0.99 [-0.0064 (-0.0218, 0.0063)] |
| | IL-6 | 1.00 [0.0013 (-0.0007, 0.0038)] | 1.00 [0.0012 (-0.0011, 0.0039)] | 1.00 [0.0006 (-0.0067, 0.0085)] | 1.00 [0.0004 (-0.0083, 0.0089)] |
| | TNF α | 1.00 [0.0002 (-0.0014, 0.0016)] | 1.00 [0.0005 (-0.0016, 0.0029)] | 0.99 [-0.0006 (-0.0041, 0.0022)] | 0.99 [-0.0002 (-0.0031, 0.0025)] |
| | TG | 1.01 [0.0058 (0.0011, 0.0157)] | 1.00 [0.0043 (-0.0004, 0.0135)] | 1.01 [0.0105 (0.0019, 0.0226)] | 1.01 [0.0068 (-0.0021, 0.0201)] |
| | HDL | 0.99 [-0.0041 (-0.0107, 0.0006)] | 0.99 [-0.0043 (-0.0111, 0.0006)] | 0.99 [-0.0045 (-0.0129, 0.0015)] | 0.99 [-0.0040 (-0.0137, 0.0023)] |
| | SBP | 0.99 [-0.0001 (-0.0085, 0.0083)] | 0.99 [-0.0018 (-0.0107, 0.0067)] | 1.00 [0.0010 (-0.0095, 0.0113)] | 1.00 [0.0001 (-0.0106, 0.0103)] |
| | DBP | 0.99 [-0.0047 (-0.0146, 0.0044)] | 0.99 [-0.0041 (-0.0146, 0.0043)] | 0.99 [-0.0051 (-0.0170, 0.0046)] | 0.99 [-0.0048 (-0.0167, 0.0042)] |
| | FBG | 0.99 [-0.0048 (-0.0134, -0.0005)] | 0.99 [-0.0052 (-0.0146, -0.0004)] | 0.99 [-0.0004 (-0.0057, 0.0043)] | 1.00 [0.0007 (-0.0051, 0.0066)] |

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| TLM | | 1.05 [0.0513 (0.0040, 0.0985)] | 1.06 [0.0555 (0.0052, 0.1057)] | 1.07 [0.0661 (0.0087, 0.1236)] | 1.07 [0.0711 (0.0097, 0.1324)] |
| | hsCRP | 0.99 [-0.0006 (-0.0033, 0.0066)] | 0.99 [-0.0013 (-0.0106, 0.0033)] | 0.99 [-0.0002 (-0.0096, 0.0069)] | 0.99 [-0.0015 (-0.0136, 0.0073)] |
| | IL-6 | 1.00 [0.0006 (-0.0039, 0.0079)] | 1.00 [0.0004 (-0.0041, 0.0081)] | 1.00 [0.0009 (-0.0039, 0.0093)] | 1.00 [0.0008 (-0.0074, 0.0125)] |
| | TNF α | 1.00 [0.0000 (-0.0035, 0.0039)] | 0.99 [-0.0011 (-0.0069, 0.0031)] | 0.99 [-0.0065 (-0.0185, 0.0020)] | 0.99 [-0.0044 (-0.0174, 0.0055)] |
| | TG | 1.01 [0.0115 (0.0020, 0.0327)] | 1.01 [0.0096 (0.0001, 0.0317)] | 1.01 [0.0115 (0.0006, 0.0275)] | 1.01 [0.0110 (-0.0016, 0.0322)] |
| | HDL | 0.99 [-0.0094 (-0.0243, 0.0015)] | 0.99 [-0.0093 (-0.0243, 0.0024)] | 0.99 [-0.0065 (-0.0200, 0.0026)] | 0.99 [-0.0051 (-0.0185, 0.0046)] |
| | SBP | 1.00 [0.0005 (-0.0044, 0.0065)] | 1.00 [-0.0010 (-0.0105, 0.0086)] | 1.00 [0.0005 (-0.0055, 0.0081)] | 1.00 [0.0009 (-0.0106, 0.0141)] |
| | DBP | 0.99 [-0.0037 (-0.0149, 0.0045)] | 0.99 [-0.0047 (-0.0187, 0.0061)] | 0.99 [-0.0034 (-0.0162, 0.0043)] | 0.99 [-0.0062 (-0.0240, 0.0068)] |
| LLM | FBG | 0.99 [-0.0078 (-0.0241, -0.0001)] | 0.99 [-0.0089 (-0.0275, -0.0001)] | 1.00 [0.0001 (-0.0045, 0.0045)] | 1.00 [0.0003 (-0.0054, 0.0058)] |
| | | 1.09 [0.0854 (-0.0105, 0.1814)] | 1.10 [0.0977 (-0.0039, 0.1994)] | 1.14 [0.1317 (0.0140, 0.2494)] | 1.16 [0.1485 (0.0230, 0.2740)] |
| | hsCRP | 1.00 [0.0001 (-0.0025, 0.0106)] | 0.99 [-0.0004 (-0.0064, 0.0074)] | 0.99 [-0.0004 (-0.0218, 0.0152)] | 0.99 [-0.0039 (-0.0299, 0.0154)] |
| | IL-6 | 0.99 [-0.0001 (-0.0094, 0.0130)] | 0.99 [-0.0003 (-0.0088, 0.0128)] | 1.00 [0.0022 (-0.0080, 0.0201)] | 1.00 [0.0019 (-0.0146, 0.0263)] |
| | TNF α | 1.00 [0.0001 (-0.0065, 0.0081)] | 0.99 [-0.0013 (-0.0128, 0.0080)] | 0.99 [-0.0127 (-0.0378, 0.0055)] | 0.99 [-0.0094 (-0.0347, 0.0114)] |
| | TG | 1.03 [0.0261 (0.0044, 0.0709)] | 1.02 [0.0205 (-0.0010, 0.0699)] | 1.03 [0.0327 (0.0057, 0.0702)] | 1.03 [0.0256 (-0.0070, 0.0709)] |
| | HDL | 0.98 [-0.0188 (-0.0495, 0.0032)] | 0.98 [-0.0191 (-0.0507, 0.0047)] | 0.99 [-0.0146 (-0.0434, 0.0065)] | 0.99 [-0.0123 (-0.0426, 0.0103)] |
| | SBP | 1.00 [0.0011 (-0.0133, 0.0172)] | 0.99 [-0.0019 (-0.0222, 0.0174)] | 1.00 [0.0018 (-0.0118, 0.0192)] | 1.00 [0.0021 (-0.0194, 0.0252)] |
| Total BMD | DBP | 0.99 [-0.0088 (-0.0348, 0.0126)] | 0.99 [-0.0104 (-0.0404, 0.0158)] | 0.99 [-0.0083 (-0.0357, 0.0094)] | 0.99 [-0.0131 (-0.0498, 0.0123)] |
| | FBG | 0.99 [-0.0123 (-0.0424, 0.0004)] | 0.99 [-0.0133 (-0.0476, 0.0003)] | 1.00 [0.0002 (-0.0094, 0.0086)] | 1.00 [0.0006 (-0.0113, 0.0117)] |
| | | 3.66 [1.2977 (-0.7296, 3.3250)] | 6.63 [1.8921 (-0.5114, 4.2957)] | 10.73 [2.3731 (0.0309, 4.7152)] | 23.57 [3.1599 (0.3525, 5.9672)] |
| | hsCRP | 1.01 [0.0147 (-0.0517, 0.2551)] | 0.97 [-0.0307 (-0.2849, 0.1122)] | 1.00 [0.0001 (-0.2711, 0.1363)] | 0.98 [-0.0231 (-0.4759, 0.2088)] |
| | IL-6 | 0.95 [-0.0554 (-0.3502, 0.0656)] | 0.97 [-0.0301 (-0.3089, 0.0948)] | 0.94 [-0.0591 (-0.3558, 0.1668)] | 1.02 [0.0198 (-0.2034, 0.3833)] |
| | TNF α | 1.08 [0.0740 (-0.2083, 0.5196)] | 1.12 [0.1175 (-0.1062, 0.5513)] | 0.92 [-0.0838 (-0.4227, 0.2000)] | 0.95 [-0.0496 (-0.3878, 0.2281)] |
| | TG | 0.90 [-0.1006 (-0.4960, 0.2084)] | 1.04 [0.0428 (-0.2921, 0.4782)] | 0.98 [-0.0218 (-0.5730, 0.4732)] | 1.36 [0.3039 (-0.0758, 1.0612)] |
| | HDL | 0.96 [-0.0396 (-0.3117, 0.1343)] | 0.95 [-0.0495 (-0.3617, 0.1299)] | 0.95 [-0.0480 (-0.4085, 0.1937)] | 0.99 [-0.0014 (-0.3009, 0.2425)] |
| Spine BMD | SBP | 0.96 [-0.0354 (-0.3896, 0.2803)] | 0.94 [-0.0598 (-0.5565, 0.3272)] | 0.90 [-0.1001 (-0.5901, 0.2980)] | 1.02 [0.0247 (-0.6175, 0.5531)] |
| | DBP | 0.99 [-0.0120 (-0.2281, 0.1841)] | 0.88 [-0.1227 (-0.6591, 0.2807)] | 1.03 [0.0266 (-0.2440, 0.3505)] | 0.82 [-0.2003 (-0.9001, 0.2438)] |
| | FBG | 0.92 [-0.0880 (-0.3857, 0.0481)] | 0.84 [-0.1782 (-0.6484, 0.0207)] | 0.99 [-0.0074 (-0.2859, 0.2723)] | 1.08 [0.0757 (-0.3235, 0.5493)] |
| | | 2.56 [0.9421 (-0.7486, 2.6328)] | 3.19 [1.1615 (-0.7140, 3.0370)] | 4.69 [1.5445 (-0.3892, 3.4782)] | 7.08 [1.9569 (-0.2076, 4.1214)] |
| | hsCRP | 1.00 [0.0040 (-0.0551, 0.1290)] | 0.98 [-0.0162 (-0.2325, 0.0588)] | 0.99 [-0.0007 (-0.2582, 0.1596)] | 0.97 [-0.0273 (-0.4151, 0.1785)] |
| | IL-6 | 0.90 [-0.1100 (-0.3668, 0.0238)] | 0.91 [-0.0890 (-0.3176, 0.0386)] | 0.98 [-0.0215 (-0.2133, 0.1280)] | 1.02 [0.0178 (-0.1747, 0.2937)] |
| | TNF α | 1.04 [0.0443 (-0.1055, 0.2933)] | 1.05 [0.0478 (-0.0928, 0.2868)] | 0.91 [-0.0917 (-0.3963, 0.1313)] | 0.96 [-0.0454 (-0.3301, 0.1690)] |
| | TG | 0.99 [-0.0046 (-0.2920, 0.2683)] | 1.06 [0.0621 (-0.1564, 0.3864)] | 1.06 [0.0549 (-0.4056, 0.4922)] | 1.22 [0.2031 (-0.1004, 0.7533)] |

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|-----|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| HDL | 0.95 [-0.0512 (-0.2901, 0.0952)] | 0.96 [-0.0439 (-0.2771, 0.1101)] | 0.96 [-0.0382 (-0.3059, 0.1807)] | 1.00 [0.0044 (-0.2141, 0.2330)] |
| SBP | 0.99 [-0.0145 (-0.2244, 0.1992)] | 1.00 [-0.0272 (-0.3054, 0.1946)] | 0.96 [-0.0414 (-0.3420, 0.2193)] | 1.02 [0.0164 (-0.3340, 0.3716)] |
| DBP | 0.99 [-0.0131 (-0.1902, 0.1403)] | 0.97 [-0.0613 (-0.4023, 0.1644)] | 1.01 [0.0107 (-0.2023, 0.2602)] | 0.91 [-0.0905 (-0.5419, 0.1669)] |
| FBG | 0.92 [-0.0869 (-0.3523, 0.0206)] | 0.87 [-0.1436 (-0.4909, 0.0170)] | 0.99 [-0.0001 (-0.2019, 0.2395)] | 1.06 [0.0558 (-0.2062, 0.4153)] |

OR – odds ratio; B – beta; CI – confidence interval; hsCRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6; TNF α – tumour necrosis factor alpha; TG – triglycerides; HDL – high-density lipoprotein cholesterol; SBP – systolic blood pressure; DBP – diastolic blood pressure; FBG – fasting blood glucose; BMI – body mass index; TFM – total fat mass; TLM – total lean mass; LLM – limb lean mass; BMD – bone mineral density.

The analyses were done in Subsample 1 with and without outliers in mediator variables. There were 15, 50, 59, 2 and 13 outliers in hsCRP, IL-6, TNF α , TG and FBG, respectively. Models were constructed using logistic regression path analysis parallel method to estimate direct effects of exposures and indirect effects of exposures through mediators on back pain episode. Odds ratio=exp(B) shows the increased odds of back pain episode for every unit increase of the exposure variable per se or via mediator. Due to small effects results are presented with four decimals. Bold results were statistically significant.

Model 1 was unadjusted and included 447 participants.

Model 2 was adjusted for age, smoking habits, hormone replacement therapy use, menopause and medication use, and included 417 participants.

Model 3 was without outliers, unadjusted and included 325 participants.

Model 4 was without outliers, adjusted for age, smoking habits, hormone replacement therapy use, menopause and medication use, and included 303 participants.