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COHORT STUDIES

Dose–response associations of clinical markers of obesity and duration of exposure to excess weight with chronic musculoskeletal pain: cross-sectional analysis at baseline of ELSA-Brasil Musculoskeletal cohort

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Abstract

The objective of this study is to investigate the association of clinical markers of obesity and weight trajectories with chronic musculoskeletal pain (CMP). This is a cross-sectional study using baseline data from ELSA-Brasil MSK cohort. CMP was evaluated at nine body sites (neck, shoulders, upper back, elbows, lower back, wrists/hands, hips/thighs, knees, ankles/feet), and defined as pain lasting > 6 months in the past year. General and abdominal obesity levels were classified according to accepted cut-offs for body mass index (BMI), waist circumference (WC) and waist–height ratio (WHtR). Binomial and multinomial logistic regressions tested for associations with CMP at any site, at ≥ 3 sites (multisite) and in upper + lower limbs + axial skeleton (generalized). A total of 2899 participants (mean age 56.0 ± 8.93) were included, 55.0% reported CMP, 19.1% had multisite, and 10.3% had generalized CMP. After adjustments for sex, age, education, physical activity and depressive symptoms, nearly all the investigated markers of obesity were associated with any CMP, multisite and generalized CMP, with strongest associations being observed for general obesity level II/III: OR 2.08 (95% CI 1.45–2.99), OR 3.19 (95% CI 2.06–4.94) and OR 3.65 (2.18–6.11), respectively. Having excess weight currently or both at age 20 and currently was also associated with all CMP presentations. Associations of greater magnitude were consistently observed at higher obesity levels and longer exposures to excess weight (dose–response). These results may support the contribution of obesity-derived mechanical and inflammatory mechanisms of CMP, and indicate a role for the accumulation of exposure to excess weight across the adult life course.

Keywords Chronic pain · Musculoskeletal pain · Body mass index · Obesity · Abdominal obesity

Introduction

Chronic musculoskeletal pain (CMP) has great impact on individuals and health care systems due to its associated disability and frequent care seeking [1, 2], with yearly costs reaching over 60 billion dollars [3]. It can be classified by the number and spatial distribution of symptoms as local, regional, multisite or widespread/generalized pain [4, 5]. The prevalence of CMP is estimated at 17–86% at any site [6–8], 17–21% at a single site [6, 9] and 4–17% at multiple sites [6, 10].

Obesity is a potential contributor to CMP. Some studies have previously demonstrated that the effect of excess weight on joint compressive and shear forces can lead to painful degenerative joint conditions [11–13], while others have

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unveiled the link between pro-inflammatory cytokines released by metabolically active adipocytes and pain [14–16].

Although the effect of obesity on CMP has typically been investigated through clinical markers of general obesity such as body mass index (BMI), the evaluation of markers of visceral adiposity/abdominal obesity is becoming more frequent in pain research [17, 18]. The latter may account for the role of both mechanical and inflammatory mechanisms as they reflect more accurately an underlying inflammation pathway [19, 20]. For example, waist–height ratio (WHtR) is a relevant surrogate marker of adiposity-driven inflammation given its superior discriminatory power to identify individuals with an increased cardiometabolic risk [21, 22].

Evidence on the relationship between certain clinical markers of obesity (e.g., WHtR) and pain is currently sparse and inconsistent [23, 24]. Additionally, modelling the cumulative effect of excess weight on CMP has only been used in studies on pain at weight-bearing regions [25–27]. This study aimed to investigate the association of multiple clinical markers of obesity and trajectories of excess weight with CMP among adult Brazilians. It was hypothesized that general and abdominal obesity would be independently associated with CMP, and that the magnitude of this association would be stronger with increasing levels of obesity, longer exposures to excess weight, and greater pain "spreadness".

Materials and methods

Study design and population

A cross-sectional study was performed using data collected at the baseline of the ELSA-Brasil Musculoskeletal cohort (ELSA-Brasil MSK), which consists of an ancillary study from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) [28].

Between 2012 and 2014, 2901 active or retired civil servants from two teaching and research institutions (Universidade Federal de Minas Gerais and Federal Center for Technological Education of Minas Gerais) were evaluated at the ELSA-Brasil Investigation Center of Minas Gerais [29]. Those who completed an interview on musculoskeletal health and underwent anthropometric examinations for the evaluation of clinical markers of obesity were considered eligible for inclusion in the present study. Two civil servants who did not provide data on CMP or at least one clinical marker of obesity were excluded, resulting in a study sample of 2899 participants.

Assessment and definitions of chronic musculoskeletal pain (CMP)

A standardized questionnaire based on the Nordic Musculoskeletal Questionnaire (NMQ) [30] was used in conjunction with a body diagram for the evaluation of CMP at nine body sites: neck, shoulders, upper back, elbows, lower back, wrists/hands, hips/thighs, knees, ankles/feet. The questionnaire was applied by trained and certified interviewers during face-to-face assessments.

Two questions were used to identify CMP: "In the last 12 months, have you experienced pain, discomfort or stiffness in the [site]?" and "Did this problem that you had in the past 12 months last more than 6 months?". Those with a positive answer to both questions for at least one of the investigated sites were considered prevalent cases of CMP at any site.

Two distinct criteria were used for the evaluation of pain "spreadness": CMP was defined as multisite when located in ≥ 3 of the nine investigated sites [31], and as generalized when present simultaneously in the upper limbs (shoulders, elbows and/or wrists/hands), lower limbs (knees, hips/thighs and/or ankles/feet) and axial skeleton (neck, upper back and/or lower back) [32].

Assessment and definitions of clinical markers of obesity and weight trajectories

Anthropometric evaluations were performed by trained and certified examiners using standardized and calibrated instruments, according to a pre-defined protocol [33]. Weight (kg) and height (cm) were measured using Toledo® scales (model 2096PP, Toledo, BR, capacity of 200 kg and accuracy of 50 g) and SECA® stadiometer (model SE-216, Hamburg, BRD, accuracy of 0.1 cm), respectively.

BMI was calculated and categorized according to WHO cut-offs as overweight (25–29.9 kg/m^2), general obesity level I (30–34.9 kg/m^2) and general obesity level II/III (≥ 35 kg/m^2) [34]. BMI ≤ 24.9 kg/m^2 was considered normal weight.

Waist circumference (WC) was measured at the midpoint between the lowest rib margin and the iliac crest by an inelastic tape (range: 0–150 cm; precision of 1 mm; Mabis-Gulick, Waukegan, IL, USA). The average of two consecutive measurements was used. Categories of WC were defined according to sex-specific WHO cut-offs as abdominal obesity$_{WC}$ level I: 80.0–87.9 cm in women and 94.0–101.9 cm in men, and abdominal obesity$_{WC}$ level II: ≥ 88.0 cm in women and ≥ 102.0 cm in men [35]. WC < 80.0 cm in women and < 94.0 cm in men were indicative of the absence of abdominal obesity$_{WC}$.

WHtR was computed by dividing WC (cm, average of two measurements) by height (cm), and abdominal obesity$_{WHtR}$ (cm/cm) was defined as values ≥ 0.5 [22].

Body weight trajectories were computed according to BMI at present and at age 20. The latter was calculated similarly to BMI at present, except for the use of data on participants' self-reported weight (kg) at age 20, which was collected at baseline of ELSA-Brasil (2008–2010)

through the question "What was your approximate weight at age 20 [excluding pregnancy among women]?". Three mutually exclusive trajectories were considered: (1) normal weight at both times; (2) current excess weight (BMI ≥ 25.0 kg/m^2); (3) excess weight at both times. Participants exhibiting excess weight only at age 20 were excluded from all analyses on body weight trajectories as this group was too small to justify the inclusion of a separate "weight loss" trajectory ($N = 27$). Merging this fourth trajectory with any of the others was also judged inappropriate as these participants could differ substantially from those classified as having a stable trajectory of normal weight, and stable or increasing trajectories of excess weight.

Assessment of covariates

At baseline of ELSA-Brasil MSK, data on sociodemographic and lifestyle/clinical characteristics were collected through structured interviews and validated questionnaires [36]. Sex, age, educational level, leisure-time physical activity (LTPA) and depressive symptoms were considered relevant confounders given consistent evidence in the literature for their effect on both obesity and pain [4, 37, 38]. Self-reported skin color/race, labor status (active or retired) and nature of current occupation (or last occupation if retired) were also considered potential confounders because they have previously shown to be associated with either obesity or pain.

According to the definitions proposed by Autor et al. [39], the nature of occupation was categorized into four groups based on the description of the work task performed as non-routine non-manual (reference), routine non-manual, routine manual and non-routine manual. For the present study, the last two categories were grouped into a single "manual" category due to the small number of cases reporting a non-routine manual occupation ($N = 23$).

LTPA was assessed by the long version of the International Physical Activity Questionnaire (IPAQ) and categorized as insufficient, moderate or vigorous [40]. Depressive symptoms were assessed by the depression section (section G) of the Clinical Interview Schedule-Revised (CIS-R), which contains a total of nine questions about the presence, frequency and duration of depressive symptoms. This section begins with two introductory questions on overall depressive symptoms in the past month (if participants feel sad or depressed, and if they are still interested in the things they used to do). If one answer is affirmative, additional comprehensive assessment is made regarding symptoms in the past 7 days, with depressive symptoms defined as a score ≥ 2 [41].

Statistical analysis

Characteristics of the sample were described as frequencies and percentages, or means and standard deviations (SD). Separate binomial logistic regressions were used to test for associations of obesity clinical markers and weight trajectories (explanatory variables) with CMP at any site (response variable). Multinomial logistic regressions investigated associations of the same explanatory variables with multisite and generalized CMP (response variables). The absence of CMP was used as the reference for all analyses.

Regression analyses were performed without (univariate) and with covariate adjustment (multivariable), and results were presented as odds ratios (OR) and 95% confidence intervals (CI). Covariates were entered one at a time into multivariable models, in the following order: sex, age, self-reported skin color/race, educational level, labor status, nature of occupation, LTPA and depressive symptoms. Covariates not reaching a pre-defined threshold of $p \leq 0.20$ were removed, except for sex, age and educational level, which were kept in final models given that they are recognized confounders of the investigated associations (theory-based approach to confounding). Statistical significance in the final regression models was set at $p < 0.05$. Multivariable models investigating the association between clinical markers of abdominal obesity and CMP were further adjusted for BMI, in an attempt to distinguish between obesity-derived mechanical and inflammatory underlying pathways.

In multinomial regression models, tests for linear trends in associations across levels of clinical markers of obesity were performed using the likelihood ratio test. This test compares two models, one that uses the categorized explanatory variable and another that considers the explanatory variable as continuous. Values of $p_{\text{-trend}} \geq 0.05$ indicate no difference between these two models, thus supporting a linear trend hypothesis.

An exploratory (post hoc) descriptive analysis was performed using area-proportional Venn diagrams to inspect the overlap of CMP across different body regions, and to explore similarities and differences of its relationship with clinical markers of obesity and weight trajectories. Venn diagrams were created using R statistical software (version 3.5.3; R Core Team, Vienna). All other analyses were performed using Stata statistical software (version 12.0; Stata Corp, College Station, TX).

Results

A total of 2899 individuals aged 39–78 years (mean age 56.0 ± 8.93) were included. The sample comprised mostly highly educated and occupationally active civil servants

(66.2% and 82.3%, respectively). The sociodemographic characteristics of included participants are listed in Table 1.

Prevalence of chronic musculoskeletal pain (CMP)

CMP was reported by 55% of the participants. The most frequently reported site of symptoms was the knee (22.5%), followed by the lower back (18.6%) and shoulders (17.8%). Considering the three investigated body regions, most participants reported pain in the lower limbs (36%). The superimposition of pain sites was highly frequent; for instance, only 22.5% of the participants reported single-sited pain; whereas, 13.2% reported pain in two sites and 19.1% in ≥ 3 sites (multisite). More than a quarter of the participants (27.6%) also had pain in more than one body region and 10.3% had generalized pain.

Participants reporting CMP at any of the investigated sites were predominantly women, aged 55–64 years, had lower levels of physical activity, and had higher prevalence of depressive symptoms. A similar pattern was observed between participants with multisite or generalized CMP compared with those with no pain (see Online Resource 1, which describes the sample according to different presentations of CMP).

Prevalence of obesity clinical markers and weight trajectories

According to currently assessed BMI, 40.7% of the participants were overweight, 16.7% had general obesity level I and 5.9% had general obesity level II/III. Prevalence of abdominal obesity$_{WC}$ level I and level II was 25.8% and 41.5%, respectively. The prevalence of abdominal obesity$_{WHtR}$ was 79.9%.

At age 20, 8.3% had excess weight (7.1% were overweight, 0.9% had general obesity level I and 0.3% had general obesity level II). The majority of participants (56.4%) exhibited a trajectory of current excess weight, changing from normal weight at age 20 to current overweight or obesity. The proportion of participants showing trajectories of excess weight and normal weight at both times was 7.4% and 36.2%, respectively.

Relationship between CMP and obesity clinical markers/weight trajectories

The prevalence of CMP at any site showed a graded increase with higher obesity levels, reaching 71% among participants with general obesity level II/III and 63% among those with level II abdominal obesity$_{WC}$. The same pattern was observed for multisite and generalized CMP (see Online Resource 2, which illustrates the prevalence of different presentations of CMP according to obesity clinical markers).

Table 1 Characteristics of included participants, ELSA-Brasil MSK (2012–2014)

Characteristic	Overall sample, $n = 2899$
Women	1534 (52.9)
Men	1365 (47.1)
Age group	
< 45	289 (10.0)
45–54	1043 (36.0)
55–64	1038 (35.8)
65+	529 (18.2)
Self-reported skin color/race[a]	
White	1416 (49.5)
Brown	997 (34.9)
Black	368 (12.9)
Yellow	64 (2.2)
Indigenous	15 (0.5)
Educational level[b]	
Higher education	1917 (66.2)
Secondary school	735 (25.4)
Primary school or lower	245 (8.4)
Work status	
Active	2386 (82.3)
Retired	513 (17.7)
Nature of occupation[c]	
NR non-manual	1746 (60.7)
R non-manual	764 (26.6)
Manual	364 (12.7)
LTPA	
Insufficient	2055 (70.9)
Moderate	604 (20.8)
Vigorous	240 (8.3)
Depressive symptoms	450 (15.5)
Chronic pain	1595 (55.0)
Multisite pain	553 (19.1)
Generalized pain	299 (10.3)
Clinical markers of general obesity	
Overweight (BMI 25–29.9 kg/m^2)	1179 (40.7)
Obesity level I (BMI 30–34.9 kg/m^2)	483 (16.7)
Obesity level II/III (BMI ≥ 35 kg/m^2)	171 (5.9)
Clinical markers of abdominal obesity	
Abdominal obesity$_{WC}$ level I[d]	749 (25.8)
Abdominal obesity$_{WC}$ level II[e]	1203 (41.5)
Abdominal obesity$_{WHtR}$[f]	2315 (79.9)
Body weight trajectories	
Current excess weight	1596 (56.4)
Excess weight at both times	210 (7.4)

Data presented as frequencies and percentages for valid cases only

NR non-routine, *R* routine, *LTPA* leisure-time physical activity

[a]Frequency of missing values: 39

[b]Frequency of missing values: 2

[c]Frequency of missing values: 25

[d]Defined as WC 80.0–87.9 cm in women and 94.0–101.9 cm in men

[e]Defined as WC ≥ 88.0 cm in women and ≥ 102.0 cm in men

[f]Defined as WHtR ≥ 0.5 cm/m

Results of binomial regression analyses concerning CMP at any site are presented in Table 2. After adjustments, all markers of general and abdominal obesity but overweight were associated with CMP, with general obesity level II/III showing the strongest association (OR 2.08; 95% CI 1.45–2.99). Additionally, the magnitude of associations indicated a dose–response relationship with increasing levels of obesity: the chances of any CMP raised from 53 to 108% ($p_{\text{-trend}} = 0.54$) and from 32 to 63% ($p_{\text{-trend}} = 0.69$) in the presence of more severe levels of general and abdominal obesity, respectively. Trajectories of excess weight were also associated with CMP at any site, with current excess weight increasing by 31% and excess weight at both times by 55% ($p_{\text{-trend}} = 0.61$) the chance of any CMP (Table 2).

Results of multinomial regression analyses on the association of clinical markers of obesity and body weight trajectories with multisite CMP are presented in Table 3. After adjustments, all markers of general and abdominal obesity were associated with multisite CMP. Similar to the analysis having any CMP as response variable, general obesity level II/III was also the clinical obesity marker showing the strongest association with multisite CMP (OR 3.19; 95% CI 2.06–4.94). The magnitude of associations was consistently stronger for multisite CMP than for local symptomatic presentations, with the most prominent increase in magnitude being observed for the association with general obesity level II/III (local CMP: OR 1.64; 95% CI 1.10–2.45 versus multisite CMP: OR 3.19; 95% CI 2.06–4.94). Dose–response relationships were also observed with increasing levels of obesity ($p_{\text{-trend}} = 0.77$ and 0.61 for current BMI and WC, respectively). Trajectories of current excess weight and excess weight at both times increased the likelihood of multisite pain by 68% and 86.0%, respectively (Table 3).

The results of analyses considering the spatial distribution of CMP are presented in Table 4. These were similar to those found for multisite CMP, except for the lack of association with overweight and abdominal obesity$_{\text{WC}}$ level I. Stronger associations were found for generalized CMP when compared to regional symptomatic presentations (Table 4). Participants presenting general obesity level II/III showed a large increase (265%) in the likelihood of generalized CMP. Dose–response relationships were also observed with increasing levels of obesity ($p_{\text{-trend}} = 0.87$ and 0.48 for current BMI and WC, respectively). Trajectories of excess weight increased by similar amounts (~ 75%) the likelihood of generalized CMP (Table 4).

According to the area-proportional Venn diagrams described in Fig. 1, generalized symptoms were present in 18.9% of participants reporting CMP, with lower limbs corresponding to the most affected region, as 65% of those with CMP presented symptoms only in the lower limbs or in combination with other regions. Graded increases in the prevalence of CMP were observed with increasing levels of obesity (general and abdominal) and with longer exposures

Table 2 Association of clinical markers of obesity and body weight trajectories with chronic musculoskeletal pain at any site ($n = 2897$), ELSA-Brasil MSK (2012–2014)

	Unadjusted model OR (95% CI)	Adjusted model[a] OR (95% CI)
Clinical markers of general obesity		
Overweight (BMI 25–29.9 kg/m^2)	1.12 (0.95–1.33)	1.15 (0.97–1.37)
Obesity level I (BMI 30–34.9 kg/m^2)	1.54 (1.24–1.92)**	1.53 (1.22–1.92)**
Obesity level II/III (BMI ≥ 35 kg/m^2)	2.41 (1.69–3.42)**	2.08 (1.45–2.99)**
Clinical markers of abdominal obesity		
Abdominal obesity$_{\text{WC}}$ level I[b]	1.45 (1.19–1.76)**	1.32 (1.08–1.61)*
Abdominal obesity$_{\text{WC}}$ level II[c]	2.05 (1.72–2.44)**	1.63 (1.36–1.96)**
Abdominal obesity$_{\text{WHtR}}$[d]	1.57 (1.31–1.88)**	1.59 (1.31–1.93)**
Body weight trajectories		
Current excess weight (BMI ≥ 25 kg/m^2)	1.31 (1.12–1.54)**	1.31 (1.11–1.54)**
Excess weight at both times	1.41 (1.04–1.91)*	1.55 (1.13–2.12)*

Body mass index reference: normal weight (BMI ≤ 24.9 kg/m^2). Waist circumference reference: WC < 80.0 cm in women and < 94.0 cm in men. Waist-height ratio reference: WHtR < 0.5 cm/m. Body weight trajectories reference: normal weight (BMI ≤ 24.9 kg/m^2) at age 20 and currently (68 missing values)

BMI body mass index, *WC* waist circumference, *WHtR* waist–height ratio

*$p < 0.05$

**$p < 0.001$

[a]Adjusted by sex, age, education, leisure-time physical activity and depressive symptoms

[b]Defined as WC 80.0–87.9 cm in women and 94.0–101.9 cm in men

[c]Defined as WC ≥ 88.0 cm in women and ≥ 102.0 cm in men

[d]Defined as WHtR ≥ 0.5 cm/m

Table 3 Association of clinical markers of obesity and body weight trajectories with local and multisite chronic musculoskeletal pain ($n = 2886$), ELSA-Brasil MSK (2012–2014)

	Unadjusted model OR (95%CI)		Adjusted model[a] OR (95% CI)	
	Local CMP (1–2 sites)	Multisite CMP (≥ 3 sites)	Local CMP (1–2 sites)	Multisite CMP (≥ 3 sites)
Clinical markers of general obesity				
Overweight (BMI 25–29.9 kg/m^2)	1.04 (0.86–1.25)	1.29 (1.02–1.63)*	1.06 (0.88–1.28)	1.35 (1.05–1.72)*
Obesity level I (BMI 30–34.9 kg/m^2)	1.38 (1.08–1.76)*	1.91 (1.42–2.55)**	1.38 (1.08–1.77)*	1.92 (1.41–2.60)**
Obesity level II/III (BMI ≥ 35 kg/m^2)	1.82 (1.22–2.70)*	3.78 (2.49–5.75)**	1.64 (1.10–2.45)*	3.19 (2.06–4.94)**
Clinical markers of abdominal obesity				
Abdominal obesity$_{WC}$ level I[b]	1.39 (1.13–1.73)*	1.57 (1.18–2.08)*	1.30 (1.05–1.62)*	1.37 (1.02–1.84)*
Abdominal obesity$_{WC}$ level II[c]	1.73 (1.42–2.10)**	2.82 (2.21–3.60)**	1.46 (1.20–1.79)**	2.03 (1.57–2.63)**
Abdominal obesity$_{WHtR}$[d]	1.46 (1.19–1.78)**	1.80 (1.38–2.35)**	1.48 (1.20–1.83)**	1.84 (1.39–2.44)**
Body weight trajectories				
Current excess weight (BMI ≥ 25 kg/m^2)	1.15 (0.97–1.37)	1.66 (1.33–2.07)**	1.16 (0.97–1.38)	1.68 (1.33–2.11)**
Excess weight at both times	1.33 (0.96–1.86)	1.61 (1.07–2.43)*	1.43 (1.02–2.01)*	1.86 (1.21–2.87)*

Body mass index reference: normal weight (BMI ≤ 24.9 kg/m^2). Waist circumference reference: WC < 80.0 cm in women and < 94.0 cm in men. Waist-height ratio reference: WHtR < 0.5 cm/m. Body weight trajectories reference: normal weight (BMI ≤ 24.9 kg/m^2) at age 20 and currently (68 missing values)

CMP chronic musculoskeletal pain, *BMI* body mass index, *WC* waist circumference, *WHtR* waist–height ratio

*$p < 0.05$

**$p < 0.001$

[a]Adjusted by sex, age, education, leisure-time physical activity and depressive symptoms

[b]Defined as WC 80.0–87.9 cm in women and 94.0–101.9 cm in men

[c]Defined as WC ≥ 88.0 cm in women and ≥ 102.0 cm in men

[d]Defined as WHtR ≥ 0.5 cm/m

to excess weight only for the lower limbs; i.e., the area of the circle corresponding to CMP in the lower limb increased when changing from less to more severe levels of obesity; whereas, the area of circles corresponding to CMP in the axial skeleton and upper limbs remained the same (or were slightly reduced) (see Online Resource 3, which illustrates the prevalence of CMP according to body regions and obesity clinical markers/weight trajectories). Additionally, a graded increase in the superimposition of painful regions (generalized CMP) was also present with increasing levels of general or abdominal obesity, but not with longer exposures to excess weight (Online Resource 3).

Discussion

The results confirmed our three hypotheses. First, we found that high levels of general and abdominal obesity were strongly associated with CMP, particularly when symptoms were spread across multiple sites or body regions. Importantly, these associations were independent of sex, age, educational level, physical activity and symptoms of depression, and also showed a dose–response gradient.

Our findings are consistent with those of longitudinal studies of effects of obesity on the development of future multisite and generalized pain [42–45], as well as with prior evidence on the association of general and abdominal obesity with chronic pain syndromes [25, 27, 46–51]. Most of these studies revealed stronger associations between higher obesity levels and pain, similarly to the dose–response observed in the current study. For example, linear increases in the risk and severity of low back pain were observed with increasing sex-specific quartiles of BMI and WC in the AusDiab cohort [50]. Additionally, Ray et al. [47] have reported a 9% increase in the odds of chronic pain for each unit increase in BMI among older adults.

To the best of our knowledge, our study is the first to investigate the association of different trajectories of excess weight with CMP located at body sites other than the lower back [27, 52] or knee [24–26]. Associations of greater magnitude were consistently found in the presence of overweight or obesity both at age 20 and currently, supporting the role of accumulation of exposure across the life course as an important risk factor for the development of CMP. Although the effect of longer exposures to excess weight on pain is frequently attributed to a mechanical pathway of chronic excess load irrespective of abdominal obesity [24, 27], we believe it

Table 4 Association of clinical markers of obesity and body weight trajectories with regional and generalized chronic musculoskeletal pain ($n = 2892$), ELSA-Brasil MSK (2012–2014)

	Unadjusted model OR (95% CI)		Adjusted model[a] OR (95% CI)	
	Regional CMP (1–2 regions)	Generalized CMP (3 regions)	Regional CMP (1–2 regions)	Generalized CMP (3 regions)
Clinical markers of general obesity				
Overweight (BMI 25–29.9 kg/m^2)	1.09 (0.91–1.29)	1.29 (0.95–1.75)	1.11 (0.93–1.33)	1.35 (0.98–1.86)
Obesity level I (BMI 30–34.9 kg/m^2)	1.43 (1.13–1.79)*	2.19 (1.52–3.14)**	1.42 (1.12–1.79)*	2.25 (1.54–3.28)**
Obesity level II/III (BMI ≥ 35 kg/m^2)	2.06 (1.42–2.99)**	4.28 (2.61–7.01)**	1.83 (1.25–2.67)*	3.65 (2.18–6.11)**
Clinical markers of abdominal obesity				
Abdominal obesity$_{WC}$ level I[b]	1.43 (1.17–1.74)**	1.55 (1.06–2.25)*	1.31 (1.07–1.62)*	1.34 (0.91–1.97)
Abdominal obesity$_{WC}$ level II[c]	1.85 (1.54–2.22)**	3.26 (2.37–4.47)**	1.52 (1.26–1.85)**	2.28 (1.64–3.19)**
Abdominal obesity$_{WHtR}$[d]	1.48 (1.23–1.80)**	2.06 (1.44–2.94)**	1.51 (1.24–1.85)**	2.12 (1.46–3.07)**
Body weight trajectories				
Current excess weight (BMI ≥ 25 kg/m^2)	1.23 (1.04–1.45)*	1.72 (1.29–2.28)**	1.23 (1.04–1.46)*	1.74 (1.29–2.34)**
Excess weight at both times	1.39 (1.02–1.91)*	1.51 (0.88–2.56)	1.51 (1.09–2.09)*	1.76 (1.01–3.05)*

Body mass index reference: normal weight (BMI ≤ 24.9 kg/m^2). Waist circumference reference: WC < 80.0 cm in women and < 94.0 cm in men. Waist-height ratio reference: WHtR < 0.5 cm/m. Body weight trajectories reference: normal weight (BMI ≤ 24.9 kg/m^2) at age 20 and currently (68 missing values)

CMP chronic musculoskeletal pain, *BMI* body mass index, *WC* waist circumference, *WHtR* waist–height ratio

*$p < 0.05$

**$p < 0.001$

[a]Adjusted by sex, age, education, leisure-time physical activity and depressive symptoms

[b]Defined as WC 80.0–87.9 cm in women and 94.0–101.9 cm in men

[c]Defined as WC ≥ 88.0 cm in women and ≥ 102.0 cm in men

[d]Defined as WHtR ≥ 0.5 cm/m

would be difficult to conclude on the relative role of obesity-derived causal pathways based solely on the investigation of trajectories of excess weight, as these pathways are known to converge in the presence of persistent excess weight. For instance, a high proportion of obese adults who are metabolically healthy tend to transition to a metabolic unhealthy status (which has chronic low-grade inflammation as one of its core component) later in their life [53]. Likewise, the use of mutual adjustments for markers of general and abdominal obesity is another approach that may have a limited ability to demonstrate the added value of one pathway over the other. Although employed in previous studies as an attempt to disentangle the effects of mechanical and inflammatory mechanisms on the development of pain [48], BMI and WC are known to be highly correlated [54]. As expected, a post hoc analysis of our data revealed a very high correlation between these measures ($r = 0.86$), and associations between abdominal obesity (WC or WHtR) and CMP were lost after mutual adjustment for BMI, regardless of the CMP presentation (data not shown).

For all the investigated pain presentations, we found associations of somewhat stronger magnitude for clinical markers of general obesity than for their corresponding levels of abdominal$_{WC}$ obesity; e.g., ORs for general obesity level I were higher than those for abdominal obesity$_{WC}$ level I, and so on. This could indicate a more prominent role of mechanical or structural components in the aetiology of CMP, even though the units of measurements of BMI and WC are very distinct. However, we also found that the magnitude of associations with each pain presentation was similar between general obesity level I and abdominal obesity$_{WHtR}$, which is a measure considered superior to WC in identifying individuals with obesity-driven inflammation and metabolic alterations [21].

Another way to gain insight on the mechanisms linking obesity and pain is to explore differences in the relationship between clinical markers of obesity and distinct pain presentations. For example, CMP originated in pathophysiological processes triggered by obesity-related inflammation, such as central sensitization, typically exhibit a generalized

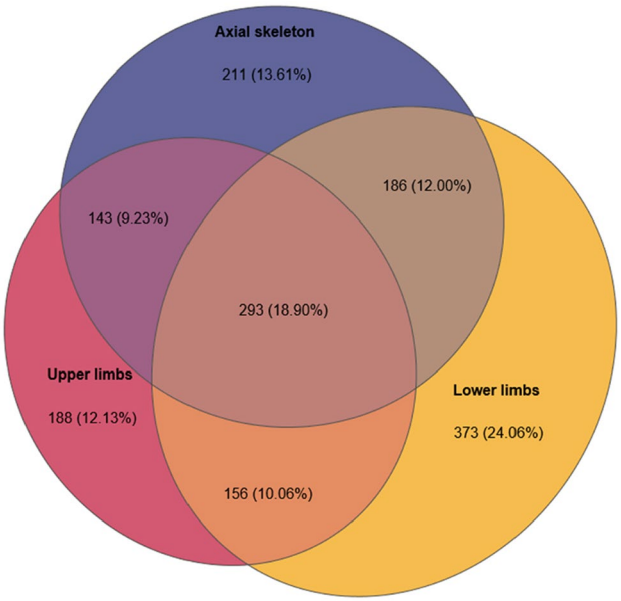

Fig. 1 Venn diagram of the frequency of chronic musculoskeletal pain according to body region: upper limbs (shoulders, elbows and/or wrists/hands), lower limbs (knees, hips/thighs and/or ankles/feet) and axial skeleton (neck, upper back and/or lower back), ELSA-Brasil MSK (2012–2014)

distribution across multiple body regions [55, 56]. On the other hand, mechanical factors would play a predominant role in the development of local joint pain [57]. According to our last hypothesis, we expected to find stronger associations between clinical markers of obesity and CMP presentations with greater pain "spreadness". This was confirmed in all analyses, regardless of definition used to indicate pain "spreadness" (multisite or generalized CMP).

When compared to other obesity clinical markers, general obesity level II/III showed the strongest associations with multisite or generalized CMP. Although this suggests at first glance that BMI would be superior to abdominal obesity in predicting multisite or generalized CMP, it could also be a result of BMI being more finely categorized (four levels) than the other obesity markers investigated in this study. Data from a cohort of older Tasmanian adults indicated a more pronounced dose–response between increasing numbers of painful sites and obesity measures that reflect an underlying inflammation pathway [45].

Our definitions for multisite and generalized CMP were similar to those used in a Norwegian longitudinal cohort [31, 32]. Multisite pain is recognizably different from generalized pain (e.g., only the latter is considered for the diagnostic of fibromyalgia), and there is currently a lack of consensus on the ideal cut-off for the definition of the former [9]. Because the body diagram used for the identification of pain sites at ELSA-Brasil MSK did not make distinctions between unilateral and bilateral pain (except for knee and hand), it was not possible to define generalized pain in this study according to the revised American College of Rheumatology (ACR) 2016 fibromyalgia criteria, which considers pain as generalized when it is present in at least four of five body regions (including four body quadrants and the axial skeleton) [5]. Nevertheless, we believe that our definition was able to identify most clinical presentations that satisfy the ACR criteria for generalized pain. For example, by considering information on bilateral knee and hand pain, misclassifications would only be possible for 12.5% of participants with regional pain and 42.8% of those with generalized pain (data not shown). Additionally, given that bilateral pain could also be present at four additional pain sites (shoulders, elbows, hips/thighs and ankles/feet), the risk of misclassification would be even lower.

Taken together, our results may support the contribution of multiple obesity-derived pathways to CMP, particularly to generalized pain presentations. Additionally, findings from our exploratory descriptive analysis provided preliminary indication of a shared role of mechanical and inflammatory mechanisms in the continuum of CMP, as they suggest that a pronounced effect of increasing levels of obesity at weight-bearing joints (lower limbs) is accompanied by the "spreadness" of pain to other sites, including non-weight bearing body regions. Nevertheless, there are some limitations to our study that need to be acknowledged. First, due to its cross-sectional observational design, reverse causality and confounding cannot be ruled out. However, previous studies have failed to demonstrate a strong direct causal effect of pain on future obesity [58, 59], thus reducing the possibility that reverse causation would have had a large impact on our estimates. Additionally, the 2-step adjustment procedure used in our analysis allowed judgmental assumptions regarding causal relationships to assist the selection of covariates for the final regression models (theory-driven approach), also reducing the risk of confounding [60]; e.g., educational level could not be considered a confounder based on statistical associations, but it was included given its recognized effect on both obesity and pain [61, 62]. Another limitation that should be considered is the possibility of measurement error in the assessment of body weight trajectories, given that they were partially computed using a subjective recall of body weight at age 20. Although overnight fasting blood samples have been collected at all rounds of examinations in ELSA-Brasil [28], until this date stored biologic specimens from baseline of ELSA-Brasil MSK have not been analyzed for the determination of profiles of serum inflammatory markers. The use of such data in future studies will further contribute to explain the role of these multiple components in the causal pathway linking obesity and chronic musculoskeletal pain.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to report.

Ethical approval This study used data from ELSA-Brasil and its ancillary musculoskeletal cohort, ELSA-Brasil MSK. ELSA-Brasil was approved by the National Committee for Ethics in Research (Comissão Nacional de Ética em Pesquisa—CONEP), Brazil [protocol 976/2006]. ELSA-Brasil MSK was approved by the ethics and research committee of Universidade Federal de Minas Gerais (UFMG), Brazil [protocol COEP/UFMG, Etic 186/06; CEP 1.160.939; CAAE 0186.1.203.000-06]. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and all participants signed a written informed consent after they had been informed of details of the study.

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