UNIVERSIDADE FEDERAL DE MINAS GERAIS
Faculdade de Medicina
Programa de Pós-Graduação em Saúde Pública

Aline Bárbara Pereira Costa

INDICADORES DE OBESIDADE: associação com a prevalência, incidência e prognóstico de dor musculoesquelética em participantes da coorte ELSA-BRASIL Musculoesquelético (ELSA-BRASIL MSK), 2012-2019

Belo Horizonte
2021

Aline Bárbara Pereira Costa

INDICADORES DE OBESIDADE: associação com a prevalência, incidência e prognóstico de dor musculoesquelética em participantes da coorte ELSA-BRASIL Musculoesquelético (ELSA-BRASIL MSK), 2012-2019

Versão Final

Tese apresentada ao Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do título de Doutora em Saúde Pública.

Orientadora: Profª. Dra. Sandhi Maria Barreto
Coorientadoras: Profª. Dra. Rosa Weiss Telles e Dra. Luciana A. Carneiro Machado

Belo Horizonte
2021

Costa, Aline Barbara Pereira.
C837i Indicadores de obesidade [manuscrito]: associação com a prevalência, incidência e prognóstico de dor musculoesquelética em participantes da coorte ELSA-BRASIL Musculoesquelético (ELSA-BRASIL MSK), 2012-2019. / Aline Barbara Pereira Costa. - - Belo Horizonte: 2021.
128f.: il.
Orientador (a): Sandhi Maria Barreto.
Coorientador (a): Rosa Weiss Telles; Luciana A. Carneiro Machado.
Área de concentração: Saúde Pública.
Tese (doutorado): Universidade Federal de Minas Gerais, Faculdade de Medicina.

1. Obesidade. 2. Sobrepeso. 3. Dor Musculoesquelética. 4. Dor Crônica. 5. Dissertação Acadêmica. I. Barreto, Sandhi Maria. II. Telles, Rosa Weiss. III. Machado, Luciana A. Carneiro. IV. Universidade Federal de Minas Gerais, Faculdade de Medicina. V. Título.

NLM: QU 248

Bibliotecário responsável: Fabian Rodrigo dos Santos CRB-6/2697

UNIVERSIDADE FEDERAL DE MINAS GERAIS
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE PÚBLICA

ATA DA DEFESA DE TESE DA ALUNA

ALINE BÁRBARA PEREIRA COSTA

Às 14:00 horas do dia 06 de outubro de 2021, através de transmissão por videoconferência pela Plataforma Lifesize (**Link da transmissão no YouTube:** https://youtu.be/WhzFgU5K09I), realizou-se a sessão pública para a defesa da Tese de **ALINE BÁRBARA PEREIRA COSTA.** A presidência da sessão coube a **Professora Sandhi Maria Barreto,** orientadora. Inicialmente, a presidente fez a apresentação da Comissão Examinadora assim constituída: **Prof(a). Rosa Weiss Telles – Coorientadora (UFMG), Prof(a). Rafael Zambelli de Almeida Pinto (UFMG), Prof(a). Fabiana de Miranda Moura dos Santos (UFMG), Prof(a). Maria del Carmen Bisi Molina (Universidade Federal do Espírito Santo) e Prof(a). Rafael Mendonça da Silva Chakr (UFRGS).** Em seguida, a candidata fez a apresentação do trabalho que constitui sua **Tese de Doutorado**, intitulada: "***INDICADORES DE OBESIDADE: ASSOCIAÇÃO COM A PREVALÊNCIA, INCIDÊNCIA E PROGNÓSTICO DE DOR MUSCULOESQUELÉTICA EM PARTICIPANTES DA COORTE ELSA-BRASIL MUSCULOESQUELÉTICO (ELSA-BRASIL MSK), 2012-2019***". Seguiu-se a arguição pelos examinadores e logo após, a Comissão reuniu-se, sem a presença da candidata e do público e decidiu considerar **aprovada** a **Tese de Doutorado**. O resultado final foi comunicado publicamente à candidata pela presidente da Comissão. Nada mais havendo a tratar, a presidente encerrou a sessão e lavrou a presente ata que, depois de lida, se aprovada, será assinada pela Comissão Examinadora.

Belo Horizonte, 06 de outubro de 2021.

Assinatura dos membros da banca examinadora:

Documento assinado eletronicamente por **Rosa Weiss Telles**, **Professora do Magistério Superior**, em 07/10/2021, às 11:37, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Rafael Mendonça da Silva Chakr**, **Usuário Externo**, em 07/10/2021, às 13:50, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Maria del Carmen Bisi Molina**, **Usuário Externo**, em 07/10/2021, às 17:13, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Sandhi Maria Barreto**, **Presidente de comissão**, em 08/10/2021, às 08:47, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Rafael Zambelli de Almeida Pinto, Usuário Externo**, em 08/10/2021, às 09:22, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

Documento assinado eletronicamente por **Fabiana de Miranda Moura dos Santos, Professora do Magistério Superior**, em 09/10/2021, às 22:15, conforme horário oficial de Brasília, com fundamento no art. 5º do Decreto nº 10.543, de 13 de novembro de 2020.

A autenticidade deste documento pode ser conferida no site https://sei.ufmg.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, informando o código verificador **0998359** e o código CRC **EBE5EA3B**.

UNIVERSIDADE FEDERAL DE MINAS GERAIS

ATA DO EXAME DE QUALIFICAÇÃO DA ALUNA

ALINE BÁRBARA PEREIRA COSTA

Realizou-se, no dia 18 de março de 2019, às 09:00 horas, Sala 526, Faculdade de Medicina. Avenida Professor Alfredo Balena, 190. Santa Efigênia., da Universidade Federal de Minas Gerais, a apresentação do exame de qualificação da aluna **ALINE BÁRBARA PEREIRA COSTA**, número de registro 2016653471, intitulado *DOR MUSCULOESQUELÉTICA CRÔNICA E OSTEOARTRITE DE JOELHOS: ASSOCIAÇÃO COM MARCADORES DE OBESIDADE E TRAJETÓRIA DE PESO CORPORAL EM PARTICIPANTES DO ELSA-BRASIL MUSCULOESQUELÉTICO(ELSA-BRASIL MSK), 2012-2014*, perante a Comissão Examinadora composta pelos professores: Prof(a). Sandhi Maria Barreto - Orientador (UFMG), Prof(a). Rosa Weiss Telles (UFMG), Prof(a). Luciana Andrade Carneiro Machado (UFMG), Prof(a). Rafael Zambelli de Almeida Pinto (UFMG), Prof(a). Silvia Nascimento de Freitas (UFOP), Prof(a). Josimari Melo de Santana (Universidade Federal de Sergipe). Terminada a apresentação, foi considerada:

(X) aprovada ( ) reprovada

e, para constar, foi lavrada a presente ata que, lida e aprovada, vai assinada pelos membros da Comissão.

Belo Horizonte, 18 de março de 2019.

Prof(a). Sandhi Maria Barreto (Doutor)

Prof(a). Rosa Weiss Telles (Doutor)

Prof(a). Luciana Andrade Carneiro Machado (Doutor) (participação por videoconferência)

Prof(a). Rafael Zambelli de Almeida Pinto (Doutor)

Prof(a). Silvia Nascimento de Freitas (Doutora)

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Reitora

Profª. Sandra Regina Goulart Almeida

Vice-Reitor

Prof. Alessandro Fernandes Moreira

Pró-Reitor de Pós-Graduação

Prof. Fábio Alves da Silva Júnior

Pró-Reitor de Pesquisa

Prof. Mario Fernando Montenegro Campos

FACULDADE DE MEDICINA

Diretor

Prof. Humberto José Alves

Vice-Diretora

Profª. Alamanda Kfoury Pereira

Coordenador Geral do Centro de Pós-Graduação

Prof. Tarcizo Afonso Nunes

Subcoordenador Geral do Centro de Pós-Graduação

Profª. Eli Iola Gurgel Andrade

Chefe do Departamento de Medicina Preventiva e Social

Prof. Raphael Augusto Teixeira de Aguiar

PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE-PÚBLICA

Coordenadora

Profª. Luana Giatti Gonçalves

Subcoordenadora

Profª. Lidyane do Valle Camelo

Colegiado

Profª. Eli Iola Gurgel Andrade (Titular) - Prof. Antônio Thomaz Gonzaga da Matta Machado (Suplente)

Profª. Luana Giatti Gonçalves (Titular) – Profª. Lidyane do Valle Camelo (Suplente)

Profª. Sandhi Maria Barreto (Titular) – Prof. Antonio Luiz Pinho Ribeiro (Suplente)

Profª. Mariângela Leal Cherchiglia (Titular) – Profª. Ilka Afonso Reis (Suplente)

Profª. Ada Ávila Assunção (Titular) – Profª Adriane Mesquita de Medeiros (Suplente)

Profª. Alaneir de Fátima dos Santos (Titular) – Prof. Rafael Moreira Claro (Suplente)

Profª. Déborah Carvalho Malta (Titular) – Profª. Amélia Augusta Friche (Suplente)

Fabiana Martins – Representante Discente (Titular)

Priscila Souza – Representante Discente (Suplente)

DEDICATÓRIA

À minha amada avó Terezinha José Mapa (*in memoriam*), que sonhou com esse momento.

AGRADECIMENTOS

À minha orientadora, Profª. Sandhi M. Barreto e às minhas coorientadoras Rosa W. Telles e Luciana A.C. Machado por todo conhecimento que compartilharam e construiram comigo, pelas oportunidades de crescimento profissional e pessoal e pela paciência que tiveram nos momentos mais desafiadores.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), que me concedeu bolsa durante boa parte do meu doutoramento.

Aos participantes do Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil), que gentilmente aceitaram doar seu tempo para o estudo e assim contribuem para o avanço da pesquisa em nosso país. Sem vocês meu trabalho e de muitos colegas não existiria.

À toda a equipe do ELSA-Brasil, especialmente a do Centro de Investigação de Minas Gerais. Vocês participaram de forma importante do meu trabalho e da minha trajetória no doutorado e na pesquisa.

Ao corpo docente e discente do Programa de Pós Graduação em Saúde Pública da Faculdade de Medicina, com quem partilhei tantos momentos e que contribuiram de forma ímpar para minha formação.

Aos meus amigos, que sempre estiveram ao meu lado, mesmo à distância, oferecendo ouvidos, ombros, palavras de incentivo e orações. Saibam que vocês são anjos em minha vida.

Aos meus pais, irmã e sobrinha, que sempre foram meu alicerce e meus maiores incentivadores. Saibam que o amor e a confiança de vocês foram fundamentais para eu chegar até aqui.

E a Deus, que me abençoou com essa oportunidade, me conduziu e capacitou a cada passo da

caminhada e me cercou de pessoas especiais que me ajudaram a seguir. Ao Senhor, toda honra e toda a glória.

RESUMO

Obesidade e dor musculoesquelética (ME) são morbidades que afetam um número significativo e crescente de indivíduos, impactando de forma negativa a qualidade de vida dessas pessoas. Estudos mostram que obesos apresentam prevalências aumentadas de dor ME, mas são escassos os trabalhos que avaliaram a população brasileira, o papel da exposição prolongada ao excesso de peso e que mensuraram o impacto da obesidade no risco e prognóstico da dor ME. Diante disso, investigamos se diferentes marcadores de obesidade estavam associados à prevalência de dor ME crônica em participantes do Estudo Longitudinal de Saúde do Adulto Musculoesquelético (ELSA-Brasil-MSK) e posteriormente avaliamos se a obesidade afetava o risco e prognóstico da dor frequente em joelhos. Esse trabalho foi desenvolvido com dados da linha de base da coorte ELSA-Brasil-MSK e as avaliações relacionadas a risco e prognóstico se basearam em dados do monitoramento telefônico anual da coorte, para identificação da ocorrência de episódios de dor. Na análise transversal observamos que entre os 2.899 participantes a obesidade, seja definida pelo índice de massa corporal, pela circunferência da cintura ou pela razão cintura-estatura, estava associada à uma probabilidade aumentada de ter dor ME crônica (OR variaram de 1,32 para obesidade abdominal nível I a 2,08 para índice de massa corporal ≥35 kg/m2), dor ME crônica em múltiplos locais (OR variaram de 1,35 para sobrepeso a 3,19 para índice de massa corporal ≥35 kg/m^2) e dor ME crônica generalizada (ORs variaram de 2,12 para razão cintura-estatura ≥0,5 a 3,65 para índice de massa corporal ≥35 kg/m^2). Quanto à trajetória de peso corporal, tanto os participantes que apresentaram excesso de peso atual, quanto os que relataram excesso de peso aos 20 anos e também foram classificados dessa forma na linha de base, apresentaram maior probabilidade de ter todos os fenótipos de dor. Na análise longitudinal, os 2.644 participantes que responderam às quatro entrevistas telefônicas de monitoramento de desfechos foram divididos em dois grupos: 1.896 compuseram a coorte de incidência (sem dor frequente e dor crônica de joelho na linha de base)

e 748 compuseram a coorte de prognóstico (com dor frequente e/ou dor crônica de joelho na linha de base). Os resultados mostraram que na coorte de incidência a obesidade aumentou o risco de ter um (OR: 1,63; IC 95% 1,13-2,37) e múltiplos episódios de dor frequente em joelhos (OR: 2,61; IC 95% 1,71-3,97), bem como o risco de ter episódios graves (OR: 2,10; IC 95% 1,50-2,95) e não graves (OR: 1,72; IC 95% 1,04-2,84). Já na coorte de prognóstico, a obesidade foi fator de risco apenas para o relato de episódios múltiplos (OR: 2,54; IC 95% 1,60-4,05) e graves (OR: 2,31; IC 95% 1,49-3,59). Esses resultados alertam para a importância de se desenvolver estratégias direcionadas ao manejo do peso tanto no âmbito coletivo, quanto no individual. Interromper, ou pelo menos desacelerar o crescimento das taxas de excesso de peso na população e incluir o manejo da obesidade no acompanhamento ambulatorial de indivíduos acometidos por dor ME são medidas importantes para prevenir a ocorrência desse agravo e promover um melhor prognóstico para pacientes que já convivem com dor ME.

Palavras-chave: Obesidade; Sobrepeso; Dor Musculoesquelética; Dor Crônica;

ABSTRACT

Obesity and musculoskeletal (MSK) pain are morbidities that affect a significant and growing number of individuals, negatively impacting their quality of life. Studies show that obese individuals have increased prevalence of MSK pain, but there are few studies evaluating the Brazilian population, the role of prolonged exposure to excess weight and measuring the impact of obesity on the risk and prognosis of MSK pain. Thus, we investigated whether different obesity markers were associated with the prevalence of chronic MSK pain in participants of the Brazilian Longitudinal Study of Adult Health Musculoskeletal (ELSA-Brasil MSK), and subsequently evaluated whether obesity affected the risk and prognosis of frequent knee pain. This work was carried out with baseline data from the ELSA-Brasil MSK cohort and the risk and prognosis assessments were based on data from the annual telephone monitoring of the cohort to identify the occurrence of pain episodes. In the cross-sectional analysis we observed that among the 2,899 participants obesity, defined by either body mass index, waist circumference or waist-to-height ratio, was associated with a higher probability of having chronic MSK pain (OR ranged from 1.32 for abdominal obesity level I to 2.08 for body mass index ≥35 kg/m^2), multisite chronic MSK pain (OR ranged from 1.35 for overweight to 3.19 for body mass index ≥35 kg/m^2) and generalized chronic MSK pain (ORs ranged from 2.12 for a waist-to-height ratio ≥0.5 to 3.65 for a body mass index ≥35 kg/m^2). Concerning the body weight trajectory, both participants who were currently overweight, and those who were overweight at age 20 and currently, were more likely to have all pain phenotypes. In the longitudinal analysis, the 2,644 participants who responded to the four monitoring outcomes telephone interviews were divided into two groups: incidence cohort (1,896 participantes without both frequent and chronic knee pain at baseline) and prognosis cohort (748 participante with frequent pain and/or chronic knee pain at baseline). The

results showed that in the incidence cohort obesity increased the risk of having one (OR: 1.63; 95% CI 1.13-2.37) and multiple episodes of frequent knee pain (OR: 2.61; 95% CI 1.71 to 3.97), as well as the risk of having severe (OR: 2.10; 95% CI 1.50-2.95) and non-severe (OR: 1.72; 95% CI 1.04-2.84) episodes. In the prognostic cohort, obesity was a risk factor only for reporting multiple (OR: 2.54; 95% CI 1.60-4.05) and severe (OR: 2.31; 95% CI 1 .49-3.59) episodes. These results highlight the importance of developing strategies focused at weight management both in the collective and individual scope. Interrupting, or at least slowing down the growth of overweight rates in the population and including the management of obesity in the outpatient follow-up of individuals suffering from MSK pain are important measures to prevent the occurrence of this problem and promote a better prognosis for patients who already live with MSK pain.

Key-words: Obesity; Overweight; Musculoskeletal Pain; Chronic Pain;

LISTA DE ABREVIATURAS

ACR	American College of Rheumatology
BMI	Body Mass Index
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CC	Circunferência da Cintura
CEFET-MG	Centro Federal de Educação Tecnológica de Minas Gerais
CI	Confidence Interval
CIS-R	Clinical Interview Schedule – Revised
CKP	Chronic Knee Pain
CMP	Chronic Musculoskeletal Pain
DECIT	Departamento de Ciência e Tecnologia
DCNT	Doenças Crônicas Não Transmissíveis
ELSA-Brasil	Estudo Longitudinal de Saúde do Adulto
ELSA-Brasil MSK	Estudo Longitudinal de Saúde do Adulto Musculoesquelético
FAPEMIG	Fundação de Amparo à Pesquisa do Estado de Minas Gerais
FINEP	Financiadora de Estudos e Projetos
FKP	Frequent Knee Pain
IASP	International Association for the Study of Pain
IMC	Índice de Massa Corporal
IPAQ	Questionário Internacional de Atividade Física

LTPA	Leisure-Time Physical Activity
ME	Musculoesquelética
MSK	Musculoskeletal
NCD	Noncommunicable Disease
NR	Non-routine
OR	Odds Ratio
R	Routine
RCE	Razão Cintura-Estatura
SD	Standard Deviations
SFKP	Severe Frequent Knee Pain
UFMG	Universidade Federal de Minas Gerais
WC	Waist Circumference
WHtR	Waist-to-Height Ratio

SUMÁRIO

1. APRESENTAÇÃO 19

2. CONSIDERAÇÕES INICIAIS 21

2.1. Definição de dor 22

2.1.1 Classificações da dor 23

2.2. Obesidade 24

2.3. Relação entre obesidade e dor musculoesquelética 26

3. OBJETIVOS 28

3.1. Objetivo Geral 27

3.2 Objetivos Específicos 27

4. HIPÓTESES 29

5. MÉTODOS 30

5.1 População em estudo 31

5.2 Variáveis resposta 31

5.3 Variáveis explicativas 34

5.4 Variáveis de ajuste 36

5.5 Análise estatística 37

5.6 Aspectos éticos 38

6. REFERÊNCIAS 39

7. ARTIGO DE RESULTADOS 1 44

8. ARTIGO DE RESULTADOS 2 86

9. CONCLUSÃO 112

10. ANEXOS 114

Anexo A – Carta de aprovação do ELSA-Brasil pelo Comitê de Ética em Pesquisa (COEP/UFMG) 114

Anexo B – Carta de aprovação do ELSA-Brasil pela Comissão Nacional de Ética em Pesquisa (CONEP) 115

Anexo C - Carta de aprovação do ELSA-Brasil MSK pelo Comitê de Ética em Pesquisa (COEP/UFMG) 117

11. APÊNDICE – Cópia da publicação do Artigo de Resultados 1 118

1. APRESENTAÇÃO

O ELSA-Brasil é financiado pelo Ministério da Saúde (Departamento de Ciência e Tecnologia) e pelo Ministério de Ciência e Tecnologia (Financiadora de Estudos e Projetos and CNPq-BR) do Brasil, 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ.

O ELSA-Brasil MSK recebe apoio e agradece o recebimento de fomento dos seguintes órgãos/fundações: CAPES-BR (SUS 054/2010), FAPEMIG-BR (APQ-00921-16) e CNPq-BR (42358520169).

O presente texto representa o volume de defesa da Tese de Doutorado da aluna Aline Bárbara Pereira Costa, intitulada: “Indicadores de obesidade: associação com a prevalência, incidência e prognóstico de dor musculoesquelética em participantes da coorte ELSA-Brasil Musculoesquelético (ELSA-Brasil MSK), 2012-2019”. A aprovação no exame de defesa de tese é um dos requisitos para a obtenção do título de doutora em Saúde Pública.

Essa Tese insere-se na linha de pesquisa *Epidemiologia das Doenças e Agravos não Transmissíveis* do Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina da Universidade Federal de Minas Gerais e integra o “Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil)”.

A apresentação deste volume está no formato de Artigo Científico e é composta pelos seguintes itens:

- Considerações Iniciais
- Objetivos
- Hipóteses
- Métodos

- Referências
- Artigo de Resultados 1
- Artigo de Resultados 2
- Conclusão
- Anexos
- Apêndice

2. CONSIDERAÇÕES INICIAIS

A população mundial vive em um cenário onde as doenças crônicas não transmissíveis (DCNT) estão entre as principais causas de incapacidade e mortalidade, afetando um número cada vez maior de indivíduos e em idades cada vez mais precoces. Isso pode ser explicado em parte pelo aumento da expectativa de vida, já que o envelhecimento é um dos fatores associados à ocorrência de DCNT. Porém, mudanças no estilo de vida das populações, que estão cada vez mais sedentárias e com padrões alimentares menos saudáveis, são fatores que favorecem o aumento das taxas de ocorrência desse grupo de doenças. Esse cenário reflete no aumento da mortalidade por DCNT e, no caso das morbidades que não aumentam o risco de morte, em piora da qualidade de vida dos pacientes (DUNCAN et al., 2012; GBD, 2018)[1].

Os distúrbios musculoesqueléticos ocupam duas posições no ranking das 25 principais causas de anos vividos com incapacidade, produzido pelo *Global Burden of Disease*: dor lombar no 9º lugar e outros distúrbios musculoesqueléticos no 19º lugar. Contudo, na análise estratificada por faixa etária observa-se que esses problemas ganham importância com o avnaçar da idade, sendo que na faixa de 25 a 49 anos a dor lombar passa a ocupar o 4º lugar, outros distúrbios musculoesqueléticos ficam no 8º e a dor no pescoço aparece em 19º (GBD 2019, 2020)[2].

Além de impactar negativamente a qualidade de vida dos indivíduos acometidos por essas morbidades, há o impacto econômico decorrente de aposentadorias precoces e dos

[1] DUNCAN, B. B. et al. Chronic Non- Communicable Diseases in Brazil: priorities for disease management and research. **Revista De Saúde Pública**, v. 46, supl. 1, p. 126-134, 2012. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. **The Lancet**, v. 392, n. 10159, p. 1859-1922, 2018.

[2] GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. **The Lancet**, v. 396, n. 10258, p. 1204-1222, 2020.

gastos com tratamento (WOOLF; PFLEGER, 2003; ABU-SAAD HUIJER, 2010)[1]

2.1. Definição de dor

Em 1979 a *International Association for the Study of Pain* (IASP) publicou pela primeira vez a definição de dor como "uma experiência sensorial e emocional desagradável, associada a dano real ou potencial ao tecido, ou descrita nos termos desse dano". No ano passado essa definição foi revisada, com intuito de refletir melhor a complexidade da dor, passando a figurar como "uma experiência sensorial e emocional desagradável, associada ou semelhante à associada a dano real ou potencial ao tecido", sendo que a IASP adicionou seis notas que complementam o entendimento desse fenômeno (RAJA et al., 2020)[2]:

- A dor é sempre uma experiência pessoal que é influenciada em vários graus por fatores biológicos, psicológicos e sociais;
- Dor e nocicepção são fenômenos diferentes. A dor não pode ser inferida apenas a partir da atividade em neurônios sensoriais;
- Através de suas experiências de vida, os indivíduos aprendem o conceito de dor.
- O relato de uma pessoa sobre uma experiência de dor deve ser respeitado.
- Embora a dor geralmente desempenhe um papel adaptativo, pode ter efeitos adversos na capacidade funcional e bem-estar social e psicológico dos indivíduos;
- A descrição verbal é apenas um dos vários meios para expressar dor. A incapacidade

[1] WOOLF, A. D.; PFLEGER, B. Burden of major musculoskeletal conditions. **Bulletin of the World Health Organization** 81, 646–656. 2003. ABU-SAAD HUIJER, H. Chronic pain: a review. **J Med Liban**, v. 58, p. 21-27, 2010.

[2] RAJA S. N.; CARR, D. B.; COHEN, M. et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. **Pain**, v.169, n. 9, p. 1976-1982, 2020.

de se comunicar não nega a possibilidade de que um indivíduo ou um animal experimenta dor (RAJA et al., 2020)[1].

Uma vez definida, a dor pode ser classificada quanto a diferentes aspectos, como sua origem, frequência de episódios e número de locais ou regiões afetadas.

2.1.1 Classificações da dor

Classificar a dor é uma estratégia importante tanto para o estudo desse fenômeno, quanto para seu tratamento, uma vez que a classificação pode indicar características desde a origem da dor até sua gravidade. Existem diversos sistemas de classificação: o anatômico, que tipifica a dor segundo o local onde ela é percebida (dor em joelho, por exemplo); o que relaciona a dor ao diagnóstico médico ou doença de base associada (dor da fibromialgia); a classificação segundo a intensidade (que envolve a apresentação de escalas para o paciente pontuar quanta dor está sentindo); e a classificação segundo a temporalidade dos episódios, que define a dor como aguda, crônica, frequente (WOESSNER, 2006; ORR et al, 2017)[2].

A dor crônica é um fenômeno persistente, que dura no mínimo de 3 a 6 meses, podendo ser contínuo ou intermitente (TREEDE et al., 2015)[3]. Sua prevalência, incluindo a dor musculoesquelética (ME) crônica, varia na literuta de 12% a 80% (BREIVIK et al., 2006; SÁ et al., 2009; ABU-SAAD HUIJER, 2010; VIEIRA et al., 2012)[4].

---

[1] RAJA, S.N.; CARR, D. B.; COHEN, M. et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. **Pain**, v.169, n. 9, p. 1976-1982, 2020.

[2] ORR, P. M.; SHANK, B.C.; BLACK, A.C. The Role of Pain Classification Systems in Pain Management. **Critical Care Nursing Clinics of North America**, v. 29, n. 4, p. 407-418, 2017. WOESSNER, J. Overview of pain: Classification and concepts. **Weiner's Pain Management: A Practical Guide for Clinicians**. p. 35-48. 2006.

[3] TREEDE, R. D. et al. A classification of chronic pain for ICD-11. **Pain**, v. 156, n. 6, p. 1003-1007, 2015.

[4] BREIVIK, H. et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. **Eur J Pain**, v. 10, n. 4, p. 287-333, 2006. SÁ, K. et al. Prevalência de dor crônica e fatores associados na população de Salvador, Bahia. **Rev Saúde Pública**, v. 43, n. 4, p. 622-630, 2009. ABU-SAAD HUIJER, H. Chronic pain: a review. **J Med Liban**, v. 58, p. 21-27, 2010. VIEIRA, E. B. M. et al. Chronic pain, associated factors, and impact on daily life: are there differences between the sexes? **Cad Saúde Pública**, v. 28, n. 8, p. 1459-1467, 2012.

Na caracterização da dor segundo a temporalidade da sua ocorrência existem subclassificações para aprimorar a caracterização do episódio doloroso. Uma subclasse é a dor primária, que compreende a dor que envolve o aparelho musculoesquelético, mas não têm causa base bem definida, como por exemplo a dor lombar e a fibromialgia. Já a dor ME secundária é aquela decorrente de um processo patológico específico, que cursa com lesões em ossos, articulações, músculos ou tecidos moles adjacentes (TREEDE et al., 2015)[1].

Há também classificações quanto ao número de locais afetados: se presente em 2 ou mais locais, pode-se classificá-la como dor em múltiplos locais; e quando presente nos quatro quadrantes corporais, denomina- se dor difusa (WOLFE et al., 1990; MAGNUSSON et al., 2014; HAUKKA et al., 2012)[2]. A dor ME em múltiplos locais é mais frequente que a dor em um único local (LARSSON et al., 2012; CARNES et al., 2007; KAMALERI et al., 2009)[3], e há indícios que até 75% dos indivíduos que têm dor ME podem apresentar sintomas sintomas em múltiplos locais (KAMALERI et al., 2008)[4].

2.2. Obesidade

A obesidade é definida como um acúmulo de gordura corporal acima do que é

[1] TREEDE, R. D. et al. A classification of chronic pain for ICD-11. **Pain**, v. 156, n. 6, p. 1003-1007, 2015.

[2] WOLFE F, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. **Arthritis Rheum.**, v.33, n.2, p. 160-72, 1990. MAGNUSSON, K. et al. No strong temporal relationship between obesity and multisite pain – results from a population-based 20-year follow-up study. **Eur J Pain**, v. 18, n. 1, p. 120–127, 2014. HAUKKA, E. et al. Physical workload, leisure-time physical activity, obesity and smoking as predictors of multisite musculoskeletal pain. A 2-year prospective study of kitchen workers. **Occup Environ Med.**, v. 69, n. 7, p. 485-492, 2012.

[3] LARSSON, B. et. al. A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. **Eur J Pain.**, v. 16, n. 8, p. 1084-93, 2012. CARNES, D. et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. **Rheumatol**, v. 46, n. 7, p. 1168–1170. 2007. KAMALERI, Y. et al. Change in the number of musculoskeletal pain sites: A 14-year prospective study. **Pain**, v. 141, n. 1-2, p. 25–30, 2009.

[4] KAMALERI, Y. et al. Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. **Eur J Pain**, v. 12, n. 6, p. 742-748, 2008.

considerado normal e, por isso, pode comprometer a saúde sob diversos aspectos (BLÜHER, 2019)[1]. Esse acúmulo excesivo de gordura é causado basicamente por um desequilíbrio entre o consumo e o gasto energético, mas os fatores que promovem esse desbalanço são variados:

- Ingestão excessiva de alimentos – pode estar associada a fatores sócio-culturais, à falta de informação sobre o que é uma alimentação saudável, a problemas emocionais, transtornos alimentares, entre outros;
- Baixo gasto energético – pode estar relacionado ao envelhecimento, a fatores genéticos, a alterações hormonais, sarcopenia, entre outros;
- Sedentarismo – impacta diretamente no gasto energético e pode estar associado a fatores sócio-culturais, a dificuldades físicas e barreiras emocionais, a ocorrência de dor musculoesquelética, entre outros (BLÜHER, 2019)[1].

Nas últimas décadas o mundo tem observado um crescimento importante e acelerado da prevalência de obesidade. Segundo dados da Organização Mundial da Saúde (OMS), esse incremento foi de 50% entre os anos de 2000 e 2016, sendo que no último o número de obesos já ultrapassava 650 milhões em todo o mundo (BLÜHER, 2019; WHO, 2021)[2]. As estatísticas da OMS mostram ainda que, apesar desse crescimento ser observado em todo o globo, as Américas (28,6%) e a Europa (23,3%) têm as maiores prevalências (WHO, 2021)[3]. No Brasil, dados da última Pesquisa Nacional de Saúde mostram que no ano de 2019 mais de uma quarto da população (25,9%) era obesa, sendo que ao incluir o sobrepeso (condição que precede a obesidade) a prevalência subiu para 60,3% (IBGE, 2020)[4].

---

[1] BLÜHER, M. Obesity: global epidemiology and pathogenesis. **Nat Rev Endocrinol**, v. 15, p.288–298, 2019.
[2] BLÜHER, M. Obesity: global epidemiology and pathogenesis. **Nat Rev Endocrinol**, v. 15, p.288–298, 2019. WHO. World health statistics 2021: monitoring health for the SDGs, sustainable development goals. Geneva: **World Health Organization**; 2021.
[3] WHO. World health statistics 2021: monitoring health for the SDGs, sustainable development goals. Geneva: **World Health Organization**; 2021.
[4] IBGE. Pesquisa Nacional de Saúde 2019: atenção primária à saúde e informações antropométricas. Brasil - IBGE, Coordenação de Trabalho e Rendimento. Rio de Janeiro: IBGE, 2020.

Nesse cenário, a obesidade que era considerada sinônimo de saúde e status social no passado, há alguns anos tornou-se um importante problema de saúde pública. Além de ser um fator de risco associado a diversas doenças, ela também pode ser abordada como uma doença crônica em si, de caráter multifatorial. A hiperplasia e a hipertrofia dos adipócitos gera diversas mudanças na homeostase do organismo do obeso que impedem a perda de peso e promovem maior ganho, criando um processo patológico que pode cursar com alterações metabólicas (LEITE; ROCHA; BRANDÃO-NETO, 2009; SARTORI-CINTRA et al., 2014; BLÜHER, 2019)[1].

2.3. Relação entre obesidade e dor musculoesquelética

Estudos têm associado a obesidade a uma maior ocorrência de dor ME, sendo que dois mecanismos são apontados como os principais responsáveis por essa associação:

- Sobrecarga mecânica das estruturas osteomusculares – esse mecanismo parece afetar principalmente estruturas que suportam o peso corporal (joelhos e quadris) e estaria relacionado à ativação de condrócitos, acelerando a degeneração da cartilagem.
- Inflamação sistêmica de baixa intensidade – esse é um fenômeno característico da obesidade. O tecido adiposo aumentado produz e libera citocinas pró-inflamatórias (como fator de necrose tumoral α, interleucinas 6 e 1β, resistina e leptina) que caem na circulação e atuam de forma sistêmica podendo gerar, entre

[1] LEITE, L. D.; ROCHA, E. D. M.; BRANDÃO-NETO, J. Obesidade: uma doença inflamatória. **Revista Ciência & Saúde**, v. 2, n. 2, p. 85-95, 2009. SARTORI-CINTRA, A. R.; AIKAWA, P.; CINTRA, D. E. Obesidade versus osteoartrite: muito além da sobrecarga mecânica. **Einstein** v. 12, n. 3, p. 374-379, 2014. BLÜHER, M. Obesity: global epidemiology and pathogenesis. **Nat Rev Endocrinol**, v. 15, p.288–298, 2019.

outros efeitos, lesões articulares e teciduais (BONAKDAR, 2013; SARTORI-CINTRA; AIKAWA; CINTRA, 2014; SIPPEL, et al., 2014; MUSUMECI et al., 2015; THIJSSEN; VAN CAAM e VAN DER KRAAN, 2015; WALSH et al., 2018)[1].

Estudos mais recentes sugerem que a inflamação associada à obesidade pode também ser um gatilho para a sensibilização central, contribuindo para o desenvolvimento de quadros de dor crônica difusa, como o observado na fibromialgia (SCHREPF et al., 2017; HARTE; HARRIS; CLAUW, 2018)[2]

Por fim, apesar de autores já tenham mostrado maiores prevalências de dor ME em obesos, quando comparados a indivíduos eutróficos (STONE; BRODERICK, 2012; BONAKDAR, 2013; MAGNUSSON et al., 2014; OKIFUJI; HARE, 2015)[3], ainda são escassos os estudos que avaliaram adultos brasileiros e investigaram o papel da exposição à obesidade na ocorrência, risco e prognóstico da dor musculoesquelética.

[1] BONAKDAR, R. A. Obesity- related pain: time for a new approach that targets systemic inflammation. **J Fam Pract**, v. 62, n. 9 Suppl CHPP, p. S22-9, 2013. SARTORI-CINTRA, A. R.; AIKAWA, P.; CINTRA, D. E. Obesidade versus osteoartrite: muito além da sobrecarga mecânica. **Einstein** v. 12, n. 3, p. 374-379, 2014. SIPPEL, C. et al. Processos inflamatórios da obesidade. **Revista de Atenção à Saúde**, v. 12, n. 42, p. 48-56, 2014. MUSUMECI, G. et al. Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression**. Int J Mol Sci**., v.16, n. 3, p. 6093-6112, 2015. THIJSSEN, E.; VAN CAAM, A.; VAN DER KRAAN, P. M. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. **Rheumatology**, v. 54, n. 4, p. 588-600, 2015. WALSH, T. P. at al. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. **BMC Musculoskelet Disord**, v. 19, n. 1, p. 233-246. 2018

[2] SCHREPF, A. et al. Improvement in the spatial distribution of pain, somatic symptoms, and depression after a weight loss intervention. **The Journal of Pain**, v. 18, n. 12, p. 1542–1550, 2017. HARTE, S.E.; HARRIS, R. E.; CLAUW, D.J. The neurobiology of central sensitization. **J Appl Behav Res**, v. 23, e121372018. Jun 2018.

[3] STONE, A. A.; BRODERICK, J. E. Obesity and pain are associated in the United States. **Obesity**, v. 20, n. 7, p. 1491-5, 2012. BONAKDAR, R. A. Obesity- related pain: time for a new approach that targets systemic inflammation. **J Fam Pract**, v. 62, n. 9 Suppl CHPP, p. S22-9, 2013. MAGNUSSON, K. et al. No strong temporal relationship between obesity and multisite pain – results from a population-based 20-year follow-up study. **Eur J Pain**, v. 18, n. 1, p. 120–127, 2014. OKIFUJI, A.; HARE, B. D. The association between chronic pain and obesity. **Journal of Pain Research**, n. 8, p. 399– 408, 2015

3. OBJETIVOS

3.1. Objetivo Geral

Investigar a associação entre marcadores de obesidade e a prevalência, incidência e prognóstico da dor musculoesquelética em participantes do Estudo Longitudinal de Saúde do Adulto Musculoesquelético (ELSA-Brasil MSK).

3.2. Objetivos Específicos

- Avaliar se as prevalências de dor ME crônica diferem segundo a presença de obesidade.
- Investigar se a magnitude da associação entre obesidade e dor ME crônica cresce com o aumento do número de locais acometidos e com o grau de obesidade.
- Avaliar se a trajetória de peso corporal ao longo da vida está associada às prevalências de dor ME crônica.
- Investigar se a obesidade aumenta o risco de desenvolver dor frequente em joelhos durante quatro anos de acompanhamento.
- Avaliar se a obesidade está associada à gravidade da dor frequente em joelhos durante quatro anos de acompanhamento.
- Investigar se a magnitude da associação entre a obesidade e a ocorrência e gravidade da dor frequente em joelhos difere segundo a presença de dor em joelhos na linha de base.

4. HIPÓTESES

- A prevalência de dor ME crônica é maior entre indivíduos obesos, quando comparados aos eutróficos.
- A magnitude da associação entre obesidade e dor ME crônica cresce com o aumento do número de locais afetados, bem como com o aumento do grau de obesidade.
- O maior tempo de exposição ao excesso de peso está associado à maior chance de ter dor ME crônica.
- Indivíduos obesos têm maior incidência de dor frequente em joelhos em quatro anos de acompanhamento.
- A obesidade está associada positivamente à gravidade da dor frequente em joelhos, identificada em quatro anos de acompanhamento.
- A magnitude da associação entre a obesidade e o risco de ter dor frequente em joelhos, bem como dor grave, é maior em indivíduos sem dor em joelhos na linha base, comparados aos que relataram ter dor.

5. MÉTODOS

Essa tese foi desenvolvida a partir dos dados da linha de base da coorte musculoesquelética do ELSA-Brasil, o ELSA-Brasil-MSK, e dos dados do monitoramento telefônico anual para identificação da ocorrência de episódios de dor.

O ELSA-Brasil é uma coorte multicêntrica que acompanha, desde 2008-2010, 15.105 servidores com idade entre 35 e 74 anos, de instituições de ensino superior e pesquisa em seis estados brasileiros: Bahia, Espírito Santo, Minas Gerais, Rio Grande do Sul, São Paulo e Rio de Janeiro. Seu objetivo principal é estudar a incidência, progressão e fatores de risco para doenças crônicas não transmissíveis, em especial as doenças cardiovasculares e o diabetes (AQUINO, et al., 2012)[1].

Entre 2012-2014, período de realização da segunda fase de exames e entrevistas do ELSA-Brasil, o centro de investigação de Minas Gerais iniciou o estudo ancilar ELSA-Brasil MSK. Trata-se de uma coorte que investiga a história natural de problemas musculoesqueléticos, em especial a dor ME crônica e a osteoartrite de mãos e joelhos, bem como os fatores associados ao seu desenvolvimento e progressão. Todos os participantes do centro de investigação mineiro (n=3.115), vivos em 2012-2014, foram convidados a participar do ELSA-Brasil MSK (MACHADO et al., 2015)[2].

Para identificação de eventos incidentes na coorte ELSA-Brasil, além das avaliações presenciais são realizadas ligações telefônicas para os participantes, com aplicação de questionários padronizados para identificação dos eventos de interesse. A primeira entrevista telefônica ocorreu de 10 a 14 meses após a visita inicial do participante ao centro de

[1] AQUINO, E. M. et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol, v. 175, n. 4, p. 315-24, 2012.

[2] MACHADO, L. A. C. et al. Perfil da Coorte ELSA-Brasil Musculoesquelético. Braz J Rheumatol, v. 56, (Suppl. 1), p. S29-30, 2015.

investigação, repetindo-se anualmente nesse mesmo intervalo de meses (BARRETO et al., 2013)[1].

A partir do ano de 2015 foi incluído no monitoramento telefônico de desfechos um questionário do ELSA-Brasil MSK para investigação de episódios de dor na região lombar, em mãos e em joelhos. Esse questionário contém perguntas sobre a ocorrência de dor nos últimos 30 dias, gravidade e incapacidade gerada pela dor, procura de assistência médica e ocorrência de lesão traumática desde a última ligação. Nas análises de incidência do presente trabalho foram avaliados somente os dados do monitoramento anual da dor em joelhos

5.1 População em estudo

Entre os 2.923 indivíduos avaliados na Onda 2 do ELSA-Brasil (192 perdas por óbitos, recusas, mudanças de estado e morbidade), participaram da linha de base do ELSA-Brasil MSK todos os que realizaram exames e entrevistas e que responderam, pelo menos, o questionário sobre dor e sintomas musculoesqueléticos (n=2.901). No presente estudo foram incluídos apenas os indivíduos com dados de pelo menos uma das variáveis explicativas e, para as análises do monitoramento telefônico anual, aqueles que responderam a quatros entrevistas sequenciais.

5.2 Variáveis resposta

A ocorrência de dor ME crônica foi avaliada em nove locais: pescoço, ombros, cotovelos, parte superior das costas, mãos, parte inferior das costas, quadris/coxas, joelhos e

[1] BARRETO, S. M. et al. Estratégias de identificação, investigação e classificação de desfechos incidentes no ELSA- Brasil. **Rev Saúde Pública**, v. 47, supl. 2, p. 79-86, 2013.

tornozelos/pés. Durante a aplicação do questionário foi apresentado ao participante um cartão contendo a figura de um homúnculo para ele pudesse indicar o local da dor (Figura 1). Para cada local os participantes responderam às seguintes perguntas: *"Nos últimos 12 meses, o(a)Sr(a) teve dor, desconforto ou rigidez no/a [local]?"* e "*Esse problema que o(a) Sr(a) teve nos últimos 12 meses durou mais de 6 meses?"*. Aqueles que positivaram ambas as perguntas, em pelo menos um dos locais avaliados, foram considerados casos prevalentes de dor ME crônica.

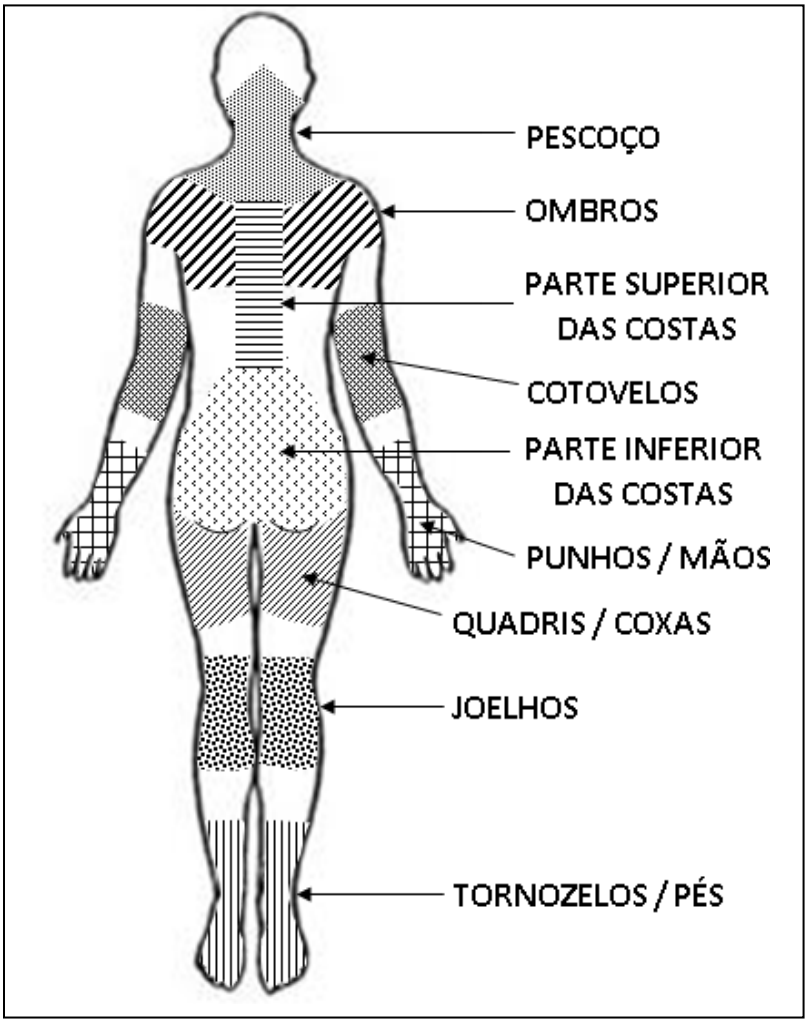


Figura 1 – Homúnculo apresentado aos participantes para indicarem os locais de apresentação da dor musculoesquelética.

A partir desses dados foram criadas três variáveis de dor ME crônica:

- Presença (sim/não) em pelo menos um dos nove locais;
- Número de locais de dor ME crônica;
- Número de regiões acometidas.

A variável número de locais de dor ME crônica foi obtida pela soma dos locais afetados (variando de 0 a 9), agrupada subsequentemente em 3 categorias: nenhum local, 1 a 2 locais e ≥ 3 locais (definida como dor em múltiplos locais). Considerando que a presença de dor crônica em mais de um local poderia, ainda sim, representar apenas uma região corporal, foi criada também a variável número de regiões de dor. Incialmente agrupou-se os locais avaliados em três regiões: membros superiores (ombros, cotovelos e/ou mãos); esqueleto axial (pescoço, parte superior das costas e/ou parte inferior das costas); e membros inferiores (quadris/coxas, joelhos e/ou tornozelos/pés). Em seguida, os participantes foram categorizados segundo o número de regiões acometidas pela dor ME crônica em: nenhuma região, uma a duas regiões e 3 regiões (definida como dor generalizada).

A incidência de dor frequente em joelhos foi avaliada a partir das entrevistas do monitoramento telefônico, mediante a aplicação da seguinte pergunta: "*Agora pense nos últimos 30 dias, desde (dia/mês) até hoje. O(a) Sr(a) teve dor, desconforto ou rigidez na maioria dos dias no joelho (esquerdo/direito)?*". Casos incidentes de dor frequente em joelhos foram aqueles que positivaram essa pergunta em pelo menos uma das quatro entrevistas de monitoramento e que na linha de base do ELSA-Brasil MSK responderam negativamente às seguintes preguntas, para ambos os joelhos: "*Esse problema que o(a) Sr(a) teve nos últimos 12 meses durou mais de 6 meses?*" (dor crônica) e "*Esse problema que o(a) Sr(a) teve nos últimos 12 meses durou a maioria dos dias de pelo menos 1 mês?*" (dor frequente).

Considerando que foram avaliadas quatro entrevistas de monitoramento telefônico anual da ocorrência de dor nos joelhos, foi criada uma variável derivada da incidência de dor, que consistiu no número de episódios de dor frequente de joelhos, categorizada como: nenhum episódio, um episódio e múltiplos episódios (dois a quatro).

A cada resposta positiva à pergunta de identificação dos casos incidentes era requisitado ao participante que respondesse outras duas perguntas para identificação da intensidade e da incapacidade ocasionada pelo episódio de dor:

- "*Quanta dor, desconforto ou rigidez o(a) Sr(a) teve no joelho (esquerdo/direito)?*" – muito leve, leve, moderada, grave ou muito grave;
- "*Agora responda pensando nos seus dois joelhos. Nos últimos 30 dias, desde (dia/mês) até hoje, o(a) Sr(a) foi impedido(a) de realizar atividades normais (por exemplo trabalho, atividades domésticas e de lazer) por causa desse problema no joelho*?" – sim ou não.

A partir dessas perguntas foi avaliada a gravidade da dor frequente de joelho, sendo que o indivíduo que relatou pelo menos um episódio de dor moderada a muito grave ou um episódio de dor frequente incapacitante foi incluído no grupo de dor grave.

5.3 Variáveis explicativas

Os marcadores de obesidade avaliados foram o índice de massa corporal (IMC) atual, a circunferência da cintura (CC) e a razão cintura-estatura (RCE). Para o cálculo do IMC o peso, em quilos, foi aferido em balança eletrônica (Toledo®, capacidade 200kg) e a altura, em metros, medida em estadiômetro com escala milimétrica (SECA®, SE-216). Posteriormente os indivíduos foram classificados segundo os pontos de corte propostos pela Organização Mundial da Saúde em: eutrófico (<25 kg/m^2); com sobrepeso (25-29,9 kg/m^2),

com obesidade grau I (≥30 kg/m^2) e com obesidade graus II/III (≥ 35 kg/m^2) (WHO, 1995)[1].

A CC foi aferida no ponto médio entre a margem mais inferior do arco costal e a crista ilíaca, utilizando trena antropométrica em aço, de 200 cm (Sanny®, C14-2). Para registro foi considerado o valor médio de duas medidas consecutivas. A obesidade abdominal foi definida considerando os seguintes pontos de corte (WHO, 2008)[2]: sem obesidade abdominal (CC <80 cm para mulheres e <94 cm para homens), obesidade abdominal grau I (≥80 cm e <88 cm para mulheres e ≥94 cm e <102 cm para homens) e obesidade abdominal grau II/III (≥88 cm para mulheres e ≥102 cm para homens).

Para o cálculo da RCE dividiu-se a cintura, em centímetros, pela altura em centímetros, sendo que valores maiores ou iguais a 0,5 foram considerados como obesidade abdominal (ASHWELL; GIBSON, 2014)[3].

Para criar a variável trajetória de peso corporal foram considerados o IMC aos 20 anos e o IMC atual. A informação sobre o peso aos 20 anos foi coletada durante a linha de base da coorte original ELSA-Brasil (2008-2010), por meio da pergunta "*Aproximadamente, quanto o(a) Sr(a) pesava aos 20 anos de idade [excluindo períodos de gravidez, no caso das mulheres]?*". O IMC aos 20 anos foi calculado dividindo-se o peso informado pelo quadrado da altura atual. Considerando a presença de excesso de peso (IMC ≥ 25 kg/m^2) em cada um dos dois momentos avaliados, três trajetórias mutualmente exclusivas foram identificadas: sem excesso de peso (nem aos 20 anos e nem atual); excesso de peso atual (eutrofia aos 20 anos que evoluiu para excesso de peso na atualidade); e excesso de peso constante (ocorrência de excesso de peso nos dois momentos).

[1] WHO (World Health Organization). Physical Status: The Use and Interpretation of Anthropometry. WHO Technical Report Series 854, Geneva 1995.

[2] WHO (World Health Organization). Waist circumference and waist–hip ratio: report of a WHO expert consultation. Geneva, p. 39, 2008.

[3] ASHWELL, M.; GIBSON, S. A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. **BMC Med**, v. 12, n. 1, p. 207, 2014.

Na criação dessa variável identificou-se 27 indivíduos que migraram do excesso de peso aos 20 anos para a eutrofia (IMC < 25 kg/m^2) atual. Devido ao pequeno número, optou-se por excluí-los da análise de trajetória.

5.4 Variáveis de ajuste

Todos os participantes responderam a questionários padronizados na coorte ELSA-Brasil por meio dos quais foram coletadas informações sociodemográficas e sobre condições de saúde. Para a descrição da amostra e ajuste das análises foram consideradas as variáveis sexo, idade (em anos), raça/cor de pele auto referida (branca, parda, preta, amarela ou indígena), escolaridade (fundamental, médio ou superior completo), status laboral (ativo ou aposentado) e natureza da ocupação (não manual não rotineira, não manual rotineira, manual não rotineira e manual rotineira). Na avaliação do status laboral foram considerados ativos os participantes que exerciam trabalho remunerado no período da entrevista, independente do local de trabalho. E para a natureza da ocupação agrupou-se as categorias manuais, devido ao pequeno número de indivíduos com atividade manual não rotineira (n=23).

O nível de atividade física e a presença de sintomas depressivos ou depressão também foram utilizados para ajuste. O Questionário Internacional de Atividade Física (IPAQ) foi aplicado para a avaliação do nível de atividade física no laser, sendo categorizado como: 1) insuficiente, quando o participante referiu não praticar atividade física ou praticar menos que as demais categorias; 2) moderado, quando a prática foi de três dias ou mais de atividade vigorosa, por no mínimo 20 min/dia; cinco ou mais dias de atividade moderada e/ou caminhada de pelo menos 30 min/dia; ou cinco ou mais dias de qualquer combinação de caminhada e atividades de intensidade moderada ou vigorosa que alcançasse, no mínimo, 600 MET-min/semana; e 3) vigoroso, quando referiu praticar atividade vigorosa por pelo menos

três dias e que acumulasse, no mínimo, 1500 MET-min/semana; ou sete dias de qualquer combinação de caminhada, atividades moderadas ou vigorosas, com acúmulo de pelo menos 3000 MET-min/semana (MATSUDO et al, 2001)[1].

Os sintomas depressivos e a depressão foram identificados a partir da aplicação da versão adaptada em português brasileiro do questionário *Clinical Interview Schedule – Revised* (CIS-R), que investiga a presença de sintomas de depressão, entre outros transtornos mentais, nos últimos sete dias (NUNES et al., 2011)[2]. Considerou-se que o indivíduo apresentava sintomas depressivos se ele positivasse pelo menos duas das sete questões da seção G do CIS-R, que se refere a depressão. Para definir a depressão foi construído um algoritmo a partir da soma de todos os sintomas de humor deprimido avaliados pelo CIS-R.

5.5 Análise estatística

A análise descritiva foi realizada mediante o cálculo de medidas de tendência central para as variáveis contínuas e distribuição de frequências para as variáveis categóricas. Para avaliar a associação independente da presença de dor ME crônica em pelo menos um local e da dor frequente em joelhos (incidente) com marcadores de obesidade foram utilizadas regressões logísticas binomiais. Regressões logísticas multinomiais foram utilizadas para avaliar a associação com os desfechos: 1) número de locais de dor ME crônica; 2) número de regiões de dor ME crônica; 3) número de episódios de dor frequente em joelhos; 4) gravidade da dor frequente em joelhos.

Em todas as situações, primeiramente foram realizadas análises de regressão univariada

[1] MATSUDO S, ARAÚJO T, MATSUDO V, et al. Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Fís Saúde, v. 6, n. 2, p. 5-18, 2001.

[2] NUNES, M. A. et al. Adaptação transcultural do CIS-R (Clinical Interview Schedule - Revised version) para o português no Estudo Longitudinal de Saúde do Adulto (ELSA). Rev HCPA, v. 31, n. 4, p. 515-8, 2011.

entre cada marcador de obesidade investigado e as variáveis desfecho. Em seguida, modelos multivariados foram utilizados para o ajuste por potenciais confundidores, inseridos no modelo na seguinte ordem: sexo, idade, raça/cor, escolaridade, status laboral, natureza da ocupação, atividade física e presença de sintomas depressivos ou depressão.

Nas análise de dor ME crônica realizou-se ainda testes de razão de verossimilhança para avaliar a presença de gradiente dose-resposta ao longo dos níveis dos marcadores de obesidade nos modelos finais de regressão. Em síntese, esse teste compara um modelo ajustado pela variável explicativa com suas categorias originais com um modelo incluindo a variável explicativa como contínua. Valores de tendência de $p>0,05$ indicam que não há diferença entre os dois modelos, apoiando a hipótese de tendência linear (gradiente dose-resposta).

Todas as análises foram conduzidas no programa estatístico *Stata* (versão 14.0; StataCorp, College Station, Texas), considerando nível de significância menor que 5%.

5.6 Aspectos éticos

ELSA-Brasil e ELSA-Brasil MSK foram aprovados pelo Comitê de Ética e Pesquisa da Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brasil [protocolo COEP / UFMG, Etic 186/06; CEP 1.160.939; CAAE 0186.1.203.000-06]. O ELSA-Brasil também foi aprovado pelo Comitê Nacional de Ética em Pesquisa, Brasil [protocolo 976/2006].

Todos os participantes assinaram um termo de consentimento livre e esclarecido após terem sido informados sobre a natureza e os detalhes do estudo.

6. REFERÊNCIAS

ABU-SAAD HUIJER, H. Chronic pain: a review. **J Med Liban**, v. 58, p. 21-27, 2010.

AQUINO, E. M. et al. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. **Am J Epidemiol**, v. 175, n. 4, p. 315-24, 2012.

ASHWELL, M.; GIBSON, S. A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. **BMC Med**, v. 12, n. 1, p. 207, 2014.

BARRETO, S. M. et al. Estratégias de identificação, investigação e classificação de desfechos incidentes no ELSA- Brasil. **Rev Saúde Pública**, v. 47, supl. 2, p. 79-86, 2013.

BLÜHER, M. Obesity: global epidemiology and pathogenesis. **Nat Rev Endocrinol**, v. 15, p.288–298, 2019.

BONAKDAR, R. A. Obesity-related pain: time for a new approach that targets systemic inflammation. **J Fam Pract**, v. 62, n. 9 Suppl CHPP, p. S22-9, 2013.

BREIVIK, H. et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain, v. 10, n. 4, p. 287-333, 2006. SÁ, K. et al. Prevalência de dor crônica e fatores associados na população de Salvador, Bahia. **Rev Saúde Pública**, v. 43, n. 4, p. 622-630, 2009.

CARNES, D. et al. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study. **Rheumatol**, v. 46, n. 7, p. 1168–1170. 2007.

DUNCAN, B. B. et al. Chronic Non- Communicable Diseases in Brazil: priorities for disease management and research. **Rev Saúde Pública**, v. 46, supl. 1, p. 126-134, 2012.

GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted

life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. **The Lancet**, v. 392, n. 10159, p. 1859-1922, 2018.

GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. **The Lancet**, v. 396, n. 10258, p. 1204-1222, 2020.

HARTE, S.E.; HARRIS, R. E.; CLAUW, D.J. The neurobiology of central sensitization. **J Appl Behav Res**, v. 23, e121372018. Jun 2018.v

HAUKKA, E. et al. Physical workload, leisure-time physical activity, obesity and smoking as predictors of multisite musculoskeletal pain. A 2-year prospective study of kitchen workers. **Occup Environ Med.**, v. 69, n. 7, p. 485-492, 2012.

IBGE. Pesquisa Nacional de Saúde 2019: atenção primária à saúde e informações antropométricas. Brasil - IBGE, Coordenação de Trabalho e Rendimento. Rio de Janeiro: IBGE, 2020.

KAMALERI, Y. et al. Number of pain sites is associated with demographic, lifestyle, and health-related factors in the general population. **Eur J Pain**, v. 12, n. 6, p. 742-748, 2008.

KAMALERI, Y. et al. Change in the number of musculoskeletal pain sites: A 14-year prospective study. **Pain**, v. 141, n. 1-2, p. 25–30, 2009.

LARSSON, B. et. al. A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. **Eur J Pain**, v. 16, n. 8, p. 1084-93, 2012.

LEITE, L. D.; ROCHA, E. D. M.; BRANDÃO-NETO, J. Obesidade: uma doença inflamatória.

Revista Ciência & Saúde, v. 2, n. 2, p. 85-95, 2009.

MACHADO, L. A. C. et al. Perfil da Coorte ELSA-Brasil Musculoesquelético. **Braz J Rheumatol**, v. 56, (Suppl. 1), p. S29- 30, 2015.

MAGNUSSON, K. et al. No strong temporal relationship between obesity and multisite pain – results from a population-based 20-year follow-up study. **Eur J Pain**, v. 18, n. 1, p. 120–127, 2014.

MATSUDO S, ARAÚJO T, MATSUDO V, et al. Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. **Rev Bras Ativ Fís Saúde**, v. 6, n. 2, p. 5-18, 2001.

MUSUMECI, G. et al. Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression. **Int J Mol Sci.**, v.16, n. 3, p. 6093-6112, 2015.

NUNES, M. A. et al. Adaptação transcultural do CIS-R (Clinical Interview Schedule - Revised version) para o português no Estudo Longitudinal de Saúde do Adulto (ELSA). **Rev HCPA**, v. 31, n. 4, p. 515-8, 2011.

OKIFUJI, A.; HARE, B. D. The association between chronic pain and obesity. **Journal of Pain Research**, n. 8, p. 399– 408, 2015

ORR, P. M.; SHANK, B.C.; BLACK, A.C. The Role of Pain Classification Systems in Pain Management. **Critical Care Nursing Clinics of North America**, v. 29, n. 4, p. 407-418, 2017.

RAJA S. N.; CARR, D. B.; COHEN, M. et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. **Pain**, v.169, n. 9, p. 1976-1982, 2020.

SARTORI-CINTRA, A. R.; AIKAWA, P.; CINTRA, D. E. Obesidade versus osteoartrite:

muito além da sobrecarga mecânica. Einstein v. 12, n. 3, p. 374-379, 2014.

SCHREPF, A. et al. Improvement in the spatial distribution of pain, somatic symptoms, and depression after a weight loss intervention. **The Journal of Pain**, v. 18, n. 12, p. 1542–1550, 2017.

SIPPEL, C. et al. Processos inflamatórios da obesidade. **Revista de Atenção à Saúde**, v. 12, n. 42, p. 48-56, 2014.

STONE, A. A.; BRODERICK, J. E. Obesity and pain are associated in the United States. **Obesity**, v. 20, n. 7, p. 1491-5, 2012.

THIJSSEN, E.; VAN CAAM, A.; VAN DER KRAAN, P. M. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. **Rheumatol.**, v. 54, n. 4, p. 588-600, 2015.

TREEDE, R. D. et al. A classification of chronic pain for ICD-11. **Pain**, v. 156, n. 6, p. 1003-1007, 2015.

VIEIRA, E. B. M. et al. Chronic pain, associated factors, and impact on daily life: are there differences between the sexes? **Cad Saúde Pública**, v. 28, n. 8, p. 1459-1467, 2012.

WALSH, T. P. at al. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. **BMC Musculoskelet Disord**, v. 19, n. 1, p. 233-246. 2018.

WHO. Physical Status: The Use and Interpretation of Anthropometry. WHO Technical Report Series 854, Geneva: World Health Organization; 1995.

WHO. Waist circumference and waist–hip ratio: report of a WHO expert consultation. Geneva: World Health Organization; 2008.

WHO (World Health Organization). World health statistics 2021: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2021.

WOESSNER, J. Overview of pain: Classification and concepts. Weiner's Pain Management: A Practical Guide for Clinicians. p. 35-48. 2006.

WOLFE F, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. **Arthritis Rheum.**, v.33, n.2, p. 160-72, 1990.

WOOLF, A. D.; PFLEGER, B. Burden of major musculoskeletal conditions. **Bulletin of the World Health Organization**, 81, 646–656. 2003.

7. ARTIGO DE RESULTADOS 1

(Publicado na revista Reumathology International – vide cópia da publicação no Apêndice)

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

Authors: Aline B P Costa[1], Luciana A C Machado[2], Rosa W Telles[1,2], Sandhi M Barreto[1,2]

Affiliations: 1Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil. 2Clinical Hospital, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

Correspondence regarding this manuscript should be addressed to: Sandhi Maria Barreto. Faculty of Medicine & Clinical Hospital, Universidade Federal de Minas Gerais, Avenida Alfredo Balena n. 190, Funcionários, Belo Horizonte, MG 30130-100, Brazil. Telephone: (+5531)3307-9140. Fax number: (+5531) 3307-9140. Email: sandhi.barreto@gmail.com

Conflict of Interest: Author Aline B P Costa, author Luciana A C Machado, author Rosa W Telles, and author Sandhi M Barreto declare that they have no conflict of interest.

Acknowledgements: We would like to thank the staff and participants of ELSA-Brasil MSK. We would also like to thank Douglas R.M. Azevedo for his support in building Venn diagrams.

Source of Funding: ELSA-Brasil has been supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and CNPq-BR), grants 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ. ELSA-Brasil

MSK has been supported by CAPES-BR (grant pós-doc/SUS 054/2010), FAPEMIG-BR (grant APQ-00921-16) and CNPq-BR (grant 42358520169). The investigation was carried out while Dr. Luciana A.C. Machado was a Postdoctoral Fellow and MSc. Aline A.B. Costa was a PhD candidate, both supported by CAPES-BR (Finance Code 001). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions: ABPC, LACM, RWT and SMB contributed to study conception and design; ABPC, RWT and SMB contributed to the analysis and interpretation of data; ABPC drafted the first version of the article; LACM, RWT and SMB revised critically the article content. All authors approved of the final version to be published.

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 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].

Two distinct criteria were used for the evaluation of pain "spreadness": chronic musculoskeletal pain was defined as multisite when located in ≥3 of the 9 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/m2), general obesity level I (30–34.9 kg/m2) and general obesity level II/III (≥ 35 kg/m2) [34]. BMI ≤ 24.9 kg/m2 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/m2); (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 col- lected 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-trend ≥ 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 par- ticipants 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).

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

Characteristic	**Overall sample *n=2,899***
Women	1,534 (52.9)
Men	1,365 (47.1)
Age group	
< 45	289 (10.0)
45-54	1,043 (36.0)
55-64	1,038 (35.8)
65+	529 (18.2)
Self-reported skin color/race[a]	
White	1,416 (49.5)
Brown	997 (34.9)
Black	368 (12.9)
Yellow	64 (2.2)
Indigenous	15 (0.5)
Educational level[b]	
Higher education	1,917 (66.2)
Secondary school	735 (25.4)
Primary school or lower	245 (8.4)
Work status	
Active	2,386 (82.3)
Retired	513 (17.7)
Nature of occupation[c]	
NR non-manual	1,746 (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

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 were 25.8% and 41.5%, respectively. The prevalence of abdominal obesityWHtR 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 were 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 obesityWC. 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).

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-trend = 0.54) and from 32 to 63% (p-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-trend = 0.61) the chance of any CMP (Table 2).

Table 2 – Association of obesity clinical markers and body weight trajectories with chronic musculoskeletal pain at any site (n = 2,897), 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$_{WC}$ level I[b]	1.45 (1.19-1.76)**	1.32 (1.08-1.61)*
Abdominal obesity$_{WC}$ level II[c]	2.05 (1.72-2.44)**	1.63 (1.36-1.96)**
Abdominal obesity$_{WHtR}$[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

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-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 obesityWC 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-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).

Table 3 – Association of clinical markers of obesity and body weight trajectories with local and multisite chronic musculoskeletal pain (n=2,886), 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	1.15 (0.97-1.37)	1.66 (1.33-2.07)**	1.16 (0.97-1.38)	1.68 (1.33-2.11)**

kg/m^2)				
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 asWHtR ≥ 0.5

Table 4 – Association of clinical markers of obesity and body weight trajectories with regional and generalized chronic musculoskeletal pain (n=2,892), 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	1.23 (1.04-1.45)*	1.72 (1.29-2.28)**	1.23 (1.04-1.46)*	1.74 (1.29-2.34)**

(BMI ≥25 kg/m^2)				
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

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 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 obe- sity 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.

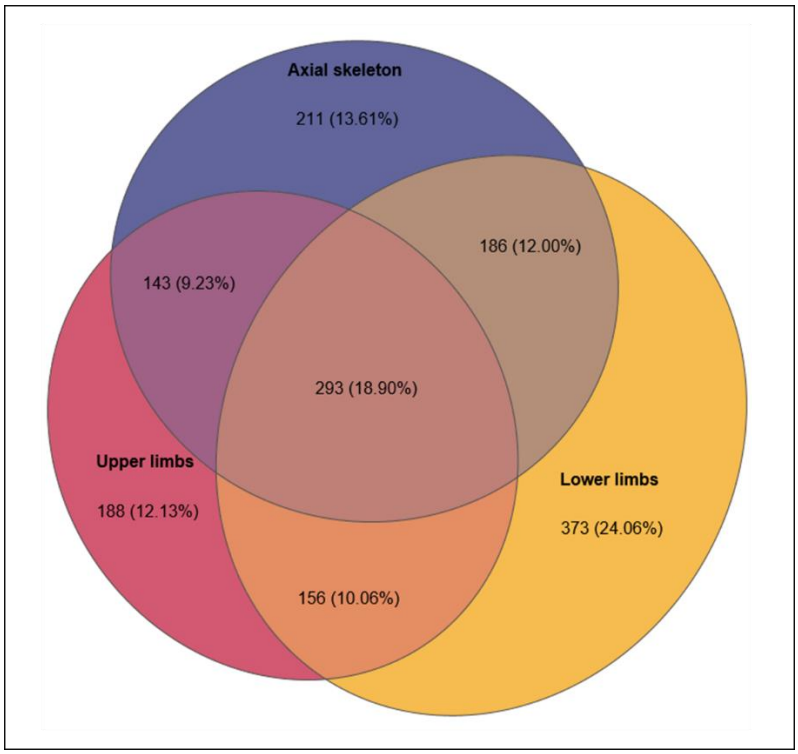


Fig. 1 Venn diagram of the frequency of chronic musculoskeletal pain according to body region: upper limbs (shoulders, elbows and/or wrists/hands), lower limbs (knees, hips/thighs and/or ankles/feet) and axial skeleton (neck, upper back and/or lower back), ELSA-Brasil MSK (2012–2014).

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 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

abdominalWC obesity; e.g., ORs for general obesity level I were higher than those for abdominal obesityWC 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 obesityWHtR, 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 pathophysio- logical processes triggered by obesity-related inflammation, such as central sensitization, typically exhibit a generalized 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 presen- tations 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 num- bers 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 observa- tional 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 statis- tical 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 measure- ment 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.

Compliance with ethical standards

The present study used data from ELSA-Brasil and ELSA-Brasil MSK, which has been 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]. ELSA-Brasil has also been approved by the National Committee for Ethics in Research, Brazil [protocol 976/2006]. 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.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1789 - 858. https://doi.org/10.1016/S0140-6736(18)32279-7

2. Torres J, da Silva S, Ferreira F, Mendes L, Machado L (2018). Chronic pain is associated with increased health care use among community-dwelling older adults in Brazil: the Pain in the Elderly (PAINEL) Study. Fam Pract. [Epub ahead of print]. https://doi.org/10.1093/fampra/cmy123.

3. Stewart WF, Ricci JA, Chee E, Morganstein, D, Lipton R. (2003) Lost productive time and cost due to common pain conditions in the US workforce. JAMA, 290(18):2443 - 54. https://doi.org/10.1093/fampra/cmy123

4. Larsson B, Bjork J, Borsbo B, Gerdle, B. (2012). A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. Eur J Pain 16(8):1084-93. https://doi.org/10.1002/j.1532-2149.2012.00117.x

5. Wolfe F, Clauw DJ, Fitzcharles MA, et al (2016). 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthitis Rheum 46(3):319-29. https://doi.org/10.1016/j.semarthrit.2016.08.012

6. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. (2008). Localized or widespread musculoskeletal pain: does it matter? Pain, 138(1):41-6. https://doi.org/10.1016/j.pain.2007.11.002

7. Miranda VS, Decarvalho VB, Machado LA, Dias JM. (2012). Prevalence of chronic musculoskeletal disorders in elderly Brazilians: a systematic review of the literature. BMC Musculoskeletal Dis 13:82. https://doi.org/10.1186/1471-2474-13-82

8. Cimas M, Ayala A, Sanz B, Agulló-Tomás MS, Escobar A, Forjaz MJ. (2018). Chronic musculoskeletal pain in European older adults: Cross-national and gender differences. Eur J Pain 22(2):333-45. https://doi.org/10.1002/ejp.1123

9. Coggon D, Ntani G, Palmer KT, et al. (2013) Patterns of multisite pain and associations with risk factors. Pain 154(9):1769-77. https://doi.org/10.1016/j.pain.2013.05.039

10. Mourao AF, Blyth FM, Branco JC. (2010). Generalised musculoskeletal pain syndromes. Best Pract Res Clin Rheumatol 24(6):829-40. https://doi.org/10.1016/j.berh.2010.10.005

11. Hajihosseinali M, Arjmand N, Shirazi-Adl A. (2015). Effect of body weight on spinal loads in various activities: a personalized biomechanical modeling approach. J Biomech 48(2):276-82. https://doi.org/10.1016/j.jbiomech.2014.11.033

12. Singh D, Park W, Hwang D, Levy MS. (2015). Severe obesity effect on low back biomechanical stress of manual load lifting. Work, 51(2):337-48. https://doi.org/10.3233/WOR-141945

13. Knarr BA, Higginson JS, Zeni JA. (2016). Change in knee contact force with simulated change in body weight. Comput Methods Biomech Biomed Engin 19(3):320-3. https://doi.org/10.1080/10255842.2015.1018193

14. Ouchi N, Parker JL, Lugus JJ. (2011). Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11(2):85-97. https://doi.org/10.1038/nri2921

15. Woolf CJ. (2011). Central sensitization: implications for the diagnosis and treatment of pain. Pain 152(3 Suppl):S2-15. https://doi.org/10.1016/j.pain.2010.09.030

16. Paley CA, Johnson MI. (2016). Physical activity to reduce systemic inflammation associated with chronic pain and obesity: A narrative review. Clin J Pain 32(4):365-70. https://doi.org/10.1097/AJP.0000000000000258

17. Shiri R, Karppinen J, Leino-Arjas P, et al. (2007). Cardiovascular and lifestyle risk factors in lumbar radicular pain or clinically defined sciatica: a systematic review. Eur Spine J 16(12):2043-54. https://doi.org/10.1007/s00586-007-0362-6

18. Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan EM. (2018). The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskelet Dis 19(1):233. https://doi.org/10.1186/s12891-018-2137-0

19. Savva SC, Lamnisos D, Kafatos AG. (2013). Predicting cardiometabolic risk: waist-to-height ratio or BMI. A meta-analysis. Diabetes Metab Syndr Obes 6:403-19. https://doi.org/10.2147/DMSO.S34220.

20. Goossens GH. (2017). The metabolic phenotype in obesity: Fat mass, body fat distribution, and adipose tissue function. Obes Facts 10(3):207-15. https://doi.org/10.1159/000471488

21. Ashwell M, Gunn P, Gibson S. (2012). Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev 13(3):275-86. https://doi.org/10.1111/j.1467-789X.2011.00952.x

22. Ashwell M, Gibson S. (2014). A proposal for a primary screening tool: 'Keep your waist

circumference to less than half your height'. BMC Med 12(1):207. https://doi.org/10.1186/s12916-014-0207-1

23. Ogwumike OO, Adeniyi AF, Orogbemi OO. (2015). Musculoskeletal pain among postmenopausal women in Nigeria: Association with overall and central obesity. Hong Kong Physiother J 34:41-6. https://doi.org/10.1016/j.hkpj.2015.06.001

24. Frilander H, Viikari-Juntura E, Heliovaara M, Mutanen P, Mattila VM, Solovieva S. (2016). Obesity in early adulthood predicts knee pain and walking difficulties among men: A life course study. Eur J Pain 20(8):1278-87. https://doi.org/10.1002/ejp.852

25. Dawson J, Juszczak, E, Thorogood M, Marks SA, Dodd C, Fitzpatrick R. (2003). An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. J Epidemiol Community Health 57(10):823-30. http://dx.doi.org/10.1136/jech.57.10.823

26. Macfarlane GJ, de Silva V, Jones GT. (2011). The relationship between body mass index across the life course and knee pain in adulthood: results from the 1958 birth cohort study. Rheumatology 50(12):2251-6. https://doi.org/10.1093/rheumatology/ker276

27. Frilander H, Solovieva S, Mutanen P, Pihlajamaki H, Heliovaara M, Viikari-Juntura E. (2015). Role of overweight and obesity in low back disorders among men: a longitudinal study with a life course approach. BMJ Open 5(8):e007805. http://dx.doi.org/10.1136/bmjopen-2015-007805

28. Aquino EM, Barreto SM, Bensenor IM, et al (2012). Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol, 175(4):315-24. https://doi.org/10.1093/aje/kwr294

29. Machado LAC, Telles RW, Costa-Silva L, Barreto SM. (2015). Perfil da Coorte ELSA-Brasil Musculoesquelético. Braz J Rheumatol. 56(Suppl 1):S29-30.

30. de Barros EM, Alexandre NM. (2003). Cross-cultural adaptation of the Nordic musculoskeletal questionnaire. Int Nurs Rev 50(2):101-8. https://doi.org/10.1046/j.1466-7657.2003.00188.x

31. Mundal I, Bjorngaard JH, Nilsen TI, Nicholl BI, Grawe RW, Fors EA. (2016). Long-term changes in musculoskeletal pain sites in the general population: The HUNT Study. J Pain 17(11):1246-56. https://doi.org/10.1016/j.jpain.2016.08.006

32. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. (2014). Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. BMC Musculoskelet Disord 15:213. https://doi.org/10.1186/1471-2474-15-213

33. Schmidt MI, Griep RH, Passos VM, et al. (2013). Strategies and development of quality assurance and control in the ELSA-Brasil. Rev Saúde Pública 47(Suppl 2):105-12. http://dx.doi.org/10.1590/S0034-8910.2013047003889

34. World Health Organization. Physical Status: The use and interpretation of anthropometry. WHO Technical Report Series 854, Geneva. 1995. Retrieved from: https://www.who.int/childgrowth/publications/physical_status/en/

35. World Health Organization. Waist circumference and waist–hip ratio: report of a WHO expert consultation. Geneva, p. 39. 2008.

36. Schmidt MI, Duncan BB, Mill JG, et al. (2015) Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol 44(1):68-75. https://doi.org/10.1093/ije/dyu027

37. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. 2000. Report. Retrieved from: https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

38. Henschke N, Kamper SJ, Maher CG. (2015). The epidemiology and economic consequences of pain. Mayo Clin Proc 90(1):139-47. https://doi.org/10.1016/j.mayocp.2014.09.010

39. Autor DH, Levy F, Murnane RJ. (2003) The skill content of recent technological change: an empirical exploration. Q J Econ 118(4):1279-333. https://doi.org/10.1162/003355303322552801

40. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, Braggion G. (2001). Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Fís Saúde 6(2):5-18. https://doi.org/10.12820/rbafs.v.6n2p5-18

41. Nunes, MA., Alves, MGM, Chor D, Schmidt MI, Duncan BB. (2011). Adaptação transcultural do CIS-R (Clinical Interview Schedule- Revised version) para o português no Estudo Longitudinal de Saúde do Adulto (ELSA). Rev HCPA 31(4):487-90. Retrieved from: https://seer.ufrgs.br/hcpa/article/view/24065/14973

42. Haukka E, Ojajarvi A, Takala EP, Viikari-Juntura E, Leino-Arjas P. (2012). Physical workload, leisure-time physical activity, obesity and smoking as predictors of multisite musculoskeletal pain. A 2-year prospective study of kitchen workers. Occup and Environ Med 69(7):485-92. https://doi.org/10.1136/oemed-2011-100453

43. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. (2014). Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study--the HUNT study. Pain

155(8):1555-61. https://doi.org/10.1016/j.pain.2014.04.033

44. Narouze S, Souzdalnitski D. (2015). Obesity and chronic pain: systematic review of prevalence and implications for pain practice. Reg Anesth Pain Med 40(2):91-111. https://doi.org/10.1097/AAP.0000000000000218

45. Pan F, Laslett L, Blizzard L, Cicuttini F, Winzenberg T, Ding C, Jones G. (2017). Associations Between Fat Mass and Multisite Pain: A Five-Year Longitudinal Study. Arthritis Care Research 69(4):509-16. https://doi.org/10.1002/acr.22963

46. Han TS, Schouten JS, Lean ME, Seidell JC. (1997). The prevalence of low back pain and associations with body fatness, fat distribution and height. Int J Obes 21(7):600-7. https://doi.org/10.1038/sj.ijo.0800448

47. Ray L, Lipton RB, Zimmerman ME, Katz MJ, Derby CA. (2011). Mechanisms of association between obesity and chronic pain in the elderly. Pain 152(1):53-9. https://doi.org/10.1016/j.pain.2010.08.04

48. Heuch I, Heuch I, Hagen K, Zwart JA. (2015). A comparison of anthropometric measures for assessing the association between body size and risk of chronic low back pain: The HUNT Study. PloS One, 10(10):e0141268. https://doi.org/10.1371/journal.pone.0141268

49. Dario AB, Ferreira ML, Refshauge K, et al. (2016). Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins. Eur Spine J 25(4):1188-95. https://doi.org/10.1007/s00586-015-4055-2

50. Hussain SM, Urquhart DM, Wang Y, Shaw JE, Magliano DJ, Wluka AE Cicuttini FM. (2017). Fat mass and fat distribution are associated with low back pain intensity and disability: results from a cohort study. Arthritis Res Ther 19(1):26. https://doi.org/10.1186/s13075-017-

1242-z

51. Shiri R, Falah-Hassani K, Heliovaara M, et al. (2019). Risk Factors for Low Back Pain: A Population-Based Longitudinal Study. Arthritis Care Res 71(2):290-9. https://doi.org/10.1002/acr.23710

52. Power C, Frank J, Hertzman C, Schierhout G, Li L. (2001). Predictors of low back pain onset in a prospective British study. Am J Public Health 91(10):1671-8. https://doi.org/10.2105/AJPH.91.10.1671

53. Kouvari M, Panagiotakos DB, Yannakoulia M, et al. (2019). Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: The ATTICA cohort study. Metabolism 93:18-24. https://doi.org/10.1016/j.metabol.2019.01.003

54. Krakauer NY, Krakauer JC. (2018) Untangling Waist Circumference and Hip Circumference from Body Mass Index with a Body Shape Index, Hip Index, and Anthropometric Risk Indicator. Metab Syndrome Relat Disord 16(4):160-5. https://doi.org/10.1089/met.2017.0166

55. Graven-Nielsen T, Arendt-Nielsen L. (2010). Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 6(10):599-606. https://doi.org/10.1038/nrrheum.2010.107

56. Harte SE, Harris RE, Clauw DJ. (2018). The neurobiology of central sensitization. J Appl Behav Res 23(2):e12137. https://doi.org/10.1111/jabr.12137

57. Davis MA, Ettinger WH, Neuhaus JM. (1990). Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). Semin Arthritis Rheum 20(3 Suppl 1):34-41. https://doi.org/10.1016/0049-0172(90)90045-H

58. Lake JK, Power C, Cole TJ. (2000). Back pain and obesity in the 1958 British birth cohort. cause or effect? J Clin Epidemiol 53(3):245-50. https://doi.org/10.1016/S0895-4356(99)00155-9.

59. Magnusson K, Osteras N, Mowinckel P, Natvig B, Hagen KB. (2014). No strong temporal relationship between obesity and multisite pain--results from a population-based 20-year follow-up study. Eur J Pain, 18(1):120-7. https://doi.org/10.1002/j.1532-2149.2013.00338.x

60. Pearl J. (2009) Causal inference in statistics: An overview. Statist Surv 3:96-146. https://doi.org/10.1002/j.1532-2149.2013.00338.x

61. Poleshuck EL, Green CR. (2008). Socioeconomic disadvantage and pain. Pain 136(3):235-8. https://doi.org/10.1016/j.pain.2008.04.003

62. Cohen AK, Rai M, Rehkopf DH, et al. (2013). Educational attainment and obesity: a systematic review. Obes Rev 14(12):989-1005. https://doi.org/10.1111/obr.12062

Note: Partial results of this paper were presented in two Congresses. The references of these presentations are listed below:

1. Costa ABP, Machado LAC, Telles RW, Silva PT, Silva LC, Barreto SM (2016). Associação entre marcadores de obesidade e a presença e número de locais de dor crônica: ELSA-Brasil Musculoesquelético (ELSA-BRASIL ME). Rev Bras Reumatol 56(supl. 1):S48 - S49.

2. Telles RW, Costa ABP, Machado LAC, Barreto SM (2018). Overweight and obesity versus chronic musculoskeletal symptoms: is there a connection? Adv Rheumatol 58(23). https://doi.org/10.1186/s42358-018-0019-7

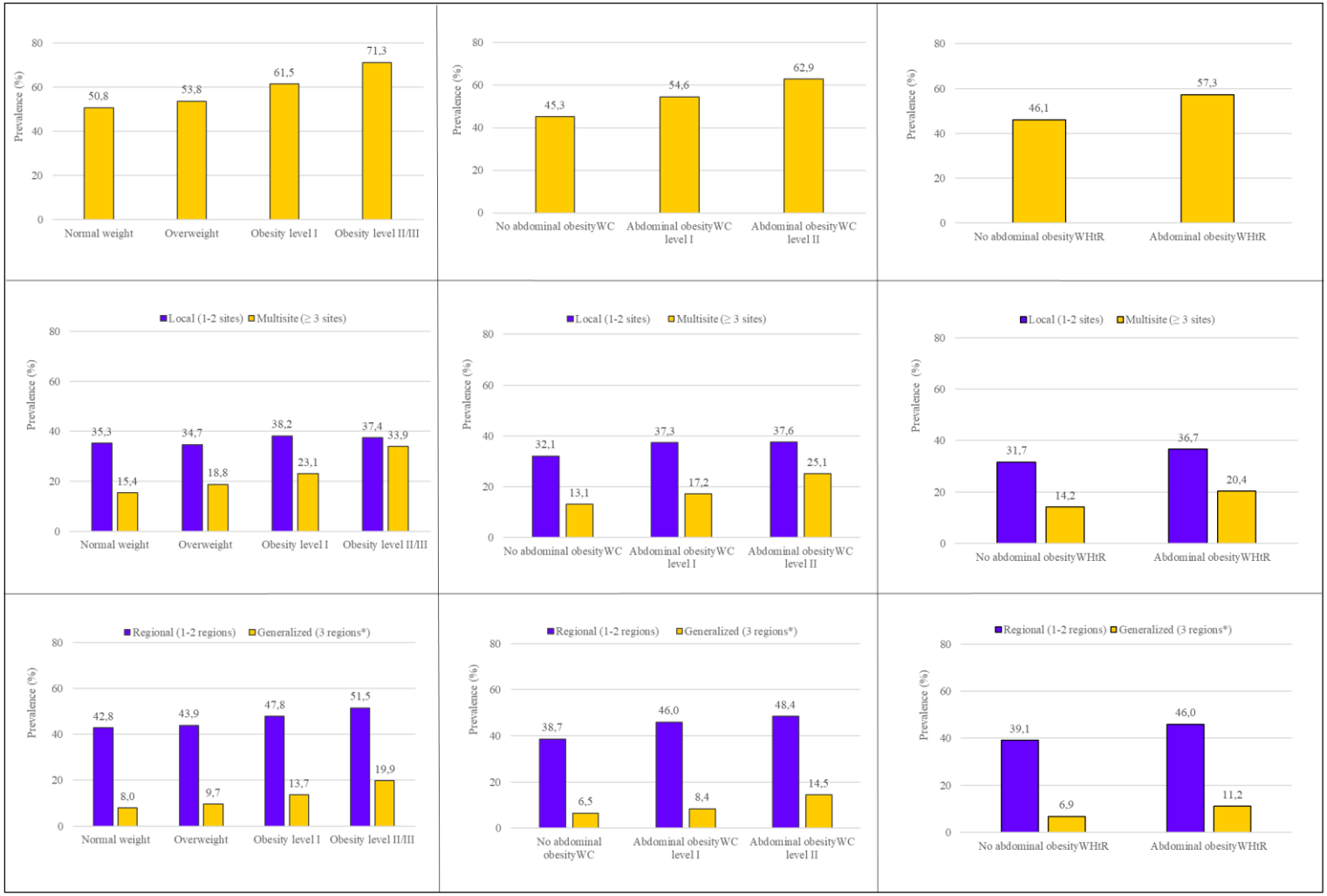
Online Resource 1 – Characteristics of included participants according to the presence, number of sites and spatial distribution of chronic musculoskeletal pain (CMP), ELSA-Brasil MSK (2012-2014)

Characteristic	No CMP n=1,304	Any CMP n=1,595	Number of sites of CMP[a]		Spatial distribution of CMP[b]	
			Local (1-2 sites) n=1,031	Multisite (≥3 sites) n=553	Regional (1-2 regions) n=1,291	Generalized (3 regions) n=299
Women	547 (41.9)	987 (61.9)	583 (56.5)	395 (71.4)	760 (58.9)	223 (74.6)
Men	757 (58.1)	608 (38.1)	448 (43.5)	158 (28.6)	531 (41.1)	76 (25.4)
Age group						
< 45	159 (12.2)	130 (8.2)	95 (9.2)	35 (6.3)	112 (8.7)	18 (6.0)
45-54	479 (36.7)	564 (35.4)	368 (35.7)	193 (34.9)	465 (36.0)	96 (32.1)
55-64	439 (33.7)	599 (37.5)	376 (36.5)	217 (39.2)	476 (36.9)	122 (40.8)
65+	227 (17.4)	302 (18.9)	192 (18.6)	108 (19.5)	238 (18.4)	63 (21.1)
Self-reported skin colour/race[c]						
White	656 (50.9)	760 (48.4)	513 (50.5)	242 (44.4)	638 (50.2)	119 (40.5)
Brown	437 (33.9)	560 (35.6)	353 (34.8)	205 (37.6)	443 (34.8)	116 (39.5)
Black	164 (12.7)	204 (13.0)	125 (12.3)	76 (14.0)	156 (12.3)	48 (16.3)
Yellow	27 (2.1)	37 (2.4)	19 (1.9)	17 (3.1)	28 (2.2)	8 (2.7)
Indigenous	5 (0.4)	10 (0.6)	5 (0.5)	5 (0.9)	7 (0.5)	3 (1.0)
Educational level[d]						
Higher education	895 (68.6)	1,022 (64.1)	676 (65.7)	341 (61.6)	832 (64.5)	187 (62.5)
Secondary school	307 (23.6)	428 (26.9)	270 (26.2)	153 (27.7)	348 (27.0)	78 (26.1)
Primary school or lower	102 (7.8)	143 (9.0)	83 (8.1)	59 (10.7)	109 (8.5)	34 (11.4)

Labour status						
Active	1,110 (85.1)	1,276 (80.0)	839 (81.4)	429 (77.6)	1,050 (81.3)	221 (73.9)
Retired	194 (14.9)	319 (20.0)	192 (18.6)	124 (22.4)	241 (18.7)	78 (26.1)
Nature of occupation[e]						
NR non-manual	818 (63.3)	928 (58.7)	607 (59.3)	316 (57.9)	748 (58.4)	177 (59.8)
R non-manual	285 (22.0)	479 (30.3)	313 (30.6)	163 (29.8)	398 (31.1)	80 (27.0)
Manual	190 (14.7)	174 (11.0)	104 (10.1)	67 (12.3)	134 (10.5)	39 (13.2)
LTPA	865 (66.3)	1,190 (74.6)	755 (73.2)	425 (76.8)	959 (74.3)	226 (75.6)
Insufficient	865 (66.3)	1,190 (74.6)	755 (73.2)	425 (76.8)	959 (74.3)	226 (75.6)
Moderate	316 (24.2)	288 (18.1)	187 (18.2)	100 (18.1)	229 (17.7)	59 (19.7)
Vigorous	123 (9.5)	117 (7.3)	89 (8.6)	28 (5.1)	103 (8.0)	14 (4.7)
Depressive symptoms						
No	1,179 (90.4)	1,270 (79.6)	857 (83.1)	405 (73.2)	1,063 (82.3)	204 (68.2)
Yes	125 (9.6)	325 (20.4)	174 (16.9)	148 (26.8)	228 (17.7)	95 (31.8)

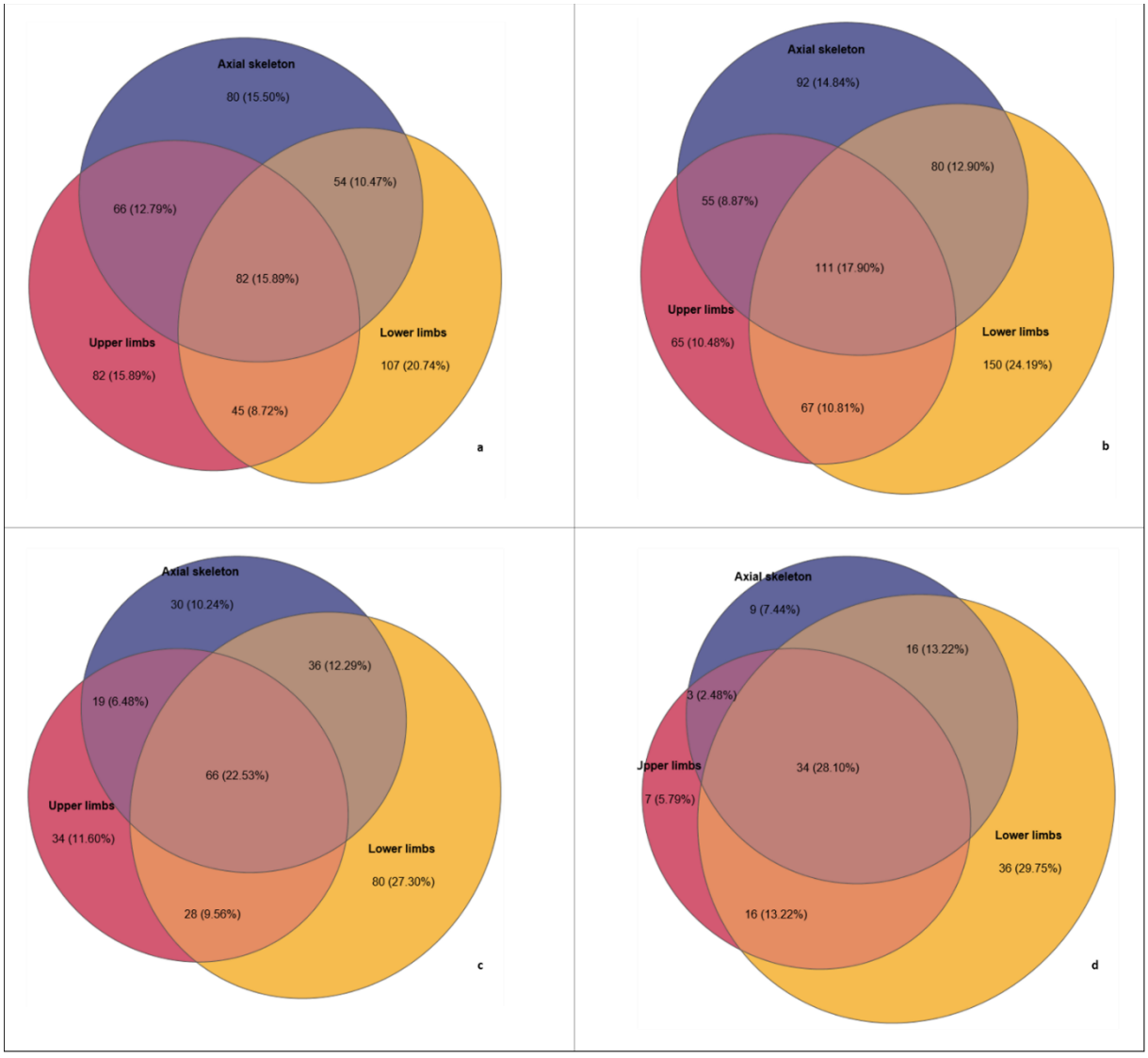
Data presented as frequencies and percentages for valid cases only.
Frequency of missing values: [a]11, [b]5, [c]39, [d]2, [e]25.
NR, Non-routine. R, routine. LTPA, leisure-time physical activity.

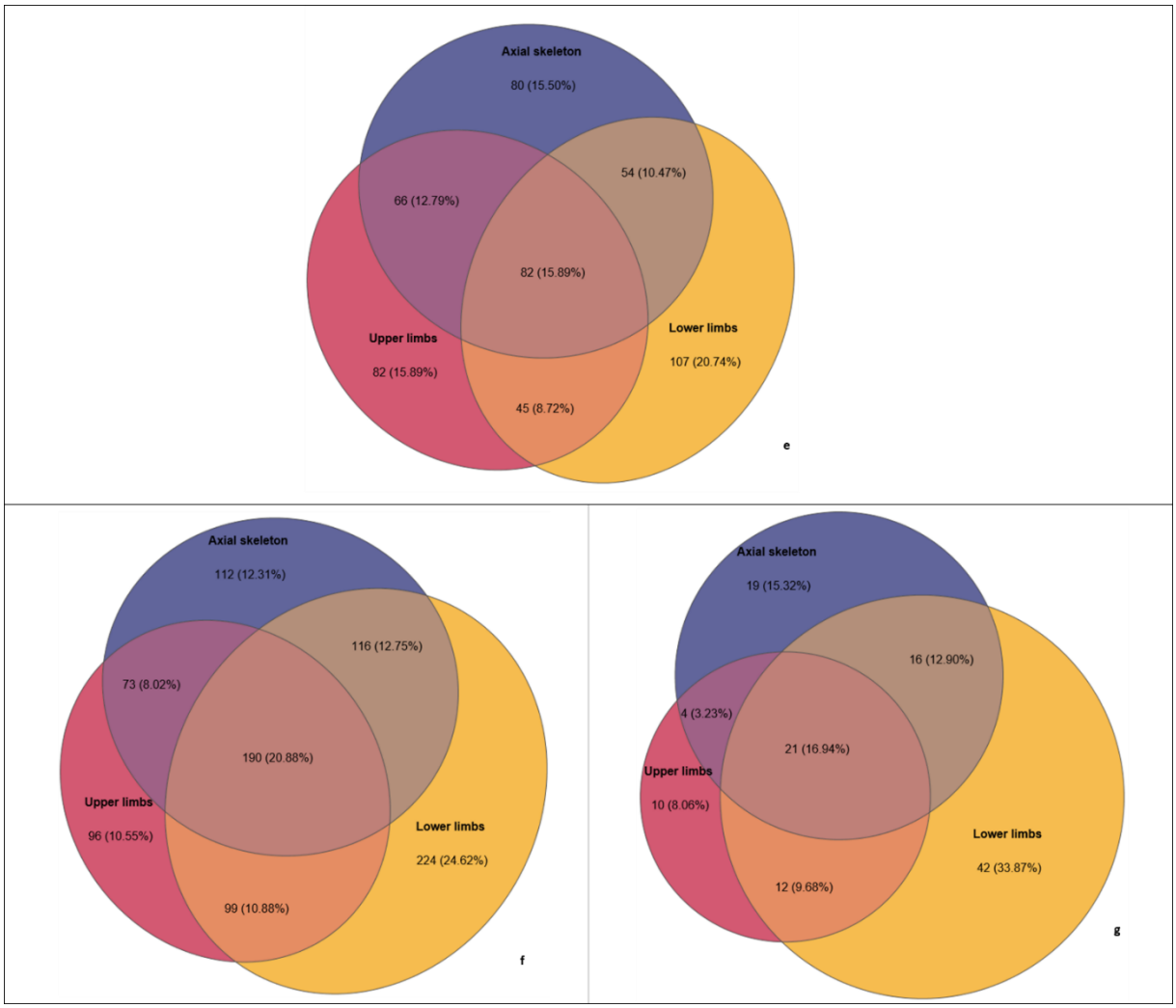
Online Resource 2 – Prevalence of chronic musculoskeletal pain at any site, at multisite and generalized pain, according to clinical markers of obesity, ELSA-Brasil MSK (2012 2014).



WC, waist circumference; WHtR, waist-to-height ratio.
a: Prevalence of chronic musculoskeletal pain at any site.
b: Prevalence of chronic musculoskeletal pain at multisite.
c: Prevalence of generalized pain.
Definitions of general obesity markers: normal weight (BMI ≤ 24.9 Kg/m2), overweight (BMI 25-29.9 kg/m2), obesity level I (BMI 30-34.9 kg/m2) and obesity level II/III
(BMI ≥35 kg/m2).
Definitions of obesity markers according to WC: no abdominal obesityWC (WC < 80.0 cm in women and < 94.0 cm in men), abdominal obesityWC level I (80.0-87.9 cm in
women and 94.0-101.9 in men), abdominal obesityWC level II (WC ≥ 88.0 cm in women and ≥102.0 cm in men).
Definitions of obesity markers according to WHtR: no abdominal obesityWHtR (WHtR < 0.5 cm/m), abdominal obesityWHtR (WHtR ≥ 0.5 cm/m).
*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)

Online Resource 3 – Venn diagrams of the frequency of chronic musculoskeletal pain according to body regions and clinical markers of obesity/weight trajectories, ELSA-Brasil MSK (2012-2014).




Axial skeleton
80 (15.50%)
54 (10.47%)
66 (12.79%)
82 (15.89%)
Upper limbs
82 (15.89%)
Lower limbs
107 (20.74%)
45 (8.72%)
e
Axial skeleton
112 (12.31%)
116 (12.75%)
73 (8.02%)
190 (20.88%)
Upper limbs
96 (10.55%)
Lower limbs
224 (24.62%)
99 (10.88%)
f
Axial skeleton
19 (15.32%)
16 (12.90%)
4 (3.23%)
21 (16.94%)
Upper limbs
10 (8.06%)
Lower limbs
42 (33.87%)
12 (9.68%)
g

a – d: Frequency of chronic musculoskeletal pain according to body region and BMI-defined obesity.
e – g: Frequency of chronic musculoskeletal pain according to body region and weight trajectories.

h – j: Frequency of chronic musculoskeletal pain according to body region and WC-defined abdominal obesity.
k – l: Frequency of chronic musculoskeletal pain according to body region and WHtR-defined abdominal obesity.
a: normal weight, BMI ≤ 24.9 Kg/m2.
b: overweight, BMI 25-29.9 kg/m2.
c: obesity level I, BMI 30-34.9 kg/m2.
d: obesity level II/III, BMI ≥ 35 kg/m2.
e: normal weight at age 20 and currently.
f: current excess weight, BMI ≥ 25 kg/m2.
g: excess weight at both times.
h: no abdominal obesityWC, WC < 80.0 cm in women and < 94.0 cm in men.
i: abdominal obesityWC level I, WC 80.0-87.9 cm in women and 94.0-101.9 in men.
j: abdominal obesityWC level II, WC ≥ 88.0 cm in women and ≥102.0 cm in men.
k: no abdominal obesityWHtR, WHtR < 0.5 cm/m.
l: abdominal obesityWHtR, WHtR ≥ 0.5 cm/m.

8. ARTIGO DE RESULTADOS 2

Obesity and risk of multiple and severe episodes of frequent knee pain in ELSA-Brasil MSK participants with or without knee pain at baseline

Aline B.P. Costa[1], MS

Luciana A.C. Machado[2], PhD

Rosa W. Telles[1,2], PhD

Sandhi M. Barreto[1,2], PhD

Affiliations: [1]Faculty of Medicine, Universidade Federal de Minas Gerais, Brazil. [2]Clinical Hospital, Universidade Federal de Minas Gerais, Brazil.

Abstract

Knee pain is an important health problem, due to its high prevalence and negative impact on daily activities, quality of life and societal burden. This longitudinal study investigated if overweight and obesity increased the risk of frequent knee pain (FKP) in the ELSA-Brasil MSK cohort. FKP (knee pain, discomfort and/or stiffness in most days of one month) was assessed during face-to-face baseline interviews (2012-2014) and during 4 yearly telephone follow-ups (2016-2018). FKP was classified as severe if rated as moderate to very severe or in the presence of self-reported knee disability. Associations of overweight and obesity at baseline with FKP (absent, present in 1 or 2-4 follow-up assessments) and FKP severity (absent, non-severe episodes, 1 or more severe episode) were verified by multinomial logistic regressions in two different groups of participants: 1) individuals without FKP/chronic knee pain (CKP - >6 months duration) at baseline

(incidence cohort, n = 1,896); 2) individuals with FKP/CKP at baseline (prognosis cohort, n=748). In total, 2,644 participated: 54.2% female, mean age 55.8 (SD 8.8) years. In the incidence cohort, obesity increased the risk of reporting FKP at one (OR: 1.63; 95%CI 1.13-2.37) and multiple follow-ups (OR: 2.61; 95%CI 1.71-3.97), as well as of non-severe (OR: 1.72; 95%CI 1.04-2.84) and severe FKP episodes (OR: 2.10; 95% CI 1.50-2.95). In the prognosis cohort, obesity was a strong independent risk factor only for the reporting of multiple (OR: 2.54; 95%CI 1.60-4.05) and severe FKP episodes (OR: 2.31; 95% CI 1.49-3.59). Overweight was not associated with any of the investigated outcomes. Results support that obesity is an important contributor to incidence and worsening of knee pain. Weight management must be prioritized in multidisciplinary knee pain prevention and treatment programs to reduce the burden of MSK disorders.

1. Introduction

Painful musculoskeletal (MSK) disorders are currently ranked among the top 20 causes of disability-adjusted life-years across all age groups [Vos et al, 2020], and have been the most common causes of years lived with disability worldwide for the last 20 years [GBD, 2020]. Knee pain is a common MSK problem that increases with age, body mass index [Fernandes et al, 2017], and could lead to physical disability and decreased quality of life [Ayis & Dieppe, 2009]. Frequent knee pain (FKP) is often defined as one that occurs on most days of a month [Leyland et al, 2018] and, although it is a common symptom of osteoarthritis, it may exist regardless of the presence or identification of this disease [Bindawas & Vennu, 2015].

Obesity is a recognized risk factor for a variety of noncommunicable diseases (NCDs) as well as a serious morbidity in itself, which may contribute to reductions of 5 to 20 years in life expectancy [Blüher, 2019]. Multiple studies conducted in high-income

countries demonstrated the association between overweight/obesity and MSK pain [Chin et al, 2020]. Concerning knee pain, studies have shown that obesity increases the risk of developing severe knee pain [Jinks et al, 2006], and that weight gain is associated with worsening pain, especially in obese individuals [Tanamas et al, 2013]. Moreover, weight loss interventions seem to be effective in reducing knee pain among overweight/obese adults [Cooper et al, 2018].

Brazil is a middle-income country facing a rapid demographic transition along with a surge in overweight/obesity prevalence [Felisbino-Mendes et al, 2020]. According to the 2019 Brazilian National Health Survey, 1 in 4 adults are obese [IBGE, 2020]. A recent cross-sectional analysis from the largest cohort investigating MSK disorders in Brazilian adults showed a dose-response association between levels of obesity and chronic MSK pain, particularly for pain at weight-bearing joints [Costa et al, 2020]. A systematic review and meta-analysis on risk factors for knee osteoarthritis estimated that overweight or obesity accounted for 25% of the new onset cases of knee pain, while only 5% of cases were related to previous knee injury [Silverwood et al, 2015].

Despite the high prevalence and incapacity associated with knee pain, most studies on the relation between excess weight and this outcome are cross-sectional or restricted to osteoarthritis patients. Longitudinal investigations with non-clinical participants are important to assess if excess weight enhances the risk and severity of knee pain in this type of population. Evidence on the role of overweight/obesity in the risk of FKP episodes can inform health care management and policy making and contribute to reduce the burden of MSK disorders, especially in countries with fast aging population.

This study investigated whether overweight and obesity increased the risk of multiple episodes of FKP and of severe FKP episodes over 4 years of follow up among two groups of participants from the Brazilian Longitudinal Study of Adult Health

Musculoskeletal (ELSA-Brasil MSK) cohort: with and without frequent/chronic knee pain at baseline. We hypothesized that overweight and obesity predict increased incidence of both multiple and severe episodes of FKP, and that the magnitude of these associations will be stronger among individuals without knee pain at baseline than among those with previous frequent/chronic knee pain episode.

2. Methods

2.1 Study design and population

A longitudinal observational study with a 4-year follow-up was conducted. ELSA-Brasil MSK is an ancillary study of the ELSA-Brasil [Aquino et al, 2012], comprising of 2,901 active or retired civil servants from UFMG and Centro Federal de Educação Tecnológica de Minas Gerais (CEFET-MG) at baseline (2012-2014) [Machado et al, 2015].

ELSA-Brasil MSK participants who completed baseline face-to-face assessments for the evaluation of knee pain and overweight/obesity, as well as 4 yearly telephone follow-ups to ascertain the presence of FKP, were eligible for inclusion in the analysis (n = 2,644). Participants were than divided into two groups, according to their pain status at baseline: (1) without FKP and chronic knee pain (CKP), namely incidence cohort, and (2) with FKP and/or CKP, namely prognosis cohort.

Knee pain at baseline was identified with the following questions: “In the last 12 months, have you experienced knee pain, discomfort or stiffness?”. Of those who answered affirmatively to this question for at least one knee, the positive answer to the question “In the last 12 months, did you have knee pain, discomfort or stiffness that lasted most days of at least 1 month?” [Leyland et al, 2018] identified those with FKP in the

previous year (N=610, 23.1%); and the positive answer to the question "Did this problem that you had in the past 12 months last more than 6 months?" [Steingrímsdóttir et al, 2017] identified those with CKP also in the previous year (n=578, 21.9%). Considering the overlaps (see Figure, Supplemental Digital Content 1, which describes the distribution of pain type at baseline), a total of 1,896 individuals were considered free from frequent and chronic knee pain at baseline (incidence cohort) and 748 reported frequent and/or chronic knee pain at baseline (prognosis cohort). Figure 1 shows the selection of study of participants.

The study was approved by the ethics and research committee of the Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil [protocol COEP/UFMG, Etic 186/06; CEP 1.160.939; CAAE 0186.1.203.000-06].

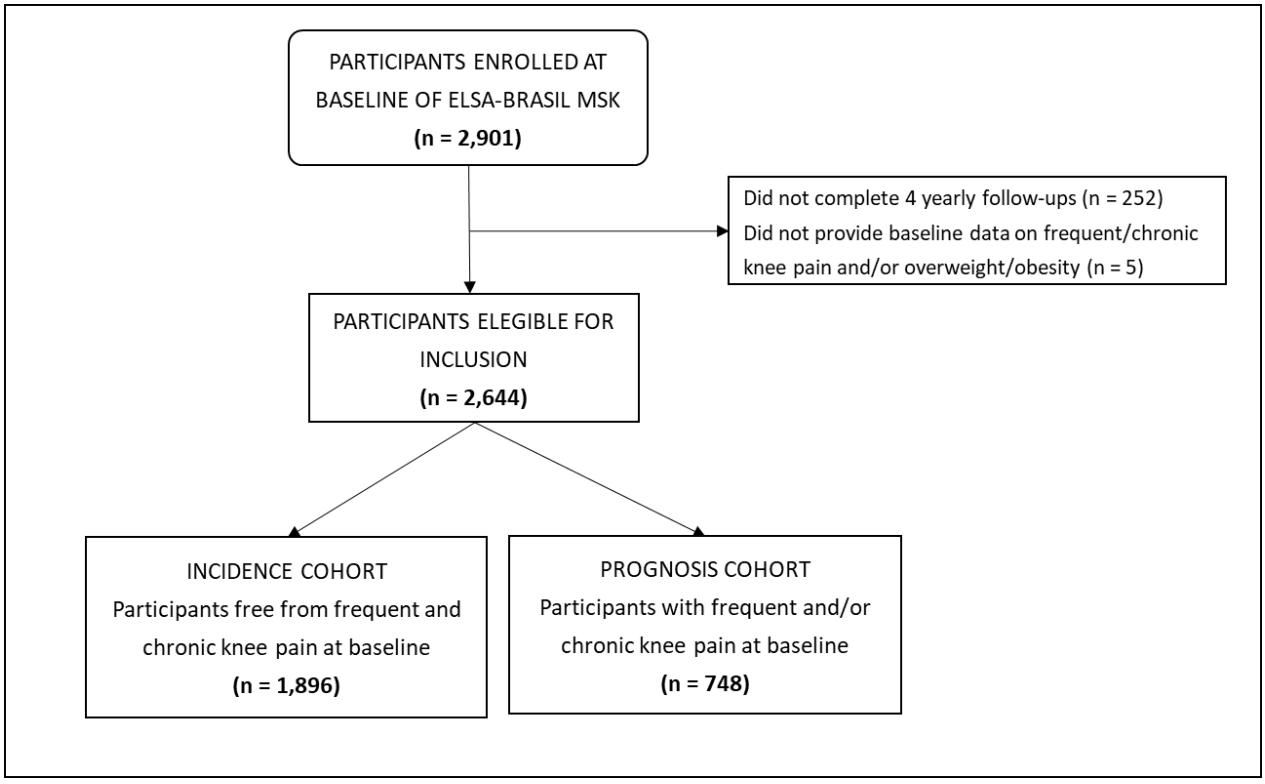


Figure 1 – Flowchart of participants included in the analysis.
ELSA-BRASIL MSK: Brazilian Longitudinal Study of Adult Health Musculoskeletal cohort

2.3 Assessment and definitions of frequent knee pain during follow up

The presence of FKP in the previous month and its characteristics (intensity and presence of associated disability) were assessed through annual telephone interviews between 2015 and 2019.

FKP was ascertained by the answer to the question “In the last 30 days did you have pain, discomfort or stiffness most days in your knee?” [Leyland et al, 2018]. Positive answers for at least one knee at each follow-up interview were computed to create the variable number of episodes of FKP in the last 30 days (0 to 4).

The intensity of FKP was assessed with the question "How much pain, discomfort or stiffness did you have in the knee?". The response in a five-points Likert scale varied from very mild to very severe. The disability associated with FKP was assessed by the question "Were you prevented from performing normal activities in the last 30 days because of this problem in your knee?". Participants who reported at least one episode of moderate, severe or very severe pain and/or one episode of disabling pain at any interview were considered cases of severe frequent knee pain (SFKP).

2.3 Assessment of obesity

Anthropometric evaluations were performed during ELSA-Brasil MSK baseline exams by trained and certified examiners using standardized and calibrated instruments, according to a pre-defined protocol [Schimidt et al, 2013]. Weight (kg) and height (cm) were measured with the participant barefoot, wearing light clothes and standing straight with the head level, 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 as weight (kg)/height $(m)^2$ and categorized as (1) normal weight: $\leq$24.9kg/m^2, (2) overweight: 25-29.9kg/m^2 and (3) obesity: $\geq$30kg/m^2 [WHO, 1995].

2.4 Assessment of potential confounders

At baseline of ELSA-Brasil MSK, data on a vast number of sociodemographic and lifestyle/clinical characteristics were collected through structured interviews and validated questionnaires [Schmidt et al, 2015]. Among those characteristics, sex, age, educational level (university degree, secondary school, elementary school or lower), leisure-time physical activity (LTPA) and depression were considered *a priori* confounders given consistent evidence on their relationship with both obesity and pain [Henschke et al, 2015; Larson et al, 2012; WHO, 1997]. Self-reported skin colour/race (White, Brown, Black) and nature of occupation at baseline (or last occupation if retired) were also considered potential confounders because they have previously shown to be associated with either obesity or pain [Henschke et al, 2015; Larson et al, 2012; Wey & Hu, 2014].

The nature of occupation was categorized into two groups based on the description of the work task performed by the participant: non-manual (reference) and manual [Autor et al, 2003)].

LTPA was assessed by the long version of the International Physical Activity Questionnaire (IPAQ) and categorized as follows: insufficient (no LTPA practice OR some LTPA, but not meeting the other two categories); moderate ($\geq$ 3 days of vigorous-intensity LTPA for at least 20 min/day, OR $\geq$ 5 days of moderate-intensity LTPA and/or walking, in combination or alone, at least 30 min/day, OR $\geq$ 5 days of any combination

of walking, moderate-or-vigorous-intensity LTPA achieving a minimum of 600 MET-min/week); or vigorous (vigorous-intensity LTPA on at least 3 days, accumulating a minimum of 1500 MET-min/week, or ≥ 7 days of any combination of walking, moderate-or-vigorous-intensity LTPA accumulating a minimum of 3000 MET-min/week) [Matsudo et al, 2001].

The presence of depression was assessed through the adapted Brazilian Portuguese version of the Clinical Interview Schedule-Revised, considering the sum of all depressive symptoms [Nunes et al, 2011].

2.5 Statistical analysis

Characteristics of the sample were described as frequencies and percentages, or as means (standard deviations - SD), according to the baseline status of knee pain and differences were assessed with chi-squared test.

Three-category response variables were computed according to the (1) number of FKP episodes: absent (reference), 1 episode, 2-4 episodes (multiple); and according to the (2) severity of frequent pain episodes: absent (reference), non-severe frequent knee pain, SFKP. The association of obesity with the number of episodes and the severity of FKP were than tested using multinomial logistic regressions.

After estimating the crude Odds Ratio (OR) and 95% confidence interval (95% CI) (unadjusted model), the covariates were included (order of inclusion in the model: sex, age, self-reported skin colour/race, educational level, nature of occupation, LTPA and depressive symptoms). Statistical significance was set at $p < 0.05$, and goodness-of-fit of the final adjusted models were assessed using a generalized Hosmer–Lemeshow

goodness-of-fit test for multinomial logistic regression models (*mlogitgof* command in Stata), with $p \geq 0.05$ meaning the models were correctly fitted.

All analyses were performed using Stata statistical software (version 14.0; StataCorp, College Station, Texas).

3. Results

From 2,644 participants included, baseline mean age 55.8 (SD 8.82) years, 54.2% were female and the majority had university education (67.5%). Table 1 shows the participants characteristics according to the knee pain status at baseline.

The average interval between the baseline exams and first follow up interview was 2.0 (SD 0.58 years); and the mean intervals between follow up interviews were 1.0 (SD 0.17) year between 1st and 2nd, 1.1 (SD 0.22) years between 2nd and 3rd and 1.0 (SD 0.23) year between 3rd and 4th.

Table 1 – Characteristics of eligible participants, according to knee pain status at baseline, ELSA-Brasil MSK (2012-2014). N=2,644.

Characteristics	**Incidence cohort*** **(n=1,896)**	**Prognosis cohort**** **(n=748)**
Men	960 (50.6)	252 (33.7)
Women	936 (49.4)	496 (66.3)
Age group		
< 45	214 (11.3)	56 (7.5)
45-54	716 (37.8)	248 (33.2)

55-64	666 (35.1)	288 (38.5)
65+	300 (15.8)	156 (20.8)
Self-reported skin colour/race[a]		
White	957 (51.2)	339 (45.6)
Brown	639 (34.2)	271 (36.6)
Black	219 (11.7)	113 (15.2)
Asian	41 (2.2)	17 (2.3)
Indigenous	14 (0.7)	1 (0.1)
Educational level		
University education	1,309 (69.0)	477 (63.8)
Secondary school	458 (24.2)	207 (27.7)
Primary school or lower	129 (6.8)	64 (8.5)
Nature of occupation[b]		
Non-manual	1,658 (88.0)	661 (89.2)
Manual	225 (12.0)	80 (10.8)
Physical activity		
Insufficient	1,321 (69.7)	544 (72.7)
Moderate	409 (21.6)	145 (19.4)
Vigorous	166 (8.7)	59 (7.9)
Depression		
No	1,812 (95.6)	685 (91.6)
Yes	84 (4.4)	63 (8.4)
BMI		
Eutrophic (< 25 kg/m^2)	761 (40.1)	217 (29.0)
Overweight (25-29.9 kg/m^2)	777 (41.0)	300 (40.1)

Obesity (≥ 30 kg/m^2)	358 (18.9)	231 (30.9)

Data presented as frequencies and percentages for valid cases only.
BMI=body mass index.
*Incidence cohort: participants free from frequent and chronic knee pain at baseline. **Prognosis cohort: participants with frequent and/or chronic knee pain at baseline. Frequency of missing values: [a]33, [b]20.

3.1 Incidence and persistence of FKP episodes and severity of FKP during follow up

Figure 2 presents the distribution of number and severity of FKP episodes during follow up, according to the pain status at baseline. FKP was reported by 24.4% of participants in the incidence cohort, with the most of them reporting only one episode. 64.3% of participants in the prognosis cohort reported at least one episode of FKP during follow up, with most of them reporting multiple episodes. Even more, participants in the prognosis cohort had SFKP more frequently than those from incidence cohort (53.5% versus 18.0%, respectively) independently of the number (one or multiple) of episodes (figure 2).

Table 2 shows the incidence (incidence cohort) or frequency (prognosis cohort) of FKP according to number of episodes, severity and baseline BMI. In the incidence cohort we observed that the incidence of both 1 and multiple episodes increased following the raise of BMI, as well as the incidence of severe pain. The incidence of multiple episodes of FKP more than doubled in the group of obese participants compared to the eutrophic participants (16.5% vs. 8.0%). The incidence of non-severe pain was higher just for obese participants, compared to the eutrophic (8.4% vs. 6.0%) in the incidence cohort. Considering the frequency of multiple FKP and SFKP episodes the prognosis cohort followed the same pattern of the incidence cohort: an increased frequency of

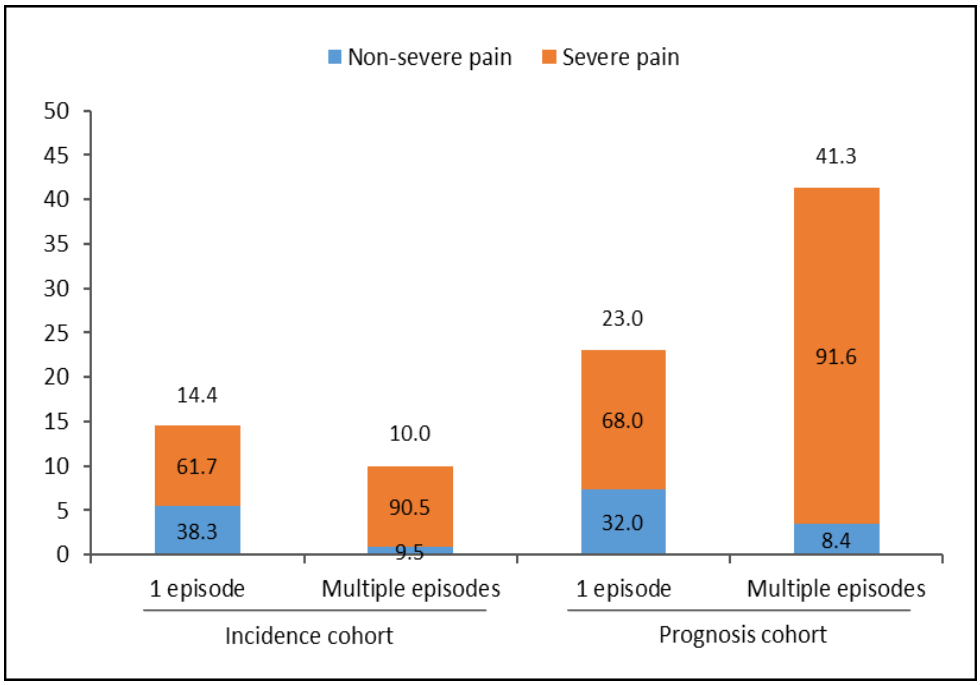


Figure 2 – Incidence, persistence and distribution of severity of frequent knee pain, considering number of episodes and presence of knee pain at baseline, ELSA-Brasil MSK follow-up (2015-2019). N=2,644.

Data presented as percentages. Numbers outside the bars represent cumulative incidence (incidence cohort) and frequency (prognosis cohort) of frequent knee pain according to the number of episodes. Numbers inside the bars represent the pain type frequency for each number of episode category.

events with overweight and obesity. However, the increase of BMI was not followed by an increase in the frequency of 1 episode or non-severe FKP (Table 2).

3.2 Relationship between body mass index and pain incidence

The fully adjusted results of the analysis between BMI and number of episodes of FKP show that the risk of having multiple episodes was higher for obese participants (Table 3). Obesity increased the risk in 139% (OR: 2.39; 95% CI 1.59-3.60) and 138% (OR: 2.38; 95% CI 1.51-3.77) among the individuals of incidence and prognosis cohorts,

respectively. However, for 1 episode of FKP, obesity increased the risk only in the incidence cohort

Similar results were observed for the adjusted analysis between BMI and type of knee pain (Table 4). For participants of the incidence cohort, obesity increased the risk of having both non-severe (OR: 1.72; 95% CI 1.05-2.81) and severe FKP (OR: 1.99; 95% CI 1.43-2.78). For participants of the prognosis cohort, obesity increased in 117% the risk of SFKP and did not change the risk of non-severe frequent pain.

Table 2 – Inicidence and persistence of frequent knee pain according to number of episodes, severity and body mass index, ELSA-Brasil MSK follow-up (2015-2019).

	Number of episodes*		**p**	**Severity****		**p**
	1 episode	**Multiple episodes**		**Non-Severe**	**Severe**	
Incidence cohort (n=1,896)			<0.001			<0.001
Body Mass Index						
Eutrophic (BMI < 25 kg/m^2)	98 (12.9)	61 (8.0)		46 (6.0)	113 (14.8)	
Overweight (BMI 25-29.9 kg/m^2)	114 (14.7)	70 (9.0)		47 (6.0)	137 (17.6)	
Obesity (BMI ≥30 kg/m^2)	62 (17.3)	59 (16.5)		30 (8.4)	91 (25.4)	
Prognosis cohort (n=748)			<0.001			<0.001
Body Mass Index						
Eutrophic (BMI < 25 kg/m^2)	52 (24.0)	74 (34.1)		29 (13.4)	97 (44.7)	
Overweight (BMI 25-29.9 kg/m^2)	76 (25.3)	112 (37.3)		36 (12.0)	152 (50.7)	
Obesity (BMI ≥30 kg/m^2)	44 (19.0)	123 (53.2)		16 (6.9)	151 (65.4)	

Data presented as frequencies and percentages. BMI, body mass index. * Annual incidence (incidence cohort) or annual frequency (prognosis cohort); **Cumulative incidence (incidence cohort) or frequency (prognosis cohort)

Table 3 – Association of body mass index with the number of episodes of frequent knee pain, ELSA-Brasil MSK follow-up (2015-2019).

	Unadjusted model *OR (95%CI)*		**Adjusted[a] model *OR (95%CI)***	
	1 episode	**Multiple episodes**	**1 episode**	**Multiple episodes**
Incidence cohort (n=1,857)				
Body Mass Index				
Eutrophic (BMI < 25 kg/m^2)	1.00	1.00	1.00	1.00
Overweight (BMI 25-29.9 kg/m^2)	1.18 (0.88-1.58)	1.16 (0.81-1.67)	1.24 (0.92-1.68)	1.17 (0.80-1.70)
Obesity (BMI ≥30 kg/m^2)	**1.61 (1.13-2.28)***	**2.46 (1.67-3.62)****	**1.63 (1.13-2.34)***	**2.39 (1.59-3.60)****
Prognosis cohort (n=734)				
Body Mass Index				
Eutrophic (BMI < 25 kg/m^2)	1.00	1.00	1.00	1.00
Overweight (BMI 25-29.9 kg/m^2)	1.19 (0.76-1.86)	1.23 (0.82-1.84)	1.16 (0.73-1.85)	1.23 (0.80-1.89)
Obesity (BMI ≥30 kg/m^2)	1.20 (0.72-2.01)	**2.36 (1.54-3.63)****	1.11 (0.65-1.88)	**2.38 (1.51-3.77)****

BMI, body mass index. [a]Adjusted by sex, age, self-reported skin colour/race, education, nature of occupation, leisure-time physical activity and depression. *p<0.05. **p≤0.001.

Table 4 – Association of body mass index with the cumulative incidence and recurrence of frequent knee pain, ELSA-Brasil MSK follow-up (2015-2019).

	Unadjusted model *OR (95%CI)*		**Adjusted[a] model *OR (95%CI)***	
	Non-Severe knee pain	**Severe knee pain**	**Non-Severe knee pain**	**Severe knee pain**
Incidence cohort (n=1,857)				
Body Mass Index				
Eutrophic (BMI < 25 kg/m^2)	1.00	1.00	1.00	1.00
Overweight (BMI 25-29.9 kg/m^2)	1.04 (0.68-1.58)	1.23 (0.94-1.62)	1.06 (0.69-1.63)	1.28 (0.96-1.70)
Obesity (BMI ≥30 kg/m^2)	**1.66 (1.02-2.69)***	**2.04 (1.49-2.80)****	**1.71 (1.05-2.81)***	**1.99 (1.43-2.78)****
Prognosis cohort (n=734)				
Body Mass Index				
Eutrophic (BMI < 25 kg/m^2)	1.00	1.00	1.00	1.00
Overweight (BMI 25-29.9 kg/m^2)	1.01 (0.57-1.77)	1.27 (0.87-1.85)	0.99 (0.55-1.77)	1.28 (0.86-1.92)
Obesity (BMI ≥30 kg/m^2)	0.78 (0.39-1.56)	**2.21 (1.47-3.33)****	0.76 (0.38-1.54)	**2.17 (1.41-3.36)****

BMI, body mass index. [a]Adjusted by sex, age, self-reported skin colour/race, education, nature of occupation, leisure-time physical activity and depression. $^{*}p<0.05$. $^{**}p\leq0.001$.

4. Discussion

The results partially confirmed our hypotheses since 1) obesity, but not overweight, increased the risk of multiple and severe episodes of FKP over 4-year follow-up at both incidence and prognosis cohort; and 2) although the magnitudes of these associations were similar in the two sub-cohorts for multiple episodes, it was slightly higher in the prognosis cohort for SFKP. Additionally, obesity was also associated with a higher risk of one episode of FKP and non-severe knee pain in the incidence cohort, but not in the prognostic cohort.

Other studies also found positive associations between obesity and the risk of developing MSK pain. Haukka et al. [2012] assessed the combined effect of obesity, physical workload, LTPA and smoking on predicting multisite pain in kitchen workers and found that obese individuals had 30% more chances of having pain compared to eutrophic after two years of follow-up. The HUNT study, an important cohort of the Norwegian population, found that obesity increased the OR of developing chronic widespread pain in 35% [Mundal et al, 2014]. Considering just knee pain, Jinks et al [2006] also found that obese, but not overweight, older adults have a risk 179% higher of developing severe pain in the knee after three years of follow up.

The results of regression models showed some differences between the incidence and prognosis sub-cohorts concerning the role of obesity on the risk of FKP episodes. While obesity increased the risk of both one and multiple episodes, non-severe and severe FKP in the incidence sub-cohort, it was associated only with the worst outcomes (multiple episodes and severe pain) in the prognosis cohort. This result indicates that obesity contributes to worsen baseline knee pain, more than simply to recurring knee pain. Bindawas [2016] observed that the combination of obesity and FKP at baseline predicted pace reduction among older adults

after six years of follow-up, and that the effect of FKP combined with obesity was greater than the isolated effects of any of these factors [Bindawas; 2016]. This could also be a result of an index event bias (or collider stratification bias), a type of selection bias that can affect research on the risk of disease sequelae when multiple risk factors for sequelae are also risk factors for having the disease in the first place, as obesity for knee pain [Choi et al, 2014].

The higher cumulative incidence of severe episodes of FKP among obese individuals in the prognosis sub-cohort is consistent with the knowledge that one of the most important risk factors for new and worst episodes of pain is the occurrence of a previous one [Larsson et al, 2012; Henschke et al, 2015]. It is worth noting that knee pain episodes of all kinds were much more frequent in the prognosis sub-cohort than the incidence sub-cohort, possibly because the former sample was older and had more women individuals, factors that also contribute to the occurrence and worsening of pain. [Ingham et al, 2011; Larsson et al, 2012; Mundal et al, 2014; Henschke et al, 2015].

How obesity increases the risk of developing knee pain has been investigated and two mechanisms are highlighted as the most likely explanations: the mechanical overload and the low grade inflammation associated to obesity [Bonakdar, 2013]. The mechanical overload of joints, especially knees and hips, activates chondrocytes and accelerates cartilage degeneration [Bonakdar, 2013; Walsh et al., 2018]. Inflammation related to obesity can also promote joint and tissue damage [Marchand et al, 2005; Bonakdar, 2013; Walsh et al., 2018], but additionally is being implicated as a trigger for central sensitization [Harte et al, 2018]. Considering the knee pain, these mechanisms probably coexists, once the inflammation related to obesity is systemic and the knees are structures that contribute to support body weight [Chin et al, 2020].

Studies that assessed if weight lost impact on knee pain, reinforces the role of obesity in its genesis [Tanamas et al, 2013; Stefanik et al, 2018; Li et al, 2019]. Although most involves post bariatric surgery patients, that face a massive weight lost, these studies observed some pain improvement with the reduction of body weight [Tanamas et al, 2013; Stefanik et al, 2018; Li et al, 2019]. Stefanik et al [2018] observed that 12 months after bariatric surgery, besides the reduction of number of pain sites, patients showed a reduced pressure pain threshold in knee and wrist, indicating improvement in central sensitization.

The strengths of our study include the large number of participants, the number of follow-up assessments, the data availability of important confusion factors to adjust the analysis and the recruitment of participants not conditioned to a pre-existing MSK disorder, what is common in cohorts evaluating knee pain. Regarding the limitations, the interval between baseline and the 1st follow-up interview (about two years) and the interval between each subsequent monitoring interview (about one year) are wide and participants were asked about pain at the previous month. These factors may have impaired the identification of some frequent knee pain episodes that occurred in the studied period.

In conclusion, we found that obesity, but not overweight, was an independent risk factor for developing multiple episodes of FKP and SFKP between adults of the ELSA-Brasil MSK study, contributing both to the incidence and prognosis of FKP. Considering that the prevalence of obesity in our study was high, representing the current global scenario, it's important to develop strategies to stop or at least slow down this phenomenon in order to reduce its negative impacts on health, including the occurrence and severity of FKP episodes.

Acknowledgements

We would like to thank the staff and participants of ELSA-Brasil MSK. ELSA-Brasil was supported by Ministério da Saúde Brasil (BR), Secretaria de Ciência Tecnologia e Insumos Estratégicos (BR), Ministério da Ciência e Tecnologia (BR), Departamento de Ciência e Tecnologia (Decit-BR), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq-BR), Financiadora de Estudos e Projetos (FINEP-BR) and by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-BR). ELSA-Brasil MSK was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-BR), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) (APQ-00921-16) and CNPq-BR (42358520169). Dr Sandhi M. Barreto is a research fellow of CNPq-BR and State of Minas Gerais Agency for Research and Technology (FAPEMIG). The investigation was carried out while Dr. Luciana A.M. was a Postdoctoral Fellow and MSc. Aline A.B. Costa was a Doctoral fellow, both supported by CAPES-BR (Finance Code 001). The contents of this manuscript are solely the responsibility of the authors. The investigators are solely responsible for the content of the manuscript and the decision to submit for publication. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have no conflict of interest to report.

Reference List

Ayis S, Dieppe P. The natural history of disability and its determinants in adults with lower limb musculoskeletal pain. J Rheumatol. 2009;36(3):583-91.

Aquino EM, Barreto SM, Bensenor IM, Carvalho MS, Chor D, Duncan BB, Lotufo PA, Mill JG, Molina Mdel C, Mota EL, Passos VM, Schmidt MI, Szklo M. Brazilian Longitudinal Study of Adult Health (ELSA-Brasil): objectives and design. Am J Epidemiol 2012;175(4):315-24.

Autor DH, Levy F, Murnane RJ. The skill content of recent technological change: an empirical exploration. Q J Econ 2003;118(4):1279-333.

Bindawas SM. Relationship between frequent knee pain, obesity, and gait speed in older adults: data from the Osteoarthritis Initiative. Clin Interv Aging. 2016;11:237-244.

Bindawas SM, Vennu V. Longitudinal effects of physical inactivity and obesity on gait speed in older adults with frequent knee pain: data from the Osteoarthritis Initiative. International Journal of Environmental Research and Public Health. 2015; 12(2):1849-1863.

Blüher, M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15:288–29.

Bonakdar RA. Obesity-related pain: time for a new approach that targets systemic inflammation. Journal of Family Practice 2013;62(9):S22-8.

Chin SH, Huang WL, Akter S, Binks M. Obesity and pain: a systematic review. Int J Obes (Lond) 2020;44(5):969-979.

Choi HK, Nguyen US, Niu J, Danaei G, Zhang Y. Selection bias in rheumatic disease research. Nat Rev Rheumatol. 2014 Jul;10(7):403-12.

Cooper L, Ryan CG, Ells LJ, Hamilton S, Atkinson G, Cooper K, Johnson MI, Kirwan JP, Martin D. Weight loss interventions for adults with overweight/obesity and chronic musculoskeletal pain: a mixed methods systematic review. Obes Rev. 2018;19(7):989-1007.

Costa ABP, Machado LAC, Telles RW, Barreto SM. 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. Rheumatology International 2020;40:881-91.

Felisbino-Mendes MS, Cousin E, Malta DC, Machado IL, Ribeiro ALP, Duncan BB, Schmidt MI, Silva DAS, Glenn S, Afshin A, Velasquez-Mendes G. The burden of non-communicable diseases attributable to high BMI in Brazil, 1990–2017: findings from the Global Burden of Disease Study. Popul Health Metrics 2020;18(Suppl 1):18.

Fernandes GS, Bhattacharya A, McWilliams DF, Ingham SL, Doherty M, Zhang W. Risk prediction model for knee pain in the Nottingham community: a Bayesian modelling approach. Arthritis Res Ther. 2017;19(1):59.

GBD 2019 Diseases and Injuries Collaborators. Musculoskeletal disorders—Level 2 cause. The Lancet 2020;396:S162-3.

Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. J Appl Behav Res 2018;23:e121372018.

Haukka E, Ojajarvi A, Takala EP, Viikari-Juntura E, Leino-Arjas P. Physical workload, leisure-time physical activity, obesity and smoking as predictors of multisite musculoskeletal pain. A 2-year prospective study of kitchen workers. Occup Environ Med 2012; 69(7):485–492.

Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. Mayo Clin Proc 2015;90(1):139-47.

IBGE. Pesquisa nacional de saúde: 2019: atenção primária à saúde e informações antropométricas: Brasil. Instituto Brasileiro de Geografia e Estatística, Coordenação de Trabalho e Rendimento. Rio de Janeiro: IBGE, 2020. 66p.

Ingham SL, Zhang W, Doherty SA, McWilliams DF, Muir KR, Doherty M. Incident knee pain in the Nottingham community: a 12-year retrospective cohort study. Osteoarthritis Cartilage 2011;19(7):847-52.

Jinks C, Jordan K, Croft P. Disabling knee pain – another consequence of obesity: results from a prospective cohort study. BMC Public Health 2006;6:258.

Larsson B, Bjork J, Borsbo B, Gerdle B. A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. Eur J Pain 2012;16(8):1084-93.

Lee S, Son C, Yeo S, Ha I. Cross-sectional analysis of self-reported sedentary behaviors and chronic knee pain among South Korean adults over 50 years of age in KNHANES 2013-2015. BMC Public Health 2019; 19(1375).

Leite LD, Rocha EDM, Brandão-Neto J. Obesidade: uma doença inflamatória. Revista Ciência & Saúde 2009; 2(2):85-95.

Leyland KM, Gates LS, Nevitt M, Felson D, Bierma-Zeinstra SM, Conaghan PG, Engebretsen L, Hochberg M, Hunter DJ, Jones G, Jordan JM, Judge A, Lohmander LS, Roos EM, Sanchez-Santos MT, Yoshimura N, van Meurs JBJ, Batt ME, Newton J, Cooper C, Arden NK. Harmonising measures of knee and hip osteoarthritis in population-based cohort studies: an international study. Osteoarthritis Cartilage. 2018 Jul;26(7):872-879.

Li JS, Tsai TY, Clancy MM, Li G, Lewis CL, Felson DT. Weight loss changed gait kinematics in individuals with obesity and knee pain. Gait Posture 2019; 68:461-465.

Machado LAC, Telles RW, Costa-Silva L, Barreto SN. Perfil da Coorte ELSA--Brasil Musculoesquelético. Braz J Rheumatol 2015;56(Supp1):S29-30.

Magnusson K, Osteras N, Mowinckel P, Natvig B, Hagen KB. No strong temporal relationship between obesity and multisite pain–results from a population-based 20-year follow- up study. Eur J Pain 2014;18(1):120–127.

Marchand F, Perreti M, Macmahon SB. Role of the immune system in chronic pain. Nature Reviews Neuroscience 2005;6: 521–532.

Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, Braggion G. (2001). Questionário internacional de atividade física (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Fís Saúde 6(2):5-18.

Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA. Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study–the HUNT study. Pain 2014; 155(8):1555– 1561.

Nunes MA, Alves MGM, Chor D, Schmidt MI, Duncan BB. Adaptação transcultural do CIS-R (Clinical Interview Schedule- Revised version) para o português no Estudo Longitudinal de Saúde do Adulto (ELSA). Rev HCPA 2011;31(4):515-8.

Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, Aquino EM, Passos VM, Matos SM, Molina Mdel C, Carvalho MS, Bensenor IM. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75.

Schmidt MI, Griep RH, Passos VM, Luft VC, Goulart AC, Menezes GM, Molina Mdel C, Vigo A, Nunes MA. Strategies and development of quality assurance and control in the ELSA-Brasil. Rev Saude Publica 2013;47 Suppl 2:105-12.

Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(4):507-15.

Stefanik JJ, Felson DT, Apovian CM, Niu J, Margaret Clancy M, LaValley MP, Neogi T. Changes in Pain Sensitization After Bariatric Surgery. Arthritis Care Res (Hoboken) 2018;70(10):1525-1528.

Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: a systematic review and meta-analysis. Pain. 2017 Nov;158(11):2092-2107.

Stone AA, Broderick JE. Obesity and pain are associated in the United States. Obesity 2012;20:1491-1495.

Tanamas SK, Wluka AE, Davies-Tuck M, Wang Y, Strauss BJ, Proietto J, Dixon JB, Jones G, Forbes A, Cicuttini FM. Association of weight gain with incident knee pain, stiffness, and functional difficulties: a longitudinal study. Arthritis Care Res (Hoboken) 2013;65(1):34-43.

Vos T et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 2020;396(10258):1204 – 1222.

Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan M. The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2018;19(1):233-246.

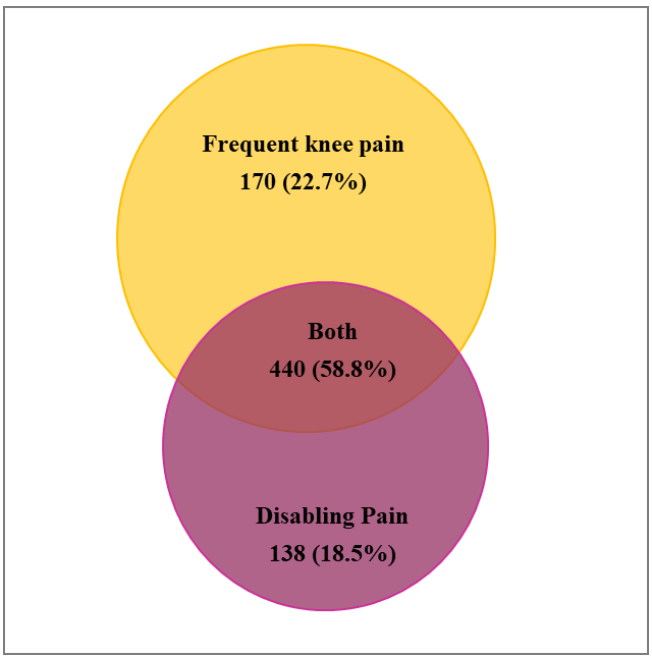
Wei L, Wu B. Racial and ethnic differences in obesity and overweight as predictors of the onset of functional impairment. J Am Geriatr Soc. 2014;62(1):61-70.

World Health Organisation (WHO). Physical Status: The use and interpretation of anthropometry. WHO Technical Report Series 854, Geneva 1995.

World Health Organization (WHO). Obesity: Preventing and Managing the Global Epidemic. Report. 1997.

Supplemental Digital Content 1

Figure - Venn diagram with the distribution of knee pain type at baseline, ELSA-Brasil MSK (2012-2014). N = 748.



9. CONCLUSÃO

O presente estudo mostrou que a obesidade se associou positivamente à prevalência de dor ME crônica, sendo que essa relação ocorreu tanto para marcadores de excesso de adiposidade global (índice de massa corporal), quanto para indicadores de excesso de adiposidade abdominal (circunferência de cintura e a razão cintura-estatura). Para todos os marcadores avaliados, quanto maior o grau de obesidade, maior foi a odds ratio, sendo que a magnitude dessa associação também foi maior na avaliação dos desfechos relacionados ao espalhamento da dor (dor ME em múltiplos locais e dor ME generalizada). Os resultados da análise de trajetória de peso corporal seguiram no mesmo sentido, mostrando que a maior exposição ao excesso de peso (aos 20 anos e na linha de base do estudo) se associou ao aumento de até 86% da chance de ter dor ME crônica.

De modo complementar, os resultados da análise descritiva exploratória apresentada no artigo um indicaram que níveis crescentes de obesidade refletiram no aumento da frequência de dor crônica, especialmente das articulações que suportam o peso (membros inferiores), sendo acompanhado também pela “propagação” da dor para outros locais.

Na avaliação do impacto da obesidade na incidência e prognóstico da dor frequente em joelhos, após quatro anos de acompanhamento, observou-se que ter um IMC $\geq 30 kg/m^2$ foi fator de risco independente para o desenvolvimento de episódios de dor, bem como para o desenvolvimento de dor grave. Contudo, o comportamento diferiu nas coortes de incidência e prognóstico. Enquanto na coorte de incidência participantes obesos apresentaram risco aumentado de desenvolver um episódio, mútiplos episódios, dor não grave e dor grave, na coorte de prognóstico a obesidade só se associou aos piores desfechos (múltiplos episódios e dor grave).

Considerados em conjunto, os resultados apresentados no presente trabalho reforçam a importância de se desenvolver estratégias para interromper ou pelo menos desacelerar o aumento das taxas de excesso de peso na população, com o objetivo de prevenir os diversos impactos negativos associados à essa condição, incluindo a ocorrência de dor ME crônica e dor frequente em joelhos. Essas estratégias devem ser direcionadas a todas as faixas etárias, mas os achados relacionados à trajetória de peso corporal sugerem que a prevenção da obesidade em idades precoces pode ser mais benéfica. Nossos resultados alertam ainda para a importância de incluir a avaliação e manejo da obesidade no acompanhamento ambulatorial de indvíduos acometidos por dor musculoesquelética, visando melhorar o prognóstico desses pacientes.

10. ANEXOS

Anexo A – Carta de aprovação do ELSA-Brasil pelo Comitê de Ética em Pesquisa (COEP/UFMG).

Universidade Federal de Minas Gerais
Comitê de Ética em Pesquisa da UFMG - COEP

Parecer nº. ETIC 186/06

Interesse: Prof. (a) Sandhi Maria Barreto
Depto. De Medicina Preventiva e Social
Faculdade de Medicina -UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP, aprovou no dia 28 de junho de 2006 o projeto de pesquisa intitulado **"ELSA - Estudo longitudinal da saúde do adulto."** bem como o Termo de Consentimento Livre e Esclarecido do referido projeto.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

pp **Profa. Dra. Maria Elena de Lima Perez Garcia**
Presidente do COEP/UFMG

Av. Presidente Antônio Carlos, 6627, Prédio da Reitoria – 7º andar sala: 7018 - 31.270-901– BH - MG
(31) 3499-4592 - FAX: (31) 3499-4027 - coep@prpq.ufmg.br

Anexo B – Carta de aprovação do ELSA-Brasil pela Comissão Nacional de Ética em Pesquisa (CONEP)

Fls. nº 109
Rubrica

MINISTÉRIO DA SAÚDE
Conselho Nacional de Saúde
Comissão Nacional de Ética em Pesquisa

CARTA Nº 976 CONEP/CNS/MS Brasília, 04 de agosto de 2006.

Senhora Coordenadora,

Tendo a CONEP recebido desse CEP o projeto de pesquisa ***"Estudo Longitudinal de Saúde do Adulto – ELSA"*** Registro CEP-HU/USP 659/06 - CAAE 0016.1.198.000-06, Registro Sipar MS: nº 25000.083729/2006-38, Registro CONEP nº 13065, verifica-se que:

Trata-se de protocolo a ser desenvolvido por consórcio vencedor da Chamada Pública DECIT/MS/FINEP/CNPq que foi constituído por sete instituições de ensino superior e pesquisa de seis estados, das regiões Nordeste (Universidade Federal da Bahia), Sudeste (FIOCRUZ/RJ, USP, UERJ, UFMG e UFES) e Sul (UFRS). Será um estudo de coorte de 15 mil funcionários de instituições públicas com idade igual ou superior a 35 anos. A coorte será acompanhada anualmente para verificação do estado geral e, a cada três anos, será chamada para avaliações mais detalhadas que incluem exames clínicos. Os sujeitos de pesquisa serão entrevistados por pessoas treinadas e certificadas e os exames serão realizados por profissionais de saúde. O estudo tem como objetivos principais: estimar a incidência do diabetes e das doenças cardiovasculares e estudar sua história natural; investigar associações entre fatores biológicos, comportamentais, ambientais, ocupacionais, psicológicos e sociais relacionados a essas doenças e complicações decorrentes, buscando compor modelo causal que contemple suas inter-relações; descrever a evolução temporal desses fatores e os determinantes dessa evolução; identificar modificadores de efeito das associações observadas; identificar diferenciais nos padrões de risco entre os centros participantes que possam expressar variações regionais relacionadas a essas doenças no país. Dentre os objetivos secundários *consta "estocar material biológico, para estudos futuros com diversos tipos de marcadores relacionados à inflamação, coagulação, disfunção endotelial, resistência à insulina, obesidade central, estresse e fatores de risco tradicionais, bem como prover a extração de DNA para exames genéticos futuros"*. De acordo com informação da pág. 11 do protocolo, item "coleta de sangue", as amostras de sangue serão estocadas para

Fls. nº 110
Rubrica

Cont. Carta CONEP nº 976/2006

exames adicionais e formação de banco de DNA. Haverá um laboratório central que fará as "determinações básicas do estudo em amostras encaminhadas pelos centros de investigação", as "determinações simples" serão feitas nos próprios laboratórios. O banco de material biológico está em fase de planejamento com local e coordenador a serem definidos.

Diante do exposto, embora nos objetivos do estudo verifica-se que haverá também pesquisa genética, pelas informações do protocolo tal pesquisa não será realizada no momento, não estando descrito ainda (nem no protocolo, nem no Termo de Consentimento Livre e Esclarecido-TCLE) os procedimentos para tal. Portanto, nesse primeiro momento do estudo não se trata de projeto da área temática especial "genética humana" (Grupo I), conforme registrado na folha de rosto, mas sim, do grupo III. Nesse caso, a aprovação ética é delegada ao Comitê de Ética em Pesquisa da instituição, devendo ser seguido o procedimento para projetos do grupo III, conforme o fluxograma disponível no site : http://conselho.saude.gov.br e no Manual Operacional para CEP. Não cabe, portanto, a referência a CONEP no 3º parágrafo da pág. 1 e no 6º parágrafo da pág.2 do TCLE. Evidenciamos, entretanto, que o armazenamento e utilização de materiais biológicos humanos no âmbito de projetos de pesquisa está regulamentado pela Resolução CNS 347/2005 e que o projeto em questão deve incluir as determinações dessa resolução. Quando for elaborado o protocolo para os estudos genéticos, deverá também ser cumprida a Resolução CNS 340/04 incluindo obtenção de TCLE específico. Em se tratando de pesquisa com funcionários de instituições públicas, cabe ressaltar o disposto no item IV.3 "b" da Res. 196/96.

Atenciosamente ,

CORINA BONTEMPO DUCA DE FREITAS
Secretária Executiva da
COMISSÃO NACIONAL DE ÉTICA EM PESQUISA

Á Sua Senhoria
Sr(a) Maria Teresa Zulini da Costa
Cordenadora Comitê de Ética em Pesquisas
Hospital Universitário da Universidade de São Paulo - HU/USP
Av. Profº Lineu Prestes, 2565
Cidade Universitária São Paulo
Cep:05.508-900

C/ cópia para os CEPs: UFBA, FIOCRUZ/RJ,UERJ, UFMG, UFES e UFRS

Anexo C - Carta de aprovação do ELSA-Brasil MSK pelo Comitê de Ética em Pesquisa (COEP/UFMG).

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Projeto: CAAE 0186.1.203.000-06

Interessado(a): Profa. Sandhi Maria Barreto
Depto. de Medicina Preventiva e Social
Faculdade de Medicina -UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP analisou e aprovou, no dia 03 de setembro de 2012, a inclusão de exames, abaixo relacionados, na 2ª. etapa de obtenção dos dados (Onda 2) do projeto de pesquisa intitulado **"ELSA - Estudo Longitudinal da Saúde do Adulto"**:

- Avaliação da força isométrica nas mãos (*handgrip*);
- Teste de força isométrica das penas (assentar/levantar repetido);
- Teste de sensibilidade com monofilamento;
- Medida de altura abdominal (diâmetro sagital abdominal);
- Avaliação radiológica das mãos e joelhos;
- Circunferência da cabeça;
- Altura do joelho.
- Termo de Consentimento Livre e Esclarecido.

A aprovação é válida por 1(um) ano (03 de setembro de 2012 a 02 de setembro de 2013).

Profa. Maria Teresa Maques Amaral
Coordenadora do COEP/UFMG

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2º andar – Sala 2005 – Cep:31270-901 – BH-MG
Telefax: (031) 3409-4592 - e-mail: coep@prpq.ufmg.br

Rheumatology International
https://doi.org/10.1007/s00296-020-04557-w

Rheumatology INTERNATIONAL

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

Aline B. P. Costa[1] · Luciana A. C. Machado[2] · Rosa W. Telles[1,2] · Sandhi M. Barreto[1,2]

Received: 9 January 2020 / Accepted: 14 March 2020

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

Data included in this manuscript were presented in part at the IASP 17th World Congress on Pain (2018), XXXII Brazilian Congress of Rheumatology [Costa ABP, Machado LAC, Telles RW, Silva PT, Silva LC, Barreto SM (2016) Associação entre marcadores de obesidade e a presença e número de locais de dor crônica: ELSA-Brasil Musculoesquelético (ELSA-BRASIL ME). Rev Bras Reumatol 56(supl. 1):S48–S49], and XXXV Brazilian Congress of Rheumatology [Telles RW, Costa ABP, Machado LAC, Barreto SM (2018) Overweight and obesity versus chronic musculoskeletal symptoms: Is there a connection? Adv Rheumatol 58(23) https://doi.org/10.1186/s42358-018-0019-7].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-020-04557-w) contains supplementary material, which is available to authorized users.

✉ Sandhi M. Barreto
sandhi.barreto@gmail.com

Extended author information available on the last page of the article

Published online: 31 March 2020

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

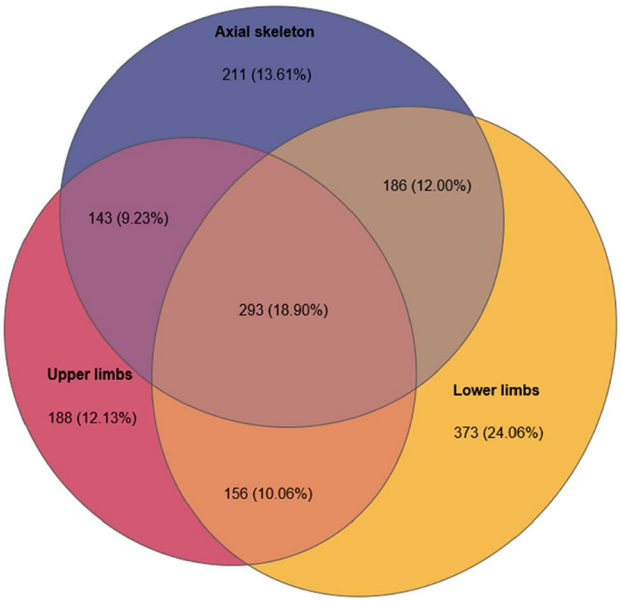


Fig. 1 Venn diagram of the frequency of chronic musculoskeletal pain according to body region: upper limbs (shoulders, elbows and/or wrists/hands), lower limbs (knees, hips/thighs and/or ankles/feet) and axial skeleton (neck, upper back and/or lower back), ELSA-Brasil MSK (2012–2014)

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.

Acknowledgements We would like to thank the staff and participants of ELSA-Brasil MSK. We would also like to thank Douglas R.M. Azevedo for his support in building Venn diagrams.

Author contributions ABPC, LACM, RWT and SMB contributed to study conception and design, and to the analysis and interpretation of data; ABPC drafted the first version of the manuscript, and LACM, RWT and SMB revised it critically for intellectual content. All authors read and approved the final version of the manuscript.

Funding ELSA-Brasil has been supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and CNPq-BR), Grants 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, 01 06 0071.00 RJ. ELSA-Brasil MSK has been supported by CAPES-BR (Grant pós-doc/SUS 054/2010), FAPEMIG-BR (Grant APQ-00921-16) and CNPq-BR (Grant 42358520169). The investigation was carried out while Dr. Luciana A.C. Machado was a Postdoctoral Fellow and MSc. Aline A.B. Costa was a PhD candidate, both supported by CAPES-BR (Finance Code 001). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet 392(10159):1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7
2. Torres J, da Silva S, Ferreira F, Mendes L, Machado L (2018) Chronic pain is associated with increased health care use among community-dwelling older adults in Brazil: the pain in the elderly (PAINEL) study. Fam Pract. https://doi.org/10.1093/fampra/cmy123 **(Epub ahead of print)**
3. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R (2003) Lost productive time and cost due to common pain conditions in the US workforce. JAMA 290(18):2443–2454. https://doi.org/10.1093/fampra/cmy123
4. Larsson B, Bjork J, Borsbo B, Gerdle B (2012) A systematic review of risk factors associated with transitioning from regional musculoskeletal pain to chronic widespread pain. Eur J Pain 16(8):1084–1093. https://doi.org/10.1002/j.1532-2149.2012.00117.x
5. Wolfe F, Clauw DJ, Fitzcharles MA et al (2016) 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 46(3):319–329. https://doi.org/10.1016/j.semarthrit.2016.08.012
6. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D (2008) Localized or widespread musculoskeletal pain: does it matter? Pain 138(1):41–46. https://doi.org/10.1016/j.pain.2007.11.002
7. Miranda VS, Decarvalho VB, Machado LA, Dias JM (2012) Prevalence of chronic musculoskeletal disorders in elderly Brazilians: a systematic review of the literature. BMC Musculoskeletal Dis 13:82. https://doi.org/10.1186/1471-2474-13-82
8. Cimas M, Ayala A, Sanz B, Agulló-Tomás MS, Escobar A, Forjaz MJ (2018) Chronic musculoskeletal pain in European older adults: cross-national and gender differences. Eur J Pain 22(2):333–345. https://doi.org/10.1002/ejp.1123
9. Coggon D, Ntani G, Palmer KT et al (2013) Patterns of multisite pain and associations with risk factors. Pain 154(9):1769–1777. https://doi.org/10.1016/j.pain.2013.05.039
10. Mourao AF, Blyth FM, Branco JC (2010) Generalised musculoskeletal pain syndromes. Best Pract Res Clin Rheumatol 24(6):829–840. https://doi.org/10.1016/j.berh.2010.10.005
11. Hajihosseinali M, Arjmand N, Shirazi-Adl A (2015) Effect of body weight on spinal loads in various activities: a personalized biomechanical modeling approach. J Biomech 48(2):276–282. https://doi.org/10.1016/j.jbiomech.2014.11.033
12. Singh D, Park W, Hwang D, Levy MS (2015) Severe obesity effect on low back biomechanical stress of manual load lifting. Work 51(2):337–348. https://doi.org/10.3233/WOR-141945
13. Knarr BA, Higginson JS, Zeni JA (2016) Change in knee contact force with simulated change in body weight. Comput Methods Biomech Biomed Eng 19(3):320–323. https://doi.org/10.1080/10255842.2015.1018193
14. Ouchi N, Parker JL, Lugus JJ (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11(2):85–97. https://doi.org/10.1038/nri2921
15. Woolf CJ (2011) Central sensitization: implications for the diagnosis and treatment of pain. Pain 152(3 Suppl):S2–15. https://doi.org/10.1016/j.pain.2010.09.030
16. Paley CA, Johnson MI (2016) Physical activity to reduce systemic inflammation associated with chronic pain and obesity: a narrative review. Clin J Pain 32(4):365–370. https://doi.org/10.1097/AJP.0000000000000258
17. Shiri R, Karppinen J, Leino-Arjas P et al (2007) Cardiovascular and lifestyle risk factors in lumbar radicular pain or clinically defined sciatica: a systematic review. Eur Spine J 16(12):2043–2054. https://doi.org/10.1007/s00586-007-0362-6
18. Walsh TP, Arnold JB, Evans AM, Yaxley A, Damarell RA, Shanahan EM (2018) The association between body fat and musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskelet Dis 19(1):233. https://doi.org/10.1186/s12891-018-2137-0
19. Savva SC, Lamnisos D, Kafatos AG (2013) Predicting cardiometabolic risk: waist-to-height ratio or BMI. A meta-analysis. Diabetes Metab Syndr Obes 6:403–419. https://doi.org/10.2147/DMSO.S34220
20. Goossens GH (2017) The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. Obes Facts 10(3):207–215. https://doi.org/10.1159/000471488
21. Ashwell M, Gunn P, Gibson S (2012) Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev 13(3):275–286. https://doi.org/10.1111/j.1467-789X.2011.00952.x
22. Ashwell M, Gibson S (2014) A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. BMC Med 12(1):207. https://doi.org/10.1186/s12916-014-0207-1

23. Ogwumike OO, Adeniyi AF, Orogbemi OO (2015) Musculoskeletal pain among postmenopausal women in Nigeria: association with overall and central obesity. Hong Kong Physiother J 34:41–46. https://doi.org/10.1016/j.hkpj.2015.06.001
24. Frilander H, Viikari-Juntura E, Heliovaara M, Mutanen P, Mattila VM, Solovieva S (2016) Obesity in early adulthood predicts knee pain and walking difficulties among men: a life course study. Eur J Pain 20(8):1278–1287. https://doi.org/10.1002/ejp.852
25. Dawson J, Juszczak E, Thorogood M, Marks SA, Dodd C, Fitzpatrick R (2003) An investigation of risk factors for symptomatic osteoarthritis of the knee in women using a life course approach. J Epidemiol Community Health 57(10):823–830. https://doi.org/10.1136/jech.57.10.823
26. Macfarlane GJ, de Silva V, Jones GT (2011) The relationship between body mass index across the life course and knee pain in adulthood: results from the 1958 birth cohort study. Rheumatology 50(12):2251–2256. https://doi.org/10.1093/rheumatology/ker276
27. Frilander H, Solovieva S, Mutanen P, Pihlajamaki H, Heliovaara M, Viikari-Juntura E (2015) Role of overweight and obesity in low back disorders among men: a longitudinal study with a life course approach. BMJ Open 5(8):e007805. https://doi.org/10.1136/bmjopen-2015-007805
28. Aquino EM, Barreto SM, Bensenor IM et al (2012) Brazilian longitudinal study of adult health (ELSA-Brasil): objectives and design. Am J Epidemiol 175(4):315–324. https://doi.org/10.1093/aje/kwr294
29. Machado LAC, Telles RW, Costa-Silva L, Barreto SM (2015) Perfil da coorte ELSA-Brasil musculoesquelético. Braz J Rheumatol 56(Suppl 1):S29–30
30. de Barros EM, Alexandre NM (2003) Cross-cultural adaptation of the Nordic musculoskeletal questionnaire. Int Nurs Rev 50(2):101–108. https://doi.org/10.1046/j.1466-7657.2003.00188.x
31. Mundal I, Bjorngaard JH, Nilsen TI, Nicholl BI, Grawe RW, Fors EA (2016) Long-term changes in musculoskeletal pain sites in the general population: the HUNT study. J Pain 17(11):1246–1256. https://doi.org/10.1016/j.jpain.2016.08.006
32. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA (2014) Prevalence and long-term predictors of persistent chronic widespread pain in the general population in an 11-year prospective study: the HUNT study. BMC Musculoskelet Disord 15:213. https://doi.org/10.1186/1471-2474-15-213
33. Schmidt MI, Griep RH, Passos VM et al (2013) Strategies and development of quality assurance and control in the ELSA-Brasil. Rev Saúde Pública 47(Suppl 2):105–112. https://doi.org/10.1590/S0034-8910.2013047003889
34. World Health Organization (1995) Physical status: the use and interpretation of anthropometry. WHO Technical Report Series 854, Geneva. https://www.who.int/childgrowth/publications/physical_status/en/. Accessed 11 May 2019
35. World Health Organization (2008) Waist circumference and waist–hip ratio: report of a WHO expert consultation. Geneva, p 39
36. Schmidt MI, Duncan BB, Mill JG et al (2015) cohort profile: longitudinal study of adult health (ELSA-Brasil). Int J Epidemiol 44(1):68–75. https://doi.org/10.1093/ije/dyu027
37. World Health Organization (2000) Obesity: preventing and managing the global epidemic. Report. https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/. Accessed 11 May 2019
38. Henschke N, Kamper SJ, Maher CG (2015) The epidemiology and economic consequences of pain. Mayo Clin Proc 90(1):139–147. https://doi.org/10.1016/j.mayocp.2014.09.010
39. Autor DH, Levy F, Murnane RJ (2003) The skill content of recent technological change: an empirical exploration. Q J Econ 118(4):1279–1333. https://doi.org/10.1162/003355303322552801
40. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, Braggion G (2001) International physical activity questionnaire (lPAQ): study of validity and reliability in Brazil. Rev Bras Ativ Fis Saude 6(2):5–18. https://rbafs.org.br/RBAFS/article/view/931/1222
41. Nunes, MA., Alves, MGM, Chor D, Schmidt MI, Duncan BB (2011) Adaptação transcultural do CIS-R (clinical interview schedule-revised version) para o português no Estudo Longitudinal de Saúde do Adulto (ELSA). Rev HCPA 31(4):487–90. https://seer.ufrgs.br/hcpa/article/view/24065/14973
42. Haukka E, Ojajarvi A, Takala EP, Viikari-Juntura E, Leino-Arjas P (2012) Physical workload, leisure-time physical activity, obesity and smoking as predictors of multisite musculoskeletal pain. A 2-year prospective study of kitchen workers. Occup Environ Med 69(7):485–492. https://doi.org/10.1136/oemed-2011-100453
43. Mundal I, Grawe RW, Bjorngaard JH, Linaker OM, Fors EA (2014) Psychosocial factors and risk of chronic widespread pain: an 11-year follow-up study–the HUNT study. Pain 155(8):1555–1561. https://doi.org/10.1016/j.pain.2014.04.033
44. Narouze S, Souzdalnitski D (2015) Obesity and chronic pain: systematic review of prevalence and implications for pain practice. Reg Anesth Pain Med 40(2):91–111. https://doi.org/10.1097/AAP.0000000000000218
45. Pan F, Laslett L, Blizzard L, Cicuttini F, Winzenberg T, Ding C, Jones G (2017) Associations between fat mass and multisite pain: a five-year longitudinal study. Arthritis Care Res 69(4):509–516. https://doi.org/10.1002/acr.22963
46. Han TS, Schouten JS, Lean ME, Seidell JC (1997) The prevalence of low back pain and associations with body fatness, fat distribution and height. Int J Obes 21(7):600–607. https://doi.org/10.1038/sj.ijo.0800448
47. Ray L, Lipton RB, Zimmerman ME, Katz MJ, Derby CA (2011) Mechanisms of association between obesity and chronic pain in the elderly. Pain 152(1):53–59. https://doi.org/10.1016/j.pain.2010.08.04
48. Heuch I, Heuch I, Hagen K, Zwart JA (2015) A comparison of anthropometric measures for assessing the association between body size and risk of chronic low back pain: the HUNT study. PLoS One 10(10):e0141268. https://doi.org/10.1371/journal.pone.0141268
49. Dario AB, Ferreira ML, Refshauge K et al (2016) Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins. Eur Spine J 25(4):1188–1195. https://doi.org/10.1007/s00586-015-4055-2
50. Hussain SM, Urquhart DM, Wang Y, Shaw JE, Magliano DJ, Wluka AE, Cicuttini FM (2017) Fat mass and fat distribution are associated with low back pain intensity and disability: results from a cohort study. Arthritis Res Ther 19(1):26. https://doi.org/10.1186/s13075-017-1242-z
51. Shiri R, Falah-Hassani K, Heliovaara M et al (2019) Risk factors for low back pain: a population-based longitudinal study. Arthritis Care Res 71(2):290–299. https://doi.org/10.1002/acr.23710
52. Power C, Frank J, Hertzman C, Schierhout G, Li L (2001) Predictors of low back pain onset in a prospective British study. Am J Public Health 91(10):1671–1678. https://doi.org/10.2105/AJPH.91.10.1671
53. Kouvari M, Panagiotakos DB, Yannakoulia M et al (2019) Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: the ATTICA cohort study. Metabolism 93:18–24. https://doi.org/10.1016/j.metabol.2019.01.003
54. Krakauer NY, Krakauer JC (2018) Untangling waist circumference and hip circumference from body mass index with a body shape index, hip index, and anthropometric risk indicator. Metab Syndr Relat Disord 16(4):160–165. https://doi.org/10.1089/met.2017.0166

55. Graven-Nielsen T, Arendt-Nielsen L (2010) Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 6(10):599–606. https://doi.org/10.1038/nrrheum.2010.107
56. Harte SE, Harris RE, Clauw DJ (2018) The neurobiology of central sensitization. J Appl Behav Res 23(2):e12137. https://doi.org/10.1111/jabr.12137
57. Davis MA, Ettinger WH, Neuhaus JM (1990) Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). Semin Arthritis Rheum 20(3 Suppl 1):34–41. https://doi.org/10.1016/0049-0172(90)90045-H
58. Lake JK, Power C, Cole TJ (2000) Back pain and obesity in the 1958 British birth cohort: cause or effect? J Clin Epidemiol 53(3):245–250. https://doi.org/10.1016/S0895-4356(99)00155-9
59. Magnusson K, Osteras N, Mowinckel P, Natvig B, Hagen KB (2014) No strong temporal relationship between obesity and multisite pain–results from a population-based 20-year follow-up study. Eur J Pain 18(1):120–127. https://doi.org/10.1002/j.1532-2149.2013.00338.x
60. Pearl J (2009) Causal inference in statistics: an overview. Stat Surv 3:96–146. https://doi.org/10.1002/j.1532-2149.2013.00338.x
61. Poleshuck EL, Green CR (2008) Socioeconomic disadvantage and pain. Pain 136(3):235–238. https://doi.org/10.1016/j.pain.2008.04.003
62. Cohen AK, Rai M, Rehkopf DH et al (2013) Educational attainment and obesity: a systematic review. Obes Rev 14(12):989–1005. https://doi.org/10.1111/obr.12062

Affiliations

Aline B. P. Costa[1] · Luciana A. C. Machado[2] · Rosa W. Telles[1,2] · Sandhi M. Barreto[1,2]

[1] Faculty of Medicine, Universidade Federal de Minas Gerais (UFMG), Avenida Alfredo Balena n. 190, Funcionários, Belo Horizonte, MG 30130-100, Brazil

[2] Clinica Hospital, UFMG, Belo Horizonte, MG, Brazil