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Osteosarcopenic adiposity (OSA) phenotype and its connection with cardiometabolic disorders: Is there a cause-and-effect?

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ABSTRACT

The objectives were to examine if there is a causal relationship between osteosarcopenic adiposity (OSA) syndrome (coexistence of osteopenia/osteoporosis, sarcopenia, and excess adiposity) and cardiometabolic disorders or if these disorders initiate the development of OSA and its worsening. The search was conducted in PubMed, Scopus, and Web of Science to include articles up to the end of 2023. Of n=539 articles retrieved, n=15 met the eligibility criteria. Only studies conducted in adults and with all three body composition compartments (bone, muscle/lean, adipose) measured were considered. The results revealed that several cardiometabolic disorders, namely, hypertension, dyslipidemia (elevated total and LDL-cholesterol, lower HDL-cholesterol), insulin resistance, hyperglycemia, lower serum vitamin D, and some inflammatory markers were accompanied by OSA. In most cases, the OSA phenotype was associated with worse outcomes than cases with healthy or less impaired body composition. Our initial questions about the reciprocal cause-and-effect relationships could be surmised with more certainty for the OSA and some cardiovascular risks (hypertension, dyslipidemia) and some metabolic abnormalities (several inflammatory markers). The results of this review underscore the importance of body composition in health and from a clinical perspective, all three body composition compartments should be measured by standardized technologies using regulated diagnostic criteria to identify OSA. Randomized trials and prospective studies in diverse groups of older and younger individuals are necessary to determine if the relationships between OSA and clinical endpoints are causal and reversible through intervention and to uncover the mechanisms.

1. Introduction

The main body composition compartments, including bone, muscle/lean, and adipose tissues, play a significant role not just in physical fitness but in overall health (Genton et al., 2011; JafariNasabian et al., 2017), and to some extent in chronic diseases risks (Wells and Shirley, 2016). Bone, muscle, and adipose are endocrine organs that secrete molecules (osteokines, myokines, and adipokines, respectively) that exert endocrine, paracrine, and local influences enabling a homeostatic crosstalk amongst themselves as well as with other tissues and organs (Ilich et al., 2020, 2014a; Moser and van der Eerden, 2018; Severinsen and Pedersen, 2020). This homeostatic crosstalk is critical for the healthy development and maintenance of each tissue. However, many factors influence and alter these homeostatic processes, the most significant being aging (inevitable), low-grade inflammation, and chronic diseases, including cardiometabolic disorders (CMD). The latter may be in a perpetual cycle: CMD contribute to the impairment of body composition and then compromised body composition contributes to CMD.

Eventually, the deterioration of each tissue leads to osteoporosis,

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sarcopenia, and adiposity (increased/redistributed body fat). In the past, these impairments used to be studied separately and in isolation, and while this approach is necessary to provide insight into the underlying mechanisms, a more integrated approach (person-as-a-whole) may improve treatment outcomes. In this context and bearing in mind the decline in quality and quantity of the three primary body composition tissues (bone, muscle/lean, and adipose), the osteosarcopenic adiposity syndrome (OSA) gets its full connotation. The elaborated proof-of-concept and identification of OSA (initially coined "osteosarcopenic obesity") was published in 2014 (Ilich et al., 2014a). Briefly, it is a condition where osteopenia/osteoporosis, sarcopenia, and excessive and/or redistributed/infiltrated adipose tissue coexist.

The interconnectedness of bone, muscle, and adipose has been recognized, and some evidence suggests that each body composition impairment worsens the other, eventually leading to OSA (Ghavipour et al., 2017; Hu et al., 2023; Ilich et al., 2020; Kelly et al., 2019). The most recent bi-directional Mendelian randomization analysis provided a cause-and-effect relationship between osteoporosis and sarcopenia; patients with osteoporosis were more susceptible to developing sarcopenia, which then further worsened bone status, indicating a perpetual causal relationship (Liu et al., 2022). Although this analysis did not directly incorporate the state of obesity and the influence of adipose tissue (there may have been infiltrated fat in bone and muscle tissues), the interdependence cannot be overlooked and supports the cause-and-effect relationships between tissues in the progression to OSA. This provides evidence that the dysfunction in one tissue could result in the deterioration of another. Consequently, it could be hypothesized that individuals with OSA might be more vulnerable to chronic poor health and that chronic disease may lead to further impairments of body composition (or OSA) through positive feedback loops. This could be particularly true for cardiometabolic disorders characterized by a cluster of metabolic abnormalities (e.g., systemic inflammation, insulin resistance, diabetes, dyslipidemia, hypertension) all increasing the risks for cardiovascular diseases (Kirk and Klein, 2009).

Although a wealth of research investigating OSA and various other disorders has been conducted across the world and in various populations; see recent reviews (Hu et al., 2023; Ilich et al., 2020; Vucic et al., 2023), the original studies reported inconsistent findings and sometimes even controversial conclusions about OSA and some cardiovascular and/or metabolic diseases. For example, having OSA syndrome was associated with greater cardiometabolic disturbances, such as hypertension (Chen et al., 2019) and dyslipidemia (Mo et al., 2018) in Chinese but not in Iranian (Ahmadinezhad et al., 2023) studies. Other researchers reported worse outcomes in rheumatoid arthritis (Yatsyshyn and Stoika, 2018) and different results in some malignancies (see review by (Carsote et al., 2016)), in patients with OSA compared to those with only one or two body composition impairments. The inferior outcomes in individuals with OSA were particularly apparent regarding some, but not all, of the functional performance measures, including markedly poorer balance, and walking abilities, higher disability and frailty scores, and morbidity and mortality (Ilich et al., 2015; Ma et al., 2020; Szlejf et al., 2017). There are various reasons for the controversy and they are addressed in relation to each study in the Discussion (Sections 4.1 and 4.2). Furthermore, the research field of body composition in clinical and health outcomes is still in its early stages. Despite that obesity, defined by body mass index (BMI), is already rooted in healthcare, muscle mass is becoming of particular interest in clinical research as it correlates with mortality and may explain the obesity paradox (Abramowitz et al., 2018). However, neither fat mass nor muscle mass are adequately assessed by BMI. Additionally, the deterioration of all three tissues is linked to inflammation (Aaron et al., 2022; Hu et al., 2023; Ilich et al., 2014b) as are other CMD parameters. Consequently, low-grade chronic inflammation might as well be the underlying common cause for both OSA and CMD and both could be considered inflammatory diseases.

Since it is reasonable to assume that dysfunction in one tissue/organ could worsen and speed up the deterioration in another, it could be speculated that individuals with OSA might be more vulnerable to chronic poor health as the metabolic health of all three body composition tissues is affected, or vice versa. Therefore, our objective was to review studies investigating the association of OSA with cardiometabolic disorders (e.g., hypertension, dyslipidemia, type 2 diabetes, inflammation) and to ascertain whether the outcomes were worse in individuals with OSA compared to those with healthy body composition, or those with only one, or two tissue impairments.

Based on the objective, our research questions are:

1) Could OSA promote the development of other comorbidities resulting in new illness and could a chronic illness worsen the body composition leading to OSA? In other words, is there a perpetual downward spiral in the relationships between OSA and cardiometabolic disorders?
2) Is it possible to determine the cause-and-effect between OSA and cardiometabolic disorders?
3) Additionally, we wanted to identify possible gaps in the research on OSA syndrome and to provide recommendations for future studies.

Of note is that the terms "adiposity" and "obesity" are used interchangeably in the literature and thus in this manuscript. There is no conventionally accepted term, although "adiposity" would be more appropriate as the term encompasses more than overt excess subcutaneous body fat (Hu et al., 2023; Ilich et al., 2020). Similarly, "muscle mass" and "lean tissue" are sometimes used interchangeably, although in most cases muscle mass, not lean tissue, is associated with health-related outcomes. The indication for all three body composition components within the normal range is referred to either as "normal" or "healthy".

2. Methods

2.1. Search strategy

The initial search, to examine relevant articles published up to October 2023, was performed in PubMed (Medline) and was then adapted for use in other databases, namely, Scopus, and Web of Science with sensitive relevant keywords and MeSH terms (osteosarcopenic obesity OR osteosarcopenic adiposity, OR osteoporotic, OR osteosarcopenia, OR osteopenia, OR osteoporosis, OR bone mineral density, AND sarcopenia, OR sarcopenic, OR dynapenia, and obesity, OR adiposity, OR body fat). These were combined with the outcome terms: cardiovascular diseases, OR coronary artery disease, OR diabetes OR dyslipidemia, OR heart disease, OR heart failure, OR hyperlipidemia, OR hypertension, OR insulin resistance, OR metabolic abnormalities/metabolic syndrome, OR NAFLD, OR non-alcohol fatty liver disease, OR stroke. To avoid overlooking applicable articles, we also reviewed the reference lists of relevant articles and reviews, as well as the applicable articles that were in print or published after the search was completed extending to the end of 2023.

The eligibility criteria were as follows: 1) Participants aged $\geq$ 18 years; 2) Studies with a clear definition of osteosarcopenic adiposity/obesity (OSA/OSO); 3) Studies in which all three tissues (bone, muscle/lean, adipose) were assessed, although OSA prevalence was not required to be reported (but could be estimated); 4) All kinds of studies, including cross-sectional, retrospective, and prospective with an observational or experimental design; 5) Adverse outcomes were defined as any of the conditions within the cardiometabolic cluster of diseases (as listed above in Introduction and Search strategy).

Articles with unusable information and studies conducted on pregnant women, children and adolescents, and animals were excluded, as was the "gray literature" (conference abstracts or abstracts only, letters, etc). The screening was performed independently by four authors (D.R.

M., A.A., S.P., V.V.). Based on the predefined inclusion and exclusion criteria, the authors selected potentially eligible articles, with a 10% double-checking. In addition, studies in which participants did not have all three components of body composition (bone, muscle/lean, and fat) measured to identify OSA, or in which all three components of body composition could not be related to the outcome/exposure variables, were excluded. The final selection of articles was made (by J.Z.I., V.V., and O.J.K.) in compliance with the inclusion/exclusion criteria listed above.

2.2. Data extraction

Two independent authors (J.Z.I., B.P.) extracted the data from the included articles (Tables 1 and 2). Assessment tools for the identification of OSA/OSO, various questionnaires, and/or lab analyses were evaluated as well. The participants with OSA/OSO having any of the conditions listed above were compared with those having the same condition and none, one, or more body composition impairments (osteoporosis, sarcopenia, obesity-only, osteopenic adiposity, sarcopenic adiposity). In some studies, the healthy participants were used for comparison and such studies were included in this review as well.

3. Results

The PRISMA flowchart illustrating the study selection process is shown in Fig. 1. Briefly, upon review of the literature, 539 articles from three databases were recognized. After removing duplicates and excluding abstracts, review papers, commentaries, and letters, 154 articles were identified. Of these, 132 articles were excluded as having no relevant outcome, upon the title and abstract screening. Twenty-two articles underwent a full review, of which 10 were excluded as being ineligible. Finally, 15 articles (12 from the original search and three, either published after the search was completed or found from reference lists), met the eligibility criteria and were evaluated in this review.

The evaluated articles were divided into two groups based on the type of disease that was investigated in relation to OSA. These included: 1) OSA and cardiovascular disease (CVD) and its risk factors with six articles evaluated (Table 1); 2) OSA and metabolic abnormalities with nine articles evaluated (Table 2). Overall, three articles did not directly report the OSA prevalence (Ilich et al., 2022; Sá et al., 2023; Stefanaki et al., 2016) but based on the included measurements of bone, lean, and adipose tissue, a full assessment could be performed and thus, these studies were included as well.

Table 1 presents the characteristics and results of studies with OSA/OSO and CVD and/or its risk factors. Despite an intensive literature search and numerous articles published examining the relationship between individual body composition compartments and CVD and/or CVD risk factors, only six studies were found with all three body composition components to allow for an estimate of OSA phenotype. The studies included two conducted in China (Chen et al., 2019; Mo et al., 2018) and one study each in the population of Iran, the USA, Brazil, and Japan (Ahmadinezhad et al., 2023; Ilich et al., 2022; Sá et al., 2023; Sasaki et al., 2020), and were published between 2018 and 2023. Altogether, studies included 7178 participants, (~78%) women. The age range was wide, particularly in the Chinese samples (20–95 years), with a mean age in most of the studies between 55 and 70 years. All studies were cross-sectional, except the Ilich et al., (Ilich et al., 2022) study which was a randomized clinical trial conducted over 6 months.

Table 2 presents an overview of the results and characteristics of nine studies with impaired metabolic health (including inflammation, albumin levels, insulin resistance, components of metabolic syndrome, hyperglycemia, hypertension, and non-alcohol fatty liver disease (NAFLD)) and its potential relationship with OSA/OSO phenotype. Three of these studies were conducted in Italy (Moroni et al., 2023; Perna et al., 2018; Stefanaki et al., 2016), one each in Japan, South Korea, China, and Taiwan (Kashiwagi et al., 2021; Lee, 2020; Nie et al., 2022; Su et al., 2021), and two in Croatia (Cvijetić et al., 2023; Keser et al., 2021) and were published between 2016 and 2023. Altogether, the studies included 14064 participants (~60% women), ranging in mean age from 19.5 to 95 years.

4. Discussion

4.1. Cardiovascular diseases (CVD)/cardiovascular risk factors and OSA

The results are presented in Table 1. Both Chinese studies (Chen et al., 2019; Mo et al., 2018) included several indigenous ethnic groups (Maonan, Mulam, Yao, Hmong, and Jing) from the Guangxi Province with significant differences in their genetic and morphological background. Mo et al. included only women stratified into younger and older cohorts (<60 and >60 years) and examined the association of OSA with dyslipidemia, while Chen et al., (Chen et al., 2019) included both women and men over 50 years and examined the association between OSA and hypertension. Although the OSA prevalence was generally low in both studies, it was comparable to that in some other studies (Kim et al., 2017; Szlejf et al., 2017) and as expected, higher in older than younger participants.

The main findings of the Mo et al., (Mo et al., 2018) study revealed the ethnic-specific differences in the prevalence of both dyslipidemia and OSA. Additionally, dyslipidemia was strongly associated with multiple adverse body composition outcomes, especially for those participants with OSA, regardless of age. There are several proposed mechanisms as to how dyslipidemia may affect bone, muscle, and adipose tissues. For example, oxidized circulating low-density lipoproteins (LDL) may shift the mesenchymal stem cell differentiation to the adipocyte lineage, away from osteoblasts and myocytes. This would promote adipocyte infiltration into bone and muscle with the resultant weakening of both tissues (Ilich et al., 2014a; Yamaguchi, 2011). Increased adiposity (local and systemic) elevates the levels of inflammatory cytokines such as interleukin (IL-6) and tumor necrosis factor (TNF-α), which may induce further lipid infiltration into the bone and muscle (Petersen et al., 2007). This suggests that fat infiltration of bone and muscle negatively affects homeostasis and at the whole-body level may induce insulin resistance (IR). Additionally, the loss of muscle mass results in decreased muscle-glycogen synthesis, possibly due to reduced type 1 fibers, mitochondrial dysfunction, and inflammation accelerating IR in skeletal muscle (Liu and Zhu, 2023). Since there is a storage limit of muscle glycogen, the remaining extra glucose may be diverted to the liver where it is converted to fat stimulating hepatic de-nuovo lipogenesis and increasing systemic inflammation.

The results from the Chen et al., (Chen et al., 2019) study showed various levels of osteoporosis, sarcopenia, and obesity and significantly different prevalence of hypertension among the ethnic groups, the latter higher in men than women and also higher than in the overall Chinese population (Lu et al., 2017) or some other minority populations (Li and Yu, 2012). As indicated by the authors, these minority groups live in poverty-stricken mountainous areas typified by the lack of healthcare access and low general knowledge about healthy lifestyles, which could help explain the differences with the general Chinese population. Although systolic and diastolic blood pressure was the highest in both women and men with OSA, hypertension was significantly higher only in women with OSA but not in men with OSA, compared to those without OSA (possibly due to the low number of participants in each group and lack of statistical power). The positive relationship between OSA and hypertension is expected considering that each of the deteriorated body composition components is independently associated with elevated blood pressure. Such relationships are well established in the obesogenic states, even in very young individuals (Kim et al., 2016) or in adults, even when adjusted for comorbidities (Movahed et al., 2016). Moreover, a study in postmenopausal women showed that over 60% of those with osteoporosis had hypertension (Rašić and Tasić, 2009) while Yang and colleagues (Yang et al., 2014) demonstrated that high blood

Table 1
Characteristics and results of studies with osteosarcopenic adiposity/obesity (OSA/OSO)[1] and cardiovascular disease (CVD) and risks in ascending order of publishing year.

Reference, Studied topic	Country, Setting	Study Design	Diagnostic criteria & Instruments Bone Lean/Muscle	Adipose		Sample size, *n* (%)/ Intervention	Age (years)	OSA/OSO Prevalence[2] *n* (%)	Assessment Tools	Compared to[3]	Outcomes in OSA group (or others if indicated)
Mo et al. (2018), OSA and dyslipidemia	Guangxi Province, China: Maonan, Mulam, Yao and Hmong ethnic groups; All Women	C-S Inclusion/ Exclusion Criteria applied (both parents of same ethnicity)	T-score ≤-1 to include osteopenia/ osteopor; With UBD	ASM/ Ht^2; Ethnic specific cutoff values; With BIA	BF%: two upper quintiles; With BIA	Total, n=2315; Maonan, n=446 (younger, n=264, older, n=182); Mulam, n=437 (younger, n=255, older, n=182); Yao, n=672 (younger, n=458, older, n=214); Hmong, n=760 (younger, n=491, older, n=269)	Overall: Range 20–95; Mean Maonan: Younger, 40.1, Older, 67.1; Mulam: Younger, 46.8; Older, 67.8 Yao: Younger, 45.0, Older, 67.8 Hmong: Younger, 44.7 Older, 69.3	Younger group: Maonan, n=1 (0.4), Mulam, n=1 (0.4), Hmong, n=3 (0.6), Yao (0) Older group: Maonan, n=9 (4.9), Mulam, n=23 (12.6), Hmong, n=31 (11.5) Yao (0)	BIA TANITA; SONOT3000; Ultrasound bone densitometer; Routine lab equipment (for blood analyses)	Ethnicities; Age and presence of dyslipidemia in each ethnicity; Body composition (OSA/two/ one/zero components)	-Signif. higher rates of OSA in older groups vs younger of Maonan, Mulam, and Hmong ethnicities; -No OSA in Yao women, thus, prevalence of OSA is ethnic-specific; -Signif. positive association with dyslipidemia and OSA in both younger and older women in ethnic groups
Chen et al. (2019), OSA and hypertension	Guangxi Province, China: Jing, Maonan, Yao and Hmong ethnic groups, M and F (91% postmeno-pausal)	C-S Inclusion/ Exclusion Criteria applied (parents mostly of same ethnicity/ group)	T-score ≤-1 to include osteopenia/ osteopor; With UBD	ASM/ Ht^2: Ethnic-specific cutoff values, With BIA	BF%: F≥32; M≥25 With BIA	Total, n=1939 (59.7% F); Jing, n=459; Maonan, n=514; Hmong n=535; Yao, n=431	Mean: F, 65.4; M, 66.8	Overall F, n=26 (2.3); M, n=7 (0.9); Jing F (0.7), Maonan F (3.2); Yao F (0.4); Hmong F (3.5); Jing M (0), Maonan M (0.9); Yao M (0), Hmong M (2.3)	BIA TANITA, MC-180 body; Achilles Express Ultrasound bone densitometer; OMRON HEM-1000 electronic sphygmomanometer; Demographic and health status questionnaires	Ethnicities; M vs. F in each ethnicity; (OSA, two/one/ zero component); Participants with hypertension vs. normal	-Signif. ethnic differences in hypertension prevalence; -Higher prevalence of hypertension in M than in F in 3 groups (Hmong, Maonan, Yao); -Signif. higher prevalence of hypertension in F with OSA than without OSA; -No higher Hypertension prevalence in M with OSA than without OSA; -Highest SBP and DBP in OSA participants in all four ethnicities; -Higher prevalence of sarcopenia in M than F in Maonan group, and lower in M than in F in

(*continued on next page*)

Table 1 (*continued*)

Reference, Studied topic	Country, Setting	Study Design	Diagnostic criteria & Instruments Bone	Lean/Muscle	Adipose	Sample size, *n* (%)/ Intervention	Age (years)	OSA/OSO Prevalence[2] *n* (%)	Assessment Tools	Compared to[3]	Outcomes in OSA group (or others if indicated)
Sasaki et al. (2020), OSA and patients with CVD	Kurume, Japan; Community dwelling (CD) adults; CVD patients admitted to University hospital	C-S; Inclusion/ Exclusion criteria applied; CD adults assessed during regular check-up; CVD patients measured within 5 days after admittance and stable	T-score ≤-1 to include osteopenia/ osteopor; With UBD	SMI: F<5.7 kg/ m^2; M<7.0 kg/ m^2; With BIA; AND low handgrip strength: F<18 kg; M<26 kg; or low gait speed <0.8 m/sec	BF%: F≥38; M≥27; With BIA	Total, n=390 CD, n=230; F, n=177; M, n=53; CVD patients, n=160; F, n=60; M, n=100	CD, 68 (range: 61–74); CVD, 67 (range: 62–73)	CVD patients, n=7 (4.4); CD adults, n=2 (0.9)	BIA; Achilles UBD; Motor function/ physical performance; dynamometer; Routine lab equipment (for 25(OH)D and TRACP-5b)	CVD *vs* CD AND F *vs* M within and between groups; No comparison with all body composition components in healthy range	Hmong, Jing and Yao groups; -Higher prevalence of osteoporosis and obesity in F than M in all four groups -Signif. higher prevalence of OSA, sarcopenia and osteosarcopenia in CVD than in CD; -Signif. higher prevalence of sarcopenia in F CVD than in M; -Signif. higher prevalence of osteosarcopenia in F CVD than F CD; -Lower BMC and T-score in F CVD than F CD; -Lower grip strength and gait speed in all CVD; -Lower serum 25 (OH)D and zinc in CVD than in CD in both F and M; -Higher body and visceral fat in M CVD than M CD; -Lower serum albumin and Ca in F CVD than F CD; -Higher TRACP-5b in F CVD
[NoP]Ilich et al. (2022), OSA and CVD risk factors; Secondary analysis to Ilich et al. (2019)	United States, CD; White, healthy postmeno-pausal women with overweight/ obesity	Inclusion/ Exclusion criteria applied; 6-month intervention with three randomized groups (dairy, Ca+vitamin D supplements, placebo); All samples blinded for analysis	T-score ≤-1 for hip and/or spine to include osteopenia (no women with osteoporos were recruited); With iDXA	Total lean mass (kg); Android lean (kg) Gynoid lean (kg); With iDXA	BF%: Average at baseline 45.9; With iDXA	At baseline: n=135 (dairy, n=64, Ca/vit D, n=62, placebo, n=62); At 6-month: n=97 (dairy, n=32, Ca/vit D, n=37, placebo, n=30); Energy (85% of total needs) to all participants	Mean 55.8 at base-line; 6.6 years since meno-pause	Not reported; All three body composition components were measured and evaluated at baseline and after 6 months of intervention	iDXA; Routine lab equipment and ELISA (for blood and urine samples); 3-day dietary records; Activity records	Baseline values; Groups after 6 months of intervention	-All participants improved (due to weight loss) in: cardiometabolic indices (BP, TC, triglycerides, insulin, leptin, adiponectin, ApoA1, ApoB) -Dairy group: Signif. decrease in BP, TC, LDL-C, TC/HDL-C, ApoB, leptin; signif. increase in adiponectin, ApoA1; Supplement group:

(*continued on next page*)

Table 1 (*continued*)

Reference, Studied topic	Country, Setting	Study Design	Diagnostic criteria & Instruments Bone	Lean/Muscle	Adipose	Sample size, *n* (%)/ Intervention	Age (years)	OSA/OSO Prevalence[2] *n* (%)	Assessment Tools	Compared to[3]	Outcomes in OSA group (or others if indicated)
						Dropout: 28.2% Imputed analyses for missing data					-Signif. decrease in BP, triglycerides, LDL-C, ApoB, leptin; signif. increase in HDL-C, adiponectin, ApoA1
[NoP]Sá et al. (2023), OSA and CVD risk factors	Recife, Brazil, University hospital; Patients in preope-rative assessment for bariatric surgery (2018–2019)	C-S; Inclusion/ Exclusion criteria applied; Patients with II, III, IV and V degrees of obesity, but less than 158 kg due to DXA limitation	BMD, 1.13 g/ cm^2; BMC, 2.3 kg; Z-score, 0.03; With DXA	Lean mass, 45.0%; Lean Mass Index, 20.4 kg/ m^2; With DXA	BF%, Mean 46.6; Abdominal fat %, Mean, 47.9; With DXA; BMI, Mean 47.3 kg/m^2; Range, 36.8–66.2 kg/ m^2	Total, n=60; F, n=47 (78); M, n=13 (22)	Mean 38.9; Range, 22–59	Not reported; Commor-bidities, n=52 (86.7); 25(OH)D Insuffi-ciency, n=42.8 (71.4)	DXA; Standard anthropo-metry; Standard biochemical analyses; Lifestyle questionnaires	Degree of obesity; Volume of abdominal fat	- Signif. positive association of abdominal fat with CVD risk; -Signif. negative correlation of LM with BMI, WC, FM, abdominal fat, fasting glucose; -Negative association of alcohol intake and physical activity with CVD risk
Ahmadi-nezhad et al. (2023), OSA and CVD risk factors	Bushehr, Iran, Bushehr Elderly Health (BEH) Program	C-S; Inclusion/ Exclusion criteria applied; (cancer patients excluded)	T-score ≤-1 for hip and/or spine to include osteopenia/ osteopor; With DXA	SMI: F<5.7 kg/ m^2; M<7.0 kg/ m^2; With DXA; AND low handgrip strength: F<18 kg; M<26 kg; or low gait speed <0.8 m/sec	BF %, F≥32; M≥25; With DXA OR BMI≥30 kg/ m^2	Total, n=2339; F, n=1202 (51); M, n=1136 (49)	Mean: OSA F, 71.7; M, 74.8; Non-OSA F, 68.3; M, 68.4	Total, n=464 (19.8) F, n=266 (22.1); M, n=198 (17.4);	DXA; Standard anthropo-metry; Standard biochemical analyses; 24-h dietary recall; Physical activity questionnaire	OSA vs non-OSA, in both F and M	- Signif. negative association of hypertriglyceri-demia and hypertension with OSA in F -Signif. positive association of diabetes with OSA in M; -Signif. positive association of age with OSA in both M and F; -Signif. negative association of education, physical activity, and protein intake with OSA in M & F

Abbreviations:
25(OH)D: 25 hydroxyvitamin D; ApoA1: apolipoprotein A1; ApoB: apolipoprotein B; ASM/Ht^2: appendicular skeletal muscle adjusted for height; BF: body fat; BIA: bioelectrical impedance analysis; BMC: bone mineral content; BMD: bone mineral density; BMI: body mass index; BP: blood pressure; Ca: calcium; CD: community dwelling; C-S: cross-sectional; CVD: cardiovascular disease; DBP: diastolic blood pressure; DXA: dual energy absorptiometry; ELISA: enzyme-linked immunosorbent assay; F: females; FM: fat mass; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; M: males; SBP: systolic blood pressure; SMI: skeletal muscle index; TC: total cholesterol; TRACP-5b: tartrate-resistant acid phosphatase 5b (marker of bone resorption); T-score: for identification of osteopenia/osteoporosis; UBD: ultrasound bone densitometer; WC: waist circumference.

[1] OSA/OSO terms are used interchangeably.

[2] Prevalence includes both pre- (with osteopenia and/or pre-sarcopenia) and full OSA/OSO.

[3] OSA/OSO participants compared to those with one or more body composition impairments (e.g., osteopenia/osteoporosis, osteosarcopenia, sarcopenia, sarcopenic obesity, obesity/adiposity alone), or normal. NoPStudies not reporting/calculating the prevalence of OSA/OSO, but still analyzing three body composition compartments from which OSA/OSO prevalence and/or its relation to exposure variables could be derived.

Table 2
Characteristics and results of studies with osteosarcopenic adiposity/obesity (OSA/OSO)[1] and metabolic abnormalities in ascending order of publishing year.

Reference, Studied topic	Country, Setting	Study Design	Diagnostic criteria & Instruments Bone Lean/Muscle Adipose			Sample size, *n* (%)	Age (years)	OSA/OSO Prevalence[2] *n* (%)	Assessment Tools	Compared to[3]	Outcomes in OSA/OSO group (others if indicated)
[NoP]Stefanaki et al. (2016), OSA in young adults and inflamma-tion	Venice, Italy; Young, healthy participants from medical centers (derived from a larger sample), both M and F	Nested case-control; Inclusion/ Exclusion Criteria applied	NR; Total bone mass ranged from 3.6 to 4.6 kg; With BIA-ACC	NR; Skeletal muscle ranged from 35.7% to 41.1%; With BIA-ACC	BF%: F >32; M >25; With BIA-ACC	Total, n=2551; Overweight/ obese, n=1479; M, n=74 (5); F, n=1405 (95); Normal weight, n=1072; M, n=900 (84); F, n=172 (16)	Mean ~19.5 for each group and sex	NoP; Overweight/ obese group had lower values for bone and muscle when adjusted for weight, compared to lean group	BIA-ACC BioTekna®; Nephelo-meter (BN 100); Automatic electrochemilumi-nescence analyzer	Healthy weight, age- and gender-matched counterparts	Overweight Group: -Signif. higher FM, IMAT, CRP, evening salivary cortisol; creatinine; -Signif. lower FFM, skeletal muscles (kg), SMI, bones (kg), phase angle, total body water, basal metabolic rate; -Signif. higher ECW (%) in F; -Signif. lower ECW (L) in M; Total sample -Signif. correlation of bone mass (kg) & muscle mass (kg)
Perna et al. (2018), OSA (including visceral and subcuta-neous fat) and metabolic profile and fracture risk	Pavia, Italy; Patients in the post-acute geriatric care unit, both M and F	C-S; Inclusion/ Exclusion Criteria applied	T-score ≤-1(to include osteopenia/ Osteopor); With DXA; FRAX index for 10-year fracture risk assessment	SMI: F <5.5 kg/ m^2; M <7.2 kg/ m^2 With DXA	BF%: F ≥38; M ≥27; VAT & SAT in android region; With DXA; Transfor-med to CT to generate VAT/ SAT ratio (>1 visceral obesity, <1 subcutan-eous obesity	Total, n=801; Healthy body comp, n=41 (5.1); Obese, n=57 (7.1); Sarcopenic, n=16 (2); Osteopenic/ osteopor., n=452 (56.4); Sarcopenic obese, n=27 (3.3); Osteopenic obese, n=63 (7.9); Osteo-sarcopenic, n=90 (11.2); Overall OSA, n=55 (6.9)	Mean ~80; Varied from 75.9 for healthy to 82.4 for OSVAT	OSA, n=55 (6.8); OSSAT, n=17 (2.1); OSVAT, n=38 (4.7)	DXA; CT; HPLC; Automatic biochemical analyzer; Dynamo-meter; Bioelectrical impedance vector analysis with single-frequency bioimpe-dance (hydration assessment)	8 groups: Healthy body comp., OSVAT, OSSAT, Other combination of OSA components	OSVAT: -Signf. higher risk of fracture (by FRAX assessment), -Trends to worse metabolic profile OSVAT & OSSAT: -Trends to higher CRP and inflammation; -Trends to lower albumin
Lee et al. (2020), OSA and insulin resistance	South Korea; KNHANES (2008–2011); Men and postmeno-pausal women	C-S; Inclusion/ Exclusion Criteria applied; Participants with diabetes excluded	T-score ≤-1 for hip and/or spine (to include osteopenia/ osteopor); With DXA	SMI: F <5.7 kg/ m^2; M <7.2 kg/ m^2 (Asian reference); With DXA	BF%: F ≥35; M ≥25; With DXA Or BMI ≥25 kg/m^2	Total, n=4500; F, n=2433 (54.1%); M, n=2067 (45.9)	Mean, 62.9 (HOMA-IR <2.5); 63.3 (HOMA-IR ≥2.5) 62.5	Based on BF % M, n=119 (5.8); F, n=175 (7.2); Based on BMI M, n= 8 (0.4);	DXA; calorimetry (glucose); IRMA (insulin)	Normal; One or two components for OSA; Divided in groups by HOMA-IR levels	-For obesity defined by BF%, odds ratio for IR were: groups with obesity and osteopenic obesity > sarcopenic obesity and OSA >osteopenia and sarcopenia > OSA; -For obesity defined by BMI, odds ratio

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Table 2 (*continued*)

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								F, n=17 (0.7)			for IR were: obesity co-existent groups > obesity non-coexistent groups; -No difference within obesity co-existent groups
Su et al. (2021), OSA components and metabolic syndrome	Taiwan; Urban areas; From Health Management Center data base (2016–2018	C-S; Inclusion/ Exclusion Criteria applied; Metabolic syndrome diagnosed by WC, blood pressure, serum glucose, and lipids	T-score ≤-1 to include osteopenia/ osteopor; With DXA	Grip strength: F <18 kg M <28 kg From Asian Working Group on Sarco-penia; With Dynamo-meter	BF%: F >35; M >25; With DXA	Total, n=2991; F, n=1258 (42.1) M, n=1733 (57.9)	Mean, 58.6; Control 55.6; OSA 64.7	Total, n=141 (4.7); F, n=68 (5.4); M, n=73 (4.2); Metabolic Syndrome prevalence: Total, n=672 (22.5); OSA, n=40 (6)	DXA; Dynamo-meter (TKK-5401); Biochemical analyzer	Controls OSA-0, no impairment; OSA-1 (osteoporosis, or sarcopenia or adiposity); OSA-2 (osteosarco-penia, or osteopenic adiposity, or sarcopenic adiposity); OSA-3 (all)	-Signif. positive relationship between metabolic syndrome with OSA-2 and OSA-3 (not with OSA-0 or OSA-1); -Other factors influencing OSA-2 and OSA-3: Older age, F sex, lack of exercise, full-time employment
Kashiwagi et al. (2021), OSA and NAFLD	University Hospital Tokyo, Japan	Retro-spective; Inclusion/ Exclusion criteria applied to include NAFLD patients and matched healthy controls	BMD at spine and femoral neck; For osteopenia 70–89% of YAM; For osteopor <70% of YAM; With DXA	ASM/Ht^2: F <5.4 kg/m^2; M <7.0 kg/m^2 (Asian references); With DXA	BF%: F ≥30; M ≥25; With DXA	Total, n=614; F, n=337 (55); M, n=277 (45)	Mean, 66.9; F, 66.7; M, 67.1	Total, n=36 (6); F, n=32 (9); M, n=4 (1)	DXA; Ultrasound (for fatty liver diagnosis); Medical records for clinical data; Lifestyle questio-nnaires	3 groups: -No NAFLD; -Obese NAFLD; -Non-obese NAFLD	-Signif. association of OSA with non-obese NAFLD in females, after controlling for confounders; -Males were not examined due to low prevalence of OSA
Keser et al. (2021), OSA and inflamma-tion in nursing home residents	Zagreb, Croatia; Nursing Home	C-S; Inclusion/ Exclusion criteria applied	T-score ≤-1 for total bone mass With BIA-ACC	S-score ≤-1 With BIA- ACC	BF%: F ≥32; M ≥25 With BIA-ACC	Total, n=84; F, n=69 (82); M, n=15 (18)	Mean, 83.5; Range 65.3–95.2	Total, n=45 (53.6); F, n=37 (53.6); M, n=8 (53.3)	BIA-ACC BioTekna® 24-h dietary recall; Other questio-nnaires	Osteopenic adiposity; Adiposity only; No normal body comp.	-Signif. higher ECW, (indicating higher inflammation); -Signif. lower phase angle (indicating lower cell integrity and muscle quality)
Nie et al. (2022), OSA and systemic inflamma-tion	Harbin Medical University China; Older adults (≥ 60 y)	C-S; Inclusion/ Exclusion criteria applied (excluded those with serious metabolic, endocrine diseases, or fractures, and use of medications affecting bone metabolism)	T-score ≤-1 for femoral neck, hip, and lumbar spine (to include osteopenia/ osteopor); With DXA	ASM/Ht^2: F <5.4 kg/m^2; M <7.0 kg/m^2 (Asian references); With DXA AND Grip strength: F<18.0 kg; M<28.0 kg; With Dynamo-meter and/or low gait speed (<1.0 m/s)	BF%: F ≥32; M ≥25; With DXA	Total, n=648; F, n=416 (64.2); M, n=232 (35.8)	Mean, 67.2; OSA-3, 69; Healthy controls (OSA-0), 64.0	OSA-3, n=107 (16.5); OSA-2, n=292 (45.1); OSA-1 n=196 (30.25); OSA-0	DXA; Dynamo-meter; 4 m walk test; Standard biochemical analyses; Standard anthropo-metries; Activity and lifestyle questio-nnaires	Controls OSA-0, no impairment; OSA-1 (osteoporosis, or sarcopenia or adiposity); OSA-2 (osteosarco-penia, or osteopenic adiposity, or sarcopenic adiposity); OSA-3 (all)	OSA-3 (adjusted for confounders): -Signif. positive association with systemic inflammation response-index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, aggregate inflammation systemic index; -Signif. inverse correlation with

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Table 2 (*continued*)

Reference, Studied topic	Country, Setting	Study Design	Diagnostic criteria & Instruments Bone Lean/Muscle Adipose			Sample size, *n* (%)	Age (years)	OSA/OSO Prevalence[2] *n* (%)	Assessment Tools	Compared to[3]	Outcomes in OSA/ OSO group (others if indicated)
											lymphocyte-to-monocyte ratio -Signif. positive correlation with age, coronary heart disease, BF%, total cholesterol and LDL; -Signif. negative correlation with alcohol consumption, regular exercise, sunlight exposure
Cvijetićet al. (2023), OSA and inflamma-tion during COVID in nursing homes residents	Zagreb, Croatia; Six Nursing Homes	C-S; Inclusion/ Exclusion criteria applied	T-score ≤-1 for total bone mass; With BIA-ACC	S-score ≤-1 With BIA- ACC	BF%: F ≥32; M ≥25; With BIA-ACC	Total, n=365; F, n=296 (81); M, n=69 (18.9)	Mean, 83.7 F, 84.3 M, 83.1	Total, n=242 (66.3); F, n=209 (70.8); M, n=33 (47.8)	BIA-ACC BioTekna®; MNA; Other questio-nnaires	Osteopor and/or sarcopenia and/or obesity alone; No normal body comp. No COVID; COVID survivors	-No difference in OSA prevalence or nutritional status in those with or without COVID; -Signif. higher ECW; -Signif. lower phase angle; -Lower total bone mass; -Higher IMAT
Moroni et al. (2023), OSA and metabolic abnormal-lities	Pavia, Italy; Patients in metabolic rehabilitation unit, University of Pavia; both M and F	C-S; Inclusion/ Exclusion Not indicated	T-score ≤-1 for femoral neck to include osteopenia/ osteopor; With DXA	SMI: F <5.5 kg/m^2; M <7.3 kg/m^2; With DXA	BF%: F ≥32; M ≥25; VAT: F>1134 g; M>1859 g; With DXA;	Total, n=1510; F, n=1100 (72.8); M, n=410 (27.2)	Mean, 75.9; Adult (<65 y); F, 50.2; M,49.9; Oldest (66–84 y); F, 77.2; M, 76.6; Oldest-old (>84 y); F, 89.5; M, 88.8	Total, n= 29 (1.9); Adult F, n=0; M,n= 2 (4.3); Oldest F, n= 8 (1.1); M, n= 14 (4.5); Oldest-old F, n= 4 (1.7); M, n= 1 (1.9)	DXA; Biochemical analyzer	Sarcopenia; Sarcopenic obesity; Osteosarco-penia;	OSA: -Signif. positively associated with glycemia and gGT; Sarcopenic Obesity: -Signif. positively associated with age, ESR; serum ferritin, and CRP; Signif. negatively with BMI, serum albumin, and iron; Osteosarcopenia: -Signif. positively associated with age and ESR; Signif. negatively with BMI, serum cholesterol, albumin, and calcium; Sarcopenia: -Signif. positively associated with age ESR and CRP; Signif. negatively with BMI, serum cholesterol, iron, albumin

Abbreviations:
ASM/Ht^2: appendicular skeletal muscle adjusted for height; BF: body fat; BIA-ACC: bioelectrical impedance analysis with BioTekna®; BMD: bone mineral density; COVID: coronavirus disease; CRP: C- reactive protein; C-S:

cross-sectional; CT: computerized tomography; DXA: dual-energy absorptiometry; ECW: extracellular water; ESR: erythrocyte sedimentation rate; F: females; FFM: fat-free mass; FM: fat mass; FRAX: fracture risk assessment tool; gGT: gamma-glutamyl transferase; HPLC: high-performance liquid chromatography; HOMA-IR: homeostatic model assessment for insulin resistance; IMAT: intermuscular adipose tissue; IR: insulin resistance; IRMA: immunoradiometric assay; KNHANES; Korea National Health and Nutrition Examination Survey; M: males; MNA: mini nutritional assessment; NAFLD: nonalcoholic fatty liver disease; NR: not reported; OSSAT: osteosarcopenic subcutaneous tissue; OSVAT: osteosarcopenic visceral adipose tissue; SAT: subcutaneous adipose tissue; SMI: skeletal muscle index; S-score for identification of sarcopenia; T-score for identification of osteopenia/osteoporosis; VAT: visceral adipose tissue; WC: waist circumference; YAM: young adult mean.

[1] OSA/OSO terms are used interchangeably.

[2] Prevalence includes both pre- (with osteopenia and/or presarcopenia) and full-blown OSA/OSO.

[3] OSA/OSO participants compared to those with one or more body composition impairments (e.g., osteopenia/osteoporosis, osteosarcopenia, sarcopenia, sarcopenic obesity, obesity/adiposity alone), or normal.

NoPStudies not reporting/calculating the prevalence of OSA/OSO, but still analyzing three body composition compartments from which OSA/OSO prevalence and/or its relation to exposure variables could be derived/estimated.

pressure was a risk factor for osteoporosis and fragility fractures. This could be attributed to the hypertension-induced loss of calcium (and other minerals) in urine and/or hyperparathyroidism, all leading to increased bone resorption (Canoy et al., 2022; Cappuccio et al., 2000, 1999). Similarly, sarcopenia and sarcopenic obesity have also been linked with hypertension. A study conducted by Park and colleagues (Park et al., 2013) revealed that the risk of hypertension was 2.5 times higher in Korean women with sarcopenia and more than 6 times higher in those with sarcopenic obesity than in the control group. This suggests that hypertension-induced arterial stiffness, as well as the presence of obesity, either leads to or worsens sarcopenia and sarcopenic obesity. There are numerous mechanisms of action for these relationships and these are out of scope for this review.

Both (Chen et al., 2019; Mo et al., 2018) studies, despite the limitations and complex analyses, show a higher presence of dyslipidemia and hypertension in women with OSA compared to those without OSA, indicating higher risks for CVD in women with OSA. In both studies, body composition indices were assessed by BIA which is a well-validated method. Bone mineral density (BMD) was estimated by an ultrasound bone densitometer which may have underestimated the prevalence of osteoporosis (Lewiecki and Lane, 2008). The ethnic differences held for the OSA prevalence as well (see Table 1). The minority groups in both studies were reported to have significant differences in their genetic and morphological background, providing the justification for studying them. However, since not much is known about the genetic, environmental, and other demographic characteristics of these specific ethnic groups, the overall relevance is hard to appreciate. Conversely, the mechanisms leading to positive relationships with OSA could hold for other ethnicities and populations.

The Sasaki et al., (Sasaki et al., 2020) study, to our knowledge, is the only one performed in Japan to determine the OSA phenotype and its components in hospitalized patients with CVD. They were compared to community-dwelling adults with medical data from their regular clinical check-ups. Not surprisingly, the hospitalized patients (clinically stable) with CVD presented with significantly more comorbidities (hypertension, dyslipidemia, type 2 diabetes) compared to the community-dwelling adults. Other markers of CVD risk factors were also more pronounced in patients, including those potentially linked to body composition, such as lower serum calcium, vitamin D, zinc, albumin, and higher bone resorption markers. The components of body composition as well as measures of functional performance were also lower in patients with CVD. The authors used non-standard terminology in naming the components of body composition; sarcopenic obesity, osteosarcopenia, and OSA were all referred to as subtypes of sarcopenia. The OSA prevalence was 4.4% in patients with CVD compared to 0.9% in community-dwelling adults. The overall prevalence of sarcopenia was 16.9% and 4.3% for patients with CVD and community-dwelling adults, respectively. The prevalence of sarcopenic obesity, osteosarcopenia, and OSA was also higher in the CVD patients, compared to community-dwelling adults (0.6% vs. 0.4%; 8.8% vs. 2.6%; and 4.4% vs. 0.9%, respectively). Notabl, the prevalence rates in Sasaki et al., study were lower than that reported in other studies in Japan (Takayama et al., 2018) or in the general population of similar age (Batsis et al., 2014). Some of the reasons could be due to the diagnostic tools (e.g., the heel ultrasound was used for bone assessment) and/or cut-offs (too high for body fat), see (Kelly et al., 2019) which excluded many participants resulting in a lower OSA prevalence. Overall, numerous variables were presented in this study with two distinct groups of participants (hospital patients vs. community-dwelling adults), each consisting of males and females. Therefore, it was sometimes hard to interpret all the measured variables and associated outcomes. Despite the evident disparities in health outcomes among patients with CVD, it was not possible to determine whether those with OSA fared worse compared to those with other body composition impairments. There was also no assessment/comparison with the group with all body composition components in the healthy range.

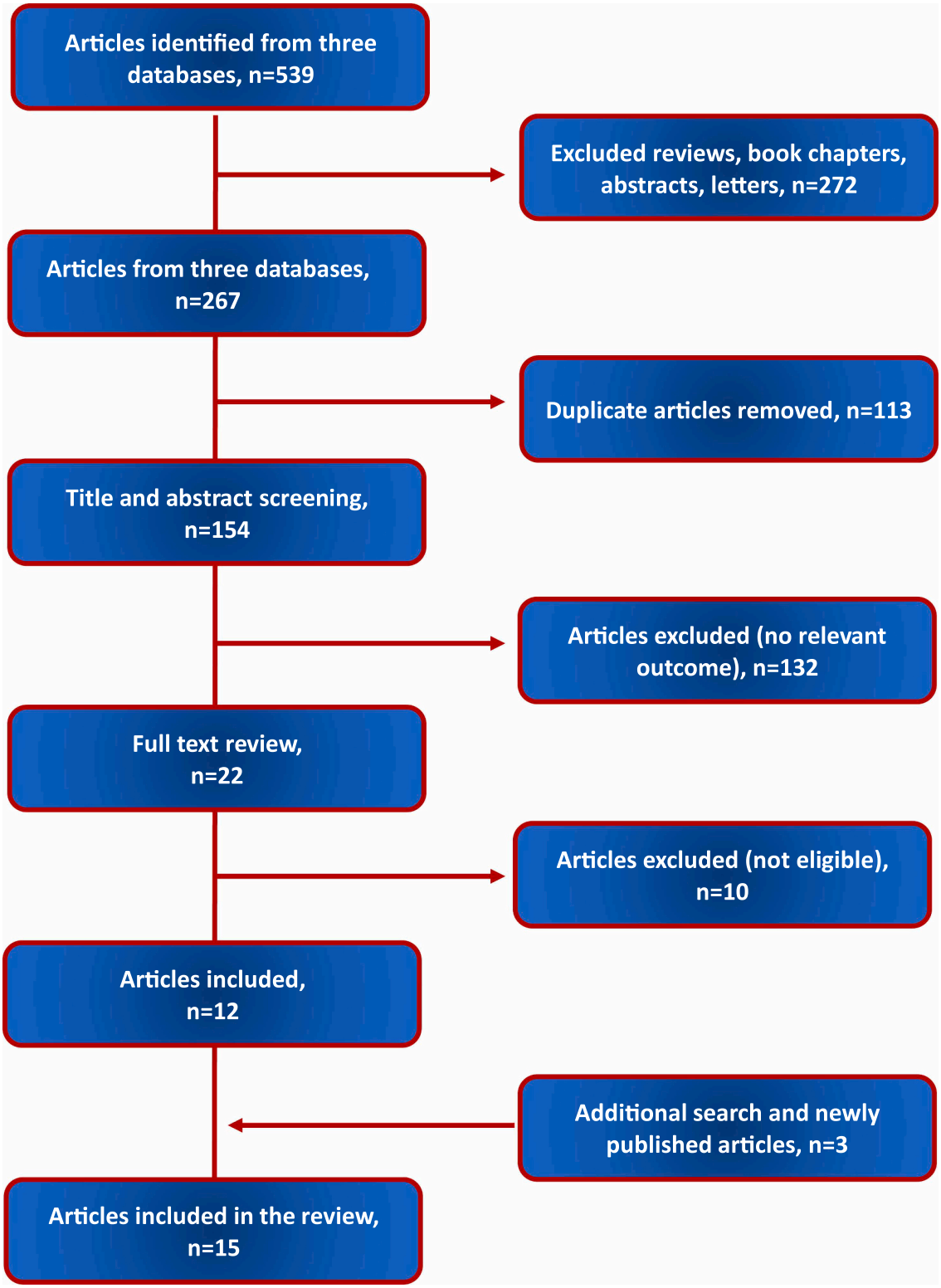

Fig. 1. Flowchart of the search process.

In both Ilich, et al., (Ilich et al., 2022) and Sa et al., (Sá et al., 2023) studies, OSA prevalences were not reported, and the studies were conducted in relatively healthy individuals, as opposed to other studies in this review where patients were included. However, since all three body composition components were reported, this enabled estimates of OSA, which showed some significant relationships with certain CVD risk factors. Additionally, the study by Ilich et al. was the only randomized clinical trial found during this search. This study was a secondary analysis of the original six-month randomized clinical trial of weight loss with either 4–5 servings/day of low-fat dairy foods or calcium+vitamin D supplements, or placebo pills (control group), investigating their effects on weight and bone health in postmenopausal women with overweight/obesity (Ilich et al., 2019). The primary results showed that all participants achieved weight loss (although moderate), but those in the

dairy group experienced greater loss of body fat and a slighter loss in lean mass (in some regions) compared to the control group or the group taking supplements. The group with calcium/vitamin D supplements showed the best improvements in BMD compared to dairy or control groups (Ilich et al., 2019). The secondary analysis revealed the remarkable effects of this moderate weight loss on improvement in CVD risk factors, namely, blood pressure, serum triglycerides, total and LDL-cholesterol, and several other cardiometabolic risk factors (each known for increasing oxidative stress and chronic inflammation). Such effects were noted in all participants but were significantly better in the dairy and/or calcium+vitamin D-supplemented groups compared to control. It is important to note that a full-blown OSA was not present in this population (as per inclusion criteria), however, it could be said that the participants had pre-OSA (osteopenia only and pre-sarcopenia, in addition to obesity). Although the participants were relatively healthy early postmenopausal women with overweight/obesity they experienced remarkable improvements in CVD risk factors after six months of intervention.

The relationship between dairy foods and CVD risk factors has been investigated, and both older (German et al., 2009) and recent (Giosuè et al., 2022) reviews indicated no adverse effects (some positive), despite the presence of saturated fatty acids in dairy foods. In this context, in the Ilich et al., (Ilich et al., 2022) study, only low-fat dairy foods were used in the intervention and resulted in positive outcomes, both in weight and other CVD risk factors (as noted above). The data examining the role of dietary or supplemental calcium intake on CVD are still controversial, although the negative relationship between calcium and blood pressure is well documented (Villa-Etchegoyen et al., 2019). For example, Larsson et al., (Larsson et al., 2013) reported a negative relationship between dietary calcium and the risk of stroke in participants with a low/moderate calcium intake and a positive in those with a high calcium intake, possibly indicating a "U" curve relationship. Other studies reported a lowering blood pressure effect of calcium supplements, while others showed that deposition of calcium in the vascular walls (associated with supplements) may be a cause of vascular disease and predictive of adverse cardiovascular events, see review (Reid et al., 2017). A recent meta-analysis evaluating the double-blind, placebo-controlled randomized clinical trials with calcium supplements found a 15% increased risk for CVD in healthy postmenopausal women (Myung et al., 2021). However, in the studies where calcium supplements were used with vitamin D (Hsia et al., 2007; Shah et al., 2010) as was also the case in the Ilich et al., (Ilich et al., 2022) study, no adverse effects were observed. Overall, although this was a secondary analysis, and in addition to other limitations (e.g., high attrition rate, missing data points counteracted by statistical manipulations), the data are valuable as they reveal possible causal relationships between body composition and CVD risk factors which can be modified by calcium+vitamin D and dairy foods. Based on these results, it can be concluded that the dietary supplementation, and accompanied weight loss, improved all three tissues (bone, muscle/lean, adipose) which in turn resulted in reduced risk of cardiovascular disease.

The Sa et al., (Sá et al., 2023) study conducted on Brazilian younger (age range 22–59 years) patients awaiting bariatric surgery describes the association between abdominal fat and CVD risks. The study was cross-sectional and was conducted in 60 patients, predominantly women, with ~72% having grade II and III obesity (no distinction between male and female cases was made). DXA was utilized for body composition measurements and Framingham Risk Score for CVD assessment. The patients in general, presented with elevated CVD risk factors such as total cholesterol (>190 mg/dL), high-density lipoprotein (HDL)-cholesterol (<50 mg/dL), fasting glucose (>100 mg/dL), and serum vitamin D (<30 ng/mL). Additionally, the results showed that patients with more abdominal fat also had even higher values for CVD risks (including higher total and LDL-cholesterol, and fasting glucose, but lower HDL-cholesterol, and serum vitamin D levels), as was reported in other studies/reviews (Kelles et al., 2015; Sjöström, 2013). These measures were also associated with lower bone and muscle indices. This study highlights the importance of body fat distribution or fat allocation when assessing associated health outcomes in young individuals with severe obesity. Although the values for the measured bone and lean mass appeared in the normal range (possibly overestimated due to weight), their total body fat, including the abdominal fat, was extremely high (>46%). This high percentage of body fat, in addition to increasing risks for several chronic diseases and poor metabolic profile (Forte et al., 2023), may also predispose these individuals to the development of OSA syndrome by fat infiltration into bone and muscle; OSA is probably inevitable in these cases (Ilich et al., 2020, 2014a). Unfortunately, the infiltrated fat was not assessed and there was no distinction between visceral and subcutaneous fat in the abdominal region.

As reported recently, obesity rates are increasing worldwide in younger people. For example, from 2009 to 2020 in the USA obesity rates increased by ~8% among the 20–44 years old individuals, accompanied by an increase in diabetes and some other cardiovascular risks (Aggarwal et al., 2023). This means that younger adults will present with a growing proportion of chronic diseases associated with obesity, including the OSA syndrome earlier, and that early detection of risk factors is of the utmost importance. For example, the Stefanaki et al., (Stefanaki et al., 2016) study conducted on over 2500 apparently healthy, young individuals, reported that those who were overweight/obese also had lower bone and muscle mass. In other words, these young individuals were presenting with the OSA phenotype which was accompanied by some unfavorable metabolic consequences (please see the details of Stefanaki et al., study in Table 2 and the accompanied text in the Discussion, Section 2). Although Sá et al., (Sá et al., 2023) did not provide a direct association between OSA and CVD risk factors, it supports the notion of OSA being designated as an "adiposity-based chronic disease" (ABCD), described earlier (Mechanick et al., 2017). ABCD reflects the true nature of the effects of adiposity (both adipose tissue expansion and redistribution) on whole-body complications and overall health (Garvey, 2022). These aspects of adiposity may often be overlooked or may not be assessed in younger individuals. Therefore, it is necessary to pay more attention to body composition in younger, apparently healthy adults, as well as to develop better technology for assessing the "hidden" fat as it can have profound negative effects.

In the Iranian study (Ahmadinezhad et al., 2023), the prevalence of OSA and its association with adverse CVD risks was evaluated in over 2000 participants (>60 years) from the Elderly Health Program. The overall mean OSA prevalence was 19.8% (slightly higher in women than men) and similar to that in other studies (De Lorenzo et al., 2024). The results showed almost a linear increase in OSA prevalence with age, particularly in women. For example, in the age groups of 60–64 years, 65–69 years, and 70–74 years, the OSA prevalence was almost double in women than in men. However, in the age group of >75 years individuals, the prevalence increased in men to 42.4%, compared to that of women at 38.9%. This could be explained by the higher rate of bone and muscle loss with very advanced age in men, as well as the higher number of comorbidities in older men compared to older women (Mitchell et al., 2012). The findings about the inverse relationship between OSA and hypertension, and OSA and hypertriglyceridemia, as reported (Ahmadinezhad et al., 2023), are quite puzzling and contradictory to other studies, including those discussed above (Chen et al., 2019; Mo et al., 2018). However, upon closer examination, the participants with hypertension comprised of those taking antihypertensive medications whereas the dyslipidemia was based on lab measurements. Therefore, the identification of participants classified as hypertensive may have been muddled by self-reporting use of medications and the participants with OSA may have been more compliant with antihypertensive and blood lipid-lowering medications. Furthermore, because the participants without OSA were not seen/recorded as overweight/obese, there may have been some bias in their clinical management; they were assumed to have normal body composition in the absence of a high body weight. Yet, fat mass (g/kg) was not significantly different either in

women or men, with or without OSA.

Some studies (although rare) have shown an inverse relationship between some individual components of body composition, e.g., sarcopenia and hypertension. Two Japanese studies (Endo et al., 2021; Kurose et al., 2020), reported an inverse relationship between hypertension and pre-sarcopenia in individuals >60 years old on a rural Japanese island. However, these two studies are unique due to the isolated and specialized population. Regarding the inverse relationship between hypertriglyceridemia and OSA, the findings could possibly be explained based on the serum lipids-bone paradox, addressed earlier (Brownbill and Ilich, 2006), again, only to the single body composition component; bone, but the mechanisms are out of scope for this review. Other findings from (Ahmadinezhad et al., 2023) included a positive relationship between OSA and diabetes in men, while education, protein intake, and physical activity were negatively associated with OSA in both women and men. The negative associations of OSA with protein intake and physical activity were corroborated earlier (Ilich, 2021; Vucic et al., 2023).

4.2. Metabolic abnormalities and OSA

The results are presented in Table 2. Stefanaki et al., (Stefanaki et al., 2016) were the first (to our knowledge) to report the existence of the OSA phenotype in young and healthy adults with overweight/obesity and relate it to some metabolic abnormalities. Since the OSA phenotype was originally identified and described as a condition of aging (Ilich et al., 2020, 2014a) and associated in younger individuals only with some chronic diseases (Guarnotta et al., 2020), the relevance of this study is considerable. This was a nested case-control study conducted on over 2550 participants (age range 18–21 years), who were stratified based on their BMI and percentage of body fat into lean/control group (16% females) and overweight/obese groups (95% females). All body composition parameters (including body water, phase angle, and intramuscular fat) were measured by the bioelectrical impedance analyzer (BIA). The surprising results were that participants with overweight/obesity presented with significantly lower muscle and bone mass compared to lean controls. Although the values of both parameters were within the normal range (masked by weight), they indicated the emergence of the OSA phenotype in this young population. In addition, participants with overweight/obesity had increased serum C-reactive protein (CRP) and evening salivary cortisol concentrations, and a lower phase angle. The greater proinflammatory state due to significantly higher levels of circulating CRP and increased evening salivary cortisol concentrations are known contributors to chronic stress-promoting obesity state and body composition derangements (Ilich et al., 2020). Phase angle, an indicator of cellular health and integrity, was also compromised in this population, implying either increased cell death or a breakdown in the cell membrane permeability, all indicating metabolic derangements during the genesis of OSA. Other results presented in this study were not as clear/convincing. For example, the extracellular water (ECW) (an indicator of inflammation), when expressed as a percent of total body water was higher, while when expressed in liters (volume), was lower in the overweight/obese female group. This relationship could be due to the high discrepancy in the number of participants with regard to both body composition and sex. For example, of a total of 2551 participants, more than half were with overweight/-obesity. Of those, only 5% were males. Consequently, only 16% of females had a normal weight (see Table 2).

Similarly, the developing OSA phenotype was observed in other studies of younger populations with chronic stress, including children with obesity (Corbalán-Tutau et al., 2015). The Stefanaki et al., (Stefanaki et al., 2016) study shows for the first time, that the OSA phenotype may exist even in very young, apparently healthy adults with overweight/obesity and that its presence is associated with worsened metabolic characteristics. This study highlights the importance of body composition analysis in medical practice and in young populations to improve prevention and management and alleviate subsequent health and economic burdens. However, little effort is made in both clinical and research settings to identify OSA development and/or presence in younger age groups.

Describing the OSA syndrome in a more complex way, Perna et al., (Perna et al., 2018) specified two distinct phenotypes based on fat mass location in the body: osteosarcopenic visceral adipose tissue (OSVAT) obesity and osteosarcopenic subcutaneous adipose tissue (OSSAT) obesity. This study was conducted on about 800 elderly subjects (mean age ~80 years, ~69% women). The body fat components were initially identified via DXA measurements of the android region and transformed to the computed tomography fat mass analysis to derive the VAT/SAT ratio. The ratio above 1 was used to identify visceral adiposity and below 1 for subcutaneous adiposity and subsequent OSVAT and OSSAT obesity, respectively. The study revealed a significantly higher risk of fracture (by FRAX assessment) in the OSVAT group and trends to higher levels of inflammation and altered metabolic profile (albumin values below the normal range, higher level of azotemia, and reduced glycemic control), compared to OSSAT. This study highlights the importance of these fat-originated locations within the body in relation to metabolic abnormalities. Such findings are supported by other studies which have shown that visceral adiposity (through the secretion of pro-inflammatory adipokines) is associated with negative effects on both bone and muscle, leading to bone resorption, muscle atrophy, and mitochondrial dysfunction and subsequently causing decreased functional performance and increased fracture risk (Abbatecola et al., 2011; Szlejf et al., 2017).

Interestingly, Perna et al., (Perna et al., 2018) refer to OSA as a "sarcopenia phenotype," although OSA also includes bone loss (osteopenia/osteoporosis) in the presence of adiposity. One of the strengths of the study is that numerous body composition and biochemical parameters were assessed/analyzed, although data for males and females were presented together. It could only be assumed that the authors performed separate analyses for each sex, as the criteria for diagnosing each of the conditions and thus, OSA, are somewhat different for men and women. Additionally, the group that was denoted as "healthy" and presumably used as a control was not explained (in which sense was the group "healthy"). That group consisted of relatively younger participants (mean age 78 years) compared to, for example, the group with OSVAT (mean age 82.4 years); age is a strong risk factor for OSA. Although this study had a small sample size (when participants were stratified into several cohorts), it was the first one to distinguish between two OSA phenotypes by adipose location. Accordingly, it is important to detect/consider the location of adipose tissue, with an emphasis on managing visceral adiposity. More studies like this will help create cut-off values, for examining further characteristics of osteosarcopenic visceral adiposity and its association with other chronic conditions.

The study by Lee (Lee, 2020) is one of many conducted in South Korea using the Korean National Health and Nutrition Survey (KNHANES) database to investigate various aspects of OSA. The KNHANES is similar to the U.S. NHANES, with a large number of generally healthy responders of various ages, thus providing a large database with the possibility of different parameters to be analyzed. The objective was to examine the associations of insulin resistance with different components of body composition, namely osteoporosis-only, sarcopenia-only, or obesity-only, or their combinations (osteopenic obesity, sarcopenic obesity, and ultimately, OSA). The study included 4500 participants (~50% women) with a mean age of ~63 years. The authors used either body fat% (BF%) or BMI to define obesity and the results showed that adiposity was the main factor driving IR, but the relationships depended on the level of adjustments with other factors. Briefly, with BF% classification and no BMI adjustment, the highest association of IR was with obesity and osteopenic obesity, followed by sarcopenic obesity and OSA, followed by osteopenia and sarcopenia, followed by osteosarcopenia (all significantly different). When BMI was used for the classification of obesity, the obesity-coexistent groups also

had stronger associations with IR than non-obesity-coexistent groups, although the associations were not significantly different among the groups. It is clear that IR presents a transitional state between obesity and type 2 diabetes, and it is increasingly recognized as an underlying cause of metabolic syndrome, as well as a risk factor for CVD, nonalcoholic fatty liver disease, and other metabolic abnormalities (Shanik et al., 2008). Although some studies have reported the associations of IR with either bone, muscle, and/or fat tissues (Conte et al., 2018; Kim and Park, 2018), the Lee (Lee, 2020) study is the first one examining that association with OSA. Considering the paucity of previous studies on associations between IR and clinical outcomes, this study provides evidence that obesity is a driving force for IR. Overall, although the OSA phenotype was not characterized by the significantly higher presence of IR, compared to other groups with obesity, this study suggests that IR may be a metabolic abnormality associated with OSA and driven by adiposity, either overt subcutaneous or hidden (ectopic/ fat infiltration).

In a cross-sectional study by Su et al., (Su et al., 2021), the relationship between metabolic syndrome and OSA was examined in almost 3000 middle-aged adults (>50 years) who were screened in the Health Management Center in Taiwan. The participants were stratified into four groups according to the severity of body composition impairment: OSA-0 (control group or no impairment); OSA-1 (the presence of one impairment, either osteoporosis, or sarcopenia or adiposity); OSA-2 (the presence of two impairments, osteopenic adiposity, or sarcopenic adiposity); and OSA-3 (the presence of all three impairments, or OSA). Metabolic syndrome was determined by the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP ATP III) (Huang, 2009) based on five factors (waist circumference, blood pressure, serum glucose, triglycerides, and HDL-cholesterol levels). DXA was used for osteopenia/osteoporosis diagnosis and BF% determination, and grip strength for the diagnosis of sarcopenia. The self-reported data about health issues, supplement intake, physical activity, and other lifestyle characteristics were collected as well. After adjustment for various confounders, the results demonstrated a significant positive relationship between metabolic syndrome and OSA-2 and OSA-3. This is the first study showing that the combination of body composition impairments and particularly OSA, is related to metabolic syndrome. Previous studies investigating metabolic syndrome showed positive relationships only with individual impaired body composition conditions; for example, with osteoporosis (Wani et al., 2019), sarcopenia (Park et al., 2019), or obesity and age (Dominguez and Barbagallo, 2016). Other research on this topic is mixed and, in most cases, also includes employment type in relation to individual body composition impairments and metabolic syndrome. For example, Bertoni et al., (Bertoni et al., 2018) showed that retired individuals with metabolic syndrome had diminished muscle strength. This is somewhat expected as these individuals are older and less active. On the contrary, another study reported that retired or those individuals working part-time (with metabolic syndrome) had a lower likelihood of having some of the body composition impairments (Dominguez and Barbagallo, 2016), compared to those working full-time. Such opposing outcomes probably depend on the type of work. While the type of work was not assessed in the Su et al., (Su et al., 2021) study, future studies are needed to investigate how employment type and retirement duration, with or without metabolic syndrome, affect OSA phenotype. The Su et al., (Su et al., 2021) study is informative but due to the way the groups were formed and analyzed, it was not possible to distinguish which specific body composition impairments were present in "OSA-1" and "OSA-2" groups, and more importantly how different body composition components, individually and/or in combination, were associated with metabolic syndrome. Further studies are needed to investigate the relationship between metabolic syndrome and the OSA phenotype.

The study by Kashiwagi et al., (Kashiwagi et al., 2021) included 614 patients (mean age ~67 years, 55% females) with non-alcohol fatty liver disease (NAFLD) who came for a health checkup at the University Hospital in Japan. Different body composition phenotypes were identified, and several groups of patients were compared, including those with non-obese (BMI<25 kg/m^2) NAFLD and obese (BMI>25 kg/m^2) NAFLD. The identification of osteopenia/osteoporosis followed the Japanese criteria, using the young adults' mean BMD values (%YAM) as cutoffs (Soen et al., 2013). The authors also used the Asian Working Group for Sarcopenia (AWGS) criteria for sarcopenia diagnosis (Chen et al., 2014). Both are more appropriate for this population, although they are not always followed in studies with Asian participants. The results are interesting because they revealed that the prevalence of OSA (although generally low) for both females and males was the highest in those with non-obese NAFLD (9% and 1%, respectively). The proportion of obese NAFLD was the highest in the obesity-alone group in both sexes, yet there were no cases of OSA in that group (that finding was not discussed by the authors). It could reflect the "U" curve relationship between obesity and bone/muscle components and even more so the hidden fat which is harder to uncover. The results may also be confounded by the obesity paradox (Amundson et al., 2010) where those with obesity fared better on various outcomes compared to those who were leaner. Additionally, this might signify yet another indicator of BMI's inadequacy as a measure of obesity (Hu et al., 2023; Ilich et al., 2020). Although the incidence of non-obese NAFLD did not change with age, the prevalence of OSA gradually increased with age, suggesting that non-obese NAFLD could be a risk factor for OSA, or vice versa. Possibly, the unfavorable body composition influenced the emergence of NAFLD as a metabolic disease (Ristic-Medic et al., 2022), but a cause or consequence here is very hard to establish. Although the sample size was relatively large, the statistical power might have not been reached for some analyses due to the eight groups being compared. Therefore, the overall conclusions of the study need to be taken cautiously. Nevertheless, this is the first study to examine the associations between OSA and NAFLD and especially the non-obese NAFLD in middle-aged and older individuals. Besides the previously reported strong association between NAFLD and metabolic syndrome, other studies reported the association with either sarcopenia, sarcopenic obesity, and/or obesity only (Bhanji et al., 2017; Kim and Choi, 2019; Wijarnpreecha et al., 2019), all indicating a strong connection between NAFLD and body composition. Since approximately 10–20% of individuals are diagnosed (also based on BMI<25 kg/m^2) with non-obese NAFLD and their metabolic risk levels are between healthy individuals and those with obese NAFLD (Wattacheril and Sanyal, 2016), this segment of the population should get more attention in clinical care, despite the lack of the overt overweight/obesity presence. In other words, this is another study that highlights the importance of fat location in the deterioration of bone and muscle. In this case, fat in the liver would be considered ectopic fat, however, obesity in this study was determined by BMI.

Both Cvijetić et al., and Keser et al., (Cvijetić et al., 2023; Keser et al., 2021) studies are similar yet very important as the researchers assessed body composition, nutritional status, and other health outcomes in residents of several nursing homes. All three body composition components were measured by BIA and both studies revealed a high prevalence of OSA. The Keser et al., study was smaller (n=69 women, n=15 men, age 65–95 years) and was conducted in only one nursing home (it started at the beginning of 2020 and was halted due to the COVID-19 pandemic). The results showed that dietary intake and nutritional status were below both European and U.S. recommendations (European Food Safety Authority. Nutrient Recommendations: Dietary Reference Values DRV n.d.) in all participants. The residents with OSA (>50% prevalence both in women and men) had significantly higher ECW, indicating a heightened inflammatory state, as well as lower phase angle, indicating lower cell integrity and muscle quality. It has been shown that there is a significant difference in phase angle between healthy and diseased states and that it decreases with worsened clinical conditions (Bellido et al., 2023; Kang et al., 2022; Shin et al., 2022). Similarly, intracellular water loss and the resulting increase in ECW disturbs muscle function and may result in sarcopenia, which was

confirmed in other studies that reported higher ECW% and/or lower phase angle (Bian et al., 2017; Doumit et al., 2014; Tanaka et al., 2020). One of the advantages of BIA (over BMI alone, for example) is that BIA can differentiate between the degree of body fat and body cell mass, and it can also be used for prognostic purposes for some chronic diseases, malnutrition, and inflammation (Gupta et al., 2004). However, the protocol for the measurements must be strictly followed (e.g., room temperature, electrode placement, exercise level, food intake, and hydration status of participants) (Kushner et al., 1996). Non-adherence to any of the protocol measures may lead to inaccuracies and subsequent inconsistent results.

The Cvijetić et al., (Cvijetić et al., 2023) study was conducted in six nursing homes just after COVID-19 pandemic restrictions were lifted, therefore, it was possible to assess the COVID-19 survivors as well. The study included 296 women and 69 men, aged >80 years. There was no difference in OSA prevalence (overall ~70%) or nutritional status in those who had COVID-19 compared to those who did not. However, a significantly higher ECW and lower phase angle were confirmed among the residents with OSA compared to those without. Additionally, a lower bone mass, and a higher intramuscular adipose tissue, were noted in residents with OSA phenotype compared to those with less severe body composition impairments. Surprisingly, the results from Cvijetić et al., (Cvijetić et al., 2023) study did not show any impact of COVID-19 infection on OSA prevalence or weight/body composition. This is in contrast to the study in French nursing homes (Ngadiarti et al., 2022), where those infected with COVID-19 experienced significant weight loss. Other studies also revealed worsened health in nursing homes in different countries during the COVID-19 pandemic (Courtois-Amiot et al., 2023). Despite the limitations of both studies (Cvijetić et al., 2023; Keser et al., 2021) (e.g., cross-sectional nature, limited number of participants), they revealed significantly poorer health status and higher inflammatory state in nursing home residents with OSA phenotype. More studies conducted in critical populations (like nursing home residents), where full body composition, as a contributor to poor health is assessed, are needed.

The Nie et al., (Nie et al., 2022) study is another one investigating some of the inflammatory markers in patients with body composition impairments, including OSA. Namely, the complete blood cell-derived inflammatory indices, including white blood cells (WBC), systemic inflammation response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), aggregate inflammation systemic index (AISI), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), were measured in apparently healthy men and women receiving annual check-ups at Harbin Medical University, China. Participants were divided into four groups based on the body composition impairments, including OSO-0 (no impairments), OSO-1 (either osteoporosis, or sarcopenia or adiposity), OSO-2 (either osteosarcopenia or osteopenic adiposity or sarcopenic adiposity), and OSO-3 (all three conditions or OSA). The results are well presented and revealed statistically significant differences (by paired analyses) in WBC, SIRI, AISI, NLR, PLR, and LMR among the four groups, where the higher number of body composition impairments resulted in worse outcomes, with the OSO-3 group being the worst. Such relationships were also confirmed in the logistic regression, where the values in the OSO-0 group were used as a normal reference. After adjustment for numerous confounders, SIRI, AISI, NLR, and PLR were positively correlated with impairments in each group and negatively with LMR. In this analysis too, the OSO-3 group fared the worst. This is a relevant study, showing that blood cell count-derived inflammatory parameters could serve as possible markers for OSA, as well as for other body composition impairments. The advantage of these indices is that they can be easily measured in most clinical settings and indicate low-grade chronic inflammation (Zinellu et al., 2020). So far, these markers have been typically used to evaluate inflammatory processes in some chronic diseases (e.g., during cancer therapy), and their use for osteoporosis, sarcopenia, and/or obesity is limited (Tuttle et al., 2020; Yilmaz et al., 2014), but could be promising for OSA, based on the results from the Nie et al., study (Nie et al., 2022). Obviously, more research must be conducted before these markers can be used for the evaluation of body composition impairments and before they can be substituted for some other inflammatory markers (e.g., CRP). Unfortunately, the stratification of participants into groups in this study precludes the distinction of the specific impairments in OSA-1 and OSO-2 groups, as was already discussed above in the study by (Su et al., 2021), where a similar way of stratification was used. Importantly, these results showed that the OSA group was associated with an elevated inflammatory state, compared to other groups and the healthy controls.

Moroni et al., (Moroni et al., 2023) investigated the association of each of the OSA components with various metabolic and health risk factors in a large pool of participants (n=1510, 72.9% females, >18 years) attending a rehabilitation unit at the University of Pavia, Italy. Unfortunately, the participants' health or demographic status was not described and neither inclusion/exclusion criteria were listed. Therefore, it is hard to compare various phenotypes, especially when participants of a wide age range are included. Nevertheless, this study is worth reviewing since numerous variables were measured and included in the analyses. The participants were divided into three age subgroups ("Adult" < 65 years; "Oldest" 66–84 years; "Oldest Old" > 84 years) and the most prevalent body composition impairment for the entire population was sarcopenia (17%), while the prevalence of OSA was 1.9%. Furthermore, and in contrast to other studies, the OSA prevalence was the highest in the "Adult" and "Oldest" males (4.3% and 4.5%, respectively). Other surprising results, when compared to most other studies, were that the OSA prevalence was lower in females than in males in each age category. Gamma-glutamyl transferase (gGT, an indicator of hepatic health) and hyperglycemia were the only serum biomarkers positively associated with OSA. The meaning of this relationship was not discussed in the article, but elevated levels of each could indicate an increased inflammatory state or some other health problems. For example, gGT may increase with high alcohol consumption and liver damage, leading to free radical production and glutathione depletion, particularly in the presence of higher serum iron (Whitfield, 2001). There are also some indications that serum gGT is linked to the risk of coronary heart disease, stroke, and type 2 diabetes. Hyperglycemia would also fit into this model. However, since not much is known about the health status and/or alcohol use of the participants in the Moroni et. al., (Moroni et al., 2023) study, it is hard to speculate. Due to other limitations (e.g., mostly females, wide age range, and heterogenous age subgroups, as well as a very low prevalence of OSA), the results need to be interpreted with caution.

5. Limitations

Limitations of this review are contingent on the limitations of the evaluated studies, which were discussed in Sections 4.1 and 4.2. Briefly, most of the studies were observational, cross-sectional, or retrospective. Randomized controlled trials were absent, except for one (Ilich et al., 2022). The limited number of studies with measures of all three body composition compartments was a major obstacle in including studies with a specific cardiovascular disease, diabetes mellitus, or autoimmune diseases (to name just a few) and their association with OSA. This was somewhat contrary to our expectations (because the technology was available in most cases) and made this review restricted. Additionally, among the 15 studies reviewed, a few did not meet some of the common methodological standards, such as listing the inclusion/exclusion criteria for the recruitment, the participants' demographics were not described, or the sample size was too small to achieve adequate statistical power. In several studies, the stratification of participants into groups based on body composition impairments was such that it was not possible to determine which impairments were present in each group. Some studies did not have a control group for the comparisons. Still, the biggest drawback was that different criteria and cut-offs were used for the diagnosis of the impairment for each tissue (except bones), thus

leading to a wide range of OSA prevalence. That was particularly true for the level of obesity and the lack of measurements of visceral and infiltrated fat. While studies have been done in both Americas continents, Europe, the Middle East, and Asia and included the respective populations, there were no studies conducted on the African continent and in African American individuals.

6. Summary and implications for future research

This comprehensive review revealed that CVD and metabolic disorders are accompanied by impaired body composition and that in most cases, the presence of OSA was associated with worse disease outcomes, compared to the conditions where only one or two impairments were present or compared to the individuals with a healthy body composition but the same disorder. Nevertheless, the initial questions we posed about the cause-and-effect relationships between OSA and examined disorders could be answered only partially, due to the limited research and most of the studies being of a cross-sectional nature. However, the scientific knowledge about numerous biochemical processes occurring in each disorder and in the OSA phenotype manifestations leads us to believe that some cardiometabolic disorders are worsened by OSA and vice versa via a positive feedback loop. Specifically, that could be speculated between OSA and hypertension, dyslipidemia, and several inflammatory markers.

Briefly, the analysis of OSA and CVD risk factors (Table 1) revealed the following: 1) Two Chinese studies reported worse cases of dyslipidemia and blood pressure/hypertension in patients with OSA compared to those without, implying OSA as a possible trigger or vice versa; 2) In contrast, hypertension was less common in participants with OSA in the Iranian older population compared to those without OSA; 3) Japanese patients hospitalized for various CVD issues had a higher prevalence of OSA compared to their community-dwelling counterparts; 4) Among Caucasian women with overweight/obesity, those with OSA phenotype had significantly worse blood pressure, serum lipid profile and adipokines compared to their counterparts with overweight/obesity-only; 5) Younger Brazilian patients with severe obesity waiting for bariatric surgery exhibited signs of rapid OSA development and those with higher abdominal fat also had higher total and LDL-cholesterol and fasting glucose, but lower HDL-cholesterol and serum vitamin D levels. This highlights the importance of body fat distribution or fat allocation when assessing associated health outcomes in young individuals with severe obesity. Overall, the relatively strong associations between OSA and some CVD risk factors suggest common mechanisms, although the data do not show if OSA triggers CVD risk factors, or if CVD risk factors trigger OSA. Nevertheless, these relationships could be bidirectional, each reinforcing the other, but more work is needed to elucidate the mechanisms.

Regarding OSA and metabolic abnormalities (Table 2), the following was noted: 1) Increased inflammatory markers (CRP, ECW, phase angle) were present in a very young Italian population with a developing OSA phenotype; 2) Poor metabolic health and higher fracture risk was observed in another Italian study with older adults having visceral OSA, compared to those with subcutaneous OSA and those without OSA; 3) Insulin resistance was related mostly to the presence of obesity and not necessarily to the OSA phenotype in older Korean population; 4) A significant positive association (in females only) was found between OSA and NAFLD, suggesting that the latter could be a risk factor for OSA, or possibly that the unfavorable body composition influenced the emergence of NAFLD in Japanese older patients; 5) Two studies conducted among Croatian nursing homes residents revealed a very high prevalence of OSA and accompanying poorer health and metabolic status (higher ECW, lower phase angle) in those with OSA; 6) The blood cell count-derived inflammatory indices in apparently healthy Chinese older adults indicated that those with the OSA phenotype had the highest level of the examined markers, compared to those in other body composition groups; 7) The results from the study in middle-aged and older Italian residents, although revealing the positive relationship between OSA and gGT and hyperglycemia, are inconclusive due to very low OSA prevalence and other limitations. These results indicate that OSA contributes to metabolic abnormalities and/or that the presence of OSA may be a result of metabolic abnormalities already present in bone, muscle, and adipose tissues. Overall, there is a great need for more research about the metabolic processes during OSA phenotype development, as well as how OSA affects metabolic pathways, as those relationships may sustain each other in a vicious cycle.

This review also revealed several other important points regarding OSA and identified the existing gaps, as well as uncovered the future research directions (some of them addressed recently (Vucic et al., 2023). These include:

1) The absence of consensus for the diagnostic criteria and officially approved indications for the treatment and management of OSA still remains the biggest obstacle in identifying individuals with OSA phenotype.
   - Unfortunately, the universal and regulated/approved guidelines are also nonexistent for sarcopenia/sarcopenic obesity (Fielding, 2024), while the cut-offs for obesity diagnosis vary as well.
2) From a clinical point of view, all three body composition compartments should be measured by standardized technologies using regulated diagnostic criteria to identify OSA and confirm its relationship with chronic diseases in diverse groups of older and younger individuals.
   - In such scenarios, patients may be classified into smaller, more homogeneous phenotypes with potential implications for therapeutic plans.
3) There should be multidisciplinary approaches for body composition assessment in the management and treatment of cardiometabolic diseases.
   - In that context, the rapid advances in medicine and medical technology may offer new opportunities, particularly in the development of new or use of some existing blood or other biomarkers for OSA identification.
4) The physiological mechanisms that link body composition with clinical events are multi-factorial and further evidence-based research, in the form of randomized clinical trials and large-scale prospective studies, is needed to determine if the relations between body composition and clinical endpoints are both causal and reversible through intervention.
   - Such research could determine the risks related to OSA syndrome more comprehensively as well as confirm the efficacy of diagnostic and treatment solutions.

CRediT authorship contribution statement

J.Z.I., O.J.K., and V.V. designed the review. V.V., D.RM., S.P. and A. A. performed the literature search, and B.P. and J.Z.I. extracted the data. J.Z.I., O.J.K., V.V., and N.V. drafted the manuscript. All authors participated in the manuscript revisions and accepted the final version.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data Availability

No data were used for the research described in the article.

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References

Aaron, N., Costa, S., Rosen, C.J., Qiang, L., 2022. The implications of bone marrow adipose tissue on inflammaging. Front. Endocrinol. (Lausanne). 13, 853765 https://doi.org/10.3389/fendo.2022.853765.

Abbatecola, A.M., Paolisso, G., Fattoretti, P., Evans, W.J., Fiore, V., Dicioccio, L., Lattanzio, F., 2011. Discovering pathways of sarcopenia in older adults: a role for insulin resistance on mitochondria dysfunction. J. Nutr. Health Aging 15, 890–895. https://doi.org/10.1007/s12603-011-0366-0.

Abramowitz, M.K., Hall, C.B., Amodu, A., Sharma, D., Androga, L., Hawkins, M., 2018. Muscle mass, BMI, and mortality among adults in the United States: a population-based cohort study. PLoS One 13, e0194697. https://doi.org/10.1371/journal.pone.0194697.

Aggarwal, R., Yeh, R.W., Joynt Maddox, K.E., Wadhera, R.K., 2023. Cardiovascular risk factor prevalence, treatment, and control in US Adults Aged 20 to 44 Years, 2009 to March 2020. JAMA 329, 899–909. https://doi.org/10.1001/jama.2023.2307.

Ahmadinezhad, M., Mansournia, M.A., Fahimfar, N., Shafiee, G., Nabipour, I., Sanjari, M., Khalagi, K., Mansourzadeh, M.J., Larijani, B., Ostovar, A., 2023. Prevalence of osteosarcopenic obesity and related factors among Iranian older people: bushehr elderly health (BEH) program. Arch. Osteoporos. 18, 137. https://doi.org/10.1007/s11657-023-01340-9.

Amundson, D.E., Djurkovic, S., Matwiyoff, G.N., 2010. The obesity paradox. Crit. Care Clin. 26, 583–596. https://doi.org/10.1016/j.ccc.2010.06.004.

Batsis, J.A., Mackenzie, T.A., Barre, L.K., Lopez-Jimenez, F., Bartels, S.J., 2014. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. Eur. J. Clin. Nutr. 68, 1001–1007. https://doi.org/10.1038/ejcn.2014.117.

Bellido, D., García-García, C., Talluri, A., Lukaski, H.C., García-Almeida, J.M., 2023. Future lines of research on phase angle: strengths and limitations. Rev. Endocr. Metab. Disord. 24, 563–583. https://doi.org/10.1007/s11154-023-09803-7.

Bertoni, M., Maggi, S., Weber, G., 2018. Work, retirement, and muscle strength loss in old age. Health Econ. 27, 115–128. https://doi.org/10.1002/hec.3517.

Bhanji, R.A., Narayanan, P., Allen, A.M., Malhi, H., Watt, K.D., 2017. Sarcopenia in hiding: the risk and consequence of underestimating muscle dysfunction in nonalcoholic steatohepatitis. Hepatology 66, 2055–2065. https://doi.org/10.1002/hep.29420.

Bian, A.-L., Hu, H.-Y., Rong, Y.-D., Wang, J., Wang, J.-X., Zhou, X.-Z., 2017. A study on the relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-α. Eur. J. Med. Res. 22, 25. https://doi.org/10.1186/s40001-017-0266-9.

Brownbill, R.A., Ilich, J.Z., 2006. Lipid profile and bone paradox: higher serum lipids are associated with higher bone mineral density in postmenopausal women. J. Women's. Health (Larchmt.). 15, 261–270. https://doi.org/10.1089/jwh.2006.15.261.

Canoy, D., Harvey, N.C., Prieto-Alhambra, D., Cooper, C., Meyer, H.E., Åsvold, B.O., Nazarzadeh, M., Rahimi, K., 2022. Elevated blood pressure, antihypertensive medications, and bone health in the population: revisiting old hypotheses and exploring future research directions. Osteoporos. Int. 33, 315–326. https://doi.org/10.1007/s00198-021-06190-0.

Cappuccio, F.P., Kalaitzidis, R., Duneclift, S., Eastwood, J.B., 2000. Unraveling the links between calcium excretion, salt intake, hypertension, kidney stones, and bone metabolism. J. Nephrol. 13, 169–177.

Cappuccio, F.P., Meilahn, E., Zmuda, J.M., Cauley, J.A., 1999. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of osteoporotic fractures research group. Lancet (Lond., Engl.) 354, 971–975. https://doi.org/10.1016/s0140-6736(99)01437-3.

Carsote, M., Albu, S.E., Gherigian, A., Valea, A., 2016. Particular types of non-age related sarcopenia: osteosarcopenic obesity and malignancy—associated muscle waste (a mini-review). Arch. Balk. Med. Union 51, 369–372.

Chen, X., Kong, C., Yu, H., Gong, Jiangu, Lan, L., Zhou, L., Gong, Jichun, Liu, P., Xu, L., Deng, Q., 2019. Association between osteosarcopenic obesity and hypertension among four minority populations in China: a cross-sectional study. BMJ Open 9, e026818. https://doi.org/10.1136/bmjopen-2018-026818.

Chen, L.-K., Liu, L.-K., Woo, J., Assantachai, P., Auyeung, T.-W., Bahyah, K.S., Chou, M.-Y., Chen, L.-Y., Hsu, P.-S., Krairit, O., Lee, J.S.W., Lee, W.-J., Lee, Y., Liang, C.-K., Limpawattana, P., Lin, C.-S., Peng, L.-N., Satake, S., Suzuki, T., Won, C.W., Wu, C.-H., Wu, S.-N., Zhang, T., Zeng, P., Akishita, M., Arai, H., 2014. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J. Am. Med. Dir. Assoc. 15, 95–101. https://doi.org/10.1016/j.jamda.2013.11.025.

Conte, C., Epstein, S., Napoli, N., 2018. Insulin resistance and bone: a biological partnership. Acta Diabetol. 55, 305–314. https://doi.org/10.1007/s00592-018-1101-7.

Corbalán-Tutau, M.D., Gómez-Abellán, P., Madrid, J.A., Canteras, M., Ordovás, J.M., Garaulet, M., 2015. Toward a chronobiological characterization of obesity and metabolic syndrome in clinical practice. Clin. Nutr. 34, 477–483. https://doi.org/10.1016/j.clnu.2014.05.007.

Courtois-Amiot, P., Allart, H., de Cathelineau, C., Legué, C., Eischen, P., Chetaille, F., Lepineux, D., Raynaud-Simon, A., Sanchez, M., 2023. Covid-19 as an independent risk factor for weight loss in older adults living in nursing homes. Gerontology. https://doi.org/10.1159/000529357.

Cvijetić, S., Keser, I., Boschiero, D., Ilich, J.Z., 2023. Osteosarcopenic adiposity and nutritional status in older nursing home residents during the COVID-19 Pandemic. Nutrients 15. https://doi.org/10.3390/nu15010227.

De Lorenzo, A., Itani, L., Gualtieri, P., Pellegrini, M., El Ghoch, M., Di Renzo, L., 2024. Association between sarcopenia and reduced bone mass: is osteosarcopenic obesity a new phenotype to consider in weight management settings? Life 14. https://doi.org/10.3390/life14010021.

Dominguez, L.J., Barbagallo, M., 2016. The biology of the metabolic syndrome and aging. Curr. Opin. Clin. Nutr. Metab. Care 19, 5–11. https://doi.org/10.1097/MCO.0000000000000243.

Doumit, J.H., Nasser, R.N., Hanna, D.R., 2014. Nutritional and health status among nursing home residents in Lebanon: a comparison across gender in a national cross-sectional study. BMC Public Health 14, 629. https://doi.org/10.1186/1471-2458-14-629.

Endo, T., Akai, K., Kijima, T., Kitahara, S., Abe, T., Takeda, M., Nabika, T., Yano, S., Isomura, M., 2021. An association analysis between hypertension, dementia, and depression and the phases of pre-sarcopenia to sarcopenia: A cross-sectional analysis. PLoS One 16, e0252784. https://doi.org/10.1371/journal.pone.0252784.

European Food Safety Authority. Nutrient Recommendations: Dietary Reference Values (DRV). [WWW Document], n.d. URL https://www.efsa.europa.eu/en/interactive-pages/drvs.

Fielding, R.A., 2024. Sarcopenia: an emerging syndrome of advancing age. Calcif. Tissue Int. https://doi.org/10.1007/s00223-023-01175-z.

Forte, Y.S., Renovato-Martins, M., Barja-Fidalgo, C., 2023. Cellular and molecular mechanisms associating obesity to bone loss. Cells 12. https://doi.org/10.3390/cells12040521.

Garvey, W.T., 2022. Is obesity or adiposity-based chronic disease curable: the set point theory, the environment, and second-generation medications. Endocr. Pract. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol. 28, 214–222. https://doi.org/10.1016/j.eprac.2021.11.082.

Genton, L., Karsegard, V.L., Chevalley, T., Kossovsky, M.P., Darmon, P., Pichard, C., 2011. Body composition changes over 9 years in healthy elderly subjects and impact of physical activity. Clin. Nutr. 30, 436–442. https://doi.org/10.1016/j.clnu.2011.01.009.

German, J.B., Gibson, R.A., Krauss, R.M., Nestel, P., Lamarche, B., van Staveren, W.A., Steijns, J.M., de Groot, L.C., Lock, A.L., Destaillats, F., 2009. A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. Eur. J. Nutr. 48, 191–203. https://doi.org/10.1007/s00394-009-0002-5.

Ghavipour, M., Sotoudeh, G., Tavakoli, E., Mowla, K., Hasanzadeh, J., Mazloom, Z., 2017. Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. Eur. J. Clin. Nutr. 71, 92–96. https://doi.org/10.1038/ejcn.2016.151.

Giosuè, A., Calabrese, I., Vitale, M., Riccardi, G., Vaccaro, O., 2022. Consumption of dairy foods and cardiovascular disease: a systematic review. Nutrients 14. https://doi.org/10.3390/nu14040831.

Guarnotta, V., Prinzi, A., Pitrone, M., Pizzolanti, G., Giordano, C., 2020. Circulating Irisin levels as a marker of osteosarcopenic-obesity in cushing's disease. Diabetes Metab. Syndr. Obes. 13, 1565–1574. https://doi.org/10.2147/DMSO.S249090.

Gupta, D., Lammersfeld, C.A., Burrows, J.L., Dahlk, S.L., Vashi, P.G., Grutsch, J.F., Hoffman, S., Lis, C.G., 2004. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. Am. J. Clin. Nutr. 80, 1634–1638. https://doi.org/10.1093/ajcn/80.6.1634.

Hsia, J., Heiss, G., Ren, H., Allison, M., Dolan, N.C., Greenland, P., Heckbert, S.R., Johnson, K.C., Manson, J.E., Sidney, S., Trevisan, M., 2007. Calcium/vitamin D supplementation and cardiovascular events. Circulation 115, 846–854. https://doi.org/10.1161/CIRCULATIONAHA.106.673491.

Hu, K., Deya Edelen, E., Zhuo, W., Khan, A., Orbegoso, J., Greenfield, L., Rahi, B., Griffin, M., Ilich, J.Z., Kelly, O.J., 2023. Understanding the consequences of fatty bone and fatty muscle: how the osteosarcopenic adiposity phenotype uncovers the deterioration of body composition. Metabolites 13. https://doi.org/10.3390/metabo13101056.

Huang, P.L., 2009. A comprehensive definition for metabolic syndrome. Dis. Model. Mech. 2, 231–237. https://doi.org/10.1242/dmm.001180.

Ilich, J.Z., 2021. Osteosarcopenic adiposity syndrome update and the role of associated minerals and vitamins. Proc. Nutr. Soc. 80, 344–355. https://doi.org/10.1017/S0029665121000586.

Ilich, J.Z., Gilman, J.C., Cvijetic, S., Boschiero, D., 2020. Chronic stress contributes to osteosarcopenic adiposity via inflammation and immune modulation: the case for more precise nutritional investigation. Nutrients 12. https://doi.org/10.3390/nu12040989.

Ilich, J.Z., Inglis, J.E., Kelly, O.J., McGee, D.L., 2015. Osteosarcopenic obesity is associated with reduced handgrip strength, walking abilities, and balance in postmenopausal women. Osteoporos. Int. a J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 26, 2587–2595. https://doi.org/10.1007/s00198-015-3186-y.

Ilich, J.Z., Kelly, O.J., Inglis, J.E., Panton, L.B., Duque, G., Ormsbee, M.J., 2014a. Interrelationship among muscle, fat, and bone: connecting the dots on cellular, hormonal, and whole body levels. Ageing Res. Rev. 15, 51–60. https://doi.org/10.1016/j.arr.2014.02.007.

Ilich, J.Z., Kelly, O.J., Kim, Y., Spicer, M.T., 2014b. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. Arh. Hig. Rada Toksikol. 65, 139–148. https://doi.org/10.2478/10004-1254-65-2014-2541.

Ilich, J.Z., Kelly, O.J., Liu, P.-Y., Shin, H., Kim, Y., Chi, Y., Wickrama, K.K.A.S., Colic-Baric, I., 2019. Role of calcium and low-fat dairy foods in weight-loss outcomes

revisited: results from the randomized trial of effects on bone and body composition in overweight/obese postmenopausal women. Nutrients 11. https://doi.org/10.3390/nu11051157.
Ilich, J.Z., Liu, P.-Y., Shin, H., Kim, Y., Chi, Y., 2022. Cardiometabolic indices after weight loss with calcium or dairy foods: secondary analyses from a randomized trial with overweight/obese postmenopausal women. Nutrients 14. https://doi.org/10.3390/nu14051082.
JafariNasabian, P., Inglis, J.E., Reilly, W., Kelly, O.J., Ilich, J.Z., 2017. Aging human body: changes in bone, muscle, and body fat with consequent changes in nutrient intake. J. Endocrinol. 234, R37–R51. https://doi.org/10.1530/JOE-16-0603.
Kang, S.H., Do, J.Y., Kim, J.C., 2022. Impedance-derived phase angle is associated with muscle mass, strength, quality of life, and clinical outcomes in maintenance hemodialysis patients. PLoS One 17, e0261070. https://doi.org/10.1371/journal.pone.0261070.
Kashiwagi, K., Takayama, M., Ichikawa, H., Takaishi, H., Iwao, Y., Kanai, T., 2021. A significant association of non-obese non-alcoholic fatty liver disease with osteosarcopenic obesity in females 50 years and older. Clin. Nutr. ESPEN 42, 166–172. https://doi.org/10.1016/j.clnesp.2021.01.045.
Kelles, S.M.B., Diniz, M. de F.H.S., Machado, C.J., Barreto, S.M., 2015. The profile of patients undergoing bariatric surgery in the Brazilian Unified National Health System: a systematic review. Cad. Saude Publica 31, 1587–1601. https://doi.org/10.1590/0102-311×00022714.
Kelly, O.J., Gilman, J.C., Boschiero, D., Ilich, J.Z., 2019. Osteosarcopenic obesity: current knowledge, revised identification criteria and treatment principles. Nutrients 11. https://doi.org/10.3390/nu11040747.
Keser, I., Cvijetić, S., Ilić, A., Colić Barić, I., Boschiero, D., Ilich, J.Z., 2021. Assessment of body composition and dietary intake in nursing-home residents: could lessons learned from the COVID-19 Pandemic Be Used to Prevent Future Casualties in Older Individuals? Nutrients 13. https://doi.org/10.3390/nu13051510.
Kim, H., Banerjee, N., Ivanov, I., Pfent, C.M., Prudhomme, K.R., Bisson, W.H., Dashwood, R.H., Talcott, S.T., Mertens-Talcott, S.U., 2016. Comparison of anti-inflammatory mechanisms of mango (Mangifera indica L.) and pomegranate (Punica granatum L.) in a preclinical model of colitis. Mol. Nutr. Food Res. 60, 1912–1923. https://doi.org/10.1002/mnfr.201501008.
Kim, J.A., Choi, K.M., 2019. Sarcopenia and fatty liver disease. Hepatol. Int. 13, 674–687. https://doi.org/10.1007/s12072-019-09996-7.
Kim, S., Lewis, J.R., Baur, L.A., Macaskill, P., Craig, J.C., 2017. Obesity and hypertension in Australian young people: results from the Australian Health Survey 2011-2012. Intern. Med. J. 47, 162–169. https://doi.org/10.1111/imj.13298.
Kim, K., Park, S.M., 2018. Association of muscle mass and fat mass with insulin resistance and the prevalence of metabolic syndrome in Korean adults: a cross-sectional study. Sci. Rep. 8, 2703. https://doi.org/10.1038/s41598-018-21168-5.
Kirk, E.P., Klein, S., 2009. Pathogenesis and pathophysiology of the cardiometabolic syndrome. J. Clin. Hypertens. (Greenwich). 11, 761–765. https://doi.org/10.1111/j.1559-4572.2009.00054.x.
Kurose, S., Nishikawa, S., Nagaoka, T., Kusaka, M., Kawamura, J., Nishioka, Y., Sato, S., Tsutsumi, H., Kimura, Y., 2020. Prevalence and risk factors of sarcopenia in community-dwelling older adults visiting regional medical institutions from the Kadoma Sarcopenia Study. Sci. Rep. 10, 19129 https://doi.org/10.1038/s41598-020-76185-0.
Kushner, R.F., Gudivaka, R., Schoeller, D.A., 1996. Clinical characteristics influencing bioelectrical impedance analysis measurements. Am. J. Clin. Nutr. 64, 423S–427S. https://doi.org/10.1093/ajcn/64.3.423S.
Larsson, S.C., Orsini, N., Wolk, A., 2013. Dietary calcium intake and risk of stroke: a dose-response meta-analysis. Am. J. Clin. Nutr. 97, 951–957. https://doi.org/10.3945/ajcn.112.052449.
Lee, K., 2020. Association of osteosarcopenic obesity and its components: osteoporosis, sarcopenia, and obesity with insulin resistance. J. Bone Miner. Metab. 38, 695–701. https://doi.org/10.1007/s00774-020-01104-2.
Lewiecki, E.M., Lane, N.E., 2008. Common mistakes in the clinical use of bone mineral density testing. Nat. Clin. Pract. Rheumatol. 4, 667–674. https://doi.org/10.1038/ncprheum0928.
Li, Z., Yu, Y., 2012. An epidemiologic study on hypertension in the aged population in Miao nationality in Duyuan city (Y.S.). J. Guiyang Med. Coll. 5.
Liu, C., Liu, N., Xia, Y., Zhao, Z., Xiao, T., Li, H., 2022. Osteoporosis and sarcopenia-related traits: a bi-directional Mendelian randomization study. Front. Endocrinol. (Lausanne). 13, 975647 https://doi.org/10.3389/fendo.2022.975647.
Liu, Z., Zhu, C., 2023. The causal relationship between insulin resistance and sarcopenia. Diabetol. Metab. Syndr. 15, 46. https://doi.org/10.1186/s13098-023-01022-z.
Lu, J., Lu, Y., Wang, X., Li, X., Linderman, G.C., Wu, C., Cheng, X., Mu, L., Zhang, H., Liu, J., Su, M., Zhao, H., Spatz, E.S., Spertus, J.A., Masoudi, F.A., Krumholz, H.M., Jiang, L., 2017. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet (Lond., Engl.) 390, 2549–2558. https://doi.org/10.1016/S0140-6736(17)32478-9.
Ma, Y., Zhang, W., Han, P., Kohzuki, M., Guo, Q., 2020. Osteosarcopenic obesity associated with poor physical performance in the elderly chinese community. Clin. Interv. Aging 15, 1343–1352. https://doi.org/10.2147/CIA.S257739.
Mechanick, J.I., Hurley, D.L., Garvey, W.T., 2017. Adiposity-based chronic disease as a new diagnostic term: the american association of clinical endocrinologists and american college of endocrinology position statement. Endocr. Pract. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol. 23, 372–378. https://doi.org/10.4158/EP161688.PS.
Mitchell, W.K., Williams, J., Atherton, P., Larvin, M., Lund, J., Narici, M., 2012. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front. Physiol. 3, 260. https://doi.org/10.3389/fphys.2012.00260.
Mo, D., Hsieh, P., Yu, H., Zhou, L., Gong, J., Xu, L., Liu, P., Chen, G., Chen, Z., Deng, Q., 2018. Osteosarcopenic obesity and its relationship with dyslipidemia in women from different ethnic groups of China. Arch. Osteoporos. 13, 65. https://doi.org/10.1007/s11657-018-0481-1.
Moroni, A., Perna, S., Azzolino, D., Gasparri, C., Zupo, R., Micheletti Cremasco, M., Rondanelli, M., 2023. Discovering the individualized factors associated with sarcopenia and sarcopenic obesity phenotypes-a machine learning approach. Nutrients 15. https://doi.org/10.3390/nu15214536.
Moser, S.C., van der Eerden, B.C.J., 2018. Osteocalcin-a versatile bone-derived hormone. Front. Endocrinol. (Lausanne). 9, 794. https://doi.org/10.3389/fendo.2018.00794.
Movahed, M.R., Lee, J.Z., Lim, W.Y., Hashemzadeh, M., Hashemzadeh, M., 2016. Strong independent association between obesity and essential hypertension. Clin. Obes. 6, 189–192. https://doi.org/10.1111/cob.12139.
Myung, S.-K., Kim, H.-B., Lee, Y.-J., Choi, Y.-J., Oh, S.-W., 2021. Calcium supplements and risk of cardiovascular disease: a meta-analysis of clinical trials. Nutrients 13. https://doi.org/10.3390/nu13020368.
Ngadiarti, I., Muntikah, M., Nurkolis, F., Gunawan, W.Ben, 2022. Malnutrition during the pandemic among home-nursed and community-dwelling elderly. Nutr. Cl. íNica Y. Diet. ética Hosp. 42.
Nie, Y.-Z., Yan, Z.-Q., Yin, H., Shan, L.-H., Wang, J.-H., Wu, Q.-H., 2022. Osteosarcopenic obesity and its components-osteoporosis, sarcopenia, and obesity are associated with blood cell count-derived inflammation indices in older Chinese people. BMC Geriatr. 22, 532. https://doi.org/10.1186/s12877-022-03225-x.
Park, S.H., Park, J.H., Song, P.S., Kim, D.K., Kim, K.H., Seol, S.H., Kim, H.K., Jang, H.J., Lee, J.G., Park, H.Y., Park, J., Shin, K.J., Kim, D. il, Moon, Y.S., 2013. Sarcopenic obesity as an independent risk factor of hypertension. J. Am. Soc. Hypertens. 7, 420–425. https://doi.org/10.1016/j.jash.2013.06.002.
Park, S.-J., Ryu, S.-Y., Park, J., Choi, S.-W., 2019. Association of sarcopenia with metabolic syndrome in korean population using 2009-2010 korea national health and nutrition examination survey. Metab. Syndr. Relat. Disord. 17, 494–499. https://doi.org/10.1089/met.2019.0059.
Perna, S., Spadaccini, D., Nichetti, M., Avanzato, I., Faliva, M.A., Rondanelli, M., 2018. Osteosarcopenic visceral obesity and osteosarcopenic subcutaneous obesity, two new phenotypes of sarcopenia: prevalence, metabolic profile, and risk factors. J. Aging Res. 2018, 6147426 https://doi.org/10.1155/2018/6147426.
Petersen, K.F., Dufour, S., Savage, D.B., Bilz, S., Solomon, G., Yonemitsu, S., Cline, G.W., Befroy, D., Zemany, L., Kahn, B.B., Papademetris, X., Rothman, D.L., Shulman, G.I., 2007. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc. Natl. Acad. Sci. U. S. A. 104, 12587–12594. https://doi.org/10.1073/pnas.0705408104.
Rašić, P.M., Tasić, I., 2009. Hypertension and osteoporosis in postmenopausal women. Acta Med. Median 48, 8–13.
Reid, I.R., Birstow, S.M., Bolland, M.J., 2017. Calcium and cardiovascular disease. Endocrinol. Metab. (Seoul., Korea) 32, 339–349. https://doi.org/10.3803/EnM.2017.32.3.339.
Ristic-Medic, D., Bajerska, J., Vucic, V., 2022. Crosstalk between dietary patterns, obesity, and nonalcoholic fatty liver disease. World J. Gastroenterol. 28, 3314–3333. https://doi.org/10.3748/wjg.v28.i27.3314.
Sá, C.M.A.T. de, Burgos, M.G.P. de A., Rabelo Filho, L.V., Calado, C.K.M., Costa, M. da C., Silva, T.C. de A., Vieira, R.A.L., Cabral, P.C., 2023. Body composition assessed by dual-energy X-ray absorptiometry on metabolic profile and cardiovascular risk in obese patients prior to bariatric surgery. Arq. Bras. Cir. Dig. ABCD = Braz. Arch. Dig. Surg. 36, e1734 https://doi.org/10.1590/0102-672020230016e1734.
Sasaki, K.-I., Kakuma, T., Sasaki, M., Ishizaki, Y., Fukami, A., Enomoto, M., Adachi, H., Matsuse, H., Shiba, N., Ueno, T., Fukumoto, Y., 2020. The prevalence of sarcopenia and subtypes in cardiovascular diseases, and a new diagnostic approach. J. Cardiol. 76, 266–272. https://doi.org/10.1016/j.jjcc.2020.03.004.
Severinsen, M.C.K., Pedersen, B.K., 2020. Muscle-organ crosstalk: the emerging roles of myokines. Endocr. Rev. 41, 594–609. https://doi.org/10.1210/endrev/bnaa016.
Shah, S.M., Carey, I.M., Harris, T., DeWilde, S., Cook, D.G., 2010. Calcium supplementation, cardiovascular disease and mortality in older women. Pharmacoepidemiol. Drug Saf. 19, 59–64. https://doi.org/10.1002/pds.1859.
Shanik, M.H., Xu, Y., Skrha, J., Dankner, R., Zick, Y., Roth, J., 2008. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? S262-8 Diabetes Care 31 (Suppl 2). https://doi.org/10.2337/dc08-s264.
Shin, J., Hwang, J.H., Han, M., Cha, R.-H., Kang, S.H., An, W.S., Kim, J.C., Kim, S.H., 2022. Phase angle as a marker for muscle health and quality of life in patients with chronic kidney disease. Clin. Nutr. 41, 1651–1659. https://doi.org/10.1016/j.clnu.2022.06.009.
Sjöström, L., 2013. Review of the key results from the Swedish Obese Subjects (SOS) trial - a prospective controlled intervention study of bariatric surgery. J. Intern. Med. 273, 219–234. https://doi.org/10.1111/joim.12012.
Soen, S., Fukunaga, M., Sugimoto, T., Sone, T., Fujiwara, S., Endo, N., Gorai, I., Shiraki, M., Hagino, H., Hosoi, T., Ohta, H., Yoneda, T., Tomomitsu, T., 2013. Diagnostic criteria for primary osteoporosis: year 2012 revision. J. Bone Miner. Metab. 31, 247–257. https://doi.org/10.1007/s00774-013-0447-8.
Stefanaki, C., Peppa, M., Boschiero, D., Chrousos, G.P., 2016. Healthy overweight/obese youth: early osteosarcopenic obesity features. Eur. J. Clin. Invest. 46, 767–778. https://doi.org/10.1111/eci.12659.
Su, Y.-H., Chang, Y.-M., Kung, C.-Y., Sung, C.-K., Foo, W.-S., Wu, M.-H., Chiou, S.-J., 2021. A study of correlations between metabolic syndrome factors and osteosarcopenic adiposity. BMC Endocr. Disord. 21, 216. https://doi.org/10.1186/s12902-021-00880-w.

Szlejf, C., Parra-Rodríguez, L., Rosas-Carrasco, O., 2017. Osteosarcopenic obesity: prevalence and relation with frailty and physical performance in middle-aged and older women, 733.e1-733.e5 J. Am. Med. Dir. Assoc. 18. https://doi.org/10.1016/j.jamda.2017.02.023.

Takayama, M., Azuma, K., Shimizu-Hirota, R., Makino, K., Seino, T., Yoshida, T., Kashiwagi, K., Hirose, H., Inoue, N., Iwao, Y., 2018. Sarcopenic obesity is associated with osteopenia among Japanese elderly women: A cross-sectional study from comprehensive health checkups. Heal. Eval. Promot. 45, 573–578.

Tanaka, S., Ando, K., Kobayashi, K., Nakashima, H., Seki, T., Ishizuka, S., Machino, M., Morozumi, M., Kanbara, S., Ito, S., Inoue, T., Kanemura, T., Ishiguro, N., Hasegawa, Y., Imagama, S., 2020. A higher extracellular water-to-total body water ratio more strongly reflects the locomotive syndrome risk and frailty than sarcopenia. Arch. Gerontol. Geriatr. 88, 104042 https://doi.org/10.1016/j.archger.2020.104042.

Tuttle, C.S.L., Thang, L.A.N., Maier, A.B., 2020. Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. Ageing Res. Rev. 64, 101185 https://doi.org/10.1016/j.arr.2020.101185.

Villa-Etchegoyen, C., Lombarte, M., Matamoros, N., Belizán, J.M., Cormick, G., 2019. Mechanisms involved in the relationship between low calcium intake and high blood pressure. Nutrients 11. https://doi.org/10.3390/nu11051112.

Vucic, V., Ristic-Medic, D., Arsic, A., Petrovic, S., Paunovic, M., Vasiljevic, N., Ilich, J.Z., 2023. Nutrition and physical activity as modulators of osteosarcopenic adiposity: a scoping review and recommendations for future research. Nutrients 15. https://doi.org/10.3390/nu15071619.

Wani, K., Yakout, S.M., Ansari, M.G.A., Sabico, S., Hussain, S.D., Alokail, M.S., Sheshah, E., Aljohani, N.J., Al-Saleh, Y., Reginster, J.-Y., Al-Daghri, N.M., 2019. Metabolic syndrome in arab adults with low bone mineral density. Nutrients 11. https://doi.org/10.3390/nu11061405.

Wattacheril, J., Sanyal, A.J., 2016. Lean NAFLD: an underrecognized outlier. Curr. Hepatol. Rep. 15, 134–139. https://doi.org/10.1007/s11901-016-0302-1.

Wells, J.C.K., Shirley, M.K., 2016. Body composition and the monitoring of non-communicable chronic disease risk. Glob. Heal. Epidemiol. Genom. 1, e18 https://doi.org/10.1017/gheg.2016.9.

Whitfield, J.B., 2001. Gamma-glutamyl transferase. Crit. Rev. Clin. Lab. Sci. 38, 263–355. https://doi.org/10.1080/20014091084227.

Wijarnpreecha, K., Panjawatanan, P., Aby, E., Ahmed, A., Kim, D., 2019. Nonalcoholic fatty liver disease in the over-60s: Impact of sarcopenia and obesity. Maturitas 124, 48–54. https://doi.org/10.1016/j.maturitas.2019.03.016.

Yamaguchi, T., 2011. Bone metabolism in dyslipidemia and metabolic syndrome. Clin. Calcium 21, 677–682.

Yang, S., Nguyen, N.D., Center, J.R., Eisman, J.A., Nguyen, T.V., 2014. Association between hypertension and fragility fracture: a longitudinal study. Osteoporos. Int. a J. Establ. Result Coop. Eur. Found. Osteoporos. Natl. Osteoporos. Found. USA 25, 97–103. https://doi.org/10.1007/s00198-013-2457-8.

Yatsyshyn, R., Stoika, I., 2018. AB0358Phenotypes of secondary sarcopenia in patients with rheumatoid arthritis. LP – 1351 Ann. Rheum. Dis. 77, 1351. https://doi.org/10.1136/annrheumdis-2018-eular.2305.

Yilmaz, H., Uyfun, M., Yilmaz, T.S., Namuslu, M., Inan, O., Taskin, A., Cakmak, M., Bilgic, M.A., Bavbek, N., Akcay, A., Kosar, A., 2014. The neutrophil-lymphocyte ratio may be superior to C-reactive protein for predicting the occurrence of postmenopausal osteoporosis. Endocr. Regul. 48, 25–33. https://doi.org/10.4149/endo_2014_01_25.

Zinellu, A., Paliogiannis, P., Sotgiu, E., Mellino, S., Mangoni, A.A., Zinellu, E., Negri, S., Collu, C., Pintus, G., Serra, A., Pistuddi, A.M., Carru, C., Pirina, P., Fois, A.G., 2020. Blood cell count derived inflammation indexes in patients with idiopathic pulmonary fibrosis. Lung 198, 821–827. https://doi.org/10.1007/s00408-020-00386-7.