



Review

Pathophysiological mechanisms linking sarcopenic obesity to mental health among older people: A state-of-the-art review linking peripheral signals to neural consequences

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Abstract: *Background:* Sarcopenia and obesity are global health concerns that usually precede the onset and development of adverse health outcomes among older people. Recent findings have shown that sarcopenic obesity is a significant risk factor for geriatric mental health conditions, especially depression. However, it remains mechanistically unclear how sarcopenic obesity-specific interactions among adipose tissues, skeletal muscles, and/or the sites of intramuscular lipid accumulation adversely affect the mental health of older adults. *Scope:* Peer-reviewed articles on both clinical (humans) and preclinical (experimental animals and cultured cells) studies primarily aiming at elucidating the associations between sarcopenic obesity and mental health and the molecular mechanisms behind, with English full-text available, were included. *Key findings:* In this review, we reviewed the definitions, diagnostic criteria [European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO)], screening and staging, and health consequences of sarcopenic obesity. We discuss potential mechanisms underlying the association between sarcopenic obesity and mental health, including dysfunction of the hypothalamic–pituitary–adrenal axis, chronic systemic low-grade inflammation (C-reactive protein, interleukin-6, and tumor

necrosis factor alpha), oxidative stress, and an imbalance between adipokines (leptin, fatty acid-binding proteins, adiponectin, and resistin) and myokines (brain-derived neurotrophic factor, irisin, fibroblast growth factor 21, and apelin). Additionally, we gain novel insights into the deficiency in store-operated Ca^{2+} entry regulatory factor in immune cells, triggering the release of proinflammatory cytokines and the influx of peripheral tissue factors into the brain via disrupting the blood–brain barrier. *Conclusions:* A deep understanding of the molecular pathways behind the onset of sarcopenic obesity-related mental disorders can provide a future perspective for the identification of evidence-based biomarkers and therapeutic targets in human clinical studies.

Keywords: sarcopenic obesity; sarcopenia; muscle loss; overweight; obesity; mental health; mental disorders; mental well-being; exercise training; resistance training

Abbreviations: ASM: appendicular skeletal muscle; ASMI: appendicular skeletal muscle index; AWGS: Asian Working Group on Sarcopenia; BBB: blood–brain barrier; BDNF: brain-derived neurotrophic factor; BIA: bioelectrical impedance analysis; BMI: body mass index; bw: body weight; Ca^{2+} : calcium ions; Cav1: L-type channels; CNS: central nervous system; CRP: C-reactive protein; DXA: dual-energy X-ray absorptiometry; EASO: European Association for the Study of Obesity; ERK1/2: Mitogen-activated protein kinase; ESPEN: European Society for Clinical Nutrition and Metabolism; EWGSOP: European Working Group on Sarcopenia in Older People; FABP: fatty acid-binding proteins; FFAs: free fatty acids; FGF21: fibroblast growth factor 21; FNHI: Foundation of the National Institutes of Health; HG: handgrip; HPA: hypothalamic-pituitary-adrenal; IGF-1: insulin-like growth factor 1; IL-4: interleukin-4; IL-6: interleukin-6; IL-18: interleukin-18; IR: insulin resistance; IWGS: International Working Group on Sarcopenia; MDD: major depressive disorder; miRNAs: microRNAs; MMP: matrix metalloproteinases; ROS: reactive oxygen species; SARAF: stored-operated calcium entry regulatory factor; SO: sarcopenic obesity; STAT3: signal transducer and activator of transcription 3; T2D: type 2 diabetes; TNF- α : tumor necrosis factor alpha; TrkB: tyrosine kinase 2; TRP: transient receptor potential; WC: waist circumference

1. Introduction

First coined by Rosenberg in 1997, sarcopenia is now defined as a muscle aging condition characterized by age-related loss of muscle mass, strength, and physical functional performance [1]. Among older people (aged ≥ 60 years), the global prevalence of sarcopenia ranged from 10% to 27%, whereas the prevalence of severe sarcopenia varied from 2% to 9% [2]. The overall prevalence estimates were similar in men and women (10%; 95% CI: 8%–13%), but higher among non-Asian than Asian individuals in both sexes [3]. The cutoff values of different definitions in the diagnosis of sarcopenia are shown in Table 1 [4–9]. Etiologic factors of sarcopenia, encompassing genetic, physiologic, and environmental aspects, include impaired muscle fiber structure, neuromuscular disconnection, altered muscle protein metabolism, protein anabolic failure, elevated production of proinflammatory cytokines [e.g., interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), and signal transducer and activator of transcription 3 (STAT3)], augmented oxidative stress and impaired mitochondrial uncoupling, poor nutritional status, and physical inactivity/sedentary lifestyles [10,11]. Sarcopenia is a critical determinant of frailty in older populations, leading to a heightened risk of

disability, hospitalization, and mortality [8,12]. Nonpharmacological approaches, including increased daily protein intake (≥ 1.0 g/kg body weight), a vitamin D-rich diet, and resistance training (e.g., >2 days/week, major muscle groups, and moderate or greater intensity), are commonly used for the management of sarcopenia [10].

Table 1. Diagnostic criteria for sarcopenia.

	ASMI, kg/m ²		ASM/BMI, kg		ASM/bw, kg/kg		Handgrip strength, kg		Gait speed, m/s	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
AWGS2014	<7.0	<5.4 (DXA) <5.7 (BIA)	—	—	—	—	<26	<18	<0.8	<0.8
AWGS2019	<7.0	<5.4 (DXA) <5.7 (BIA)	<0.789	<0.512	—	—	<28	<18	<1.0	<1.0
EWGSOP1	<6.52	<5.44	—	—	—	—	≤ 28	≤ 18	≤ 0.8	≤ 0.8
EWGSOP2	<7.0	<5.5	—	—	—	—	<27	<16	≤ 0.8	≤ 0.8
IWGS	≤ 7.23	≤ 5.67	—	—	—	—	—	—	<1.0	<1.0
FNIH	—	—	<0.789	<0.512	—	—	<26	<16	—	—

Note: Abbreviations: ASM, appendicular skeletal muscle; ASMI, appendicular skeletal muscle index; AWGS, Asian Working Group on Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; bw, body weight; DXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; FNIH, Foundation of the National Institutes of Health; IWGS, International Working Group on Sarcopenia.

1.1. Sarcopenic obesity (SO)

1.1.1. Definitions and diagnostic criteria

Sarcopenia and obesity are global concerns that usually precede the onset and development of adverse health outcomes in older people. Globally, more than one-third of older people aged 60 and older are living with obesity [13], which is characterized by excessive accumulation of fat inside the body. According to the consensus statement on the definition and diagnostic criteria by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), SO is defined as the co-occurrence of both sarcopenia (low muscle mass and function) and obesity (excess fat mass) on the basis of sex-, ethnicity- and age-adjusted cutoff points (Table 2) [14]. The impact of sarcopenia on body fat gain can be explained by reduced total energy expenditure and/or positive energy balance, whereas obesity-related metabolic abnormalities usually contribute to impaired muscle metabolism, especially protein anabolism. The interrelationship between obesity and sarcopenia has been evidenced by the significant correlation between visceral adiposity and sarcopenia, and greater visceral fatness exhibited a higher likelihood of sarcopenia and SO [15,16]. Current evidence has also shown that patients with SO had a higher risk of type 2 diabetes (T2D) than those with obesity or sarcopenia alone [17], implicating a synergistic adverse effect of co-occurring sarcopenia and obesity. Like sarcopenia, the treatment of SO is

mainly nonpharmacological, including exercise (e.g., resistance training) and nutritional (e.g., dietary antioxidant) interventions [18–20].

Table 2. Criteria for diagnosing sarcopenic obesity according to the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) consensus statement.

1. Body composition				
(a) Low muscle mass	Cutoff points		References	
	<u>Men</u>	<u>Women</u>		
(i) Skeletal muscle mass adjusted by weight (assessed by DXA)	CLASS I of Sarcopenia (1–2 SD): 31.5%–37%; CLASS II of Sarcopenia (< 2 SD): <31.5%	CLASS I of Sarcopenia (1–2 SD): 22.1%–27.6%; CLASS II of Sarcopenia (< 2 SD): <22.1%	[21]	
(ii) Appendicular lean mass adjusted to body weight (assessed by BIA)	<25.7%	<19.4%	[22]	
(b) Obesity	Cutoff points		References	
	<u>Men</u>	<u>Women</u>		
(i) BMI	<u>Non-Asians:</u> >29.9 kg/m ²	<u>Non-Asians:</u> >29.9 kg/m ²	[23]	
(ii) WC	<u>Asians:</u> >24.9 kg/m ²	<u>Asians:</u> >24.9 kg/m ²	[24]	
	<u>Non-Asians:</u> >102 cm	<u>Non-Asians:</u> >88 cm	[25]	
	<u>Asians:</u> >90 cm	<u>Asians:</u> >80 cm	[26]	
(iii) Fat mass	<u>Caucasians:</u> 20–39y: >26%	<u>Caucasians:</u> 20–39y: >39%	[27]	
	40–59 y: >29%	40–59 y: >41%		
	60–79y: >31%	60–79y: >43%		
	<u>Asians:</u> 20–39y: >28%	<u>Asians:</u> 20–39y: >40%		
	40–59 y: 29%	40–59 y: >41%		
	60–79y: 29%	60–79y: >41%		
	<u>African-Americans:</u> 20–39y: >26%	<u>African-Americans:</u> 20–39y: >38%		
	40–59 y: >27%	40–59 y: >39%		
	60–79y: >29%	60–79y: >41%		
	2. Low muscle strength			
HG	Cutoff points		References	
	<u>Men</u>	<u>Women</u>		
	<u>Caucasians:</u> <27 kg	<u>Caucasians:</u> <16 kg		[28]
	<u>Asians:</u> <28 kg	<u>Asians:</u> <18 kg		[7]

Continued on next page

3. Low physical performance	Cutoff values		References
	<u>Men</u>	<u>Women</u>	
Chair stand	≥17 s for 5 rises	≥17 s for 5 rises	[29]

Note: Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HG, handgrip; WC, waist circumference.

1.1.2. Prevalence and health consequences

Recent meta-analytic results have shown that SO affected approximately 1 in 10 older people worldwide, with a wide regional variation in prevalence ranging from 3% to 29% [30–37]. SO was more prevalent among individuals aged 75+ years (23%), hospitalized (16%), and residing in South and North American countries (40%) [31,38]. A population-based cohort study on older people (n = 5888) has shown that both SO and sarcopenia were associated with an approximately 2- to 3-fold higher risk of all-cause mortality independent of age and sex [38]. Among at-risk individuals (e.g., hospitalized older adults), the risk of all-cause mortality associated with SO versus age-matched non-SO counterparts could be as high as 5-fold [39]. Other negative clinical consequences include metabolic impairments (e.g., dyslipidemia and hyperglycemia) [14,40,41], osteoporosis [41,42], frailty and functional disabilities [14,40], cardiovascular and respiratory diseases [14,40], and cognitive impairments [43].

1.1.3. Screening, diagnosis, and staging

The ESPEN and EASO consensus statement has suggested three steps for screening and diagnosing SO: 1) screening of obese individuals with either high body mass index (BMI) or waist circumference (WC) coexisting with surrogate parameters for sarcopenia [clinical symptoms, clinical suspicion, or screened by questionnaires (e.g., 5-item SARC-F)], 2) diagnosis of impaired muscle functional parameters (e.g., handgrip strength) followed by physical examination of body composition [e.g., dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA)], and 3) staging of SO based on the presence of complications attributable to altered body composition and impaired skeletal muscle functional parameters [stage I: no complications; stage II: presence of ≥1 SO-related complications (e.g., functional disabilities, cardiometabolic diseases, and respiratory diseases)] [14].

Screening: Woo (2017) suggested the use of a rapid screening tool, namely the 5-item SARC-F questionnaire (strength, assistance in walking, rise from a chair, stair climbing, and history of falls), as the first step in the large-scale screening of sarcopenia in community or primary care settings, followed by resource-intensive physical examinations [10]. However, the SARC-F has poor sensitivity (13.7%–50.0%) yet excellent specificity (82%) for screening sarcopenia, so researchers have recently proposed using SARC-F by adding calf circumference (SARC-CalF), which has better sensitivity (25.0%–54.5%) and diagnostic accuracy (90%–98%) for detecting sarcopenia [10,44–47]. A SARC-F score of ≥4 suggests sarcopenia, whereas a SARC-CalF score of ≥11 indicates probable sarcopenia (Table 3). Besides, Benz et al. (2024) suggested the use of handgrip strength (i.e., an indicator for muscle strength) as the first screening step of SO, given its strong association with premature mortality among older adults in a large-scale, population-based cohort study (n = 5888) [38]. The sensitivity and practicality (time, availability, cost) of using SARC-F, SARC-CalF, and handgrip strength are in line with the ESPEN and EASO consensus statement that SO screening should target the largest possible number

of at-risk individuals and also be easily applied in a variety of clinical settings (e.g., outpatient clinics, hospitals, and nursing homes) by health care professionals who may not have specialized training in the field of obesity or sarcopenia [14]. For obesity screening, the consensus group supports the use of both BMI and WC in routine clinical practice. Of note, older people aged 70+ years overweight and presenting obesity should be immediately considered at risk of SO and are recommended to have regular SO screening by using muscle functional tests (e.g., handgrip strength and chair stand).

Table 3. SARC-F questionnaire with the calf circumference measurement.

Components	Questions	Scoring
Strength	How much difficulty do you have lifting and carrying 10 pounds?	None = 0; some = 1; a lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0; some = 1; a lot, use aids, or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair or bed?	None = 0; some = 1; a lot or unable without help = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0; some = 1; a lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0; 1–3 falls = 1; 4 or more falls = 2
CC	Measure the patient's exposed right CC with the legs relaxed and feet 20 cm apart from each other	Females: >33 cm = 0; ≤33 cm = 10; Males: >34 cm = 0; ≤34 cm = 10

Note: Abbreviations: CC, calf circumference.

Diagnosis: Assessment of muscle functional parameters should be considered as the first step of diagnosis prior to body composition examination by BIA or DXA [14]. This is because impaired muscle functions can adversely affect the quality of life and treatment regimens of SO patients. Another concern is the lower practicality of body composition examination, which requires tools that may not be accessible in clinical and research settings. The ESPEN/EASO consensus group has suggested the use of maximal handgrip strength and maximal knee extensor strength of both limbs, because other physical performance tests (e.g., usual gait speed) may be confounded by impaired or degenerative joint conditions such as knee osteoarthritis. For body composition examination, the consensus group has advocated the use of DXA rather than BIA, which should be considered as the second choice. This is because BIA lacks direct measurement of body composition and is easily confounded by some factors (e.g., hydration status, physical activity levels, and menstruation). The ESPEN/EASO consensus group has suggested the use of skeletal muscle mass normalized with body weight (kg) as the primary index, yet the muscle mass adjusted for body weight is not commonly used for examining body composition in various definitions and diagnostic criteria of sarcopenia (Table 2). Thus, the body weight normalization method requires further studies to validate its use in routine clinical practice. Recently, the Asia–Oceania consensus on definitions and diagnostic criteria for SO has recommended the use of appendicular skeletal muscle index (kg/m^2) [48], of which the cutoff values for defining sarcopenia have been widely adopted across various diagnostic criteria suggested by different consensus groups, including the

Asian Working Group on Sarcopenia, the European Working Group on Sarcopenia in Older People, and the International Working Group on Sarcopenia.

Staging: SO staging after diagnosis is primarily based on the presence or absence of clinical consequences attributable to altered body composition and impaired skeletal muscle functional parameters. Based on this risk stratification, SO patients can be timely triaged so that older adults at a higher risk for poor outcomes can receive more aggressive treatment and monitoring.

1.1.4. Cellular and molecular crosstalk between sarcopenia and obesity

Mechanistically, myosteatorsis and lipotoxicity in muscle may exacerbate impaired skeletal muscle mass, strength, and anabolic sensitivity, thereby giving rise to several severe syndromes and diseases, including frailty, cachexia and wasting disorders, and sarco-osteoporosis [10]. Axelrod et al. (2023) highlighted that the sole intercept point between lipid accumulation in obesity and age-related sarcopenia is systemic energy metabolic burden, so the adverse interaction between sites of lipid accumulation and contractile force generation/myogenesis/muscle protein synthesis may dictate the onset and progression of SO in older adults [11]. Potential mechanisms of lower muscle mass and quality in the context of obesity include overexpression of systemic proinflammatory cytokines (e.g., IL-6, TNF- α , and STAT3) causing muscle wasting, impaired leptin and adiponectin sensitivity in skeletal muscle triggering protein degradation, deficiencies in testosterone hindering muscle protein synthesis, impaired regenerative capacity of skeletal muscle by reducing the number and proliferative capacity of resident stem cells, impaired bioenergetic capacity of skeletal muscle by lowering the number and function of mitochondria, and accumulation of intramyocellular lipids in the development of muscle resistance to anabolic stimuli [11]. Therapeutically targeting these myocellular pathways may help to preserve muscle mass and quality and hence alleviate SO-associated adverse outcomes (e.g., impaired activities of daily living) in older adults. Figure 1 summarizes the potential factors for lowering muscle mass and quality in the context of obesity.

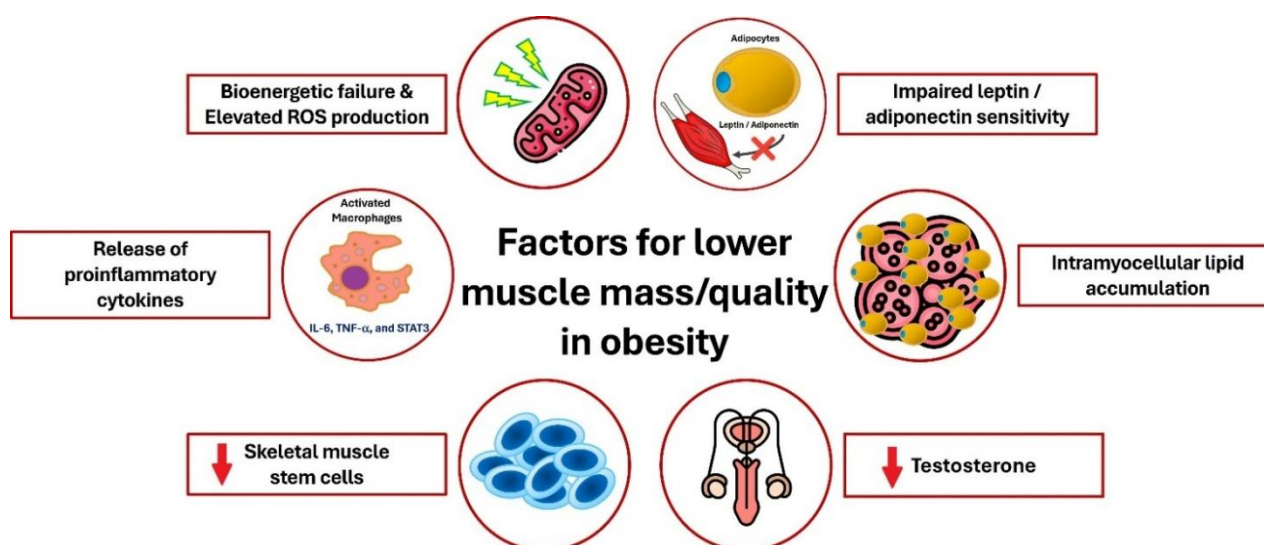


Figure 1. Obesity-related risk factors for lower muscle mass and quality. Abbreviations: IL-6, interleukin-6; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF- α , tumor necrosis factor alpha.

1.2. *SO and mental health*

1.2.1. Mental health

According to the World Health Organization, mental health is defined as more than the absence of mental disorders: it is a state of mental well-being that enables people to realize their own capabilities to confront normal stresses of life, learn and work well, and contribute to their community [49]. In the present review, a wide definition of mental health, spanning from mental well-being to clinically relevant mental health symptoms, was adopted.

1.2.2. SO-related mental health

A prospective cohort study over a 6-year follow-up has shown that older adults comorbid with probable sarcopenia and obesity (defined based on handgrip strength and BMI) ($n = 3862$) had a 79% greater risk of new onset depressive symptoms than their non-sarcopenic, non-obese counterparts [50]. Further, obese older adults showing the largest decline in handgrip strength (an indicator for impaired muscle function) over time had the greatest risk of depressive symptoms (OR = 1.97, 95% CI: 1.22–3.17) relative to non-obese counterparts who had stable handgrip strength. Meanwhile, sarcopenia has been shown to be positively and independently associated with a greater risk of depression by almost 3-fold among obese individuals ($n = 373$) [51]. Recent cross-sectional evidence has also shown that SO was significantly associated with increased likelihoods of mild and severe depression in adults ($n = 7262$) [52] and compromised quality of life in older women ($n = 95$) [53]. A recent systematic review has further supported the bidirectional relationships between SO and mental health [54], implicating a potential role of coexisting sarcopenia and obesity in the onset of mental disorders. However, further high-quality experimental studies, for example, randomized controlled trials (RCTs), are imperatively needed to verify the causal inference of SO with mental health in older adults.

1.3. *Knowledge gap and research objectives*

Although a few relevant narrative reviews and book chapters have been published on the relationship between SO and mental health/disorders [55–58], no comprehensive review has thoroughly discussed the cellular/molecular mechanisms behind this relationship thus far. Besides, previous reviews primarily focused on human clinical studies but fell short in addressing the clinical significance of preclinical studies on experimental animals and *in vitro* models, which are useful to elucidate the underlying mechanisms of action and usually serve as a milestone for future human clinical trials. Even though Blum et al. (2021) mechanistically studied the involvement of catecholaminergic pathways in the association between SO and mental health, the study was only confined to substance-seeking behavior (e.g., carbohydrate cravings) [59]. As such, the findings could not be easily generalized to other populations or mental health outcomes. A comprehensive review on the cellular/molecular mechanisms behind the relationships between SO and mental health is imperatively needed, as the perspectives gained through the review process are clinically relevant to the identification of empirically proven biomarkers and therapeutic targets to alleviate the two global healthcare burdens (sarcopenia and obesity) in the rapidly ageing population, who is projected to double (i.e., 2.1 billion) globally by 2050 and exceed 30% of the general population in some places

(e.g., Japan and Hong Kong) [60]. In the present study, a state-of-the-art narrative review approach was adopted, which attempts to summarize recently published literature concerning a specific current matter [61]. Therefore, the objective of this study was to synthesize current evidence on the molecular pathways involved in the crosstalk between SO phenotypes and the onset and progression of various mental disorders. Taken together, a deep understanding of the underlying molecular pathways can pinpoint the understudied research areas that require further investigation and hence probe for a future perspective for the identification of evidence-based biomarkers and therapeutic targets in human clinical studies.

2. Literature search strategy

Given that no formal guidelines or no consensus on standard structure are available for developing narrative reviews, this narrative review study protocol was constructed primarily based on the recommendations given by several reviews [61–63], namely that the development of narrative reviews can benefit from the methodological rigor of systematic reviews, especially regarding the selection of articles for review (e.g., search terms, study inclusion/exclusion criteria, and study selection flowchart). The narrative review checklist proposed by the Academy of Nutrition and Dietetics for the present study is shown in Appendix 1 [64].

2.1. Eligibility criteria

The eligibility criteria of retrieved records were screened for relevancy based on the population/concept/context framework [65] (Table 3). In short, peer-reviewed articles on both clinical (humans) and preclinical (experimental animals and cultured cells) studies primarily aiming at elucidating the relationships between SO and mental health and the molecular mechanisms behind, with English full-text available, were included. A wide definition of mental health outcomes, spanning from mental well-being to clinically relevant mental health symptoms, was used [49]. Cognitive functions, which generally refer to the brain's abilities to function (e.g., learning, reasoning, and memory), were not considered as a mental health outcome in the present study. Studies other than primary research, including reviews, book chapters, errata/corrections, study protocols, editorials, and commentaries, were excluded. Retracted articles or preprints were also excluded.

2.2. Information sources and search strategy

Similar to our previous review [66], studies published in the past five years from 2020 through 2025 were searched using the PubMed database, which is a free full-text archive of biomedical and life sciences journal literature from MEDLINE, life science journals, and online books. The text word terms used for the database search were piloted twice before implementation. The text word terms were (sarcopenia OR sarcopenic OR “muscle loss”) for sarcopenia, and (obesity OR obese OR overweight) for obesity, and (mental OR psychological OR depress* OR anxiety OR stress OR distress OR mood OR emotion* OR affect* OR sleep OR insomnia OR resilience OR “quality of life” OR satisfaction) for mental health. The search strategy is shown in Appendix 2.

2.3. Selection process

The retrieved records were screened using a two-stage approach by first reviewing their titles and abstracts, followed by their full texts. Duplicates were removed manually using an Excel spreadsheet. Additional eligible studies were also identified by a manual search among the cited references of the included studies. Additionally, relevant studies were identified based on the expert suggestions by Leung WKC and Yau SSY, who have nearly 20 years of research experience in the field of molecular biology and neuroscience.

2.4. Data collection and synthesis

The results of the included studies relevant to our study aims (SO and mental health) were charted chronologically in a calibrated data extraction form. Similar to our previous narrative review [66], the findings related to the neurobiological mechanisms or cell signaling pathways behind the relationships between SO and mental health were also schematically and narratively summarized. The data extraction process was conducted by two authors (Leung WKC and Yau CYC) and independently verified by three co-authors (Yau SSY, Lam SC, and Suen LKP). Disagreement among the authors was resolved through discussion.

3. Neural pathophysiological mechanisms linking SO to mental health

3.1. Study selection

By March 24, 2025, our PubMed search for records published from 2021 to 2025 yielded a total of 531 records, of which the titles and abstracts were initially screened. In total, 463 studies that did not meet the eligibility criteria were excluded. Altogether, 68 studies were retrieved for full-text assessment. Finally, three primary studies that met the eligibility criteria were included for review and reporting. The molecular mechanisms that were related to SO-linked mental disorders or brain functions were systemic low-grade inflammation [67], oxidative stress [68], and deficiency in store-operated calcium ions (Ca^{2+}) entry regulatory factor [69]. For the included studies, there were no concerns about multiple reports or double result counting because they were completely different from each other in terms of publication details (e.g., authors' names and locations), subjects' characteristics (e.g., sample sizes and medical conditions), and main findings. The three included studies were mainly used to supplement the main content of this review. Tables 4 and 5 summarize the characteristics and main findings of the three included studies. Figure 2 shows the study selection process. Studies that were found irrelevant to our study aims after full-text assessment are listed in Appendix 3.

Table 4. Eligibility criteria based on the population/concept/context framework.

	Inclusion and exclusion criteria
Population	Human participants, experimental animals, and in vitro models
Concept	Mental health outcomes (e.g., depression, anxiety, stress, affect, distress, sleep, subjective psychological well-being, and life satisfaction) pertaining to sarcopenic obesity; studies examining cognitive functions, which generally refer to the brain's abilities to function (e.g., learning, reasoning, and memory), were excluded
Context	Clinical and preclinical settings
Study design	Peer-reviewed original research journal articles published in English with full text available; retracted articles, preprints, and studies other than primary research, including reviews, book chapters, errata/corrections, study protocols, editorials, and commentaries, were excluded.

Table 5. Summary of studies published from 2021 to 2025 examining the relationships between sarcopenic obesity and mental disorders (n = 3).

Authors	Subjects	Context	Main findings
Lee et al. (2024); South Korea; interventional study [68]	<u>Experimental animals:</u> High-fat diet-induced obese male C57BL/6 mice	<i>Solanum melongena</i> (SME) extract (200 mg/kg BW/daily, orally for 12 weeks) supplementation 6-weeks after obesity induction	Muscle and hippocampal expressions of muscle-derived myokines (BDNF, PGC1a, irisin, and FGF21) increased after SME administration
Gataulin et al. (2023); Israel; interventional study [69]	<u>Experimental animals:</u> SARAF-deficient mice <u>Tissue cell culture:</u> Primary hepatocytes isolated from the SARAF-deficient mice	General and spatially specific genetically SARAF knocked-out male mice aged 8–12 weeks	Age-dependent sarcopenic obesity manifested (e.g., reduced energy expenditure, lean mass, and locomotion without affecting food consumption) in the mice after SARAF ablation; reduced hippocampal proliferation, altered activity of the HPA axis and anxiety-related behaviors in the mice after SARAF ablation; elevated store-operated calcium entry, increased vasopressin-induced Ca^{2+} oscillations, and increased mitochondrial spare respiratory capacity in the hepatocytes after SARAF ablation
Pasco et al. (2023); Australia; retrospective cohort study [67]	<u>Human subjects:</u> Middle-aged and older women aged 47.6 years (35.9–60.7): n = 808	Women aged 20–84 years were followed for a median of 16.1 years.	19.9% (161/808) women developed an MDD episode; women with both sarcopenic obesity/obesity and systemic low-grade inflammation (i.e., increased serum concentration of high-sensitivity CRP) were at increased risk of subsequent MDD by >60% at follow-up.

Note: Abbreviations: BDNF, brain-derived neurotrophic factor; BW, body weight; CRP, C-reactive protein; FGF21,

fibroblast growth factor 21; SME, *Solanum melongena*; PGC1 α , peroxisome proliferator-activated receptor gamma coactivator 1- α ; SARAF, stored-operated calcium entry regulatory factor.

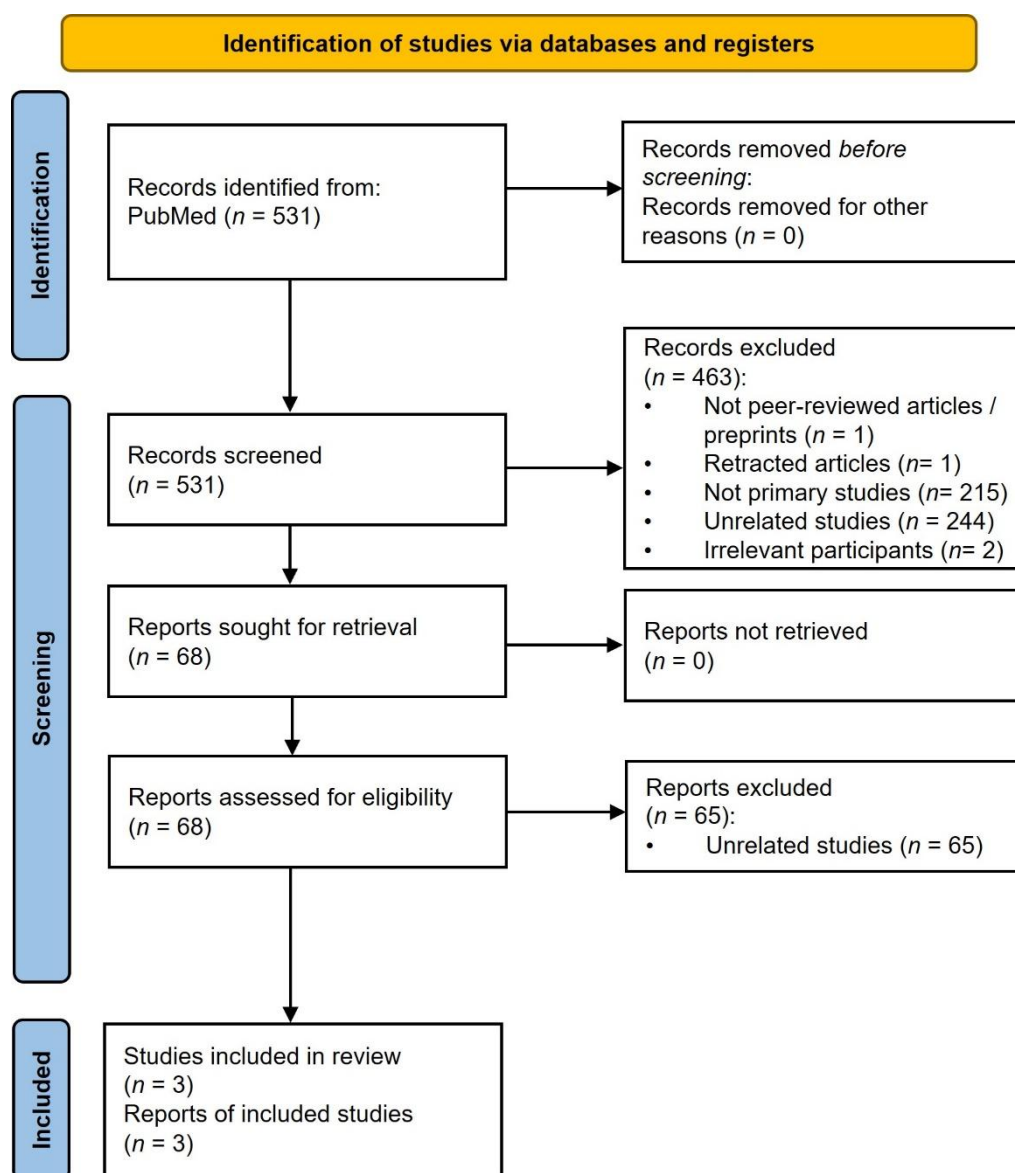


Figure 2. Study selection process.

3.2. Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis

The HPA axis is a primary neuroendocrine system in humans in response to stress, challenge, and threat. In response to stress, the system produces several glucocorticoid hormones, mainly cortisol in humans. In older adults, altered diurnal cortisol secretion might explain why older adults are more likely to suffer from negative mental health outcomes [70]. Mechanistically, prolonged exposure to high glucocorticoid levels due to chronic stress leads to reduced glucocorticoid receptor sensitivity, resulting in less negative feedback and hence a long-term high level of cortisol “signal”. Therefore, altered cortisol awakening response and a “flattened” morning-to-evening diurnal cortisol rhythm is a

key indicator for HPA dysregulation. In sarcopenia, excessive HPA axis hyperactivity results in consistently elevated circulatory cortisol, which in turn binds to glucocorticoid receptors in skeletal muscle, thereby triggering muscle protein degradation via activating the ubiquitin-proteasome system and autophagy-lysosomal pathway [71]. Other possible mechanisms linking HPA axis hyperactivation to skeletal muscle damage include chronic systemic low-grade inflammation (e.g., increased TNF- α and IL-6) and oxidative stress (to be discussed). Obesity-induced inflammation and/or insulin resistance may further exacerbate the HPA axis dysregulation, increasing the susceptibility for depression in older adults with SO [55]. The linkage between SO and adverse mental health outcomes due to obesity could be explained by hypermethylation of the glucocorticoid receptor promoter that “turns off” the brain’s stress responses, thereby leading to elevated physiological reactivity and heightened risk for mental disorders. In patients with generalized anxiety disorder, reduced glucocorticoid receptor sensitivity and increased methylation of the glucocorticoid receptor promoter in peripheral blood were very commonly seen [72]. Although the HPA axis dysregulation characterized by higher morning cortisol levels (i.e., HPA axis hyperactivity at awakening) and a less dynamic awakening response was also concomitantly observed in depressed older adults [73,74], the evidence on the direct relevance of HPA axis activity to SO-related mental health in older adults is still very scarce.

3.3. *Chronic systemic low-grade inflammation*

Intramuscular expansion of adipose tissue is usually accompanied by an increase in inflammatory cell types [75]. Infiltration of immune cells into adipose tissues, especially activated macrophages (aka adipose tissue macrophages), further exacerbates intramuscular infiltration of adipose tissue, aggravates the release of proinflammatory cytokines, and accelerates the atrophy of skeletal muscle [75–77]. The major molecular mechanisms linking chronic low-grade inflammation to the occurrence of SO included TNF signaling pathway (pyroptosis), ubiquitin/proteasome system (muscle proteolysis), AKT/mTOR signaling pathway (skeletal muscle synthesis), and autophagy and p53 signaling pathway (programmed cell death) [78–80]. Peripheral systematic inflammation has also been experimentally shown to trigger disruptive blood–brain barrier (BBB) alterations (e.g., tight junction modification, endothelial dysfunction/damage, and glycocalyx degradation) [81]. Hence, BBB changes allow the invasion of peripheral proinflammatory cytokines and chemokines into the brain and interfere with its balanced environment, thereby causing neuroinflammation and, more severely, a number of psychiatric disorders, including schizophrenia, bipolar disorder, and depression.

Compelling evidence from 43 meta-analyses comprising 704 publications has supported the neurobiological relevance of inflammatory biomarkers and their diagnostic potential for differentiating psychiatric disorders [82]. For instance, 30 inflammatory factors [e.g., TNF- α , IL-6, insulin-like growth factor 1 (IGF-1), and C-reactive protein (CRP)] show significant alterations in at least one psychiatric disorder, whereas a few inflammatory biomarkers (e.g., elevated IL-4 in bipolar disorder) reveal disease specificity as evidenced by unique changes in specific psychiatric disorders. In a recent large-scale prospective cohort study ($n = 585,279$), inflammation-related factors (e.g., leukocytes, haptoglobin, and CRP) were also shown to be associated with a heightened risk of psychiatric disorders, for example, depression, anxiety, and stress-related disorders [83]. Recent evidence has also shown that middle-aged and older women with both SO and systemic low-grade inflammation (i.e., increased serum concentration of high-sensitivity CRP) ($n = 808$) were at a >60% increased risk of subsequent major depressive disorder (MDD) at a median 16.1-year follow-up [67]. Further, anti-inflammatory

medications, including Celecoxib, Pioglitazone, and statins, have been proven to be effective in treating bipolar disorder or MDD [84]. Among persistently depressed patients with baseline inflammatory abnormalities, anti-inflammatory drugs (e.g., anti-TNF- α) also demonstrated superior effectiveness to classical antidepressants [85].

3.4. Oxidative stress

SO was associated with oxidative stress through mitochondrial dysfunction, endoplasmic reticulum stress, and dysregulation of the skeletal muscle mass control pathways [86]. Oxidative stress has been suggested to cause BBB disruption through damaging a variety of cellular components and structures, including brain microvascular endothelial cells, astrocytes, pericytes, and basement membrane, increased matrix metalloproteinases (MMP) expression, altered transporter expression and BBB permeability, and activated autophagy in the hippocampus [87]. In humans, oxidative stress has been implicated in a number of mental disorders, including anxiety, depression, schizophrenia, and bipolar disorder, likely via disrupted oxidation-antioxidant pathways (e.g., increased ERK1/2 expression, proinflammatory IL-1 β and TNF- α augmentation, and hampered antioxidant enzyme activity) [88]. Recent evidence has shown that daily supplementation with *Solanum melongena*, an eggplant antioxidant extract, could alleviate oxidative stress and inflammation and confer neuroprotection by modulation of the brain-derived neurotrophic factor (BDNF)/peroxisome proliferator-activated receptor gamma coactivator-1 alpha/irisin pathway via brain function-related myokines in high-fat-diet-induced obese mice [68]. Chronic ferulic acid consumption has also been shown to alleviate depressive-like symptoms through increased activities of superoxide dismutase in the blood, catalase in the blood, and glutathione in the cerebral cortex among experimental animals [89]. Besides, hesperetin, a cholesterol-lowering flavonoid predominantly found in citrus juices, has been suggested to attenuate diabetes-associated anxiety and depression-like behaviors in an experimental rat model via activation of the Nrf2-ARE pathway [90], which is a known intrinsic mechanism of defense against oxidative stress. Consistently, a systematic review and meta-analysis on 82 studies comprising 205 adult human patients showed that patients with psychiatric disorders (e.g., psychotic and bipolar disorders) had higher oxidative stress levels than age-matched healthy controls [91]. Figure 3 shows the mechanistic overview of SO-induced oxidative stress in terms of cellular apoptotic pathways and BBB damage and dysfunction in the development of neurological diseases.

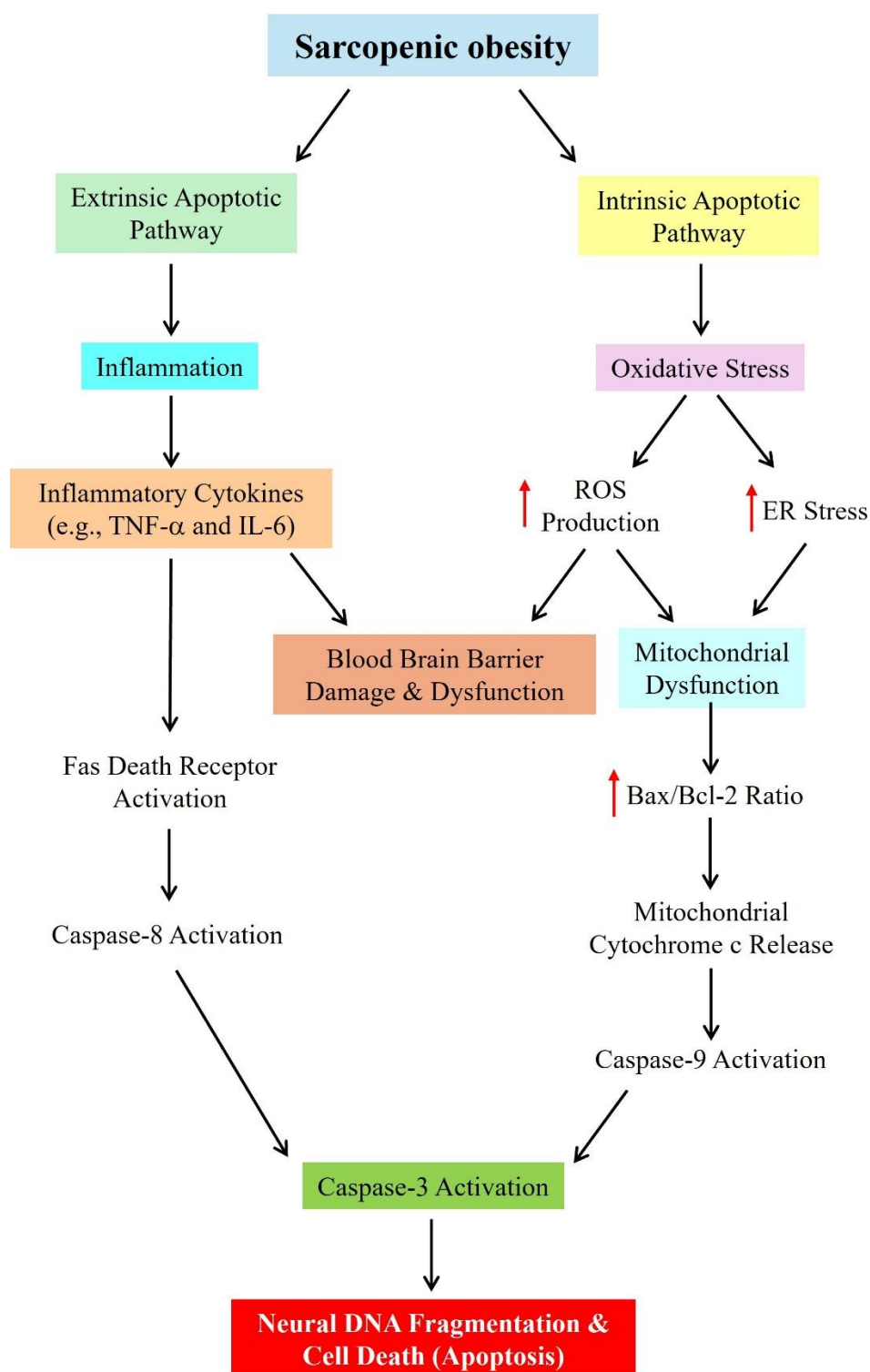


Figure 3. Roles of oxidative stress and inflammation in the development of sarcopenia, obesity-associated neurological diseases via apoptosis, and blood–brain barrier destruction. Abbreviations: ER, endoplasmic reticulum; IL-6, interleukin-6; ROS, reactive oxygen species; TNF- α , tumor necrosis factor alpha.

3.5. Myosteatosis/lipotoxicity and adipokines

Excessive intramuscular/intramycellular infiltration of lipids (aka “myosteatosis”) in the form of free fatty acids (FFAs) induces mitochondrial dysfunction, impairs the process of FFA β -oxidation, and stimulates reactive oxygen species production, thereby leading to insulin resistance (IR) in skeletal muscle and altered adipokine/myokine secretions such as low serum irisin and high circulatory myostatin [75,76,92]. The putative role of lipotoxicity in driving skeletal muscle atrophy can be due to impaired muscle protein synthesis and translation via suppressing 4E-binding protein 1 phosphorylation [75]. Worsening of peripheral IR in the context of SO can be explained by lipotoxic induction of impaired insulin-mediated glycogen synthesis and glucose uptake via a reduced protein kinase B/AKT phosphorylation. The combined lipotoxic effects of dysregulated adipokines and FFAs on skeletal muscle cells have been evidenced both in vivo and in vitro [93]. In this section, we provide an in-depth discussion on the mental health roles of three adipokines, namely leptin, adiponectin, and adipocyte fatty acid-binding proteins (FABP), because the detrimental impacts of sarcopenic visceral obesity reside largely in the interference with the downstream signaling cascades of these adipokines [75].

Leptin: In older obese people, the expansion of adipose tissue is usually accompanied by increased expression of leptin, a peripheral adipocyte-secreted proinflammatory hormone to suppress appetite. Plasma levels of leptin were found to be higher among middle-aged and older adults with SO than age-matched counterparts with either sarcopenia or central obesity alone [94]. Mechanistically, the upregulation of leptin induces low levels of persistent inflammation via the release of proinflammatory cytokines such as TNF- α and IL-6, which in turn negatively regulate IGF-1 and adiponectin, which are responsible for skeletal muscle protein synthesis, hence leading to the onset and progression of obesity-associated sarcopenic phenotypes [76,95].

In MDD patients, plasma/serum levels of leptin were generally increased [96–98], implicating a potential role of leptin in the pathophysiology of MDD. The increased levels of leptin were shown to predict the occurrence of the atypical MDD subtype [98] and coexisting “somatic anxiety” symptoms [97]. In T2D patients, higher serum levels of leptin were consistently observed among those with depressive and moderate-severe anxiety symptoms, and the likelihood of developing depressive symptoms among T2D patients in the highest leptin level group versus the lowest was almost 6-fold [99]. The involvement of leptin in mood and psychiatric disorders could be explained by its potential linkages to neural nitric oxide synthase activity and serotonin metabolism [100]. In schizophrenia or mood disorders, increased production of nitric oxide due to loss of inhibition by leptin (aka “leptin resistance”) contributes to serotonin inactivation, despite high levels of leptin. However, mixed findings were found regarding different levels of circulating leptin among patients with mental disorders, such as low/high in MDD and high in schizophrenia [96–98,101–103]. Zhu et al. (2022) attributed the heterogeneity in circulating leptin levels to age, sex, body weight status, treatment with antipsychotics, and different clinical subtypes or symptomatic profiles [97,98].

Adiponectin: Adiponectin, a protein adipokine predominantly secreted by white adipose tissue, serves as a key regulator for blood glucose control and fatty acid breakdown. Reduced gene expression and circulatory levels of adiponectin have been consistently observed among individuals and experimental animals with obesity [104–106]. A meta-analysis of 30 eligible studies examining serum/plasma adiponectin levels showed that patients with mental disorders ($n = 19,178$), including anxiety and bipolar disorder, had lower peripheral adiponectin levels than age-matched healthy counterparts [107]. In MDD patients, the serum concentration of adiponectin was lowered by >30%

compared with healthy controls, and serum adiponectin was shown to have a good predictive performance (AUC: 0.895) for MDD [108]. Mechanistically, intracerebrovascular injection of exogenous adiponectin in diet-induced obese diabetic mice could alleviate depressive-like behaviors via glucocorticoid-mediated negative feedback on the HPA axis [109], which is a major neuroendocrine signaling system that regulates the sympathetic nervous system in response to stress. Other potential mechanisms underlying the integral role of adiponectin in mental disorders, especially depressive and anxiety symptoms, include restored hippocampal neuroplasticity accompanying increased peripheral and hippocampal levels of BDNF [110–112], immune-inflammatory activation [113], and dysregulation of the microbiota–gut–brain axis [113]. However, a meta-analysis showed that sarcopenic participants ($n = 1389$) had a 20% higher level of adiponectin than healthy controls [114]. Thus, we postulate that the effects of adiponectin on SO-associated mental disorders are dependent not only on the net changes of peripheral/hippocampal adiponectin levels, but also on its altered sensitivity of binding with AdipoR1/R2 receptors.

FABP: Released primarily by adipocytes and macrophages, FABP is another key regulator in the pathogenesis of SO [75]. The involvement of circulating FABP in brain functions could be due to MMP9-mediated BBB disruption [115]. Further, experimental evidence showed that *Fabp7* knockout mice had impaired prepulse inhibition of acoustic startle reflex and longer time to erase fear memory, which are endophenotypic markers for psychiatric illnesses such as schizophrenia and bipolar disorder and anxiety-like behavior, respectively [116]. In addition, FABPs seem to be a downstream effector of the NOTCH (neurogenic locus notch homolog proteins) signaling, which was associated with an increased risk for posttraumatic stress disorder based on the findings derived from integrated genetic, epigenetic, and gene set enrichment analyses among survivors of war and genocide [117]. However, serum FABP levels were higher in SO patients than non-SO counterparts, and multiple regression also confirmed its independent/predictive role in determining the prevalence of SO [118], yet what FABP members were examined was not clearly specified. Given that FABPs are members of the superfamily of lipid-binding proteins comprising nine different members, a comprehensive analysis of FABP members at different levels (genetic, epigenetic, translational, posttranslational, tissue distribution, and cellular localization) should be conducted to elucidate the precise role of circulating FABP in SO-associated psychiatric illnesses.

Resistin: Resistin, an adipocyte-derived hormone, has been suggested to play an important role in obesity, IR, and diabetes [119]. In humans, resistin was the first to be described as a contributing factor to IR and diabetes. It was shown that serum levels of resistin were consistently higher in both high-fat-diet-induced and genetically modified obese mice than age-matched counterparts [120]. Meanwhile, treatments targeting resistin, such as antidiabetic medication, immunoneutralization, and gene repression, could significantly improve insulin sensitivity and glucose metabolism in experimental obese mouse models and T2D patients [119,121,122].

In older adults, circulating resistin levels were associated with low muscle mass [123,124], increased sarcopenia/frailty risk [125,126], and higher serum levels of proinflammatory cytokines (e.g., CRP, IL-18, and TNF- α) [124,127]. Recently, an observational study has shown that the resistin G-A haplotype at single nucleotide polymorphism-420/-358 was independently associated with SO, independent of age and sex, with adjustment for other confounding factors [128]. In MDD and bipolar disorder, serum resistin levels were significantly higher in patients than in healthy controls [129,130], underlying its possible role in the pathogenesis of mental disorders, especially depression and bipolar disorder. Clinically, serum resistin also had a fairly predictive performance for MDD (AUC: 0.746).

3.6. Altered myokine secretions

Synthesized and secreted by myocytes, myokines are important mediators that show potentially pleiotropic influences on non-muscle tissues or organs, including the brain. Myokines act through autocrine, paracrine, and endocrine signaling to elicit diverse biological functions at the cellular level, in skeletal muscle and other organs. Current reviews highlighted 14 myokines [e.g., apelin, BDNF, fibroblast growth factor 21 (FGF21), IGF-1, IL-6, irisin, myostatin] that are highly associated with age-related muscle atrophy. Dysregulation of myokine secretion (e.g., BDNF, irisin, FGF21, apelin, and myostatin) triggered by excessive myocellular infiltration of lipids has also been largely implicated in various central nervous system (CNS) diseases [131–136]. Although myostatin has been extensively studied to be an accurate diagnostic marker for discriminating sarcopenic patients, it is mostly reported to be associated with cognitive defects, but not mental disorders [137], and its signaling downstream (presenilin 1) has been shown to have no association with late-onset depressive disorder subsequent to Alzheimer's disease [138]. Therefore, in this section, we only focus on four myokines (BDNF, irisin, FGF21, and apelin) that are highly associated with mental illnesses.

BDNF: Dysfunction of neural plasticity due to neurotrophic factor deficiency, especially within the hippocampus, is a key mechanism in the onset of depression. Contracting skeletal muscle is a major source of neurotrophic factors that are known to play a central role in mood and behavior. BDNF is among the most representative neurotrophic factors for depression [132]. In sarcopenia, low levels of BDNF were also significantly associated with reduced muscle protein synthesis, increased muscle protein degradation, impaired mitochondrial function, augmented oxidative stress, and impaired neuromuscular junction integrity [139]. Within the hippocampus, BDNF is mainly responsible for neurogenesis, neural growth and development, neuronal survival, neuroplasticity, and synaptogenesis through neurotrophic receptor tyrosine kinase 2 (TrkB) signaling (e.g., Ras/MAPK or PI3K/Akt pathways). In pathophysiology, reduced expression or increased promoter methylation of BDNF was associated with early onset and greater severity of depression in humans and rodents [131,132]. Evidence from meta-analyses has shown that low circulating BDNF concentrations are observed in untreated depressed patients versus antidepressant-treated patients and healthy controls [140,141]. By successful treatment with antidepressant medications or electroconvulsive therapy, serum BDNF levels in depressed patients can be effectively normalized [131,132]. Of note, over the course of antidepressant treatment, larger alleviation of depressive symptom severity has been brought about by a larger increase in blood/serum BDNF levels, suggesting an association between increased BDNF levels and successful antidepressant treatments [141]. These observations strongly suggest an important role of BDNF-involved pathways in the pathogenesis of depression and in typical antidepressant treatments.

Irisin: Secretion of irisin is mediated through the enzymatic cleavage of the membrane-bound precursor fibronectin type III domain-containing protein 5. In healthy elderly, serum irisin was suggested to be a valid biomarker for improved muscle strength [142]. On the other hand, low circulatory levels of irisin were shown to be a significant predictor for sarcopenia and sarcopenia-associated health consequences (e.g., accidental falls) in older people with or without co-morbidities, including obesity and T2D [143–145]. On the other hand, the exogenous administration of recombinant irisin has been proven effective to alleviate age-related sarcopenia in experimental animals [92], substantiating its clinical relevance in sarcopenia and its potential therapeutic roles against muscle wasting. In a chronically stressed rodent model, exogenous irisin injection could suppress depressive-

like behavior through regulation of glucose metabolism in the prefrontal cortex [146,147]. In ischemic stroke patients, serum irisin is a powerful biomarker for post-stroke depression due to a greater discriminatory ability when the irisin levels are added in receiver operating characteristic analysis (from 0.77 to 0.81, 95% CI [0.76, 0.86]) [146,148].

FGF21: FGF21 is an endocrinal hormone-like or paracrine signaling molecule derived from multiple organs (e.g., liver, adipose tissue, and muscle) primarily involved in energy metabolism. Through targeting specific cell surface Trk receptors (e.g., FGF receptor 1c) with Beta-Klotho as a cofactor, FGF21 triggers a multitude of intracellular signaling cascades, for example, PI3K/Akt, MAPK, and STAT pathways, in a tissue-specific manner [149]. In T2D rodents, an 8-week resistance training was suggested to increase skeletal muscle levels (soleus and extensor digitorum longus) of FGF21 [150]. Meanwhile, the muscle levels of FGF21 showed positive correlations with grip strength. Further, our earlier study has provided evidence of antidepressant effects of exercise in rodents through the FGF21–adiponectin axis in hippocampal amelioration of neuroinflammation, neurogenesis, and synaptic plasticity [151]. Other studies also resonated well with our findings that exogenous FGF21 injection could alleviate depressive-like behavior in vivo via microglial suppression of proinflammatory signaling [152]. These findings have important implications for the potential central actions of FGF21 in the genesis and symptom severity of mental disorders.

Apelin: Apelin is an endogenous ligand for the G-protein-coupled receptor APJ (APLNR). The apelin/APJ system is involved in a number of physiological and pathological processes, including energy metabolism, fluid homeostasis, heart failure, hypertension, and cardiovascular diseases. Of note, apelin is an exercise-induced myokine capable of countering age-related loss of skeletal muscle mass, quality, and strength. Recently, functional experiments using both knockout and ectopic-expressing approaches in rodents have illustrated that apelin is an essential peptide in delaying and reversing age-related sarcopenia [153]. In older adults, after 6 months of exercise training, plasma levels of apelin were significantly augmented, and the levels were positively correlated with short physical performance battery scores (i.e., higher scores indicate better mobility). A systematic review also highlighted that exercise interventions (resistance, aerobic, and combined) favored the production of serum apelin, and exercise effects were apparently observed in older adults [154]. Since *APNR* mRNA is abundantly found in the CNS (especially amygdala, hypothalamus, Ammon's horn, and dentate gyrus) [136], the apelin/APJ system is highly speculated to play an important role in brain functions, especially emotional behavior. In rodents, brain infusion of apelin-13 was shown to abrogate chronic stress-induced depressive-like behavior via upregulation of BDNF in the amelioration of HPA axis and hippocampal glucocorticoid receptor dysfunctions [155,156]. Serum apelin levels were also associated with depressive disorders in patients with chronic conditions [157,158]. This substantial body of evidence constitutes a potential link among physical activity/exercise, skeletal muscle capacities, and depressive symptoms, likely through the apelin/APJ system.

3.7. Novel insights gained from an experimental animal study: dysregulated cellular store-operated calcium entry

Store-operated calcium entry is a vital process to maintain intracellular metabolic homeostasis in response to the depletion of Ca^{2+} [159]. Cellular Ca^{2+} imbalance, especially aberrantly increased intracellular Ca^{2+} entry, has been implicated in endothelial dysfunction [160], cardiovascular

diseases [160,161], dysregulated immune responses [162], and acute/chronic neurodegenerative diseases (e.g., brain ischemia, Alzheimer's disease, and Parkinson's disease) [163].

Homozygous deletion of store-operated calcium entry regulatory factor (SARAF) has been shown to induce age-dependent symptoms resembling SO with body weight gain, increased fat mass, reduced lean mass, lower metabolic rate, reduced locomotion, and abdominal fat accumulation in experimental elderly mice [69]. Deficiency of SARAF has also led to reduced hippocampal cell proliferation, HPA axis activation, and anxiety-like behaviors. However, the peripheral-central linkage(s) of SARAF remain to be explored, because a whole-body SARAF-knockout approach was adopted. In other words, whether the SARAF ablation occurred in the brain and peripheral tissues independently or whether the consequences associated with SARAF deficiency in central and peripheral tissues exacerbate one another remains largely elusive. One possible explanation is the involvement of circulatory immune cells with SARAF deficiency that produces proinflammatory cytokines, triggering BBB disruption and hence favoring the influx of peripheral tissue factors (e.g., adipokines) into the brain [81,162]. In immune cells, stimulation of Ca^{2+} channels, including transient receptor potential (TRP) ion channels, Orai1/stromal interaction molecule 1, and L-type channels (Cav1), has been suggested to induce production and release of proinflammatory cytokines through orchestrating a number of intracellular signaling cascades, such as JNK/STAT1/6, AKT/MAPK/NF- κ B, AKT/mTOR, and JAK/STAT3 [160,164,165] (Figure 4). As aforesaid, systemic inflammatory factors (e.g., TNF- α , IL-6, IGF-1, and CRP) demonstrated neurobiological relevance to the occurrence of psychiatric disorders [82]. The interaction has also been substantiated by previous findings reporting the effects of anti-inflammatory drugs (e.g., anti-TNF- α) superior to or comparable with classical medications in treating mental disorders [84,85]. Figure 5 summarizes how BBB destruction induced by peripheral inflammation, oxidative stress, and SARAF-deficient immune cell responses allows the flow of peripheral tissue factors (e.g., leptin, adiponectin, FABP, resistin, BDNF, irisin, FGF21, and apelin) into the brain, causing CNS diseases, including mental disorders.

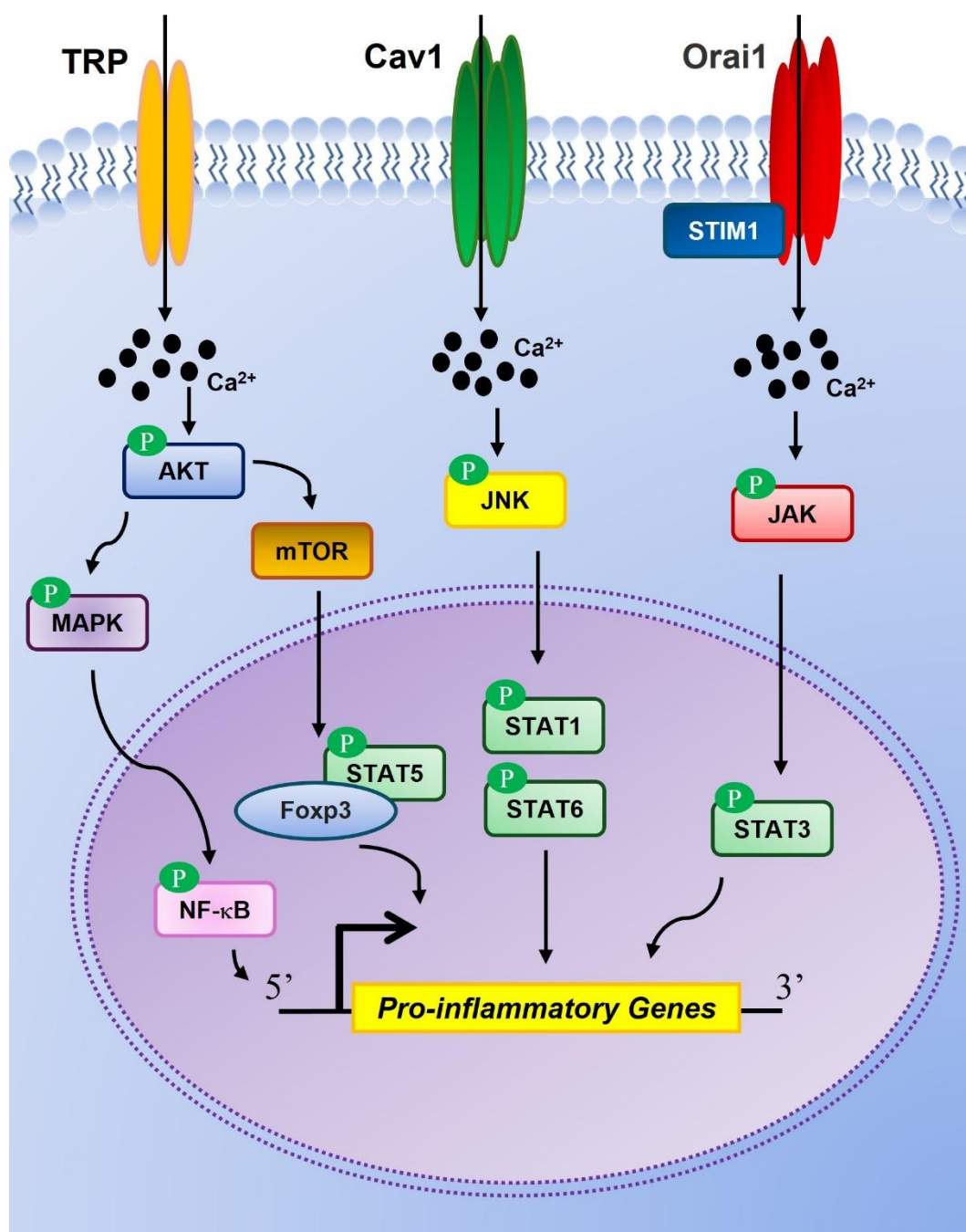


Figure 4. Role of store-operated Ca^{2+} entry and inflammation. Influx of calcium ions into immune cells triggers phosphorylation and nuclear translocation of NF- κ B by the activation of MAPK pathways, phosphorylation of JNK/STAT1 or STAT6, and activation of AKT/mTOR/STAT5-Foxp3 pathway, resulting in proinflammatory gene transcription. Abbreviations: AKT, protein kinase B; Cav1, L-type channels; Foxp3, forkhead box P3; JAK; Janus kinase; JNK, Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor kappa B; STAT, signal transducer and activator of transcription; STIM1, stromal interaction molecule 1; TRP, transient receptor potential ion channels.

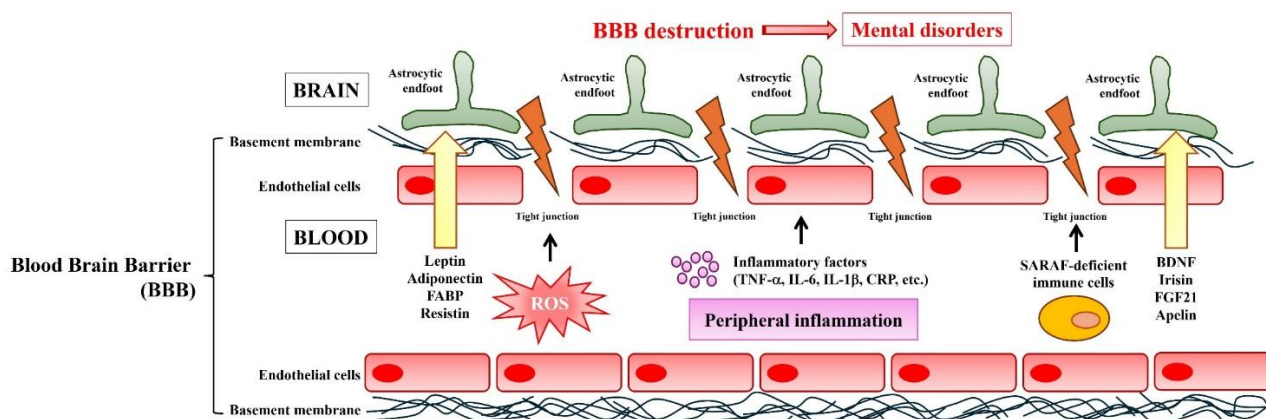


Figure 5. Blood–brain barrier destruction caused by peripheral inflammation, oxidative stress, and store-operated calcium entry regulatory factor-deficient immune cells, leading to the influx of peripheral tissue factors (e.g., leptin, adiponectin, FABP, resistin, BDNF, irisin, FGF21, and apelin) into the brain. Potential mechanisms of BBB destruction include alterations in tight junctions, endothelial damage, penetration of peripheral immune cells, and altered receptors and transport pathways. Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; FABP, fatty acid–binding proteins; FGF21, fibroblast growth factor 21; IL-1 β , interleukin-1beta; IL-6, interleukin-6; ROS, reactive oxygen species; SARAF, store-operated calcium entry regulatory factor; TNF- α , tumor necrosis factor alpha.

4. Conclusion

This paper provides a comprehensive review of the intricate relationship between SO and mental health among older adults, highlighting the pathophysiological mechanisms involved linking peripheral signals to mental health consequences. The evidence reviewed indicates that SO significantly increases the risk of mental disorders, particularly depression, through various mechanisms such as HPA axis dysregulation, chronic systemic low-grade inflammation, oxidative stress, an imbalance between adipokines and myokines, and BBB disruption caused by store-operated calcium entry regulatory factor-deficient immune cells. Our earlier review has also highlighted an emerging research area on linking the microbiota–gut–brain axis to psychiatric outcomes, especially depression and anxiety [166]. However, scientific evidence of how the axis works and contributes to psychiatric disease onset and progression in SO is still very limited, although epigenetic aberrations and microRNAs (miRNAs) may play a role in modulating the causal relationship between microbiota composition and depressive and anxiety behaviors. Future clinical studies under well-controlled experimental conditions, especially adjusted for confounding lifestyle factors (e.g., physical activity, diet, and medication), targeting specific brain regions, including the prefrontal cortex, hippocampus, dorsal raphe nucleus, and amygdala, that are associated with mental disorders, should be conducted. Meanwhile, targeted interventions on gut microbiota–associated miRNA alterations (e.g., miR-137, miR-124, and miR-34a) that demonstrated strong implications for depression and anxiety could pave the way for new therapeutic targets and/or novel biomarker identification in the context of SO-related mental health.

The contributions of this review are twofold: first, it consolidates recent research on mechanistic pathways linking SO to mental health, paving the way for future investigations and targeted interventions. Second, since recent evidence has supported muscle strengthening as the most powerful intervention among other physical training to stimulate the release of myokines (e.g., BDNF and irisin) in response to skeletal muscle contraction [167], which are strongly associated with lower prevalence of mental disorders, peripheral interventions specifically targeting the myokine secretion pathways may shed light on possible future therapeutic options in SO.

Despite the strengths of this review, including a thorough examination of both clinical and preclinical studies, several limitations are acknowledged. The reliance on studies conducted over the past five years may not capture all relevant literature; also, variations in methodology among the included studies and limited clinical studies in human beings could influence the generalizability of the findings. Further high-quality interventional studies (e.g., RCTs) are imperatively needed to verify the pathophysiological mechanisms and clinical outcomes in older adults with SO. Additionally, while the complex interplay of factors contributing to SO and mental health was addressed, the exploration of potential confounding variables remains limited. Besides, interpretation of the findings should be cautious because only a few relevant, current studies were identified. Therefore, the molecular mechanisms proposed here across different populations (e.g., T2D patients, MDD patients, younger human cohorts, and experimental animals) deserve further investigation.

In conclusion, understanding the cellular/molecular mechanisms underlying the connections between SO and mental health is crucial for developing effective therapeutic strategies. This review also highlights the need for continued research in this area, focusing on evidence-based biomarker identification and therapeutic strategies to improve health outcomes for the aging population facing the dual challenges of sarcopenia and obesity.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Authors' contributions

Leung WKC, Yau SSY, Lam SC, and Suen LKP conceived and designed the study. Leung WKC and Yau SSY designed search strategies. Leung WKC and Yau CYC conducted literature search and data extraction. Leung WKC prepared figures 1–5, tables 1–5, and appendices 1–3. Leung WKC, Yau SSY, Yau CYC, Lam SC, and Suen LKP reviewed, commented on, and edited the main content. All authors read and approved of the final manuscript.

Conflict of interest

Lorna Kwai Ping Suen is an editorial board member for AIMS Public Health and was not involved in the editorial review or the decision to publish this article. The authors declare no financial or non-financial competing interests.

References

1. Rosenberg IH (1997) Sarcopenia: origins and clinical relevance. *J Nutr* 127: 990S–991S. <https://doi.org/10.1093/jn/127.5.990S>
2. Petermann-Rocha F, Balntzi V, Gray SR, et al. (2022) Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 13: 86–99. <https://doi.org/10.1002/jcsm.12783>
3. Shafiee G, Keshtkar A, Soltani A, et al. (2017) Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population studies. *J Diabetes Metab Disord* 16: 21. <https://doi.org/10.1186/s40200-017-0302-x>
4. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. (2010) Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 39: 412–423. <https://doi.org/10.1093/ageing/afq034>
5. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. (2019) Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 48: 601. <https://doi.org/10.1093/ageing/afz046>
6. Chen LK, Liu LK, Woo J, et al. (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>
7. Chen LK, Woo J, Assantachai P, et al. (2020) Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 21: 300–307.e2. <https://doi.org/10.1016/j.jamda.2019.12.012>
8. Fielding RA, Vellas B, Evans WJ, et al. (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 12: 249–256. <https://doi.org/10.1016/j.jamda.2011.01.003>
9. Studenski SA, Peters KW, Alley DE, et al. (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 69: 547–558. <https://doi.org/10.1093/gerona/glu010>
10. Woo J (2017) Sarcopenia. *Clin Geriatr Med* 33: 305–314. <https://doi.org/10.1016/j.cger.2017.02.003>

11. Axelrod CL, Dantas WS, Kirwan JP (2023) Sarcopenic obesity: emerging mechanisms and therapeutic potential. *Metabolism* 146: 155639. <https://doi.org/10.1016/j.metabol.2023.155639>
12. Landi F, Cruz-Jentoft AJ, Liperoti R, et al. (2013) Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age Ageing* 42: 203–209. <https://doi.org/10.1093/ageing/afs194>
13. McKee AM, Morley JE (2000) Obesity in the elderly. [cited 2026 April 29]. Available from: <https://www.ncbi.nlm.nih.gov/sites/books/NBK532533/>.
14. Donini LM, Busetto L, Bischoff SC, et al. (2022) Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Obes Facts* 15: 321–335. <https://doi.org/10.1159/000521241>
15. Li J, Lin Y, Deng H, et al. (2024) Association of visceral adiposity index with sarcopenia based on NHANES data. *Sci Rep* 14: 21169. <https://doi.org/10.1038/s41598-024-72218-0>
16. De Lorenzo A, Itani L, El Ghoch M, et al. (2024) The association between sarcopenic obesity and DXA-Derived Visceral Adipose Tissue (VAT) in adults. *Nutrients* 16: 1645. <https://doi.org/10.3390/nu16111645>
17. Lu Z, Hu Y, He H, et al. (2024) Associations of muscle mass, strength, and quality with diabetes and the mediating role of inflammation in two national surveys from China and the United States. *Diabetes Res Clin Pract* 214: 111783. <https://doi.org/10.1016/j.diabres.2024.111783>
18. Collazo-Castineira P, Sanchez-Izquierdo M, Reiter LJ, et al. (2024) Analysis of behavioral change techniques used in exercise and nutritional interventions targeting adults around retirement age with sarcopenic obesity in a systematic review. *Arch Gerontol Geriatr* 123: 105437. <https://doi.org/10.1016/j.archger.2024.105437>
19. Zhang N, He J, Qu X, et al. (2024) Research hotspots and trends of interventions for sarcopenic obesity: a bibliometric analysis. *Cureus* 16: e64687. <https://doi.org/10.7759/cureus.64687>
20. Wu H, Chen X, Shi Z, et al. (2024) The L-shaped relationship between composite dietary antioxidant index and sarcopenic obesity in elderly adults: a cross-sectional study. *Front Nutr* 11: 1428856. <https://doi.org/10.3389/fnut.2024.1428856>
21. Janssen I, Heymsfield SB, Ross R (2002) Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 50: 889–896. <https://doi.org/10.1046/j.1532-5415.2002.50216.x>
22. Batsis JA, Barre LK, Mackenzie TA, et al. (2013) Variation in the prevalence of sarcopenia and sarcopenic obesity in older adults associated with different research definitions: dual-energy X-ray absorptiometry data from the National Health and Nutrition Examination Survey 1999–2004. *J Am Geriatr Soc* 61: 974–980. <https://doi.org/10.1111/jgs.12260>
23. WHO (2000) Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 894: i–xii, 1–253.
24. Consultation WHOE (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 363: 157–163. [https://doi.org/10.1016/S0140-6736\(03\)15268-3](https://doi.org/10.1016/S0140-6736(03)15268-3)
25. National Institutes of Health (1998) Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res* 6 Suppl 2: 51S–209S.

26. Misra A, Vikram NK, Gupta R, et al. (2006) Waist circumference cutoff points and action levels for Asian Indians for identification of abdominal obesity. *Int J Obes (Lond)* 30: 106–111. <https://doi.org/10.1038/sj.ijo.0803111>
27. Gallagher D, Heymsfield SB, Heo M, et al. (2000) Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr* 72: 694–701. <https://doi.org/10.1093/ajcn/72.3.694>
28. Dodds RM, Syddall HE, Cooper R, et al. (2014) Grip strength across the life course: normative data from twelve British studies. *PLoS One* 9: e113637. <https://doi.org/10.1371/journal.pone.0113637>
29. Cesari M, Kritchevsky SB, Newman AB, et al. (2009) Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. *J Am Geriatr Soc* 57: 251–259. <https://doi.org/10.1111/j.1532-5415.2008.02126.x>
30. Guimaraes NS, Reis MG, Tameirao DR, et al. (2024) Factors associated with sarcopenic obesity in Brazilian adults and older people: Systematic review and meta-analysis of observational studies. *Geriatr Gerontol Int* 24: 661–674. <https://doi.org/10.1111/ggi.14918>
31. Gao Q, Mei F, Shang Y, et al. (2021) Global prevalence of sarcopenic obesity in older adults: A systematic review and meta-analysis. *Clin Nutr* 40: 4633–4641. <https://doi.org/10.1016/j.clnu.2021.06.009>
32. Yang J, Wang Y, Shi X, et al. (2024) Prevalence of sarcopenic obesity among older adults in communities of China: A multicenter, cross-sectional study. *Nutr Clin Pract* 39: 1375–1387. <https://doi.org/10.1002/ncp.11214>
33. Baygi F, Buhl SF, Thilsing T, et al. (2024) Sarcopenia and sarcopenic obesity among older adults in the nordic countries: a scoping review. *BMC Geriatr* 24: 421. <https://doi.org/10.1186/s12877-024-04970-x>
34. Habboub B, Speer R, Gosch M, et al. (2025) The diagnosis and treatment of sarcopenia and sarcopenic obesity. *Dtsch Arztebl Int* 122: 121–126. <https://doi.org/10.3238/arztebl.m2025.0004>
35. Diago-Galmes A, Guillamon-Escudero C, Tenias-Burillo JM, et al. (2023) Sarcopenic obesity in community-dwelling spanish adults older than 65 years. *Nutrients* 15: 4932. <https://doi.org/10.3390/nu15234932>
36. Lu L, He X, Song Y, et al. (2022) Prevalence and risk factors of sarcopenia without obesity and sarcopenic obesity among Chinese community older people in suburban area of Shanghai: A cross-sectional study. *Front Aging Neurosci* 14: 1034542. <https://doi.org/10.3389/fnagi.2022.1034542>
37. Verma M, Kapoor N, Chaudhary A, et al. (2022) Prevalence and determinants of sarcopenic obesity in older adults: secondary data analysis of the longitudinal ageing study in India (LASI) wave 1 survey (2017–18). *Adv Ther* 39: 4094–4113. <https://doi.org/10.1007/s12325-022-02216-z>
38. Benz E, Pinel A, Guillet C, et al. (2024) Sarcopenia and sarcopenic obesity and mortality among older people. *JAMA Netw Open* 7: e243604. <https://doi.org/10.1001/jamanetworkopen.2024.3604>
39. Atmis V, Yalcin A, Silay K, et al. (2019) The relationship between all-cause mortality sarcopenia and sarcopenic obesity among hospitalized older people. *Aging Clin Exp Res* 31: 1563–1572. <https://doi.org/10.1007/s40520-019-01277-5>
40. Atkins JL, Wannamathée SG (2020) Sarcopenic obesity in ageing: cardiovascular outcomes and mortality. *Br J Nutr* 124: 1102–1113. <https://doi.org/10.1017/S0007114520002172>

41. Du Y, Wang X, Xie H, et al. (2019) Sex differences in the prevalence and adverse outcomes of sarcopenia and sarcopenic obesity in community dwelling elderly in East China using the AWGS criteria. *BMC Endocr Disord* 19: 109. <https://doi.org/10.1186/s12902-019-0432-x>
42. Bauer JM, Cruz-Jentoft AJ, Fielding RA, et al. (2019) Is there enough evidence for osteosarcopenic obesity as a distinct entity? A critical literature review. *Calcif Tissue Int* 105: 109–124. <https://doi.org/10.1007/s00223-019-00561-w>
43. Booranasuksakul U, Tsintzas K, Macdonald I, et al. (2024) Application of a new definition of sarcopenic obesity in middle-aged and older adults and association with cognitive function: Findings from the National Health and Nutrition Examination Survey 1999–2002. *Clin Nutr ESPEN* 63: 919–928. <https://doi.org/10.1016/j.clnesp.2024.08.017>
44. Bahat G, Oren MM, Yilmaz O, et al. (2018) Comparing SARC-F with SARC-CalF to screen sarcopenia in community living older adults. *J Nutr Health Aging* 22: 1034–1038. <https://doi.org/10.1007/s12603-018-1072-y>
45. da Luz MCL, Pinho CPS, Bezerra GKA, et al. (2021) SARC-F and SARC-CalF in screening for sarcopenia in older adults with Parkinson's disease. *Exp Gerontol* 144: 111183. <https://doi.org/10.1016/j.exger.2020.111183>
46. Barreto de Lima A, Dos Santos Ribeiro G, Henriques-Neto D, et al. (2023) Diagnostic performance of SARC-F and SARC-CalF in screening for sarcopenia in older adults in Northern Brazil. *Sci Rep* 13: 11698. <https://doi.org/10.1038/s41598-023-39002-y>
47. Guo JY, Yu K, Li CW, et al. (2024) The application of Chinese version of SARC-F and SARC-CalF in sarcopenia screening against five definitions: a diagnostic test accuracy study. *BMC Geriatr* 24: 883. <https://doi.org/10.1186/s12877-024-05460-w>
48. Chen TP, Kao HH, Ogawa W, et al. (2025) The Asia–Oceania consensus: Definitions and diagnostic criteria for sarcopenic obesity. *Obes Res Clin Pract* 19: 185–192. <https://doi.org/10.1016/j.orcp.2025.05.001>
49. WHO (2022) Mental health. [cited 2026 April 29]. Available from: https://www.who.int/health-topics/mental-health#tab=tab_1.
50. Hamer M, Batty GD, Kivimaki M (2015) Sarcopenic obesity and risk of new onset depressive symptoms in older adults: English Longitudinal Study of Ageing. *Int J Obes (Lond)* 39: 1717–1720. <https://doi.org/10.1038/ijo.2015.124>
51. Venant V, Pouget M, Lahaye C, et al. (2019) Depression severity as a risk factor of sarcopenic obesity in morbidly obese patients. *J Nutr Health Aging* 23: 761–767. <https://doi.org/10.1007/s12603-019-1218-6>
52. Ye C, Chen G, Huang W, et al. (2025) Association between skeletal muscle mass to visceral fat area ratio and depression: A cross-sectional study based on the National Health and Nutrition Examination Survey. *J Affect Disord* 372: 314–323. <https://doi.org/10.1016/j.jad.2024.12.041>
53. Fonfria-Vivas R, Perez-Ros P, Barrachina-Igual J, et al. (2023) Assessing quality of life with SarQol is useful in screening for sarcopenia and sarcopenic obesity in older women. *Aging Clin Exp Res* 35: 2069–2079. <https://doi.org/10.1007/s40520-023-02488-7>
54. Pilati I, Slee A, Frost R (2022) Sarcopenic obesity and depression: A systematic review. *J Frailty Aging* 11: 51–58. <https://doi.org/10.14283/jfa.2021.39>
55. Khatoon BS, Saravanan D, Ganamurali N, et al. (2023) A narrative review on the impact of sarcopenic obesity and its psychological consequence in quality of life. *Diabetes Metab Syndr* 17: 102846. <https://doi.org/10.1016/j.dsx.2023.102846>

56. Kumari M, Khanna A (2023) Sarcopenic obesity and its impact on quality of life: A concise review. *Curr Aging Sci* 16: 194–198. <https://doi.org/10.2174/1874609816666230525161020>
57. Roh E, Choi KM (2020) Health consequences of sarcopenic obesity: A narrative review. *Front Endocrinol (Lausanne)* 11: 332. <https://doi.org/10.3389/fendo.2020.00332>
58. Cheah LJ, Cheah KJ (2024) The interplay of sarcopenic obesity and mental health: a complex relationship, In: Himmerich H, editor, *Weight Loss – A Multidisciplinary Perspective*. <https://doi.org/10.5772/intechopen.1004582>
59. Blum K, Gold MS, Llanos-Gomez L, et al. (2021) Hypothesizing nutrigenomic-based precision anti-obesity treatment and prophylaxis: should we be targeting sarcopenia induced brain dysfunction? *Int J Environ Res Public Health* 18: 9774. <https://doi.org/10.3390/ijerph18189774>
60. WHO (2024) Ageing and health. [cited 2026 April 29]. Available from: <https://www.who.int/news-room/fact-sheets/detail/ageing-and-health>.
61. Sukhera J (2022) Narrative reviews: flexible, rigorous, and practical. *J Grad Med Educ* 14: 414–417. <https://doi.org/10.4300/JGME-D-22-00480.1>
62. Ferrari R (2015) Writing narrative style literature reviews. *Medical Writing* 24: 230–235. <https://doi.org/10.1179/2047480615Z.000000000329>
63. Baethge C, Goldbeck-Wood S, Mertens S (2019) SANRA—a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* 4: 5. <https://doi.org/10.1186/s41073-019-0064-8>
64. JAND (2024) Research Reporting Checklists: Narrative Review. [cited 2026 April 29]. Available from: https://legacyfileshare.elsevier.com/promis_misc/ANDJ%20Narrative%20Review%20Checklist.pdf.
65. Pollock D, Peters MDJ, Khalil H, et al. (2023) Recommendations for the extraction, analysis, and presentation of results in scoping reviews. *JBI Evid Synth* 21: 520–532. <https://doi.org/10.11124/JBIES-22-00123>
66. Leung WK, Gao L, Siu PM, et al. (2016) Diabetic nephropathy and endothelial dysfunction: Current and future therapies, and emerging of vascular imaging for preclinical renal-kinetic study. *Life Sci* 166: 121–130. <https://doi.org/10.1016/j.lfs.2016.10.015>
67. Pasco JA, Berk M, Penninx B, et al. (2023) Obesity and sarcopenic obesity characterized by low-grade inflammation are associated with increased risk for major depression in women. *Front Nutr* 10: 1222019. <https://doi.org/10.3389/fnut.2023.1222019>
68. Lee H, Kim SY, Lim Y (2024) Solanum melongena extract supplementation protected skeletal muscle and brain damage by regulation of BDNF/PGC1alpha/irisin pathway via brain function-related myokines in high-fat diet induced obese mice. *J Nutr Biochem* 124: 109537. <https://doi.org/10.1016/j.jnutbio.2023.109537>
69. Gataulin D, Kuperman Y, Tsoory M, et al. (2023) Store-operated Ca(2+) entry regulatory factor alters murine metabolic state in an age-dependent manner via hypothalamic pathways. *PNAS Nexus* 2: pgad068. <https://doi.org/10.1093/pnasnexus/pgad068>
70. Gaffey AE, Bergeman CS, Clark LA, et al. (2016) Aging and the HPA axis: Stress and resilience in older adults. *Neurosci Biobehav Rev* 68: 928–945. <https://doi.org/10.1016/j.neubiorev.2016.05.036>
71. Gao LL, Chen Y, Dai T, et al. (2025) Gut-muscle axis crosstalk in age-related sarcopenia: mechanisms and therapeutic targets. *Front Microbiol* 16: 1638880. <https://doi.org/10.3389/fmicb.2025.1638880>

72. Wang W, Feng J, Ji C, et al. (2017) Increased methylation of glucocorticoid receptor gene promoter 1(F) in peripheral blood of patients with generalized anxiety disorder. *J Psychiatr Res* 91: 18–25. <https://doi.org/10.1016/j.jpsychires.2017.01.019>
73. Iob E, Kirschbaum C, Steptoe A (2020) Persistent depressive symptoms, HPA-axis hyperactivity, and inflammation: the role of cognitive–affective and somatic symptoms. *Mol Psychiatry* 25: 1130–1140. <https://doi.org/10.1038/s41380-019-0501-6>
74. Rhebergen D, Korten NC, Penninx BW, et al. (2015) Hypothalamic-pituitary-adrenal axis activity in older persons with and without a depressive disorder. *Psychoneuroendocrinology* 51: 341–350. <https://doi.org/10.1016/j.psyneuen.2014.10.005>
75. Armandi A, Rosso C, Caviglia GP, et al. (2021) The impact of dysmetabolic sarcopenia among insulin sensitive tissues: a narrative review. *Front Endocrinol (Lausanne)* 12: 716533. <https://doi.org/10.3389/fendo.2021.716533>
76. Antuna E, Cachan-Vega C, Bermejo-Millo JC, et al. (2022) Inflammaging: Implications in sarcopenia. *Int J Mol Sci* 23: 15039. <https://doi.org/10.3390/ijms232315039>
77. Chen YF, Lee CW, Wu HH, et al. (2022) Immunometabolism of macrophages regulates skeletal muscle regeneration. *Front Cell Dev Biol* 10: 948819. <https://doi.org/10.3389/fcell.2022.948819>
78. Cheng Y, Lin S, Cao Z, et al. (2025) The role of chronic low-grade inflammation in the development of sarcopenia: Advances in molecular mechanisms. *Int Immunopharmacol* 147: 114056. <https://doi.org/10.1016/j.intimp.2025.114056>
79. Franco-Romero A, Sandri M (2021) Role of autophagy in muscle disease. *Mol Aspects Med* 82: 101041. <https://doi.org/10.1016/j.mam.2021.101041>
80. Beberashvili I, Azar A, Khatib A, et al. (2023) Sarcopenic obesity versus nonobese sarcopenia in hemodialysis patients: differences in nutritional status, quality of life, and clinical outcomes. *J Ren Nutr* 33: 147–156. <https://doi.org/10.1053/j.jrn.2022.05.003>
81. Varatharaj A, Galea I (2017) The blood-brain barrier in systemic inflammation. *Brain Behav Immun* 60: 1–12. <https://doi.org/10.1016/j.bbi.2016.03.010>
82. Yuan N, Chen Y, Xia Y, et al. (2019) Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl Psychiatry* 9: 233. <https://doi.org/10.1038/s41398-019-0570-y>
83. Zeng Y, Chourpiliadis C, Hammar N, et al. (2024) Inflammatory biomarkers and risk of psychiatric disorders. *JAMA Psychiatry* 81: 1118–1129. <https://doi.org/10.1001/jamapsychiatry.2024.2185>
84. Fitton R, Sweetman J, Heseltine-Carp W, et al. (2022) Anti-inflammatory medications for the treatment of mental disorders: A scoping review. *Brain Behav Immun Health* 26: 100518. <https://doi.org/10.1016/j.bbih.2022.100518>
85. Fond G (2014) Inflammation in psychiatric disorders. *Eur Psychiatry* 29: 551–552. <https://doi.org/10.1016/j.eurpsy.2014.09.347>
86. Gonzalez A, Simon F, Achiardi O, et al. (2021) The critical role of oxidative stress in sarcopenic obesity. *Oxid Med Cell Longev* 2021: 4493817. <https://doi.org/10.1155/2021/4493817>
87. Song K, Li Y, Zhang H, et al. (2020) Oxidative stress-mediated Blood-Brain Barrier (BBB) disruption in neurological diseases. *Oxid Med Cell Longev* 2020: 4356386. <https://doi.org/10.1155/2020/4356386>
88. Salim S (2014) Oxidative stress and psychological disorders. *Curr Neuropharmacol* 12: 140–147. <https://doi.org/10.2174/1570159X11666131120230309>

89. Lenzi J, Rodrigues AF, Ros Ade S, et al. (2015) Ferulic acid chronic treatment exerts antidepressant-like effect: role of antioxidant defense system. *Metab Brain Dis* 30: 1453–1463. <https://doi.org/10.1007/s11011-015-9725-6>
90. Zhu X, Zhang YM, Zhang MY, et al. (2021) Hesperetin ameliorates diabetes-associated anxiety and depression-like behaviors in rats via activating Nrf2/ARE pathway. *Metab Brain Dis* 36: 1969–1983. <https://doi.org/10.1007/s11011-021-00785-6>
91. Jorgensen A, Baago IB, Rygner Z, et al. (2022) Association of oxidative stress-induced nucleic acid damage with psychiatric disorders in adults: a systematic review and meta-analysis. *JAMA Psychiatry* 79: 920–931. <https://doi.org/10.1001/jamapsychiatry.2022.2066>
92. Paoletti I, Coccurello R (2024) Irisin: A multifaceted hormone bridging exercise and disease pathophysiology. *Int J Mol Sci* 25: 13480. <https://doi.org/10.3390/ijms252413480>
93. Coles CA (2016) Adipokines in healthy skeletal muscle and metabolic disease. *Adv Exp Med Biol* 900: 133–160. https://doi.org/10.1007/978-3-319-27511-6_6
94. Kohara K, Ochi M, Tabara Y, et al. (2011) Leptin in sarcopenic visceral obesity: possible link between adipocytes and myocytes. *PLoS One* 6: e24633. <https://doi.org/10.1371/journal.pone.0024633>
95. Barakat B, Almeida MEF (2021) Biochemical and immunological changes in obesity. *Arch Biochem Biophys* 708: 108951. <https://doi.org/10.1016/j.abb.2021.108951>
96. Burrows K, McNaughton BA, Figueroa-Hall LK, et al. (2023) Elevated serum leptin is associated with attenuated reward anticipation in major depressive disorder independent of peripheral C-reactive protein levels. *Sci Rep* 13: 11313. <https://doi.org/10.1038/s41598-023-38410-4>
97. Zhu Y, Wei Y, Duan J, et al. (2022) The role of leptin in indirectly mediating “somatic anxiety” symptoms in major depressive disorder. *Front Psychiatry* 13: 757958. <https://doi.org/10.3389/fpsy.2022.757958>
98. Milaneschi Y, Lamers F, Bot M, et al. (2017) Leptin dysregulation is specifically associated with major depression with atypical features: evidence for a mechanism connecting obesity and depression. *Biol Psychiatry* 81: 807–814. <https://doi.org/10.1016/j.biopsych.2015.10.023>
99. Cernea S, Both E, Hutanu A, et al. (2019) Correlations of serum leptin and leptin resistance with depression and anxiety in patients with type 2 diabetes. *Psychiatry Clin Neurosci* 73: 745–753. <https://doi.org/10.1111/pcn.12922>
100. Farr OM, Tsoukas MA, Mantzoros CS (2015) Leptin and the brain: influences on brain development, cognitive functioning and psychiatric disorders. *Metabolism* 64: 114–130. <https://doi.org/10.1016/j.metabol.2014.07.004>
101. Antonijevic IA, Murck H, Frieboes RM, et al. (1998) Elevated nocturnal profiles of serum leptin in patients with depression. *J Psychiatr Res* 32: 403–410. [https://doi.org/10.1016/S0022-3956\(98\)00032-6](https://doi.org/10.1016/S0022-3956(98)00032-6)
102. Kraus T, Haack M, Schuld A, et al. (2001) Low leptin levels but normal body mass indices in patients with depression or schizophrenia. *Neuroendocrinology* 73: 243–247. <https://doi.org/10.1159/000054641>
103. Jow GM, Yang TT, Chen CL (2006) Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *J Affect Disord* 90: 21–27. <https://doi.org/10.1016/j.jad.2005.09.015>

104. Daniele A, Cammarata R, Masullo M, et al. (2008) Analysis of adiponectin gene and comparison of its expression in two different pig breeds. *Obesity (Silver Spring)* 16: 1869–1874. <https://doi.org/10.1038/oby.2008.275>
105. De Rosa A, Monaco ML, Capasso M, et al. (2013) Adiponectin oligomers as potential indicators of adipose tissue improvement in obese subjects. *Eur J Endocrinol* 169: 37–43. <https://doi.org/10.1530/EJE-12-1039>
106. Nigro E, Scudiero O, Monaco ML, et al. (2014) New insight into adiponectin role in obesity and obesity-related diseases. *Biomed Res Int* 2014: 658913. <https://doi.org/10.1155/2014/658913>
107. Vuong E, Nothling J, Lombard C, et al. (2020) Peripheral adiponectin levels in anxiety, mood, trauma- and stressor-related disorders: A systematic review and meta-analysis. *J Affect Disord* 260: 372–409. <https://doi.org/10.1016/j.jad.2019.09.050>
108. Islam S, Islam T, Nahar Z, et al. (2022) Altered serum adiponectin and interleukin-8 levels are associated in the pathophysiology of major depressive disorder: A case-control study. *PLoS One* 17: e0276619. <https://doi.org/10.1371/journal.pone.0276619>
109. Liu J, Guo M, Zhang D, et al. (2012) Adiponectin is critical in determining susceptibility to depressive behaviors and has antidepressant-like activity. *Proc Natl Acad Sci U S A* 109: 12248–12253. <https://doi.org/10.1073/pnas.1202835109>
110. Yau SY, Li A, Hoo RL, et al. (2014) Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. *Proc Natl Acad Sci U S A* 111: 15810–15815. <https://doi.org/10.1073/pnas.1415219111>
111. Lee TH, Christie BR, van Praag H, et al. (2021) AdipoRon treatment induces a dose-dependent response in adult hippocampal neurogenesis. *Int J Mol Sci* 22. <https://doi.org/10.3390/ijms22042068>
112. Formolo DA, Lee TH, Yu J, et al. (2023) Increasing adiponectin signaling by sub-chronic AdipoRon treatment elicits antidepressant- and anxiolytic-like effects independent of changes in hippocampal plasticity. *Biomedicines* 11: 249. <https://doi.org/10.3390/biomedicines11020249>
113. Fu X, Wang Y, Zhao F, et al. (2023) Shared biological mechanisms of depression and obesity: focus on adipokines and lipokines. *Aging (Albany NY)* 15: 5917–5950. <https://doi.org/10.18632/aging.204847>
114. Komici K, Dello Iacono A, De Luca A, et al. (2021) Adiponectin and sarcopenia: a systematic review with meta-analysis. *Front Endocrinol (Lausanne)* 12: 576619. <https://doi.org/10.3389/fendo.2021.576619>
115. Liao B, Geng L, Zhang F, et al. (2020) Adipocyte fatty acid-binding protein exacerbates cerebral ischaemia injury by disrupting the blood-brain barrier. *Eur Heart J* 41: 3169–3180. <https://doi.org/10.1093/eurheartj/ehaa207>
116. Matsumata M, Inada H, Osumi N (2016) Fatty acid binding proteins and the nervous system: Their impact on mental conditions. *Neurosci Res* 102: 47–55. <https://doi.org/10.1016/j.neures.2014.08.012>
117. Conrad D, Wilker S, Schneider A, et al. (2020) Integrated genetic, epigenetic, and gene set enrichment analyses identify NOTCH as a potential mediator for PTSD risk after trauma: Results from two independent African cohorts. *Psychophysiology* 57: e13288. <https://doi.org/10.1111/psyp.13288>

118. Kim TN, Won JC, Kim YJ, et al. (2013) Serum adipocyte fatty acid-binding protein levels are independently associated with sarcopenic obesity. *Diabetes Res Clin Pract* 101: 210–217. <https://doi.org/10.1016/j.diabres.2013.05.014>
119. Jamaluddin MS, Weakley SM, Yao Q, et al. (2012) Resistin: functional roles and therapeutic considerations for cardiovascular disease. *Br J Pharmacol* 165: 622–632. <https://doi.org/10.1111/j.1476-5381.2011.01369.x>
120. Tripathi D, Kant S, Pandey S, et al. (2020) Resistin in metabolism, inflammation, and disease. *FEBS J* 287: 3141–3149. <https://doi.org/10.1111/febs.15322>
121. Owecki M, Miczke A, Nikisch E, et al. (2011) Serum resistin concentrations are higher in human obesity but independent from insulin resistance. *Exp Clin Endocrinol Diabetes* 119: 117–121. <https://doi.org/10.1055/s-0030-1263111>
122. Lee JH, Chan JL, Yiannakouris N, et al. (2003) Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab* 88: 4848–4856. <https://doi.org/10.1210/jc.2003-030519>
123. de Luis D, Primo D, Izaola O, et al. (2023) Relationship of circulating resistin levels with muscle mass determined by bioelectrical impedance in females with obesity. *Endocrinol Diabetes Nutr (Engl Ed)* 70: 468–475. <https://doi.org/10.1016/j.endien.2023.03.023>
124. Gao J, Deng M, Li Y, et al. (2022) Resistin as a systemic inflammation-related biomarker for sarcopenia in patients with chronic obstructive pulmonary disease. *Front Nutr* 9: 921399. <https://doi.org/10.3389/fnut.2022.921399>
125. Kwak MK, Baek JY, Park SJ, et al. (2024) Higher circulating resistin levels linked to increased sarcopenia risk in older adults. *J Clin Endocrinol Metab* 110: e2994–e3001. <https://doi.org/10.1210/clinem/dgae894>
126. Kim BJ, Jo Y, Baek JY, et al. (2025) Higher serum resistin levels and increased frailty risk in older adults: Implications beyond metabolic function. *J Nutr Health Aging* 29: 100521. <https://doi.org/10.1016/j.jnha.2025.100521>
127. Demirci S, Aynali A, Demirci K, et al. (2017) The serum levels of resistin and its relationship with other proinflammatory cytokines in patients with Alzheimer's disease. *Clin Psychopharmacol Neurosci* 15: 59–63. <https://doi.org/10.9758/cpn.2017.15.1.59>
128. Ikeda Y, Kawamura R, Takata Y, et al. (2023) Resistin G-A haplotype at SNP-420/-358 is associated with the latent sarcopenic obesity index in the toon genome study. *J Diabetes Investig* 14: 686–694. <https://doi.org/10.1111/jdi.13998>
129. Rahman S, Shanta AA, Daria S, et al. (2022) Increased serum resistin but not G-CSF levels are associated in the pathophysiology of major depressive disorder: Findings from a case–control study. *PLoS One* 17: e0264404. <https://doi.org/10.1371/journal.pone.0264404>
130. Yumru M, Gergerlioglu HS, Savas HA, et al. (2012) Serum resistin levels and metabolic changes in bipolar disorder. *J Mood Disord* 2: 47–50. <https://doi.org/10.5455/jmood.20120516040842>
131. Castren E, Monteggia LM (2021) Brain-derived neurotrophic factor signaling in depression and antidepressant action. *Biol Psychiatry* 90: 128–136. <https://doi.org/10.1016/j.biopsych.2021.05.008>
132. Yang T, Nie Z, Shu H, et al. (2020) The role of BDNF on neural plasticity in depression. *Front Cell Neurosci* 14: 82. <https://doi.org/10.3389/fncel.2020.00082>

133. Goncalves RA, Sudo FK, Lourenco MV, et al. (2023) Cerebrospinal fluid irisin and lipoxin A4 are reduced in elderly Brazilian individuals with depression: Insight into shared mechanisms between depression and dementia. *Alzheimers Dement* 19: 2595–2604. <https://doi.org/10.1002/alz.12893>
134. Chen K, Wang K, Wang T (2022) Protective effect of irisin against Alzheimer's disease. *Front Psychiatry* 13: 967683. <https://doi.org/10.3389/fpsyt.2022.967683>
135. Mason BL, Minhajuddin A, Czysz AH, et al. (2022) Fibroblast growth factor 21 (FGF21) is increased in MDD and interacts with body mass index (BMI) to affect depression trajectory. *Transl Psychiatry* 12: 16. <https://doi.org/10.1038/s41398-021-01679-y>
136. Lv SY, Chen WD, Wang YD (2020) The Apelin/APJ system in psychosis and neuropathy. *Front Pharmacol* 11: 320. <https://doi.org/10.3389/fphar.2020.00320>
137. Lin YS, Lin FY, Hsiao YH (2019) Myostatin is associated with cognitive decline in an animal model of Alzheimer's disease. *Mol Neurobiol* 56: 1984–1991. <https://doi.org/10.1007/s12035-018-1201-y>
138. Ohara K, Suzuki Y, Ohta D, et al. (2000) Presenilin-1 in late-onset depressive disorder. *Psychiatry Res* 95: 83–86. [https://doi.org/10.1016/S0165-1781\(00\)00167-0](https://doi.org/10.1016/S0165-1781(00)00167-0)
139. Susanto E, Kusuma S (2024) The role of brain-derived neurotrophic factor (BDNF) in the pathogenesis of sarcopenia: a meta-analysis of molecular mechanisms. *BioSci Med J Biomed Transl Res* 8: 5736–5748. <https://doi.org/10.37275/bsm.v8i12.1148>
140. Brunoni AR, Lopes M, Fregni F (2008) A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharmacol* 11: 1169–1180. <https://doi.org/10.1017/S1461145708009309>
141. Molendijk ML, Spinhoven P, Polak M, et al. (2014) Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (N = 9484). *Mol Psychiatry* 19: 791–800. <https://doi.org/10.1038/mp.2013.105>
142. Planella-Farrugia C, Comas F, Sabater-Masdeu M, et al. (2019) Circulating irisin and myostatin as markers of muscle strength and physical condition in elderly subjects. *Front Physiol* 10: 871. <https://doi.org/10.3389/fphys.2019.00871>
143. Oguz A, Sahin M, Tuzun D, et al. (2021) Irisin is a predictor of sarcopenic obesity in type 2 diabetes mellitus: A cross-sectional study. *Medicine (Baltimore)* 100: e26529. <https://doi.org/10.1097/MD.00000000000026529>
144. Zhang L, Peng Y, Qie Y, et al. (2025) Relationship of irisin and apelin levels with sarcopenia and body Composition in community-dwelling older adults: a paired case-control study. *Appl Physiol Nutr Metab* 50: 1–11. <https://doi.org/10.1139/apnm-2024-0473>
145. Liang H, Qi W, Jiajue R, et al. (2023) Serum Irisin level is associated with fall risk, muscle strength, and cortical porosity in postmenopausal women. *Front Endocrinol (Lausanne)* 14: 1096950. <https://doi.org/10.3389/fendo.2023.1096950>
146. Jodeiri Farshbaf M, Alvina K (2021) Multiple roles in neuroprotection for the exercise derived myokine irisin. *Front Aging Neurosci* 13: 649929. <https://doi.org/10.3389/fnagi.2021.649929>
147. Wang S, Pan J (2016) Irisin ameliorates depressive-like behaviors in rats by regulating energy metabolism. *Biochem Biophys Res Commun* 474: 22–28. <https://doi.org/10.1016/j.bbrc.2016.04.047>

148. Tu WJ, Qiu HC, Liu Q, et al. (2018) Decreased level of irisin, a skeletal muscle cell-derived myokine, is associated with post-stroke depression in the ischemic stroke population. *J Neuroinflammation* 15: 133. <https://doi.org/10.1186/s12974-018-1177-6>
149. Tezze C, Romanello V, Sandri M (2019) FGF21 as modulator of metabolism in health and disease. *Front Physiol* 10: 419. <https://doi.org/10.3389/fphys.2019.00419>
150. Kim HJ, Song W (2017) Resistance training increases fibroblast growth factor-21 and irisin levels in the skeletal muscle of Zucker diabetic fatty rats. *J Exerc Nutrition Biochem* 21: 50–54. <https://doi.org/10.20463/jenb.2017.0008>
151. Liu Y, Yau SSY, Liang Q, et al. (2020) FGF21 mediates the anti-depressant effects of exercise by coordinating the crosstalk between central and peripheral organs. *Hum Behav Brain* 1: 1–15. <https://doi.org/10.37716/HBAB.2020010102>
152. Wang X, Zhu L, Hu J, et al. (2020) FGF21 attenuated LPS-induced depressive-like behavior via inhibiting the inflammatory pathway. *Front Pharmacol* 11: 154. <https://doi.org/10.3389/fphar.2020.00154>
153. Vinel C, Lukjanenko L, Batut A, et al. (2018) The exerkin apelin reverses age-associated sarcopenia. *Nat Med* 24: 1360–1371. <https://doi.org/10.1038/s41591-018-0131-6>
154. Bae JH, Kwak SE, Lee JH, et al. (2019) Does exercise-induced apelin affect sarcopenia? A systematic review and meta-analysis. *Hormones (Athens)* 18: 383–393. <https://doi.org/10.1007/s42000-019-00157-x>
155. Dai TT, Wang B, Xiao ZY, et al. (2018) Apelin-13 upregulates BDNF against chronic stress-induced depression-like phenotypes by ameliorating HPA axis and hippocampal glucocorticoid receptor dysfunctions. *Neuroscience* 390: 151–159. <https://doi.org/10.1016/j.neuroscience.2018.08.018>
156. Tian SW, Xu F, Gui SJ (2018) Apelin-13 reverses memory impairment and depression-like behavior in chronic social defeat stressed rats. *Peptides* 108: 1–6. <https://doi.org/10.1016/j.peptides.2018.08.009>
157. Gok Oguz E, Akoglu H, Ulusal Okyay G, et al. (2016) Serum apelin is associated with affective disorders in peritoneal dialysis patients. *Ren Fail* 38: 1059–1066. <https://doi.org/10.1080/0886022X.2016.1193873>
158. Wang Y, Liu W, Xiao Y, et al. (2020) Association of apelin and apelin receptor polymorphisms with the risk of comorbid depression and anxiety in coronary heart disease patients. *Front Genet* 11: 893. <https://doi.org/10.3389/fgene.2020.00893>
159. Venkatachalam K, van Rossum DB, Patterson RL, et al. (2002) The cellular and molecular basis of store-operated calcium entry. *Nat Cell Biol* 4: E263–272. <https://doi.org/10.1038/ncb1102-e263>
160. Lu T, Zhang Y, Su Y, et al. (2022) Role of store-operated Ca²⁺ entry in cardiovascular disease. *Cell Commun Signal* 20: 33. <https://doi.org/10.1186/s12964-022-00829-z>
161. Bonilla IM, Belevych AE, Baine S, et al. (2019) Enhancement of cardiac store operated calcium entry (SOCE) within novel intercalated disk microdomains in arrhythmic disease. *Sci Rep* 9: 10179. <https://doi.org/10.1038/s41598-019-46427-x>
162. Letizia M, Wang YH, Kaufmann U, et al. (2022) Store-operated calcium entry controls innate and adaptive immune cell function in inflammatory bowel disease. *EMBO Mol Med* 14: e15687. <https://doi.org/10.15252/emmm.202215687>

163. Secondo A, Bagetta G, Amantea D (2018) On the role of store-operated calcium entry in acute and chronic neurodegenerative diseases. *Front Mol Neurosci* 11: 87. <https://doi.org/10.3389/fnmol.2018.00087>
164. Yan Q, Gao C, Li M, et al. (2024) TRP ion channels in immune cells and their implications for inflammation. *Int J Mol Sci* 25. <https://doi.org/10.3390/ijms25052719>
165. Badou A, Jha MK, Matza D, et al. (2013) Emerging roles of L-type voltage-gated and other calcium channels in T lymphocytes. *Front Immunol* 4: 243. <https://doi.org/10.3389/fimmu.2013.00243>
166. Rosa JM, Formolo DA, Yu J, et al. (2022) The role of microRNA and microbiota in depression and anxiety. *Front Behav Neurosci* 16: 828258. <https://doi.org/10.3389/fnbeh.2022.828258>
167. Zunner BEM, Wachsmuth NB, Eckstein ML, et al. (2022) Myokines and resistance training: a narrative review. *Int J Mol Sci* 23. <https://doi.org/10.3390/ijms23073501>



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