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Associations between Sarcopenic Obesity and Cognitive Function

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Abstract

Background: Sarcopenia, characterised by decreased muscle mass and muscle function, and obesity (excessive fat mass) have been linked to negative health outcomes and brain health. The coexistence of sarcopenia and obesity, called sarcopenic obesity (SO), may have a synergistic or additive negative impact on cognition. Sarcopenia, obesity, and cognitive impairment are prevalent conditions among older individuals. The definitions of SO remain inconsistent across studies. **Aim:** The main aim of this thesis was to review and investigate the association between SO, cognitive impairment and dementia risk. **Methods:** This thesis contains 4 main chapters, including a narrative review (Chapter 2), a systematic review and meta-analysis of longitudinal studies (Chapter 3), and two analyses based on observational data from the National Health and Nutrition Examination Survey (NHANES) (Chapters 4 and 5). In Chapter 4, SO phenotypes were created based on several definitions and cutoffs (high adiposity-low muscle mass (HA-LM), high fat mass-fat free mass ratio (FM/FFM), high trunk fat mass-appendicular skeletal muscle mass ratio (TrFM/ASM), and high waist circumference-low hand grip strength (WC-HGS)) to investigate the association between SO and cognitive impairment (low neuropsychological tests scores) in older adults. In Chapter 5, the new SO definition (screening: sign of sarcopenia (high SARC-F score) with high body mass index (BMI) and/or high WC; diagnostic phase I: added low muscle strength; diagnostic phase II: added low muscle mass and high fat mass) implemented by the European Society for Clinical Nutrition and Metabolism and the European Association for the Study of Obesity (ESPEN-EASO) was used to investigate its association with cognitive impairment (low digit symbol substitution test (DSST) score) in middle-aged and older adults. **Results:** The findings from the narrative review revealed the complex link between SO and brain function deterioration. The interrelated mechanisms that may be involved include impaired muscle glucose metabolism, reduced secretion of neuroprotective myokines, negatively impacted cerebral

blood flow, obesity-related insulin resistance, oxidative stress, and neuroinflammation, all contributing to impaired brain signalling, memory loss, and cognitive impairment. The systematic review and meta-analysis revealed a positive association between SO and all-cause dementia (ACD) risk, with no studies on Alzheimer's Disease (AD) and vascular dementia (VaD). Sarcopenia itself showed a positive association with ACD, AD and VaD, whereas obesity was associated with an increased risk of AD and VaD, but not with ACD. In Chapter 4, the findings support the positive association between low DSST scores and SO using FM/FFM (OR 2.0, CI 95% 1.3–3.1) and WC-HGS (OR 2.5, CI 95% 1.6–4.0) models in individuals aged 60-85 years. In Chapter 5, the new ESPEN-EASO SO phenotypes were associated with lower DSST scores at diagnostic phase I (OR 2.3, CI 95% 1.4–3.8) and phase II (OR 2.7, CI 95% 1.5–4.9) in individuals aged 60-85 years. **Conclusions:** SO was associated with cognitive impairment and dementia risk. The nature of this association may vary based on the definitions of SO used. The updated ESPEN-EASO definition of SO should be adopted in future research. Furthermore, the interrelated mechanisms linking SO to cognitive impairment warrant further investigation through clinical and epidemiological studies to inform the design of effective prevention strategies.

Publications

Booranasuksakul U, Tsintzas K, Macdonald IA, Pereira L, Guan Z, Donini L, Johnstone A, Sim M, Stephan BC, Siervo M. Association of Sarcopenia, Obesity and Sarcopenic Obesity with Dementia Risk in Cohort Studies: A Systematic Review and Meta-Analysis. *International Journal of Obesity.* Under review.

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Booranasuksakul U, Tsintzas K, Macdonald I, Stephan BC, Siervo M. 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. *Clinical Nutrition ESPEN*. 2024 Oct 1;63:919-28.

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Abbreviations

ACD	All-cause dementia
AD	Alzheimer’s disease
AF	The Animal Fluency
ALM	Appendicular lean mass
ALM/W	Appendicular lean mass per body weight
ALMI	Appendicular lean mass index
ASM	Appendicular skeletal mass
ASMI	Appendicular skeletal muscle mass index
ASMM	Absolute skeletal muscle mass
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CDC	The Center for Disease Control and Prevention
CERAD-DR	The Consortium to Establish a Registry for Alzheimer's Disease-Delayed Recall test
CERAD-WL	The Consortium to Establish a Registry for Alzheimer's Disease-Word Learning subtest
CI	Confidence intervals
CRP	C-reactive protein
CSGLM	Complex Samples General Linear Model
CSL	Complex Samples Logistic
DSST	Digit symbol substitution test
DXA	Dual energy x-ray absorptiometry
EASO	The European Association for the Study of Obesity
ESPEN	The European Society for Clinical Nutrition and Metabolism
EWGSOP	The European Working Group on Sarcopenia in Older People
FFM	Fat free mass
FMR	Fat-to-muscle mass ratio
HA-HM	High adiposity-High muscle mass
HA-LM	High adiposity-Low muscle mass
HGS	Hand grip strength
HOMA-IR	Homeostatic Model of Assessment for Insulin Resistance
HR	Hazard ratio
ICD	The International Statistical Classification of Diseases and Related Health Problems
IGF-1	Insulin-like growth factor-1
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6

KES	Knee extensor strength
KES/W	Knee extensor strength per body weight
kPCr	Post-exercise phosphocreatine recovery rate
LA-HM	Low adiposity-High muscle mass
LA-LM	Low adiposity-Low muscle mass
MCI	Mild cognitive impairment
MEC	Mobile examination centre
MMSE	The Mini Mental State Examination
MoCA	The Montreal Cognitive Assessment
MQ	Memory-related question
NHANES	The National Health and Nutrition Examination Survey
NOS	The Newcastle Ottawa Scale
NVC	Neurovascular coupling
OR	Odds ratio
PHQ	Patient Health Questionnaire
ROS	Reactive oxygen species
RR	Relative risk
SARC-F	Sarcopenia screening questionnaires
SE	Standard error
SMM/W	Total skeletal muscle mass per body weight
SMMI	Skeletal muscle mass index
SO	Sarcopenic obesity
SOGLI	The Sarcopenic Obesity Global Leadership Initiative
SPSM	The Short Portable Sarcopenia Measure
SVR	Visceral fat area ratio
TNF-α	Tumour Necrosis Factor-alpha
TrFM	Trunk fat mass
TUG	Timed Up and Go
VaD	Vascular dementia
WC	Waist circumference

CHAPTER 1: Introduction

Significant alterations in body composition with ageing (i.e., skeletal muscle mass loss, decreased muscle strength, and increased fat mass) have been linked to negative health outcomes (1). Body composition changes have been identified by different terms, such as sarcopenia, obesity, and sarcopenic obesity (SO), which is the coexistence of sarcopenia and obesity in the same individual. Sarcopenia is defined as a progressive loss of skeletal muscle mass and muscle strength that occurs with ageing or disease, leading to low physical performance and increased risk of adverse health outcomes such as falls and mortality (2). SO is the coexistence of sarcopenia and obesity, characterised by the co-occurrence of loss of muscle mass, strength, and function and the increase of body fat stores (3). Age-related loss of skeletal muscle mass is mainly attributed to a decrease in the size of muscle fibres, particularly type II muscle fibres (4). At the cellular level, muscle metabolic dysregulation, such as impaired mitochondrial function, chronic low-grade inflammation, insulin resistance, and impaired satellite cell activity, diminishes protein synthesis and promotes muscle degradation, causing muscle atrophy (5). Reduced functional capacity may lead to infiltration of fat within (intramyocellular) and between (intermuscular) muscle fibres, interrupting normal muscle structure and function (6). The smaller size of muscle fibres and increased infiltration of fat tissue lead to diminished contractile efficiency. In addition, age-related neurological deterioration (e.g., loss of motor neurones and reduction of motor unit number and function, degeneration of neuromuscular junctions) plays a major role in the initiation of the reduction of nerve communication with the muscle fibre, leading to sarcopenic muscle atrophy (7). Fat infiltration in skeletal muscle disrupts muscle homeostasis (i.e., excess intramuscular and intermuscular fat impairs muscle contractile strength), metabolism (i.e., lipid intermediates impair insulin signalling and reduce glucose uptake, which interferes with muscle repair and

contraction), and signalling (i.e., inflammatory cytokines inhibit anabolic signalling, which impairs muscle protein synthesis and regeneration). Collectively, these adverse effects weaken muscle function, promote inflammation, and worsen insulin resistance, creating a self-reinforcing cycle of muscle atrophy and fat accumulation (6).

Sarcopenia and obesity represent independently significant public health challenges globally, with prevalence estimates in high income countries ranging from 10% to 27% for sarcopenia (2) and 12% to 34% for obesity (8). These conditions not only affect quality of life but also place a substantial burden on healthcare systems (9, 10). Sarcopenia is the age-related loss of muscle mass, strength, and function, typically initiated in individuals aged 30s or 40s and accelerating after the age of 60 (11, 12). Sarcopenia has been associated with health conditions such as cognitive impairment, falls and fractures, functional decline, metabolic syndrome and diabetes, hypertension, and depression (13). Factors such as lower physical activity, hormonal changes, poor nutrition, and chronic diseases contribute to sarcopenia's development (14). Obesity is defined as excessive fat accumulation that is related to various health risks such as type 2 diabetes, heart disease, hypertension, stroke, and cancers (15, 16). SO is a condition that combines sarcopenia and obesity, leading to greater health risks than either condition alone. SO often occurs in older adults but can also happen in younger individuals with poor lifestyle habits. SO has been linked to chronic inflammation, metabolic conditions, cardiovascular consequences, and cognitive impairment (17, 18).

Age-related cognitive decline was associated with body composition changes (19, 20). Sarcopenia and cognitive decline are prevalent conditions among older individuals, and it has been suggested that sarcopenia is a risk factor for cognitive decline (20). Obesity during middle age has been linked to an increased risk of developing dementia later in life (21). Specifically, individuals with a body mass index (BMI) of 30 or higher at age 50 had a higher risk of developing dementia (22). In addition, abdominal obesity was associated with metabolic

dysregulation (i.e., insulin resistance and inflammation), which could contribute to cognitive decline (18). However, the association between obesity and cognitive decline remains complex in older individuals. The use of BMI to classify obesity has limitations that do not differentiate between muscle mass and fat mass (FM) changes, which can lead to uncertain outcomes (23). There are various techniques to assess body composition, from basic anthropometric measurements (e.g., BMI, waist circumference (WC)) to more advanced methods, such as bioelectrical impedance analysis (BIA) and dual energy x-ray absorptiometry (DXA), each offering different levels of precision and complexity (24, 25). While body composition measures are more accurate than BMI for assessing obesity, they still have limitations in older adults due to physiological changes with ageing (e.g. altered distribution of visceral vs. subcutaneous fat), tool limitations (e.g. hydration effects), difficulty with mobility, variability in assessment methods (e.g., lack of universal cut-off, ethnic and sex differences), and costs. An increase in visceral fat (fat around organs) and a decrease in subcutaneous fat have been observed in older adults, even if the overall weight and BMI remain stable (26, 27). Moreover, men have a higher ratio of intra-abdominal visceral fat to subcutaneous fat area than women (27).

Sarcopenia, obesity, and cognitive decline share interrelating metabolic, vascular, and inflammatory mechanisms. Multiple studies reveal that both sarcopenia and obesity independently increase the risk of cognitive decline and dementia, but evidence of the combined condition (SO) remains fragmented and has not shown consistent outcomes. Several previous studies have provided evidence linking SO to a higher risk of cognitive impairment and dementia compared to sarcopenia or obesity alone (28, 29). However, the strength and consistency of this association vary across studies.

The overall aim of this thesis was to review and investigate the association between SO and cognitive impairment and dementia risk using standardised definitions, and identify shared

biological pathways, enabling the design of future preventive and therapeutic strategies to promote healthy ageing.

This thesis includes a literature review, a systematic review and two observational studies using data from the National Health and Nutrition Examination Survey (NHANES).

Specific Aims:

(a) The literature review aims to critically review the current evidence on the association between SO with cognitive outcomes and dementia risk through the discussion of the biological mechanisms that may link the SO phenotype with deterioration of brain functions.

(b) The systematic review aims to investigate the associations between sarcopenia, obesity, and SO with the risk of dementia (i.e., all-cause dementia (ACD), Alzheimer's disease (AD), and vascular dementia (VaD)) in cohort studies. In addition, the potential roles of baseline age of the population, sex, and differences in SO diagnostic protocols in the associations between body composition phenotypes and dementia risk were explored.

(c) The first observational study aims to explore the association of body composition and SO phenotypes with cognitive function in older adults.

(d) The second observational study aims to estimate the prevalence of SO using the definition of SO endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) in a representative sample of middle-aged and older adults and to explore the association of the new SO definition with cognitive function and appraise whether this association is different between age groups.

CHAPTER 2: Literature review: Sarcopenic Obesity and Brain Health

Introduction

SO has emerged as a significant public health concern, particularly among older adults (30). SO is a clinical condition that can reveal an interrelated negative impact from both sarcopenia and obesity on various health systems, including the brain (17, 18).

There is an increasing global ageing population, and almost a quarter of the total global burden of disease was in individuals aged 60 years and older (31). Meanwhile, the prevalences of sarcopenia (13), obesity (32), and dementia (33) are also found in the ageing population. Therefore, the prevalence of SO may be found to be increasing in older individuals, with larger impacts on cognitive function and dementia.

Both obesity and sarcopenia have independently been associated with increased risk of cognitive impairment and dementia (20, 21). However, the mechanisms by which SO influences brain structure and function remain complex.

A review of the prevalence of SO and previous studies showing the associations between SO and cognitive function in part of SO diagnosis and interrelated mechanisms may help to better understand the link between SO and the brain.

Aim

To critically review the current evidence on the association between SO with cognitive outcomes and dementia risk through the discussion of the biological mechanisms that may link the SO phenotype with deterioration of brain functions.

Methodology

A narrative review of the literature was conducted to explore the evidence surrounding the links between SO and brain health. Relevant studies were searched through electronic databases such as PubMed, Scopus, and Ovid MEDLINE following research purposes. The key terms of the search strategy used to ensure broad and comprehensive coverage of the research topic included "sarcopenia", "obesity", "sarcopenic obesity", "brain health", "pathogenesis", "diagnosis", "risk", "cognition", and "dementia". The Boolean operators "AND", "OR", and "Asterisk (*)" were used in database searches to combine or refine keywords to help broaden, narrow, or focus search results. Relevant studies published in English and focusing on human populations were prioritised. Additional references were identified through manual screening of bibliographies from key articles. The selected studies were carefully reviewed, and their main findings, methodologies, and conclusions were integrated. A coherent narrative synthesis was then developed to summarise existing knowledge and identify the gaps in the literature that warrant further investigation.

Results and Discussion

Sarcopenia, derived from the Greek words "sarx" (flesh) and "penia" (loss), describes a significant loss of skeletal muscle mass and strength (34). The identification of sarcopenia involves various methods based on single or combined assessments of muscle mass and function using body composition methods (i.e., DXA, BIA) and physical performance tests (i.e., timed up and go, walking speed, hand grip strength (HGS)) (35). Recent consensus definitions, such as the European Working Group on Sarcopenia in Older People (EWGSOP2), have emphasized the importance of muscle strength as a key component in the diagnosis of sarcopenia (36).

Obesity is characterised by a substantial increase in FM and is commonly assessed using simple anthropometric measures like BMI and WC (37). However, these methods have limitations, including modest sensitivity for predicting disease risk and inability to differentiate between body components such as FM and fat-free mass (FFM) (37, 38).

SO is a body composition phenotype characterized by a substantial decrease in muscle mass and/or function occurring concomitantly with an increase in adipose tissue (39). This concept aims to integrate the independent risks associated with obesity and sarcopenia (40). The term was first introduced by Heber et al. in 1996 (41) and refined in 1998 by Baumgartner et al. (42), who proposed a normative approach to SO classification using DXA measurements. Since then, research on SO has grown exponentially, with over 3,800 publications indexed in PubMed since 1996 (**Figure 2-1**). However, less than 5% of those have discussed and/or investigated links between SO and cognitive function.

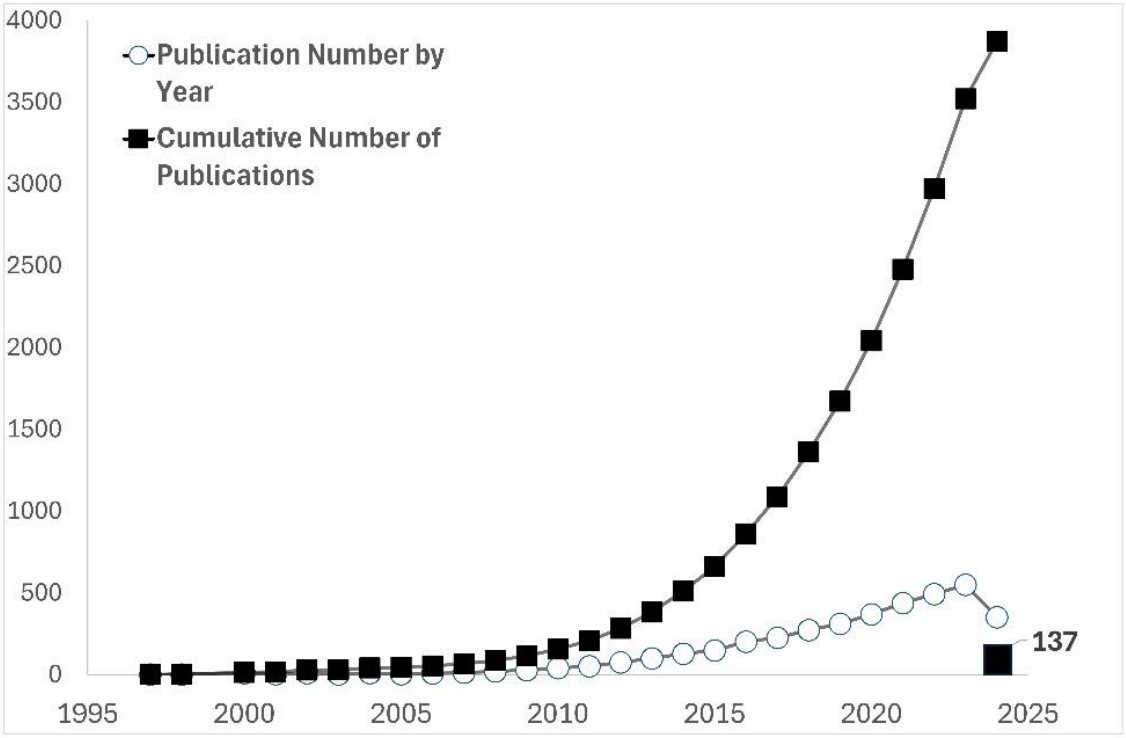


Figure 2- 1 *The number of publications indexed in PubMed of links between SO and cognitive function since 1996*

The increasing number of publications has led to the proposition of several diagnostic models for SO classification, contributing to heterogeneity in prevalence estimates and mixed associations with health outcomes (39, 43). This variability in definitions and diagnostic criteria has complicated the comparison of results across published studies and made it difficult to establish a clear consensus on the public health burden and clinical implications of SO. In 2022, the Sarcopenic Obesity Global Leadership Initiative (SOGLI) proposed a new diagnostic algorithm to reach expert consensus on the definition and diagnostic criteria for SO (44). The SOGLI definition aims to provide a more comprehensive and standardised stepwise approach to diagnosing SO, incorporating measures of muscle mass, muscle strength, and adiposity (44). This model is currently undergoing validation, with initial reports indicating good sensitivity and prevalence estimates ranging from 4% to 15% (44-48).

Diagnosis of SO

A sensitive and specific diagnostic strategy is crucial for accurately identifying SO cases and enabling effective risk stratification for predicting adverse health outcomes and designing targeted interventions. The diagnostic approach has evolved significantly since the initial definition proposed by Heber et al in 1996 (41), which identified SO in subjects with the lowest tertiles of FFM assessed by BIA and a BMI≥30kg/m^2. The definition by Baumgartner et al. (42, 49) diagnosed SO by identifying low appendicular skeletal muscle mass index (ASMI) (<7.26 kg/m^2 in men and <5.45 kg/m^2 in women) coupled with high fat mass percentage (FM% >28% in men and >38% in women) using DXA. This approach led to a prevalence of 5.8% in older individuals aged 60 years and above. While this definition provided a more comprehensive assessment of body composition, it still relied solely on muscle mass and did not account for differences in muscle function or strength.

Recent studies have explored SO diagnosis using criteria associated with low muscle mass, low muscle strength, and/or performance (29, 39, 50). For instance, a classification utilising low skeletal muscle mass index, low physical performance, and/or low HGS with high BMI revealed a prevalence of 11% in a study of people aged over 65 years in Turkey (50). The application of the Short Portable Sarcopenia Measure (SPSM), which incorporates assessments of muscle mass, muscle strength and physical performance, for the diagnosis of SO resulted in prevalence estimates ranging from 14.3% to 37.2% in 353 older subjects (mean age 69 years) when combined with BMI ≥30 kg/m^2 or with the highest two quintiles of FM%, respectively (29). In 2022, the SOGLI initiative, endorsed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), proposed new diagnostic criteria for SO (39). This collaborative effort aimed to establish unified definitions and diagnostic criteria for SO, recognizing it as a distinct clinical entity with significant health implications. The consensus statement emphasized the importance of using both muscle mass and function measures alongside adiposity assessments to diagnose SO. The ESPEN-EASO consensus proposed a two-step approach for diagnosing SO including a first screening and second diagnostic stage. At the screening stage of the protocol, simple anthropometric measures (e.g., BMI, WC) and self-reported assessment of sarcopenia (i.e., sarcopenia screening questionnaires (SARC-F) or presence of physical disability) can be used to identify individuals at risk of SO. At the diagnostic stage, suspected cases of SO can be confirmed with more detailed body composition analysis (e.g., DXA, BIA) and comprehensive assessments (e.g., HGS, gait speed) of skeletal muscle function. This approach aims to balance clinical practicality with diagnostic accuracy, allowing for easier identification of at-risk individuals in primary care settings while reserving more resource-intensive assessments for specialist clinics. Since its publication, the SOGLI protocol has been applied in an increasing

number of studies (44-48), which have showed significant associations of SO with cardio-metabolic outcomes (44, 45) and risk of mortality (48, 51).

Pathogenesis of SO and its links with brain health

Dementia and mild cognitive impairment (MCI) rates continue to rise as the population ages (52). Dementia results from damage to brain cells and neurodegeneration affecting cognitive processes. There are several types of dementia including AD (most common), VaD (second most common), Lewy body dementia, Frontotemporal dementia, Parkinson's disease dementia, mixed dementia, and other types (less common) (52). MCI is a stage of cognitive ageing that falls between normal ageing and dementia. There are four different types of MCI, including amnestic, non-amnestic, single-domain, and multi-domain subtypes (53).

The current clinical diagnostic criteria for dementia use coding systems which provide universal and standardised labels for diseases and disorders, including the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) and ICD-11 for each dementia type. The ICD-11 represents a conceptual advance over the ICD-10 in the classification of dementias. ICD-10 classifies dementia primarily as a psychiatric syndrome, while ICD-11 categorises dementia under neurodegenerative dementias (54).

The etiological factors and pathogenetic mechanisms of SO are still largely unknown. These likely involve multiple, inter-related mechanisms with possible bi-directional associations, making the understanding of causal relationships challenging.

SO could be the result of progressive and marked age-related changes in body composition (i.e., increased FM and decreased lean body mass) and skeletal muscle function. These changes may be associated with decreased physical activity, which could contribute to skeletal muscle loss and ectopic fat accumulation via alteration of muscle anabolic signalling and impact on energy balance (55). However, it could be also conceivable that factors (e.g., in-built

environment, behaviour and lifestyle) affecting the capacity to perform physical activity could interact with the ageing process and modify body composition trajectories, leading to an increased risk of developing the SO phenotype. This cycle can be influenced by external factors such as poor dietary habits, rate and extent of changes in energy balance, pathogenic features of chronic diseases, and medications that affect muscle or adipose tissue metabolism.

Obesity and sarcopenia have been independently linked to an increased risk of cognitive impairment and dementia (19, 56, 57). Both conditions are associated with insulin resistance, endothelial dysfunction, altered secretion of myokines and adipokines and inflammation (58-61), which are all mechanisms associated with an increased risk of cognitive impairment and dementia (62, 63). The relationship between brain metabolism and SO involves alterations in myokine and adipokine secretion and signalling, impacting both musculoskeletal and brain functions (58, 64, 65). Skeletal muscles produce myokines that play a role in muscle-brain communication, while adipokines secreted by adipose tissue interact with the blood brain barrier (BBB), affecting central nervous system integrity and function (66, 67).

Several biological pathways have been proposed to explain how SO may influence or interact with cognitive impairment and dementia. These include mitochondrial dysfunction, endothelial dysfunction, insulin resistance, oxidative stress, inflammation, gut microbiota, endocrine factors, skeletal muscle plasticity, neuro-humoral control, adipokines and myokines, and autophagy. A description of some of the putative mechanisms linking SO to cognitive impairment is provided in **Figure 2-2**.

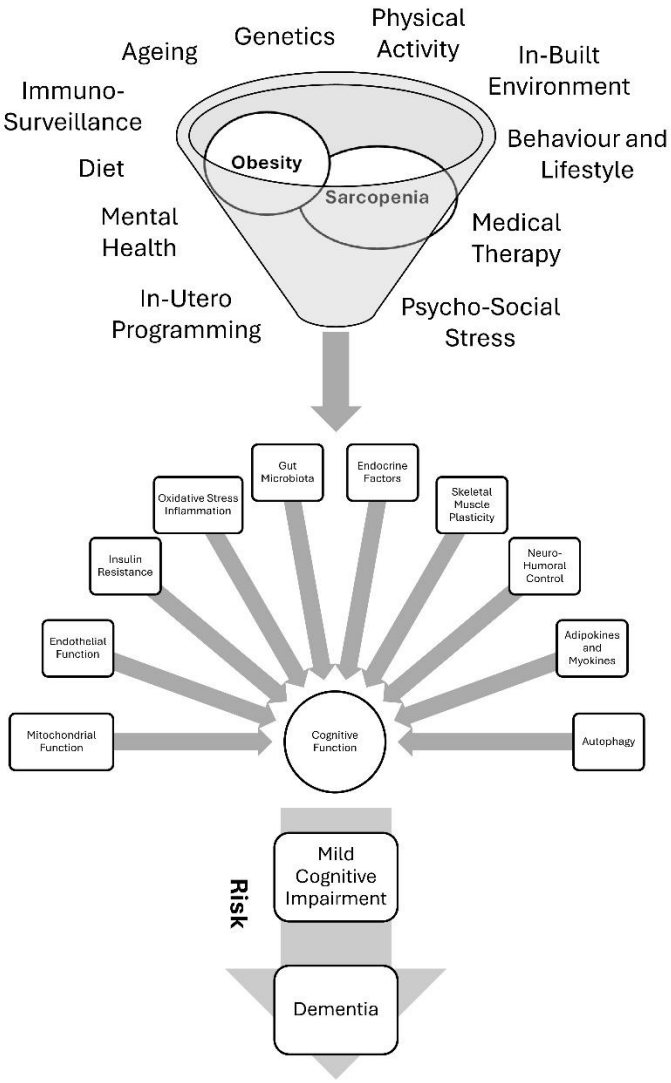


Figure 2- 2 *The mechanisms linking SO to cognitive impairment*

Mitochondrial Dysfunction: Both sarcopenia and obesity can lead to muscle mitochondrial dysfunction through several mechanisms (i.e., decreased mitochondrial biogenesis, increased oxidative stress, disrupted mitochondrial dynamic), which is crucial for energy metabolism in neurons (68, 69). SO promotes chronic low-grade inflammation, insulin resistance, oxidative stress, and physical inactivity, which contribute to muscle mitochondrial dysfunction through multiple mechanisms, including decreased mitochondrial biogenesis, increased oxidative stress and reactive oxygen species (ROS), and disrupting mitophagy (70-72). Impaired muscle mitochondrial function, can result in reduced ATP production and increased oxidative stress, potentially contributing to neurodegeneration (73). In addition, impaired muscle mitochondria contribute to insulin resistance and reduced glucose utilization, that could lead to impaired synaptic plasticity and cognitive decline (74). Higher skeletal muscle mitochondrial function was associated with lower risk of cognitive impairment. Using magnetic resonance spectroscopy, post-exercise phosphocreatine recovery rate (kPCr) was measured as a marker of muscle mitochondrial function. Higher kPCr levels were associated with significantly lower risk of mild cognitive impairment (MCI) or dementia, reduced amyloid accumulation in multiple brain regions, and decreased neuroinflammation markers (75). The mechanisms linking mitochondrial function to cognitive impairment may involve increased ROS production and a pro-inflammatory response (76). In addition, mitochondrial dysfunction may involve altered expression of genes (i.e., SDHB, SDHD, ATP5F1A, and ATP5F1B) (77) that regulate energy production, mitochondrial dynamics, and oxidative stress. Their dysregulation reduces ATP production and induces muscle mitochondrial damage, contributing to muscle atrophy, fat infiltration, and neuronal decline, forming a shared biological pathway between metabolic and cognitive ageing (77).

Endothelial Dysfunction: SO can lead to endothelial dysfunction and reduced cerebral blood flow, potentially contributing to cognitive decline through neurovascular and

neuroinflammatory pathways (3, 59). SO-related factors (i.e., systematic inflammation, oxidative stress, insulin resistance, and physical inactivity) negatively affect vascular endothelial cells and increase endothelial dysfunction (i.e., increased vascular inflammation, reduced nitric oxide bioavailability, and increased BBB permeability) (78). Fantin et al (79) investigated the relationship between sarcopenia, SO, and arterial stiffness in 77 older adults (average age 78.7 years) and showed that SO individuals had the highest central arterial stiffness, while sarcopenic patients had the highest peripheral arterial stiffness. Endothelial dysfunction, characterised by reduced nitric oxide bioavailability, contributes to dementia risk through multiple mechanisms (80). In particular, impaired nitric oxide production leads to decreased cerebral blood flow, compromised BBB integrity, and increased oxidative stress (81). This promotes neuroinflammation, amyloid-β accumulation, and tau hyperphosphorylation (82, 83). Endothelial dysfunction also exacerbates vascular risk factors, further compromising cerebral perfusion and potentially accelerating cognitive decline and neurodegeneration (81, 83). Endothelial and lysosomal stress triggers cathepsin release (e.g., cathepsins B, D, and O) in both vascular and neural cells (84). Cathepsin-mediated lysosomal stress disrupts the efficient degradation of misfolded proteins (i.e., amyloid-beta, tau), affecting their accumulation in neurones and cerebral vessels (84).

Insulin Resistance: SO is associated with increased insulin resistance, which can impair insulin signalling in the brain (85). This can lead to reduced glucose uptake and utilisation by neurons, potentially contributing to cognitive decline (17, 18, 86). Insulin resistance in the brain has been associated with reduced cerebral glucose metabolism and cognitive impairment in older adults (87). Brain insulin resistance has also been associated with AD pathology, even in individuals without diabetes (88).

Oxidative Stress: SO is associated with increased oxidative stress, which can damage neurons and contribute to cognitive impairment through several mechanisms, including adipose tissue

inflammation-related ROS production, and decreased antioxidant defence capacity. SO is characterised by higher levels of oxidative stress markers and lower antioxidant capacity compared to those without SO (89). Elevated levels of the lipid peroxidation marker 8,12-iso-iPF(2alpha)-VI in cerebrospinal fluid, plasma, and urine were found in individuals with MCI and early AD, suggesting increased brain oxidative damage may precede symptomatic dementia onset (90).

Inflammation: Chronic low-grade inflammation is a hallmark of SO. Pro-inflammatory cytokines such as Interleukin-6 (IL-6), Tumour Necrosis Factor-alpha (TNF-α), and C-reactive protein (CRP) are elevated in individuals with SO (91). These inflammatory markers can cross the blood brain barrier and activate microglia, leading to neuroinflammation (92). Chronic inflammation can impair synaptic plasticity and contribute to cognitive decline (93). In three hundred patients with mild to severe AD, increases in serum TNF-α concentrations were associated with an increase in cognitive decline (94).

Altered Gut Microbiome: Emerging evidence suggests that SO-related factors (i.e., poor dietary patterns, physical inactivity, chronic inflammation, metabolic disturbances) may be associated with changes in the gut microbiome, which can influence brain health through the gut-brain axis (95). Both obesity and sarcopenia have been associated with reduced gut microbiome diversity, which could contribute to inflammation and metabolic dysfunction (96, 97). Dysbiosis can lead to increased intestinal permeability, triggering systemic inflammation and neuroinflammation. Altered microbial metabolites, including short-chain fatty acids, affect brain function and neuroplasticity (98). The gut-brain axis modulates neurotransmitter production, immune responses, and amyloid metabolism. Microbiome changes can also impact vascular health and insulin sensitivity, indirectly affecting cognitive function and neurodegeneration risk (99, 100).

Hormonal Dysregulation: SO may contribute to age-related hormonal deficiency, including growth hormone, insulin-like growth factor-1 (IGF-1), and sex hormones (i.e., androgens and oestrogens) (30, 101). These hormonal changes can affect brain function and cognitive performance (102, 103). Older adults had significantly lower IGF-1 levels, which correlated with decreased cerebral blood flow and impaired neurovascular coupling (NVC) responses during cognitive tasks (104). SO-related factors (i.e., decreased muscle mass, increased adiposity, and physical inactivity) could affect IGF-1 production and suppress IGF-1 synthesis (105, 106). The magnitude of IGF-1 decline predicted the extent of NVC impairment (104). These findings suggest that age-related IGF-1 deficiency contributes to neurovascular ageing, potentially impacting cognitive function in older adults by reducing the brain's ability to adjust blood flow to meet metabolic demands (104). SO is also associated with hormonal imbalances, particularly in androgens like testosterone (3). Reduced androgen levels can exacerbate muscle loss and fat gain, creating a vicious cycle. These hormonal shifts may impact brain health through various mechanisms, including decreased neuroprotection, altered neurotransmitter function, and reduced neuroplasticity (102). Androgens also influence cognitive processes, mood, and memory (107). The combination of SO and androgen deficiency may synergistically contribute to cognitive impairment and increased risk of neurodegenerative diseases.

Neurotrophins: Brain-derived neurotrophic factor (BDNF), produced by muscles and the brain, plays a crucial role in neuronal development, memory formation, and neuroprotection (108). Exercise increases muscle BDNF, promoting motor neuron regeneration and muscle fibre specification (109). BDNF also influences energy homeostasis, appetite regulation, and fat metabolism (110). Its levels are negatively correlated with obesity and type 2 diabetes (111, 112). BDNF interacts with hormones like leptin and adiponectin, potentially improving metabolic health and insulin sensitivity (113). BDNF plays a crucial role in neuroplasticity and

cognitive function (108). Lower serum BDNF levels were associated with smaller hippocampal volumes and poorer memory performance in older adults (114).

Myokines and Adipokines Secretion: SO-related factors (i.e., decreased muscle mass, adiposity, inflammation, and physical inactivity) contribute to a decrease in myokines production and increase in secretion of inflammatory adipokines (115, 116). Skeletal muscles produce various myokines that play crucial roles in muscle-brain communication (60). Irisin, secreted during exercise, crosses the BBB and promotes neurogenesis in the hippocampus, potentially enhancing cognitive function (117). Irisin is secreted by skeletal muscle, offering advantageous effects for skeletal muscle, metabolic function, and the brain (118). Low levels of irisin have been identified as an independent risk factor for SO (119). IL-6, while often associated with inflammation, can have anti-inflammatory effects when derived from muscle and may protect against cognitive decline (120). Another notable myokine is cathepsin B, which has been shown to increase BDNF levels and improve spatial memory in mice (121). Adipose tissue, particularly in excess as seen in obesity, secretes various adipokines that can interact with the BBB and affect central nervous system function. Leptin, primarily known for its role in appetite regulation, also influences hippocampal synaptic plasticity and has been associated with improved cognitive function at normal levels (122). However, in obesity, leptin resistance can develop, potentially negating these beneficial effects (123). Adiponectin, an adipokine with anti-inflammatory properties, has been linked to improved insulin sensitivity (124). Lower levels of adiponectin, as often seen in obesity, have been associated with an increased risk of cognitive decline (125). TNF-α, elevated in obesity, can promote inflammation and oxidative stress in the brain, potentially contributing to neurodegeneration (126). Similarly, Interleukin-1 beta (IL-1β), another pro-inflammatory adipokine increased in obesity, has been associated with impaired synaptic plasticity and cognitive function (127).

Skeletal Muscle Plasticity: The capacity of muscle to undergo structural and functional adaptations (e.g., hypertrophy, atrophy, metabolic flexibility, and regeneration) in response to physiological and environmental stimuli is characterised as skeletal muscle plasticity (128). Skeletal muscle adaptability is partially controlled by myokines (i.e., irisin) and neurotrophins (i.e., BDNF), which regulate anabolic signalling, mitochondrial biogenesis, satellite cell activity, and neuromuscular function (129). Sarcopenia and obesity suppress the secretion of beneficial myokines such as irisin and BDNF, which may impair skeletal muscle plasticity (118, 130). Skeletal muscle mass loss during ageing caused by muscle fibre atrophy is linked to impaired mitochondrial biogenesis, systemic inflammation, oxidative stress, and brain insulin resistance, affecting neuroinflammation and cognitive decline (131).

Impaired Autophagy: Autophagy, a cellular process responsible for degrading and recycling cellular components, is crucial for maintaining neuronal health (132). Impaired autophagy could be triggered by oxidative stress, chronic inflammation, and metabolic disorder (133). SO has been associated with impaired autophagy in both muscle and adipose tissue, which may extend to the brain (134). Impaired autophagy in skeletal muscle was associated with sarcopenia (135) and insulin resistance (136) and has been linked with the pathogenesis of neurodegenerative diseases such as AD and Parkinson's Disease (137).

SO and risk of cognitive impairment

The relationship between SO and cognitive function is receiving increasing attention supported by the independent associations of both sarcopenia and obesity with increased risk of MCI and dementia. Peng et al. found in a meta-analysis that individuals with sarcopenia had a 2.2-fold higher risk of cognitive impairment compared to those without sarcopenia (138). This analysis included 12 observational studies, providing robust evidence for the association. A manual

search of the reference lists of the eligible articles was also conducted to identify additional, relevant articles (18, 29, 56, 139-147) (**Table 2-1**).

Table 2- 1 Summary of key observational studies that have explored the association between sarcopenic obesity (SO), cognitive impairment and dementia risk in humans.

Author (year of publication)	Study design	Age (year)	Sarcopenia	Obesity	SO Definition	Cognitive Test	Main Findings
Levine (2012)	Cross-sectional	60+	Low SMM (<48.37 kg for men and 34.57 kg for women)	High WC (> 102 cm for men and 88 cm for women)	Low SMM and high WC	DSST	SO (beta = -7.08, p<0.0001), sarcopenia alone (beta = -4.19, p<0.0001), and obesity alone (beta = -1.43, p<0.0001) were associated with cognitive impairment.
Noh (2017)	Cross-sectional	65+	Low lean mass (1st tertile)	High FM (2nd and 3rd tertiles)	Low lean mass and high FM	K-MMSE	Only in women, the highest fat mass was associated with lower risk for cognitive impairment (OR = 0.23; 95% CI:0.04–0.88).
Tolea (2018)	Cross-sectional	40+	Low SPSM derived from three components, low HGS + low chair stands + low MM	High BMI (≥30 kg/m^2) FM% (top two quintiles)	Lowest two quintiles of SPSM+BMI ≥30 kg/m^2	MoCA and Animal naming	SO, sarcopenia, and obesity were associated with the cognitive impairment (Coefficient ± SE (Est.). SO_I=−2.85±1.38, p=0.039); Sarcopenia (Est.SO_I=−1.88±0.79, p=0.017); Obesity (Est.SO_I=−1.10±0.81, p=0.175).
Wang (2019)	Cross-sectional	60-92	Low ASMI (<7.0 kg/m^2 for men and <5.7 kg/m^2 for women)	High FM%	Low ASMI and High FM%	MMSE	SO (OR = 2.55, 95% CI 1.19-5.43) and obesity (OR = 2.14, 95%CI:1.23-3.73) had significantly increased risk for cognitive impairment in fully adjusted model.
Low (2020)	Cross-sectional	45+	Low FFM	High FM	High FM/FFM ratio, normal, <0.40; and SO, > 0.80.	RBANS and MMSE	FM/FFM ratio was significantly associated with cognitive impairment (beta -1.44, 95%CI: -2.82 to -0.06, p=0.041).
Batsis (2021)	Longitudinal	65+	Low HGS (men <35.5 kg for men and <20 kg for women)	High BMI (≥30 kg/m^2, high WC (≥102 cm for men and ≥88 cm for women)	Low HGS and High BMI and/or High WC	AD-8	SO (HR = 1.20, 95% CI:1.03–1.40) and Sarcopenia (HR = 1.60, 95%CI:1.42–1.80) was associated with the risk of cognitive impairment.
Tou (2021)	Cross-sectional	21-90	Low ALMI (<7.0 kg/m^2 for men and 5.4 kg/m^2 for women) with low HGS (<28 kg for men and <18 kg for women) and/or low GS (<1.0 metre per second)	High FMI (≥ 7.63 kg/m^2 for men and ≥ 9.93 kg/m^2 for women)	Low ALMI + Low HGS and/or Low HGS + High FMI	RBANS	Obesity was significantly associated with cognitive impairment (OR = 2.05, 95%CI:1.12–3.82).

Table 2- 1 Summary of key observational studies that have explored the association between sarcopenic obesity (SO), cognitive impairment and dementia risk in humans.

Author (year of publication)	Study design	Age (year)	Sarcopenia	Obesity	SO Definition	Cognitive Test	Main Findings
Someya (2022)	Cross-sectional	65-84	Low HGS (<28 kg for men and <18 kg for women)	High BMI (≥25 kg/m^2)	Low HGS and High BMI	MoCA and MMSE	SO was independently associated with MCI and dementia compared with the control (MCI, OR = 2.11, 95%CI:1.12–3.62; dementia, OR = 6.17, 95%CI:2.50–15.27).
Cavazzotto (2022)	Cross-sectional	Older adults with AD (mean age 77±7)	Low ASMI (<7.2 for men and <5.7 for women)	High FM% (>28% for men and >39% for women)	Low ASMI and high FM%	MMSE	Men with obesity and aged >75 years had better cognitive performance compared with men with normal weight.
Yu (2022)	Cross-sectional	65+	Low MM	High FM	(1) Low AMM/FM (aMFR), (2) Low total MM/FM (tMFR)	MoCA	No significant associations were found with MoCA scores.
Low (2024)	Cross-sectional	45+ with T2DM	Low appendicular skeletal muscle mass (ASM, g)	High Visceral Fat Area (cm^2)	Skeletal MM to visceral fat area ratio (SVR, g/cm^2)	RBANS total score	The corresponding coefficients for quartiles 1 (lowest) and 2 of SVR were −3.79 (95 % CI:−5.39 to −2.19; p < 0.001) and −1.47 (95 % CI:−2.86 to −0.07; p = 0.039) in fully adjusted analysis.
Zhang (2024)	Longitudinal	60-69	The combination of low ASMI (< 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women) and low HGS (< 27 kg in men and < 16 kg in women)	BMI ≥ 30 kg/m^2	Met both criteria of obesity and sarcopenia	Dementia diagnosis based on linked hospital-admission data	SO was associated with higher dementia risk (HR women = 1.42, 95%CI:1.22–1.65; HR men = 1.98, 95%CI:1.70–2.32.

Abbreviations: AD: Alzheimer's disease, ALMI: appendicular lean mass index, aMFR: appendicular muscle/fat ratio, AMM: appendicular muscle mass, ASMI: appendicular skeletal muscle mass index, BMI: body mass index, DSST: Digit Symbol Substitution Test, FFM: fat free mass, FM: fat mass, FMI: fat mass index, HGS: hand grip strength, HR: hazard ratio, K-MMSE: Korean-the Mini Mental State Examination, MMSE: The Mini Mental State Examination, MoCA: Montreal Cognitive Assessment, OR: Odds ratio, RBANS: Repeatable Battery for the Assessment of Neuropsychological Status, SMM: skeletal muscle mass, SO: sarcopenic obesity, SPSM: short portable sarcopenia measure, SVR: Skeletal MM to visceral fat area ratio, tMFR: total muscle/fat ratio, WC: waist circumference

The studies have demonstrated a significant association between the SO phenotype with risk of cognitive impairment and dementia in eight studies (18, 29, 139, 141, 142, 144, 145, 147), whilst three studies reported non-significant associations (56, 143, 146), and one study observed a significant reduction in risk of cognitive impairment in subjects with the SO phenotype (140) (**Table 2-2**).

Cavazzotto et al. (2022) conducted on SO elderly participants with AD (mean age 77 years) found that body fat had a protective effect on cognition (140). This finding shows that the association between fat and cognitive function could vary with age and supports the "obesity paradox", in which higher adiposity appears paradoxically protective in certain age groups and disease states (148, 149). However, the association between obesity and cognitive impairment in very old adults is inconsistent across studies. The complex interactions among sex, ageing, obesity measurements, and cognitive assessments may influence the outcomes of the association between obesity and the cognitive risk evaluations in very old populations.

Only two longitudinal studies (139, 147) have looked at the relationship between SO and cognitive decline and dementia risk. Using data from the National Health and Aging Trends Survey, Batsis et al. analysed 5,822 participants over 8 years (139). Sarcopenia was defined by grip strength, and obesity by BMI. The study found that compared to those without sarcopenia or obesity, individuals with sarcopenia alone and SO had a significant higher risk of cognitive impairment, while obesity alone did not increase the risk. A recent longitudinal analysis conducted on the UK Biobank data in 208,867 participants aged 60-69 years at baseline explored the relationship between obesity, sarcopenia, SO, and dementia risk (147). SO consistently increased dementia risk and advanced onset in both sexes. Brain imaging showed that men with SO had a lower grey matter volume and a higher white matter hyperintensity volume than normal participants.

Table 2- 2 *The summary of the associations between the sarcopenic obesity phenotype with risk of cognitive impairment and dementia in the individual studies.*

Author	Cognitive Impairment	Dementia
	Risk	
Levine, 2012	⇧	
Noh, 2017	⇔	
Tolea, 2018	⇧	
Wang, 2019	⇧	
Low, 2020	⇧	
Batsis, 2021	⇧	
Tou, 2021	⇔	
Someya, 2022	⇧	⇧*
Cavazzotto, 2022	⇩	
Yu, 2022	⇔	
Low, 2024	⇧	
Zhang, 2024		⇧

Arrows indicate the direction and statistical significance of the associations.
↑ = increased risk and statistically significant.
↔ = no significant association.
↓ = reduced risk and statistically significant.
*This was a cross-sectional study with dementia cases identified using Mini-Mental State Examination cut off.

Ten cross-sectional studies (18, 29, 56, 140-146) have examined the association between SO and cognitive function and impairment. For example, a cross-sectional study examined the relationship between skeletal muscle mass to visceral fat area ratio (SVR) and cognitive function in 1,326 patients with type 2 diabetes (141). Lower SVR was associated with poorer cognitive performance across multiple domains, even after adjusting for confounding factors such as age or physical activity. Tolea et al. found that individuals with SO performed worse on cognitive tests compared to those without SO, with the association stronger than for sarcopenia or obesity alone (29).

Overall, the current evidence shows an association between SO and cognitive decline in older adults. However, the link between SO and cognitive function has mostly been investigated in cross-sectional studies, which are susceptible to confounding and reverse causality and are unable to determine causality. More longitudinal studies and randomised controlled trials are needed to clarify the direction and causality of the associations observed in these studies and explore biological mechanisms that may enhance the understanding of the links between SO and dementia risk.

Conclusion

The multiple interrelated mechanisms that link SO to neural homeostasis include reduced myokine–brain signalling, increased cytokine-related neuroinflammation, enhanced muscle–brain insulin resistance, disrupted hormone-related cerebral blood flow and neurovascular function, impaired muscle and brain mitochondrial and cellular function, and alterations in gut–brain axis communication. Further research is required to enhance the understanding of the pathogenesis of SO and its impact on brain metabolism and dementia risk. To lower the risk of cognitive impairment and dementia in older adults with SO, the design and implementation of effective prevention strategies and personalised management approaches are required.

Implication for further research

A new strategic emphasis is needed to develop the study of SO and its effects on brain health. Standardisation of diagnostic criteria is essential and therefore the adoption of the SOGLI diagnostic protocol is encouraged. It is crucial to conduct longitudinal research on how SO affects cognitive performance over time, incorporating repeated measures of body composition, physical function, cognitive performance, and dementia incidence. Additionally, mechanistic research that focuses on understanding the underlying processes and mechanisms is required to investigate the molecular and cellular links between SO and cognitive impairment, focusing on multiple mechanisms such as inflammation, oxidative stress, insulin resistance, endothelial dysfunction or altered mitochondrial function.

CHAPTER 3: Systematic Reviews and Meta-Analyses: Association of Sarcopenia, Obesity and Sarcopenic Obesity with Dementia Risk in Cohort Studies: A Systematic Review and Meta-Analysis

Introduction

Dementia is a leading cause of mortality globally and can be characterized by abnormal brain changes that can trigger cognitive and functional impairment (150). In general, the prevalence of dementia increases with age and mostly affects individuals 65 years and over (33, 52). Early-onset dementia is found in people before the age of 65 years and is associated with high healthcare burden (151).

Increased risk of dementia has been linked to body composition changes including sarcopenia, obesity, and SO (29, 138, 152). Sarcopenia was strongly associated with cognitive impairment (adjusted pooled OR 2.25, 95%CI 1.70–2.97) (138). A previous study suggested that obesity in middle age increases the risk of future dementia (Hazard ratio (HR) 1.74, 95%CI 1.34 - 2.26) (21). In addition, SO was more associated with cognitive impairment than sarcopenia or obesity alone (29). Studying findings across studies requires careful consideration of context and factors such as classification criteria based on the age of the population (i.e., middle-aged and older adults) and measurement techniques (anthropometrics, DXA, BIA) (35, 153). Additionally, various factors influence the association between sarcopenia, obesity, SO and dementia such as sex, ethnicity, education, chronic conditions (e.g., type 2 diabetes, cardiovascular disease, hypertension, stroke, depression, etc.), and lifestyle (physical activity, alcohol consumption, nutrition) (139, 154, 155). Identifying the link between sarcopenia, obesity, and/or SO and dementia could lead to more effective dementia risk reduction, prevention and treatment plans.

Aims

(a) To investigate the associations between sarcopenia, obesity, and SO with risk of dementia (i.e., all cause dementia (ACD), Alzheimer's Disease (AD) and vascular dementia (VaD)) in cohort studies.

(b) To explore the potential roles of baseline age of the population, sex, and differences in SO diagnostic protocols in the associations between body composition phenotypes and dementia risk.

Methodology

The protocol of this systematic review was registered with PROSPERO (CRD42024509396). The article selection process was performed using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

Study Design: This review adopted a Population, Exposure, Comparator, and Outcome (PECO) format. Cohort studies were included. Cross-sectional studies, case control studies, non-original research (reviews, editorials, and commentaries), and randomised controlled trials were excluded.

Search strategy: Four electronic databases including MEDLINE, EMBASE, Cochrane Database, and PsycINFO were searched using combinations of relevant search terms until January 2025. No language restrictions were applied to the searches. Cohort studies with at least one year of follow-up and investigating dementia risk (ACD, AD, VaD) in participants with sarcopenia, obesity, or SO were included. A manual search of the reference lists of included studies was conducted to find additional, eligible studies.

Participants and Exposures: Cohort studies involving adult participants aged 18 years and over, and exploring the association between sarcopenia, obesity, and SO were included.

Sarcopenia: Applying defined diagnostic methods based on quantitative data (i.e., BIA, DXA) to identify sarcopenia measures of muscle mass or muscle functional measurements (e.g., hand grip strength (HGS), walking speed) assessments of muscle strength/function, used alone or in combination.

Obesity: Studies using validated diagnostic models of obesity, for instance, anthropometric (i.e., BMI, WC) or body composition measures (fat mass) of excess adiposity, were included.

SO: Use of validated diagnostic models of SO based on muscle measurements (i.e., BIA, DXA) or functional measurements (e.g., HGS, walking speed) of lean body mass and adiposity. Self-

reported assessment or measures of sarcopenia and obesity (e.g., self-reported body weight or sarcopenia screening questionnaires (SARC-F)) were excluded.

Outcomes: Dementia diagnosis (ACD but also sub-types of dementia such as AD, VaD or mixed dementia) performed using validated diagnostic models. Studies that did not present risk estimates (e.g., Relative risk (RR) or HR) were excluded. Studies that used cognitive questionnaires for diagnosing dementia (i.e., The Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA)) were excluded.

Study selection: All citations were managed using the bibliographic software EndNote 20 (Clarivate, Philadelphia, PA, USA) to conduct the screening procedure of article selection. Initially, duplicate references were removed. Titles and abstracts of the remaining articles were subsequently reviewed independently based on the eligibility criteria. The full texts of the selected publications were obtained, and two reviewers evaluated each publication for inclusion independently. Any disagreements between the reviewers regarding inclusion decisions were addressed through discussion.

Data extraction: The first reviewer extracted data from the qualifying publications, which was later confirmed for accuracy by the second reviewer. The following information was extracted from each publication: study characteristics (e.g., first author, year, study design, duration of follow up), participants (e.g., sample size, age, sex, ethnicity), exposure (e.g., definition, assessment tool, cut-offs of exposure, control group), outcome (e.g., dementia type, diagnostic definition), results (e.g., key results, risk estimates (HR, Odds ratio (OR), RR) and 95% confidence intervals (95%CIs), and covariates used in multivariate models.

Risk of bias: The Newcastle Ottawa Scale (NOS) for cohort studies was modified and applied to evaluate quality of the publications (156). The NOS contains three domains and eight sub-domains to evaluate the risk of bias. These include the selection domain ((1) representativeness

of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at start of study), comparability domain ((1) comparability of cohorts on the basis of the design or analysis controlled for confounders), outcome domain ((1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow-up of cohorts). The publications were graded independently by two reviewers (i.e., good quality, fair quality, and poor quality).

Meta-analysis: Results were pooled when two or more unique studies investigated the association between sarcopenia, obesity, and SO with dementia risk including ACD, AD and VaD. Several studies investigated associations between various body composition phenotypes and dementia risk, reporting results from different diagnostic protocols and measurement methods within the same paper. The results were analysed independently when calculating pooled estimates, which accounts for the discrepancy between the number of analyses and the number of studies included in this review.

The meta-analysis was performed using the Comprehensive Meta-Analysis for Windows, Version 2 (Biostat, Englewood, NJ, USA). Pooled estimates for the HRs with 95%CIs were calculated for each body composition phenotype (i.e., sarcopenia, obesity, SO) using random-effect models and stratified by dementia type (ACD, AD and VaD). Analyses were also stratified by age (<65 years, ≥65 years), sex (men and women) and by method of assessment of sarcopenia (muscle, function, muscle plus function) and obesity (BMI, measures of central adiposity). Sarcopenia and obesity assessments were used to define SO. Heterogeneity was assessed using the Chi-squared test and quantified with the I^2 statistic. Publication bias for each body composition phenotype was visually inspected using funnel plots. Funnel plot asymmetry was tested using Egger's regression test. Statistical significance was set at a P-value less than 0.05.

Results

Overview: The electronic search resulted in the retrieval of 13,235 references. After removing duplicates, 11,886 references remained for the screening of titles and abstracts. 11,708 references were excluded after screening titles and abstracts. 184 full-text publications were examined, and 80 publications (84 studies) were considered eligible to be included in the systematic review; these included 12 articles on sarcopenia (157-168) 69 articles on obesity (21-23, 157, 161, 168-231) and 3 articles on SO (157, 168, 232) **(Figure 3-1).** There are 2 publications with three studies on sarcopenia, obesity, and SO. The search terms are shown in **Table 3-1**.

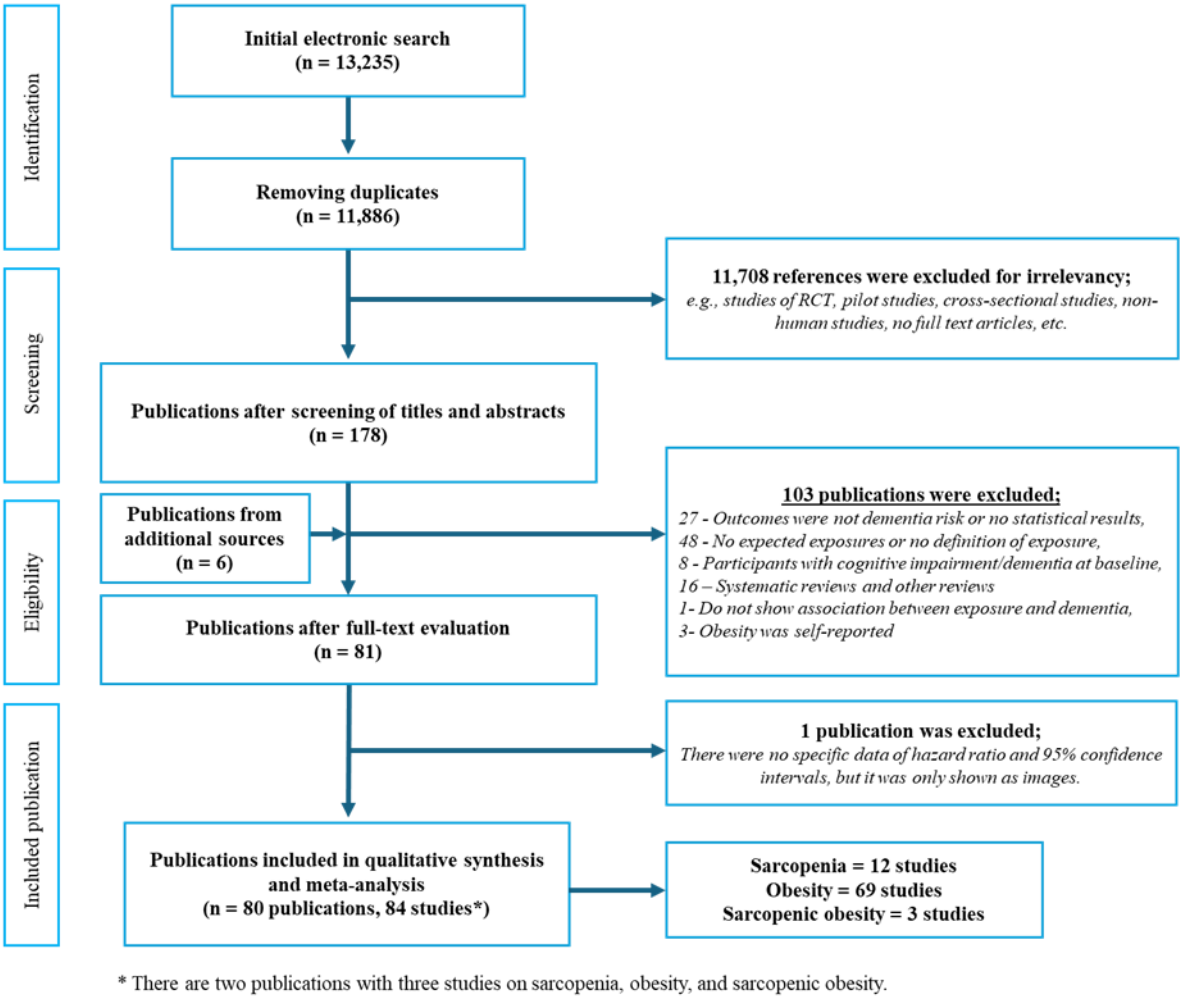


Figure 3- 1 *A PRISMA flowchart presenting the article selection process*

Table 3- 1 Search terms of the systematic review

#	**Query**
1	dementia.af. or dementia.mh. or Alzheimer.af. or Alzheimer.mh.
2	risk.af. or risk.mh. or epidemiology.af. or epidemiology.mh. or incidence.af. or incidence.mh.
3	sarcopeni*.af. or sarcopeni*.mh. or obes*.af. or obes*.mh. or muscle mass.af. or muscle mass.mh. or adiposity.af. or adiposity.mh.
4	cohort.af. or cohort.mh. or longitudinal.af. or longitudinal.mh. or observational.af. or observational.mh.
Abbreviations: af: all fields of the database, mh: main heading	

Study characteristics: This search identified 80 publications (84 studies) that were published between 2005 and 2025. Twelve studies examined the relationship between sarcopenia measures and dementia (157-168) and followed participants for 2.6 (159) to 24 (164) years, with sample sizes varying from 344 (161) to 483,637 (166) participants. Baseline mean/median age ranged from 56.5 (163) to 93 (159) years. Studies primarily assessed sarcopenia using HGS (157, 158, 160, 161, 163, 164, 166-168), with cut offs typically <27kg for men and <16kg for women. Other measures included skeletal muscle mass index (SMMI) (157, 158), appendicular lean mass (ALM) (161), appendicular lean mass index (ALMI) (161), and physical performance tests (i.e., walking speed, Timed Up and Go (TUG), chair stands, and standing balance) (159, 160, 162, 165, 167). Overall, all studies reported significant associations between at least one sarcopenia measure and dementia risk. Lower HGS consistently predicted higher dementia risk across most studies (157, 160, 162-164, 166-168), with HRs ranging from 1.34 to 2.27. Studies examining AD (158, 160, 164-166) and VaD (164-166) separately found similar associations, with VaD showing slightly stronger associations **(Table 3-2).**

Table 3- 2 Individual characteristics for 12 studies that examined the relationship between sarcopenia and dementia risk

First Author, Year (reference)	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results Hazard ratio (HR) and (95% CI)
Beeri, 2021 (158)	5.6	1,507	81	1. SMMI (men <8.87 kg/m^2, women <6.42 kg/m^2), 2. HGS (men <30 kg, women <20 kg), 3. Higher scores of the composite sarcopenia average[#]	1. SMMI (men ≥8.87 kg/m^2, women ≥6.42 kg/m^2), 2. HGS (men ≥30 kg, women ≥20 kg), 3. Lower scores of the composite sarcopenia average	AD	1. SMMI, HR = 0.96 (0.83–1.11), 2. HGS, HR = 0.66 (0.55–0.78)*, 3. Composite Sarcopenia, HR = 1.50 (1.20–1.86)*
Bullain, 2016 (159)	2.6	630	93	Performance tests (HGS, 4-m walk, Chair stands, Standing balance) Q 1	Performance tests Q 4	Dementia	1. HGS, HR = 1.01 (0.61–1.65), 2. 4-m walk, HR = 1.65 (1.00–2.2), 3. Chair stands, HR = 1.48 (0.92–2.40), 4. Standing balance, HR = 1.92 (1.13–3.25)*
Camargo, 2016 (160)	6.5	3,539	62	1. HGS ≤10th sex-specific percentile, 2. Walking speed ≤1 m/s	1. HGS >10th sex-specific percentile (corresponding to cut-offs of 15 kg in women and 30 kg in men), 2. Walking speed >1 m/s	1. Dementia 2 AD	1. Dementia: HGS, HR = 2.17 (1.00–4.69)*, Walking speed, HR = 2.53 (1.11–5.74)*; 2. AD: HGS, HR = 2.75 (1.18–6.39)*, Walking speed, HR = 2.92 (1.19–7.14)*
Cui, 2020 (161)	6	344	78	1. HGS (men <27 kg, women <16 kg), 2. ALM (men <20 kg, women <15 kg), 3. ALMI (men <7 kg/m^2, women < 5.5 kg/m^2)	1. HGS (men ≥27 kg, women ≥16, 2. ALM (men ≥20 kg, women ≥15 kg), 3. ALMI (men ≥7 kg/m^2, women ≥ 5.5 kg/m^2)	Dementia	1. HGS, men HR = 0.47 (0.14-1.62), women HR = 0.50 (0.22-1.13), 2. ALM, men HR = 3.38 (1.85-6.18)*, women HR = 1.45 (0.92-2.30), 3. ALMI, men HR = 2.28 (1.23-4.23)*, women HR = 0.81 (0.52-1.28)
Doi, 2019 (162)	3.6	4,086	72	Physical Performance (HGS, FTSS, TUG) = C 4 (lowest)	Physical Performance = C 1 (highest)	Dementia	1. HGS, HR = 1.39 (0.89-2.17), 2. FTSS, HR = 1.69 (1.10-2.59)*, 3. TUG, HR = 1.54 (1.01-2.35)*
Esteban, 2022 (163)	9.1	466,788	56.5	HGS = Q 1 (lowest)	HGS = Q 5 (highest)	Dementia	HR = 1.72 (1.55; 1.92)*
Hatabe, 2020 (164)	24.0	1,055	68	Low tertile HGS	High tertile HGS	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 1.66 (1.29–2.13)*, 2. AD, HR = 1.94 (1.41–2.67)*, 3. VaD, HR = 2.07 (1.32–3.25)*
Lee, 2018 (165)	3.8	49,283	40-79	Impaired TUG[##], >10 seconds	Normal TUG, ≤10 seconds	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 1.34 (1.14–1.57)*, 2. AD, HR = 1.26 (1.06–1.51)*, 3. VaD, HR = 1.65 (1.19–2.30)*
Ling, 2024 (166)	13.6	483,637	58.0	Probable sarcopenia; 1. HGS (men <27 kg, women <16 kg) and/or 2. ALMI (men <7.0 kg/m2, women <5.5 kg/m2) or 3. Gait speed ≤0.8 m/s	No sarcopenia; 1. HGS (men ≥27 kg, women ≥16 kg) and/or 2. ALMI (men ≥7.0 kg/m2, women ≥5.5 kg/m2) or 3. Gait speed >0.8 m/s	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 1.54 (1.46–1.62)*, 2. AD, HR = 1.32 (1.21–1.43)*, 3. VaD, HR = 1.69 (1.52–1.89)*
Radavelli, 2023 (167)	14.5	1,225	75.1	1. HGS = Q 1, 2. TUG = Q 4	1. HGS = Q 4, 2. TUG = Q 1	Dementia	1. HGS, HR = 2.27 (1.54–3.35)*, 2. TUG, HR = 2.10 (1.42–3.10)*
Yao, 2024 (168)	12.4	279,884	62.5	HGS (men <27 kg, women <16 kg)	HGS (men ≥27 kg, women ≥16 kg)	Dementia	HR = 1.56 (1.43-1.70)*
Zhang, 2024 (147)	13.4	208,867	63.5	HGS (men <27 kg, women <16 kg) and SMMI (men <7.0 kg/m^2, women <5.5 kg/m^2)	HGS (men ≥27 kg, women ≥16 kg) and SMMI (men ≥7.0 kg/m^2, women ≥5.5 kg/m^2)	Dementia	Men HR = 1.44 (1.24-1.67)*, Women HR = 1.16 (1.02-1.32)*

Table 3- 2 Individual characteristics for 12 studies that examined the relationship between sarcopenia and dementia risk

First Author, Year (reference)	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results Hazard ratio (HR) and (95% CI)
Abbreviations: AD: Alzheimer's disease, ALM: Appendicular lean mass, ALMI: Appendicular lean mass index, C: Category, FTSS: Times Sit-to-Stand Test, HGS: Hand grip strength, HR: Hazard ratio, Q: Quartile, SMMI: Skeletal muscle mass index, TUG: Timed Up & Go Test, VaD: Vascular dementia * Statistical significance ($P < 0.05$). # The composite sarcopenia average is calculated as the mean sex-specific z-score, where z scores for SMMI and for HGS are computed separately for men and women and then multiplied by -1 so higher scores represent more sarcopenia. ## Timed Up and Go Test (TUG) is rising from a chair, walked at a comfortable pace to a line on the floor 3 m away, turned and walked back to the chair, and sat down again. The person wore regular footwear and used his/her customary walking aid.							

Sixty-nine studies examined the association between obesity and dementia risk (157, 161, 168-176) (21-23, 177-231). Study follow-up periods ranged from 2.0 (180) to 53.1 (221) years, with sample sizes varying from 344 (161) to 5,669,488 (203) participants. Baseline mean/median age ranged from 18 (221) to 83 (215) years, with many studies focusing on middle-aged and older populations. Obesity was primarily assessed using BMI ≥30 kg/m² (21-23, 157, 161, 168-170, 174-178, 181-185, 187, 188, 191, 194-201, 205, 207-209, 211, 213-216, 218, 220, 222, 224-230, 233). Many studies also measured WC and sagittal abdominal diameter (SAD) which were re-classified into one category (central adiposity) (176, 178, 182, 184, 186, 192, 206, 207, 210, 212, 216, 226, 228, 231, 233, 234). Only one study explored the association between fat mass and dementia risk (182). Results showed contrasting associations between obesity and dementia risk. Midlife obesity was associated with increased dementia risk (21, 22, 183-185, 193, 200, 201, 209, 220), while late-life obesity often showed protective associations (161, 171, 174, 187, 210). Sex differences were observed in several studies, with some studies showing stronger associations between obesity and dementia risk in women (161, 178, 207, 229). In particular, vascular dementia appeared to have stronger association with obesity (23, 185, 186, 192-194, 196, 206, 211, 227) **(Table 3-3).**

Table 3- 3 Individual characteristics for 69 studies that examined the association between obesity and dementia risk

First Author, Year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
Albanese, 2015 (169)	26.2	5,764	50	BMI ≥30kg/m^2	BMI 18.5–24.9 kg/m^2	Dementia	RR = 0.91 (0.49 - 1.72)
Arnoldussen, 2018 (170)	10.0	924	74	BMI ≥30kg/m^2	BMI 20–24.9 kg/m^2	Dementia	OR = 0.93 (0.39-2.22)
Atti, 2008 (171)	9.0	1,810	81	BMI ≥25kg/m^2	BMI 20.0–24.9 kg/m^2	Dementia	HR = 0.75 (0.59–0.96)*
Batty, 2016 (172)	50.6	9,547	20.5	BMI ≥25kg/m^2	BMI <25kg/m^2	Dementia death	HR = 0.93 (0.49, 1.79)
Beydoun, 2008 (173)	23.4	3,005	52	1. BMI ≥30 kg/m^2, 2. WC = Q 5	1. BMI 18.5–24.9 kg/m^2, 2. WC = Q 1	AD	1. At baseline 30 years, 1.1 BMI, men HR = 0.70 (0.25, 1.96), women HR = 2.44 (0.85, 7.00), 1.2 WC, men HR = 0.64 (0.28, 1.46), women HR = 4.60 (1.28, 16.43)*; 2. At baseline 50 years, 2.1 BMI, men HR = 0.52 (0.13, 2.17), women HR = 2.43 (0.84, 7.02), 2.2 WC, men HR = 0.48 (0.95, 1.07), women HR = 3.04 (0.87, 10.59)
Bowen, 2012 (174)	5.0	808	78	BMI ≥30 kg/m^2	BMI 18.6–24.9 kg/m^2	Dementia	OR = 0.43 (0.25-0.76)*
Bowman, 2019 (175)	12.5	1. A = 257,523 2. B = 161,927	68	BMI ≥30 kg/m^2	BMI 18.5–25 kg/m^2	Dementia	1. Group A, HR = 1.17 (1.03, 1.32)*; 2. Group B, HR = 0.82 (0.69, 0.97)*
Brian, 2011 (176)	13.4	12,047	72	1. BMI ≥30kg/m^2, 2. WC ≥102 cm	1. BMI <25 kg/m^2, 2. WC <94 cm	Dementia	1. BMI: HR = 0.82 (0.67–1.01), 2. WC: HR = 0.88 (0.74–1.04)
Cao, 2020 (177)	8.1	466,980	57	BMI ≥30 kg/m^2	BMI 18.5 - <25 kg/m^2	Dementia	HR = 0.78 (0.68–0.88)*
Cho, 2019 (178)	6.5	872,082	70	1. BMI ≥30 kg/m^2, 2. WC ≥110 cm for men and women	1. BMI 18.5 - <23 kg/m^2, 2. WC 85-<90 cm for men and 80-<85 cm for women	Dementia	1. BMI, men HR = 0.74 (0.68-0.81)*, women HR = 0.75 (0.72-0.79)*; 2. WC, men HR = 1.63 (1.37-1.94)*, women HR = 1.58 (1.36-1.84)*
Cho, 2021 (180)	2.0	136,847	67	MUO, BMI ≥25 kg/m^2 with ≥2 metabolic risk factors[#]; (1) HTN, (2) DLP, (3) DM, or (4) Low HDL-C	MHNO, BMI <25 kg/m^2 with ≤1 metabolic risk factor	AD	HR = 1.08 (0.77-1.51)
Cho, 2022 (179)	10.0	148,534	71	BMI ≥25 kg/m^2	BMI 18.5–22.9 kg/m^2	AD	HR = 0.83 (0.80, 0.85)*
Cui, 2020 (161)	6.0	344	78	BMI >30 kg/m^2	BMI 20-25 kg/m^2	Dementia	Men, HR = 0.14 (0.02, 0.80)*, Women, HR = 1.19 (0.64, 2.19)
de Bruijn, 2015 (181)	8.9	RS-I = 7,003, RS-II = 2,953	RS-I = 69.4, RS-II = 65.0	BMI >30 kg/m^2	BMI 18.5–25 kg/m^2	Dementia	RS-I, HR = 0.84 (0.65–1.08), RS-II, HR = 0.81 (0.48–1.36)
Deng, 2022 (182)	8.7	322,336	62.2	1. BMI 30-34.9 kg/m^2, 2. WC (men >95 cm, women >85 cm), 3. FM (men >25 kg, women >30 kg),	1. BMI 18.5-24.9 kg/m^2, 2. WC (men ≤95 cm, women ≤85 cm), 3. FM (men ≤25 kg, women ≤30 kg),	Dementia	1. BMI, HR = 0.81 (0.73–0.89)*, 2. WC, HR = 2.21 (1.31–3.74)*, 3. FM, HR = 0.76 (0.68–0.84)*, 4. FM%, HR = 0.37 (0.27–0.51)*, 5. TrFM% HR = 0.52 (0.41–0.65)*

Table 3- 3 Individual characteristics for 69 studies that examined the association between obesity and dementia risk

First Author, Year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
				4. FM% (men >27%, women >35%), 5. TrFM% (men >28%, women >38.5%)	4. FM% (men ≤27%, women ≤35%), 5. TrFM% (men ≤28%, women ≤38.5%)		
Ding, 2024 (183)	21.1	295, 823	54.7	MAO, BMI ≥30 kg/m^2 with ≥2 metabolic risk factors[#]; (1) HTN, (2) DLP, (3) DM, or (4) Low HDL-C	MNNO, BMI <30 kg/m^2 with <2 metabolic risk factors	Dementia	HR = 1.48 (1.16-1.89)*
Exalto, 2014 (184)	36.1	9,480	46	1. BMI >30 kg/m^2, 2. SAD >25 cm	1. BMI ≤30 kg/m^2, 2. SAD ≤25 cm	Dementia	1. BMI, HR = 1.19 (0.96–1.48), 2. SAD, HR = 1.27 (1.04–1.56)*
Fitzpatrick, 2009 (23)	5.4	2,798	74.7	BMI > 30 kg/m^2	BMI 20-25 kg/m^2	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 1.36 (0.94-1.95), 2. AD, HR = 1.25 (0.74-2.11), 3. VaD, HR = 1.33 (0.78-2.29)
Floud, 2020 (185)	18.0	1,136,846	56	BMI ≥30 kg/m^2	BMI 20-24.9 kg/m^2	1. Dementia, 2. AD, 3. VaD	1. Dementia, RR = 1.31 (1.23-1.39)*, 2. AD, HR = 1.01 (0.93-1.08), 3. VaD, HR = 1.41 (1.29-1.56)*
Forti, 2010 (186)	3.9	749	1. Group 1 (<75 y) = 69.3, 2. Group 2 (≥75 y)= 79.8	WC (men >102 cm, women >88 cm)	WC (men ≤102 cm, women ≤88 cm)	1. Dementia, 2. AD, 3. VaD	1. Group 1, Dementia, HR = 0.80 (0.38–1.66), AD HR = 0.62 (0.21–1.76), VaD HR = 1.08 (0.32–3.64); 2. Group 2, Dementia, HR = 0.53 (0.28–0.98)*, AD HR = 0.61 (0.29–1.30), VaD HR = 0.30 (0.08–1.00)
Garcia, 2014 (187)	2.5	11,398	78.5	BMI >30 kg/m^2	BMI 18.5-22.9 kg/m^2	Dementia death	HR = 0.68 (0.59-0.78)*
Gong, 2021 (188)	11.8	502,226	56.5	BMI ≥30 kg/m^2	BMI 18.5–24.9 kg/m^2	Dementia	1. Men, HR = 0.92 (0.85-1.00), 2. Women, HR = 1.08 (0.99-1.18)
Gontie, 2022 (189)	2.0	46,141	≥50	High BMI	NA	Dementia	RR = 0.56 (0.44-0.70)*
Gottesman, 2017 (190)	23.0	15,744	54.2	High BMI	NA	Dementia	HR = 1.14 (0.99-1.31)
Guo, 2023 (191)	5.8	1,673	69.4	BMI ≥30 kg/m^2	BMI <25 kg/m^2	Dementia	HR = 2.61 (1.09−5.54)*
Gustafson, 2009 (192)	32.0	1,462	38	1. BMI ≥25 kg/m^2, 2. WC >88 cm	Per kg/m^2	Dementia, AD, and VaD	1. BMI, HR = 0.84 (0.59–1.21), 2. WC, HR = 1.25 (0.67–2.35)
Hassing, 2009 (193)	40.0	1,152	52.5	BMI highest quartile	BMI lowest quartile	1. Dementia, 2. AD, 3. VaD	1. Dementia, OR = 1.55 (1.18–2.04)*, 2. AD, OR = 1.68 (1.21–2.33)*, 3. VaD, OR = 1.36 (0.82–2.56)
Hayden, 2006 (194)	3.2	3,123	73.7	BMI ≥30 kg/m^2	NA	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 1.76 (1.03–2.88)*, 2. AD, HR = 1.93 (1.05–3.36)*, 3. VaD, HR 1.16 (0.37–3.12)
Hessler, 2016 (195)	6.7	3,547	67.3	BMI ≥30 kg/m^2	BMI <25 kg/m^2	Dementia	HR = 0.77 (0.55–1.07)

Table 3- 3 Individual characteristics for 69 studies that examined the association between obesity and dementia risk

First Author, Year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
Jacob, 2022 (196)	10.0	296,767	70.2	BMI ≥30 kg/m^2	BMI 18.5-<25 kg/m^2	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 0.98 (0.94-1.02), 2. AD, HR = 0.82 (0.73-0.91)*, 3. VaD, HR = 1.10 (1.01-1.21)*
Kang, 2021 (197)	2.7	45,076	60-79	BMI ≥30 kg/m^2	BMI 18.5-25 kg/m^2	AD	4-year BMI change, HR = 1.13 (0.85–1.50)
Karlsson, 2020 (198)	13.0	The STR = 22,156, The HRS = 25,698	The STR = 66.8, The HRS = 62.9	BMI >30 kg/m^2	BMI 18.5-25 kg/m^2	Dementia	The STR: 20-34 y, HR = 0.92 (0.39-2.17), 35-49 y, HR = 1.36 (1.06-1.74)*, 50-64 y, HR = 1.37 (1.09-1.73)*, 65-79 y, HR = 0.92 (0.79-1.06), 80+ y, HR = 0.79 (0.58-1.07); The HRS: 50-64 y, HR = 0.95 (0.80-1.12), 65-79 y, HR = 0.83 (0.73-0.93)*, 80+ y, HR = 0.91 (0.77-1.09)
Kivimaki, 2018 (199)	16.1	1,349,857	69.1	BMI >30 kg/m^2	BMI 20.0-24.9 kg/m^2	Dementia	HR = 0.84 (0.75–0.94)*
Kivipelto, 2005 (200)	21.0	2,000	50.6	BMI >30 kg/m^2	BMI ≤25 kg/m^2	Dementia	OR = 1.88 (0.76-4.63)
Kivipelto, 2006 (201)	20.9	2,000	50.4	BMI >30 kg/m^2	BMI ≤30 kg/m^2	Dementia	OR = 1.84 (0.98–3·45)
Kontari, 2023 (202)	1. ELSA = 12.2 2. HRS = 11.6 3. CHARLS = 6.8	1. 4, 511 2. 5 ,112 3. 9, 022	1. 65.7, 2. 66.7, 3. 58.6	Obesity hypertension: 1. ELSA and HRS, WC (men ≥94 cm, women ≥80 cm), 2. CHARLS, WC (men ≥90 cm, women ≥80 cm); And hypertension: Systolic BP ≥130 mm Hg and raised diastolic BP ≥85 mm Hg	Healthy obesity	Dementia	1. ELSA, HR = 1.02 (0.78, 1.33), 2. HRS, HR = 1.16 (0.94, 1.43), 3. CHARLS, HR = 1.28 (1.04, 1.57)*
Lee, 2019 (203)	5.4	5,669,488	67.1	MUO, BMI ≥25 kg/m^2 with ≥2 metabolic risk factors[#]; (1) HTN, (2) DLP, (3) DM, or (4) Low HDL-C	MHNO, BMI <25 kg/m^2 with ≤1 metabolic risk factor	Dementia	Dementia, HR = 1.01 (0.99–1.02), AD, HR = 1.29 (1.25–1.32)*, VaD, HR = 1.33 (1.29–1.36)*
Lei, 2022 (204)	5.3	1,627	71.3	BMI ≥24.0 kg/m^2	BMI 18.5 - 24.0 kg/m^2	Demntia	HR = 1.04 (0.63,1.71)
Li, 2021 (205)	38.0	3,632	43.5	BMI >30 kg/m^2	BMI <25 kg/m^2	Dementia	1. At 40-49 y, HR = 3.15 (1.35-7.33)*, 2. At 50-59 y, HR = 0.82 (0.53-1.27), 3. At 60-69 y, HR = 0.76 (0.50-1.14), 4. At ≥70 y, HR = 0.65 (0.40-1.04)
Luchsinger, 2007 (206)	5.1	1,117	77	1. BMI >29.6 kg/m^2, 2. WC > 97 cm	1. BMI <23.4 kg/m^2, 2. WC ≤83 cm	1. Dementia, 2. AD, 3. VaD	1. BMI: 1.1 Dementia, HR = 0.8 (0.5-1.2), 1.2 AD, HR = 0.9 (0.5-1.6), 1.3 VaD, HR = 0.8 (0.4-1.7); 2. WC: 2.1 Dementia, HR = 1.1 (0.7-1.8), 2.2 AD, HR = 1.0 (0.6-1.8), 2.3 VaD, HR = 2.3 (1.0-5.1)

Table 3- 3 Individual characteristics for 69 studies that examined the association between obesity and dementia risk

First Author, Year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
Ma, 2019 (235)	NA	1,199	73.5	MUO, BMI ≥25 kg/m^2 with ≥2 metabolic risk factors[#]; (1) HTN, (2) DLP, (3) DM, or (4) Low HDL-C	MHNO, BMI <25 kg/m^2 with ≤1 metabolic risk factor	AD	HR = 0.93(0.70-1.24)
Ma, 2020 (207)	11.4	BMI = 6129, WC = 5,106	BMI = 61.9, WC = 62.7	1. BMI ≥30 kg/m^2, 2. WC (men >102 cm, women >88 cm)	1. BMI 18.5–24.9 kg/m^2, 2. WC (men ≤102 cm, women ≤88 cm)	Dementia	1. BMI, HR = 1.31 (1.03-1.59)*, 2. WC men, HR = 0.84 (0.55-1.13), 3. WC women, HR = 1.39 (1.12-1.66)*
Machado, 2023 (208)	1. 20.8, 2. 10.3, 3. 4.2	1. 4,301, 2. 3,117, 3. 1,244	1. 55.0, 2. 65.0, 3. 73.9	MUO, BMI ≥30 kg/m^2 with ≥2 metabolic risk factors[#]; (1) HTN, (2) DLP, (3) DM, or (4) Low HDL-C	MHNO, BMI <30 kg/m^2 with ≤1 metabolic risk factor	Dementia	1. Age < 60 y, HR = 1.46 (1.02-2.08)*, 2. Ages 60 - < 70 y, HR = 1.47 (1.05-2.04)*, 3. Age ≥ 70 y, HR = 1.20 (0.82-1.74)
Mehlig, 2014 (209)	34.0	1,448	38-60	BMI ≥30 kg/m^2 and Low LTPA[##]	BMI < 30 kg/m^2 and High LTPA	Dementia	HR = 3.31 (1.43–7.66)*
Muller, 2007 (210)	4.4	1,833	76.1	WC (men ≥102 cm, women ≥88 cm)	WC (men <102 cm, women <88 cm)	Dementia	HR = 0.7 (0.5–0.9)*
Neergaard, 2016 (211)	11.9	4,920	70.1	BMI ≥30 kg/m^2	BMI 18.5 - <25 kg/m^2	1. Dementia, 2. AD, 3. VaD	1. Dementia, HR = 0.79 (0.62–1.01), 2. AD, HR = 0.74 (0.51–1.09), 3. VaD, HR = 1.28 (0.57–2.86)
Ng, 2016 (212)	3.8	2,042	64.9	WC (men ≥90 cm, women ≥80 cm)	WC (men <90 cm, women <80 cm)	Dementia	HR = 2.97 (0.85-10.40)
Osler, 2020 (213)	43.0	377,598	18-30	BMI ≥30 kg/m^2	BMI 18.5 - < 25 kg/m^2	Dementia	1. Age 41-60 y, HR = 0.98 (0.67–1.45), 2. Age 61-78 y, HR = 0.85 (0.52–1.45)
Park, 2019 (214)	5.3	67,219	65.4	1. BMI %gain, >10%, 2. BMI ≥30 kg/m^2	1. BMI stable, ±5%, 2. BMI 23–25 kg/m^2	Dementia	1. BMI %gain, HR = 1.25 (1.08-1.45)*, 2. BMI, HR = 0.76 (0.57-1.01)
Pham, 2022 (215)	9.0	39,066	1. 71.6, 2. 83.8	BMI ≥30 kg/m^2 or a physician diagnosis of obesity	BMI 20 - <30 kg/m^2	Dementia	1. 65-79 y, HR = 0.93 (0.82–1.05), 2. 80+ y, HR = 0.92 (0.76–1.12)
Power, 2011 (216)	9.7	12,047	72.1	1. BMI ≥30 kg/m^2, 2. WC ≥102 cm	1. BMI <25 kg/m^2, 2. WC <94 cm	Dementia	1. BMI, HR = 0.82 (0.67–1.01), 2. WC, HR = 0.88 (0.74–1.04)
Power, 2013 (217)	5.9	12,203	75.3	1. BMI gain >1 unit 2. BMI gain >2 units	1. BMI gain ≤1 unit 2. BMI gain ≤2 units	Dementia	1. HR = 1.28 (0.82–2.01), 2. HR = 0.79 (0.40–1.54)
Qizilbash, 2015 (218)	9.1	1,958,191	55	1. Class I, BMI 30–34.9 kg/m^2, 2. Class II, BMI 35–39.9 kg/m^2, 3. Class III, BMI ≥40 kg/m^2	BMI 20-24.9 kg/m^2	Dementia	Class I, HR = 0.74 (0.72–0.76)*, Class II, HR = 0.69 (0.66–0.74)*, Class III, HR = 0.67 (0.60–0.74)*
Qureshi, 2024 (234)	12.3	176,249	64.1	WC (men ≥102 cm, women ≥88 cm)	WC (men <102 cm, women <88 cm)	Dementia	HR = 1.02 (0.97-1.09)
Rosengren, 2005 (220)	23.0	7,402	51.5	BMI ≥30 kg/m^2	BMI 20-22.49 kg/m^2	Dementia	HR = 1.84 (1.01-3.34)*
Russ, 2019 (221)	53.1	32,692	18	BMI >25 kg/m^2	BMI ≤25 kg/m^2	Dementia-related deaths	HR = 0.36 (0.18-0.73)*
Singh, 2018 (22)	26.7	9,974	44.8	BMI ≥30 kg/m^2	BMI 18.5–24.9 kg/m^2	Dementia	1. BMI at 50 y, HR = 1.93 (1.35–2.75)*, 2. BMI at 60 y, HR = 1.31 (0.89–1.92), 3. BMI at 70 y, HR = 0.87 (0.56–1.34)

Table 3- 3 Individual characteristics for 69 studies that examined the association between obesity and dementia risk

First Author, Year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
Strand, 2017 (222)	9.0	43,721	42	BMI ≥30 kg/m^2	BMI 20–24.9 kg/m^2	Dementia-Related Mortality	HR = 1.04 (0.84-1.29)
Tashiro, 2023 (223)	10.0	37,414	49	BMI 27.0 - 39.9 kg/m^2	BMI 23.0 - 24.9 kg/m^2	Disabling dementia	1. Men, HR = 1.17 (0.96-1.44), 2. Women, HR = 1.20 (1.02-1.42)*
Tolppanen, 2014 (224)	26.0	2,000	50.2	BMI >30 kg/m^2	BMI < 25kg/m^2	1. Dementia, 2. AD	1. Dementia, HR = 0.55 (0.23-1.34), 2. AD, HR = 0.40 (0.15-1.08)
Wang, 2025 (225)	7.3	30,113	66.04	BMI ≥30 kg/m^2	NA	Dementia	OR = 1.11 (1.01-1.22)*
West, 2009 (226)	5.6	1,351	70	1. BMI >30 kg/m^2, 2. WC hight tertile	1. BMI <25 kg/m^2, 2. WC low tertile	Dementia	1. BMI, HR = 0.24 (0.10-0.54)*, 2. WC, HR = 2.7 (1.2-6.0)*
Whitmer, 2005 (21)	27.0	10,276	42.5	BMI ≥30 kg/m^2	BMI 18.5-24.9 kg/m^2	Dementia	HR = 1.74 (1.34-2.26)*
Whitmer, 2007 (227)	36.0	10,136	42	BMI ≥30 kg/m^2	BMI 18.5-24.9 kg/m^2	1. AD 2. VaD	1. AD, HR = 3.10 (2.19-4.38)*, 2. VaD, HR = 5.01 (2.98-8.43)*
Whitmer, 2008 (228)	36.0	6,583	42	BMI ≥30 kg/m^2 and SAD ≥25 cm	BMI 18.5-24.9 kg/m^2 and SAD <25 cm	Dementia	HR = 3.60 (2.85-4.55)*
Yao, 2024 (168)	12.4	279,884	62.5	BMI ≥30 kg/m^2	BMI <30 kg/m^2	Dementia	HR = 1.03 (0.97-1.10)
Zakharova, 2023 (229)	8.0	13,802	59	BMI ≥30 kg/m^2	BMI 22.7 - 24.9 kg/m^2	Dementia	1. Men, HR = 0.69 (0.16–2.96), 2. Women, HR = 2.33 (0.77–6.99)
Zeki, 2021 (230)	7.9	15,001	1. 20-49, 2. 50-69, 3. 70-89	BMI >30 kg/m^2	BMI <25 kg/m^2	Dementia	1. Age 20-49 y, Men OR = 2.47 (1.46-4.19)*, Women OR = 2.45 (1.47-4.06)*, 2. Age 50-69 y, Men OR = 2.00 (1.16-3.42)*, Women OR = 0.70 (0.42-1.19), 3. Age 70-89 y, Men OR = 0.37 (0.24-0.59)*, Women OR = 0.52 (0.36-0.76)*
Zeng, 2025 (236)	1. 5.8, 2. 5.3	1. 9,222, 2. 3,806	1. 58, 2. 72.6	1. BMI ≥28 kg/m^2, 2. WC ≥ 90 cm for men and ≥ 85 women	1. BMI 18.5-24 kg/m^2, 2. WC <90 cm for men and <85 women	Dementia	1. Mid-life: BMI, HR = 1.77 (1.26-2.47)*, WC, HR = 1.56 (1.23-1.98)*; 2. Late-life: BMI, HR = 1.14 (0.74-1.74), WC, HR = 1.11 (0.88-1.40)
Zhang, 2024 (147)	13.4	208,867	63.5	BMI ≥30 kg/m^2	BMI <30 kg/m^2	Dementia	Men HR = 1.04 (0.96-1.14), Women HR = 0.92 (0.83-1.02)

Abbreviations: AD: Alzheimer's disease, BMI: Body mass index, BP: Blood pressure, DLP: Dyslipidemia, DM: Diabetes mellitus, FM: Fat mass, HDL-C: HDL cholesterol, HR: Hazard ratio, HTN: Hypertension, LTPA: Leisure time physical activity, MAO: Metabolically abnormal obesity, MHNO: Metabolically healthy non-obesity, MNNO: Metabolically normal non-obesity, MUO: Metabolically unhealthy obesity, OR: Odds ratio, Q: Quartiles, RR: Relative Risk, SAD: Sagittal abdominal diameter, TrFM%: Trunk fat mass%, VaD: Vascular dementia, WC: Waist circumference.

* Statistical significance (P < 0.05).

[#] Metabolic risk factors; (1) HTN = systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or taking antihypertensive medications; (2) DLP = TG ≥150 mg/dL or taking lipid-lowering medications; (3) DM = FPG ≥100 mg/dL or taking antidiabetic medications; or (4) HDL-C <40 mg/dL in men and <50 mg/dL in women.

[##] LTPA (Leisure time physical activity) was assessed in 4 categories, ranging from 'almost inactive' (reading, watching TV, etc.), 'some physical activity at least 4 h/week' (cycling, walking, etc.) and 'regular exercise' (tennis, running, heavy gardening, etc.) to 'regular training and competitive sports'.

Three studies examined the relationship between SO and dementia risk (157, 168, 232). Studies followed participants for 8.7-13.4 years with sample sizes ranging from 2,000-279,884 participants (mean/median baseline age: 56.7-63.5 years). Assessments included combined measures of body composition and muscle strength such as fat-to-muscle mass ratio (FMR) (232), BMI with HGS (168), and combined use of HGS, SMMI, and BMI (157). Results showed contrasting associations as a higher FMR was protective against dementia (232), while the combination of low muscle strength, low muscle mass, and obesity significantly increased dementia risk (157, 168) (**Table 3-4**). The forest plots on the association between sarcopenia, obesity, and SO in the different definitions and age groups were shown in **Figures 3-2 – 3-12**.

Table 3- 4 Individual characteristics for 3 studies that examined the relationship between sarcopenic obesity (SO) and dementia risk

First Author, year	Follow Up (Mean, years)	Baseline Sample Size	Baseline Mean/ Median Age (years)	Definition	Control group	Type of dementia Outcome	Key Results
Wang, 2022 (232)	8.7	491,420	56.7	Highest FMR (Q 5)	Lowest FMR (Q 1)	1. Dementia, 2. AD, 3. VaD	1. Dementia: Men HR = 0.65 (0.51-0.84)*, Women HR = 0.55 (0.40-0.76)*, 2. AD: Men HR =0.51 (0.33-0.79)*, Women HR = 0.72 (0.43-1.20), 3. VaD: Men HR = 0.83 (0.50-1.07), Women HR = 0.50 (0.23-1.09)
Yao, 2024 (168)	12.4	279,884	62.5	BMI ≥30 kg/m^2 and HGS (men <27 kg, women <16 kg)	BMI <30 kg/m^2 and HGS (men ≥27 kg, women ≥16 kg)	Dementia	HR = 1.67 (1.44-1.94)*
Zhang, 2024 (147)	13.4	208,867	63.5	HGS (men <27 kg, women <16 kg) and SMMI (men <7.0 kg/m^2, women <5.5 kg/m^2) and BMI ≥30 kg/m^2	HGS (men ≥27 kg, women ≥16 kg) and SMMI (men ≥7.0 kg/m^2, women ≥5.5 kg/m^2) and BMI <30 kg/m^2	Dementia	Men HR = 1.99 (1.70-2.32)*, Women HR = 1.42 (1.23-1.65)*

Abbreviations: AD: Alzheimer's disease, BMI: Body mass index, FMR: Fat-to-muscle mass ratio, HGS: Hand grip strength, HR: Hazard ratio, Q: Quartiles, SMMI: Skeletal muscle mass index, VaD: Vascular dementia
* Statistical significance (P < 0.05).

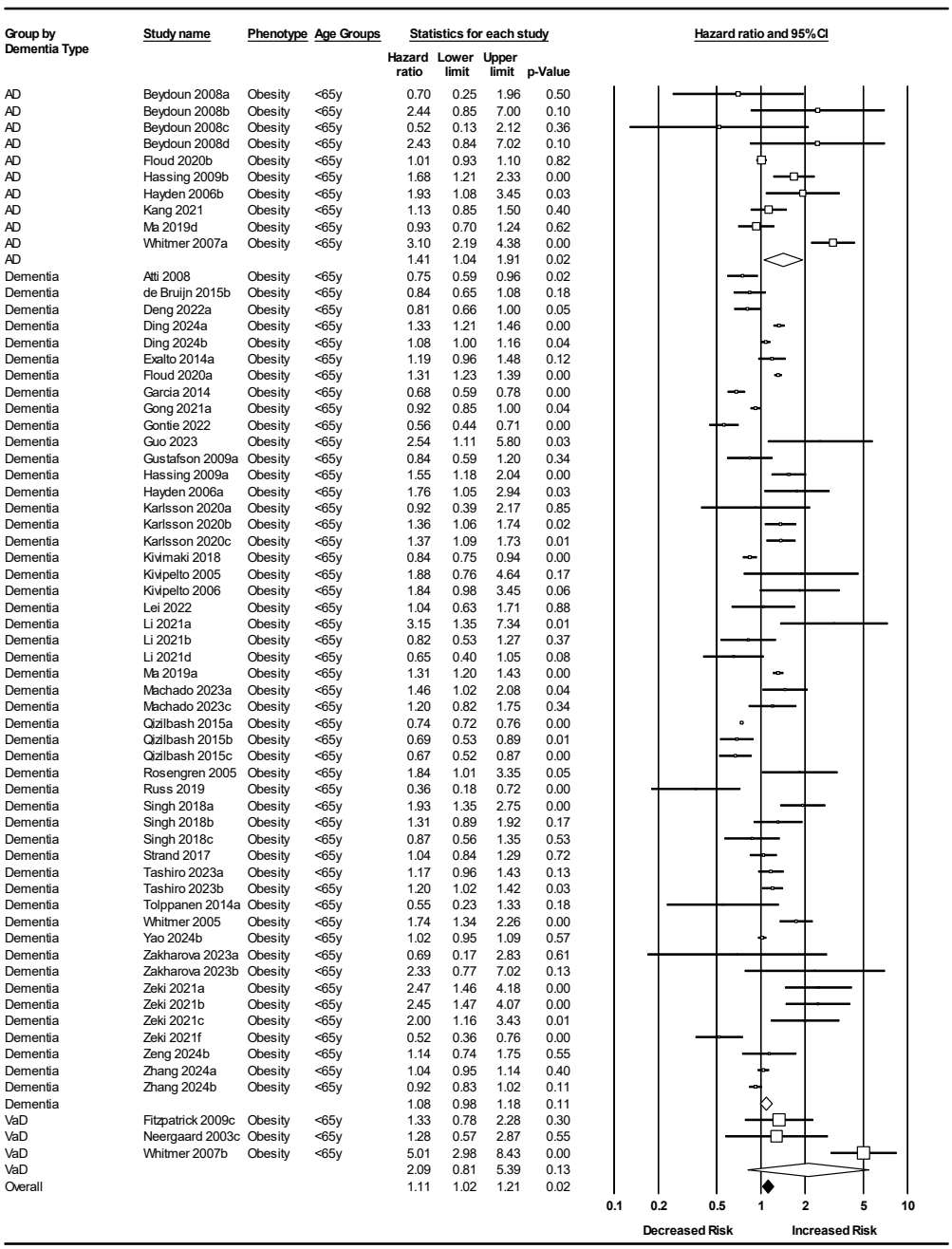


Figure 3- 2 *Forest plot on the association between obesity, assessed by BMI, and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

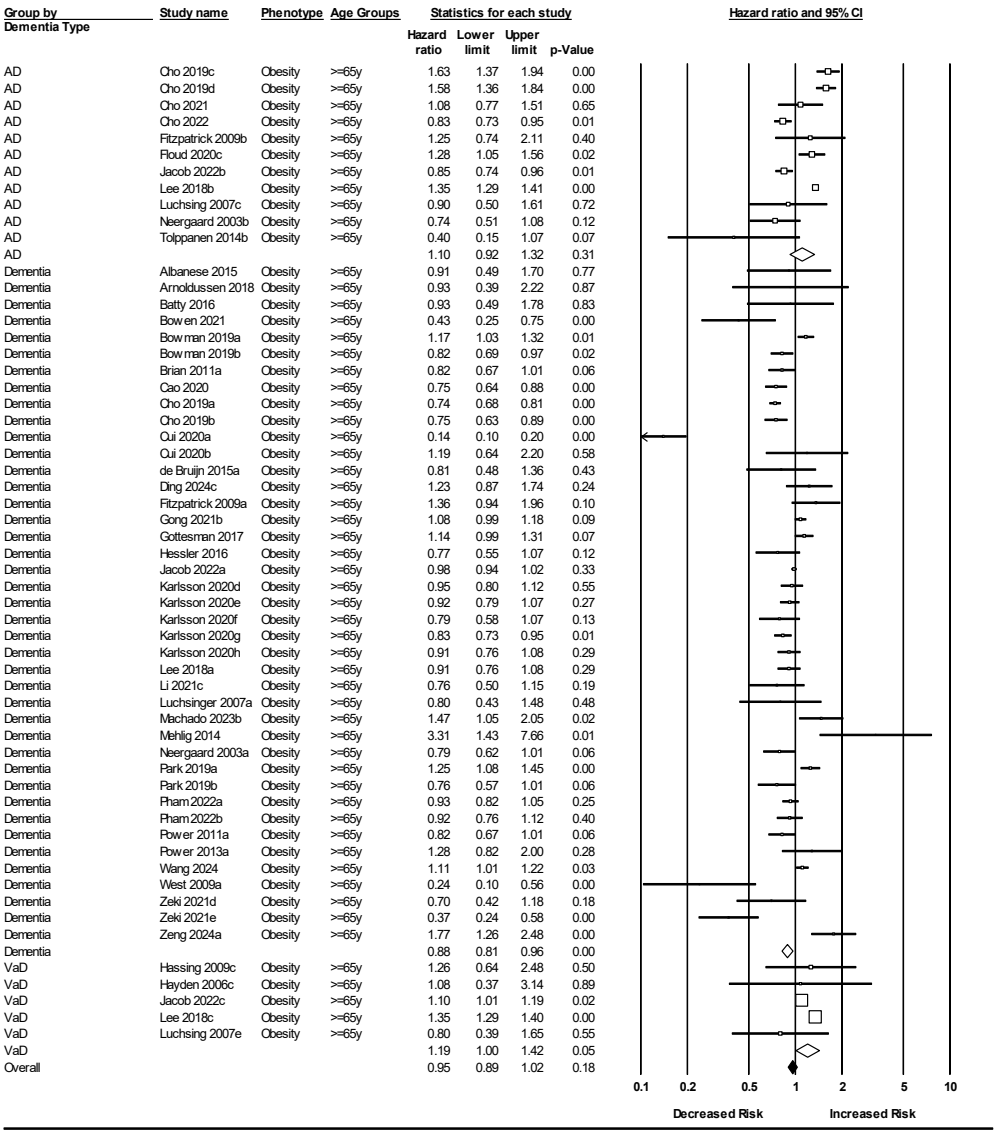


Figure 3- 3 *Forest plot on the association between obesity, assessed by BMI, and dementia risk, stratified by dementia type, in subjects older than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

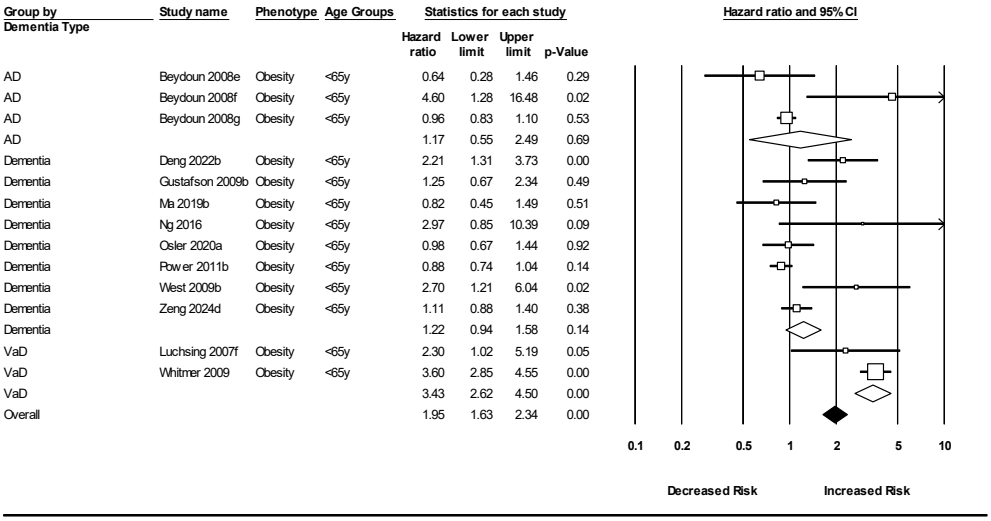


Figure 3- 4 *Forest plot on the association between central obesity and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

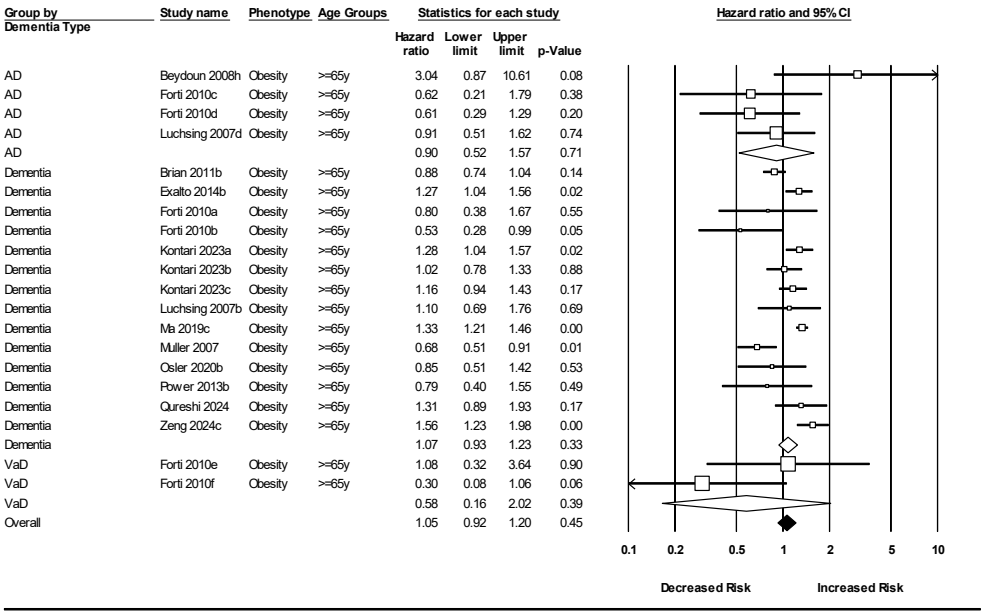


Figure 3- 5 *Forest plot on the association between central obesity and dementia risk, stratified by dementia type, in subjects older than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

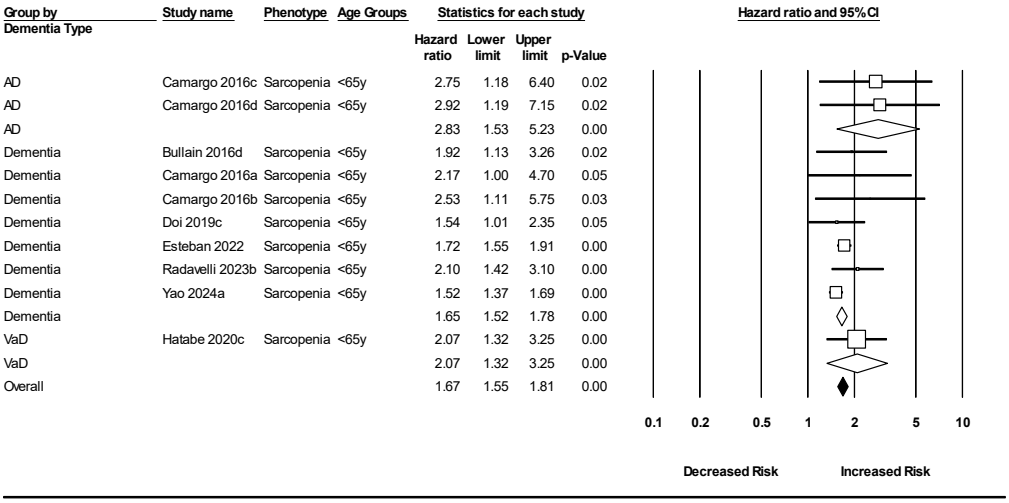


Figure 3- 6 *Forest plot on the association between sarcopenia, assessed using functional methods, and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

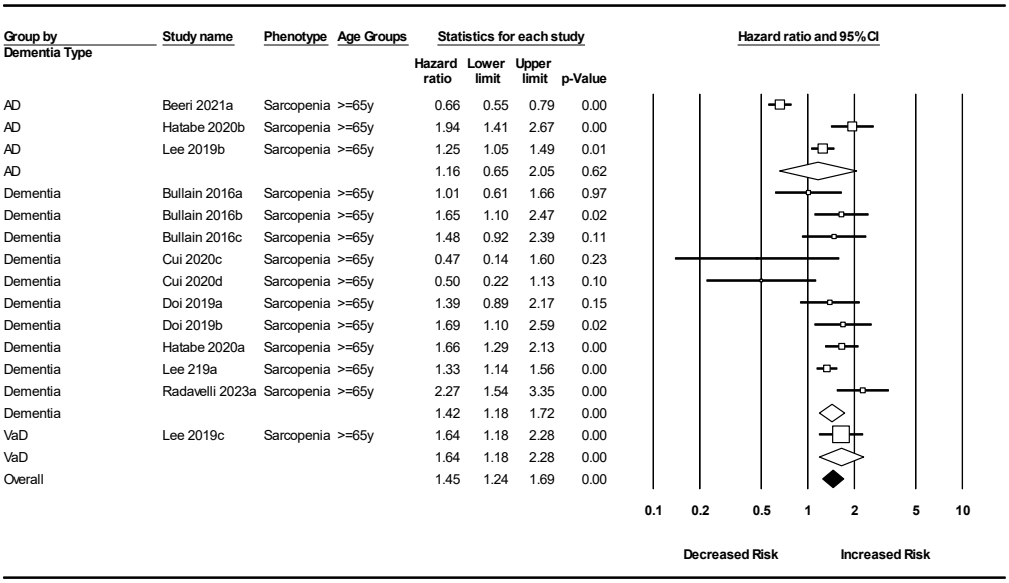


Figure 3- 7 *Forest plot on the association between sarcopenia, assessed using functional methods, and dementia risk, stratified by dementia type, in subjects older than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

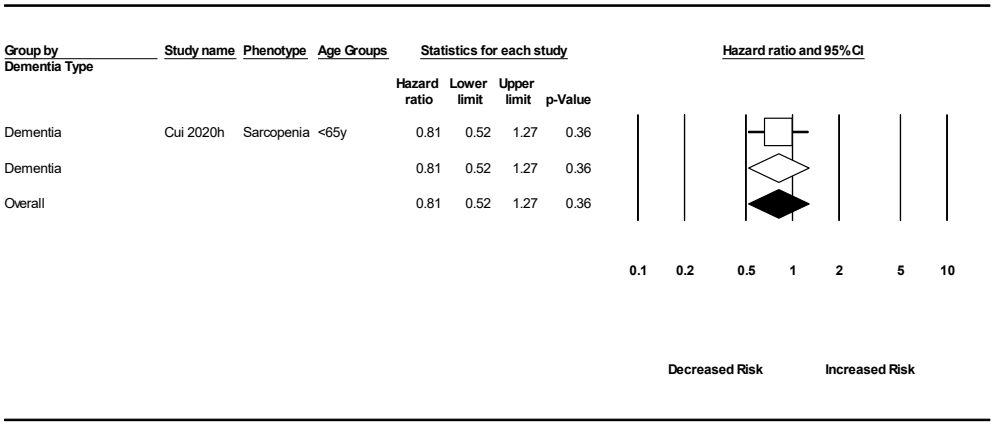


Figure 3- 8 *Forest plot on the association between sarcopenia, assessed using quantitative methods, and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

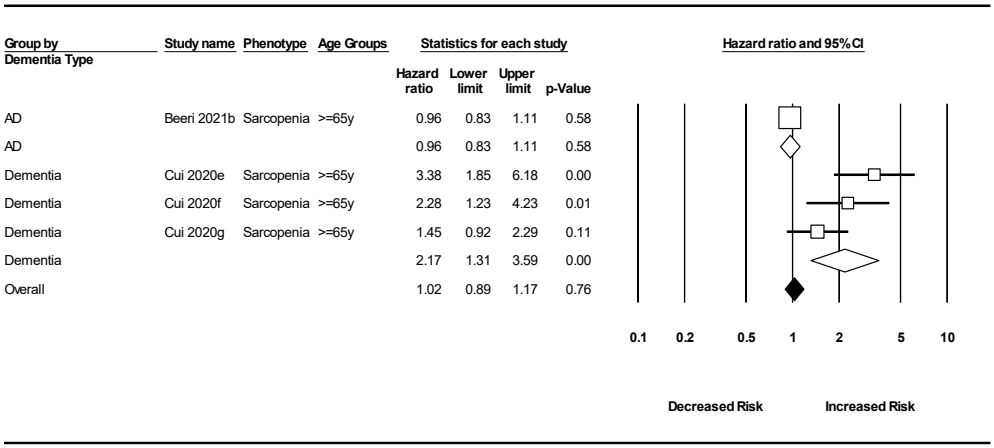


Figure 3- 9 *Forest plot on the association between sarcopenia, assessed using quantitative methods, and dementia risk, stratified by dementia type, in subjects older than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

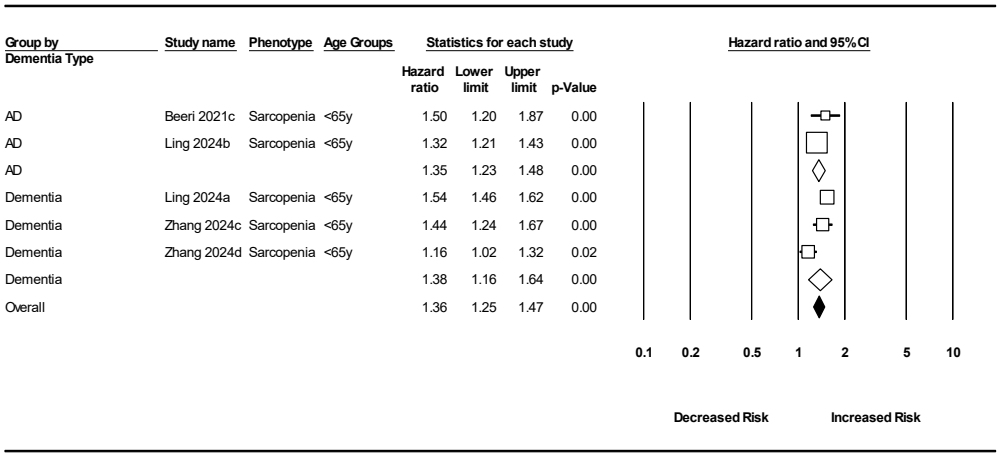


Figure 3- 10 *Forest plot on the association between sarcopenia, assessed using quantitative+functional methods, and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*



Figure 3- 11 *Forest plot on the association between sarcopenia, assessed using quantitative+functional methods, and dementia risk, stratified by dementia type, in subjects older than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

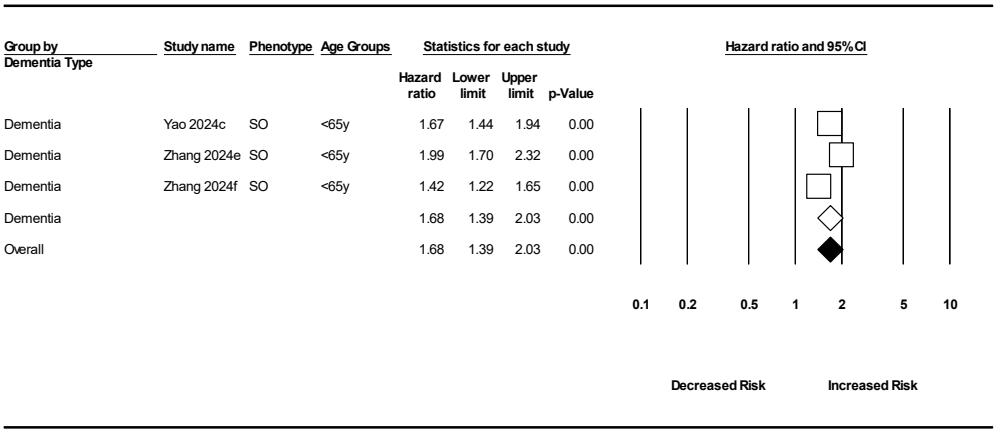


Figure 3- 12 *Forest plot on the association between sarcopenic obesity (SO) and dementia risk, stratified by dementia type, in subjects younger than 65 years. AD, Alzheimer's disease; VaD, vascular dementia.*

Risk of bias Assessment: NOS scores ranged from 5 to 8 points **(Figure 3-13)**, with the majority (68 studies, 81%) receiving "Good" quality ratings (7-8 points) (21-23, 157, 159-164, 166-170, 173-183, 185-188, 190-192, 194-200, 202-206, 209, 211, 212, 214, 215, 217, 218, 220, 223-229, 231, 232, 234) and 16 studies (19%) rated as "Fair" quality (5-6 points) (158, 165, 171, 172, 184, 189, 193, 201, 207, 208, 210, 213, 216, 221, 222, 230). No studies were rated as "Poor" quality. The highest-scoring studies (8 points) accounted for approximately 29% of all publications (157, 164, 166, 168, 169, 173, 175, 176, 179, 180, 183, 188, 192, 195, 196, 214, 225, 234), demonstrating generally robust methodological quality across the cohort studies.

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE, COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) Truly representative (one star)

b) Somewhat representative (one star)

c) Selected group

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort (one star)

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) (one star)

b) Structured interview (one star)

c) Written self-report

d) No description

e) Other

4) Demonstration that outcome of interest was not present at start of study

a) Yes (one star)

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for age (one star)

b) Study controls for other factors (list) sex, marital status, education, hypertension, etc. (one star)

c) Cohorts are not comparable based on the design or analysis controlled for confounders

d) No statement

Outcome

1) Assessment of outcome

a) Independent blind assessment (stated in the paper, or confirmation of the outcome by reference to secure records, health records, etc.) (one star)

b) Record linkage (e.g. identified through ICD codes on database records) (one star)

c) Self report (i.e. no reference to original health records or documented source to confirm the outcome)

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur (≥10 years)

a) Yes (one star)

b) No

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)

c) Follow up rate less than 80% and no description of those lost

d) No statement

Note:

The quality of each study was rated using the following scoring algorithms: ≥7 points were considered as "good", 2 to 6 points were considered as "fair", and ≤1 point was considered as "poor" quality.

Figure 3- 13 *Newcastle - Ottawa Quality Assessment Scale (NOS), Cohort Studies*

Meta-analysis: The meta-analysis revealed complex associations between body composition phenotypes and dementia risk, with distinct patterns emerging for sarcopenia, obesity, and SO. Sarcopenia demonstrated more consistent associations across age groups. The overall association of sarcopenia with ACD was significant (HR 1.51, 95% CI 1.38-1.65), with similar magnitudes of associations observed in both sex and age groups. Sarcopenia was also significantly associated with VaD (HR 1.70, 95% CI 1.53-1.88) for the whole group, suggesting potential vascular mechanisms may play a role. The method of sarcopenia assessment influenced the strength of the associations. Functional measures of sarcopenia showed stronger associations with dementia outcomes compared to quantitative measures alone. Combined functional and quantitative assessments demonstrated more consistent risk patterns, suggesting that comprehensive evaluation of sarcopenia might provide more reliable risk assessment **(Table 3-5)**.

SO showed the association with all-cause dementia (HR 1.67, 95% CI 1.38-2.02). In addition, sex-stratified analyses showed that SO was associated with all-cause dementia in both men (HR 1.99, 95% CI 1.70-2.32) and women (HR 1.42, 95% CI 1.23-1.65). However, this finding should be interpreted with caution due to the limited number of studies (n=3) **(Table 3-5).** The substantial heterogeneity observed across studies, particularly for obesity-related associations (I^2 ranging from 71% to 93%), highlights the complexity of these associations and suggests the influence of additional confounding factors not captured in the primary analyses. This heterogeneity was generally lower for sarcopenia-related associations (I^2 ranging from 0% to 93%), particularly for VaD outcomes, indicating more consistent associations **(Table 3-5)**.

Obesity was not associated with all-cause dementia (HR 0.99, 95% CI 0.94-1.05), however, subgroup analyses showed significant associations with AD (HR 1.16, 95% CI 1.02-1.32) and VaD (HR 1.57, 95% CI 1.22-2.00). The association between obesity and dementia suggested the existence of age-dependent associations. In individuals under 65 years, obesity was

associated with increased risk across all dementia types, with HR of 1.32 (95% CI 1.05-1.66) for AD, and a substantial increase in risk for VaD (HR 2.46, 95% CI 1.47-4.13). Conversely, in those aged 65 and older, obesity seemed to be protective for all-cause dementia (HR 0.92, 95% CI 0.85-0.99), while associations with AD and VaD were not significant.

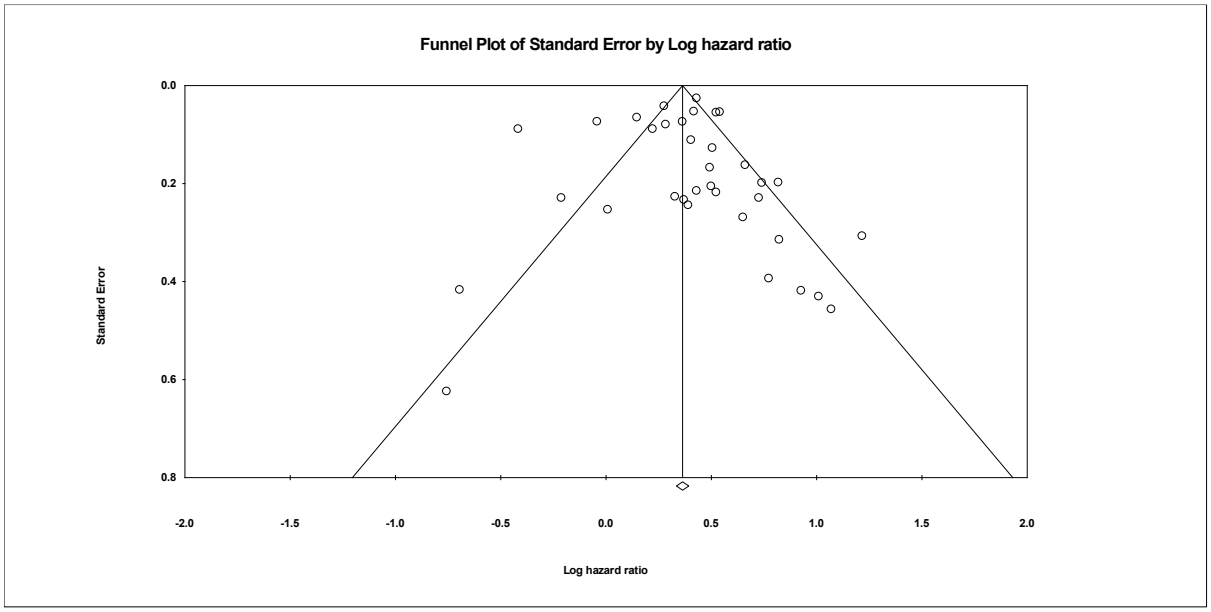
The method of obesity assessment influenced the observed associations**.** BMI-defined obesity demonstrated stronger relationships with VaD (HR 1.38, 95% CI 1.12-1.71) compared to other dementia types. Central adiposity measures showed similar directional relationships but with wider confidence intervals, suggesting less precision in these estimates. Moreover, sex-stratified analyses showed that SO was associated with decreased risk of all-cause dementia in men (HR 0.84, 95% CI 0.72-0.99), but increased risk of AD in women (HR 1.73, 95% CI 1.05-2.86) **(Table 3-5).**

Table 3- 5 Pooled estimates of the associations between obesity, sarcopenia and sarcopenic obesity with dementia risk.

Results are presested for all studies and stratified by age (<65 years, ≥65 years), measurements used to assess obesity (body mass index (BMI), central adiposity (CA) meaurements including waist circumference or waist-hip ratio), measurements for the assessment of sarcopenia (muslce, function, muscle+function) and sex (men only, women only and men+women)						
Phenotype	**Sample Categories**	**Outcome**	**N**	**HR**	**95%CIs**	**I^2**
Sarcopenia	All	ACD	24	1.51	1.38, 1.65	64%
		AD	8	1.30	1.02, 1.65	91%
		VaD	3	1.70	1.53, 1.88	0%
	<65years	ACD	11	1.50	1.35, 1.66	72%
		AD	4	1.51	1.21, 1.89	55%
		VaD	1	2.07	1.31, 3.24	0%
	≥65years	ACD	13	1.52	1.27, 1.83	59%
		AD	4	1.09	0.76, 1.57	93%
		VaD	2	1.68	1.51, 1.86	0%
	Muslce measurements	ACD	4	1.68	0.92, 3.09	81%
		AD	1	0.96	0.83, 0.96	0%
	Functoinal measurements	ACD	17	1.57	1.41, 1.75	47%
		AD	5	1.49	0.90, 2.49	92%
		VaD	2	1.77	1.36, 2.32	0%
	Muslce + Functional	ACD	3	1.37	1.15, 1.64	87%
	Measurements	AD	2	1.35	1.22, 1.48	12%
		VaD	1	1.69	1.51, 1.88	0%
	Men	ACD	4	1.51	1.32, 1.74	75%
	Women	ACD	6	1.25	1.12, 1.39	80%
	Men+Women	ACD	14	1.55	1.49, 1.61	91%
		AD	8	1.18	1.11, 1.23	6%
		VaD	3	1.70	1.53, 1.88	0%
Obesity	All	ACD	113	0.99	0.94, 1.05	90%
		AD	28	1.16	1.02, 1.32	86%
		VaD	12	1.57	1.22, 2.00	91%
	<65years	ACD	58	1.09	1.00, 1.19	93%
		AD	13	1.32	1.05, 1.66	81%
		VaD	5	2.46	1.47, 4.13	79%
	≥65years	ACD	55	0.92	0.85, 0.99	86%
		AD	15	1.07	0.90, 1.27	88%
		VaD	7	1.15	0.96, 1.38	76%
	BMI	ACD	91	0.97	0.92, 1.04	91%
		AD	21	1.20	1.04, 1.38	88%
		VaD	8	1.38	1.12, 1.71	84%
	Central Adiposity	ACD	22	1.10	0.97, 1.24	71%
		AD	7	0.97	0.67, 1.41	50%
		VaD	4	1.47	0.55, 3.90	83%
	Men	ACD	20	0.84	0.72, 0.99	90%
		AD	5	0.99	0.65, 1.51	84%
	Women	ACD	15	1.05	0.90, 1.22	85%
		AD	6	1.73	1.05, 2.86	74%
		VaD	1	1.28	0.57, 2.86	0%
	Men+Women	ACD	78	1.02	0.96, 1.10	91%
		AD	17	1.12	0.96, 1.31	89%
		VaD	11	1.59	1.23, 2.05	91%
Sarcopenic Obesity	All	ACD	3	1.67	1.38, 2.02	78%
	Men	ACD	1	1.99	1.70, 2.32	0%
	Women	ACD	1	1.42	1.23, 1.65	0%
	Men+Women	ACD	1	1.67	1.44, 1.94	0%
ACD: all cause dementia; AD: Alzheimer's Disease; VaD: vascular dementia; N: numbr of independent analyses; HR: hazard ratio; 95%Cis: 95% confidence intervals; I^2: heterogeneity.						

Publication Bias: Funnels plots showed overall symmetrical distributions of the risk estimates (as a function of the respective SEs) for sarcopenia **(Figure 3-14)**, obesity **(Figure 3-15)** and SO **(Figure 3-16)**. These results were confirmed by the non-significant associations found by the Egger's regression test for obesity (P=0.26), sarcopenia (P=0.84) and SO (P=0.52).

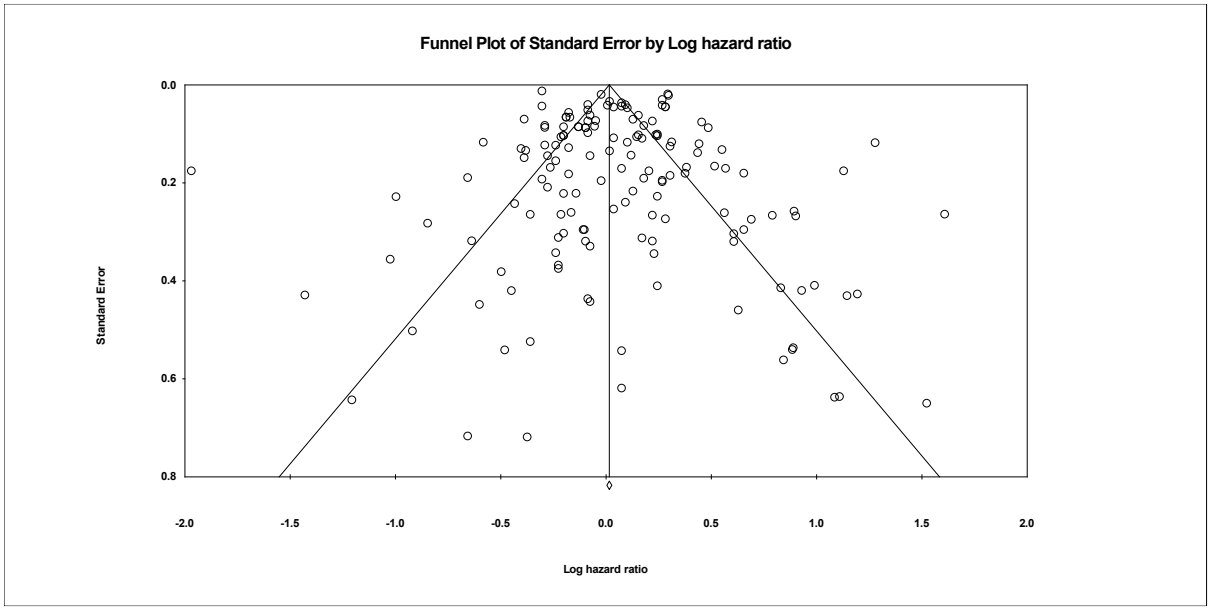
.



Egger's regression intercept

Intercept	0.12622
Standard error	0.63181
95% lower limit (2-tailed)	-1.15920
95% upper limit (2-tailed)	1.41165
t-value	0.19978
df	33.00000
P-value (1-tailed)	0.42144
P-value (2-tailed)	0.84288

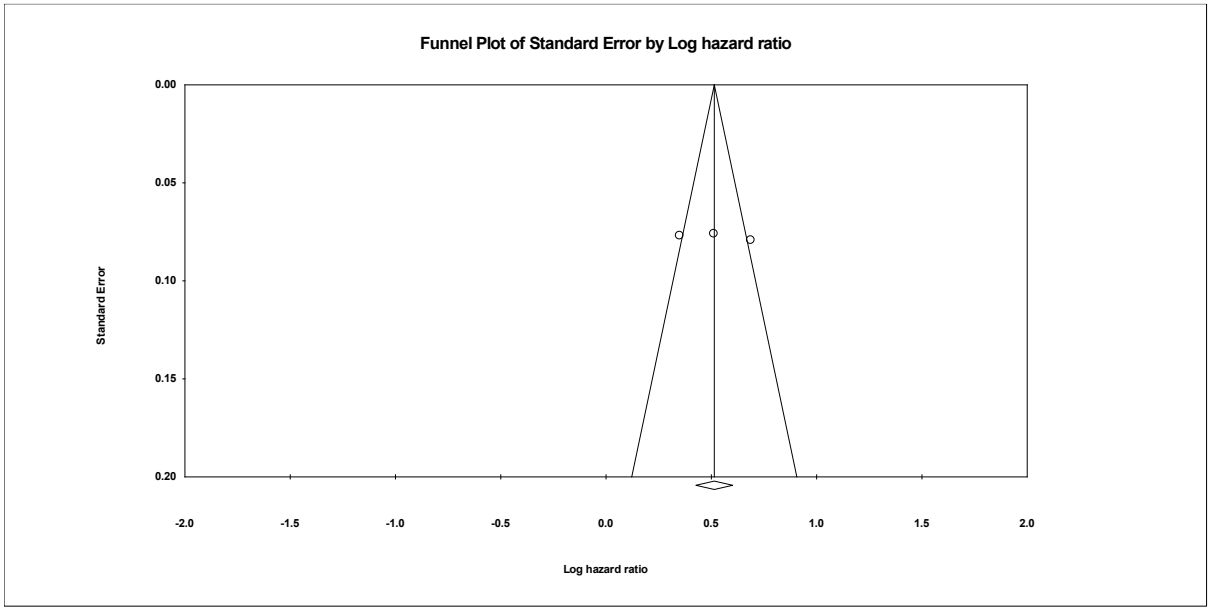
Figure 3- 14 *Funnel's plot and Egger's regression test to evaluate publication bias in all sarcopenia cohort studies included in the systematic review.*



Egger's regression intercept

Intercept	0.45062
Standard error	0.40111
95% lower limit (2-tailed)	-0.34188
95% upper limit (2-tailed)	1.24313
t-value	1.12345
df	151.00000
P-value (1-tailed)	0.13151
P-value (2-tailed)	0.26303

Figure 3- 15 *Funnel's plot and Egger's regression test to evaluate publication bias in all obesity cohort studies included in the systematic review.*



Egger's regression intercept

Intercept	68.34538
Standard error	72.79249
95% lower limit (2-tailed)	-856.57090
95% upper limit (2-tailed)	993.26167
t-value	0.93891
df	1.00000
P-value (1-tailed)	0.26003
P-value (2-tailed)	0.52005

Figure 3- 16 *Funnel's plot and Egger's regression test to evaluate publication bias in all sarcopenic obesity cohort studies included in the systematic review.*

Discussion

Several previous systematic review studies mostly focused on the association between sarcopenia and cognitive impairment using cross-sectional designs (20, 138, 237). There are a few studies focusing on the association between obesity and dementia risk outcomes using cohort designs (19, 238, 239). A systematic review and meta-analysis in 2025 studied the association of SO with cognitive dysfunction and dementia, but case-control and cross-sectional studies were included (240). This systematic review and meta-analysis presented, for the first time, a comprehensive comparison of the associations between sarcopenia, obesity, and SO with dementia risk reported in cohort studies. This study excluded literature with incomplete methodological details and standardised data that could affect the quality and reliability of the evidence synthesis. This study primarily reported associations using HRs, which compare the instantaneous risk of an event between groups at any point in time. In contrast to HRs, incidence rate ratios (IRRs) compare the overall event rate per person-time between groups.

Sarcopenia showed a strong association with all-cause dementia, AD, and VaD, whereas SO was associated with all-cause dementia, with no studies investigating the associations with AD and VaD. Sarcopenia was consistently associated with increased VaD and all cause dementia risk in both middle-aged and older subjects. The links between sarcopenia and dementia risk observed in this analysis are supported with evidence from previous studies (241-243). However, earlier studies focused mostly on cross-sectional associations between sarcopenia and cognitive impairment (241-243) whereas the current analysis provides more robust evidence derived from longitudinal cohort studies. In addition, this study shows that sarcopenia defined using functional methods, including assessments of muscle strength and physical performance, showed a stronger association with dementia risk than definitions based only on muscle mass, which is consistent with findings from a previous study suggesting the cognitive

relevance of functional assessments in sarcopenia diagnosis (158). The findings from this study are consistent with the recommendation of the EWGSOP2 consensus that muscle strength (especially HGS) should be prioritised as the primary indicator of sarcopenia, which is a better predictor of adverse health outcomes than muscle mass alone (36).

This study shows that obesity was associated with an increased risk of AD and VaD, but not with all-cause dementia. In addition, obesity in individuals ≥65 years showed protective effects for all-cause dementia, while there was increased risk for AD and VaD in individuals with obesity aged <65 years. The protective effect of obesity in older individuals against dementia aligns with the "obesity paradox" previously documented in several studies (171, 174, 179, 187, 199, 210, 230). The current analysis provides evidence for this relationship through its larger sample size and more rigorous methodology. However, the methods for the diagnosis of obesity should be also considered because associations were mostly based on BMI assessment (178, 182, 226). The increased risk associated with mid-life obesity for all-cause dementia confirms findings from previous studies (152, 244, 245). The current study extends these findings by demonstrating a strong association with VaD, suggesting the importance of the vascular component in the obesity-dementia link. This builds upon work by Whitmer et al. (2007), who first highlighted the significance of distinguishing between mid-life and late-life obesity effects on risk for AD and VaD (227). The age-stratified analyses in this study also provide important context to previous findings. While earlier studies often treated obesity as a single entity, this analysis clearly demonstrates age-dependent effects, with significant heterogeneity between mid-life and late-life associations with dementia risk. This helps to reconcile apparently contradictory findings in the literature and suggests that the timing of obesity exposure is crucial for the prediction of dementia risk. Moreover, survival bias and competing risks may affect the association between obesity and dementia because individuals

with obesity may die from other causes before dementia, reducing the chance of being diagnosed with dementia later in life.

This meta-analysis represents a significant advance in understanding the biological and clinical complexity of the SO phenotype. SO has been linked to impaired cognitive function and three longitudinal studies have explored the association of the SO phenotype with dementia risk (157, 168, 232). However, a significant increased risk was found when SO was defined using diagnostic models based on assessment of muscle strength, muscle mass and fat mass (157, 168). In one study, the application of FMR showed an inverse relationship between the ratio and dementia risk (232); however, this study was not included in the current meta-analysis as a clear diagnosis of the SO phenotype was not reported. This meta-analysis provides the first robust pooled estimate of longitudinal risk, indicating that SO and sarcopenia were associated with a higher risk of dementia than obesity alone.

This study extends previous evidence by observing sex-specific effects, particularly in the context of sarcopenia, obesity, and SO, where sex differences in obesity may also influence cognitive outcomes. It was shown that men with obesity had a lower risk of dementia, whereas women with obesity had a higher risk of AD. Similarly, one Japanese longitudinal study in participants aged 40–74 years showed a lower dementia risk in men with high BMI, but higher risk in women with high BMI (246). Zhang et al. (2024) first highlighted potential sex and genetic differences in the association between obesity and dementia risk; women with high polygenic risk scores had a lower risk of dementia, while men with low polygenic risk had a higher risk of dementia (157). Several previous studies report contrasting findings, with older women with obesity showing a lower risk of developing cognitive impairment and dementia, while in older men, obesity was linked to cognitive decline or dementia risk (196, 247). However, the current meta-analysis did not stratify the associations by age group within each sex.

Biological Mechanisms: The relationship between sarcopenia, obesity, and dementia risk varies significantly across the life course through multiple interacting biological pathways. Mid-life obesity may elevate dementia risk through several mechanisms. Adipose tissue functions as an endocrine organ, secreting pro-inflammatory cytokines that contribute to chronic systemic inflammation and neuroinflammation (248-250). This inflammatory state can initiate neurodegenerative processes (251). Additionally, obesity-induced insulin resistance affects brain insulin signalling, potentially increasing amyloid-beta accumulation and tau hyperphosphorylation—all hallmarks of AD (61, 252, 253). The cardiovascular risk factors linked to obesity may contribute to cerebrovascular damage (254), explaining the particularly stronger association with VaD.

Conversely, late-life obesity appears protective through different mechanisms. A higher BMI may confer a greater metabolic reserve against catabolic processes common in preclinical dementia (255). Adipose tissue also produces oestrogen, which may have neuroprotective effects in older adults (256, 257). However, this apparent protection might reflect reverse causation, as weight loss often occurs in early dementia stages (258).The length of the follow-up period should be considered when examining the association between obesity and dementia risk. Kivimaki et al. (199) found that a higher BMI was associated with increased dementia risk in individuals followed for more than 20 years, whereas a shorter follow-up time (<20 years) reversed the association between BMI and dementia risk. The results need to be interpreted with caution. BMI is unable to quantify body fat, distinguish fat distribution patterns, and it provides no insight into underlying metabolic disturbances. This one-dimensional measurement oversimplifies obesity's complex nature, missing crucial factors like body composition, nutritional status, hormonal alterations, and systemic health impacts.

Sarcopenia consistently increases dementia risk across the life course. As an endocrine organ, skeletal muscle secretes beneficial myokines like irisin and brain-derived natriuretic factor

(BDNF) with neuroprotective properties (60, 259). Reduced muscle mass may decrease production of these protective factors (259). As skeletal muscle is one of the largest sites of insulin-stimulated glucose uptake, sarcopenia affects whole body glucose disposal, potentially contributing to brain insulin resistance (74). In addition, sarcopenia related to low physical activity also impacts cerebral blood flow and neuroplasticity (260, 261).

SO presents a higher risk for all cause dementia. This metabolic "double-hit" phenotype may combine obesity's pro-inflammatory state with sarcopenia's reduced protective myokine production. The coexistence of high adiposity and low muscle mass/function creates heightened insulin resistance, as these tissues have similar effects on insulin sensitivity (17, 262). Fat infiltration into muscle tissue exacerbates local inflammation and metabolic dysfunction further exacerbating insulin resistance (263).

Strengths and Limitations: This meta-analysis offers a comprehensive scope, rigorous methodology, and large sample sizes for the analyses of the three phenotypes. The comparison of the different body composition phenotypes and consideration of age-dependent effects provides valuable insights into the complex relationships between body composition and dementia risk. The inclusion of studies using validated diagnostic models for both exposures and outcomes enhanced the reliability of the findings. However, potential heterogeneity still exists across studies in measurement methods and definitions of exposures, particularly for sarcopenia and SO, and classification of dementia types (i.e., ACD, AD or VaD). This systematic review included both prospective and retrospective cohort studies. Distinguishing prospective and retrospective cohort designs, particularly in register-based research, is challenging because data are collected prospectively by the registries but analysed retrospectively by the new research questions. However, the risk of bias assessment of this study (NOS) indicated that register-based cohort studies scored lower on the domains of exposure ascertainment and follow-up, reflecting the methodological uncertainty inherent in

differentiating prospective from retrospective designs. The relatively small number of studies on SO (only 3) limits the robustness of conclusions. The observational nature of included studies prevents causal inference, and residual confounding cannot be ruled out.

Conclusion

This meta-analysis demonstrates complex and some cases age-dependent relationships between body composition and dementia risk. SO and sarcopenia consistently increase all-cause dementia risk, with SO showing particularly strong associations. The assessment of sarcopenia should combine functional methods with body composition assessments to better understand its association with cognitive decline and dementia risk. Obesity was linked to a higher risk of AD and VaD. While presence of obesity at mid-life increases dementia risk, its presence at late life appears to be protective. These findings emphasise the importance of life-course approaches to body composition management for dementia prevention and highlight the need for age-appropriate interventions and definitions. The results support public health strategies focusing on maintaining a healthy body composition and suggest that combined preventative and therapeutic approaches addressing both muscle mass and adiposity may be most effective for reducing dementia risk.

Implication for further research

Future research should prioritise standardising definitions and measurement methods for sarcopenia and SO, investigating mechanisms underlying the protective effect of late-life obesity, developing targeted interventions for different age groups and body composition phenotypes, conducting longer-term follow-up studies to better understand temporal relationships, and exploring sex-specific effects and potential moderating factors. This study also highlights important gaps in previous research, particularly regarding the limited longitudinal studies of SO and the need for standardised definitions and measurement

approaches. Clinical recommendations emphasise regular monitoring of body composition changes across the lifespan, early intervention for mid-life obesity prevention, implementation of exercise and nutrition programs to prevent sarcopenia and SO.

CHAPTER 4: Body Composition, Sarcopenic Obesity and Cognitive Function in Older Adults: Findings from the National Health and Nutrition Examination Survey (NHANES) 1999-2002 and 2011-2014

Introduction

SO was associated with a greater risk for adverse health outcomes compared to either sarcopenia or obesity independently in older individuals (29, 264).

The SO definition used could impact the study of SO in older individuals (265). SO phenotype was established by Prado et al. (2014) for appendicular skeletal muscle and fat mass indices using the National Health and Nutrition Examination Survey (NHANES) data, with the finding that the prevalence of individuals (mean age 44.57 ± 0.33 in men and 46.8 ± 0.36 in women) with SO phenotype (high adiposity-low muscle mass (HA-LM)) was 15.2% in men and 10.3% in women (266). Baumgartner's cutoffs are some of the first and most commonly referenced standards for defining sarcopenia and obesity (42), with widely use especially in epidemiological studies, to identify SO with various prevalence (40, 267). An integrated diagnostic method has been developed by Siervo et al. (2015) to define body composition phenotypes applying a load–capacity model (FM/FFM and TrFM/ASM), which could be beneficial for identifying cases of SO (268).

Several studies have investigated the association between SO and cognitive function with various results, which could be explained by differences in body composition methods, diagnostic definitions of SO, study design, and phenotypic characteristics of the populations (18, 29, 139, 140, 144, 146).

In addition, the mechanisms underlying this association remain unclear. Two prominent factors, such as insulin resistance and chronic low-grade inflammation, have been linked as potential mediators linking SO to neurocognitive outcomes in older individuals (18).

Understanding these pathways is required to identify modifiable approaches for prevention and intervention strategies aimed at mitigating SO and cognitive impairment in older adults.

Aim

(a) To explore the association of body composition and SO phenotypes with cognitive function in older adults using the data from two consecutive cycles of the NHANES 1999-2002 and 2011-2014.

(b) To explore the mediating role of mediatic factors (i.e., insulin resistance and inflammation) in the associations between body composition and cognitive impairment

Methodology

Data and study population*:* Data collected from the 1999-2002 and 2011-2014 waves of the NHANES programme were used to investigate the association between body composition and cognitive function in individuals aged 60 to 85 years. The datasets are released by NHANES on the CDC website (https://www.cdc.gov/nchs/nhanes/index.html). Ethical approval was obtained from the NHANES Institutional Review Board and the NCHS Research Ethics Review Board. The protocol number of NHANES 1999-2002 is Protocol #98-12 and Protocol #2011-17 for NHANES 2011-2014 (https://www.cdc.gov/nchs/nhanes/about/erb.html). Individuals with incomplete cognitive test, DXA data, and anthropometric data were excluded.

Anthropometry and body composition assessment

NHANES (1999–2002): Body measurements were recorded for all participants by a trained examiner in the mobile examination centre. In situations where participants had to leave the mobile examination centre early and were unable to complete the body measurement component, at a minimum, weight and standing height or recumbent length were measured. Body weight, height, and BMI were included in the dataset. Height (cm) was measured using a stadiometer. Weight (kg) was measured using an electronic digital scale calibrated in kilograms (kg). BMI was calculated as weight (kg) divided by height in meters (m) squared.

Body composition assessment was undertaken by DXA (Hologic QDR 4500A). Participants were not eligible for a DXA scan if they were pregnant, weighed more than 136 kg or if they were taller than 1.96 m. In addition, participants were not eligible if they had been exposed to radiographic contrast material in the past 7 days or nuclear medicine in the past 3 days. Only complete DXA data of eligible participants were included. The DXA scans provided bone and soft tissue measurements for the total body, arms and legs, trunk, and head. Body composition variables derived from DXA measurements included FM, Lean Body Mass (LBM) and Bone Mineral Mass (BMM). Fat free mass (FFM) was calculated as the sum of LBM and BMM.

Appendicular skeletal mass (ASM) was calculated as the sum of LBM in arms and legs. FM, FFM and ASM indexes were calculated by dividing each variable by height (m) squared (266, 268).

NHANES (2011–2014): body measurements were collected by trained health technicians in the mobile examination centre. Body weight (kg) and height (cm) were measured, and BMI calculated. Waist circumference (cm) was measured just above the uppermost lateral border of the right ilium.

Participants were stratified by BMI and WC according to recommended cut offs. BMI categories included underweight (<18.5 kg/m^2), normal weight (≥18.5 and <25 kg/m^2), overweight (≥25 and <30 kg/m^2) and obesity (≥30 kg/m^2). For men, a WC below 102 cm was defined as 'normal or moderately high WC' and greater than or equal to 102 cm was 'high WC'. For women, below 88 cm was 'normal or moderately high WC' and more than or equal to 88cm was 'high WC' (269).

Hand grip Strength (HGS) assessment

NHANES (2011–2014)

Muscle strength was assessed from the isometric grip strength using a handgrip dynamometer (Takei Hand Grip Dynamometer, Japan). Participants were asked to remove hand and wrist jewellery. The grip size of the dynamometer was also adjusted to ensure optimal performance and participants completed two warm-up exercises. Participants were then asked to squeeze hand-grip dynamometer as hard as possible for three times of each hand (alternating hands between trials with a 60 second rest between measurements on the same hand). The average of the combined hand-grip strength was calculated and used in the analysis and stated in kg. This variable was not calculated for participants who only performed the test on one hand. HGS cut

offs for men and women to identify individuals at-risk of sarcopenia in older adults were less than 30 kg and 20 kg, respectively (2).

SO phenotype assessment

NHANES (1999–2002)

Three models were used to define the SO phenotype:

Baumgartner Model (42, 265): The model was derived using DXA data from the New Mexico Elder Health Survey, 1993-1995. Sarcopenia was identified if appendicular skeletal muscle mass index (ASMI) was lower than 7.26 kg/m^2 in men and 5.45 kg/m^2 in women. Obesity was defined if FM% were greater than 27% in men and 38% in women. The cut offs for ASMI corresponded to the lower 2SD value derived from the distribution of ASMI in a healthy young normal weight population. The following body composition phenotypes can be derived: 1) sarcopenic (low ASMI and low FM%), normal (high ASMI and low FM%), obese (high ASMI and high FM%) and SO (low ASMI and high FM%).

Prado-Siervo Model (266): This model used DXA body composition data to operationalize the large variability in body-composition phenotypes by taking into account the individual effects of age, gender, and body mass on body components. Age, gender, and BMI-specific reference curves were derived for each body composition variable using the DXA data from the 1999-2004 NHANES survey. The Prado-Siervo model includes the following four phenotypes: LA-HM (low adiposity-high muscle mass), HA-HM (high adiposity-high muscle mass), LA-LM (low adiposity-low muscle mass), and HA-LM (high adiposity-low muscle mass). The cut-offs applied for each phenotype are LA-HM (FMI: 0–49.99; ASMI: 50–100); HA-HM (FMI: 50–100; ASMI: 50–100); LA-LM (FMI: 0–49.99; ASMI: 0–49.99), and HA-LM (FMI: 50–100; ASMI: 0–49.99).

Siervo-Prado Model (268): This model used DXA body composition data to calculate the ratio between FM and FFM (FM:FFM) and between trunk fat mass (TrFM) and ASM (TrFM:ASM). Age, gender, and BMI-specific reference curves were developed for both ratios. Individuals were classified as low (<15th centile), normal (15-84.99th centile) or high (≥85th centile), with the higher category indicating the SO phenotype.

NHANES (2011–2014)

Age (≥60 years old) and gender specific cut-offs for HGS and gender-specific cut offs for WC were used to derive body composition phenotypes which include 1) low HGS – high WC (SO phenotype), 2) high HGS – high WC, 3) low HGS – low WC and 4) high HGS – low WC (reference group). The ratio between WC and HGS (WC-HGS-R) was also used as a simple method to classify SO (high WC to low HGS). The WC-HGS-R was analysed as a continuous variable or divided into tertiles with the highest tertile indicating the SO phenotype and the lowest tertile used in the analysis as a reference group.

Cognitive assessment

NHANES (1999–2002)

In the 1999-2002 cohort, cognition was assessed using the Digit Symbol Substitution Test (DSST). In this test, participants copied symbols that were paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. Sample items were provided for initial practice. Participants who were unable to complete any of the sample items did not continue to the definitive test. The score was calculated as the number of correct symbols drawn within 120 seconds. One point was given for each correctly drawn symbol completed within the time limit. The maximum score was 133 with higher scores indicating greater cognitive function. The DSST did not assume that participants who had a physical or mental impairment would be unable to do the sample,

and there was no medical condition data of participants about dementia or AD in NHANES 1999-2002 (only relevant stroke). Thus, this analysis included adults aged 60 years and older with all cognitive states (i.e., with and without dementia). DSST provides information on multiple cognitive domains including response speed (motor skills), sustained attention, visual spatial skills, associative learning, and memory. DSST scores were entered in the analyses as a continuous variable. A DSST cut off of < 40 was applied to identify subjects with impaired cognitive function (270).

NHANES (2011–2014)

In 2011-2014, a series of assessments were re-introduced, including: 1) word learning and recall modules from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD); 2) the Animal Fluency (AF) test; and 3) the DSST. Cognitive outcomes were entered in the analyses as continuous variables. Cognitive outcomes were run as separate models including AF, DSST, CERAD Word Learning subtest (CERAD-WL), and CERAD Delayed Recall test (CERAD-DR). The AF test examined categorical verbal fluency, a component of executive function. Scores have been shown to discriminate between persons with normal cognitive functioning compared with those with MCI and more severe forms of cognitive impairment, such as AD. CERAD-WL assessed immediate and delayed learning ability for new verbal information (memory sub-domain). Following CERAD-WL trials, CERAD-DR was administered 8–10 minutes after the completion of both other cognitive exercises (AF and DSST). However, cognitive outcomes were also stratified by specific cut offs for each cognitive outcome to classify individuals as cognitive impaired and non-impaired. The cognitive scores were stratified by cut offs, and lower scores were considered as impaired, depending on the type of cognitive test. Cognitive impairment was defined by applying the following cut offs to each cognitive test: AF <14, DSST <40, CERAD-WL <17, and CERAD-DR <5 (270).

Covariates: Socio-demographic, lifestyle, and laboratory biomarkers

Covariates included: age, gender, education, marital status, annual household income, number of morbidities (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy consumption, CRP (only for NHANES 1999-2002), and metabolic markers (fasting glucose and insulin, both cohorts). Fasting glucose and insulin concentrations were used to calculate the Homeostatic Model of Assessment for Insulin Resistance (HOMA-IR). In NHANES 1999-2002, CRP was quantified by latex-enhanced nephelometry, plasma glucose was calculated by an enzymatic hexokinase method, and plasma insulin was assessed by radioimmunoassay. In NHANES 2011-2014, plasma glucose was calculated by the HK method, and plasma insulin was assessed by a Roche chemiluminescent immunoassay performed on the Elecsys 2010 analyser.

Statistical analysis

All data were analysed using SPSS complex sample module version 28.0 (IBM Corp, Armonk, NY). *P*-value <0.05 was considered as statistically significant. Complex-survey analysis was applied to account for the sampling strategy of the NHANES survey and conducted according to NHANES approved protocols. Analysis of the NHANES datasets followed the Center for Disease Control and Prevention (CDC) guidelines as multiple survey cycles were combined and specific population-weights were applied according to the suggested weighting methodology. The results were presented as means ± standard deviation (SD) or frequency (%) according to the characteristics of the variables. Complex Samples General Linear Model (CSGLM) regression analysis was used to analyse the association between body composition variables and cognitive variables. Complex Samples Logistic (CSL) regression analysis was performed to evaluate the association of body composition with odds of cognitive impairment.

Distribution of residuals was checked to ensure validity of the regression models. Analyses were adjusted for potential confounding variables which were available in two consecutive cycles of the NHANES (1999–2002 and 2011-2014). Analyses were conducted in both cohorts after stratification by age (60-70 years and >70 years).

Mediation analysis was conducted in both analyses to quantify the extent to which biological variables (CRP and HOMA-IR for NHANES 1999–2002, HOMA-IR for NHANES 2011-2014) influence the association between body composition and cognitive function by using the SPSS Macro developed by Preacher and Hayes (271).

Results

NHANES 1999-2002: The final dataset consisted of 2,544 participants (43.3% men). Their mean age (±SE) was 70.44±0.27 years, and 70.1% had a BMI≥25 kg/m^2 **(Table 4-1).**

The prevalence of the phenotypes derived from the body composition models is shown in **Figure 4-1**. The difference between Baumgartner and Prado-Siervo models is noticeable in estimating the prevalence of the SO phenotype in the cohort (14.5% vs 21.9%, respectively).

When all participants were taken into account and after adjustment for confounding variables, DSST scores differed between the body composition phenotypes based on Baumgartner's model (P=0.022) with the HA-LM phenotype having significantly lower scores than the HA-HM phenotype (P<0.05; **Table 4-2**) and therefore a significant risk of cognitive impairment (HA-LM vs LA-HM, OR = 1.9; CI 95% 1.0–3.7, P=0.027; **Table 4-3**). No significant differences between body composition phenotypes and DSST scores were identified for the Prado-Siervo and the two ratio (FM/FFM, TrFM/ASM) models after adjustment for confounding variables **(Table 4-2)**. However, the CSL regression analysis showed that the highest FM/FFM centile (≥85th) had a greater risk of cognitive impairment (OR = 2.0; CI 95% 1.3–3.1, P=0.004) compared to the normal centile group (15-84.9th) (**Table 4-3**).

When analysis was performed based on age-dependent associations, the HA-LM phenotype for both Baumgartner and Prado-Siervo models (HA-LM vs. LA-HM) was significantly associated with cognitive impairment in subjects younger than 70 years old, but associations were not significant in subjects older than 70 years **(Table 4-4).**

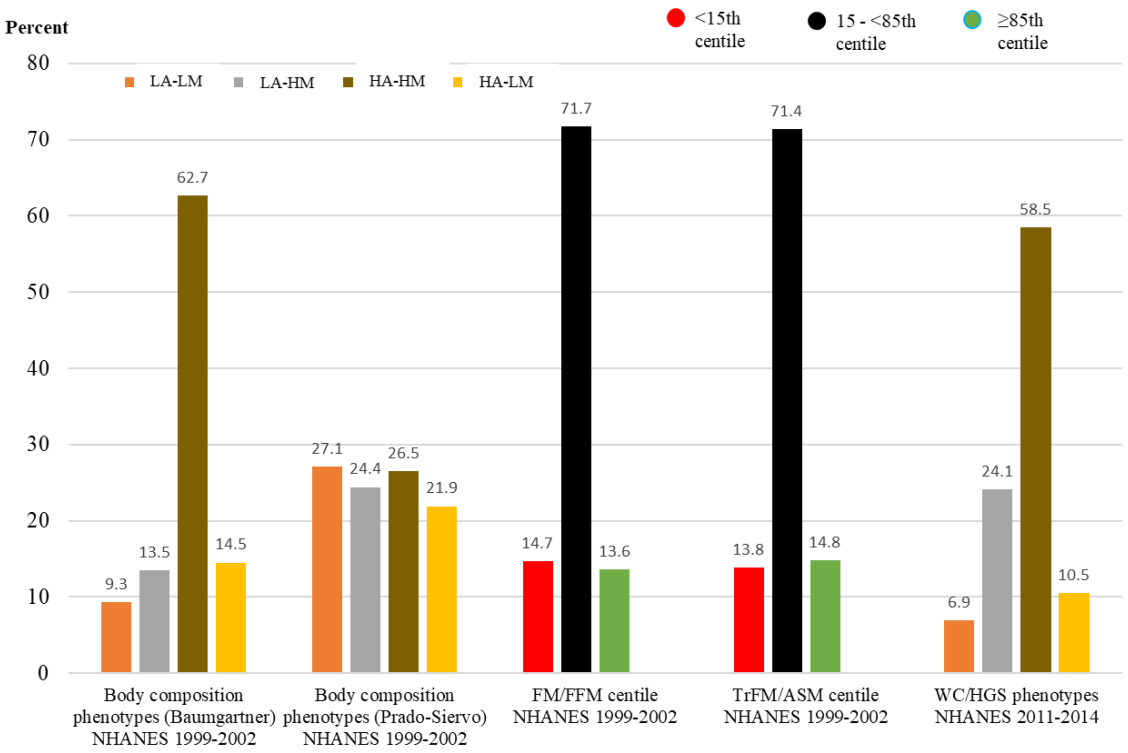


Figure 4- 1 *The prevalence of body composition phenotype in the NHANES 1999-2002 and the NHANES 2011-2014.*

The numbers on the bar graph are displayed as percentages (%).
Abbreviations: ASM: appendicular skeletal mass, FFM, fat free mass, FM: fat mass, HGS: hand grip strength, HA-HM: high adiposity-high muscle mass, HA-LM: high adiposity-low muscle mass, LA-HM: low adiposity-high muscle mass, LA-LM: low adiposity-low muscle mass, TrFM: truncal fat mass; WC: waist circumference.

Table 4- 1 Characteristics of study participants included in the analyses of the 1999-2002 and 2011-2014 datasets.

Characteristic	NHANES 1999-2002		NHANES 2011-2014	
	Total N = 2,544	**Missing data**	**Total N = 3,395**	**Missing data**
Age at screening (year)	70.44 ± 0.27	0	69.58±0.19	0
BMI (kg/m^2), %		0		0
<18.5	1.7		1.6	
18.5-24.9	28.2		25.3	
25-29.9	38.3		36.1	
≥30	31.8		37.0	
Gender, % Men	43.3	0	45.1	0
Ethnicity, %		0		0
Non-Hispanic White	83.8		77.3	
Non-Hispanic Black	6.8		9.1	
Mexican American	2.8		3.8	
Other Race	2.2		5.9	
Other Hispanic	4.4		3.9	
Education, %		5		0
Less Than High School	29.2		18.9	
High School Diploma	29.6		22.0	
More Than High School	41.2		59.0	
Marital Status, %		125		0
Married	64.3		61.1	
Widowed	22.6		18.4	
Divorced	8.3		12.4	
Separated	1.2		1.2	
Never married	2.4		4.4	
Living with partner	1.2		2.4	
[1]Annual Household Income, %		340		29
$ 0 to $ 4,999	0.8		0.8	
$ 5,000 to $ 9,999	8.5		3.1	
$10,000 to $14,999	12.1		7.0	
$15,000 to $19,999	8.8		5.9	
$20,000 to $24,999	9.5		7.0	
$25,000 to $34,999	16.0		10.7	
$35,000 to $44,999	10.0		10.5	
$45,000 to $54,999	8.7		7.5	
$55,000 to $64,999	6.1		6.7	
$65,000 to $74,999	4.4		6.3	
$75,000 and over	15.1		31.5	
Co-Morbidities				
Diabetes, % yes	14.0	2	24.7	1
Kidney problems, % yes	3.7	9	5.7	1
Anaemia past 3 months, % yes	3.1	2	4.7	1
Arthritis, % yes	49.3	3	46.7	1
Congestive heart failure, % yes	5.8	22	6.8	1
Coronary heart disease, % yes	9.9	37	9.5	1
Cancer or malignancy, % yes	21.0	2	19.5	1

Table 4- 1 Characteristics of study participants included in the analyses of the 1999-2002 and 2011-2014 datasets.

Characteristic	NHANES 1999-2002		NHANES 2011-2014	
	Total N = 2,544	**Missing data**	**Total N = 3,395**	**Missing data**
Stroke, % yes	5.6	7	7.2	0
[2]Physical activity, %		9		0
Sedentary	24.8		35.0	
Light	59.0		5.5	
Moderate	14.1		38.7	
Vigorous	2.1		20.8	
[3]Medications, % yes	15.7	519	25.6	0
Smoking, % yes	26.1	1112	13.9	105
[4]Depression, % yes	8.5	0	7.2	0
Blood pressure, % yes	49.8	7	60.0	7
CRP (mg/dL)	0.52 ± 0.02	118	NA	NA
Plasma glucose (mmol/L)	6.13 ± 0.13	1913	6.31±0.09	1,781
Insulin (pmol/L)	85.81 ± 3.51	1928	79.00±2.39	1,850
Alcohol use (time a year)	5.65 ± 0.93	538	6.76±1.36	792
Energy consumption (kcal)	1779.10 ± 20.33	80	1868.52 ±18.16	379

All information except as noted is given in data using sample weights. Percentages shown as estimate percent of total ± standard error (SE): gender, ethnicity, education, marital status, annual household income, number of morbidities, stroke, physical activity, medications related cognitive interactions, smoking, depression, blood pressure.

Data shown as mean ± SE:.age, BMI, SBP, DBP, CRP, plasma glucose, insulin, alcohol use, energy consumption.

[1]Annual household income in 2011-2014, percentage of "refused" and "don't know answer" = 2.9%

[2]Physical activity level; 1. Sedentary: sit during the day/ not walk about very much, 2. Light activity: stand or walk a lot during the day, but do not have to carry or lift things very often, walk or bicycle, 3. Moderate activity: lift light load or have to climb stairs or hills often, moderate work and recreational activity, 4. Vigorous activity: do heavy work or carry heavy loads, vigorous work and recreational activity.

[3]Self-reported medications related cognitive interactions include (catechol-O-methyltransferase (COMT) inhibitor, alkylating agents, alpha/beta adrenergic agonists, analgesics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, anorectics or anorexigenics, antibiotic drug, anticonvulsants, antidepressants, antidiabetics, anti-emetics, antihistamine, antihypertensive agents, antimanic agents, antimetabolites, antipsychotics, benzodiazepines, carbonic anhydrase inhibitors, central nervous system (CNS) depressants, CNS stimulants, CNS agents, cholinesterase inhibitors, conventional antipsychotics, corticosteroids, decarboxylase inhibitors, decongestants, diuretics, dopamine agonists, ergot alkaloids, hormones, hypnotics, lipase inhibitors, long-acting dopamine agonist, monoamine oxidase inhibitors (MAOIs), muscarinic antagonist, nasal decongestants, opiate/opioid analgesics, opiate antagonists, peripherally acting μ-receptor opioid antagonist drugs, proton pump inhibitors (PPIs), psychotherapeutic agents, pyrazolidines, rauwolfia alkaloids, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), SSR agonists, steroid drug, stimulants, sympathomimetic amines).

[4]Depression: Total PHQ-9 score (0 to 27) were classified clinically relevant depression based on a cut-off score of ≥10 (272, 273). Abbreviations; CRP: C-reactive protein, NA: not available.

Abbreviations: BMI: Body Mass Index

Table 4- 2 Complex Samples General Linear Model (CSGLM) to test the association between the classifications of body composition (factor) and cognitive function (dependent variable) before (model A) and after adjustment for confounding variables (model B) in the NHANES 1999-2002 dataset

Classifications of body composition	**DSST score Mean (Lower, Upper 95% CI)**			
	Model A	***p*-value**	**Model B**	***p*-value**
BMI (kg/m^2)		0.286		0.221
<18.5	41.6 (36.2, 47.0)		39.9 (31.5, 48.2)	
18.5-24.9	46.9 (44.8, 49.0)		45.2 (41.1, 49.3)	
25-29.9	47.0 (45.0, 49.0)		46.4 (43.7, 49.1)	
≥30	46.8 (45.3, 48.3)		47.4 (45.2, 49.6)	
Body composition phenotypes (Baumgartner)		0.418		0.022
LA-LM	44.8 (41.5, 48.1)		43.7 (39.3, 48.2)	
LA-HM	47.2 (45.1, 49.2)		46.7 (42.8, 50.6)	
HA-HM	47.4 (45.8, 49.0)		47.6 (45.5, 49.8)[a]	
HA-LM	45.2 (42.1, 48.3)		42.2 (38.3, 46.1)	
Body composition phenotypes (Prado-Siervo)		0.048		0.666
LA-LM	47.8 (45.9, 49.7)		46.4 (43.2, 49.7)	
LA-HM	45.3 (43.4, 47.1)[b]		45.8 (42.2, 49.5)	
HA-HM	47.6 (45.5, 49.7)		47.5 (44.9, 50.1)	
HA-LM	46.4 (43.8, 49.0)		45.2 (41.7, 48.7)	
FM/FFM centile		0.011		0.131
<15th	43.6 (41.4, 45.7)[c]		45.6 (42.6, 48.7)	
15 – 84.9th	47.6 (46.1, 49.1)		47.1 (44.7, 49.5)	
≥85th	46.1 (44.0, 48.2)		43.1 (39.3, 46.9)	
TrFM/ASM centile		0.014		0.226
<15th	43.8 (41.6, 46.0)[c]		46.4 (43.6, 49.2)	
15 – 84.9th	47.5 (45.9, 49.1)		46.9 (44.4, 49.4)	
≥85th	46.3 (44.2, 48.4)		43.7 (40.3, 47.0)	

All information except as noted is given in data using sample weights. Data shown as mean (min, max). Model A: before adjusted variables, Model B: after adjusted variables (age, gender, education, marital status, annual household income, number of morbidity (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake).

Abbreviations: ASM: appendicular skeletal muscle, BMI: Body Mass Index, FFM: fat free mass, FM: fat mass, HA: high adiposity, HM: high muscle mass, LA: low adiposity, LM: low muscle mass, TrFM: truncal fat mass, DSST: Digit Symbol Substitution Test, CI: Confidence interval.

[a] $P < 0.05$ between HA-HM and HA-LM within model B

[b] $P < 0.05$ between LA-HM and LA-LM within model A

[c] $P < 0.05$ between <15th and 15- 84.9th within model A

Table 4- 3 Complex Samples Logistic (CSL) regression analysis of the association between the classifications of body composition (factor) and cognitive function (dependent variable) before (model A) and after adjustment for confounding variables (model B) in the NHANES 1999-2002 dataset

Classifications of body composition	**DSST score Odds Ratios (Lower, Upper) (<40)**			
	Model A	**P-value**	**Model B**	**P-value**
BMI (kg/m^2)		0.366		0.332
<18.5 vs. 18.5-24.9	1.5 (0.6, 3.4)		1.1 (0.3, 5.0)	
25-29.9 vs. 18.5-24.9	0.9 (0.7, 1.2)		0.9 (0.5, 1.6)	
≥30 vs. 18.5-24.9	0.9 (0.7, 1.1)		0.6 (0.4, 1.1)	
Body composition phenotypes (Baumgartner)		0.042		0.027
LA-LM vs LA-HM	1.6 (1.0, 2.6)		2.1 (0.9, 4.7)	
HA-HM vs LA-HM	1.0 (0.7, 1.3)		1.0 (0.5, 1.9)	
HA-LM vs LA-HM	1.3 (0.9, 2.0)		1.9 (1.0, 3.7) [c]	
Body composition phenotypes (Prado-Siervo)		0.177		0.267
LA-LM vs LA-HM	0.8 (0.7, 1.1)		1.2 (0.7, 2.0)	
HA-HM vs LA-HM	0.8 (0.6, 1.0)		0.8 (0.5, 1.6)	
HA-LM vs LA-HM	0.9 (0.7, 1.3)		1.4 (0.9, 2.2)	
FM/FFM centile		0.006		0.004
<15th vs 15 – 84.9th	1.5 (1.2, 2.0)*		1.2 (0.7, 2.0) [c]	
≥85th vs 15 – 84.9th	1.2 (1.0, 1.5)		2.0 (1.3, 3.1)*	
TrFM/ASM centile		0.101		0.200
<15th vs 15 – 84.9th	1.4 (1.0, 2.0)		1.2 (0.8, 1.8)	
≥85th vs 15 – 84.9th	1.2 (0.8, 1.6)		1.5 (1.0, 2.5)	

All information except as noted is given in data using sample weights. Data shown as mean (min, max).

* Statistical significance ($P < 0.05$).

Model A: before adjusted variables, Model B: after adjusted variables (age, gender, education, marital status, annual household income, number of morbidity (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake).

Abbreviations: ASM: appendicular skeletal muscle, BMI: Body Mass Index, FFM: fat free mass, FM: fat mass, HA: high adiposity, HM: high muscle mass, LA: low adiposity, LM: low muscle mass, TrFM: truncal fat mass, DSST: Digit Symbol Substitution Test.

[c] $P < 0.05$ between <15th and 15- 84.9th within model

Table 4- 4 Age-stratified Complex Samples Logistic (CSL) regression analysis of the association between the classifications of body composition (factor) and cognitive function (dependent variable) after adjustment for confounding variables in the NHANES 1999-2002 cohort

Classifications of body composition	**DSST score (<40)**			
	Odds Ratios (Lower, Upper)			
	60-70 y (n=1352)	**P-value**	**>70 -85 y (n=1192)**	**P-value**
Body composition phenotypes (Baumgartner)		0.039		0.569
HA-HM vs. LA-HM	2.0 (0.8, 5.2)		0.7 (0.3, 1.3)	
HA-LM vs. LA-HM	3.9 (1.2, 12.7)*		1.0 (0.5, 2.1)	
LA-LM vs. LA-HM	4.0 (1.5, 10.5)*		1.1 (0.4, 3.2)	
Body composition phenotypes (Prado-Siervo)		0.011		0.653
HA-HM vs. LA-HM	2.0 (1.0, 3.9)		0.6 (0.2, 1.5)	
HA-LM vs. LA-HM	2.7 (1.2, 6.1)*		0.9 (0.4, 1.9)	
LA-LM vs. LA-HM	2.9 (1.5, 5.6)*		0.8 (0.4, 1.5)	
FM/FFM centile		0.099		0.590
$<15^{th}$ vs 15 – 84.9^{th}	1.1 (0.5, 2.2)		1.2 (0.5, 2.5)	
$\geq 85^{th}$ vs 15 – 84.9^{th}	2.5 (1.1, 5.7)*		1.6 (0.6, 4.0)	
TrFM/ASM centile		0.242		0.904
$<15^{th}$ vs 15 – 84.9^{th}	0.9 (0.4, 2.0)		1.1 (0.6, 2.1)	
$\geq 85^{th}$ vs 15 – 84.9^{th}	1.8 (0.9, 3.7)		1.1 (0.5, 2.4)	

All information except as noted is given in data using sample weights.
* Statistical significance ($P < 0.05$).
Models adjusted for age, gender, education, marital status, annual household income, comorbidity (diabetes, kidney problems, anemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake.
Abbreviations: ASM: appendicular skeletal muscle, FFM: fat free mass, FM: fat mass, HA: high adiposity, HM: high muscle mass, LA: low adiposity, LM: low muscle mass, TrFM: truncal fat mass, DSST: Digit Symbol Substitution Test.

NHANES 2011-2014: The final dataset included 3,395 participants (men = 45.1%). Participants mean age (±SE) was 69.5±0.1 years and 73.1% of participants had a BMI ≥ 25 kg/m^2. Descriptive characteristics of the sample are provided in **Table 4-1.**

When all participants were taken into account and after adjustment for confounding variables, a higher WC was characterised by significantly higher CERAD-WL scores compared to lower WC (score 20.0 and 19.5, respectively; P=0.019). The LWC-LHGS and HWC-LHGS were also characterised by significantly lower scores for the AF, DSST, CERAD-WL and CERAD-DR (P<0.001) cognitive tests. The highest tertile of WC-HGS-R index had significantly lower AF and DSST scores (P<0.001 and P<0.001, respectively) **(Table 4-5).**

A higher WC (≥102 cm in men and ≥88 cm in women) had a lower risk of cognitive impairment (CERAD-WL, OR= 0.6; CI 95%: 0.5–0.8; P<0.001) compared to low WC. However, the LWC-LHGS (AF, OR= 2.2; CI 95%: 1.2–4.0; DSST, OR= 2.9; CI 95%: 1.8–4.9; CERAD-DR, OR= 2.1; CI 95%: 1.2–3.4; all P<0.05) and the HWC – LHGS (AF, OR= 2.2; CI 95%: 1.4–3.5; DSST, OR= 2.5; CI 95%: 1.6–4.0; CERAD-WL, OR= 1.6; CI 95%: 1.1–2.4; CERAD-DR, OR= 1.6; CI 95%: 1.1–2.5; all P<0.05) phenotypes had a higher risk of cognitive impairment compared to LWC – HHGS. The highest WC-HGS-R tertile had a greater risk of cognitive impairment (AF, OR= 1.6; CI 95%: 1.1–2.1; DSST, OR= 1.4; CI 95%: 1.0–1.9; all P<0.05) compared to lowest tertile 1 **(Table 4-6).**

When analysis was performed based on age-dependent associations, the LWC – LHGS phenotype was significantly associated with greater risk of cognitive impairment assessed by the DSST and CERAD-WL and DR in subjects younger than 70 years old **(Table 4-7).**

Table 4- 5 Complex Samples General Linear Model (CSGLM) regression analysis of the association between the classifications of body composition and grip strength (factor) and cognitive function (dependent variable) before (model A) and after adjustment for confounding variables (model B) in the NHANES 2011-2014 cohort

Body composition	Sig.	Cognitive functioning score Mean (Lower, Upper)							
		Model A				Model B			
		AF	DSST	CERAD-WL	CERAD-DR	AF	DSST	CERAD-WL	CERAD-DR
BMI (kg/m^2)									
	P	*0.390*	*0.861*	*0.126*	*0.013*	*0.908*	*0.879*	*0.204*	*0.008*
<18.5		16.3 (14.2, 18.5)	50.8 (42.9, 58.6)	18.0 (16.0, 19.9)	5.6 (4.9, 6.4)	17.7 (15.2, 20.2)	51.5 (43.8, 59.2)	18.1 (15.6, 20.5)	5.6 (4.7, 6.4)
18.5 – 24.9		17.8 (17.0, 18.7)	51.4 (48.9, 53.8)	19.5 (18.9, 20.1)	6.1 (5.9, 6.4)	18.4 (17.4, 19.3)	52.9 (50.2, 55.7)	19.8 (19.1, 20.4)	6.3 (6.0, 6.6)
25-29.9		17.9 (17.4, 18.5)	52.5 (50.9, 54.1)	19.4 (18.9, 19.9)	6.0 (5.8, 6.2)	18.5 (17.9, 19.1)	53.9 (52.2, 55.6)	19.7 (19.2, 20.2)	6.1 (5.9, 6.3)
≥30		18.1 (17.6, 18.6)	52.2 (50.8, 53.6)	19.8 (19.3, 20.2)	6.3 (6.1, 6.6)[b]	18.5 (18.0, 19.1)	53.4 (51.9, 54.9)	20.0 (19.5, 20.5)	6.5 (6.2, 6.7)[a, b]
WC[1] (cm)									
	P	*0.849*	*0.349*	*0.003*	*0.006*	*0.721*	*0.354*	*0.019*	*0.073*
Low WC		18.2 (17.4, 19.0)	51.9 (49.5, 54.2)	19.2 (18.6, 19.8)	6.1 (5.8, 6.3)	18.7 (17.9, 19.5)	53.0 (50.5, 55.5)	19.5 (18.8, 20.1)	6.2 (5.9, 6.5)
High WC		18.1 (17.7, 18.5)	52.9 (51.9, 54.0)	19.9 (19.4, 20.3)[c]	6.3 (6.1, 6.5)[c]	18.6 (18.1, 19.0)	54.2 (53.1, 55.2)	20.0 (19.6, 20.5)[c]	6.4 (6.2, 6.6)
WC-HGS[2] Phenotypes									
	P	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
LWC-LHGS		15.8 (15.1, 16.6)	42.5 (39.6, 45.4)	17.6 (16.6, 18.7)	5.2 (4.7, 5.6)	16.4 (15.6, 17.2)	44.0 (41.2, 46.8)	18.3 (17.1, 19.4)	5.5 (5.0, 6.0)
LWC-HHGS		19.0 (18.1, 19.9)[d]	54.7 (52.0, 57.3)[d]	19.7 (19.0, 20.4)[d]	6.3 (6.1, 6.6)[d]	19.3 (18.4, 20.3)[d]	55.4 (52.6, 58.2)[d]	19.9 (19.2, 20.5)[d]	6.4 (6.1, 6.7)[d]
HWC-HHGS		18.7 (18.3, 19.1)[d, f]	55.1 (53.9, 56.3)[d, f]	20.3 (19.8, 20.7)[d, e, f]	6.5 (6.3, 6.7)[d, f]	19.0 (18.5, 19.5)[d, f]	55.9 (54.7, 57.1)[d, f]	20.3 (19.9, 20.8)[d, f]	6.5 (6.3, 6.7)[d, f]
HWC-LHGS		16.0 (15.1, 16.9)[e]	44.0 (41.7, 46.4)[e]	18.2 (17.3, 19.0)[e]	5.6 (5.2, 6.1)[e]	16.4 (15.4, 17.5)[e]	45.6 (42.6, 48.7)[e]	18.6 (17.6, 19.6)[e]	5.9 (5.4, 6.3)[e]
WC-HGS-R[3]									
	P	*<0.001*	*<0.001*	*0.038*	0.162	*<0.001*	*<0.001*	*0.359*	*0.536*
Tertile1		19.2 (18.6, 19.8)	54.1 (52.3, 55.9)	19.8 (19.3, 20.4)	6.3 (6.0, 6.6)	19.4 (18.7, 20.0)	54.4 (52.5, 56.2)	19.8 (19.2, 20.4)	6.3 (6.0, 6.6)
Tertile2		18.6 (18.1, 19.1)	55.4 (54.0, 56.8)	20.1 (19.6, 20.5)	6.4 (6.2, 6.7)	18.9 (18.4, 19.5)	56.1 (54.7, 57.5)	20.2 (19.7, 20.7)	6.4 (6.2, 6.7)
Tertile3		17.1 (16.5, 17.6)[g, h]	49.7 (48.1, 51.2)[g, h]	19.3 (18.7, 19.9)[h]	6.1 (5.8, 6.4)	17.7 (17.0, 18.3)[g, h]	51.8 (50.3, 53.3)[g, h]	19.8 (19.1, 20.5)	6.4 (6.1, 6.7)

All information except as noted is given in data using sample weights. Data shown as mean (min, max). Model A: before adjusted variables, Model B: after adjusted variables (age, gender, education, marital status, annual household income, number of morbidity (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake).

Abbreviations: HGS: Hand grip strength, WC: Waist circumference, WC-HGS-R: Waist-to-hand grip ratio, LWC: Low waist circumference, LHGS: Low hand grip strength, HWC: High waist circumference, HHGS: High hand grip strength, AF: Animal Fluency, DSST: Digit Symbol Score Test, CERAD-WL: The Consortium to Establish a Registry for Alzheimer's Disease - Word Learning test, CERAD-DR: The Consortium to Establish a Registry for Alzheimer's Disease - Delayed Recall test.

[1] WC: Waist circumference cut-off used diagnosis and management of the metabolic syndrome.

[2] HGS: Hand grip strength cut-off used the most relevant index in men and women that effectively identified individuals at risk of sarcoprnia in older adults.

[3] WC-HGS-R: Waist-to-hand grip ratio was devided into 3 tertiles including tertile1 (<2.987), tertile2 (2.987-<3.974), and tertile3 (≥3.974).

[a] P < 0.05 significant differences with BMI <18.5 kg/m^2: [b] P < 0.05 significant differences with BMI 25-29.9 kg/m^2

[c] P < 0.05 significant differences with Low WC; [d] P < 0.05 significant differences with LWC-LHGS; [e] P < 0.05 significant differences with LWC-HHGS; [f] P < 0.05 significant differences with HWC-LHGS

[g] P < 0.05 significant differences with Tertile1; [h] P < 0.05 significant differences with Tertile2

Table 4- 6 Complex Samples Logistic (CSL) regression analysis of the association between the classifications of body composition and grip strength (factor) and cognitive function (dependent variable) before (model A) and after adjustment for confounding variables (model B) in the NHANES 2011-2014 cohort

Body composition		**Cognitive functioning score Odds Ratios (Lower, Upper)**							
		Model A				**Model B**			
	Sig.	**AF (<14)**	**DSST (<40)**	**CERAD-WL (<17)**	**CERAD-DR (<5)**	**AF (<14)**	**DSST (<40)**	**CERAD-WL (<17)**	**CERAD-DR (<5)**
BMI (kg/m^2)									
	P	*0.545*	*0.739*	*0.010*	*0.043*	*0.691*	*0.793*	*0.011*	*0.041*
<18.5 vs. 18.5-24.9		1.4 (0.6, 3.0)	1.2 (0.6, 2.6)	2.1 (0.9, 4.9)	1.8 (0.7, 4.6)	1.2 (0.4, 3.2)	1.5 (0.7, 3.4)	2.6 (0.9, 6.9)	2.3 (0.9, 6.0)
25-29.9 vs. 18.5-24.9		0.9 (0.7, 1.2)	0.9 (0.6, 1.2)	1.0 (0.7, 1.3)	1.2 (0.9, 1.6)	0.9 (0.6, 1.3)	1.0 (0.7, 1.4)	0.9 (0.6, 1.4)	1.3 (0.9, 1.8)
≥30 vs. 18.5-24.9		0.8 (0.6, 1.2)	0.9 (0.6, 1.2)	0.8 (0.6, 1.0)	0.9 (0.7, 1.1)	0.8 (0.6, 1.2)	1.0 (0.7, 1.5)	0.7 (0.5, 1.0)	0.8 (0.6, 1.1)
WC[1] (cm)									
	P	*0.628*	*0.088*	*<0.001*	*0.039*	*0.844*	*0.172*	*<0.001*	*0.113*
High WC vs Low WC		1.0 (0.7, 1.2)	0.8 (0.6, 1.0)	0.6 (0.5, 0.8)	0.9 (0.7, 1.0)	1.0 (0.7, 1.3)	0.8 (0.6, 1.1)	0.6 (0.5, 0.8)	0.9 (0.7, 1.0)
WC-HGS[2] Phenotypes									
	P	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.005*
LWC – LHGS vs LWC – HHGS		2.5 (1.6, 3.9)*	3.4 (2.1, 5.4)*	1.9 (1.2, 3.2)*	2.8 (1.7, 4.5)*	2.2 (1.2, 4.0)*	2.9 (1.8, 4.9)*	1.6 (0.9, 2.7)	2.1 (1.2, 3.4)*
HWC – LHGS vs LWC – HHGS		2.5 (1.7, 3.7)*	2.9 (2.0, 4.2)*	1.7 (1.3, 2.3)*	1.9 (1.4, 2.6)*	2.2 (1.4, 3.5)*	2.5 (1.6, 4.0)*	1.6 (1.1, 2.4)*	1.6 (1.1, 2.5)*
HWC – HHGS vs LWC – HHGS		1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	0.6 (0.5, 0.8)	1.0 (0.8, 1.2)	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	0.6 (0.4, 0.8)	0.9 (0.7, 1.2)
WC-HGS-R[3]									
	P	*<0.001*	*0.001*	*0.106*	*0.074*	*0.016*	*0.012*	*0.769*	*0.922*
Tertile2 vs 1		1.1 (0.9, 1.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.2)	1.0 (0.7, 1.5)	1.1 (0.8, 1.6)	0.9 (0.6, 1.1)	1.0 (0.7, 1.3)	0.9 (0.6, 1.4)
Tertile3 vs 1		1.8 (1.3, 2.5)*	1.7 (1.2, 2.3)*	1.4 (1.0, 1.9)	1.4 (1.0, 1.9)	1.6 (1.1, 2.1)*	1.4 (1.0, 1.9)	1.1 (0.8, 1.7)	1.0 (0.7, 1.5)

All information except as noted is given in data using sample weights. Data shown as mean (min, max).

* Statistical significance (P < 0.05).

Model A: before adjusted variables, Model B: after adjusted variables (age, gender, education, marital status, annual household income, number of morbidity (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake).

[1] WC: Waist circumference cut-off used diagnosis and management of the metabolic syndrome.

[2] HGS: Hand grip strength cut-off used the most relevant index in men and women that effectively identified individuals at risk of sarcoprnia in older adults.

[3] WC-HGS-R: Waist-to-hand grip ratio was devided into 3 tertiles including tertile1 (<2.987), tertile2 (2.987-<3.974), and tertile3 (≥3.974).

Abbreviations: HGS: Hand grip strength, WC: Waist circumference, WC-HGS-R: Waist-to-hand grip ratio, LWC: Low waist circumference, LHGS: Low hand grip strength, HWC: High waist circumference, HHGS: High hand grip strength, AF: Animal Fluency, DSST: Digit Symbol Score Test, CERAD-WL: The Consortium to Establish a Registry for Alzheimer's Disease - Word Learning test, CERAD-DR: The Consortium to Establish a Registry for Alzheimer's Disease - Delayed Recall test.

Table 4- 7 Complex Samples Logistic (CSL) regression analysis of the association between the classifications of body composition and grip strength (factor) and cognitive function (dependent variable) after adjustment for confounding variables

Body composition	**Sig.**	**Cognitive functioning scores**							
		Odds Ratios (Lower, Upper)							
		60-70 y (n=1910)				**>70 - 85 y (n=1485)**			
		AF	**DSST**	**CERAD-WL**	**CERAD-DR**	**AF**	**DSST**	**CERAD-WL**	**CERAD-DR**
		(<14)	**(<40)**	**(<17)**	**(<5)**	**(<14)**	**(<40)**	**(<17)**	**(<5)**
WC-HGS[1] Phenotypes									
	P	*0.217*	*<0.001*	*0.006*	*0.067*	*0.061*	*0.002*	*<0.001*	*0.034*
LWC – LHGS vs LWC – HHGS		2.5 (0.9, 6.7)	4.0 (1.6, 9.9)*	2.5 (1.1, 5.9)*	3.4 (1.3, 8.9)*	1.0 (0.5, 2.1)	1.6 (0.9, 2.8)	0.6 (0.3, 1.1)	3.4 (1.3, 8.9)*
HWC – LHGS vs LWC – HHGS		1.9 (0.8, 4.8)	1.9 (0.9, 4.1)	1.8 (0.9, 4.0)	1.2 (0.3, 4.1)	1.1 (0.7, 2.0)	1.7 (0.9, 3.1)	0.7 (0.4, 1.2)	1.2 (0.3, 4.1)
HWC – HHGS vs LWC – HHGS		1.4 (0.9, 2.4)	0.9 (0.5, 1.4)	0.7 (0.5, 1.1)	1.4 (1.0, 2.0)	0.7 (0.4, 1.0)	0.8 (0.5, 1.4)	0.4 (0.3, 0.6)	1.4 (1.0, 2.0)
WC-HGS-R[2]									
	P	*0.915*	*0.029*	*0.468*	*0.254*	*0.211*	*0.270*	*0.710*	*0.123*
Tertile2 vs 1		1.0 (0.6, 1.6)	0.6 (0.4, 0.9)	0.8 (0.5, 1.2)	0.7 (0.4, 1.1)	1.1 (0.7, 1.7)	1.2 (0.7, 1.9)	0.9 (0.6, 1.4)	1.1 (0.7, 1.6)
Tertile3 vs 1		0.9 (0.5, 1.7)	0.9 (0.6, 1.5)	0.9 (0.5, 1.4)	0.8 (0.5, 1.5)	1.5 (0.9, 2.7)	1.3 (0.9, 1.9)	0.8 (0.5, 1.4)	0.7 (0.4, 1.2)

All information except as noted is given in data using sample weights.

* Statistical significance (P < 0.05).

Models were adjusted for age, gender, education, marital status, annual household income, number of morbidity (diabetes, kidney problems, anemia, arthritis, congestive heart failure, coronary heart disease, cancer or malignancy), stroke, blood pressure, physical activity, medications related cognitive interactions, smoking, depression, alcohol use, energy intake.

[1] WC: Waist circumference cut-off used diagnosis and management of the metabolic syndrome, HGS: Hand grip strength cut-off used the most relevant index in men and women that effectively identified individuals at risk of sarcoprnia in older adults.

[2] WC-HGS-R: Waist-to-hand grip ratio was devided into 3 tertiles including tertile1 (<2.987), tertile2 (2.987-<3.974), and tertile3 (≥3.974).

Abbreviations: HGS: Hand grip strength, WC: Waist circumference, WC-HGS-R: Waist-to-hand grip ratio, LWC: Low waist circumference, LHGS: Low hand grip strength, HWC: High waist circumference, HHGS: High hand grip strength, AF: Animal Fluency, DSST: Digit Symbol Score Test, CERAD-WL: The Consortium to Establish a Registry for Alzheimer's Disease - Word Learning test, CERAD-DR: The Consortium to Establish a Registry for Alzheimer's Disease - Delayed Recall test.

Mediation Analysis

NHANES 1999-2002

The mediation analysis showed a significant indirect effect of both CRP (FM/FFM, b=-0.5, TrFM/ASM, b = -0.3) and HOMA-IR (FM/FFM, b = -1.4, TrFM/ASM, b = -1.9) in explaining the impact of FM/FFM and TrFM/ASM on DSST. Furthermore, the direct effect of FM/FFM and TrFM/ASM on DSST was also significant; hence, CRP or HOMA-IR may partially mediate the association between FM/FFM and TrFM/ASM and DSST (**Table 4-8**). The mediation model 2 (**Figure 4-2**) assessed the concomitant role of both CRP and HOMA-IR on the association between body composition variables and cognitive function (DSST) in the NHANES 1999-2002 cohort. The analysis showed a significant indirect effect on FM/FFM and TrFM/ASM on DSST, but this was only mediated by HOMA-IR (FM/FFM, b = -1.4, TrFM/ASM, b = -1.9). A direct effect of FM/FFM (b = 12.2, $P < 0.005$) and TrFM/ASM (b =8.9, $p < 0.05$) on DSST was also found; hence, a partial mediation of the association between FM/FFM and TrFM/ASM and DSST was found for HOMA-IR (**Table 4-8**).

NHANES 2011-2014

The study assessed the mediating role of HOMA-IR on the association between body composition variables (WC-HGS-R) and cognitive function in NHANES 2011-2014. The results show there were no significant indirect effects of impact of HOMA-IR on cognitive performance (AF, DSST, CERAD-WL, and CERAD-DR). However, the direct effect of body composition (WC-HGS-R) on cognitive function was significant (AF, DSST, CERAD-WL, and CERAD-DR). Therefore, HOMA-IR was a mediator of the association between body WC-HGS-R and cognitive function in the NHANES 2011-2014 cohort (**Table 4-8**).

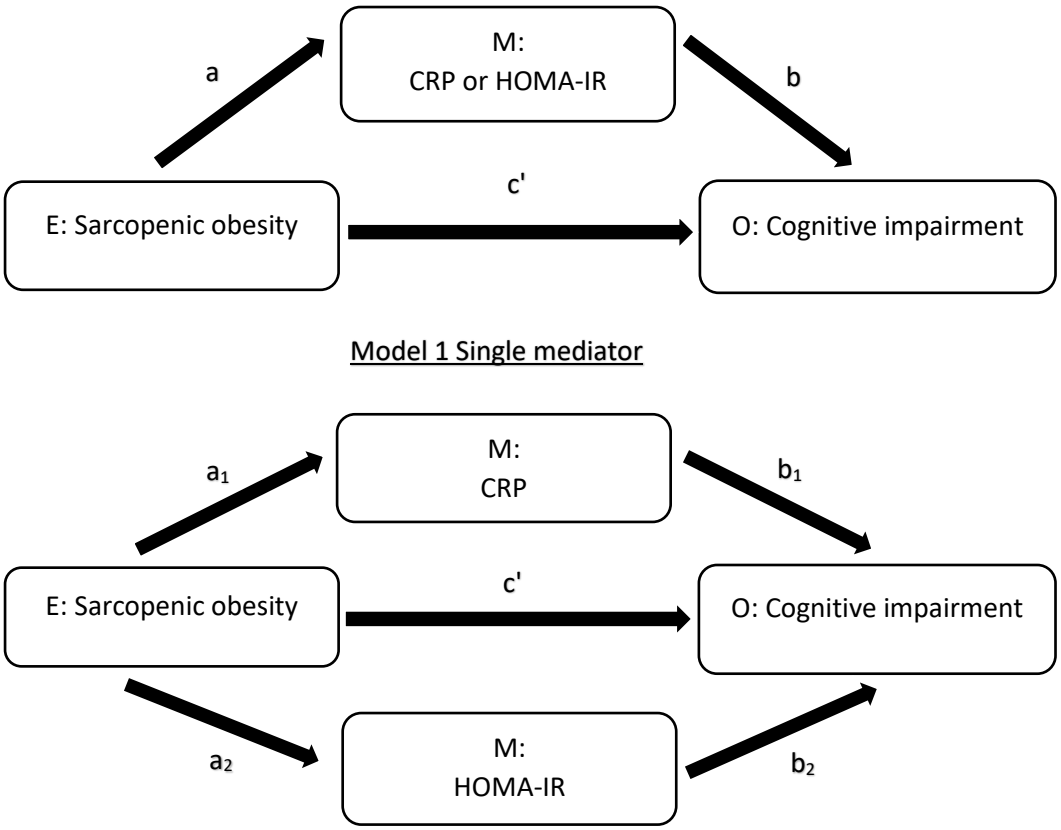


Figure 4- 2 *Mediation model for the association between sarcopenic obesity and cognitive impairment and sarcopenic obesity with insulin resistance (IR) or inflammation as mediators (Model 1 and 2).*

a= E predicting M, b= M predicting O controlling for E, c'= direct effect
Abbreviations: E: exposure, M: mediator, O: outcome

Table 4- 8 Mediation analysis of CRP and HOMA-IR on the association between body composition variables and cognitive function (NHANES 1999-2002)

Relationship	Total effect (P value)	Direct effect (P value)	Indirect effect	Confidence interval (CI*)	
				Lower	Upper
NHANES 1999-2002					
Model 1					
FM/FFM➔CRP➔DSST	7.1 (0.0002)	7.6 (0.0001)	-0.5	-1.1	-0.1
TrFM/ASM ➔CRP➔DSST	4.0 (0.004)	4.3 (0.002)	-0.3	-0.8	-0.1
FM/FFM➔HOMA-IR➔DSST	10.8 (0.005)	12.2 (0.001)	-1.4	-2.7	-0.6
TrFM/ASM ➔HOMA-IR➔DSST	7.0 (0.01)	8.9 (0.002)	-1.9	-3.1	-1.1
Model 2					
FM/FFM➔CRP and HOMA-IR➔DSST	10.7 (0.005)	12.2 (0.001)	H1 (HOMA-IR) : -1.4 H2 (CRP) : $-3.0x10^{-2}$	-2.7 -1.5	-0.6 0.5
TrFM/ASM ➔CRP and HOMA-IR➔DSST	7.0 (0.018)	8.9 (0.003)	H1 (HOMA-IR) : -1.9 H2 (CRP) : $-1.0x10^{-2}$	-3.1 -1.0	-1.1 0.3
NHANES 2011-2014					
WC-HGS-R➔HOMA-IR➔AF	-0.6 (<0.001)	-0.6 (<0.001)	$-1.5x10^{-3}$	$-2.7x10^{-2}$	$1.4x10^{-2}$
WC-HGS-R➔HOMA-IR➔DSST	-1.6 (<0.001)	-1.5 (<0.001)	$-3.1x10^{-2}$	$-8.1x10^{-2}$	$1.0x10^{-2}$
WC-HGS-R➔HOMA-IR➔CERAD-WL	-0.3 (0.005)	-0.3 (0.006)	$-5x10^{-4}$	$-1.4x10^{-2}$	$7.1x10^{-3}$
WC-HGS-R➔HOMA-IR➔CERAD-DR	-0.2 (0.004)	-0.2 (0.004)	$5x10^{-4}$	-4.0×10^{-3}	4.9×10^{-3}

*CIs: Confidence intervals (Lower and Upper) were based on indirect effect model; significant value was based on indirect effect model (no zero between lower CI and upper CI). The level of significance was set at P<0.05. Model 1: Analyse as single mediator (CRP or HOMA-IR), Model 2: Analyse as multiple mediators (CRP and HOMA-IR).

The indirect effect constitutes the extent to which the exposure influences the outcome through the mediator. A positive sign indicates the same direction (complimentary mediator) of the association between the exposure and outcome, whereas a negative sign was considered having an opposite effect (competitive mediator).

Abbreviations; ASM: appendicular skeletal muscle mass, FFM: Fat free mass, FM: Fat mass, TrFM: Trunk fat mass, CRP: C Reactive protein, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, WC-HGS-R: Waist-to-hand grip ratio, AF: Animal Fluency, DSST: Digit Symbol Score Test, CERAD-WL: The Consortium to Establish a Registry for Alzheimer's Disease - Word Learning test, CERAD-DR: The Consortium to Establish a Registry for Alzheimer's Disease - Delayed Recall test, CI: Confidence interval.

Discussion

Overall, the results showed that BMI was poor predictors of cognitive impairment. The SO phenotype, based on the concomitant measurement of FM and muscle mass and/or muscle function, was more closely associated with cognitive functions in both NHANES cohorts. The mediation analysis showed that insulin resistance, assessed by HOMA-IR, may explain (at least in part) the associations between the SO phenotype and cognitive function.

In the present study, older adults (≥60 years) with obesity (BMI ≥30 kg/m^2) tended to have higher cognitive scores than other BMI groups. In addition, BMI was not significantly associated with an increased risk of cognitive impairment. BMI alone may not be a good tool to predict cognitive impairment in older adults, while abdominal obesity (measured by WC) had better prognostic value (21, 178). The predictive role of obesity for cognitive and dementia risk has been challenged in other studies as statistical significance of the associations may vary with age and obesity measurement tools. Obesity assessment in older people using only BMI may not be appropriate for predicting dementia risk as does not provide information on variations in body composition components, such as muscle mass and fat mass (23). An older individuals may present with a normal BMI while having increased body fat mass and decreased muscle mass (SO) (274). The findings from the present study showed an association between high WC and cognitive impairment (low CERAD-WL score).

Sarcopenia, defined as a decrease in muscle strength, muscle function (i.e., HGS), and muscle mass, was associated with a higher risk of cognitive impairment in middle-aged and older adults (153, 241). In the present study, HGS was combined with WC to represent the SO phenotype in the NHANES 2011-2014 cohort, with a positive association with cognitive impairment. The finding from this study is consistent with the recommendation of the EWGSOP2 consensus that muscle strength is a better predictor of adverse health outcomes than muscle mass alone (36).

The SO phenotype attempts to integrate the physiological effects of both obesity and sarcopenia into a single diagnostic definition, which may provide a greater predictive sensitivity to estimate risk for impaired cardio-metabolic and brain health compared to obesity or sarcopenia alone (39). The present study showed that SO phenotypes, regardless of definition (e.g., HA-LM, high FM/FFM, high TrFM/ASM, and high WC- low HGS), were associated with cognitive impairment. The body composition ratio model was confirmed by previous studies which reported a significant association with impaired cognitive functions (i.e., low ASM/FM (146) and high FM/FFM (275)). The results from this study revealed for the first time that the WC-HGS ratio may represent a better risk predictor compared to the measurement of WC or HGS alone.

Differences in the definitions of SO, population characteristics, study design and methods of body composition and cognitive function assessment, may explain some of the inconsistent findings between published studies regarding the associations with various measures of cognitive domains. Body composition was frequently assessed using BMI (29), WC (18), BIA (29) or DXA (18). Sarcopenia was defined using muscle strength alone (i.e., HGS (139, 144)), muscle mass alone (i.e., ASMI (145), SMM (18)), or a combination between muscle mass and muscle strength (i.e., ASMI+HGS (147)). Obesity was classified using BMI alone (29, 144, 147), WC alone (18), or body fat mass alone (145).

The present study showed an association between SO and cognitive impairment in participants aged between 60–69 years but not in participants aged 70 years and older. This may be affected by the inconsistent outcomes regarding obesity and cognitive function in the very old adults, with some studies showing a protective effect (171, 174, 187, 230) and one indicating an adverse effect (18). Some studies reported a protective effect of obesity in the very old men (140, 161).

The mediation analysis from this study showed that HOMA-IR was a strong competitive mediator of the association between SO ratios and cognitive function, more so than CRP. The role of inflammation in the pathogenesis of insulin resistance is well known, which may suggest that insulin resistance could represent the "effector" mechanism linking SO to the deterioration of cognitive functions (61, 74). This is supported by previous studies showing that age-related cognitive impairment was independently associated with HOMA-IR (276), which was also a significant mediator of the association of SO with DSST scores for individuals aged 70 years and over (18).

The study has several strengths including a large sample size representative of the US population, a cross-comparison of body composition methods and approaches to define SO and validated cognitive tests. This study minimised the effects of potential confounding variables (i.e., demographics, comorbidity, blood pressure, physical activity, medications related to cognitive interactions, smoking, depression, alcohol use, and energy consumption) by including them in the models as covariates to obtain more accurate estimates. Adjusting for multicollinearity strengthens the validity of associations. There are also some limitations. The cross-sectional design does not allow the ascertainment of the causality of the associations between body composition phenotypes and cognitive outcomes. Adapting a case-control design from cross-sectional data has limitations. The association is unclear since exposure and outcome are measured at the same time. Retrospective classification of cases and controls may lead to selection and misclassification biases. Reporting ORs for common outcomes (not rare) tends to overestimate the strength of association compared with risk ratios, leading to potential misinterpretation.

Depression was included as a covariate in the analyses; however, in the 1999-2002 cohort, patients with depression were identified only if they were taking antidepressant medications, leading to a possible underestimation of depression prevalence. Classifying depression by

antidepressant medication use leads to misclassification of non-depressed individuals as depressed because antidepressants are prescribed for other conditions (e.g., anxiety disorders, chronic pain, insomnia, and menopausal symptoms) without depression. On the other hand, some individuals with depression remain undiagnosed or untreated, resulting in underestimation of true cases.

Conversely, in the 2011-2014 cohort depression was identified by using a validated depression screening questionnaire (Patient Health Questionnaire (PHQ)-9) (277). A single cognitive test was used in the 1999-2002 cohort, which may allow for a thorough assessment of multiple cognitive domains. However, the DSST is a sensitive measure of various cognitive domains and DSST scores correlate with the diagnosis of cognitive dysfunction and changes in cognitive function across a wide range of clinical populations (278). Some of the significant differences in cognition between body composition phenotypes were small and the biological and clinical relevance of these significant results needs to be interpreted with caution.

Conclusion

Overall, to the best of our knowledge, SO was associated with cognitive impairment in both cohorts, but SO definitions differed in their associations with cognitive impairment. This further emphasises the need for a standardised diagnostic approach for the identification of SO cases. Insulin resistance may represent a key mechanism linking SO to the development of cognitive impairment, and possibly, dementia onset.

Implication for further research

Further study requires a standardised diagnostic method for identifying cases of SO.

CHAPTER 5: Application of the New ESPEN-EASO Definition of Sarcopenic Obesity in Middle-Aged and Older Adults (50+ years old) and Evaluation of its Association with Cognitive Function

Introduction

SO has been associated with an increased risk of cognitive impairment compared with sarcopenia or obesity alone (28, 29). There is growing evidence suggesting an association between SO, cognitive impairment and dementia from the previous Chapters (18, 140). However, there has also been difference of research findings around the association of SO with cognitive impairment and dementia risk. These various outcomes can be mostly attributed to the lack of a standardised definition of SO, which has negatively affected the consistency and comparability of research findings supporting the predictive role of SO.

Sarcopenia has been defined using quantitative measures of muscle mass such as appendicular skeletal mass measured by DXA or functional measures of muscular performance such as hand-grip strength (36). For example, Baumgartner et al. defined sarcopenia using appendicular skeletal mass index (ASMI), (cut-offs, <7.26 kg/m^2 for men and 5.45 kg/m^2 for women) and the prevalence of sarcopenia increased from 24 % in those under 70 years of age to more than 60 % in those over 80 years (42). Obesity is typically assessed in SO definitions using BMI, WC or body composition variables (e.g., visceral fat, FM, FM%) (19, 59). The application of different methods to define SO, and consequent inconsistencies across epidemiological studies, has led to the development of a consensus statement for the diagnosis of SO in 2022, recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), with the aim to complement research practice and corroborate the predictive roles of SO for disease risk (39). The new SO definition has been applied in five studies between 2022-2023 (44-48). SO prevalence was 4-5% in older Japanese participants (aged ≥ 65 years) using cut-offs specific for an Asian

population (47, 48). The prevalence of SO was 4.5% in 998 German participants (aged ≥ 65 years) (45) and about 9% in 1,705 Australian men (≥ 70 years) (46) and 76 Italian participants (> 65 years) (44). However, no studies so far have explored the association of the new SO definition with health outcomes including cardiovascular, metabolic or cognitive health.

Aims

(a) To estimate the prevalence of SO as applied by the new ESPEN-EASO definition of SO in a representative sample of middle-aged and older adults (50-85 years old) from the 1999-2002 National Health and Nutrition Examination Survey (NHANES), and

(b) To explore the association of the new SO definition with cognitive function and appraise whether this association is different between age groups (50-59 years vs 60-85 years).

Methodology

Data and study population

Data from participants aged 50 years and over were collected from the NHANES conducted between 1999 and 2002 (https://www.cdc.gov/nchs/nhanes/index.htm). Ethics approval was obtained from NCHS Research Ethics Review Board. The protocol number of NHANES 1999-2002 is Protocol #98-12 (https://www.cdc.gov/nchs/nhanes/irba98.htm). Participants aged 50 to 85 years with complete key variables, including BMI, SARC-F, knee extensor strength (KES) and cognitive data (i.e., DSST and/or memory question), were included in the analysis and categorised following the ESPEN-EASO SO diagnostic algorithm **(Figure 5-1)** and the suggested cut-offs in supplementary material described in the previous paper (39).

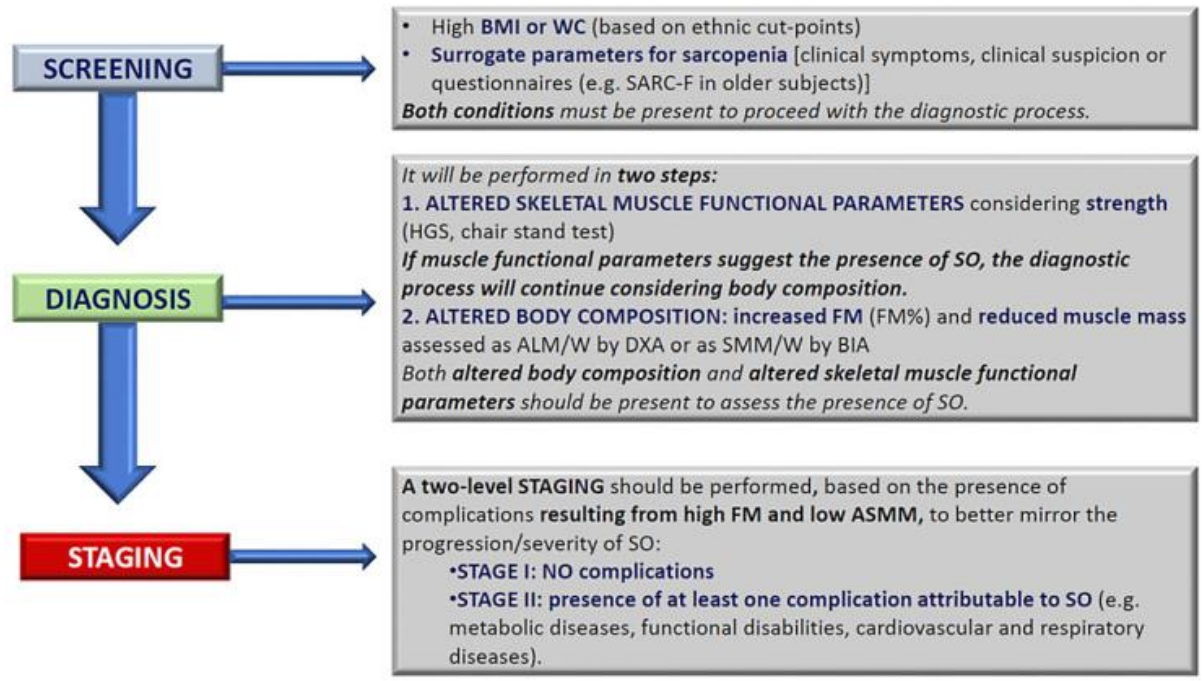


Figure 5- 1 *Diagnostic procedure for the assessment of sarcopenic obesity (SO). Reproduced with permission from Mario Siervo (original author of Donini et al., 2022 (39))*

Abbreviations: ALM/W: appendicular lean mass adjusted to body weight, ASMM: absolute skeletal muscle mass, BIA: bioelectrical impedance analysis, BMI: body mass index, DXA: dual X-ray absorptiometry, FM: fat mass, HGS: handgrip strength, SMM/W: total skeletal muscle mass adjusted by weight, SO: sarcopenic obesity, WC: waist circumference, SARC-F: strength, assistance with walking, rising from a chair, climbing stairs and falls.

ESPEN-EASO SO definition: The ESPEN-EASO SO diagnostic algorithm includes three assessment phases: 1) Screening, 2) Diagnosis I and 3) Diagnosis II.

Screening phase: Participants with high SARC-F and high BMI and/or high WC were identified as potential SO cases. SARC-F cut-offs (≥1 and ≥4) were used to identify participants with signs of sarcopenia (high SARC-F) (279-281). BMI ≥25 kg/m^2 (24) and BMI ≥30 kg/m^2 (282) were used to identify obesity in participants aged ≥ 60 years and 50-59 years, respectively. Participants with high WC were assesses using cut-offs 1 (WC ≥102 cm for men and ≥88 cm for women, participants aged 50-59 years) (283) and cut-offs 2 (WC ≥97. 6 cm for men and ≥87.4 cm for women, participants aged ≥ 60 years) (24). Participants with 'high BMI and/or high WC' were those who either had high values for both BMI and WC or had a high value for either one of them.

Diagnosis phase I: Participants with potential SO identified at screening were confirmed as SO cases if they presented a low KES. Values of KES (kg) per Weight (kg) (KES/W) <0.40 for men, <0.31 for women (for participants aged ≥ 60 years) (284) and KES (Newtons) < 390.9 for men, <266.4 for women (for participants aged 50-59 years) were used to classify sarcopenia (285).

Diagnosis phase II: Participants with SO at phase I were confirmed as SO cases if they presented a low ALM and a high FM%. Established cut-offs were used for ALM (%ALM/W (ALM x 100/body weight) including cut-offs 1 (<25.7% for men and <19.4% for women) (265, 286) and cut-offs 2 (<28.27% for men and <23.47% for women) (287). Excess adiposity was classified using cut-offs 1 (FM% >27% for men and >38% for women) (42) and cut-offs 2 (FM% >25% for men and >32% for women) (288).

Anthropometry and body composition

Anthropometry: Height was measured once in centimetres using a fixed stadiometer with a vertical backboard, a fixed floorboard, and a moveable headboard. Weight was measured once by using an electronic load-cell digital scale calibrated in kilograms to two decimal places with a weight capacity limit of 130 kg. WC was measured at the uppermost lateral border of the ilium using a measuring tape. BMI was calculated by dividing weight (kg) by squared height (m^2). Body measurements were recorded by a trained examiner at a mobile examination centre (MEC).

Body composition: Body composition assessment was undertaken by DXA (Hologic QDR 4500A). Participants were not eligible for a DXA scan if they were pregnant, weighed more than 136 kg (289), or were taller than 1.96 m. In addition, participants were not eligible if they had been exposed to radiographic contrast material in the past 7 days or nuclear medicine in the past 3 days. Body composition variables included ALM and FM%. ALM was calculated from the sum of the lean body mass in upper and lower limbs.

Sarcopenia questionnaire: The SARC-F questionnaire was used to screen for sarcopenia. This includes five self-reported domains from physical functioning and fall data, including 1) strength, 2) assistance with walking, 3) rise from a chair, 4) climb stairs, and 5) falls. Scores range from 0 to 10 (i.e., 0–2 points for each component; 0 = best to 10 = worst) (280, 281).

Muscle strength assessment: Muscle strength was assessed by measuring the isokinetic strength of the KES. A Kin Com MP dynamometer (Chattanooga Group, Inc., Chattanooga, TN, USA) was used to evaluate the isokinetic strength of the knee extensors (quadriceps). An average peak force (Newtons) was used to represent KES.

Cognitive assessment: In participants aged ≥60 years, the DSST (Wechsler Adult Intelligence Scale, Third Edition, The Psychological Corporation) was administered. Participants who were

unable to complete any of the sample items did not continue to the test. In middle-aged adults (50-59 years), a self-reported memory-related question (MQ, 'Are you limited in any way because of difficulty remembering or because you experience periods of confusion?') from the physical functioning questionnaire was used to characterize cognitive impairment (yes-no question). MQ has been analysed using a chi-squared test and shown to be significantly associated with the DSST score in participants aged 60-85 years ($P<0.001$). Cognitive impairment was defined as a DSST score <40 in participants aged ≥60 years and presence of self-reported memory complaint in participants aged 50-59 years.

Covariates: The following variables were included in the analysis. Socio-demographic variables included age, sex (men, women), race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other Race - Including Multi-Racial), education (less than high school, high school, more than high school), marital status (married, widowed, divorced, separated, never married, living with partner), and annual household income (under $20,000, $20,000 and over). Health-related variables included disease comorbidity (diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart failure, cancer or malignancy), stroke (yes, no), physical activity (sedentary, light, moderate, vigorous), medications related cognitive interaction, smoking (cigarettes, pipe, cigars, snuff, chewing tobacco), depression (participants with antidepressants use), alcohol use, blood pressure, and total energy intake. All covariates were collected by household interview and MEC interview. Data were recorded electronically with the use of computerized questionnaire forms. Total energy intake was assessed once by 24-hour dietary recall. Dietary recall interviews were conducted in person by trained dietary interviewers in a private room with a standard set of measuring guides in the MEC.

Statistical analysis

The results were analysed using SPSS complex sample module version 29.0 (IBM Corp, Armonk, NY). A P-value < 0.05 was considered statistically significant. Complex-survey analysis was applied to account for the sampling strategy of the NHANES survey and conducted according to NHANES approved protocols. Analysis of the NHANES dataset follows the CDC guidelines using weighting methodology to represent of the U.S. civilian noninstitutionalized resident population. This analysis combines multiple survey cycles (1999-2000 and 2001-2002), and the appropriate multi-year interview weight, as described in the following section, "Constructing Weights for Combined NHANES Survey Cycles", needs to be created. The study population was described using simple descriptive statistics (the results are presented as means ± SD or percentage (%) for continuous or categorical variables, respectively). The prevalence of SO in each phase (screening, diagnosis I, diagnosis II) was calculated. The differences between age groups were analysed by Complex Samples Crosstabs Analysis (chi-square test) for nominal/ordinal data and Complex Samples Descriptive tests (t-test) for continuous data.

Complex Samples Logistic Regression Odds Ratios was used to explore the association between factors (the SO phenotypes) and dependent variable (cognitive impairment, DSST score <40 or 'YES' answer to MQ) at each diagnostic phase of the ESPEN-EASO SO diagnostic algorithm. Analyses were adjusted for potential confounding factors including age, sex, race/ethnicity, education, marital status, annual household income, comorbidity, stroke, hypertension, physical activity, medications, smoking, depression, alcohol use, and total energy consumption. Analyses were also stratified by age to evaluate whether associations were different between age groups (50-59 vs 60-85 years). The cognitive variables and SO phenotypes are categorical. All SO phenotypes were evaluated by comparing them to their reference categories (normal phenotypes). This study considered using covariates that have

been linked to cognitive impairment and dementia risk in previous studies (169, 177, 290-292). Results are presented as Odds Ratio (OR) with their 95% confidence intervals (95% CI).

Results

Baseline characteristics of all 2,356 participants (mean age 66.7 years, 44.7% men) are presented in **Table 5-1**.

Table 5-2 shows the prevalence of sarcopenia, obesity and cognitive variables using the new ESPEN-EASO cut-offs. Participants with signs of sarcopenia (SARC-F ≥1) represented more than 40% of the sample. Most participants (~60-70%) had a high BMI (BMI≥25 kg/m^2) and high WC (≥102 cm for men, ≥88 cm for women for 50-59 years, and ≥97.6 cm for men, ≥87.4 cm for women for 60-85 years). More than 50% of participants had a low KES in both cut-offs. Muscle mass (ALM/W%, <28.27% for men and <23.47% for women) and excess adiposity (FM%, >27% for men and >38% for women) were found in more than 50% and 70% of the sample, respectively. The prevalence of the other cut-offs for SARC-F, ALM/W% and FM% were higher, with a few samples in the normal groups. The prevalence of cognitive impairment was 14.8% in participants aged 50-59 and 28.6% in participants aged 60-85.

The selected SO model was created using the cut-offs based on age group-related values according to the ESPEN-EASO SO recommendations. In addition, the prevalence and number of individuals with both the SO and normal phenotypes, which were sufficient for investigating the association, were considered. The diagnosis phase II model for this study was SO phenotype, defined by High SARC-F (≥1 for all age) + High BMI (≥30 kg/m^2 for 50-59 years and ≥25 kg/m^2 for 60-85 years) and/or High WC (≥102 cm for men, ≥88 cm for women for 50-59 years and ≥97.6 cm for men, ≥87.4 cm for women for 60-85 years) + Low KES (KES <390.9 Newtons for men, <266.4 Newtons for women for 50-59 years, and KES/W <0.40 kg/kg for men, <0.31 kg/kg for women for 60-85 years) + Low ALM/W% (<28.27% for men and <23.47% for women of all ages) + High FM% (>27% men and >38% for women of all ages). The prevalence of the SO phenotypes using the new ESPEN-EASO definition criteria is shown in **Table 5-2**.

Overall, the prevalence of SO was 32.3%, 21.2% and 15.0% at screening, diagnosis phase I and diagnosis phase II, respectively. At all phases, the prevalence of SO was higher in middle-aged participants (18.1%) compared to older participants (14.2%) **(Table 5-2 and Figure 5-2)**.

Table 5- 1 Characteristics of participants aged 50-85 years in NHANES 1999-2002.

Characteristics		Total 50-85 years (N=2,356)		Age group			
				50-59 years (n=297)		60-85 years (n=2,059)	
Name	**Categories**						
Continuous variables		**Mean**	**SE**	**Mean**	**SE**	**Mean**	**SE**
Age (year)#		66.7	0.3	54.2	0.1	69.9	0.3
SARC-F score (1-10)#		1.0	0.0	1.4	0.1	0.9	0.4
BMI (kg/m^2), mean#		28.2	0.2	29.5	0.5	27.8	0.1
WC (cm), mean#		99.3	0.4	100.4	1.2	99.0	0.3
KES (Newtons), mean#		260.4	3.6	282.6	4.4	254.6	4.3
ALM (kg), mean#		20.2	0.1	21.6	0.3	19.8	0.1
FM (%), mean#		29.2	0.2	37.2	0.8	36.7	0.2
Dietary, mean	Energy (kcal)#	1848.4	20.8	1972.1	47.8	1816.0	23.1
DSST score, mean		48.5	0.7	-	-	48.5	0.7
Categorical variables		**%**	**SE**	**%**	**SE**	**%**	**SE**
Gender	Men	44.7	0.7	42.5	2.0	45.3	0.7
Race/Ethnicity	Mexican American	2.9	0.6	3.0	0.7	2.8	0.6
	Other Hispanic	5.0	1.6	7.0	2.5	4.5	1.5
	Non-Hispanic White	80.9	2.0	74.7	3.5	82.5	1.9
	Non-Hispanic Black	7.7	1.2	8.8	1.6	7.4	1.2
	Other - multi-racial	3.6	0.7	6.6	1.6	2.8	0.7
Education#	Less Than High School	28.2	1.7	26.0	3.1	28.8	1.7
	High School, Diploma	27.3	1.6	22.2	2.7	28.6	1.8
	More Than High School	44.4	1.7	51.9	3.4	42.4	1.8
Marital status#	Married	63.3	1.5	63.7	2.6	63.2	1.5
	Widowed	63.3	1.5	2.9	1.0	20.1	1.5
	Divorced	16.5	1.2	13.9	2.6	7.7	0.8
	Separated	9.0	0.9	2.9	1.1	1.0	0.2
	Never married	1.4	0.3	5.7	1.1	2.6	0.5
	Living with partner	3.2	0.5	6.4	1.6	1.1	0.3
Annual household income	Under $20,000	23.4	1.9	21.3	3.3	23.9	2.4
	Over $20,000	64.8	1.5	66.7	3.6	64.4	1.8
HBP	Yes	46.0	1.6	42.0	3.3	47.1	1.5
Alcohol (≥12drinks/year) #	Yes	62.7	2.6	69.0	2.9	61.1	2.7
Stroke	Yes	1.0	0.2	0.9	0.6	1.0	0.3
Comorbidity*#	No	34.8	1.4	42.7	3.5	32.8	1.3
	> 1 condition	63.6	0.7	56.2	1.5	65.6	0.7
Physical activity**#	Sedentary	24.0	1.4	33.4	2.8	21.5	1.3
	Light	58.6	1.5	48.5	3.5	61.2	1.2
	Moderate	13.8	1.2	11.8	1.9	14.3	1.2
	Vigorous	3.2	0.5	5.7	1.6	2.6	0.4
Smoke#	Yes	58.6	1.4	64.5	2.6	57.0	1.4
Medications***#	Yes	13.8	0.9	19.9	1.7	12.2	0.9
Depression#	Yes – Antidepressant use	9.5	0.7	16.5	1.9	7.7	0.7

All information is given in data using sample weights and complex analysis.
Abbreviation: ALM/W: appendicular lean mass per body weight, BMI: body mass index, DSST: the Digit Symbol Substitution Test, EASO: the European Association for the Study of Obesity, ESPEN: the European Society for Clinical Nutrition and Metabolism, FM: total body fat mass, KES: knee extensors strength, MQ: memory related question (one question about experience confusion/memory problems), SARC-F: sarcopenia screening questionnaire, SE: standard error, WC: waist circumference.
*Comorbidity: diabetes, kidney problems, anaemia, arthritis, congestive heart failure, coronary heart failure, cancer or malignancy
** Physical activity level; 1. Sedentary: sit during the day/ not walk about very much, 2. Light activity: stand or walk a lot during the day, but do not have to carry or lift things very often, walk or bicycle, 3. Moderate activity: lift light load or have to climb stairs or hills often, moderate work and recreational activity, 4. Vigorous activity: do heavy work or carry heavy loads, vigorous work and recreational activity.
*** Medications related cognitive interaction: (catechol-O-methyltransferase (COMT) inhibitor, alkylating agents, alpha/beta adrenergic agonists, analgesics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, anorectics or anorexigenics, antibiotic drug, anticonvulsants, antidepressants, antidiabetics, anti-emetics, antihistamine, antihypertensive agents, antimanic agents, antimetabolites, antipsychotics, benzodiazepines, carbonic anhydrase inhibitors, central nervous system (CNS) depressants, CNS stimulants, CNS agents, cholinesterase inhibitors, conventional antipsychotics, corticosteroids, decarboxylase inhibitors, decongestants, diuretics, dopamine agonists, ergot alkaloids, hormones, hypnotics, lipase inhibitors, long-acting dopamine agonist, monoamine oxidase inhibitors (MAOIs), muscarinic antagonist, nasal decongestants, opiate/opioid analgesics, opiate antagonists, peripherally acting μ-receptor opioid antagonist drugs, proton pump inhibitors (PPIs), psychotherapeutic agents, pyrazolidines, rauwolfia alkaloids, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), SSR agonists, steroid drug, stimulants, sympathomimetic amines).
# statistically significant difference between groups ($P < 0.05$).

Table 5- 2 Prevalence of sarcopenia, obesity, and SO using cut-offs of the new ESPEN-EASO definition criteria in the 1999-2002 cohort.

Variables		Total			Age group					
		50-85 years (N=2,356)			50-59 years (n=297)			60-85 years (n=2,059)		
		%	SE	N	%	SE	N	%	SE	N
Body variables and cut-offs										
SARC-F	< 4	91.2	0.7	2131	88.4	1.8	254	91.9	0.7	1877
	≥ 4 (Sarcopenia)	8.8	0.7	225	11.6	1.8	43	8.1	0.7	182
	< 1	57.4	1.2	1382	42.8	2.8	122	61.2	1.1	1260
	≥ 1 (Sarcopenia)	42.6	1.2	974	57.2	2.8	175	38.8	1.1	799
BMI (kg/m^2)	< 30	68.1	1.3	1637	58.1	4.1	173	70.8	1.3	1464
	≥ 30 (Obesity)	31.9	1.3	719	41.9	4.1	124	29.2	1.3	595
	< 25	29.6	1.4	680	26.0	2.8	73	30.6	1.7	607
	≥ 25 (Obesity)	70.4	1.4	1676	74.0	2.8	224	69.4	1.7	1452
WC (cm)	< 102 men, < 88 women	36.6	1.6	903	33.7	3.3	106	37.3	1.7	797
	≥ 102 men, ≥ 88 women (Obesity)	62.5	1.7	1431	65.8	3.4	190	61.6	1.9	1241
	< 97.6 men, < 87.4 women	30.3	1.4	724	28.9	3.1	87	30.7	1.5	637
	≥ 97.6 men, ≥ 87.4 women (Obesity)	69.7	1.4	1610	71.1	3.1	209	69.3	1.5	1401
KES/W (kg/kg)	< 390.9 men, < 266.4 women (Sarcopenia)	77.6	1.7	1902	65.7	3.1	201	80.7	1.7	1701
	≥ 390.9 men, ≥ 266.4 women	22.4	1.7	454	34.3	3.1	96	19.3	1.7	358
KES (Newtons)	< 0.40 men, < 0.31 women (Sarcopenia)	51.8	1.9	1275	46.8	3.4	142	53.2	2.1	1133
	≥ 0.40 men, ≥ 0.31 women	48.2	1.9	1081	53.2	3.4	155	46.8	2.1	926
ALM/W (%)	< 28.27 men, < 23.47 women (Sarcopenia)	50.7	1.7	1156	49.7	3.6	135	51.0	1.8	1021
	≥ 28.27 men, ≥ 23.47 women	48.8	1.8	1191	49.7	3.7	160	48.6	1.8	1031
	< 25.7 men, < 19.4 women (Sarcopenia)	5.6	0.7	124	3.2	1.1	8	6.3	0.8	116
	≥ 25.7 men, ≥ 19.4 women	93.9	0.2	2223	96.3	1.2	287	93.3	0.8	1936
FM (%)	≤ 25 men, ≤ 32 women	8.3	0.6	232	7.7	1.5	29	8.4	0.6	203
	> 25 men, ≤ 32 women (Obesity)	91.7	0.6	2115	92.3	1.5	266	91.6	0.6	1849
	≤ 27 men, ≤ 38 women	23.6	1.3	586	21.6	3.3	67	24.1	1.2	519
	> 27 men, ≤ 38 women (Obesity)	76.4	1.3	1761	78.4	3.3	228	75.9	1.2	1533
Cognitive variables and cut-offs										
MQ	Yes	9.5	0.7	239	14.8	1.8	49	8.1	0.8	190
	No	90.5	0.7	2115	85.2	1.8	248	91.9	0.8	1867
DSST	DSST <40	22.7	1.4	758	0	0	0	28.6	1.9	758
	DSST ≥40	51.1	1.9	1090	0	0	0	64.4	1.8	1090
Mapping with the new definitions (ESPEN and EASO):										
Screening phase: SARC-F+BMI/WC										
Normal: L SARC-F+Normal BMI and L WC		13.7	0.8	319	10.6	1.7	27	14.5	1.0	292
SO: H SARC-F +H BMI and/or H WC		32.3	1.2	743	42.3	3.3	125	29.7	1.1	618
Diagnosis phase I: SARC-F+BMI/WC+KES										
Normal: L SARC-F+Normal BMI and L WC+H KES		8.5	0.8	196	3.6	1.1	9	9.7	0.9	187
SO: H SARC-F+H BMI and/or H WC+L KES		21.2	1.1	507	27.5	3.2	83	19.6	1.0	424
Diagnosis phase II: SARC-F+BMI/WC+KES+ALM/W%+FM%										
Normal: L SARC-F+Normal BMI and L WC+H KES+H ALM/W%+L FM%		5.4	0.6	125	2.7	1.0	7	6.1	0.7	118
SO: H SARC-F+H BMI and/or H WC+L KES+L ALM/W%+H FM%		15.0	0.9	349	18.1	2.8	52	14.2	0.9	297

All information is given in data using sample weights and complex analysis.
SO phenotype, H SARC-F (≥1) + H BMI (≥30 kg/m^2 for 50-59 years and ≥25 kg/m^2 for 60-85 years) and/or H WC (≥102 cm men, ≥88 cm women for 50-59 years and ≥97.6 cm men, ≥87.4 cm women for 60-85 years) + L KES (KES <390.9 Newtons men, <266.4 Newtons women for 50-59 years and KES/W <0.40 kg/kg men, <0.31 kg/kg women for 60-85 years) + L ALM/W% (<28.27% men, <23.47% women) + H FM% (>27% men, >38% women).
Normal phenotype, L SARC-F (<1) + Normal BMI (18.5-24.9 kg/m^2) and/or L WC (<102 cm men, <88 cm women for 50-59 years and <97.6 cm men, <87.4 cm women for 60-85 years) + H KES (KES ≥390.9 Newtons men, ≥266.4 Newtons women for 50-59 years and KES/W ≥0.40 kg/kg men, ≥0.31 kg/kg women for 60-85 years) + H ALM/W% (≥28.27% men, ≥23.47% women) + L FM% (≤27% men, ≤38% women).
Abbreviation: ALM/W: appendicular lean mass per body weight, BMI: body mass index, DSST: the Digit Symbol Substitution Test, EASO: the European Association for the Study of Obesity, ESPEN: the European Society for Clinical Nutrition and Metabolism, FM: total body fat mass, H: high, KES/W: knee extensors strength per body weight, MQ: memory related question (one question about experience confusion/memory problems), L: low, N: number of samples, SARC-F: sarcopenia screening questionnaire, SE: standard error, SO: sarcopenic obesity, WC: waist circumference.

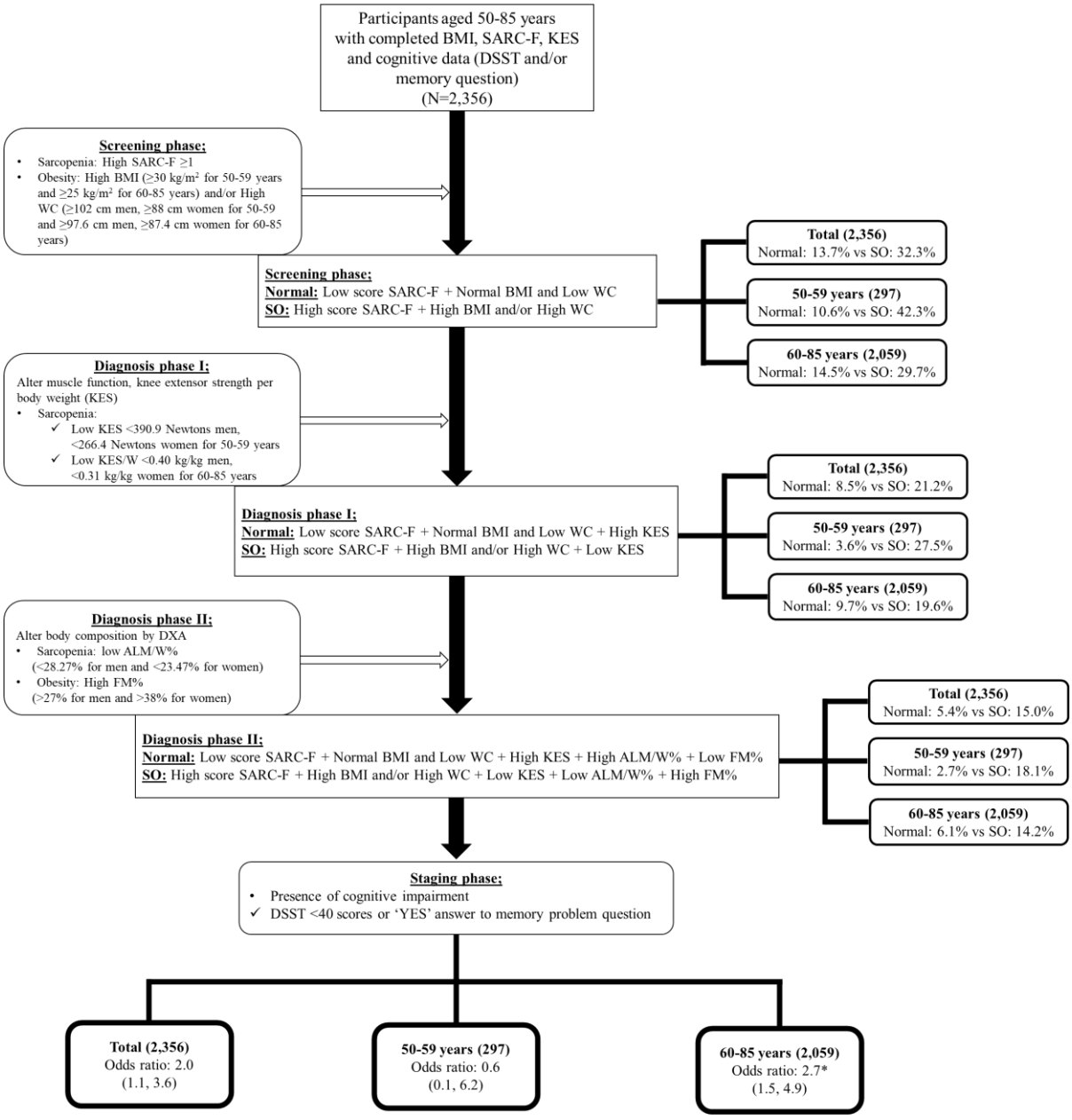


Figure 5- 2 *The prevalence and odds ratios of mapping the new ESPEN-EASO definition of SO in participants aged 50-85 years in NHANES 1999-2002*

At the screening phase, the SO phenotype was not associated with cognitive impairment in any of the groups when compared to the normal phenotype (reference group: Low score SARC-F + Normal BMI and Low WC), including participants aged 50-85 years (OR: 1.1, 95%CI 0.8-1.6, P=0.447), participants aged 50-59 years (OR: 0.6, 95%CI 0.2-1.9, P=0.343), and participants aged 60-85 years (OR: 1.4, 95%CI 0.9-2.2, P=0.082). The odds of cognitive impairment in all participants (50-85 years) were 1.6 times higher with SO at Phase I (95% CI: 1.0–2.5, P = 0.055) and 2 times higher with SO at Phase II (95% CI: 1.1-3.6, P= 0.059).

The SO phenotype was significant associated with cognitive impairment in older participants (60-85 years) at diagnosis phase I (OR: 2.3, 95%CI 1.4-3.8, P=0.007) and diagnosis phase II (OR: 2.7, 95%CI 1.5-4.9, P=0.004). However, there was no association between the SO phenotype and cognitive impairment in participants aged 50-59 years at all phases **(Table 5-3).**

Table 5- 3 The association between cognitive impairment (low DSST or having memory problem) using the new ESPEN-EASO definition criteria compared to normal phenotype model in 1999-2002 cohort.

Phase	Low DSST score (cut-off <40) or Having memory problem[#] (SO vs Normal phenotype)	Adjusted** OR 95%CI (Lower, Upper), P Value		
		50-85 years	50-59 years	60-85 years
Screening phase (n=1,062)	SARC-F+ BMI/WC			
	SO: High score SARC-F + High BMI and/or High WC vs **Normal:** Low score SARC-F + Normal BMI and Low WC	1.1 (0.8, 1.6), 0.447	0.6 (0.2, 1.9), 0.343	1.4 (0.9, 2.2), 0.082
Diagnosis phase I (n=703)	SARC-F+ BMI/WC+ KES			
	SO: High score SARC-F + High BMI and/or High WC + Low KES vs **Normal:** Low score SARC-F + Normal BMI and Low WC + High KES	1.6 (1.0, 2.5), 0.055	0.5 (0.1, 2.8), 0.419	2.3* (1.4, 3.8), 0.007
Diagnosis phase II (n=474)	SARC-F+ BMI/WC+ KES + ALM/W%+ FM%			
	SO: High score SARC-F + High BMI and/or High WC + Low KES + Low ALM/W% + High FM% vs **Normal:** Low score SARC-F + Normal BMI and Low WC + High KES + High ALM/W% + Low FM%	2.0 (1.1, 3.6), 0.059	0.6 (0.1, 6.2), 0.632	2.7* (1.5, 4.9), 0.004

All information is given in data using sample weights and complex analysis.
Abbreviation: ALM/W: appendicular lean mass per body weight, BMI: body mass index, CI: confidence interval, DSST: the Digit Symbol Substitution Test, EASO: the European Association for the Study of Obesity, ESPEN: the European Society for Clinical Nutrition and Metabolism, FM: total body fat mass, KES/W: knee extensors strength per body weight, MQ: memory related question (one question about experience confusion/memory problems), N: number of samples, OR: odds ratio, SARC-F: sarcopenia screening questionnaire, SE: standard error, SO: sarcopenic obesity, WC: waist circumference.
* P-value < 0.05 is statistically significant.
**Adjusted covariates: age, gender, race/ethnicity, education, marital status, annual household income, blood pressure, alcohol intake, stroke, comorbidity, physical activity, smoke, medications related cognitive interactions, depression, dietary energy.
[#] This comparison was done by using memory problem data in cases where DSST data was missing for participants aged 60 years and above.

Discussion

Overall, the finding shows a high prevalence of the SO phenotype in participants aged 50-85 years at each phase of the new definition (15% at diagnosis phase II). When stratified by age group, higher prevalence of SO was observed in individuals aged 50-59 years in comparison to those aged 60-85 years. Furthermore, this study found a tendency for the association between SO and cognitive impairment in participants aged 50-85 years at diagnostic phases I and II. However, when stratified by age group, SO phenotypes were significantly associated with cognitive impairment in participants aged ≥60 years at screening and both diagnostic phases I and II, whereas no association was observed in participants aged 50-59 years.

In the present study, the prevalence of the SO phenotype was greater than prevalence values reported in previous studies which followed the ESPEN-EASO algorithm of individuals aged ≥65 years (range: 4.3% to 9%) (44-48). These variability in results may be due to study differences in sample size used in those studies (range: 76 to 1,416 participants) (44-48), type of participants (healthy older, post-stroke patients, older adults undergoing rehabilitation), type of measurements and body composition methods used to define sarcopenia and obesity at each phase (44, 45, 47, 48).

In the present study, a higher prevalence of SO was observed in individuals aged 50-59 years in comparison to those aged 60-85 years. A decline in the prevalence of obesity (classified using BMI, WC, and FM%) among older individuals in the present study may explain the decrease in the prevalence of SO, despite the increased presence of sarcopenia in older individuals. However, BMI and FM% do not differentiate between subcutaneous fat (beneath the skin) and visceral fat (around internal organs) (293). Abdominal fat distribution may play an important role in the association between SO and cognitive decline (21, 178), especially visceral fat (141, 294).

Sarcopenia in the present study, defined as low KES and ALM/W%, show a higher prevalence in the older age group. A previous study by Liu et al. showed the prevalence of sarcopenia (low ASMI, low HGS, and low gait speed) tends to increase with increasing age (295). In addition, Liu et al. showed that the prevalence of SO rises with age (295). The SO phenotype studied by Liu et al. was classified using low muscle mass (ASMI, <7.0 kg/m^2 in men, 5.7 kg/m^2 in women), low muscle strength (HGS, <26 kg in men, 18 kg in women), low physical performance (gait speed <0.8 m/s), and high FM% (>34.3% in men, >42.1% in women). The prevalence of SO may vary due to the use of various methods and cut-off criteria.

The large difference in sample sizes between groups (297 participants aged 50-59 years and 2,059 participants aged 60-85 years) might impact the accuracy and reliability of prevalence outcomes. Bastis et al. showed that the prevalence of SO, as defined by different research definitions based on body composition data using DXA from the NHANES 1999–2004, varied from 4.4% to 84.0% in men and from 3.6% to 94.0% in women (265). In addition, the variety of obesity assessments used, and sex could impact the prevalence of obesity. it was previously shown that absolute visceral adipose tissue mass and the FM trunk/limbs ratio increased significantly with age for both men and women (296).

The present study found an association between SO and cognitive impairment only in participants aged ≥60 years at screening and both diagnostic phases after adjustment for relevant covariates. However, there was no association between SO and cognitive impairment in participants aged 50-59 years. Several previous studies show the association between SO and cognitive impairment in older adults (18, 29, 45, 139, 144). For example, Schluessel et al. found that older participants (aged ≥65 years) with a SO phenotype (low HGS, low skeletal muscle mass per weight, and high fat mass) had a higher risk of cognitive impairment (OR: 3.0, 95%CI 1.5–6.1) compared to subjects without the SO phenotype (45). Another longitudinal study in participants aged ≥65 years (n=5,822, 8-year follow-up period) reported that

individuals with SO had a significantly higher risk of developing cognitive dysfunction over the follow-up period compared to those without SO (HR 1.20; 95% CI 1.03–1.40) (139). While there is growing research exploring the associations between SO and cognitive function in older adults, there is still a limited number of longitudinal studies investigating these associations and none of these studies have applied the new ESPEN-EASO definition.

In addition, the different outcomes between groups 50-59 years and 60-85 years may be explained by the fact that cognition was assessed using a self-reported memory question only in participants aged 50-59 years. Self-reported cognitive questions may lack internal validity when compared to scores obtained from neuropsychological tests (297). DSST scores could have potentially offered a more precise assessment of cognitive impairment in comparison to self-reported memory questions, therefore strengthening the associations between SO and cognitive function in middle-aged participants.

The interrelated mechanisms that connect SO with cognitive impairment are still tentative, and several potential links have been suggested, including reduced secretion of relevant myokines, increased secretion of pro-inflammatory cytokines, insulin resistance, oxidative stress, and hormonal dysfunction (60, 87, 89, 92, 101, 102). High adipose tissue leading to systemic insulin resistance and inflammation, may contribute to brain insulin resistance, neuroinflammation, brain mitochondrial dysfunction, oxidative stress, BBB damage, and reduced neuroprotective signalling (61). One mechanism may involve the development of insulin resistance and adipose tissue dysfunction that may further contribute to the inflammatory cascade, as altered adipokine secretion and adipocyte dysfunction perpetuate a pro-inflammatory state. Mitochondrial dysfunction may represent another potential mechanism, which links SO and cognitive function (68, 69). Sarcopenia, defined as low skeletal muscle mass and function, was associated with reduced myokine-brain signalling (i.e., irisin, BDNF) (60, 259), impaired brain insulin signalling (88). In addition, sarcopenia related

to low physical activity also adversely impacts cerebral blood flow and neuroplasticity (260, 261). Therefore, the synergistic effects of the concurrence of sarcopenia and obesity may contribute to greater deterioration in neural homeostasis and brain function.

A study conducted on individuals aged ≥65 years showed an association between SO and high levels of inflammatory markers (IL-6, C-reactive protein, IL-1 receptor antagonist, and soluble IL-6 receptor) (298). Long-term chronic inflammation is known to play a role in the development and progression of cognitive impairment and dementia (91). Additionally, hormonal dysregulation is identified as a key factor contributing to the increased risk of cognitive impairment associated with SO. This dysregulation could result in changes in hormone levels, such as growth hormone and insulin, which are known to impact cognitive function. It has been demonstrated that individuals with SO have reduced growth hormone secretion, which is particularly important for metabolism and body composition, such as muscle mass and adiposity (299, 300). This decrease in growth hormone secretion may have implications for brain health and cognitive function (301).

Strengths and Limitations: This is the first study to estimate the prevalence of SO using the ESPEN-EASO definition for SO and its association with cognitive function in the US population. This study used SARC-F as a marker for sarcopenia, following the new criteria suggested by ESPEN and EASO. Additionally, KES and KES/W were used to assess muscle strength because there was a lack of data on HGS. a previous study has shown a strong sensitivity of KES in identifying clinically significant muscle weakness (284). The European Working Group on Sarcopenia in Older People (EWGSOP) recommends evaluating lower limb isometric strength in cases where hand impairment is present (e.g., advanced arthritis or stroke) (36). However, evaluating both upper and lower extremity muscle strength is crucial for comprehensively assessing muscle function and accurately diagnosing sarcopenia. Furthermore, using a SARC-F cut-off of ≥1 in this study demonstrated high sensitivity in

screening for sarcopenia (279-281). The association observed in this study is considered robust due to the adjustment for covariates, which enhanced the reliability of the findings. As mentioned in Chapter 4, for common outcomes (not rare), ORs may inflate associations relative to risk ratios. This study was cross-sectional. Therefore, longitudinal studies are necessary to investigate causal associations between SO and cognitive impairment. A further limitation is that the study used two different methods to assess presence of cognitive impairment (self-reported memory complaint vs DSST test), which could have explained the differences in associations between SO and risk of cognitive impairment in the two age groups studied. DXA scans may be limited by hydration status variations impacting lean mass readings, as the scan cannot separate between lean tissue and water. There are still ongoing discussions regarding the most appropriate method for evaluating body composition in older individuals. The reliability of self-reported memory impairment is limited due to individuals' answers could be influenced by personality, mood, education, and health awareness, particularly depression and anxiety, which may lead to an overestimation of memory problems. Reporting the analysis in individuals aged 50-59 years may be less reliable than in those individuals aged 60 years and older due to individuals aged 50-59 often having greater variability in health status, lifestyle, and cognitive function, which could increase measurement inaccuracy in self-reported outcomes. Despite potential age-related cognitive decline in individuals aged 60 years and older, they often show more consistent patterns of chronic disease and healthcare utilisation, which may improve the stability of reported data.

Conclusion

The prevalence of SO in a large cohort of participants aged 50 to 85 was 15.0% at diagnosis phase II using the new ESPEN-EASO definition, with higher prevalence in individuals aged 50-59 years in comparison to those aged 60-85 years. SARC-F and KES/W represented the measures for the screening and diagnosis of sarcopenia, respectively. The study also found a significant association between SO and cognitive impairment in individuals aged 60 and above. SO diagnosis should be implemented among middle-aged and older individuals as part of clinical assessments, especially for those who have cognitive conditions or are at risk of cognitive dysfunction.

Implication for further research

Longitudinal studies are required to establish the causal links between SO and the risk of cognitive impairment and dementia in middle-and older-aged populations. To study the link between cognitive function and SO, it is imperative to adopt a consistent approach to diagnose SO, tailored to different age groups, genders, and ethnicities as indicated in the latest ESPEN and EASO guidelines.

CHAPTER 6: General Discussion

Sarcopenia and obesity are increasingly identified as risk factors for cognitive impairment and dementia. The coexistence of sarcopenia and obesity as SO may synergistically accelerate cognitive impairment and neurodegeneration processes.

The association between sarcopenia and cognitive impairment could be explained by impaired muscle glucose metabolism and reduced secretion of neuroprotective myokines (such as irisin and BDNF) (259). These factors can negatively impact cerebral blood flow, synaptic plasticity, and brain signalling, contributing to memory loss and cognitive impairment (118). Obesity is linked to increased proinflammatory cytokines, insulin resistance, and oxidative stress, which are established contributors to neuroinflammation and cognitive impairment (126). When sarcopenia and obesity coexist in individuals with SO, their underlying mechanisms may interact and further disrupt neural homeostasis, leading to more rapid cognitive decline and increasing the risk of dementia (302).

In a systematic review and meta-analysis of this thesis, the association (HRs) between dementia and sarcopenia, particularly when assessed using quantitative combined with functional methods, was stronger than the comparable association with obesity alone. The findings revealed a positive association between SO and all-cause dementia risk, but there is a lack of studies on AD and VaD. The evidence of the association between SO and dementia risk is still needed to explain the complex links of the combination between sarcopenia and obesity on dementia risk. These findings support the associations previously described between sarcopenia and obesity with neurodegeneration (302). Sarcopenia showed an association with all-cause dementia, AD, and VaD, confirming outcomes from a previous systematic literature review and meta-analysis of mixed studies (71 cross-sectional, 4 cohort, and 2 interventional studies) on the association between sarcopenia and MCI, AD, and other forms of dementia

(242). The findings from the present thesis also showed that impaired muscle function (e.g., low grip strength and slow gait speed) had a stronger and more consistent association with dementia risk than low muscle mass alone. This finding indicates neuromuscular integrity (i.e., muscular movement) is more closely linked to brain health than static measurements (i.e., muscle volume) (303). Furthermore, it was shown that midlife obesity is a stronger predictor of late-life dementia (i.e., AD and VaD) than obesity in older age. Previous systematic literature reviews and meta-analyses of longitudinal studies on the risk of obesity and central obesity in midlife and late life for the development of dementia and its subtypes confirmed these findings (19, 152). Obesity may exert a cumulative influence on dementia and its subtypes gradually over the course of a lifetime. The long-term impact of obesity-related inflammation, insulin resistance, and metabolic dysfunction may contribute to chronic vascular damage and altered brain signalling. In line with this, a previous study indicated that the associations between obesity and incident AD and vascular dementia were stronger in studies with long follow-up (>10 years) and baseline age less than 60 years (19).

The differences observed between ACD, AD, and VaD risks in the systematic review and meta-analysis of this thesis further highlight the heterogeneity of dementia pathophysiology and risk outcomes. These associations in individuals with sarcopenia and obesity were mostly strongest for VaD risk, which is possibly linked to metabolic and vascular disorders related to their underlying conditions (164-166, 185, 227). These results indicate that vascular and metabolic pathways (e.g., inflammation, oxidative stress, and insulin resistance) may play an important role in mediating the impact of sarcopenia and obesity on cognitive impairment. These variations indicate that the impact of sarcopenia, obesity, and their coexistence differs across dementia subtypes, with vascular-related pathways particularly linked to explaining the stronger associations observed.

Collectively, the finding from chapter 4 shows that the association with cognitive impairment (ORs) observed for SO was stronger than the association for obesity assessed by BMI alone. Consistent with previous evidence, the association (ORs and HRs) between cognitive impairment/dementia and SO was stronger than that observed for obesity alone (29, 139, 147, 304). Furthermore, insulin resistance may be a potential mediating factor linking SO to the development of cognitive impairment and lead to the onset of dementia.

The findings from this thesis (Chapter 4 and 5) provide emerging evidence that supports the positive association between SO (in particular the FM/FFM, WC-HGS, and SO ESPEN-EASO models) and cognitive impairment in participants aged 60-85 years from the NHANES (305, 306). This association was also particularly significant in participants aged 60-70 years, in line with previous findings (147). However, it has to be noted that the two NHANES studies presented in this thesis are cross-sectional in nature, capturing associations at a single time point and therefore not allowing for conclusions about causal relationships. In the trajectory of dementia among individuals with SO, it is suggested that when obesity develops during midlife, sarcopenia, and hence SO, typically become clinically evident in early older age (between the ages 60 and 70 years) (36). At this stage, the cumulative metabolic and inflammatory effects of midlife obesity are already well established. In addition, sarcopenia compounds the burden by reducing physical function, exacerbating insulin resistance, and promoting inflammation. Together, these synergistic effects of sarcopenia and obesity increasingly deteriorate brain health.

This thesis also highlights the influence of SO definitions on cognitive outcomes. Obesity assessment beyond BMI (i.e., WC) combined with low muscle strength (low HGS) to generate the SO phenotype was associated with worse cognitive outcome (Chapter 4). This is consistent with the SO definition of ESPEN-EASO (Chapter 5) (39), which combines the use of WC with BMI along with muscle strength for SO screening and preliminary diagnosis, and was

associated with cognitive impairment in older individuals (60-85 years). Defining SO solely on muscle mass is insufficient, just as relying exclusively on BMI fails to accurately capture obesity. Incorporating measurements of muscle function, abdominal adiposity (e.g., WC, visceral fat), and body composition assessments will enhance the identification of SO and strengthen observed associations with cognitive impairment and dementia risk (307). The definition of SO proposed by ESPEN-EASO, which combines functional measurements with body composition assessments, provides a robust framework for SO classification and warrants broader adoption (39).

Investigating the association between SO and cognitive impairment is challenging because there are many confounders. Including relevant confounders as covariates in the statistical models enhances the robustness of the observed association. Comorbidities and potential medication-related confounders, particularly in participants who have health conditions and/or receive immune suppressive/anti-inflammatory drugs, may affect inflammatory profiles and potentially influence cognitive outcomes. However, analyses were adjusted for potential confounding factors, including age, gender, race/ethnicity, education, marital status, annual household income, comorbidity, stroke, hypertension, physical activity, medication-related cognitive interactions, smoking, depression, alcohol use, and energy consumption. The comorbidity term used in the analyses encompasses health conditions potentially affecting the association, including diabetes, kidney disease, anaemia, arthritis, congestive heart failure, coronary heart failure, and cancer or malignancy. However, most of those health conditions rely on self-reported physician diagnoses (only anaemia is self-reported treatment behaviour). Finally, anti-inflammatory/immunosuppressive medication use for comorbidity was not adjusted in this thesis. Consequently, some residual confounding related to chronic inflammatory and/or immunosuppressive conditions and their medications may persist.

Based on the findings from this thesis, several modifiable factors should be considered to design efficient therapeutic interventions targeting both an increase in muscle mass and a decrease in adiposity. These factors include lifestyle modifications, such as nutrition management (e.g., consuming sufficient energy combined with adequate protein intake), exercise strategies (e.g., resistance training), and pharmacological approaches (308). However, several limitations moderate the potential efficacy of these interventions. Weight loss interventions from caloric restriction risk further muscle loss if not carefully balanced, and long-term adherence is challenging (308). Exercise strategies in older people, although effective, may be limited by mobility limitations or comorbidities. Pharmaceutical medications could be cautiously considered for the treatment procedure in cases of severe SO or failure to improve SO through nutrition and exercise approaches. Some of the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (a class of widely used drugs for the treatment of T2DM and obesity) have been shown to induce a greater lean body mass loss than low-calorie diets (309). This result also fluctuates based on factors such as sex, age, dose of medications, and the severity of calorie restriction, which could be an issue in the context of SO. However, evidence for drug use, particularly in older people, is limited, and side effects or safety concerns may restrict their use.

Cross-sectional analyses used in parts of this study revealed associations between SO and cognitive impairment. Nevertheless, they are limited in establishing causal relationships and determining whether SO contributes to cognitive impairment or early cognitive impairment leads to SO being affected by reduced physical activity, poor nutrition, and subsequent muscle loss and fat accumulation (reverse causation). Moreover, a cross-sectional study could not fully account for unmeasured confounders that may influence both SO and cognitive outcomes. For future designs, Mendelian randomisation could be considered to offer a potential solution to these limitations. Using genetic variants as natural instruments may help to establish causality

by investigating whether genetic traits linked to SO are associated with an increased risk of dementia (310).

There are fourteen potentially modifiable factors for cognitive impairment and dementia that can be targeted through lifestyle, medical, or social interventions, including alcohol consumption, body weight, depression, diabetes mellitus, diet, hypertension, less education, physical inactivity, sensory loss, sleep disturbance, smoking, social isolation, traumatic brain injury, and vitamin D deficiency (311). Due to their strong association with cognitive decline and dementia risk, sarcopenia and SO could be considered as additional modifiable risk factors for dementia.

Further epidemiological and clinical research is required to elucidate the underlying mechanisms linking SO with cognitive impairment and dementia to inform the design of effective prevention strategies. Future longitudinal studies should combine standardised assessments of sarcopenia and obesity, comprehensive cognitive evaluation, and cautious adjustment for potential confounders to reveal a causal link between SO and dementia risk and explore the potential of targeted interventions (e.g., resistance training, diet modifications, and interventions that improve insulin sensitivity and reduce chronic low-grade inflammation) to slow cognitive impairment and prevent dementia risk in individuals with SO. Other key factors that should also be considered in the statistical model include age groups, medication use, comorbidity, and follow-up duration. In addition, integrating genetic methods to assess causality with interventional studies targeting muscle and body fat may provide stronger evidence for effective strategies to slow cognitive deterioration and reduce dementia risk. To better understand the mechanisms underlying the association between SO and cognitive impairment, prospective clinical studies should incorporate comprehensive biological, neurological, and functional markers before and after lifestyle interventions (e.g. resistance exercise and nutritional modifications) aiming to reverse sarcopenia and reduce adiposity.

The findings of this thesis carry important public health implications, particularly as older populations and the global burden of cognitive impairment and dementia continue to rise. Early detection of SO by routine screening as a risk factor for cognitive impairment and dementia risk in primary care could help identify individuals at higher risk before symptoms emerge. Public health programmes promoting physical activity, adequate protein intake, and metabolic risk management could play a key role in delaying cognitive impairment and preventing dementia risk. Dementia-prevention policies beyond cardiovascular and metabolic risk factors may include sarcopenia/SO as potentially modifiable risk factors to strengthen prevention frameworks. Furthermore, the findings support the development of targeted interventions for individuals in higher-risk groups (in midlife and older adults) to launch public health messages and clinical guidelines to encourage individuals to maintain their muscle health and be aware of maintaining low body fat for healthy cognition.

The key strengths of this thesis include the incorporation of a systematic review and meta-analysis, along with the analyses of large-scale national health surveys (i.e., NHANES), enhancing its population-level relevance. However, limitations arise from the reliance on cross-sectional and retrospective cohort designs, which limit the ability to infer causality between SO and cognitive impairment. Additionally, the retrospective nature of the cohort data may limit the availability or completeness of key variables necessary to accurately classify SO and cognitive impairment.

In summary, this thesis has examined the positive association between SO and cognitive impairment in middle-aged and older adults and the implications for clinical practice and future research. Variations of the SO definition may impact the strength and consistency of the association observed with cognitive impairment. The SO definition by ESPEN–EASO, which was developed through international consensus, needs to be implemented in future research to ensure greater consistency and applicability across diverse ethnicities and regions. In addition,

the complex interplay between biological mechanisms (e.g., neuromuscular degradation, chronic inflammation, insulin resistance, and hormonal dysregulation), which may contribute to the association between SO and cognitive impairment, warrants further research. Comprehensive longitudinal research and clinical prospective studies are essential to elucidate these pathways and to guide the development of targeted, evidence-based interventions to gradual cognitive impairment and prevent dementia in ageing populations.

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