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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

Uraiporn Booranasuksakul[a], Ian A. Macdonald[a], Blossom C. M. Stephan[b,c], and Mario Siervo[a,c,d]

[a]School of Life Sciences, The University of Nottingham Medical School, Queen's Medical Centre, Nottingham, UK; [b]Institute of Mental Health, The University of Nottingham Medical School, Nottingham, UK; [c]Faculty of Health Sciences, Curtin enAble Institute, Curtin University, Perth, Australia; [d]School of Population Health, Curtin University, Perth, Australia

ABSTRACT

Objective: Sarcopenic-obesity (SO) is characterized by the concomitant presence of low muscle mass and high adiposity. This study explores the association of body composition and SO phenotypes with cognitive function in older adults.

Methods: Cross-sectional data in older adults (≥60 years) from NHANES 1999–2002 and 2011–2014 were used. In the 1999–2002 cohort, phenotypes were derived from body mass index (BMI) and dual-X-ray-absorptiometry, and cognition was assessed the by Digit-Symbol-Substitution-Test (DSST). In the 2011–2014 cohort, phenotypes were derived from BMI, waist-circumference (WC), and hand-grip-strength (HGS). Cognition was assessed using four tests: DSST, Animal Fluency, the Consortium-to-Establish-a-Registry-for-Alzheimer's-Disease-Delayed-Recall, and Word Learning. Mediation analysis was conducted to evaluate the contribution of inflammation (C-reactive-protein, CRP) and insulin resistance (Homeostatic-Model-Assessment-for-Insulin-Resistance, HOMA-IR) to the association between body composition and cognitive outcomes.

Results: The SO phenotype had the lowest DSST mean scores ($p < 0.05$) and was associated with a significant risk of cognitive impairment [Odds Ratio (OR) = 1.9; 95%CI 1.0–3.7, $p = 0.027$] in the 1999–2002 cohort. A higher ratio of fat mass and fat free mass (FM/FFM) also showed a greater risk of cognitive impairment (OR = 2.0; 95%CI 1.3–3.1, $p = 0.004$). In the 2011–2014 cohort, the high WC-Low HGS group showed significantly lower scores on all four cognitive tests ($p < 0.05$) and a higher risk of cognitive impairment. CRP and HOMA-IR were significant partial mediators of the association between FM/FFM and DSST in the 1999–2002 cohort.

Conclusions: The SO phenotype was associated with a higher risk of cognitive impairment in older adults. Insulin resistance and inflammation may represent key mechanisms linking SO to the development of cognitive impairment.

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Sarcopenia; obesity; cognition; dementia; aging

Introduction

Obesity is linked to metabolic and vascular dysregulation (i.e., insulin resistance, inflammation, loss of endothelial integrity), which may contribute to the impairment of brain health and increase the risk of dementia (1). However, the strength and direction of the associations between adiposity and brain health appear to be influenced by factors, such as aging, gender, and body fat distribution (i.e., central *vs* peripheral). For example, middle-age obesity is a potential risk factor for later-life dementia (2, 3) and adiposity appears to have a health protective role in very old individuals (>80 years old), a phenomenon that has been termed the "obesity paradox." A cross-sectional study indicated that a higher body mass index (BMI ≥25 kg/m^2) and visceral adiposity [measured by computerized tomography (CT)] were associated with lower cognitive performance in individuals <70 years, but not in those ≥70 years (4). The association between BMI and dementia risk was inverted in 2,798 participants from the Cardiovascular Health Study (CHS) Cognition Study as overweight status was not associated with dementia risk whereas obesity (BMI > 30 kg/m^2) was associated with a reduced risk of dementia (Hazard Ratio (HR), 0.63; 95% Confidence Interval (CI), 0.44–0.91) compared to a normal BMI (20–25 kg/m^2) (5). However, adiposity indices, such as BMI or waist circumference (WC) do not provide information on individual body components (i.e., mass, distribution); hence, the assessment of body composition may provide greater accuracy in the prediction of cognitive impairment and dementia risk (6).

A significant reduction in skeletal muscle mass (SMM) and function is defined as sarcopenia (7), which has been linked to cognitive impairment and dementia (8, 9). Bae et al (10) found in 840 older Japanese individuals (≥65 years)

CONTACT Mario Siervo mario.siervo@curtin.edu.au School of Population Health, Curtin University, Perth, WA, Australia.
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that a lower fat free mass (FFM) and appendicular muscle mass were associated with an increased risk of mild cognitive impairment (MCI) in men and a higher lean body mass (LM), which did not include bone mineral mass, was associated with reduced risk of cognitive impairment in older adults (11, 12).

The co-existence in the same individual of reduced muscle mass and/or strength with an increased adiposity characterizes the phenotype of sarcopenic obesity (SO) (13), which may be associated with a greater risk for adverse health outcomes compared to either sarcopenia or obesity independently (13, 14). The concomitant occurrence of obesity and sarcopenia could synergistically amplify their independent effects on inflammation, insulin resistance, and vascular dysfunction which, in turn, could promote additional losses of muscle mass (15) and predispose to further weight gain. Several studies have investigated the association between SO and cognitive function with contrasting results, which could be explained by differences in body composition methods, diagnostic definitions of SO, study design, and phenotypic characteristics of the populations (16–22).

This study explores the association between body composition and cognitive function in older adults (≥60 years) from the NHANES 1999–2002 and 2011–2014 cohorts. The aim was to explore and compare the independent associations of two different approaches for the assessment of SO with cognition and whether the SO the phenotype might confer a greater risk for cognitive impairment in both cohorts. In the 1999–2002 cohort, the association between dual X-ray absorptiometry (DXA)-based measurements of lean body mass and adiposity with measures of executive function, assessed by the Digit-Symbol-Substitution-Test (DSST) scores, was explored. Age, gender, and BMI specific DXA-based body composition models of SO (23–25) were applied and the association with DSST scores was investigated. In the 2011–2014 cohort, adiposity was assessed by anthropometry (BMI, WC), and hand-grip strength (HGS) was used as a functional measure of muscle mass. The independent and interactive effects of adiposity and HGS on domains of cognitive function (i.e., memory, attention, executive) were evaluated. A mediation analysis was conducted to evaluate the influence of inflammation (C-reactive-Protein: CRP) and insulin resistance (Homeostatic Model Assessment for Insulin Resistance: HOMA-IR) on the associations between SO and cognitive function.

Methods

Data and study population

Cross-sectional data from the 1999–2002 and 2011–2014 waves of the NHANES programme were used to examine the association between body composition and cognitive function in individuals aged 60–85 years. All DXA datasets are released by NHANES on the CDC website (26). 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 the number of NHANES 2011–2014 is Protocol #2011-17 (27). Individuals with incomplete cognitive test and body composition (e.g., DXA and/or anthropometric) data were excluded.

Anthropometry

NHANES (1999–2002)

Body measurements were recorded for all participants by a trained examiner in the mobile examination center. In situations where participants had to leave the mobile examination center 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 (24, 25).

NHANES (2011–2014)

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

In both cohorts, 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) (28). For men, a waist circumference (WC) below 102 cm was defined as "normal or moderately high WC" and ≥102 cm was "high WC." For women, below 88 cm was "normal or moderately high WC," and more than or equal to 88 cm was "high WC" (29).

Hand-grip strength (HGS)

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 jewelry. 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 on each hand (alternating hands between trials with a 60 s rest between measurements on the same hand). The average of the combined grip strength (the sum of the largest reading from each hand) 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 <30 and 20 kg, respectively (30).

Assessment of body composition phenotypes

NHANES (1999–2002)

Baumgartner model (23, 31). 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% was >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 (24). 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 cutoffs 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 (25). 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 cutoffs 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 analyzed 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 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 s. 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 Alzheimer's Disease (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 (32).

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 into 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) (33). 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 min 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 cognitively 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. A brief description of the cognitive scores and calculations is provided in the Online Supplementary Material (Table S1). 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 (32, 34).

Covariates: socio-demographic, lifestyle, and laboratory biomarkers

Covariates included: age, gender, education, marital status, annual household income, number of morbidities (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 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 (HOMA-IR) of insulin resistance (12). In NHANES 1999–2002, CRP was quantified by latex-enhanced nephelometry, plasma glucose was calculated by an enzymatic hexokinase (HK) method and plasma insulin was assessed by radioimmunoassay (RIA). 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 analyzer.

Statistical analysis

All data were analyzed using the SPSS complex sample module (35) version 28.0 (IBM Corp, Armonk, NY, USA). 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 Centers 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 (36). The results were presented as means ± standard deviation or frequency (%) according to the characteristics of the variables. Complex Samples General Linear Model (CSGLM) regression analysis was used to analyze 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. The distribution of residuals was checked to ensure the 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 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 (37, 38). The mediation analysis model is described in Figure 1. A full list of the covariates and mediators entered in each analysis is provided in the Online Supplementary Material (OSM) (Table S2).

Results

The flowcharts describing the selection of participants included in the final analysis for the NHANES 1999–2002 (Figure S1) and NHANES 2011–2014 (Figure S2) cohorts are reported in the OSM. The body composition characteristics of the population stratified according to the models of body composition phenotypes are shown in Table S3 of the OSM.

NHANES 1999–2002: The final dataset consisted of 2,544 participants with 43.3% as men. Participants mean age (±SE) was 70.44 ± 0.27 years, and 70.1% had a BMI ≥ 25 kg/m^2. 83.8% of participants were non-Hispanic white and ~70% of the participants completed high school or above. Descriptive characteristics of the sample are provided in Table 1. The prevalence of the phenotypes derived from the body composition models is shown in Figure 2. There was a difference between the Baumgartner and the Prado-Siervo models in estimating the prevalence of the SO phenotype in the cohort (14.5 *vs* 21.9%, respectively).

In adjusted models, FM (kg), FM (%), FMI (kg/m^2), and FM/FFM ratio were significantly associated with the DSST score (Beta Coefficient ± SE = 0.1 ± 0.1, 0.2 ± 0.1, 0.3 ± 0.1, and 8.6 ± 2.8, respectively; all $p < 0.05$) (Table S4 of the OSM). 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 ($p < 0.05$). No significant differences between phenotypes were identified for the Prado-Siervo and the two ratios (FM/FFM, TrFM/ASM) models (Table 2). The SO phenotype identified by Baumgartner's model had a significant risk of cognitive impairment compared to the reference group (HA-LM *vs* LA-HM, OR = 1.9; CI 95% 1.0–3.7, $p = 0.027$). In addition, the highest FM/FFM centile (≥85th) also showed 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 3). The HA-LM phenotype for both Baumgartner and Prado-Siervo models 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 S5 of the OSM).

NHANES 2011–2014: The final dataset included 3,395 participants (men = 45.1%). Participant mean age (±SE) was 69.5 ± 0.1 years and 73.1% of participants had a BMI ≥

Table 1. Characteristics of study participants included in the analyses of the 1999–2002 and 2011–2014 datasets.[a]

	NHANES 1999–2002		NHANES 2011–2014	
Characteristic	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	
[b]Annual household income, %		340		29
$0–$4,999	0.8		0.8	
$5,000–$9,999	8.5		3.1	
$10,000–$14,999	12.1		7.0	
$15,000–$19,999	8.8		5.9	
$20,000–$24,999	9.5		7.0	
$25,000–$34,999	16.0		10.7	
$35,000–$44,999	10.0		10.5	
$45,000–$54,999	8.7		7.5	
$55,000–$64,999	6.1		6.7	
$65,000–$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
Anemia 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
Stroke, % yes	5.6	7	7.2	0
[c]Physical activity, %		9		0
Sedentary	24.8		35.0	
Light	59.0		5.5	
Moderate	14.1		38.7	
Vigorous	2.1		20.8	
[d]Medications, % yes	15.7	519	25.6	0
Smoking, % yes	26.1	1112	13.9	105
[e]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

CRP = C-reactive protein, NA = not available, BMI = body mass index.

[a]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.

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

[c]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.

[d]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).

[e]Total PHQ-9 score (0–27) were classified clinically relevant depression based on a cutoff score of ≥10.

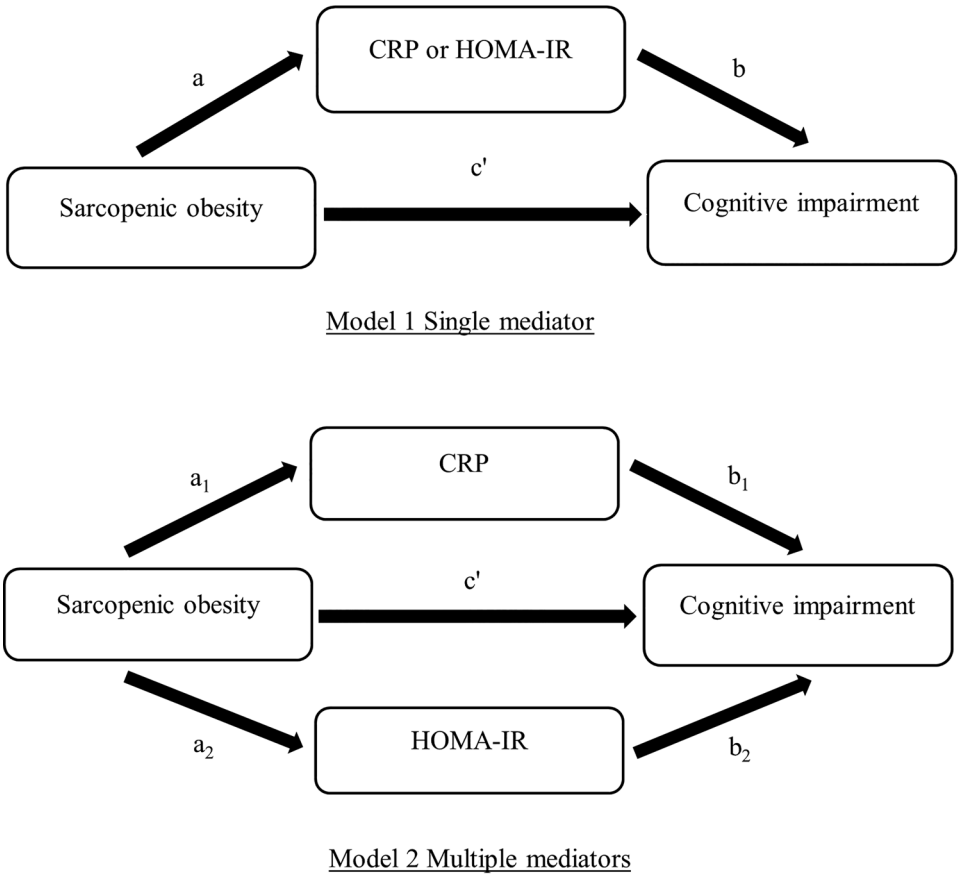

Figure 1. Mediation model for the association between sarcopenic obesity and cognitive impairment and sarcopenic obesity with insulin resistance (IR) or inflammation as mediators (Models 1 and 2). The direct effect was identified as c path, indirect effect by the b path, total effect (C′) was the combination of direct and indirect effects. The direct effect measures the extent to which the dependent variable changes when the independent variable increases by one unit and the mediator variable remains unaltered. In contrast, the indirect effect measures the extent to which the dependent variable changes when the independent variable is held constant and the mediator variable changes by the amount it would have changed had the independent variable increased by one unit. The indirect effect constitutes the extent to which the X variable influences the Y variable through the mediator. In linear systems, the total effect is equal to the sum of the direct and indirect (C′ + AB in the model above). 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).

25 kg/m^2. Descriptive characteristics of the sample are provided in Table 1.

A higher WC was characterized 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 characterized 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).

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 5). The LWC–LHGS phenotype was significantly associated with a greater risk of cognitive impairment assessed by the DSST and CERAD-WL and DR in subjects younger than 70 years old (Table S6 of the OSM).

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 mediating 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 6). The mediation model 2 (Figure 1) 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

Table 2. Complex samples general linear model (CSGLM) to test the association between the classifications of body composition (factor) and cognitive function (dependent variable) before and after adjusted model 1999–2002.*

	DSST score mean (lower, upper 95% CI)			
Classifications of body composition	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)	

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.

*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, 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].

[a]$p < 0.05$ between HA-HM and HA-LM.

[b]$p < 0.05$ between LA-HM and LA-LM.

[c]$p < 0.05$ between <15th and 15–84.9th.

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 6).

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 the 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 6).

Discussion

The results showed that BMI, WC, and other individual body composition parameters (FM, FFM, ASM) were overall 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 the associations between the SO phenotype and cognitive function.

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 in independent analyses conducted in the 1999–2002 and 2011–2014 NHANES cohorts. Hou et al. (39) showed that a BMI between 24.0 and 27.9 kg/m^2 was significantly related to a decreased risk of cognitive impairment (OR = 0.5, 95% CI = 0.3–0.7, $p < 0.001$) in 1,100 Chinese subjects aged 60–98 years; however, a significant association was found between abdominal obesity, measured by WC, and increased risk of cognitive impairment. The predictive role of BMI for cognitive and dementia risk has been challenged in other studies as the statistical significance of the associations may vary with age (5). Middle-aged obesity has been associated with increased dementia risk in later life (older than 65 years) (2) but having a BMI > 30 kg/m^2 in older age does not necessarily predict dementia risk (5).

Measures of central adiposity, such as WC or truncal FM, have been considered as better adiposity risk factors due to the closer role played by central adiposity in the pathogenesis of cardiovascular and metabolic diseases (40). However, the association of WC with risk for cognitive impairment

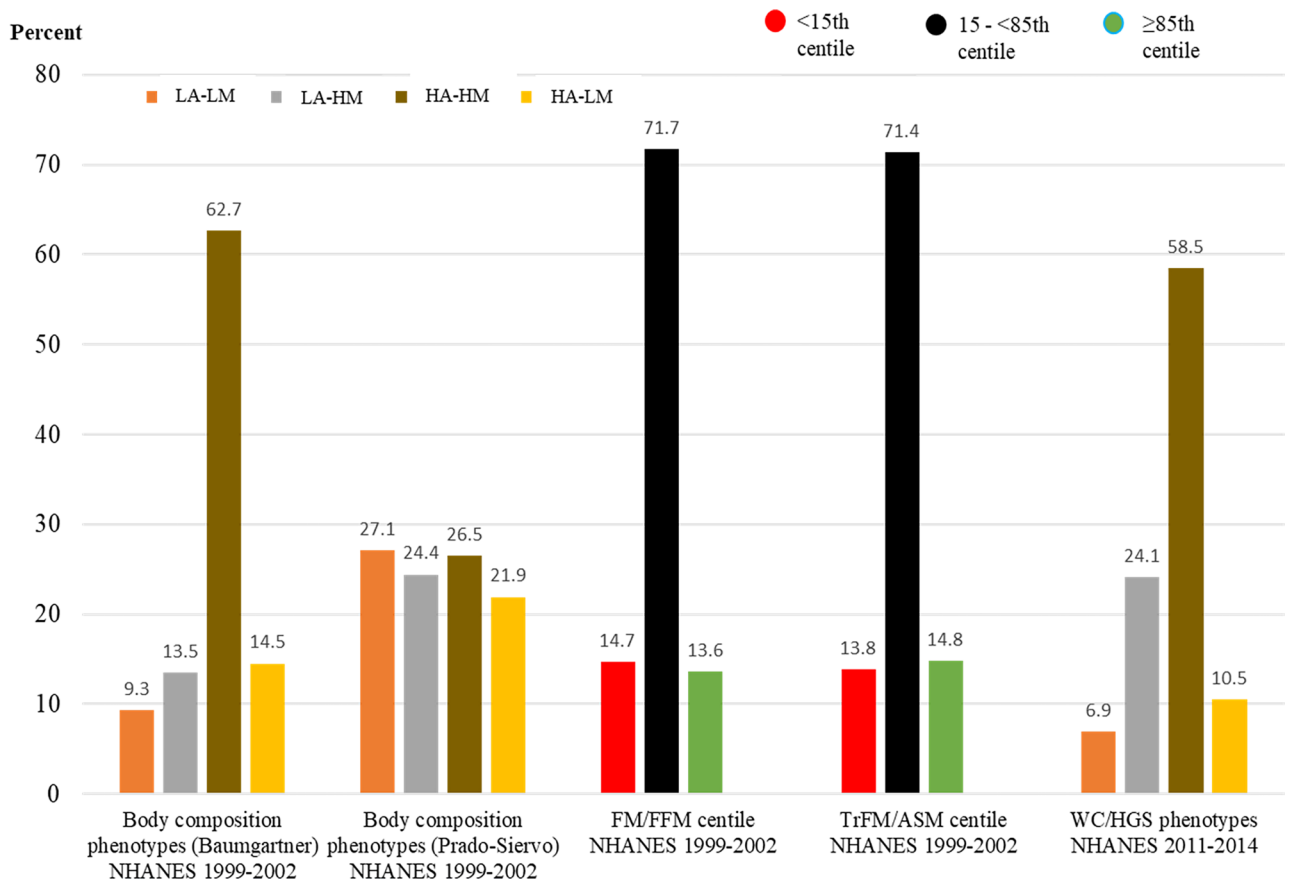

Figure 2. The prevalence of body composition phenotype in the NHANES 1999–2002 and the NHANES 2011–2014. FM = fat mass, FFM = fat free mass, TrFM = truncal fat mass, ASM = appendicular skeletal mass, WC = waist circumference, HGS = hand grip strength.

Table 3. Complex samples logistic (CSL) regression analysis of the association between the classifications of body composition (factor) and cognitive function (dependent variable) before and after adjusted model 1999–2002.*

	DSST score odds ratios (lower, upper) (<40)			
Classifications of body composition	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)	
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)	
≥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)	

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.

*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, 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].

has been inconsistent across studies (41, 42), which was also reported in the analysis conducted in the NHANES 2011–2014 cohort as we found an inverse association between WC and CERAD-WL.

High FM, measured by different body composition methods (i.e., DXA, bioelectrical impedance), has been inconsistently associated with the risk of cognitive impairment (43–48). In a cross-sectional analysis using data from

Table 4. 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 and after adjusted model 2011–2014.*

		Cognitive functioning score mean (lower, upper)							
		Model A				Model B			
Body composition	Sig.	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)

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.

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

[2]HGS: Hand grip strength cutoff 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 5. 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 and after adjusted model 2011–2014.*

		Cognitive functioning score odds ratios (lower, upper)							
		Model A				Model B			
Body composition	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)

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.
*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, 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 cutoff used diagnosis and management of the metabolic syndrome.
[2]HGS: Hand grip strength cutoff 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).

Table 6. Mediation analysis of CRP and HOMA-IR on the association between body composition variables and cognitive function (NHANES 1999–2002).

				Confidence interval (CI*)	
Relationship	Total effect (*p*-value)	Direct effect (*p*-value)	Indirect effect	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	−2.7	−0.6
			H2 (CRP): -3.0×10^{-2}	−1.5	0.5
TrFM/ASM→CRP and HOMA-IR→DSST	7.0 (0.018)	8.9 (0.003)	H1 (HOMA-IR) : −1.9	−3.1	−1.1
			H2 (CRP): -1.0×10^{-2}	−1.0	0.3
		NHANES 2011–2014			
WC-HGS-R→HOMA-IR→AF	−0.6 (<0.001)	−0.6 (<0.001)	-1.5×10^{-3}	-2.7×10^{-2}	1.4×10^{-2}
WC-HGS-R→HOMA-IR→DSST	−1.6 (<0.001)	−1.5 (<0.001)	-3.1×10^{-2}	-8.1×10^{-2}	1.0×10^{-2}
WC-HGS-R→HOMA-IR→CERAD-WL	−0.3 (0.005)	−0.3 (0.006)	-5×10^{-4}	-1.4×10^{-2}	7.1×10^{-3}
WC-HGS-R→HOMA-IR→CERAD-DR	−0.2 (0.004)	−0.2 (0.004)	5×10^{-4}	-4.0×10^{-3}	4.9×10^{-3}

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.
*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: Analyze as single mediator (CRP or HOMA-IR), Model 2: Analyze as multiple mediators (CRP and HOMA-IR).

the Canadian Longitudinal Study on Aging ($N = 30,097$), a higher total FM measured by DXA was associated with lower cognitive performance on the AF, Stroop interference, and reaction time tasks (43). In another cross-sectional analysis of more than 9,000 middle-aged and older participants, DSST cognitive scores were lower

with increasing FM percentage and visceral adipose tissue measured by bioelectrical impedance analysis (BIA) and magnetic resonance imaging (MRI), respectively (44). An analysis conducted on more than 20,000 individuals in the UK Biobank cohort showed that FM% measured by BIA was linked to lower cortical thickness, gray matter, and subcortical structure volumes and to lower working memory (45). Several studies have also observed that a higher FM was associated with a lower risk of cognitive impairment in older individuals (>70 years) (46–48), suggesting the existence of an age-interaction for the association of adiposity with cognitive function and dementia risk (49). Low FFM or other similar functional or quantitative measurements of muscle mass (i.e., lean body mass, ASM, HGS) have been more frequently associated with a higher risk of cognitive impairment in different age groups (50–54). A prospective analysis conducted in the Canadian Longitudinal Study on Aging showed that the presence of low appendicular lean soft tissue mass at baseline was associated with faster 3-year cognitive decline in executive functions and psychomotor speed (50). However, several studies have shown that functional measures of muscle mass (i.e., HGS, gait speed) may be better predictors of cognitive function compared to quantitative measures (51–53).

The SO phenotype attempts to amalgamate the physiological effects of both high FM and low muscle mass into a single diagnostic definition, which may provide a greater predictive sensitivity to estimate risk for impaired cardio-metabolic and brain health compared to FM or sarcopenia alone (13). This analysis showed that DXA-based models of the SO phenotype defined by different definitions [HA-LM (Baumgartner), HA-LM (Prado-Siervo), FM/FFM centile ≥85th, TrFM/ASM centile ≥85th] tended to have lower DSST scores and were associated with higher risk of cognitive impairment in the NHANES 1999–2002 cohort. Due to the lack of quantitative measures of body composition (i.e., DXA or BIA) in the 2011–2014 cohort, a different approach was adopted to operationalize the definition of SO. This was based on WC data as a measure of central obesity and HGS data were used as functional parameters of sarcopenia, allowing to test the predictive value of these two user-friendly and affordable measurements. In fact, the LWC-LHGS and HWC-LHGS phenotypes were significantly associated with a higher risk of cognitive impairment, which may suggest a greater predictive role of low muscle function. The results also revealed that the highest tertile for the FM: muscle strength ratio (higher FM and lower muscle strength) was associated with a greater risk of cognitive impairment, suggesting that the WC-HGS Ratio may represent a better risk predictor compared to the individual measurement of WC or HGS. A previous study used a similar approach by evaluating the association of the handgrip/bodyweight ratio (HGS/BW) with the risk of metabolic syndrome in 5,026 participants (mean age 51.2 years) and found that participants in the lowest tertile of HGS/BW had a higher risk of metabolic impairment (55). To our knowledge, no study has so far evaluated the association of the WC-HGS Ratio with cognitive function. However, the association of SO with cognitive function has been explored in other studies, which overall found a superior predictive value of the SO phenotype for risk of cognitive impairment compared to obesity or sarcopenia alone (16, 17, 19–22, 53, 56, 57). However, studies showed large differences in the definitions of SO, population characteristics, study design and methods of body composition, and cognitive function assessment, which may explain some of the differences between studies regarding the associations with various measures of cognitive domains. Five studies (16, 21, 22, 56, 57) used BIA to assess body composition followed by DXA which was used in three studies (19, 20, 53). Three studies (16, 19, 53) used HGS as a functional measure of sarcopenia which was combined in two studies (16, 53) with measurements of FFM obtained from BIA or DXA. The only prospective analysis used data from 5822 older participants recruited as part of the National Health and Aging Trends study. Baseline data on HGS and BMI and prospective data on cognitive function collected over an 8-year follow-up were included in the analysis; the study found that the risk of impaired cognitive function was not significant in obesity alone (HR 0.98; 95% CI 0.82–1.16), but was significantly higher in sarcopenia (low HGS, HR 1.60; 95% CI 1.42–1.80) and SO (low HGS and high BMI, HR 1.20; 95% CI 1.03–1.40) (17). Another paper used data from the NHANES 1999–2002 cohort (1127 older participants) to test the association between DSST scores and SO, which was based on waist circumference and DXA measurements of muscle mass (19). The analysis was stratified by age (60–69 and ≥70 years) and found that the SO was associated with lower DSST scores only in adults aged 70 years and over, which was not found in our study. The study also found an inverse relationship between HOMA-IT with DSST scores which accounted for ~20% of the association between SO and cognitive function (19). Three studies found a significant association between ASM/FM (22) (lowest tertile) and FM/FFM (56, 57) (highest tertile) ratios with impaired global (MoCA) or domain-specific (i.e., attention, language, visuospatial abilities, and immediate and delayed memory recall) cognitive functions.

The mediation analysis showed that CRP and HOMA-IR may account partially for the association between FM/FFM and TrFM/ASM ratios and DSST scores. However, if both CRP and HOMA-IR were entered in the mediation analysis, HOMA-IR was the only competitive mediator of the association between SO ratios and cognitive function. The role of inflammation in the pathogenesis of insulin resistance is known (58), which may suggest that insulin resistance could represent the "effector" mechanism linking SO to the deterioration of cognitive functions. Age-related cognitive impairment was independently associated with HOMA-IR (59) and was a significant mediator of the association of SO with DSST scores for subjects aged 70 years and over (19).

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 minimized the effects of potential confounding variables (i.e., demographics, comorbidity, blood pressure, physical activity, medications

related cognitive interactions, smoking, depression, alcohol use, and energy consumption) by including them in the models as covariates to obtain more accurate estimates. 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. 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. Conversely, in the 2011–2014 cohort depression was identified by using a validated depression screening questionnaire (Patient Health Questionnaire (PHQ)-9) (60, 61). 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 (62). 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.

Conclusions

This is the first study to test in two independent cohorts of older individuals the association of body composition phenotypes and different definitions of SO with global and domain-specific measures of cognitive function. Overall, to the best of our knowledge, SO was associated with a greater risk of cognitive impairment in both cohorts but SO definitions differed in their associations with cognitive impairment. This further emphasizes the need for a standardized 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.

Author contributions

MS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MS and UB conceived and designed the study. UB and MS conducted the analysis and wrote the manuscript. All authors contributed to the analysis, discussion, and interpretation of data, and reviewed/critically edited the manuscript. All authors have read and approved the final manuscript.

Disclosure statement

I.A.M. was a member of the UK Government Scientific Advisory Committee on Nutrition, the Mars Scientific Advisory Council, the Mars Europe Nutrition Advisory Board, the Nestle Research Scientific Advisory Board, the Novozymes Scientific Advisory Board, and was a Scientific Adviser to the Waltham Center for Pet Nutrition until 2020. On August 1, 2020, he became Professor Emeritus at the University of Nottingham and took up the post of Scientific Director of the Nestle Institute of Health Sciences in Lausanne, Switzerland, which terminated in August 2022. Other authors: no conflicts to declare.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The NHANES data are publicly available at https://wwwn.cdc.gov/Nchs/Nhanes.

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