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Body fat and components of sarcopenia relate to inflammation, brain volume, and neurometabolism in older adults

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ABSTRACT

Obesity and sarcopenia are associated with cognitive impairments at older age. Current research suggests that blood biomarkers may mediate this body-brain crosstalk, altering neurometabolism and brain structure eventually resulting in cognitive performance changes. Seventy-four older adults (60–85 years old) underwent bioimpedance body composition analysis, handgrip strength measurements, 8-Foot Up-and-Go (8UG) test, Montreal Cognitive Assessment (MoCA), blood analysis of interleukin-6 (IL-6), kynurenine, and insulin-like growth factor-1 (IGF-1), as well as brain magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS), estimating neurodegeneration and neuroinflammation. Normal fat% or overweight was associated with larger total gray matter volume compared to underweight or obesity in older adults and obesity was associated with higher N-acetylaspartate/Creatine levels in the sensorimotor and dorsolateral prefrontal cortex. Muscle strength, not muscle mass/physical performance, corresponded to lower kynurenine and higher N-acetylaspartate/Creatine levels in the dorsal posterior cingulate and dorsolateral prefrontal cortex. The inflammatory and neurotrophic blood biomarkers did not significantly mediate these body-brain associations. This study used a multimodal approach to comprehensively assess the proposed mechanism of body-brain crosstalk.

1. Introduction

Age-related cognitive decline (i.e. cognitive aging) is one of the major concerns of the presently aging society (Kronschnabl et al., 2021). Poor cognitive function is associated with a loss of independence (Tucker-Drob, 2019; Zhu et al., 2008), social withdrawal (Sartori et al., 2012), and decreased quality of life (Stites et al., 2018). Even mild declines in cognitive abilities can impel an individual to alter his/her activities of daily living, and may lead to frustrations (Sartori et al., 2012). It seems inevitable that the big majority of our population will someday experience functional deficits due to cognitive aging (Petersen, 2011). However, there is a large interindividual variability in the age at which people start to experience these functional deficits (Nyberg et al., 2020; Tucker-Drob, 2019). This interindividual variability can be explained by genetic and environmental risk factors. Importantly, it has been reported that around 1 in 3 cases of Alzheimer's disease worldwide could be

Abbreviations: ^{1}H-MRS, proton magnetic resonance spectroscopy; BMI, body mass index; CRP, C-reactive protein; DLPFC, dorsolateral prefrontal cortex; DPCC, dorsal posterior cingulate cortex; ELISA, enzyme-linked immunosorbent assay; EWGSOP, European Working Group on Sarcopenia in Older People; FDR, false discovery rate; fat%, body fat percentage; FFM, fat-free mass; FWHM, full width at half maximum; Glx, glutamate-glutamine complex; GMV, gray matter volume; HPC, hippocampal cortex; ICC, intraclass correlation coefficient; IFN-γ, interferon-γ; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; LCModel, linear combination of model spectra; mIns, myoinositol; MoCA, Montreal Cognitive Assessment; MPRAGE, magnetization prepared gradient echo; MTC, medial temporal cortex; PRESS, Point RESolved Spectroscopy; SM1, primary sensorimotor cortex; SMI, skeletal muscle mass index; tCho, total choline; tCr, total creatine; tNAA, total N-acetyl aspartate; TNF-α, tumor necrosis factor-α; 8UG, 8-Foot Up-and-Go.

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prevented if we would optimize modifiable risk factors (Livingston et al., 2020; Norton et al., 2014). Two well-known modifiable risk factors of cognitive decline are obesity and sarcopenia. Both are important contributors to functional deficits at older age, as they are not only risk factors of cognitive decline, but also directly contribute to physical disabilities (Baumgartner, 2000; Chang et al., 2016; Cipolli et al., 2019; Cournot et al., 2006; Mrak, 2009; Peng et al., 2020; Sartori et al., 2012; Tolea and Galvin, 2015). A better understanding of the link between cognitive aging and modifiable risk factors, such as obesity and sarcopenia, may direct researchers to specific targets for preventing cognitive aging.

Obesity is a major health problem in current society. The prevalence of overweight and obesity is increasing worldwide (Blüher, 2019). Especially in Europe (Peralta et al., 2018) and the USA (Ogden et al., 2014), obesity prevalence in older adults has reached epidemic proportions. Of importance, a longitudinal study discovered that middle-aged obese adults suffer accelerated cognitive aging when compared with non-obese counterparts over a 10-year follow-up period (Singh-Manoux et al., 2012). It has been suggested that the link between obesity and cognitive decline is mediated by a chronic state of inflammation (Beilharz et al., 2016; Tang et al., 2015). Indeed, adipose tissue is found to be one of the largest sources of inflammatory markers in the human body (Woods et al., 2012; Yudkin, 2007). These inflammatory markers readily cross the blood-brain barrier and may result in neuroinflammation (Agudelo et al., 2014; Banks et al., 1995; Fukui et al., 1991). Neuroinflammatory processes can subsequently damage neurons in the central nervous system, resulting in a loss of neural integrity or density (i.e. neurodegeneration), eventually leading to cognitive decline (Bourgognon and Cavanagh, 2020; Sartori et al., 2012; Scheiblich et al., 2020). To estimate the level of neuroinflammation and neurodegeneration in vivo, proton magnetic resonance spectroscopy (^{1}H-MRS) can be adopted. However, only a few studies have used this technique in the context of obesity. For example, Gonzales et al. (2012), reported that a higher body mass index (BMI) was associated with higher levels of neuroinflammation, as expressed by an elevation of the ratio of myoinositol (mIns) to creatine (Cr), in the occipitoparietal cortex, which was indirectly related to decreased memory performance (Gonzales et al., 2012). Another ^{1}H-MRS study example was published by Coplan et al. (2014), who discovered that a higher BMI was associated with decreased levels of neural integrity, as expressed by reduced levels of N-acetylaspartate (NAA) in the hippocampus (Coplan et al., 2014). Neuroinflammation is also considered to explain the increased rate of age-related brain volume loss in the context of obesity, as reviewed by García-García et al. (2022). However, the authors of this review only refer to animal studies and not to ^{1}H-MRS research when it comes to neuroinflammation. Anyway, the negative effects of obesity on brain volume have been described by multiple longitudinal magnetic resonance imaging (MRI) studies (Bobb et al., 2014; Shaw et al., 2017). Of interest, a meta-analysis of 10 cross-sectional studies reported lower brain gray matter volume (GMV) of the left, middle, and right inferior frontal gyrus, the left precentral gyrus, the left middle temporal cortex, and the cerebellum, while there was a larger GMV of the left cuneus, left middle frontal gyrus, left inferior occipital gyrus and corpus callosum in obese young and older adults (Herrmann et al., 2019). Another longitudinal study using whole-body MRI reported that specifically liver fat, muscle fat infiltration, and weight-to-muscle ratio were predictors of accelerated brain aging (Beck et al., 2022).

Sarcopenia is another health concern with increasing societal prevalence (Ethgen et al., 2017). Importantly, older adults with sarcopenia are six times more likely to have a combined cognitive and physical impairment compared to healthy controls (Tolea and Galvin, 2015). Tolea and Galvin (2015) discovered that lower muscle strength, and not muscle mass, was related to cognitive impairment (Tolea and Galvin, 2015). Other studies have also recognized muscle strength as a better predictor of other adverse outcomes, which has led to the decision to revise the 2010 European Working Group on Sarcopenia in Older People (EWGSOP) definition of sarcopenia. In the new definition that was published in 2019, muscle strength is now the principal determinant of sarcopenia instead of muscle mass (Cruz-Jentoft et al., 2019). There is abundant evidence that muscle strength and muscle mass should be considered separate health markers that are regulated differently (Clark and Manini, 2008). This warrants the need to investigate each of the components of sarcopenia separately. Similar to obesity, sarcopenia has also been linked to chronic inflammation (Beyer et al., 2012; Tuttle et al., 2020). However, to our knowledge, no human ^{1}H-MRS studies exist that have examined the link between (components of) sarcopenia and neuroinflammation. Concerning the link between (components of) sarcopenia and brain volume, the literature is also limited. However, some studies have shown a positive correlation between brain volume and muscle mass (Burns et al., 2010; Kilgour et al., 2014) or physical performance assessed as gait speed (Rosano et al., 2005; Silbert et al., 2008). We also found one longitudinal study with a 4-year follow-up that showed associations between sarcopenia at baseline and increased parietal GMV atrophy, lower muscle strength at baseline and larger age-related decreases in total brain GMV, and lower muscle mass at baseline and larger age-related decreases in total GMV, frontal GMV, and occipital GMV (Yu et al., 2021). In addition to its link with inflammation, sarcopenia has also been associated with lower levels of insulin-like growth factor-1 (IGF-1) (Bian et al., 2020). This hormone is considered to be critical for neuroplastic processes in the adult brain (Frater et al., 2018; Vints et al., 2022b). Like the age-related increases in inflammation in our blood circulation, the age-related reduction in circulating IGF-1 levels is also suggested to play a role in cognitive aging (Frater et al., 2018).

The aim of the current study was to provide a comprehensive overview on the proposed mechanisms underlying body-brain crosstalk in the context of obesity and sarcopenia (Fig. 1) by assessing how (1) body fat percentage (fat%), and (2) muscle strength, muscle mass, and physical performance are associated with serum inflammatory and neurotrophic factor levels, markers of neuroinflammation and neural integrity, total and regional brain GMV and general cognitive function. In accordance with the literature provided above, we hypothesized that high fat%, low muscle strength, low muscle mass, and poor physical performance would be associated with high serum inflammatory and low neurotrophic factor levels, high markers of neuroinflammation and low neural integrity, low total and regional brain volumes, and poor general cognitive function (Gonzales et al., 2012; Herrmann et al., 2019; Scheiblich et al., 2020; Tang et al., 2015; Tolea and Galvin, 2015; Yudkin, 2007). Finally, we predicted that the blood serum biomarkers would be possible mediators of the relationship between the body and brain/cognitive function. We hypothesized that the neurotrophic marker insulin-like growth factor-1 (IGF-1) would play a role in mediating the relationship between strong older adults or older adults with large muscular volume and markers of brain health or high cognitive test scores (Bian et al., 2020; Frater et al., 2018; Vints et al., 2022b), while we hypothesized that the inflammatory blood biomarkers interleukin-6 (IL-6) and kynurenine would play a role in mediating the relationship of high fat%, poor strength, low muscle mass or poor physical performance with poor brain health measures and poor cognitive performance (Beyer et al., 2012; Sartori et al., 2012; Tang et al., 2015; Vints et al., 2022a).

To the best of our knowledge, we are the first to profoundly explore the mediating effect of blood biomarkers on brain health and general cognition in the concept of the link between fat% and the brain and the link between components of sarcopenia and the brain in older adults. This paper may lead to a better understanding of the

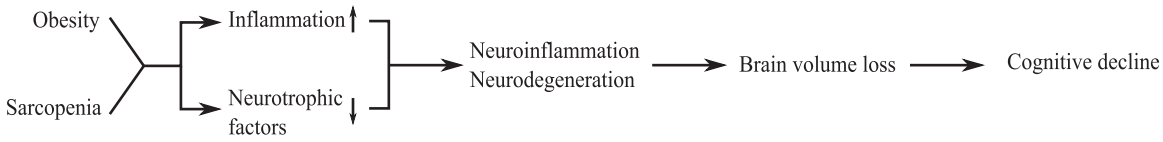

Fig. 1. Schematic hypothetical framework of the relationship between obesity or sarcopenia and cognitive aging via alterations in blood biomarkers, neurometabolites, and brain volume.

influential effect of different aspects of body composition and muscular fitness on brain health and cognitive function. Ultimately, this knowledge may serve in designing treatment strategies aiming to prevent age-related cognitive decline.

2. Material and methods

2.1. Participants and setting

Participants were 74 apparently healthy male and female adults aged from 60 to 85 years old that were from the same pool of participants as in the study of Vints et al. (2022a) recruited as described previously (Vints et al., 2022a). The exclusion criteria included a diagnosis of a psychiatric or neurological disorder or the use of centrally acting medication in the last 5 years. Participants were physically healthy and able to perform 10 sit-ups, but they did not participate in any regular exercise program in the last 6 months. We excluded participants with current alcohol or drug abuse. Additionally, excluded participants were those with diabetes mellitus, or with oncologic disorders, or a history of chemotherapy treatment. At last, we followed the exclusion criteria for MRI scanning derived from a checklist provided by the department of radiology at the Lithuanian University of Health Science. This list excluded participants with MRI-incompatible implants, claustrophobia, or a weight over 130 kg. Participants could voluntarily withdraw from the study at any time. The study was approved by the Kaunas Regional Biomedical Research Ethics Committee (No. BE-10–7) and a written informed consent was obtained from all participants prior to their inclusion in the study.

2.2. Demographic characteristics

All participants were asked to report age, sex, smoking status, and educational level (i.e. basic education, secondary education, or higher education). Furthermore, the Montreal Cognitive Assessment (MoCA) test was conducted by a qualified health care specialist in psychiatry (co-author SK) to evaluate the cognitive status of the participants. The MoCA test is a reliable and sensitive screening tool to evaluate the risk of mild cognitive impairment in the geriatric population (Bruijnen et al., 2020; Nasreddine et al., 2005). It consists of an assessment of 7 cognitive domains: executive functioning/visuospatial abilities; naming; memory; attention, language; abstract reasoning; and orientation. The maximum total score is 30 points, where a higher score indicates better cognitive functioning. As indicated on the MoCA test instructions, 1 point was added to the score if a participant did not complete a higher education. Nasreddine et al. (2005) proposed that total MoCA scores of 25 or below indicate a high risk for mild cognitive impairment (Nasreddine et al., 2005). Based on this cutoff, 52.1% of the included participants had mild cognitive impairment. The lowest MoCA test score in our study was 19. None of the included participants were considered to have Alzheimer's dementia, based on MoCA test cut-offs and clinical evaluation by a psychiatrist (co-author SK).

At last, we assessed the participants' body mass index (BMI) and measured their body fat percentage (fat%) and fat-free mass using leg-to-leg bio-impedance analysis (BIA, Tanita TBF-300-A). Standing leg-to-leg BIA, also called bipolar or foot-to-foot BIA, measures impedance through an electronic pathway of the lower extremities, and is widely used as an easy, noninvasive, and inexpensive method to estimate whole-body composition (Wu et al., 2015). It is considered a valid method for the estimation of total body fat-free mass (Cable et al., 2001) and total body fat% (Ritchie et al., 2005). Analysis with fat% is considered an improved phenotypic characteristic over BMI when assessing participants' health (Gallagher et al., 2000). For non-Asian adults aged 60 years and over, a healthy fat% lies between 24% and 36% for women and 13% and 25% for men. Any values below correspond to underweight, and above correspond to overweight. Obesity as a measure of fat% starts from 42% for women and 30% for men (Gallagher et al., 2000).

2.3. Functional assessment

Based on the revised European Working Group on Sarcopenia in Older People 2019 (EWGSOP2) criteria (Cruz-Jentoft et al., 2019), participants were categorized in three groups, (1) probable sarcopenia (i.e. low muscle strength), (2) confirmed sarcopenia (i.e. low muscle strength + low muscle quality or quantity) or (3) severe sarcopenia (i.e. low muscle strength + low muscle mass + low physical performance). We used handgrip strength of the right hand as a measure for muscle strength, BIA-estimated skeletal muscle mass index (SMI, see formula below) as a measure of muscle quantity, and the 8UG test as a measure of physical performance, using cut-off values presented in Table 1 (Cruz-Jentoft et al., 2019).

2.3.1. Measures of muscle mass

Skeletal muscle mass index (kg/m²): leg-to-leg BIA was used to estimate the SMI. First, absolute skeletal muscle mass was calculated using the BIA equation from a previous study (Janssen et al., 2000): Absolute skeletal muscle mass (kg) = [0.401 × (height²/resistance) + (3.825 × sex) − (0.071 × age) + 5.102], where height is in cm; resistance is in ohms; for sex, men = 1 and women = 0; and age is in years. Absolute skeletal muscle mass measured with leg-to-leg BIA was shown to provide accurate results on a group level (Bosy-Westphal et al., 2008). Second, SMI was calculated by dividing absolute skeletal muscle mass by height in meters squared (kg/m²) (Chien et al., 2008). Third, we also reported the fat-free mass (kg) as given by the BIA.

2.3.2. Measures of muscle strength

Handgrip strength (kg): Participants' handgrip strength of the right hand was measured using a dynamometer (JAMAR 11940248 Adjustable Hand Grip Strength Testing System) in standing position. The grip size was adjusted so that the second joint of the index finger was at a 90° angle on the handle. After a first try at submaximal effort, participants were instructed to squeeze the handle as hard as they can. The test was performed 2 times with 1 min rest period between trials, and the highest value was used for analysis.

Table 1
Variables and cut-off values for diagnosis of sarcopenia

Criterion	**Measurement method**	**Cut-off points by sex**
Muscle strength	Handgrip strength	-Men: < 27.0 kg-Women: < 16.0 kg
Muscle mass	BIA-predicted SMI	-Men: ≤8.9 kg/m²-Women: ≤6.4 kg/m²
Physical performance	8-foot Up-and-Go test (2.44 m)	-Men: > 9.2 s-Women: > 10.0 s

Cut-off values were based on EWGSOP2 consensus recommendations (Cruz-Jentoft et al., 2019). Cut-off values for handgrip strength were derived from the study of Dodds et al. (2014). The EWGSOP2 describes a cut-off for SMI derived from a dual-energy X-ray absorptiometry (DXA) study, while in our study BIA was used to estimate SMI. They also suggest the 3m Timed Up-and-Go test, while we used the American alternative, the 8-foot Up-and-Go test. Therefore, we calculated the cut-off values for the BIA-predicted SMI and 8-foot Up-and-Go test from the studies of Janssen et al. (2000) and Rikli and Jones (1999) respectively, according to the EWGSOP2 recommendation to place cut-off points at two standard deviations from the mean reference value.
Key: BIA, bio-impedance analysis; EWGSOP2, European Working Group on Sarcopenia in Older People; SMI, skeletal muscle mass index

2.3.3. Measures of physical performance

8-Foot Up-and-Go test (s): the 8UG test was performed as described for the Fullerton Fitness Test and assessed a person's agility and dynamic balance (Kirschke et al., 2006). The test result is the time required for a person to rise from an armless chair, walk 8 feet (2.44 m), turn around a cone, and return to the sitting position as fast as possible. Participants were given two trials with 1 min rest period in seated position, and the trial with the shortest time was used for analysis.

In addition, we described self-reported physical activity level based on self-reported light/moderate/high intense exercise time per week. Based on the time participants described to perform a specific type of physical activity, the total calories burned during exercise per week were estimated. The following equation was used based on previous research from Sjostrom et al. (2005): Total kcal/week burned during exercise = the sum of days performing light/moderate/vigorous intense exercise × average time/day performing light/moderate/vigorous intense exercise × F, where F is 8.0 for vigorous intense exercise, 4.0 for moderate intense exercise, and 3.3 for light intense exercise. Total weekly kcal burned with exercise was used to estimate the physical activity level of the participants, with participants burning < 600 kcal/week defined as sedentary, 600–3000 kcal/week defined as moderately physically active, and participants burning > 3000 kcal/week defined as highly physically active (Sjostrom et al., 2005).

2.4. Blood serum analysis

Blood samples were drawn between 9 a.m. and 1 p.m. by a qualified medical professional. Blood was collected at the antecubital vein in 5 mL serum separator tubes. Immediately after collection, tubes were gently inverted 8–10 times and allowed to clot for 30 min at room temperature. Then, the tubes were centrifugated at 4000*g* for 15 min. Finally, blood serum was aliquoted into 1.5 mL polypropylene tubes and stored at −80 °C in the refrigerator compartment of the laboratory of the Lithuanian Sports University until further analysis with enzyme-linked immunosorbent assay (ELISA). After completion of the study, ELISA tests for IL-6, kynurenine, and IGF-1 were analyzed with a spectrophotometer (Spark 10M, Tecan Group Ltd., Zürich, Switzerland) by an experienced lab technician.

IL-6 levels were analyzed using a commercially available ELISA kit purchased from DIAsource ImmunoAssays S.A., Belgium (KAP1216). The lower limit of detection was 2 pg/mL.

Kynurenine levels were analyzed using a commercially available ELISA kit purchased from MyBiosource, Inc., USA. The lower limit of detection was 45.7 ng/mL.

IGF-1 levels were measured using a commercially available ELISA kit purchased from IBL International, GMBH, Germany (MD58011). The lower limit of detection was 0.03 ng/mL.

2.5. Brain imaging and ^{1}H-MRS

Whole brain MRI and ^{1}H-MRS scanning was performed using a 3 Tesla Skyra scanner (Siemens Healthineers, Erlangen, Germany) with a 32-channel receiver head coil. Total scanning duration was 90 min per participant.

Total and regional gray matter volumes (GMV) were calculated from 3D magnetization prepared gradient echo (MPRAGE) images acquired from high-resolution T1-weighted (T1W) structural MRI (repetition time (TR) = 2200 ms, echo time (TE) = 2.48 ms, 0.9 × 0.9 × 1.0 mm³ voxels, field of view: 230 × 256 mm, number of sagittal slices = 176) using the FreeSurfer software v7.1.1 (Harvard, MA, USA, http://surfer.nmr.mgh.harvard.edu/). Regions of interest were the dorsal posterior cingulate cortex (DPCC), left and right hippocampal cortex (HPC), left middle temporal cortex (MTC), left primary sensorimotor cortex (SM1) and right dorsolateral prefrontal cortex (DLPFC). A detailed description of the FreeSurfer regions was presented previously in Vints et al. (2022a).

Regional voxel-based neurometabolite levels were calculated from ^{1}H-MRS spectra using a Point RESolved Spectroscopy (PRESS) sequence (TR = 2000 ms, TE = 30 ms, number of averages = 128, spectral bandwidth = 2000 Hz, data size = 1024 points) with chemical shift selective water suppression (sequence svs_se_30). A detailed description of the ^{1}H-MRS methods is presented in Appendix A based on the minimum reporting standards of the MRSinMRS experts' consensus recommendations (Lin et al., 2021). Voxels were placed on the DPCC, left HPC, left MTC, left SM1, and right DLPFC; see Fig. 2. A detailed description of the voxel position was described previously in Vints et al. (2022a). Voxel sizes were: (i) 1.6 × 1.6 × 1.6 cm³ in the DPCC, left SM1 and right DLPFC voxels, (ii) 20 × 12 × 16 cm^3 in the left MTC, and (iii) 26 × 12 × 12 cm^3 in the left HPC. Voxel-specific shimming was performed using automated B0-field mapping followed by manual adjustment to reduce the water signal full width at half maximum (FWHM) below 15 Hz. The MR spectra were processed using the linear combination of model spectra (LCModel, version 6.3.1-R). In total, 340 spectra (i.e. 68 participants × 5 voxels of interest) were acquired. Only spectra with FWHM < 15 Hz, signal-to-noise ratio > 5 were considered of sufficient quality to be included. All included neurometabolites were quantified with a Cramér-Rao lower bound < 20%. ^{1}H-MRS spectra were visually checked to ensure the absence of artifacts prior to quantification. This resulted in the elimination of 57 spectra (8.4%). The number of participants (n = 74) from whom good quality measurements could be attained ranged from 56 (75.7%) for the left MTC to 67 (90.5%) for the right DLPFC. The number of retained spectra per voxel of interest is presented in Supplementary Table A.1. ^{1}H-MRS quantifiable neurometabolites were (1) total NAA (tNAA) composed of N-acetylaspartate and N-acetylaspartylglutamate, (2) total creatine (tCr) composed of creatine and phosphocreatine, (3), total

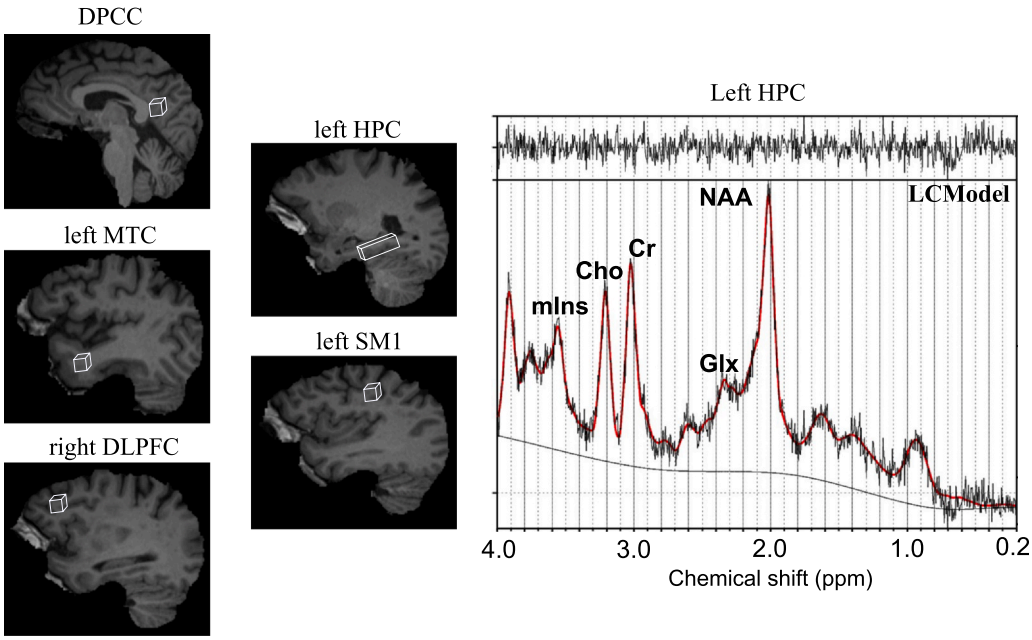

Fig. 2. Example voxel positions and spectra from a representative participant Voxel positions are presented on the left side of the figure. Raw (black curve) and fitted (red curve) spectra from LCModel are illustrated for the left HPC on the right side of the figure. Abbreviations: Cho, total choline; Cr, creatine + phosphocreatine; DLPFC, dorsolateral prefrontal cortex; DPCC, dorsal posterior cingulate cortex; Glx, glutamate-glutamine complex; HPC, hippocampal cortex; mIns, myoinositol; MTC, medial temporal cortex; NAA, N-acetyl aspartate; SM1, primary sensorimotor cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

choline (tCho) composed of phosphorylcholine and glycerophosphocholine, (4) mIns, and (5) Glx composed of glutamate and glutamine. Both water-referenced levels of tNAA, tCr, tCho, mIns, and Glx and ratios relative to tCr were calculated for each voxel location. For tNAA also, the ratio relative to mIns was calculated. The main outcome measures were tNAA/tCr, as a marker of neural integrity or neural density, mIns/tCr, as a marker of glial cell proliferation or neuroinflammation, and the ratio of tNAA/mIns. Results from analyses with the other neurometabolites (namely tCho and Glx) are only presented in Appendix A. We noted that in general the same conclusions could be drawn from the relative and absolute, water-referenced, neurometabolite levels. Therefore, observations including the water-referenced neurometabolite levels are also only presented in Appendix A.

2.6. Statistical analysis

Statistical analysis was performed using SPSS Statistics version 27 (IBM Inc, Chicago USA). The data were first checked for extreme outliers (defined as lying more than 3 times interquartile range from the mean) and normal distribution (defined as kurtosis and skewness between −2 and +2 and checked graphically using PP plots and histograms) (George and Mallery, 2010). IL-6 levels were log transformed, as they did not meet the normality assumption.

2.6.1. Investigation of sex differences

To evaluate the effect of sex differences on nominal variables, we used $\chi 2$ or Fisher Exact statistics. To compare continuous variables between sexes, a two-sided independent t-test was performed.

2.6.2. Investigations of body-brain or body-blood biomarker associations

Multiple linear regression adjusted for age and sex was used to assess how fat% was related to serum levels of IL-6, kynurenine and IGF-1, brain total and regional GMV measures and cognition. In addition, each association with brain volume measurements in this paper was adjusted for intracranial volume. Assessments of relationships with SMI were not adjusted for age and sex, as the formula used to calculate absolute skeletal muscle mass already contains these factors. Associations with right handgrip strength as well as with performance on the 8UG test were adjusted for age, sex, and body fat%. Appendix A also includes these associations adjusted for age, sex, and BMI.

2.6.3. Mediation analysis

We investigated if differences in blood biomarker levels could be part of the underlying mechanism responsible for relationships between body and brain outcome measures by using mediation analysis. Blood biomarkers that showed significant associations with fat%, handgrip strength, SMI, or the 8UG test result (significant body-blood biomarker associations) were considered possible mediators of the significant associations between fat%, handgrip strength, SMI or 8UG test results, and brain volume or neurometabolite levels. Mediation analysis was performed using model 4 of the SPSS macro named PROCESS, developed by Hayes (2022), including age, sex, and fat% as covariates. This macro was used to calculate the indirect effect of the blood biomarker on the body-brain interaction. The indirect effect was presented as a 95% confidence interval determined using 5000 stratified bootstrap samples. Effect sizes were R^2_{med} values, representing the proportion of variance attributed to the indirect effect by the mediator, which is calculated by subtracting the R^2 of the model including the mediator by the R^2 of the model without the mediator (Fairchild et al., 2009). The direct effects between the variables included in the mediation model were derived from the multiple regression analysis described in Section 2.6.2.

2.6.4. Interpretation of statistical significance

For the purpose of this exploratory study, *p*-values below 0.05 were considered statistically significant. In addition, we tested if these *p*-values survived correction for multiple testing with false discovery rate (FDR) analysis (Benjamini and Hochberg adjustment) (Benjamini and Hochberg, 1995). The FRD procedure was done

Table 2
Participant characteristics and sex differences

	Men (n = 34)	Women (n = 40)	Total (n = 74)	*p*-value
Age	70.8 (6.0)	68.2 (6.1)	69.4 (6.2)	0.069
Montreal Cognitive Assessment	25.0 (3.1)	25.3 (2.7)	25.2 (2.9)	0.747
Education				0.953
Higher	26 (35.6%)	31 (42.5%)	57 (78.1%)	
Secondary	7 (9.6%)	7 (9.6%)	14 (19.2%)	
Basic	1 (1.4%)	1 (1.4%)	2 (2.7%)	
Smoker	1 (1.4%)	2 (2.7%)	3 (4.1%)	0.562
Body mass index (kg/m²)	28.6 (5.4)	27.5 (4.5)	28.0 (4.9)	0.361
Fat%	26.3 (8.7)	35.8 (7.8)	31.4 (9.4)	< 0.001***
Sarcopenia	0 (0%)	0 (0%)	0 (0%)	NA
Possible sarcopenia	1 (1.4%)	2 (2.9%)	3 (3.3%)	
Confirmed sarcopenia	0 (0%)	0 (0%)	0 (0%)	
Severe sarcopenia	0 (0%)	0 (0%)	0 (0%)	
Skeletal muscle mass index (kg/m²)	10.9 (1.3)	8.5 (1.0)	9.6 (1.7)	< 0.001***
Absolute skeletal muscle mass (kg)	32.9 (4.6)	22.2 (2.8)	27.1 (6.6)	< 0.001***
Fat-free mass (kg)	62.5 (7.0)	44.8 (3.6)	52.9 (10.4)	< 0.001***
Handgrip strength (kg)	42.4 (6.1)	25.0 (4.5)	31.8 (10.0)	< 0.001***
8-Foot Up-and-Go test (s)	4.9 (1.4)	4.7 (0.9)	4.8 (1.1)	0.273
Self-reported kcal/week burned with physical activity	5600 (4025)	3534 (2512)	4353 (3322)	0.273
Estimated physical activity level				0.754
Sedentary	2 (2.8%)	3 (4.2%)	5 (6.9%)	
Moderately active	12 (16.7%)	17 (23.6%)	29 (39.2%)	
Highly active	19 (26.4%)	19 (26.4%)	38 (51.4%)	

Continuous parameters are expressed as mean values (standard deviation); categorical parameters are expressed as n (% of total). *$p < 0.05$, ** $p < 0.01$, ***$p < 0.001$ (not FDR corrected). Key: NA, not applicable.

multiple times for each of the independent variables (fat%, right handgrip strength, SMI, and 8UG test) for all *p*-values presented in Supplementary Tables A.2–A.17. It should be noted that the results surviving the multiple testing adjustment are strong, whereas interpretation of the remaining results should be made with caution. The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials, see Appendix A.

3. Results

3.1. Participant characteristics

Participant characteristics are described in Table 2. The difference between sexes found for fat%, SMI, absolute skeletal muscle mass, fat-free mass, and handgrip strength survived FDR correction for multiple testing. Of all 74 participants, only 1 man and 2 women were diagnosed with probable sarcopenia according to the EWGSOP2 criteria, based on low muscle strength. None of the participants was diagnosed with confirmed sarcopenia. In total, 3 participants scored below the sarcopenia cut-off level for muscle quantity measured as SMI with BIA and 1 scored above the sarcopenia cut-off time for physical performance based on the 8UG test. Of note, multiple linear regression analysis showed that higher fat% was correlated with a higher right handgrip strength ($p = 0.022$) after adjusting for age and sex, but with a lower SMI ($p = 0.017$).

3.2. Higher fat% correlates with decreases in brain volume and ^{1}H-MRS markers of neural integrity

Multiple linear regression analysis did not reveal any significant correlations between fat% and serum IGF-1, IL-6 or kynurenine levels, between fat% and brain volume, nor between fat% and MoCA scores, see Table 3 and Supplementary Table A.2. However, total GMV seemed to be non-linearly related to fat%. Graphical representation showed that participants with underweight based on measures of fat% (Gallagher et al., 2000) in our study (n = 2) have lower total GMV, indicating there is most probably a hyperbolic relationship between fat% and total GMV, see Fig. 3. Therefore, we repeated the linear analysis after excluding the 2 participants that fell into the underweight category. After exclusion of the two underweight participants, higher levels of fat% were associated with lower total GMV ($p = 0.021$), right HPC GMV ($p = 0.005$), and left MTC GMV ($p = 0.040$). The negative association between fat% after exclusion of the two underweight participants and total GMV, right HPC GMV and left MTC GMV survived the FDR correction for multiple testing.

Some neurometabolite levels were associated with fat% in specific brain regions. The most notable was the significant association between higher fat% and lower tNAA/tCr levels in 3 of the 5 regions of interest, a negative association for the left SM1 and right DLPFC, but a positive association for the left MTC, see Table 4 and Supplementary Table A.3. None of these significant results survived correction for multiple testing with the FDR procedure.

Table 3
How fat%, skeletal muscle mass index, right handgrip strength, and physical performance on the 8-Foot Up-and-Go test relate to brain gray matter volume and peripheral inflammation

		β	p-value
Fat%[a]	–	–	–
Fat% after exclusion of underweight participants[a]	Total GMV	−0.190	0.021
	Right HPC GMV	−0.374	0.005
	Left MTC GMV	−0.421	0.040
SMI	–	–	–
Right handgrip strength[b]	KynurenineTotal GMV	−0.4980.334	0.0450.018
8UG time o.e.[b]	–	–	–

Only statistically significant correlations (not FDR corrected) are presented. See Supplementary Tables A.2, A.4, A.8, and A.16 for all results. β represents the standardized regression coefficient. Additionally, associations with GMV were adjusted for total intracranial volume. Key: DLPFC, dorsolateral prefrontal cortex; DPCC, dorsal posterior cingulate cortex; GMV, gray matter volume; HPC, hippocampal cortex; mIns, myoinositol; MTC, medial temporal cortex; o.e., outlier excluded; SMI, skeletal muscle mass index; SM1, primary sensorimotor cortex; tCho, total choline; tCr, total creatine, tNAA, total N-acetyl aspartate; 8UG, 8-Foot Up-and-Go test.
[a] adjusted for age and sex.
[b] adjusted for age, sex, and fat%.

3.3. Higher skeletal muscle mass index is associated with decreased levels of neural integrity markers

Linear regression analysis found no correlation between SMI and IGF-1, IL-6 or kynurenine levels, nor between SMI and MoCA test scores. Multiple linear regression analysis did also not result in any significant associations between SMI and brain volume in any of the regions of interest, see Table 3 and Supplementary Table A.4. In contrast to what we expected, SMI was negatively associated with tNAA/tCr in the left SM1 ($p = 0.011$), see Table 4; for all results see Supplementary Table A.5. However, this result did not remain significant after correction for multiple testing with the FDR procedure.

3.4. Increased handgrip strength is associated with higher markers of neural integrity, and lower levels of peripheral and neural inflammatory markers

Multiple regression analysis showed that higher right handgrip strength was associated with lower kynurenine levels ($p = 0.045$) and larger total GMV ($p = 0.018$). Additionally, a positive association was found between right handgrip strength and tNAA/tCr levels in the DPCC ($p = 0.006$) and right DLPFC ($p = 0.022$) and between right handgrip strength and mIns/tCr levels in the left MTC ($p = 0.012$), see Tables 3 and 4, and Supplementary Tables A.8 and A.9. None of the results remained significant after correction for multiple testing with the FDR procedure.

3.5. Better physical performance on the 8UG test was associated with lower markers of neural integrity and higher levels of neuroinflammation

Before analysis of associations with 8UG test results, we excluded an extreme outlier. Results from multiple linear regression analysis before exclusion of the outlier are described in Supplementary Tables A.10-A.13. Multiple linear regression analysis did not show any significant associations between 8UG test time and serum biomarker levels or scores on the MoCA test, nor with any of the brain volumes after exclusion of this outlier. Associations with neurometabolic biomarkers showed that a longer time needed to complete the 8UG test was associated with higher levels of tNAA/mIns in the left MTC ($p = 0.039$), see Table 4 and Supplementary Tables A.16 and A.17. However, this result did not remain significant after correction for multiple testing with the FDR procedure.

3.6. The mediating effect of blood biomarkers on the body-brain crosstalk

Based on our hypotheses and the associations presented above, kynurenine was considered a possible mediator of the relationships between right handgrip strength and the following brain outcome measures: (1) total GMV (direct effect: b = 1577.053, $p = 0.018$), (2) tNAA/tCr levels in the DPCC (b = 0.007, $p = 0.006$) and right DLPFC (b = 0.006, $p = 0.022$), and (3) mIns/tCr levels in the left MTC (b = 0.010, $p = 0.012$). Our data showed that the indirect effect of the mediation analysis was not significant for all aforementioned outcome measures (all R^2_{med} values ≤0.011). Thus, we found no evidence for a mediating effect of kynurenine on any of the above-mentioned associations. The indirect and direct effects are presented in Fig. 4.

4. Discussion

This paper is original in its holistic view on examining body fat% and components of sarcopenia (muscle strength, muscle mass, and physical performance) and the relationship with brain volume, neurometabolite levels, and general cognition. The investigation was complemented with the assessment of inflammatory biomarkers (IL-6 and kynurenine) and the neurotrophic blood biomarker IGF-1 as possible mediators of the link between the body and brain. Mediation analysis did not confirm a significant indirect effect of the blood biomarkers on any of the outcomes and the nonsignificant findings had low effect sizes.

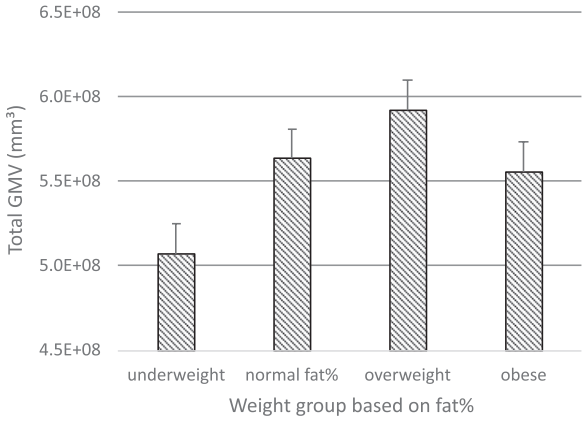

Fig. 3. How body fat percentage relates to total gray matter volume. The bars display the mean and the whiskers the standard errors of total gray matter volume (mm³) for underweight (n = 2), normal fat% (n = 29), overweight (n = 23), and obese (n = 17) participants, based on fat% based weight categories defined by Gallagher et al. (2000). The figure shows that underweight and obese participants have lowest gray matter volumes.

Our results suggest a hyperbolic relationship between fat% and total GMV, with lowest levels of total GMV in the two underweight participants included in our study. This is in line with a study that reported that participants with anorexia nervosa have lower GMV. Following weight gain, these participants showed a significant increase in their GMV in this study (Roberto et al., 2011). After excluding the two underweight participants from our study, higher fat% was significantly associated with lower total GMV, right HPC GMV, and left MTC GMV. These findings remained significant after correction for multiple testing. Similar results have also been reported in several other studies (Dekkers et al., 2019; Hamer and Batty, 2019; Opel et al., 2020). One of these studies reported that higher fat% is also associated with decreased subcortical GMV (Dekkers et al., 2019).

Table 4
How fat%, skeletal muscle mass index, right handgrip strength, and physical performance on the 8-Foot Up-and-Go test relate to neurometabolite levels

		β	p-value
Fat%[a]	tNAA/tCr l SM1	−0.362	0.016
	tNAA/tCr l MTC	0.330	0.044
	tNAA/tCr r DLPFC	−0.338	0.026
SMI	tNAA/tCr l SM1	−0.316	0.011
Right handgrip strength[b]	tNAA/tCr DPCC	0.647	0.006
	mIns/tCr l MTC	0.667	0.012
	tNAA/tCr r DLPFC	0.524	0.022
8UG time o.e.[b]	tNAA/mIns l MTC	0.305	0.039

Only statistically significant correlations (not FDR corrected) are presented. See Supplementary Tables A.3, A.5, A.9, and A.17 for all nonsignificant results. β represents the standardized regression coefficient. Key: DLPFC, dorsolateral prefrontal cortex; DPCC, dorsal posterior cingulate cortex; GMV, gray matter volume; HPC, hippocampal cortex; l, left; mIns, myoinositol; MoCA, Montreal Cognitive Assessment; MTC, medial temporal cortex; o.e., after exclusion of an influential outlier; r, right; SMI, skeletal muscle mass index; SM1, primary sensorimotor cortex; tCho, total choline; tCr, total creatine, tNAA, total N-acetyl aspartate; 8UG, 8-Foot Up-and-Go test.
[a] Adjusted for age and sex.
[b] Adjusted for age, sex, and fat%.

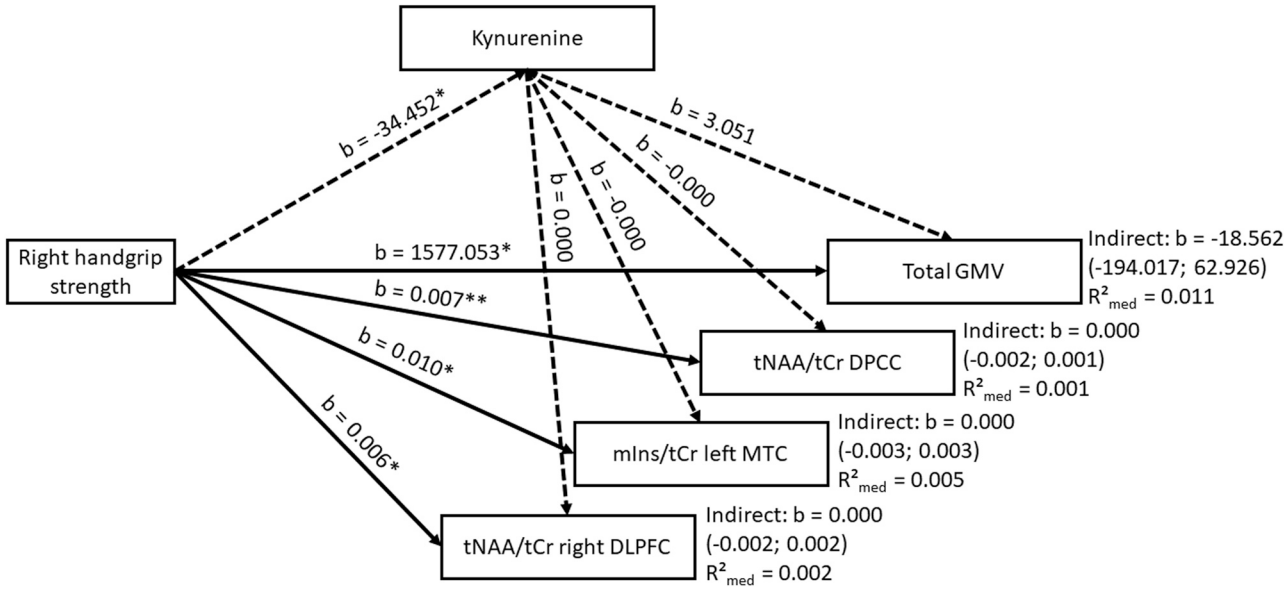

Fig. 4. Mediation model Effect of right handgrip strength on total GMV, tNAA/tCr DPCC, mIns/tCr left MTC and tNAA/tCr right DLPFC with kynurenine as a potential mediator. Solid arrows indicate direct pathways, the dashed arrows indicate the indirect pathways. Correlation coefficients with the respective *p*-values are presented, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (not FDR corrected). The correlation coefficient of the indirect effect is presented with a 95% confidence interval and R^2_{med} effect sizes, representing the proportion of variance attributed to the indirect effect by the mediator. Abbreviations: DLPFC, dorsolateral prefrontal cortex; DPCC, dorsal posterior cingulate cortex; GMV, gray matter volume; mIns, myoinositol; MTC, medial temporal cortex; tCr, total creatine, tNAA, total N-acetyl aspartate.

Our analysis revealed only weak associations between body composition, muscular fitness, and physical performance measures and the ^{1}H-MRS measures. None of our results survived the FDR procedure to correct for multiple testing. This may be due to the exploratory nature of this study, including a large number of statistical tests. Taken together, our observations provide evidence for plausible underlying effects of high body fat% and components of sarcopenia on brain health. However, our results not surviving correction for multiple testing, should be interpreted with caution, especially if they are not supported by further research, as will be discussed below.

An interesting finding from our study was that higher fat%, adjusted for age and sex, was associated with lower levels of neural integrity biomarker tNAA/tCr in the left SM1, and right DLPFC, but an increase in tNAA/tCr levels in the left MTC. Lower levels of neural integrity in overweight adults have also been described in another study, but this study only investigated tNAA levels in the HPC (Coplan et al., 2014).

At this point, we cannot explain why the opposite relationship was found concerning the fat% to tNAA/tCr relationship in the left MTC compared to the left SM1 and right DLPFC. Furthermore, we could not find the link we expected between fat% and peripheral or neural inflammation, and we did not discover an association with MoCA scores. In previous studies, obesity has been advocated as a possible cause of chronic low-grade inflammation (Mangge et al., 2014; Woods et al., 2012; Yudkin, 2007), associated with neuroinflammation in the hypothalamus, hippocampus, amygdala, cerebral cortex, and cerebellum in diet-induced obesity animal models (Beilharz et al., 2016; Guillemot-Legris et al., 2016; Lu et al., 2011; Tapia-González et al., 2011) and in the occipitoparietal cortex in a human ^{1}H-MRS study (Gonzales et al., 2012). Furthermore, obesity has been associated with cognitive decline after adjusting for age and educational level (Cournot et al., 2006), and with an increased risk of Alzheimer's disease (Mrak, 2009). Taken together, our observations suggest that while higher fat% has been linked to lower neuronal density, estimated by tNAA/tCr in the left SM1 and right DLPFC, the association with cognition and (neuro)inflammatory processes were less visible in our sample of older adults.

Muscle strength, as measured with right handgrip dynamometry, was associated with higher levels of tNAA/tCr in the right DLPFC, and the DPCC. This indicates that muscle strength is associated with higher levels of neural integrity in these brain regions (Castillo et al., 1998). Contrary to what we expected, mIns/tCr levels in the left MTC were positively related to handgrip strength, which may indicate a link between muscle strength and neuroinflammation (Castillo et al., 1998). To our knowledge, no other studies have previously reported a link between muscle strength and brain ^{1}H-MRS results, making it impossible to compare our results with existing literature.

Contradictory to the association with neuroinflammation in the left MTC, muscle strength was associated with lower serum IL-6 levels (adjusted for BMI, see Supplementary Table A.6.) and kynurenine levels (both when adjusted for BMI or fat%). IL-6 is considered an important mediator of inflammatory processes, being involved both in pro- and anti-inflammatory processes (Smith and Miles, 2000). It is typically elevated in a state of chronic inflammation, which is often seen at older age and is called 'inflammaging' (Ershler, 1993; Franceschi et al., 2000; Maggio et al., 2006). The negative relationship between handgrip strength and serum IL-6 is in line with previous studies (Visser et al., 2002). Furthermore, we reported previously that serum kynurenine is associated with ^{1}H-MRS signs of neurodegeneration and neuroinflammation (Vints et al., 2022a). Serum kynurenine levels are increased in a state of elevated inflammation, as is commonly found at an older age (Allison et al., 2017). It is considered a robust marker of inflammation, as the enzyme indolamine-2,3-dioxygenase, which converts tryptophan into kynurenine, is upregulated by a wide array of pro-inflammatory cytokines, including C-reactive protein (CRP), IL-1β, IL-6, IL-8, tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) and downregulated by anti-inflammatory cytokines like IL-4 and IL-10 (Allison et al., 2017; Chiarugi et al., 2001; Kindler et al., 2019; Lustgarten and Fielding, 2017; Pedraz-Petrozzi et al., 2020). Notably, aging-associated elevations of serum kynurenine have previously

been suggested to play a role in the development of sarcopenia in mice, possibly by increasing oxidative stress markers. In this study, administration of kynurenine caused a reduction in muscle protein synthesis, leading to a reduction in muscle size and mass (Kaiser et al., 2019). Furthermore, in adults with heart failure, plasma kynurenine levels were found to be elevated, and this elevation was negatively associated with handgrip strength (Konishi et al., 2016). The latter is in line with the findings from our study.

In contrast to muscle strength, we discovered that higher SMI and better performance on the 8UG test were associated with signs of neurodegeneration, as expressed by the negative association between SMI and levels of tNAA/tCr in SM1 and the positive association between time on the 8UG test and tNAA/mIns in the left MTC. This would indicate that having more muscle mass or being able to perform better on physical tasks would be detrimental for brain metabolism, which was contradictory to our hypothesis.

Overall, our results suggest that muscle strength rather than muscle mass or physical performance is positively associated with a healthy brain neurometabolism, even though we did not find an association between muscle strength and cognitive function as measured with the MoCA scale. Other studies reported that muscle strength in older adults is a good predictor of cognitive function, physical performance, and risk of falls. These studies also indicated that muscle strength is a better predictor of mental and physical health than muscle mass (Menant et al., 2017; Sui et al., 2020; Tolea and Galvin, 2015), which is in line with our findings. Menant et al. (2017), who measured muscle strength as a measure of maximal isometric knee extension force, even proposed that a simple muscle strength measurement is to be preferred as a predictor of health-related outcomes in older people instead of assessing if a person has sarcopenia (defined as the combination of low muscle strength and muscle mass by the EWGSOP2 (Cruz-Jentoft et al., 2019)).

Limitations of this study include the exploratory nature of our design. As a consequence, our results needed to be corrected for multiple testing with FDR analysis. Findings that did not survive FDR correction should be interpreted as possible trends. We should note that our sample size was relatively small for the elaborate statistical analysis performed, including mediation analysis. Furthermore, we only included older adults (60–85 years old) and excluded participants weighing more than 130 kg because this was an exclusion criterium for MRI scanning. This limits the interpretation of the results related to age and fat%. Moreover, we cannot make causal inferences about the effects of a change in age, fat%, or sarcopenia-related measures in this study. Finally, cognitive function was assessed only with the MoCA test, which should be considered a global cognition screening tool and cannot accurately be used to capture variations in cognitive subdomains.

In conclusion, our results in older adults suggest that a healthy fat % and muscle strength are associated with correlates of brain health, measured as larger brain volumes or neural integrity. Based on these findings, researchers may consider longitudinal studies to investigate if maintaining a healthy fat% and muscle strength throughout life may be part of preventive measures to combat cognitive decline at older age. We invite other researchers to investigate fat% and muscle strength in their relationship to neural integrity in older adults. From a mechanistical point of view, the role of serum kynurenine and other inflammatory blood biomarkers as possible mediators of both a decrease in muscle strength and neurodegeneration in older adults would be a relevant topic to investigate again in larger study cohorts.

Verification

This paper has not been previously published and is not currently under consideration in another journal. However, in the text, we refer to another study done on the same cohort of older adults that has already been published elsewhere. There is no conflict of interest for any of the contributing co-authors. All authors have approved of and have agreed to submit the manuscript to Neurobiology of Aging. The sponsor indicated in the manuscript was not involved in study design; collection, analysis and interpretation of the data; in writing of the report; nor in the decision to submit the article for publication.

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Author contributions

WV, SK, VC, OL, and NM contributed to conception and design of the study. WV, SK, SS, KV, RG, VC, OL, and NM were involved in data collection and/or analysis. WV performed the statistical analysis. WV wrote the first draft of the manuscript. SK, and UH wrote sections of the manuscript. WV and OL prepared the figures. RG, MP, OL, JV, and NM had a role in supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nerijus Masiulis reports financial support was provided by Research Council of Lithuania.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.02.011.

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