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Original Article

Effects of Sarcopenia and Frailty on Cognitive Function, Brain Volume, and Dementia Risk: A Prospective Cohort Study Based on UK Biobank

Seok-Jae Heo [1], **Min Young Chun** [2,3,4]

[1]Division of Biostatistics, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, Korea
[4]Yonsei Beyond Lab, Yongin, Korea

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Correspondence to
Min Young Chun
Department of Neurology, Yongin Severance Hospital, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea.
Email: myc5198@gmail.com

ORCID iDs
Seok-Jae Heo
https://orcid.org/0000-0002-8764-7995
Min Young Chun
https://orcid.org/0000-0003-3731-6132

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ABSTRACT

Background and Purpose: Despite the rising prevalence of sarcopenia, frailty, and dementia, their interrelationships remain unclear. This study investigated the associations of sarcopenia and frailty with cognitive function, brain structure, incident dementia, and their longitudinal changes.
Methods: This study included 390,903 participants aged 40–70 years from the UK Biobank. Sarcopenia was assessed using hand grip strength, muscle mass index, and gait speed; frailty was measured based on weight loss, exhaustion, physical activity, gait speed, and grip strength. Outcomes included cognitive test scores, magnetic resonance imaging-derived brain volumes, and incident dementia. Linear regression, Cox proportional hazards models, and linear mixed effects models were used.
Results: Frailty was associated with poorer performance across cognitive domains (all $p<0.05$), while sarcopenia was associated with slower reaction time ($p<0.001$). Frailty, but not sarcopenia, was associated with reduced cortical volume. Both conditions increased all-cause dementia risk: frailty with a dose-response gradient (hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.87 to 2.38) and particularly strong associations with vascular dementia (VaD, HR, 2.39; 95% CI, 1.85 to 3.07); sarcopenia with a moderate increase (HR, 1.53; 95% CI, 1.09 to 2.12). Longitudinally, sarcopenia—but not frailty—was associated with accelerated cognitive decline.
Conclusions: Sarcopenia and frailty show overlapping but non-identical patterns of association with neurocognitive outcomes: sarcopenia was linked to longitudinal cognitive decline, whereas frailty was associated with cortical volume reduction and VaD. Early identification of these conditions is crucial for mitigating neurodegenerative decline and reducing dementia risk.

Keywords: Sarcopenia; Frailty; Cognitive Function; Brain Atrophy; Dementia

Conflict of Interest

Min Young Chun serves as an Editorial Board member of *Dementia and Neurocognitive Disorders*. However, she was not involved in the peer review or decision-making process for this manuscript. The authors declare no other potential conflicts of interest relevant to this article.

Data Sharing Statement

The data used in this study are owned by the UK Biobank (www.ukbiobank.ac.uk) and legal constraints do not permit public sharing of the data. The UK Biobank, however, is open to all bona fide researchers anywhere in the world. Data may be obtained from a third party and are not publicly available. Data are available through the UK Biobank (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access) and can be applied for through the UK Biobank Access Management System (AMS).

Author Contributions

Conceptualization: Heo SJ, Chun MY; Data curation: Heo SJ; Formal analysis: Heo SJ; Investigation: Chun MY; Methodology: Heo SJ; Project administration: Chun MY; Writing - original draft: Heo SJ, Chun MY.

INTRODUCTION

With the global increase in life expectancy, the prevalence of age-related conditions such as sarcopenia and frailty has risen substantially.[1,2] While both conditions reflect a state of increased vulnerability to adverse outcomes, including falls, hospitalization, and mortality,[3-6] they represent distinct physiological deficits. Sarcopenia primarily involves the age-related loss of muscle mass and function,[7] whereas frailty characterizes a broader multisystem dysregulation resulting in diminished physiological reserve and resilience.[8]

Dementia represents a growing global health burden,[9] and there is an urgent need to identify modifiable risk factors capable of attenuating or postponing cognitive decline. Accumulating evidence indicates that sarcopenia and frailty are closely linked to cognitive impairment and may promote neurodegeneration via overlapping mechanisms, including chronic systemic inflammation, vascular dysfunction, endocrine dysregulation, and disrupted myokine signaling.[10-13] Several studies have reported associations between sarcopenia or frailty and poorer cognitive function, or increased risk of dementia.[14,15] However, previous studies have rarely simultaneously examined the contributions of these conditions to specific dementia subtypes and structural brain integrity.

The UK Biobank presents a valuable resource for addressing these gaps. This large, well characterized prospective cohort includes detailed information on physical function, lifestyle factors, comorbidities, cognitive performance, brain magnetic resonance imaging (MRI), and long term follow up for incident dementia.[16,17] Using these data, it is possible to derive operational definitions of sarcopenia and frailty and to examine their associations with multiple dimensions of brain health.

The present study aimed to investigate the effects of sarcopenia and frailty on cognitive function, brain volume, and dementia risk in the UK Biobank. First, we evaluated associations of sarcopenia and frailty with cognitive function and brain volume. Second, we examined their association with the incidence of all-cause dementia, as well as Alzheimer's disease dementia (ADD) and vascular dementia (VaD). Third, we assessed whether sarcopenia and frailty were related to longitudinal changes in cognition and brain structure.

METHODS

Data source and study population

This study utilized data from the UK Biobank, a large, prospective cohort study aimed at understanding the health of middle-aged and older adults. Between 2006 and 2010, more than 500,000 participants aged 40 to 70 visited 22 assessment centers across England, Wales and Scotland.[18] At the initial assessment visit (baseline), participants completed a questionnaire on sociodemographic factors, lifestyle, and medical history, and underwent physical measurements and biological sampling.

Longitudinal follow-up assessments have been conducted, including a first repeat assessment visit for approximately 20,000 participants between 2012 and 2013. The UK Biobank Imaging Study, including brain MRI, commenced in 2014 with a pilot phase involving approximately 5,000 participants to finalize protocols. This was followed by the main phase, extending to 100,000 participants with data collection estimated to be completed by 2023. A repeat

imaging visit began in 2019. Additionally, subsets of participants have taken web-based assessments, including online cognitive tests. Further details are about the UK Biobank protocol available online (https://www.ukbiobank.ac.uk/).[18]

For the present study, the date of the initial assessment center visit (2006–2010) was defined as the baseline. We established a dementia-free cohort by excluding participants who had a diagnosis of dementia (International Classification of Diseases, 10th Revision [ICD-10] codes F00–F04). We further excluded individuals who withdrew consent or had missing data on key demographic or socioeconomic covariates. From this eligible population, we applied specific exclusion criteria based on the availability of data for sarcopenia and frailty components. Consequently, a total of 390,903 participants were included in the sarcopenia analysis, and 316,562 participants were included in the frailty analysis (**Supplementary Fig. 1**).

The UK Biobank study received ethical approval from the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent. For the present analysis, additional approval was obtained from the Institutional Review Board (IRB) of Yongin Severance Hospital, Korea (IRB 9-2023-0187).

Independent variables

Assessment of sarcopenia

To define sarcopenia, we applied the clinical criteria established by the 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) guidelines.[19] Sarcopenia was identified by the presence of both low muscle strength and low muscle mass, while severe sarcopenia was defined by the combination of low muscle strength, low muscle mass, and low physical performance.

Muscle strength was assessed via handgrip strength using a Jamar J00105 hydraulic dynamometer. Isometric grip force was measured from a single 3-second maximal effort, separately for the right and left hands, with the participant seated upright and the elbow flexed at 90°. The mean of the right and left values was used for analysis. Low grip strength was defined as <27 kg for men and <16 kg for women.[19]

Muscle mass was evaluated using the muscle mass index (MMI), calculated as appendicular skeletal muscle mass (ASM) divided by height squared (m^2). ASM was estimated using the Janssen equation[20] based on bioelectrical impedance analysis data obtained via a Tanita BC-418MA device. Low muscle mass was defined as MMI <7.0 kg/m^2 in men and <5.5 kg/m^2 in women.[19,21]

Physical performance was assessed using self-reported walking pace (slow, average, brisk) as a proxy for gait speed, which has been shown to reliably predict functional outcomes.[22] Walking pace was dichotomized into slow versus steady/brisk.[21]

Consequently, participants were classified into 2 groups for analysis: sarcopenia and severe sarcopenia.

Assessment of frailty

Frailty was assessed using the 5 components of the frailty phenotype—unintentional weight loss, exhaustion, low physical activity, slow walking speed, and low grip strength—originally proposed by Fried et al.[23] These criteria were adapted to fit the available UK Biobank data,[21] following the methodology described by Hanlon et al.[24] and Petermann-Rocha et al.[25]

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Specifically, the components were defined based on the touchscreen questionnaire and physical measurements at the assessment center as follows: (1) Unintentional weight loss was defined as a self-reported weight loss in the past year. (2) Exhaustion was identified if participants reported feeling tired or lethargic for "more than half the days" or "nearly every day" in the last 2 weeks. (3) Low physical activity was defined based on the International Physical Activity Questionnaire[26] or reporting no moderate or vigorous physical activity in a typical week. (4) Slow walking speed was defined as a self-reported "slow" walking pace. (5) Low grip strength was defined using the same cut-off points as the sarcopenia assessment (<27 kg for men and <16 kg for women).

Participants were classified into 3 categories based on their total score (range 0–5): robust (0 points), pre-frail (1–2 points), and frail (3–5 points).

Outcome variables

In this cohort study, the primary outcome was the cognitive test scores, brain MRI volume, the incidence of newly developed dementia following the index date, and longitudinal changes in cognitive test scores and brain MRI volume.

Cognitive assessments

Cognitive function was evaluated through a series of computerized tasks completed during the assessment center visits. Based on data availability for large numbers of participants and their relevance to neurodegeneration, we selected 3 key tests[27]: (1) Visual memory, assessed using the pairs matching test (number of incorrect matches) [Field ID 339]. (2) Reasoning, evaluated through fluid intelligence, a verbal-numerical reasoning test (score range: 0–13) [Sum of 4935, 4946, 4957, 4968, 4979, 4990, 5001, 5012, 5556, 5699, 5779, 5790, and 5866]. (3) Processing speed, assessed using the Reaction Time test (mean time to correctly identify matches in the "Snap" game) [404].

For analysis, test scores were coded such that higher values reflected better performance where appropriate (for example, higher fluid intelligence) and worse performance for reaction time (longer time) and error counts. Where necessary, scores were transformed to approximate normal distributions.

Brain MRI measures

All brain images were obtained on a 3T Siemens Skyra platform in accordance with the standardized UK Biobank neuroimaging protocol described previously.[28] Image-Derived Phenotypes were generated using the Freesurfer image analysis suite (version 6.0).[29] Cortical and subcortical volumes were derived from T1-weighted structural images using ASEG (Automatic Segmentation).

Two primary imaging outcomes were examined: cortex volume, derived as the bilateral hemisphere average [Field IDs 26552 and 26583], and total white matter volume, extracted from T2-weighted FLAIR sequences using the BIANCA algorithm [Field ID 25781]. Estimated total intracranial volume [Field ID 26521] was entered as a covariate in all volumetric models to account for individual differences in head size.

Dementia incidence

Incident dementia cases were identified through linkage to hospital inpatient records (Hospital Episode Statistics) and death registries provided by the National Health Service

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(NHS) Information Centre and the NHS Central Register. All diagnoses were coded using the ICD-10.[30]

The primary outcomes were defined using the following ICD-10 codes: (1) All-cause dementia: comprising Alzheimer's disease (G30), dementia in Alzheimer's disease (F00), VaD (F01), dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), and other degenerative diseases of the nervous system (G31). (2) ADD: defined by codes G30 and F00. (3) VaD: defined by codes F01 and I67.

For the incidence analysis, the follow-up period was calculated from the date of the baseline assessment to the date of first dementia diagnosis, death, or the end of the follow-up period (censoring date), whichever occurred first.

Longitudinal follow-up

Longitudinal follow-up assessments included a first repeat assessment visit (2012–2013), the first imaging visit (from 2014 onwards), and the first repeat imaging visit (from 2019 onwards). For the longitudinal analyses, we included participants who completed the relevant cognitive assessments or MRI scans at both the first imaging visit (defined as the baseline for these analyses) and the subsequent repeat imaging visit.

Covariates

To control for potential confounding factors, we adjusted for sociodemographic, lifestyle, genetic, and health-related covariates in the multivariable models. Sociodemographic factors included age (categorized into 40–49, 50–59, and 60–69 years), sex (male or female), race/ethnicity (grouped into White, Black, Asian, and Mixed/Other), educational attainment (dichotomized as below high school vs. high school or above), and socioeconomic status (assessed using the Townsend Deprivation Index (TDI) as a continuous variable. Lifestyle factors included body mass index (BMI; classified into 5 groups: <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2), smoking status (never, past, or current), and alcohol consumption frequency (dichotomized as ≥5 vs. <5 times/week). Genetic risk was assessed by *APOE* ε4 carrier status (carrier vs. non-carrier). *APOE* genotype was derived from UK Biobank genetic the rs429358 and rs7412 single nucleotide polymorphisms, and participants were classified as ε4 carriers (ε2/ε4, ε3/ε4, ε4/ε4) or non-carriers (ε2/ε2, ε2/ε3, ε3/ε3). Comorbidities included hypertension, myocardial infarction, congestive heart failure, cerebrovascular disease, diabetes, dyslipidemia, chronic kidney disease, and cancer.

Statistical analyses

Baseline characteristics are presented as means ± standard deviations for continuous variables and as frequencies with percentages for categorical variables. Differences in baseline characteristics according to sarcopenia and frailty status were assessed using analysis of variance for continuous variables and the χ^2 test for categorical variables.

For cross-sectional associations with cognitive function and brain MRI volumes at baseline, we used multivariable linear regression models. Regression coefficients (β) and corresponding 95% confidence intervals (CIs) were estimated after adjustment for age group, sex, education, race, TDI, BMI group, smoking, alcohol consumption, comorbidities, and *APOE* ε4 carrier status.

To assess the risk of incident dementia, cumulative incidence curves were estimated using the Kaplan-Meier method, and differences between groups were compared using

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the log-rank test. Cox proportional hazards regression models were subsequently used to estimate hazard ratios (HRs) and 95% CIs for the associations of sarcopenia and frailty status with the risk of all-cause and subtype-specific dementia, including ADD and VaD. The time scale was defined as the interval from the baseline assessment to the date of dementia diagnosis, death, or censoring, whichever occurred first.

To further examine the overlap between sarcopenia and frailty, we performed supplementary analyses including mutually adjusted models, joint exposure analyses, and descriptive assessment of overlap between the 2 constructs.

Longitudinal associations with cognitive function and brain volumes were assessed using linear mixed-effects models with subject-specific random intercepts to account for within-subject correlations. An interaction term between exposure (sarcopenia/frailty) and time (follow-up visits since baseline) was included to assess group differences in longitudinal changes.

All statistical analyses were conducted using R software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Study population

Baseline characteristics of the study population are summarized in **Table 1**. For the sarcopenia analyses, 390,903 participants were included, of whom 1,198 (0.31%) met criteria for sarcopenia and 269 (0.07%) for severe sarcopenia. Participants with sarcopenia were older than those without sarcopenia (mean age 62.1 vs. 55.5 years), and the proportion aged 60 years or older was markedly higher in the sarcopenia and severe sarcopenia groups (p<0.001). Women were more common among participants with sarcopenia or severe sarcopenia groups (p<0.001). Participants with sarcopenia and severe sarcopenia were predominantly underweight or of normal weight, whereas obesity was significantly less common compared to those without sarcopenia (p<0.001). Participants with sarcopenia or severe sarcopenia characterized by lower educational attainment, a higher proportion of non-White ethnicity, and greater socioeconomic deprivation than those without sarcopenia (all p<0.001). The distribution of *APOE* ε4 status was broadly similar across sarcopenia categories. Comorbidities, including hypertension, congestive heart failure, cerebrovascular disease, diabetes, dyslipidemia, chronic kidney disease, and cancer, were more prevalent among participants with severe sarcopenia.

For the frailty analyses, 316,562 participants were included; 254,623 (80.4%) were classified as robust, 46,364 (14.65%) as pre-frail, and 15,575 (4.92%) as frail. Mean age was similar across frailty categories, but the frail group contained a higher proportion of participants aged 60 years or older. Women were over-represented among pre-frail and frail participants (58.7% and 62.9%, respectively, vs. 50.7% in the robust group). Frail participants were much less often of normal weight (17.4% vs. 38.0% in the robust) and more frequently obese or severely obese (47.2% vs. 18.3% in the robust), with pre-frail individuals showing intermediate proportions (p<0.001). Frailty was also associated with lower educational attainment, non-White, and higher social deprivation (all p<0.001). Frailty was associated with a greater burden of comorbidities, including hypertension, myocardial infarction,

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Table 1. Baseline characteristics of the study population according to sarcopenia and frailty status

Characteristic	Sarcopenia status					Frailty status				
	Overall	Normal	Sarcopenia	Severe sarcopenia	*p*-value	Overall	Robust	Pre-frail	Frail	*p*-value
Number	390,903	389,436	1,198	269		316,562	254,623	46,364	15,575	
Age (yr)	55.52±8.04	55.50±8.04	62.10±5.74	60.60±6.75	<0.001	55.39±8.05	55.47±8.04	54.90±8.06	55.61±8.01	<0.001
Age group (yr)					<0.001					<0.001
<50	105,514 (27.0)	105,450 (27.1)	43 (3.6)	21 (7.8)		87,230 (27.6)	69,560 (27.3)	13,595 (29.3)	4,075 (26.2)	
50–59	137,764 (35.2)	137,421 (35.3)	272 (22.7)	71 (26.4)		111,683 (35.3)	89,104 (35.0)	16,841 (36.3)	5,738 (36.8)	
≥60	147,625 (37.8)	146,565 (37.6)	883 (73.7)	177 (65.8)		117,649 (37.2)	95,959 (37.7)	15,928 (34.4)	5,762 (37.0)	
Sex					<0.001					<0.001
Male	178,126 (45.6)	178,034 (45.7)	66 (5.5)	26 (9.7)		150,336 (47.5)	125,404 (49.3)	19,159 (41.3)	5,773 (37.1)	
Female	212,777 (54.4)	211,402 (54.3)	1,132 (94.5)	243 (90.3)		166,226 (52.5)	129,219 (50.7)	27,205 (58.7)	9,802 (62.9)	
BMI					<0.001					<0.001
Underweight	2,044 (0.5)	1,938 (0.5)	88 (7.3)	18 (6.7)		1,600 (0.5)	1,328 (0.5)	193 (0.4)	79 (0.5)	
Healthy weight (normal)	134,737 (34.5)	133,688 (34.3)	861 (71.9)	188 (69.9)		110,313 (34.8)	96,871 (38.0)	10,730 (23.1)	2,712 (17.4)	
Overweight	165,263 (42.3)	164,965 (42.4)	245 (20.5)	53 (19.7)		134,807 (42.6)	109,673 (43.1)	19,697 (42.5)	5,437 (34.9)	
Obesity	64,133 (16.4)	64,122 (16.5)	3 (0.3)	8 (3.0)		51,028 (16.1)	36,269 (14.2)	10,681 (23.0)	4,078 (26.2)	
Severe obesity	24,726 (6.3)	24,723 (6.3)	1 (0.1)	2 (0.7)		18,814 (5.9)	10,482 (4.1)	5,063 (10.9)	3,269 (21.0)	
Education					<0.001					<0.001
Below high school level	79,805 (20.4)	79,342 (20.4)	382 (31.9)	81 (30.1)		61,057 (19.3)	46,934 (18.4)	10,185 (22.0)	3,938 (25.3)	
High school level and above	311,098 (79.6)	310,094 (79.6)	816 (68.1)	188 (69.9)		255,505 (80.7)	207,689 (81.6)	36,179 (78.0)	11,637 (74.7)	
Race					<0.001					<0.001
White	370,552 (94.8)	369,242 (94.8)	1,068 (89.1)	242 (90.0)		301,283 (95.2)	244,291 (95.9)	43,037 (92.8)	13,955 (89.6)	
Non-white	20,351 (5.2)	20,194 (5.2)	130 (10.9)	27 (10.0)		15,279 (4.8)	10,332 (4.1)	3,327 (7.2)	1,620 (10.4)	
Townsend Deprivation Index					<0.001					<0.001
Q1	105,595 (27.0)	105,264 (27.0)	267 (22.3)	64 (23.8)		86,769 (27.4)	72,121 (28.3)	11,530 (24.9)	3,118 (20.0)	
Q2	101,162 (25.9)	100,752 (25.9)	349 (29.1)	61 (22.7)		82,450 (26.0)	67,555 (26.5)	11,557 (24.9)	3,338 (21.4)	
Q3	97,858 (25.0)	97,479 (25.0)	314 (26.2)	65 (24.2)		79,428 (25.1)	63,688 (25.0)	11,757 (25.4)	3,983 (25.6)	
Q4	86,288 (22.1)	85,941 (22.1)	268 (22.4)	79 (29.4)		67,915 (21.5)	51,259 (20.1)	11,520 (24.8)	5,136 (33.0)	
Smoking					<0.001					<0.001
Never	222,384 (56.9)	221,459 (56.9)	771 (64.4)	154 (57.2)		179,324 (56.6)	145,834 (57.3)	25,577 (55.2)	7,913 (50.8)	
Past	131,098 (33.5)	130,682 (33.6)	343 (28.6)	73 (27.1)		107,411 (33.9)	86,394 (33.9)	15,604 (33.7)	5,413 (34.8)	
Current	37,421 (9.6)	37,295 (9.6)	84 (7.0)	42 (15.6)		29,827 (9.4)	22,395 (8.8)	5,183 (11.2)	2,249 (14.4)	
Alcohol consumption frequency					<0.001					<0.001
None	111,024 (28.4)	110,382 (28.3)	508 (42.4)	134 (49.8)		85,493 (27.0)	62,165 (24.4)	16,028 (34.6)	7,300 (46.9)	
1–2/week	99,512 (25.5)	99,203 (25.5)	252 (21.0)	57 (21.2)		80,495 (25.4)	65,086 (25.6)	11,915 (25.7)	3,494 (22.4)	
3–4/week	95,524 (24.4)	95,282 (24.5)	213 (17.8)	29 (10.8)		79,336 (25.1)	67,340 (26.4)	9,631 (20.8)	2,365 (15.2)	
≥5/week	84,843 (21.7)	84,569 (21.7)	225 (18.8)	49 (18.2)		71,238 (22.5)	60,032 (23.6)	8,790 (19.0)	2,416 (15.5)	
APOE e4 status					0.259					0.009
e4 non-carrier	279,538 (71.5)	278,508 (71.5)	833 (69.5)	197 (73.2)		226,451 (71.5)	181,844 (71.4)	33,430 (72.1)	11,177 (71.8)	
e4 carrier	111,365 (28.5)	110,928 (28.5)	365 (30.5)	72 (26.8)		90,111 (28.5)	72,779 (28.6)	12,934 (27.9)	4,398 (28.2)	
Comorbidity										
Hypertension	26,211 (6.7)	26,067 (6.7)	90 (7.5)	54 (20.1)	<0.001	20,467 (6.5)	13,763 (5.4)	4,113 (8.9)	2,591 (16.6)	<0.001
Myocardial infarction	1,603 (0.4)	1,593 (0.4)	8 (0.7)	2 (0.7)	0.260	1,290 (0.4)	852 (0.3)	244 (0.5)	194 (1.2)	<0.001
Congestive heart failure	1,254 (0.3)	1,246 (0.3)	3 (0.3)	5 (1.9)	<0.001	1,003 (0.3)	586 (0.2)	213 (0.5)	204 (1.3)	<0.001
Cerebrovascular disease	2,903 (0.7)	2,882 (0.7)	10 (0.8)	11 (4.1)	<0.001	2,231 (0.7)	1,446 (0.6)	437 (0.9)	348 (2.2)	<0.001
Diabetes	6,665 (1.7)	6,646 (1.7)	7 (0.6)	12 (4.5)	<0.001	5,228 (1.7)	2,948 (1.2)	1,224 (2.6)	1,056 (6.8)	<0.001
Dyslipidemia	10,626 (2.7)	10,579 (2.7)	32 (2.7)	15 (5.6)	0.016	8,417 (2.7)	5,660 (2.2)	1,655 (3.6)	1,102 (7.1)	<0.001
Chronic kidney disease	970 (0.2)	960 (0.2)	3 (0.3)	7 (2.6)	<0.001	765 (0.2)	398 (0.2)	191 (0.4)	176 (1.1)	<0.001
Cancer	13,550 (3.5)	13,460 (3.5)	62 (5.2)	28 (10.4)	<0.001	10,808 (3.4)	8,110 (3.2)	1,828 (3.9)	870 (5.6)	<0.001

Data are presented as mean ± standard deviation or number (%). The *p*-values were calculated using analysis of variance for continuous variables and χ^2 test for categorical variables.
BMI: body mass index.

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congestive heart failure, cerebrovascular disease, diabetes, dyslipidemia, chronic kidney disease, and cancer, with a clear gradient from robust to pre-frail and frail participants.

Cross-sectional associations of sarcopenia and frailty with cognitive function

In fully adjusted linear regression models, both sarcopenia and frailty were associated with poorer cognitive performance (**Table 2**). Sarcopenia was associated with longer reaction time (β, 28.16 ms; 95% CI, 21.53 to 34.79; p<0.001), compared to participants without sarcopenia. Severe sarcopenia was associated with lower fluid intelligence (β, −0.39; −0.78 to −0.01; p=0.043) and slower reaction time (β, 38.71 ms; 24.76 to 52.65; p<0.001).

Frailty was consistently associated with poorer cognitive performance. Compared with robust participants, pre-frail participants showed worse performance on fluid intelligence (β, −0.09; −0.12 to −0.06; p<0.001) and reaction time (β, 7.07 ms; 5.91 to 8.22; p<0.001). Frail participants had lower scores on the pairs matching test (β, −0.26; −0.42 to −0.11; p<0.001), lower fluid intelligence (β, −0.25; −0.30 to −0.19; p<0.001), and showed slower reaction time (β, 22.33 ms; 20.41 to 24.24; p<0.001).

Cross-sectional associations of sarcopenia and frailty with brain volume

In the cross-sectional analysis of brain MRI measures (**Table 3**), sarcopenia was not significantly associated with cortical or white matter volumes. In contrast, pre-frail and frail individuals had progressively smaller cortical volumes (β, −428.03 mm^3; −847.44 to −86.1; p<0.001; and β, −964.29 mm^3; −1,796.37 to −132.22; p<0.001) compared with robust participants. However, white matter volume did not differ significantly according to frailty status.

Table 2. Cross-sectional associations of sarcopenia and frailty with cognitive test scores

Variable	Paired associate learning		Fluid intelligence score		Reaction time	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Sarcopenia status						
Normal	Reference		Reference		Reference	
Sarcopenia	−0.10 (−0.65, 0.45)	0.714	−0.14 (−0.30, 0.03)	0.112	28.16 (21.53, 34.79)	<0.001
Severe sarcopenia	−0.96 (−2.59, 0.67)	0.247	−0.39 (−0.78, −0.01)	0.043	38.71 (24.76, 52.65)	<0.001
Frailty status						
Robust	Reference		Reference		Reference	
Pre-frail	−0.07 (−0.15, 0.00)	0.062	−0.09 (−0.12, −0.06)	<0.001	7.07 (5.91, 8.22)	<0.001
Frail	−0.26 (−0.42, −0.11)	<0.001	−0.25 (−0.30, −0.19)	<0.001	22.33 (20.41, 24.24)	<0.001

All β estimates are from multivariable linear regression models adjusted for age group, sex, education, race, Townsend Deprivation Index, body mass index group, smoking, alcohol consumption, comorbidities, and *APOE* ε4 carrier status.
CI: confidence interval.

Table 3. Cross-sectional associations of sarcopenia and frailty with brain magnetic resonance imaging measures

Variable	Cortex		White matter	
	β (95% CI)	p-value	β (95% CI)	p-value
Sarcopenia status				
Normal	Reference		Reference	
Sarcopenia	658.56 (−2,072.96, 3,390.08)	0.637	115.68 (−2,989.13, 3,220.50)	0.942
Severe sarcopenia	1,745.98 (−4,892.30, 8,384.26)	0.606	−3,399.42 (−10,944.90, 4,146.05)	0.377
Frailty status				
Robust	Reference		Reference	
Pre-frail	−428.03 (−847.44, −8.61)	0.045	−140.80 (−619.58, 337.98)	0.564
Frail	−964.29 (−1,796.37, −132.22)	0.023	−490.91 (−1,440.76, 458.95)	0.311

All β estimates are from multivariable linear regression models adjusted for age group, sex, education, race, Townsend Deprivation Index, body mass index group, smoking, alcohol consumption, comorbidities, *APOE* ε4 carrier status, and intra-cranial volume.
CI: confidence interval.

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Table 4. Association of sarcopenia and frailty with the risk of incident dementia

Variable	Dementia		Alzheimer's disease dementia		Vascular dementia	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Sarcopenia status						
Normal	Reference		Reference		Reference	
Sarcopenia	1.53 (1.09, 2.12)	0.013	1.53 (0.84, 2.78)	0.165	1.72 (0.76, 3.87)	0.192
Severe sarcopenia	1.71 (0.89, 3.30)	0.108	1.39 (0.35, 5.59)	0.640	-	-
Frailty status						
Robust	Reference		Reference		Reference	
Pre-frail	1.35 (1.23, 1.48)	<0.001	1.06 (0.88, 1.27)	0.577	1.37 (1.11, 1.68)	0.003
Frail	2.11 (1.87, 2.38)	<0.001	1.34 (1.02, 1.77)	0.038	2.39 (1.85, 3.07)	<0.001

HRs and 95% CIs were estimated using Cox proportional hazards models, with time since baseline as the time scale. All models adjusted for age group, sex, education, race, Townsend Deprivation Index, body mass index group, smoking, alcohol consumption, comorbidities, and *APOE* ε4 carrier status.
HR: hazard ratio, CI: confidence interval.

Incidence of all-cause and subtype-specific dementia

In Cox proportional hazards models adjusted for demographic factors, socioeconomic status, lifestyle variables, comorbidities, and *APOE* ε4, both sarcopenia and frailty were associated with increased risk of incident all-cause dementia (**Table 4**). Sarcopenia was associated with a 53% higher risk of dementia (HR, 1.53; 1.09 to 2.12; p=0.013), whereas the estimate for severe sarcopenia did not reach statistical significance (HR, 1.71; 0.89 to 3.30; p=0.108), probably owing to small numbers.

Frailty showed a clear gradient in dementia risk. Compared with robust participants, pre-frail participants had a 35% higher risk of all-cause dementia (HR, 1.35; 1.23 to 1.48; p<0.001), and frail participants had more than a 2-fold increased risk (HR, 2.11; 1.87 to 2.38; p<0.001). When dementia subtypes were examined, pre-frail participants had an elevated risk of VaD (HR, 1.37; 1.11 to 1.68; p=0.003), while frail participants had an HR of 1.34 (1.02 to 1.77; p=0.038) for ADD and an HR of 2.39 (1.85 to 3.07; p<0.001) for VaD.

The Kaplan-Meier curves showed similar patterns (**Fig. 1**). Dementia-free survival differed significantly across sarcopenia groups for all-cause dementia and ADD (both log-rank p<0.001), but not for VaD (log-rank p=0.069). Likewise, frailty status showed clear graded separation for all-cause dementia and VaD (both log-rank p<0.001), whereas ADD-free survival did not differ significantly across frailty groups (log-rank p=0.080).

Supplementary analyses addressing the overlap between sarcopenia and frailty, including mutually adjusted models and joint exposure analyses, are presented in **Supplementary Tables 1-4**.

Longitudinal changes in cognitive function and brain structure

In linear mixed-effects models assessing longitudinal change in cognitive function (**Table 5**), sarcopenia was associated with a faster decline in fluid intelligence (β for sarcopenia–time interaction −0.54, −1.07 to −0.01; p=0.046). Severe sarcopenia was associated with a steeper increase in reaction time over the follow-up period (β, 109.69 ms; 50.24 to 169.13; p<0.001). However, longitudinal changes in cognitive performance did not differ significantly across frailty categories.

Longitudinal analyses of brain MRI measures showed no significant associations between sarcopenia or frailty status and changes in cortical or white matter volumes over time (**Table 6**).

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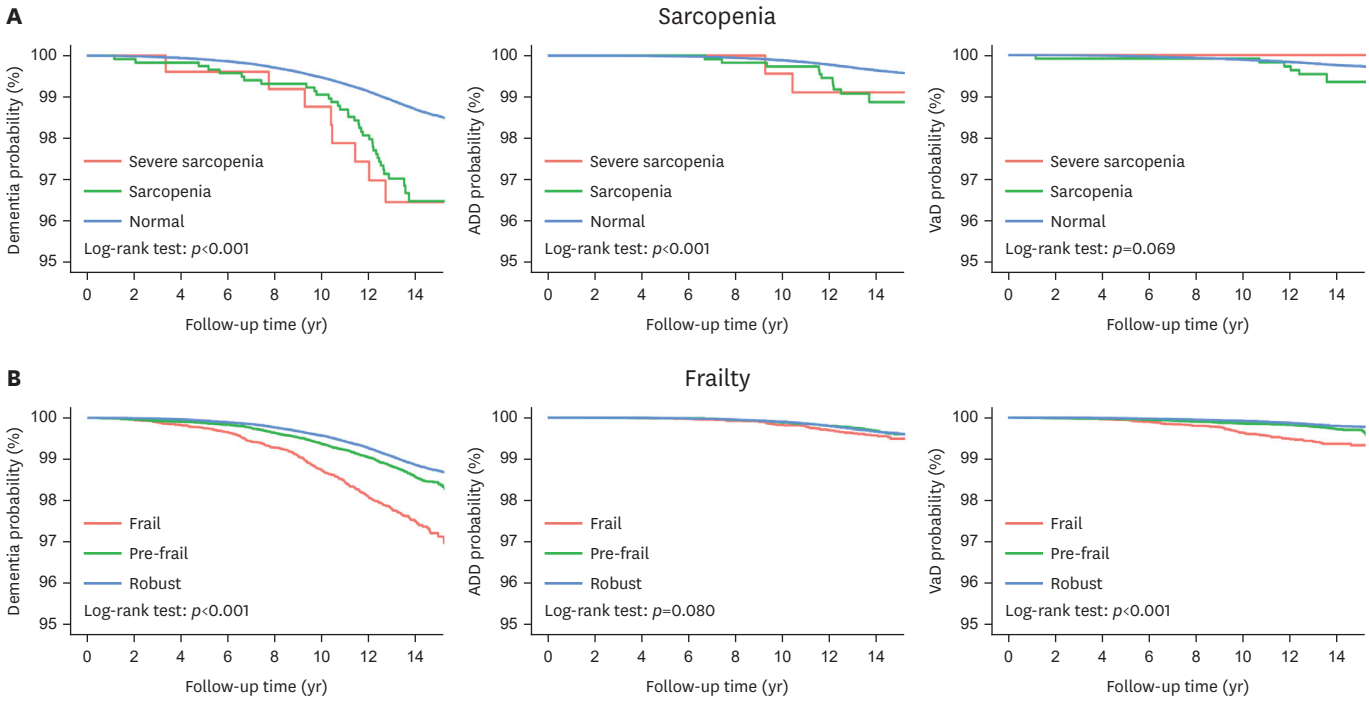

Fig. 1. Kaplan-Meier curves for incident dementia according to sarcopenia and frailty status. (A) Dementia risk by sarcopenia status (no sarcopenia, sarcopenia, severe sarcopenia). (B) Dementia risk by frailty status (robust, pre-frail, frail). The left, middle, and right panels show curves for all-cause dementia, ADD, and VaD, respectively. Curves compare cumulative incidence across exposure groups over follow-up time (years); the *p*-values are from log-rank tests.
ADD: Alzheimer's disease dementia, VaD: vascular dementia.

Table 5. Longitudinal changes in cognitive test scores according to sarcopenia and frailty status

Variable	Paired associate learning		Fluid intelligence score		Reaction time	
	β (95% CI)	*p*-value	*β* (95% CI)	*p*-value	*β* (95% CI)	*p*-value
Sarcopenia status						
Normal	Reference		Reference		Reference	
Sarcopenia	0.76 (−1.69, 3.22)	0.542	−0.54 (−1.07, −0.01)	0.046	−13.33 (−40.79, 14.13)	0.341
Severe sarcopenia	1.65 (−2.66, 5.95)	0.454	−0.40 (−1.60, 0.79)	0.510	109.69 (50.24, 169.13)	<0.001
Frailty status						
Robust	Reference		Reference		Reference	
Pre-frail	0.12 (−0.10, 0.33)	0.284	0.04 (−0.05, 0.14)	0.367	−3.45 (−8.09, 1.20)	0.146
Frail	−0.12 (−0.59, 0.36)	0.637	−0.05 (−0.22, 0.12)	0.545	−1.78 (−9.93, 6.37)	0.668

Values are beta coefficients (*β*) representing the difference in change in cognitive test scores across visits associated with the interaction between group status and time. All linear mixed-effects adjusted for age group, sex, education, race, Townsend Deprivation Index, body mass index group, smoking, alcohol consumption, comorbidities, *APOE* ε4 carrier status.
CI: confidence interval.

Table 6. Longitudinal changes in brain magnetic resonance imaging measures according to sarcopenia and frailty status

Variable	Cortex		White matter	
	β (95% CI)	*p*-value	*β* (95% CI)	*p*-value
Sarcopenia status				
Normal	Reference		Reference	
Sarcopenia	−4,166.863 (−12,638.969, 4,305.243)	0.335	1,493.652 (−3,927.064, 6,914.369)	0.589
Severe sarcopenia	−4,381.181 (−19,075.749, 10,313.386)	0.559	1,326.158 (−8,064.862, 10,717.179)	0.782
Frailty status				
Robust	Reference		Reference	
Pre-frail	−56.114 (−795.496, 683.267)	0.882	−275.233 (−748.923, 198.457)	0.255
Frail	−77.827 (−1,738.482, 1,582.827)	0.927	−688.255 (−1,752.985, 376.474)	0.205

Values are beta coefficients (*β*) representing the difference in change in brain magnetic resonance imaging measures across visits associated with the interaction between group status and time. All linear mixed-effects models adjusted for age group, sex, education, race, Townsend Deprivation Index, body mass index group, smoking, alcohol consumption, comorbidities, *APOE* ε4 carrier status, and intra-cranial volume.
CI: confidence interval.

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DISCUSSION

This large-scale cohort study confirms that sarcopenia and frailty are not merely markers of physical aging but are intrinsically linked to neurocognitive health. Our major findings are as follows. First, both sarcopenia and frailty were associated with poorer cognitive performance, particularly in domains related to reasoning and psychomotor slowing; moreover, sarcopenia was associated with longitudinal decline in these domains. Second, frailty, but not sarcopenia, was associated with reduced cortical volume. Third, both conditions were associated with an increased risk of incident all-cause dementia, with frailty showing a dose-response gradient and a particularly strong association with VaD. Taken together, these findings indicate that sarcopenia and frailty represent overlapping but non-identical pathways linking physical vulnerability to neurodegeneration and dementia, underscoring the importance of assessing both conditions in strategies aimed at the early identification and prevention of dementia.

Our first major finding was that sarcopenia and frailty are associated with cognitive impairment, and sarcopenia predicts longitudinal cognitive decline. Both conditions were cross-sectionally associated with slower reaction time and lower fluid intelligence after comprehensive covariate adjustment, consistent with earlier studies linking muscle weakness to impaired processing speed and reasoning.[31] Frailty showed a broader and more graded pattern of association across cognitive domains, which may reflect the multisystem dysregulation captured by the frailty phenotype,[10] in contrast to the more circumscribed neuromuscular deficit represented by sarcopenia. Notably, sarcopenia—but not frailty—was associated with accelerated longitudinal cognitive decline in fluid intelligence and psychomotor speed. This observation aligns with earlier findings from the Rush Memory and Aging Project, which highlighted the central contribution of muscle function as a mediating factor between sarcopenia and progressive cognitive deterioration.[32] A plausible mechanism involves the muscle–brain axis, whereby skeletal muscle functions as an endocrine organ and releases myokines, including brain-derived neurotrophic factor, irisin, and cathepsin B, that support neurogenesis, synaptic plasticity, and neuronal resilience.[33-35] Progressive muscle loss and function may reduce muscle-derived neurotrophic signaling, thereby increasing neuronal vulnerability to age-related cognitive decline.[36,37] The absence of longitudinal cognitive decline in frail participants, despite its clear cross-sectional associations with poorer cognition, may reflect several factors. Frailty may be more strongly related to baseline cognitive vulnerability and accumulated deficit burden than to short-term rate of decline. In addition, the longitudinal sample represents a healthier subset of participants who returned for repeat assessments, which may have attenuated differences in cognitive trajectories. The relatively limited follow-up duration and number of repeated cognitive assessments may also have reduced sensitivity to detect small differences in slope. Finally, because frailty is a dynamic condition that may change over time, a single baseline frailty assessment may not fully capture longer-term cognitive decline trajectories.

Our second major finding was that frailty is associated with graded reductions in cortical volume, whereas sarcopenia showed no significant association with brain volume measures. Frailty may be more closely linked than sarcopenia to macroscopic structural brain changes detectable at the population level, consistent with previous studies in the UK Biobank and other cohorts showing that frailty is associated with lower grey matter volume and other adverse structural brain markers.[38,39] One possible explanation is that frailty reflects a broader accumulation of physiological deficits across vascular, metabolic, inflammatory, and

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endocrine systems, which together may have a greater impact on brain structure.[10] By contrast, the absence of a significant association between sarcopenia and cortical volume should be interpreted cautiously. It may reflect limited statistical power due to the low prevalence of EWGSOP2-defined sarcopenia in this cohort,[40] or the possibility that sarcopenia is more strongly related to functional or microstructural brain changes than to global cortical volume. Although a recent Mendelian randomization study suggested that genetically predicted sarcopenia-associated traits may influence brain cortical structure,[41] our study did not detect a significant association between categorical sarcopenia and cortical volume. This discrepancy may reflect differences in exposure definition and imaging phenotype, as the prior study examined continuous sarcopenia-related traits and regional cortical surface area/thickness, whereas we used EWGSOP2-defined sarcopenia and global cortical volume. Accordingly, our imaging findings do not exclude a relationship between sarcopenia and brain structural vulnerability, but rather suggest that such associations may be subtler or less readily detectable using the measures available in the present study. The lack of significant longitudinal brain volume change associated with either condition may be related to the relatively short imaging follow-up interval in this predominantly middle-aged cohort.

Our final major finding was that both conditions were associated with an increased risk of incident all-cause dementia, with frailty showing a particularly strong association with VaD. These findings are broadly consistent with earlier studies showing that both frailty and sarcopenia are associated with future dementia risk.[42-44] A notable finding was that frailty showed a stronger association with VaD than with ADD, consistent with the possibility that frailty captures a higher burden of vascular and systemic vulnerability.[45,46] Given that frailty is closely linked to cardiovascular risk factors, endothelial dysfunction, impaired cerebral perfusion, and chronic inflammation, this pattern is biologically plausible.[47] In contrast, sarcopenia was associated with all-cause dementia, but its associations with individual dementia subtypes did not reach statistical significance. Of note, although Kaplan-Meier analysis showed significant differences in ADD-free survival across sarcopenia groups (log-rank $p<0.001$), this association was attenuated to non-significance in the fully adjusted Cox model, suggesting that the unadjusted association may have been substantially confounded by factors such as age, comorbidities, and socioeconomic status. This may in part reflect limited statistical power, given the very low prevalence of sarcopenia in this cohort, but it also suggests that the subtype-specific relationship of sarcopenia with dementia remains less clearly defined than that of frailty. Therefore, our findings support a more robust and graded association between frailty and dementia subtypes, particularly VaD, whereas the dementia profile associated with sarcopenia appears more modest and requires further clarification in future studies.

The strengths of our study include the large sample, concurrent assessment of sarcopenia and frailty, availability of brain MRI data, and comprehensive covariate adjustment including *APOE* ε4 genotype. However, several limitations should be acknowledged. First, because the UK Biobank relies on voluntary participation, its members are generally healthier and of higher socioeconomic standing than the broader UK population, which may attenuate observed effect sizes and constrain the external validity of our findings. Second, the proxy measures used to define sarcopenia and frailty were necessarily limited to the data fields collected within the UK Biobank framework and may not encompass the full clinical spectrum of either condition. Additionally, physical performance was assessed using self-reported walking pace rather than objectively measured gait speed, which may introduce misclassification. Although this measure has been validated as a reliable proxy for physical

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performance in the UK Biobank and other community-based cohorts,[22] our findings should be replicated in studies with objective gait speed data. Third, an important limitation is the partial overlap in the operational definitions of sarcopenia and frailty, particularly with respect to grip strength and walking pace, which limits interpretation of their associations as fully independent effects. Fourth, residual confounding cannot be excluded despite adjustment for many covariates. Finally, participants with brain MRI and repeated assessments represent a selected subset of the cohort, which may introduce additional selection bias in longitudinal analyses.

In conclusion, both sarcopenia and frailty were associated with impaired cognitive function and elevated dementia risk, but their profiles of association differed in important ways. Sarcopenia was linked to longitudinal cognitive decline, while frailty was associated with reduced cortical brain volume and a particularly strong predisposition to VaD. These complementary patterns suggest overlapping but non-identicalpathways to neurodegeneration and support the systematic assessment of both conditions for the early identification and prevention of dementia in clinical practice. Given that sarcopenia and frailty are at least partly modifiable through resistance exercise, nutritional supplementation, and management of comorbidities, our findings support the development and testing of targeted interventions aimed at improving muscle strength and physical function as potential strategies to reduce dementia risk.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Overlap between sarcopenia and frailty in the analytic sample

Supplementary Table 2
Cognitive outcomes: mutual adjustment and joint exposure analyses of sarcopenia and frailty

Supplementary Table 3
Brain magnetic resonance imaging: mutual adjustment and joint exposure analyses of sarcopenia and frailty

Supplementary Table 4
Incident dementia: mutual adjustment and joint exposure analyses of sarcopenia and frailty

Supplementary Fig. 1
Study flow chart.

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