Blood biomarkers of Alzheimer's disease and 12-year muscle strength trajectories in community-dwelling older adults: a cohort study

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Summary

Background Age-related muscle function decline is a major impediment to healthy ageing. We aimed to investigate the association between a panel of Alzheimer's disease-related biomarkers and longitudinal trajectories of muscle strength, while exploring the influence of cognitive function.

Methods In this cohort study, we gathered data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), an ongoing prospective study that includes adults aged 60 years and older, from central Stockholm, Sweden. We included data from baseline to the fourth follow-up (March 21, 2001, to Dec 31, 2016). Seven Alzheimer's disease-related blood biomarkers were measured in dementia-free, community dwelling participants: total tau, phosphorylated tau181 (p-tau181), phosphorylated tau217 (p-tau217), amyloid β 40 and 42, neurofilament light chain, and glial fibrillary acidic protein (GFAP). Muscle strength was measured through the handgrip strength and chair-stand tests. Linear mixed models were used to explore the association between baseline Alzheimer's disease-related biomarkers and muscle strength trajectories.

Findings The baseline SNAC-K cohort included 3363 individuals, of whom 1953 participants were included in our analyses (mean age 70·2 [SD 9·1] years; 780 [39·9%] male and 1173 [60·1%] female participants). In adjusted models, higher concentrations of p-tau181 (β per year 0·93 [95% CI 0·71 to 1·16]; p<0·0001), p-tau217 (β per year 1·31 [1·03 to 1·58]; p<0·0001), neurofilament light chain (β per year 0·76 [0·56 to 0·96]; p<0·0001), and GFAP (β per year 0·37 [0·21 to 0·53]; p<0·0001) were associated with an accelerated decline of chair-stand performance over time. The adjustment for Mini-Mental State Examination (MMSE) score led to the attenuation of these associations. Higher concentrations of p-tau181 (β per year –0·12 [95% CI –0·17 to –0·07]; p<0·0001), p-tau217 (β per year –0·13 [–0·20 to –0·07]; p<0·0001), and neurofilament light chain (β per year –0·05 [–0·09 to –0·001]; p=0·047) were also associated with faster handgrip strength decline, with no attenuation after adjusting for MMSE score. Sex-specific differences were observed, with female participants showing a stronger association between biomarker concentrations and muscle strength decline than male participants, particularly in the chair-stand test.

Interpretation Our findings suggest that blood Alzheimer's disease-related biomarkers might help estimate progressive muscle strength decline among older adults, elucidating the influence of brain pathology and cognitive ageing on this association. These Alzheimer's disease-related biomarkers could aid in identifying individuals for early intervention to prevent sarcopenia.

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Introduction

A decline in muscle function, a central element of sarcopenia, is common during ageing.[1] Sarcopenia is a geriatric condition characterised by low muscle strength and low muscle mass.[2] Research has shown that muscle strength is a better predictor of adverse health outcomes than muscle mass.[3,4] Therefore, early identification of individuals at risk of muscle strength decline and a better understanding of the underlying mechanisms are essential for effective sarcopenia prevention.

Skeletal muscle performance is influenced by a complex interplay of factors related to the nervous, muscular, and skeletal systems, all of which are modulated by lifestyle and biological and psychosocial aspects across the lifespan.[5,6] The decline in muscle performance results not only from age-related functional, metabolic, and structural muscle changes but also from the negative effects of several chronic diseases,[7,8] such as cardiovascular and cerebrovascular diseases, diabetes, and respiratory diseases. These conditions contribute to endocrine dysfunction, metabolic alterations,

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Research in context

Evidence before this study

Skeletal muscle performance is influenced by a complex interplay of factors related to endocrine, metabolic, and nervous system functions. There has been growing interest in exploring muscle–brain crosstalk, yet the exact mechanisms underlying this relationship remain incompletely defined. We conducted a comprehensive search of PubMed using the terms ("neurofilament*" OR "nfl" OR "Aβ*" OR "abeta*" OR "amyloid beta" OR "tau" OR "GFAP" OR "glial fibrillary acidic protein") AND ("muscle strength" OR "handgrip" OR "hand strength" OR "grip strength" OR "chair stand test" OR "sit to stand test" OR "sit to stand") from database inception to Sept 6, 2024, with no language restrictions. This search identified several studies investigating the association between blood-based biomarkers of Alzheimer's disease and physical performance. However, only a few studies specifically focused on muscle strength, with several limitations and mixed findings. As a result, there is limited research examining the role of Alzheimer's disease-related biomarkers in the decline of muscle strength over time, particularly among community-dwelling individuals.

Added value of this study

To our knowledge, this is the first study to investigate the association between a panel of blood-based Alzheimer's disease-related biomarkers and trajectories of muscle strength measured by two distinct tests in a large sample of community-dwelling older adults.

Implications of all the available evidence

These findings suggest the potential utility of easily accessible, blood-based, Alzheimer's disease-related biomarkers to estimate the progressive decline of muscle strength among older adults. More research is needed to further elucidate muscle–brain crosstalk, including a more in-depth exploration of the mediating role played by cognitive function.

and increased systemic inflammation.[9–11] Furthermore, biological differences substantially contribute to sex-based disparities, with women having earlier and more pronounced strength decline with ageing than men.[12]

Brain pathology has been linked to poorer motor performance and faster functional decline.[13,14] Neurodegeneration alters neuromuscular signalling, impairing muscle fibre recruiting and promoting atrophy.[15] In individuals with Alzheimer's disease, this process contributes to muscle deterioration, even in the preclinical stages.[16] The *APOE* ε4 genotype, the strongest genetic risk factor for Alzheimer's disease, is also linked to poorer motor function.[17,18] Moreover, reduced muscle strength correlates with increased risk of Alzheimer's disease and a faster rate of cognitive decline.[19,20] These findings suggest an underlying relationship, the mechanisms of which have not yet been fully defined, fostering growing interest in muscle–brain crosstalk.[19,21]

Several studies have investigated the association between motor function and biomarkers of Alzheimer's disease, including amyloid β (Aβ), total tau (t-tau), phosphorylated tau (p-tau), neurofilament light chain, and glial fibrillary acidic protein (GFAP).

Cerebral amyloid deposition has been linked to reduced walking speed and lower limb strength in older adults.[22,23] However, studies examining Alzheimer's disease-related biomarkers in cerebrospinal fluid and blood remain few and heterogeneous. Lower cerebrospinal fluid Aβ42 concentrations have been associated with slower walking speed and poorer performance on the timed up and go test, but not with handgrip strength, and no significant associations have been reported for cerebrospinal fluid tau or p-tau181.[24,25] Regarding blood biomarkers, higher neurofilament light chain concentrations have been negatively associated with handgrip strength.[26] Additionally, elevated neurofilament light chain concentrations and a low ratio of Aβ42 to Aβ40 have been linked to a greater decline in gait speed, although no association with handgrip strength has been observed.[27,28] Higher p-tau181 and neurofilament light chain concentrations have also been associated with a more rapid decline in Short Physical Performance Battery (SPPB) scores.[29] However, the longitudinal relationship between Alzheimer's disease-related biomarkers and muscle strength in dementia-free, community-dwelling older adults remains insufficiently investigated.

We aimed to explore the relationship between blood concentrations of Alzheimer's disease-related biomarkers and changes in muscle strength over time in dementia-free, community-dwelling, older adults. Specifically, we aimed to explore the association between Alzheimer's disease-related biomarkers and muscle strength assessed by two tests, the handgrip strength test and the chair-stand test, and investigate the role played by cognitive function and other clinically relevant factors in this association.

Methods

Study population

In this cohort study, we gathered data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), an ongoing prospective study that includes adults aged 60 years and older, from central Stockholm, Sweden. The initial phase (2001–04) of the study included individuals from 11 age cohorts (ages 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and ≥99 years), who were followed up every 6 years (those aged <78 years) or every 3 years (those aged ≥78 years).

This study included data from baseline to the fourth follow-up (March 21, 2001, to Dec 31, 2016). From the

For **SNAC-K** see https://www.snac-k.se/

baseline cohort, we excluded individuals residing in institutions and those with dementia, Parkinson's disease or parkinsonism, or multiple sclerosis. Additionally, participants without data for baseline handgrip strength, chair-stand tests, or at least one of the Alzheimer's disease-related biomarkers were excluded. Sex data were self-reported by participants at baseline through standardised questionnaires.

SNAC-K was approved by the Regional Ethical Review Board in Stockholm (ethical permit approval numbers KI 01-114, 2001-114, 2004-929/3, 2007/279-31, 2010/2:4, 2013/3:6, 2016/730-31/1), and all participants or next of kin provided written informed consent. The study results are reported following STROBE recommendations (appendix p 7).

Procedures

A multidisciplinary team carried out a comprehensive data collection at each visit following consistent protocols. The chair-stand test was performed once by asking the participant to stand up from a chair five times as quickly as possible. It is measured in seconds, and a shorter time indicates greater lower limb strength. The worst recorded value of 75 s was assigned to participants unable to perform the test due to physical limitations. Muscle strength was defined as low if the test required 15 s or more to be completed.[2]

The handgrip strength test was conducted using a dynamometer to assess the maximum force exerted when squeezing a handle. The test was performed seated, with the arm at 90°, once per hand, and the highest obtained value was registered; higher scores indicate greater strength. A value of 0 kg was assigned to participants unable to perform the test. The cutoffs for low handgrip strength were set at less than 27 kg for men and less than 16 kg for women, based on the European Working Group on Sarcopenia in Older People 2 guidelines.[2]

For blood biomarkers and *APOE* genotype, non-fasting venous blood samples were collected. Blood was allowed to clot, and the serum was stored at –80°C at the Karolinska Institutet BioBank, Stockholm, Sweden. Biomarker analysis was carried out at the Affinity Proteomics Stockholm Unit (SciLifeLab, Stockholm, Sweden) using Quanterix Single Molecule Arrays (Simoa). Neurofilament light chain and GFAP were assayed using Simoa Neuro 2-plex B Kit. Aβ40, Aβ42, and t-tau were measured using Simoa Neuro 3-plex A Kit. p-tau181 was quantified using Simoa pTau-181 Advantage V2 Kit, and serum p-tau217 was measured using the commercial assay Simoa ALZpath p-tau217. For each kit, 25 µL of sample was diluted 1:4 and the assays were done according to manufacturer instructions. All the kits were manufactured at Quanterix Corporation, Billerica, MA, USA. The Quanterix instrument provides average enzyme per bead values for calibrators, controls, and samples. Curve-fitting, extrapolation of concentrations, and graphical representations are automatically performed within the Quanterix SR-X integrated software (version 1.2.0) using the calibrators, a series of known concentrations of an analyte, and a four-parameter logistic curve fit. The averages of intracoefficient and intercoefficient variations were calculated on a pool of samples representative of the whole SNAC-K sample set. The pool was analysed in three replicates. Intra-assay and interassay coefficient variations are shown in the appendix (p 8). Data below the limit of detection were replaced using a not missing at random strategy, through single-value imputation, with a value of 0 (imputed: four for Aβ42, 14 for p-tau181, three for p-tau217, and 14 for t-tau). The ratio of Aβ42 to Aβ40 was calculated. Alzheimer's disease-related biomarkers were used as continuous variables and Z scored for standardised comparisons.

IL-6 concentrations were measured using Simoa CorPlex Human Cytokine Panel 1 on a Quanterix SP-XTM imaging and analysis platform (Quanterix Corporation, Billerica, MA, USA). IL-6 was used as a continuous variable and dichotomised at the population median. DNA was extracted from peripheral blood mononuclear cells and the *APOE* alleles were genotyped. Participants were then classified as either ε4-carriers (at least one ε4 allele) or ε4-non-carriers.

See Online for appendix

Covariates

Several personal, lifestyle, and anthropometric data were measured at baseline, including age, sex, education (elementary school, high school, and university or above), marital status (partnered or unpartnered), smoking status (never, former, or current smoker), alcohol intake (no or occasional, light to moderate, and heavy, based on self-reported number of drinks per week), and BMI. 99% of the individuals in the SNAC-K cohort were White; therefore, ethnicity was not considered in this study. Based on a questionnaire in which participants self-reported frequency and intensity of engagement in physical activities, an active physical level was defined as engaging in light or moderate-to-intense activity at least once per week. Chronic diseases were identified through clinical interviews, examinations, laboratory parameters, medication use, and the National Patient Register, and coded according to the ICD 10th revision. For this study, we considered cerebrovascular and cardiovascular diseases (ie, stroke, atrial fibrillation, ischaemic heart disease, and heart failure), chronic kidney disease, and diabetes as covariates. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, following a three-step procedure by three trained physicians.[30] Incident dementia was defined as a new diagnosis made during the follow-up. The Mini-Mental State Examination (MMSE), a validated tool for assessing global cognition, was used at both baseline and follow-up. The MMSE evaluates several cognitive domains, including orientation (time and place), registration and short-term recall (memory), attention and calculation, language skills, and visual–spatial abilities. Its comprehensive yet concise structure makes it suitable for repeated assessments and monitoring cognitive trajectories.

Statistical analysis

Baseline characteristics were reported using numbers and percentages, and either mean (SD) or median (IQR).

	Total (n=1953)	Male (n=780)	Female (n=1173)	p value
Age, years	70·2 (9·1)	69·1 (8·8)	70·9 (9·3)	<0·0001
BMI, kg/m^2	26·1 (3·9)	26·4 (3·3)	25·9 (4·3)	0·0023
Level of education	..	..	..	<0·0001
Elementary	249 (12·7%)	98 (12·6%)	151 (12·9%)	..
High school	938 (48·0%)	319 (40·9%)	619 (52·8%)	..
University	766 (39·2%)	363 (46·5%)	403 (34·4%)	..
Mini-Mental State Examination at baseline	28·96 (1·41)	28·98 (1·47)	28·94 (1·37)	0·59
*APOE ε*4 carrier status	569 (30·0%)	235 (31·4%)	334 (29·0%)	0·29
Chronic diseases				
Number of chronic diseases	3·4 (2·1)	3·3 (2·1)	3·5 (2·1)	0·018
Hypertension	1343 (68·8%)	531 (68·1%)	812 (69·2%)	0·63
Heart disease	346 (17·7%)	180 (23·1%)	166 (14·2%)	<0·0001
Atrial fibrillation	123 (6·3%)	62 (7·9%)	61 (5·2%)	0·019
Heart failure	93 (4·8%)	43 (5·5%)	50 (4·3%)	0·25
Ischaemic heart disease	225 (11·5%)	121 (15·5%)	104 (8·9%)	<0·0001
Cerebrovascular disease	75 (3·8%)	33 (4·2%)	42 (3·6%)	0·54
Chronic kidney disease	527 (27·0%)	146 (18·7%)	381 (32·5%)	<0·0001
Diabetes	153 (7·8%)	87 (11·2%)	66 (5·6%)	<0·0001
Dyslipidaemia	1022 (52·3%)	373 (47·8%)	649 (55·3%)	0·0013
Depression or mood disorders	147 (7·5%)	39 (5·0%)	108 (9·2%)	0·0008
Musculoskeletal disease	353 (18·1%)	126 (16·2%)	227 (19·4%)	0·082
Inflammatory arthropathies	64 (3·3%)	27 (3·5%)	37 (3·2%)	0·81
Osteoarthrosis	241 (12·3%)	74 (9·5%)	167 (14·2%)	0·0022
Other musculoskeletal joint diseases	89 (4·6%)	38 (4·9%)	51 (4·3%)	0·67
Number of drugs	3·3 (3·1)	2·7 (3·0)	3·7 (3·1)	<0·0001
Functional status				
One or more ADLs lost	22 (1·1%)	5 (0·6%)	17 (1·4%)	0·15
Walking speed at baseline, m/s	1·1 (0·4)	1·2 (0·3)	1·1 (0·4)	<0·0001
Handgrip strength at baseline, kg	26·7 (11·7)	37·3 (9·7)	19·7 (6·4)	<0·0001
Impaired test	441 (22·6%)	113 (14·5%)	328 (28·0%)	<0·0001
Physical limitation	7 (0·4%)	1 (0·1%)	6 (0·5%)	0·25
Chair-stand test time at baseline, s	19·6 (19·8)	17·3 (17·8)	21·1 (20·9)	<0·0001
Impaired test	614 (31·4%)	197 (25·3%)	417 (35·5%)	<0·0001
Physical limitation	209 (10·7%)	64 (8·2%)	145 (12·4%)	0·0046
Active physical level	1541 (78·9%)	613 (78·6%)	928 (79·1%)	0·83
Serum biomarkers				
Aβ40, pg/mL	128·23 (96·26–160·59)	126·92 (96·29–156·09)	129·82 (96·24–162·62)	0·29
Aβ42, pg/mL	7·17 (5·44–8·93)	6·90 (5·29–8·56)	7·32 (5·54–9·06)	0·0023
Ratio Aβ42 to Aβ40	0·06 (0·05–0·07)	0·06 (0·05–0·07)	0·06 (0·05–0·07)	0·0019
Total tau, pg/mL	0·80 (0·51–1·12)	0·78 (0·50–1·09)	0·81 (0·52–1·14)	0·16
Phosphorylated tau181, pg/mL	1·08 (0·70–1·65)	1·17 (0·73–1·75)	1·04 (0·69–1·58)	0·0005
Phosphorylated tau217, pg/mL	0·09 (0·05–0·15)	0·10 (0·06–0·17)	0·09 (0·05–0·14)	0·0015
Neurofilament light chain, pg/mL	16·47 (12·04–24·18)	16·26 (11·64–23·84)	16·61 (12·14–24·54)	0·20
GFAP, pg/mL	112·28 (74·97–165·94)	98·60 (65·54–144·29)	121·23 (85·05–185·03)	<0·0001
IL-6, µg/mL	1·45 (0·87–2·53)	1·54 (0·90–2·73)	1·42 (0·85–2·39)	0·016

Data are mean (SD), n (%), or median (IQR). p values represent a comparison between male and female individuals. All the statistical tests were two-sided. A mismatch between total numbers and sample sizes is due to missing data. Missing values for women: BMI=6; Mini-Mental Sate Examination=5; walking speed=8; IL-6=1; *APOE ε*4=22. Missing values for men: Mini-Mental State Examination=2; walking speed=4; IL-6=1; *APOE ε*4=32. Aβ=amyloid β. ADL=activity of daily living. GFAP=glial fibrillary acidic protein.

Table 1: **Baseline characteristics**

Characteristics' comparisons were performed by χ^2 test or Fisher exact test for categorical variables and either analysis of variance, Kruskal–Wallis H, or Mann–Whitney U test for continuous variables.

Linear mixed models with random intercept and random slope were used to assess the association between baseline levels of Alzheimer's disease-related biomarkers and changes in muscle strength over time, as measured by the chair-stand and handgrip strength tests. The β coefficients of the linear mixed models indicate the annual change of the muscle strength tests for 1 SD increase in Alzheimer's disease-related biomarker concentrations. These coefficients

	Handgrip strength test		Chair-stand test	
	Model I: β per year (95% CI)	Model II: β per year (95% CI)	Model I: β per year (95% CI)	Model II: β per year (95% CI)
Phosphorylated tau181	−0·12 (−0·17 to −0·07)	−0·11 (−0·16 to −0·06)	0·93 (0·71 to 1·16)	0·63 (0·41 to 0·85)
Phosphorylated tau217	−0·13 (−0·20 to −0·07)	−0·12 (−0·18 to −0·05)	1·31 (1·03 to 1·58)	0·82 (0·55 to 1·09)
Total tau	−0·02 (−0·05 to 0·01)	−0·02 (−0·05 to 0·01)	0·11 (−0·06 to 0·27)	0·07 (−0·09 to 0·23)
Neurofilament light chain	−0·05 (−0·09 to −0·001)	−0·04 (−0·09 to 0·004)	0·76 (0·56 to 0·96)	0·56 (0·37 to 0·76)
Ratio Aβ42 to Aβ40	0·003 (−0·03 to 0·03)	0·001 (−0·03 to 0·03)	−0·05 (−0·19 to 0·10)	−0·02 (−0·16 to 0·12)
GFAP	−0·004 (−0·04 to 0·03)	−0·001 (−0·03 to 0·03)	0·37 (0·21 to 0·53)	0·27 (0·12 to 0·42)

The table shows the results from fitting linear mixed effect models with longitudinal muscle strength as the outcome and baseline biomarker Z scores. β coefficients are interpreted as handgrip strength decline per year per each SD change in biomarker Z score values or chair-stand test time increase per year per SD change in biomarker Z score values. p values are shown in appendix pp 10–13. Model I adjusted for age, sex, education, smoking and alcohol intake, diabetes, chronic kidney disease, cerebrovascular disease, heart disease, and IL-6. Model II is the same as model I plus adjustment for time-varying Mini-Mental State Examination score. There were ten missing values for smoking habits, six for alcohol consumptions, two for IL-6, and seven for Mini-Mental State Examination. Aβ=amyloid β. GFAP=glial fibrillary acidic protein.

Table 2: **Association between blood-based Alzheimer's disease biomarker Z scores and annual change in handgrip strength test and chair-stand test over the 12-year follow-up**

represent the average rate and direction of muscle strength changes over time (ie, trajectory) across the entire sample. Figures showing trajectories for mean, plus 1 SD, and minus 1 SD biomarker concentrations were derived from the principal model. Covariates were selected based on clinical judgement, previous research on muscle strength and neurodegeneration, and established literature. The principal model adjustments include age, sex, education, chronic kidney disease, diabetes, cerebrovascular disease, heart disease, smoking, alcohol consumption, and serum IL-6 concentrations. Further adjustments of the principal model with *APOE* genotype, time-varying MMSE score, BMI, physical activity, and incident dementia were conducted to explore their potential effects on the association. Specifically, the time-varying MMSE score was used to explore how changes in global cognitive function might influence the association between Alzheimer's disease-related biomarkers and muscle strength.

Stratified and interaction analyses were conducted to investigate potential effect modifiers. Specifically, sex, age, IL-6 concentration, *APOE* genotype, and physical activity were tested as potential moderators and used in further stratified analyses to evaluate changes in the direction of the association.

A linear mixed model adjusted for age and sex was also used to assess the annual rate of cognitive decline, taking the MMSE score as the dependent variable.

Sensitivity analyses were performed to assess the robustness of study findings and the effect of different methodological approaches. First, we excluded individuals diagnosed with musculoskeletal disease at baseline; diagnosed with cerebrovascular disease at baseline; with missing handgrip strength data across all follow-up; with missing chair-stand test data across all follow-up; with missing data for both outcomes across all follow-up; with a baseline chair-stand test time of 75 s; and with either a chair-stand test time of 75 s or missing values at every follow-up. Furthermore, we repeated the analyses after recoding the chair-stand score of 75 s as a missing value, and as 51 s (ie, second worst value).

Data were analysed using R software (version 4.2.3) with the level of statistical significance set at $p<0·05$.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The baseline SNAC-K cohort included 3363 individuals, of whom we excluded 1410 participants for one or more of the following reasons: 191 residing in institutions, 322 with dementia, 40 with Parkinson's disease or parkinsonism, four with multiple sclerosis, 421 without data for baseline handgrip strength, 22 without baseline data for chair-stand tests, and 763 without at least one of the Alzheimer's disease-related biomarkers (appendix p 2). After applying these criteria, 1953 participants remained in the study sample (mean age 70·2 [SD 9·1] years); of these, 780 (39·9%) were male and 1173 (60·1%) were female (table 1). Low handgrip strength was observed in 113 (14·5%) male participants and 328 (28·0%) female participants; impaired chair-stand test was observed in 197 (25·3%) male participants and 417 (35·5%) female participants. 256 (13·1%) participants had low strength detected with both tests. Cohen's κ value for the agreement between physical tests in detecting individuals with low muscle strength was 0·3 ($p<0·0001$). Blood-based Alzheimer's disease-related biomarkers showed different distributions between sexes (table 1). Furthermore, participants with low muscle strength had higher concentrations of p-tau181, p-tau217, t-tau, neurofilament light chain, and GFAP, along with a lower ratio of Aβ42 to Aβ40 (appendix pp 3–4). Excluded participants were older, predominantly women, with more chronic conditions, reduced muscle strength, and higher Alzheimer's disease-related biomarker concentrations than included participants (appendix pp 5–6). The baseline characteristics of the study population by age are shown in the appendix (pp 8–9).

Participants were followed up for mean 9·3 years (SD 3·6). During the follow-up, the mean annual MMSE score decrease was 0·24 (95% CI −0·27 to −0·22; $p<0·0001$). 235 (12·0%) individuals were diagnosed with incident

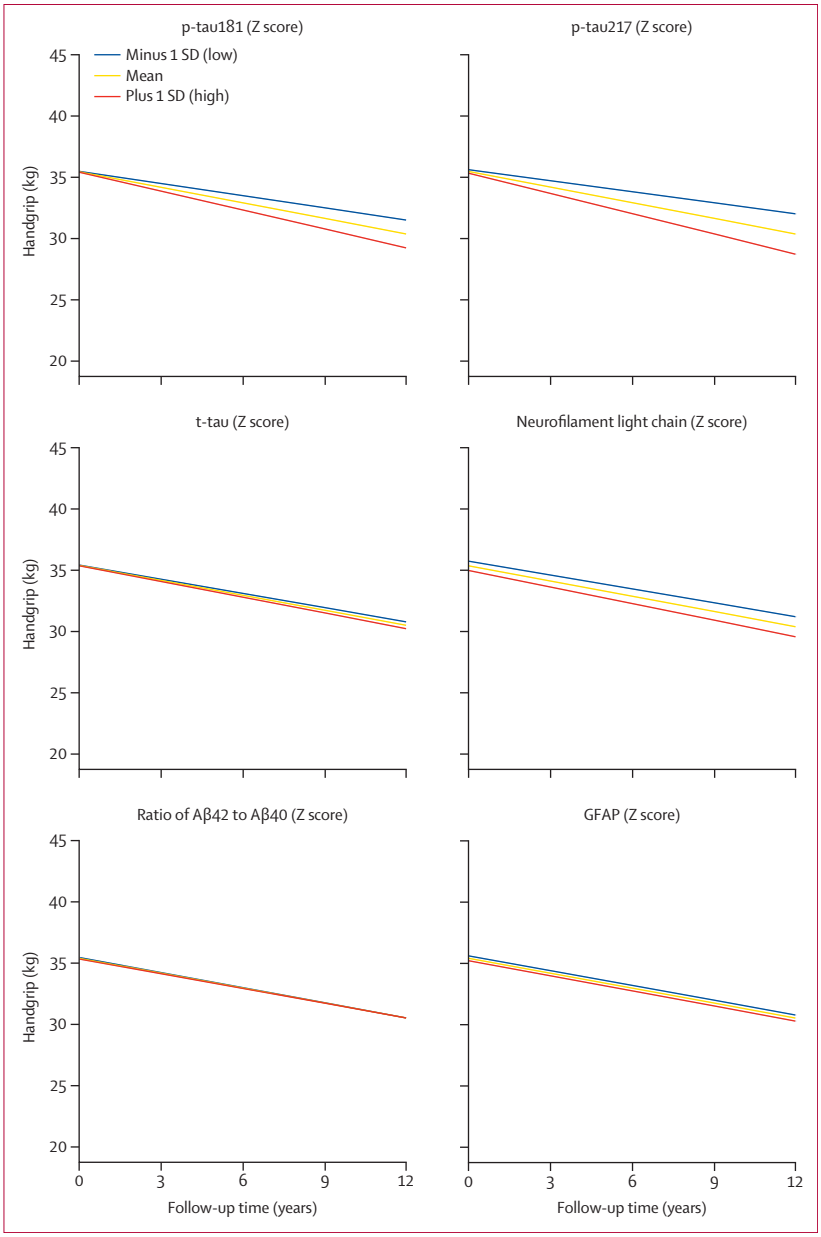

Figure 1: **Longitudinal changes in handgrip strength**
Predicted handgrip strength decline from linear mixed models adjusted for age, sex, education, smoking and alcohol habits, diabetes, chronic kidney disease, cerebrovascular diseases, heart diseases, and IL-6. Aβ=amyloid β. GFAP=glial fibrillary acidic protein. p-tau=phosphorylated tau. t-tau=total tau.

dementia; of these, 152 (64·7%) were female. 558 participants had only baseline assessment of the handgrip strength test, and 411 had only baseline assessment of the chair-stand test; of these, 409 participants had only baseline assessment for both tests.

In the 12-year longitudinal analyses, increases of 1 SD in p-tau181 (β per year –0·12 [95% CI –0·17 to –0·07]; p<0·0001), p-tau217 (β per year –0·13 [–0·20 to –0·07]; p<0·0001), and neurofilament light chain (β per year –0·05 [–0·09 to –0·001]; p=0·047) were associated with a faster decline in handgrip strength after adjusting for potential confounders (table 2 and figure 1). Notably, estimates from this model did not differ significantly from the basic adjusted one (appendix pp 10–11). Results also remained consistent after adjusting for MMSE score introduced as a time-varying measure (model II in table 2). Specifically, there was no attenuation of the association between biomarker concentrations of p-tau181 and p-tau217 and the rate of change in handgrip strength; however, for neurofilament light chain the association was not significant. The same changes in the associations between Alzheimer's disease-related biomarker concentrations and handgrip strength decline were found after adjustment for incident dementia (appendix pp 10–11). When muscle strength was measured through the chair-stand test, increases of 1 SD in p-tau181 (β per year 0·93 [95% CI 0·71 to 1·16]; p<0·0001), p-tau217 (β per year 1·31 [1·03 to 1·58]; p<0·0001), neurofilament light chain (β per year 0·76 [0·56 to 0·96]; p<0·0001), and GFAP (β per year 0·37 [0·21 to 0·53]; p<0·0001) were associated with a faster worsening of performance over time (table 2 and figure 2). Further adjustment of the model for the time-varying MMSE score led to an attenuation of the associations, resulting in a reduction of the rate of lower limb strength decline per year (p-tau181 β per year 0·63 [0·41 to 0·85]; p<0·0001, p-tau217 β per year 0·82 [0·55 to 1·09]; p<0·0001, neurofilament light chain β per year 0·56 [0·37 to 0·76]; p<0·0001, and GFAP β per year 0·27 [0·12 to 0·42]; p=0·0004). The same trend was observed after adjusting the primary model for incident dementia (appendix pp 12–13).

In sex-stratified analyses, a slightly stronger association between GFAP and handgrip strength decline was observed in women compared with men (table 3). Similarly, for the chair-stand test duration, several associations, including with t-tau, neurofilament light chain, and GFAP, were more pronounced among female participants than among male participants (table 3).

When stratifying by IL-6 concentration, no significant differences were observed in the association between Alzheimer's disease-related biomarkers and handgrip strength between groups (table 4). By contrast, for the chair-stand test, a stronger association between decline in muscle strength and both neurofilament light chain and GFAP was observed in the group with higher IL-6 concentrations than in the group with lower IL-6 concentrations.

After stratifying by *APOE* genotype, results appeared to be more heterogeneous than in the main analysis (appendix p 14). Specifically, p-tau181 was associated with a faster worsening in the chair-stand test performance in *APOE* ε4 carriers than in non-*APOE* ε4 carriers. Conversely, neurofilament light chain and GFAP were associated with a faster worsening of the test performance in *APOE* ε4 non-carriers than in *APOE* ε4 carriers. There were no significant differences in the association between Alzheimer's disease-related biomarkers and handgrip strength between groups.

When stratifying by age and physical activity, the association between specific Alzheimer's disease-related biomarkers and muscle strength decline in both tests was more pronounced in younger participants and in inactive participants (appendix pp 15–16).

Excluding individuals with musculoskeletal (n=353) or cerebrovascular diseases (n=75) at baseline, or missing follow-up data for handgrip strength (n=558), chair-stand test (n=411), or both (n=409) yielded results consistent with the main findings (appendix pp 17–18). Further exclusion of individuals with physical limitation (ie, a chair-stand test of 75 s) at baseline (n=209) or follow-up, as well as those with missing chair-stand test evaluation at every follow-up (n=152), resulted in a slight strengthening of the estimates while remaining consistent with our main results. Finally, recoding a chair-stand test score of 75 s as a missing value resulted in a loss of information due to the increase of missing data, whereas replacing 75 s with 51 s led to a slight reduction of the estimates, but the trend remained consistent with the main results (data not shown).

Discussion

We identified significant associations of p-tau181, p-tau217, neurofilament light chain, and GFAP serum concentrations with steeper trajectories of muscle strength decline in older adults without dementia. When accounting for time-varying cognitive performance, the association between the biomarkers and muscle strength trajectories was attenuated when strength was measured through the chair-stand test. Several factors modifying these associations were identified, including age, sex, genetic predisposition for Alzheimer's disease, and systemic inflammation.

We found that study participants with the highest biomarker concentrations showed an independent annual decrease of 0·05–0·13 kg in handgrip strength and increase of 0·37–1·31 s in the chair-stand test. Although there is no established consensus on clinically relevant changes for these muscle strength measures, the functional decline observed for some biomarkers appears to be greater than expected based solely on aging.[31,32] Although previous studies explored the association between blood-based Alzheimer's disease-related biomarkers and physical performance, only a few focused on muscle strength, yielding mixed results. A cross-sectional study of 300 middle-aged and older adults from Ireland's GenoFit study showed a negative association between neurofilament light chain and handgrip strength.[26] However, the study relied on a single biomarker and was conducted cross-sectionally in a relatively small sample. Two longitudinal studies investigating this association among older adults with subjective memory complaints reported inconsistent results. He and colleagues,[27] using data from 452 adults aged 70 years and older of the Multidomain Alzheimer's Preventive Trial (MAPT), found that those with combined low plasma Aβ42 to Aβ40 ratio and high neurofilament light chain had a greater decline in gait speed over time. No association was observed for the chair-stand test. Another study, conducted in 507 MAPT participants, found no longitudinal associations between Aβ42 to Aβ40 ratio or neurofilament light chain and physical performance, assessed through the SPPB and handgrip strength.[28] Both studies had limitations, including relatively small sample sizes, a small biomarker panel, the potential effect of the multidomain intervention on concentrations of Alzheimer's disease-related biomarkers, and a relatively short follow-up. Moreover, the use of study-specific cutoffs for low plasma Aβ42 to Aβ40 ratio and high neurofilament light chain classification restricts the generalisability of the results. These limitations might

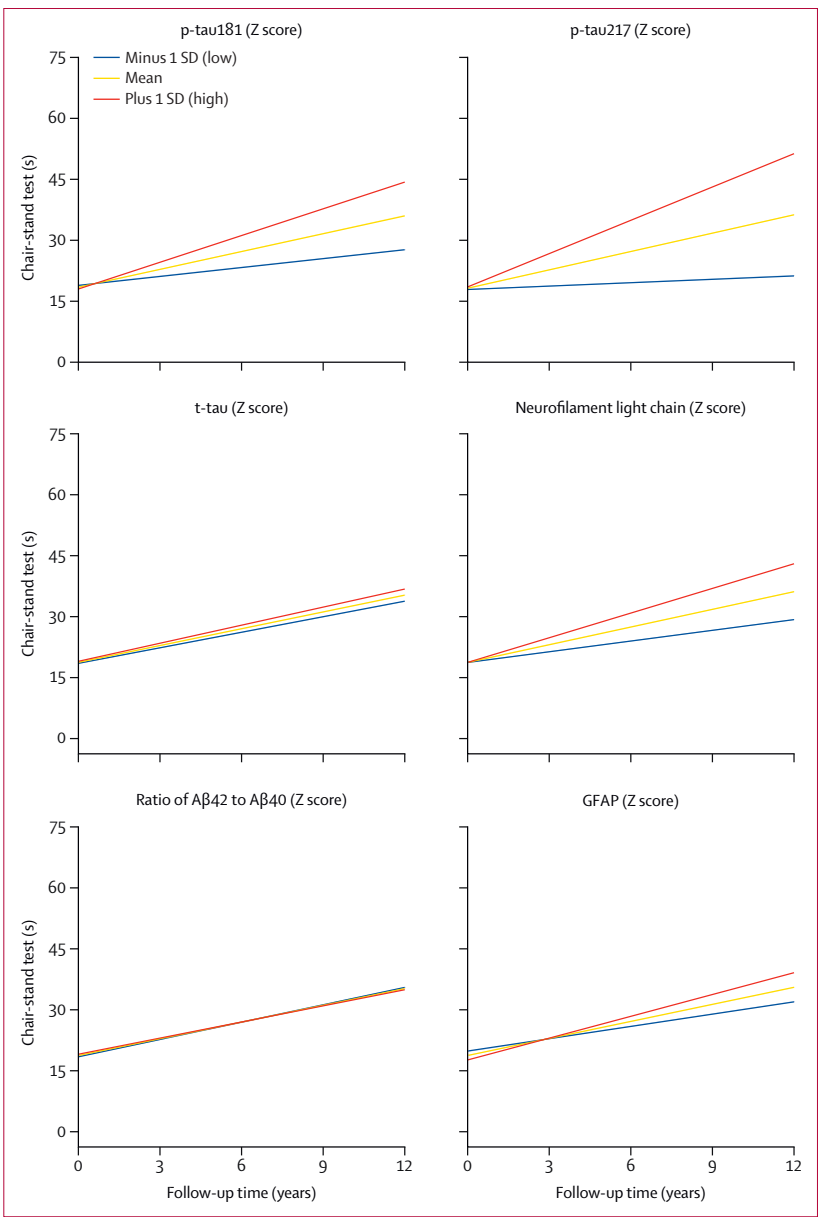

Figure 2: **Longitudinal changes in chair-stand test performance**
Predicted chair-stand test performance decline from linear mixed models adjusted for age, sex, education, smoking and alcohol habits, diabetes, chronic kidney disease, cerebrovascular disease, heart disease, and IL-6. Aβ=amyloid β. GFAP=glial fibrillary acidic protein. p-tau=phosphorylated tau. t-tau=total tau.

	Handgrip strength test			Chair-stand test		
	Males: β per year (95% CI)	Females: β per year (95% CI)	p value for interactions	Males: β per year (95% CI)	Females: β per year (95% CI)	p value for interactions
Phosphorylated tau181	−0·12 (−0·21 to −0·04)	−0·07 (−0·13 to −0·02)	0·33	0·94 (0·60 to 1·28)	1·02 (0·71 to 1·33)	0·66
Phosphorylated tau271	−0·15 (−0·26 to −0·04)	−0·04 (−0·12 to 0·03)	0·066	1·24 (0·81 to 1·67)	1·50 (1·13 to 1·88)	0·30
Total tau	−0·01 (−0·05 to 0·04)	−0·04 (−0·08 to 0·002)	0·25	−0·08 (−0·31 to 0·15)	0·35 (0·10 to 0·60)	0·013
Neurofilament light chain	−0·02 (−0·08 to 0·03)	−0·09 (−0·17 to −0·01)	0·14	0·52 (0·25 to 0·79)	1·12 (0·81 to 1·44)	0·0038
Ratio Aβ42 to Aβ40	−0·01 (−0·06 to 0·05)	−0·01 (−0·04 to 0·02)	0·93	0·15 (−0·09 to 0·38)	−0·17 (−0·36 to 0·02)	0·048
GFAP	0·01 (−0·03 to 0·04)	−0·07 (−0·14 to −0·004)	0·045	0·13 (−0·05 to 0·32)	1·34 (0·99 to 1·69)	<0·0001

The table shows the results from fitting linear mixed effect models with longitudinal muscle strength as the outcome and baseline biomarker Z scores stratified by sex. β coefficients are interpreted as handgrip strength decline per year per each SD change in biomarker Z score values or chair-stand test time increase per year per each SD change in biomarker Z score values. Models adjusted for age, education, smoking and alcohol intake, diabetes, chronic kidney disease, cerebrovascular disease, heart disease, and IL-6. There were ten missing values for smoking habits, six for alcohol consumption, and two missing values for IL-6. Aβ=amyloid β. GFAP=glial fibrillary acidic protein.

Table 3: **Association between blood-based Alzheimer's disease biomarker Z scores and annual change in handgrip strength test and chair-stand test over the 12-year follow-up in males (n=780) and females (n=1173)**

	Handgrip strength test			Chair-stand test		
	IL-6 concentration less than the median: β per year (95% CI)	IL-6 concentration equal to or greater than the median: β per year (95% CI)	p value for interactions	IL-6 concentration less than the median: β per year (95% CI)	IL-6 concentration equal to or greater than the median: β per year (95% CI)	p value for interactions
Phosphorylated tau181	−0·13 (−0·19 to −0·06)	−0·12 (−0·20 to −0·05)	1·0	0·96 (0·67 to 1·26)	0·83 (0·48 to 1·18)	0·48
Phosphorylated tau217	−0·13 (−0·22 to −0·04)	−0·16 (−0·26 to −0·07)	0·48	1·42 (1·05 to 1·80)	1·15 (0·73 to 1·57)	0·31
Total tau	−0·02 (−0·06 to 0·02)	−0·03 (−0·09 to 0·03)	0·80	0·10 (−0·10 to 0·29)	0·23 (−0·07 to 0·52)	0·49
Neurofilament light chain	−0·05 (−0·10 to 0·01)	−0·09 (−0·18 to −0·002)	0·41	0·42 (0·16 to 0·68)	1·02 (0·70 to 1·33)	0·0046
Ratio Aβ42 to Aβ40	0·01 (−0·03 to 0·04)	0·01 (−0·04 to 0·05)	0·97	−0·03 (−0·21 to 0·14)	−0·09 (−0·33 to 0·16)	0·76
GFAP	−0·01 (−0·04 to 0·03)	−0·02 (−0·10 to 0·06)	0·81	0·13 (−0·04 to 0·31)	0·84 (0·50 to 1·18)	0·0002

The table shows the results from fitting linear mixed effect models with longitudinal muscle strength as the outcome and baseline biomarker Z scores stratified by IL-6. β coefficients are interpreted as handgrip strength decline per year per each SD change in biomarker Z score values or chair-stand test time increase per year per each SD change in biomarker Z score values. Model adjusted for age, sex, education, smoking and alcohol habits, diabetes, chronic kidney disease, cerebrovascular disease, and heart disease. IL-6 data were missing for two participants. Aβ=amyloid β. GFAP=glial fibrillary acidic protein.

Table 4: **Association between blood-based Alzheimer's disease biomarker Z scores and annual change in handgrip strength test and chair-stand test over the 12-year follow-up in participants with low (n=975) and high (n=976) IL-6 concentrations**

explain the differences from our study, in which baseline neurofilament light chain concentrations were associated with more accelerated muscle strength decline observed for both tests.

With growing evidence supporting a substantial neurological contribution to skeletal muscle regulation in older adulthood,[33,34] our findings contribute to a better understanding of the mechanisms underlying the muscle–brain crosstalk within a dementia-free, community-based population. Elevated serum neurofilament light chain and GFAP concentrations indicate axonal degeneration and astroglial activation, respectively,[35] while increased serum Aβ and tau concentrations reflect Alzheimer's disease neuropathology.[36] Brain pathology might impair motor input transmission at the neuromuscular junction, reducing motor unit recruitment and muscle trophism.[15] In turn, reduced muscle trophism might disrupt release of myokines, cytokines, and chemokines, crucial for maintaining neuroplasticity. The resulting dysregulation weakens the muscle–brain interaction, potentially accelerating cognitive and motor decline.[19,21] These mechanisms could partially explain the association we observed between Alzheimer's disease-related biomarkers and muscle strength trajectories. Notably, although performance on both tests was associated with Alzheimer's disease-related biomarkers, a stronger association was found for the chair-stand test. Unlike the handgrip test, it involves a more complex movement requiring strength, coordination, and balance. Thus, its stronger association might reflect the neural demands of the task, including cognitive status, motor control, and muscle synergies. Supporting the greater cognitive component, the association was attenuated after adjusting for MMSE score or incident dementia, an effect not observed for handgrip strength.

The presence of the *APOE* ε4 allele strengthened the association between p-tau181 and declining performance on the chair-stand test. No significant differences were observed for p-tau217, although the association followed a similar trend. These findings highlight the possible influence of Alzheimer's disease pathology on decline in lower limb strength.[37] On the other hand, the absence of the *APOE* ε4 allele strengthened the association between neurofilament light chain and GFAP and decline in muscle strength detected by the chair-stand test, suggesting that other aspects related to neurodegeneration might be implicated. Again, no changes in the associations due to the *APOE* ε4 allele were observed for handgrip strength.

These differences highlight that the two tests, although both evaluating muscular strength, are not interchangeable, with the chair-stand test being more influenced by cognitive impairment and neurodegeneration than the handgrip test. This aspect, if confirmed by further studies, could have implications for clinical practice, in which the two tests are currently used interchangeably to evaluate muscle strength and investigate the presence of sarcopenia.

Additionally, a stronger association was found in women than in men, especially for the chair-stand test. Sex-specific pathways could be influenced by hormonal, inflammatory, and metabolic aspects.[12] Another noteworthy aspect of our study is the stronger association between Alzheimer's disease-related biomarkers and muscle strength decline in participants with higher IL-6 serum concentrations. This finding aligns with the concept of inflammaging, whereby the increase in chronic inflammation with ageing contributes to the development of frailty, multimorbidity, and sarcopenia.[11] A stronger association was also observed between neurofilament light chain and chair-stand test decline, as well as GFAP and declines in both handgrip and chair-stand tests, among participants with an inactive lifestyle. These findings suggest the role of physical activity in preserving muscle strength even in the context of neurodegeneration, possibly mitigating neuroinflammation, supporting muscular function, and promoting the release of neuroprotective myokines.[21] Last, heterogeneous results were found in the analysis stratified for age, with only minimal differences observed between groups, warranting further investigation to clarify potential age-related effects.

Strengths of the study include the large population-based sample with a 12-year follow-up, enabling both cross-sectional and longitudinal analyses. The use of a large panel of blood-based Alzheimer's disease-related biomarkers and two different muscle strength tests allowed us to evaluate diverse aspects of their potential association. Finally, analyses were adjusted for multiple confounders and the robustness of the findings was confirmed through sensitivity analyses. Some limitations need to be acknowledged. SNAC-K participants are healthier and of higher socioeconomic status compared with the general Swedish population, potentially affecting the generalisability of our results. Moreover, the considerable amount of missing data led to the exclusion of more than 1000 participants who were older, more multimorbid, and with poorer functional status, likely introducing an underestimation of the associations we tested. Not including compulsory fasting for blood sampling might have influenced the biomarker concentrations. Additionally, the use of serum rather than plasma might have contributed to lower biomarker concentrations. The absence of longitudinal Alzheimer's disease-related biomarker data prevented us from exploring closer the dynamic relationship between biomarkers and muscle strength.

In conclusion, this study highlights a significant association between several blood-based Alzheimer's disease-related biomarkers and trajectories of muscle strength decline, shedding light on the influence of cognitive function. Our findings suggest the potential utility of easily accessible, blood-based Alzheimer's disease-related biomarkers to anticipate progressive muscle strength decline among older adults. Nevertheless, more research is needed to further elucidate this relationship, including a more in-depth exploration of the mediating role played by cognitive function and other factors, to further clarify their potential clinical relevance.

Contributors

DLV and AMO developed the study concept and design. CF and SA conducted the biomarkers analyses. AMO did the data analyses. DLV and AC-L accessed and verified the data. All authors had access to the data and contributed to the interpretation of the results. AMO drafted the first version of the manuscript. All authors provided critical revisions and approved the final version for publication. All authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data are from the SNAC-K project, a population-based study on ageing and dementia (http://www.snac-k.se/). Access to these original data is available to the research community on approval by the SNAC-K organisation. Applications for accessing these data can be submitted through http://www.snac-k.se/.

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