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Original Article

Trajectories of muscle strength and physical performance preceding dementia in older US and European populations

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ABSTRACT

Background: The association between muscle function and dementia risk remains elusive, as studies suggest that impaired muscle function may act as both a risk factor for and a consequence of dementia, hindering causal inference.
Objectives: We aimed to clarify the temporal relationship between muscle function and incident dementia by investigating non-linear trajectories of muscle function in the years preceding dementia onset in older US and European populations.
Design: Case-control study.
Setting: Data were combined from the English Longitudinal Study of Ageing (ELSA, 2004–2018, waves 2–9), Health and Retirement Study (HRS, 2004–2018, waves 7–14), and Survey of Health, Ageing and Retirement in Europe (SHARE, 2004–2017, waves 1–7).
Participants: For handgrip strength analysis, 18,335 participants aged 60 and older were included from the ELSA, HRS, and SHARE cohorts. For gait speed analysis, 11,690 participants aged 60 and older were included from the ELSA and HRS cohorts.
Measurements: Muscle strength was assessed by handgrip strength using a Smedley dynamometer, and physical performance was evaluated by gait speed using the Timed 8-Foot Walk test, with assessments conducted biennially or quadrennially. Dementia was diagnosed using self-reported physician diagnosis and cognitive-functional assessments. Trajectories of muscle strength and physical performance were analyzed on a backward timescale using latent-process mixed models within a nested case-control design.
Results: Significant differences in muscle function trajectories were observed between cases and controls 12 and 13 years prior to dementia onset (handgrip strength: coefficient [SE], -0.23 [0.05], $P < 0.001$; gait speed: coefficient [SE], -0.24 [0.08], $P = 0.003$). The pathological trajectories of handgrip strength and gait speed revealed periods of acceleration beginning 6 and 8 years prior to diagnosis, respectively. After adjusting for pre-dementia acceleration, greater handgrip (per 1-kg increment) was associated with a modest reduction in

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dementia risk (hazard ratio, 0.98; 95 % CI, 0.97–0.99), while faster gait speed (per 1-m/s increment) markedly lowered risk (hazard ratio, 0.35; 95 % CI, 0.23–0.53).
Conclusions: These findings highlight muscle function as a cost-effective tool for early detection and dynamic monitoring of dementia risk and identify it as a modifiable target for prevention. Muscle function may also assist in identifying high-risk groups for preferential enrollment into clinical trials for dementia prevention and treatment.

1. Introduction

Dementia currently impacts over 57 million people worldwide, predominantly those aged 60 and older [1]. This figure is expected to triple by 2050, propelled by aging population and intensifying risk factors [2]. Given the absence of curative therapies, modifiable risk factors of cognitive impairment continue to be the most promising avenues to mitigate the escalating burden.

Muscle function, a proxy for sarcopenia, emerges as a compelling candidate for early detection and intervention [3]. The 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) guidelines redefined sarcopenia by prioritizing muscle function, comprised muscle strength (e.g., handgrip strength) and physical performance (e.g., gait speed), over muscle mass as the primary diagnostic criterion [4]. Prior studies have consistently demonstrated that impaired muscle function is strongly associated with adverse health outcomes, including frailty, disability, and increased risk of mortality. In contrast to muscle mass and other indicators for muscle function, evaluations of handgrip strength and gait speed provide objective and cost-effective measures, thereby improving their applicability in clinical settings.

Previous research has investigated the association between muscle strength, physical performance, and dementia risk. However, the findings remain inconsistent due to potential reverse causality [5–7] While previous studies with follow-up durations of 6-14 years have identified muscle strength and physical performance as risk factors for dementia, [6,8] other research has shown that muscle strength declines before incident dementia as early manifestations of underlying neurodegenerative processes [5,9,10]. The temporal relationship between muscle function and incident dementia is likely complicated and varies in different stages of dementia progression.

Notably, a life-course perspective on muscle strength has been established in previous research, revealing that muscle strength measured as handgrip strength peaks in early adulthood, plateaus, and subsequently declines with age [11–13]. Given the existence of potential reverse causality, it is plausible to hypothesize that muscle function decline accelerates prior to dementia, a phenomenon not captured by previous studies that relied solely on linear trajectory models [9,10]. These studies likely overestimated the absolute rate of muscle function decline in dementia cases, leading to an erroneous perception of earlier divergence between dementia and non-dementia groups. Such miscalculation may distort the role of muscle function as a risk factor by inflating the perceived duration of its manifestation. Recently, studies emerged that discussed potential reverse causality in the acceleration stage of the non-linear trajectories of other risk factors, including depressive symptoms, body mass index (BMI), and frailty in individuals who later developed dementia [14–17]. However, the non-linear trajectories of muscle function preceding dementia have not been investigated.

Prior research has established distinct muscle function trajectories across the life course in healthy individuals, stratified by factors such as gender [4,11]. However, heterogeneity in these trajectories among those who later develop dementia remains underexplored. Beyond gender, which shows significant differences in normative muscle function values, obesity and physical activity are critical due to their potential to concurrently enhance muscle function and cognition at low cost. These modifiable factors may enable dementia-prone individuals with functional vulnerabilities to maintain independence before dementia onset, thereby reducing the substantial disability burden associated with the condition.

Therefore, utilizing harmonized longitudinal data from three large-scale cohorts across the US and Europe, this study aims to [1] investigate the non-linear trajectories of muscle strength and physical performance in the 14 years preceding dementia, [2] examine the association between muscle strength, physical performance, and incident dementia while accounting for the influence of pre-dementia acceleration, [3] detect the heterogeneity in the trajectories among subgroups according to gender, obesity status, and physical activity habit.

2. Methods

2.1. Study population

Data were drawn from three sister longitudinal cohorts with similar protocols to facilitate cross-country comparisons and harmonization: the English Longitudinal Study of Ageing (ELSA) waves 2-9 (2004-2018), the Health and Retirement Study (HRS) waves 7-14 (2004-2018), and the Survey of Health, Ageing and Retirement in Europe (SHARE) waves 1-7 (2004-2017). The study procedures were evaluated and approved by local institutional review boards, and all participants provided written informed consent. Full methodological details have been published elsewhere [18–20]. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2. Muscle function

Muscle function comprised muscle strength (measured as handgrip strength) and physical performance (measured as gait speed).

Handgrip strength was measured using a Smedley dynamometer biennially in HRS and SHARE and quadrennially in ELSA, following standardized protocols. Measurements were taken with the elbow flexed at 90°, either standing or seated for those unable to stand, while maintaining a neutral wrist position. Each hand was tested multiple times, and handgrip strength was defined as the maximum recorded value from either hand. Participants with recent hand injuries, inflammation, or severe pain were excluded [21–23].

Physical performance was evaluated biennially using a gait speed test in participants aged 60 years and older in ELSA and HRS. SHARE was excluded because gait speed testing was limited to waves 1 and 2. Following an initial assessment of walking ability and contraindications, participants completed a timed 8-foot (2.44-meter) walk at their usual pace, as demonstrated by the examiner. Each participant performed two trials, with time recorded to the nearest 0.01 seconds for valid attempts. Any incomplete trials and their reasons were documented. Gait speed was calculated as the 8-foot distance divided by the average time across both trials.

2.3. Incident dementia

In ELSA and SHARE, dementia was classified as "Yes" if: [1] a physician diagnosis was self-reported; or [2] the cognitive impairment and the functional impairment were assessed positive simultaneously. Specifically, for cognitive impairment assessments, memory (immediate and delayed word recall tasks), executive function (animal-naming

fluency task), and orientation (date-naming test) were included. Standardized z-scores were calculated for each of the three cognitive domains using their respective baseline means and standard deviations. These domain-specific z-scores were then averaged and subsequently rescaled based on the baseline mean and standard deviation to derive global cognitive z-scores. Cognitive impairment was defined positive if the individual scored 1.5 standard deviations below the population mean, adjusted for educational attainment and country [24–26]. Functional impairment was identified positive if the individual reported difficulties in one or more activities of daily living, including bathing, eating, dressing, transferring, or walking.

Similarly in HRS, dementia was identified as "Yes" if: [1] a physician diagnosis was self-reported; or [2] a cognitive summary score $\leq$6 (on a 0-27 scale), reflecting significant cognitive and functional impairments [26–28].

These criteria were well-established and consistently applied in previous research [16,26–28].

2.4. Covariates

Baseline covariates included sociodemographic, behavioral, and health-related factors. Sociodemographic variables comprised age, gender, ethnicity (White vs. non-White), study cohort (ELSA, HRS, SHARE), education level (below upper secondary, upper secondary, tertiary), and total household wealth (categorized into quintiles, with the highest quintile indicating the greatest wealth). Behavioral factors included current smoking status, alcohol consumption (classified as none-to-moderate [$\leq$2 drinks/day for men or $\leq$1 drink/day for women] or heavy,[29]) physical activity (classified as weekly moderate-to-vigorous activity [MVPA] if the individual participates in both moderate and vigorous activity at least weekly, or less-than-weekly MVPA otherwise,[25]) body mass index (BMI), and social contact, assessed via the 5-item Social Isolation Index; participants scoring in the top 40 % of the distribution were defined as socially active [30,31]. Health-related conditions were based on self-reported physician diagnoses of hypertension, diabetes, cancer, pulmonary disease, heart disease, stroke, and depression (assessed using the Center for Epidemiologic Studies Depression Scale [CES-D]). Missing data was imputed using multiple imputation chain-equation (MICE).

2.5. Nested case-control approach

ELSA, HRS and SHARE data were pooled for analysis. Among the 59736 participants assessed at baseline, 30283 were excluded due to being younger than 60 years (n = 21227), having a diagnosis of dementia at baseline, or lacking at least one follow-up assessment for dementia diagnosis (n = 9056). The analytical sample comprised 29453 individuals, of whom 4635 developed incident dementia during follow-up (Fig. S1).

Each dementia case was matched to four controls at the wave when the diagnosis was established, following procedures described in prior research [15,17,32]. Controls were required to be dementia-free, with no replacement allowed either within or between waves. Matching was performed on age ($\pm$ 3 years), gender, ethnicity, educational attainment, and cohort origin. For handgrip strength analysis, 3667 (79.1 %) of the 4635 dementia cases were successfully matched to four controls, resulting in a final nested case-control sample of 18335 individuals. For gait speed analysis, 2338 (72.8 %) of the 3213 dementia cases were successfully matched, resulting in a final sample of 11690 individuals.

2.6. Statistical analysis

Trajectories of handgrip strength and gait speed over 14 years were modeled using a backward timescale with latent-process mixed models to handle non-Gaussian longitudinal markers [17,33]. For cases, the year 0 was the year of dementia diagnosis; for controls, it was the year of censoring or three years before death. The three-year censoring rule was implemented to address the well-documented phenomenon of terminal decline—marked deterioration across multiple health domains typically occurring in the final years of life [34–37]. This approach helps mitigate confounding from end-of-life decline and improves the comparability of muscle function trajectories before incident dementia with those observed in normal aging. The fixed effects of the models included dementia status, time, time-squared, time-cubed, and their interactions, adjusted by matching covariates (age, gender, ethnicity, educational attainment, and cohort origin); the random effects included intercept and time [14]. The non-linear function is a basis of quadratic I-splines with 5 knots placed at the quantiles of the distribution of muscle function. The models were selected based on Akaike Information Criterion (AIC) [17].

First, a global test was conducted to evaluate overall differences over time. Subsequently, we tested for time-specific differences in muscle function's trajectories between cases and controls, by applying Wald tests to dementia status and its interactions with time terms (i.e., time, time-squared, time-cubed). The starting point of difference was defined as the earliest time point at which a significant difference was observed and remained significant at all subsequent time points.

The starting point of acceleration was defined as the first time point when the second derivative of the annually computed differences in predicted muscle function values became significantly negative and remained negative thereafter. This definition was chosen over the starting point of difference to reflect the point where dementia begins to independently accelerate muscle function decline, distinct from covariate-driven differences (e.g., age, stroke, diabetes) observed in our cohort design. This approach mitigates confounding from baseline imbalances and aligns with the clinical manifestation of dementia in late life.

Finally, we examined the association between muscle function and incident dementia using Cox proportional hazards models adjusted by wealth, hypertension, diabetes, cancer, pulmonary disease, cardiovascular disease, stroke, CES-D scores, BMI, smoking status, alcohol consumption, moderate-to-vigorous physical activity (MVPA), and social contact, in the total sample, the subgroup before the acceleration period, and the subgroup within the acceleration period [16]. The proportional hazards assumption was assessed using weighted Schoenfeld residuals. Non-linear associations were explored using restricted cubic splines with five knots, applied to subgroups where the proportional hazards assumption was met.

Sensitivity analyses for the main analyses were performed using non-imputed datasets, employing the same latent-process mixed models as in the main analyses and fitting the Cox proportional hazards models adjusted for covariates with less than 5 % missing data.

To explore the heterogeneous progression of muscle function within participants who developed dementia, we stratified the trajectory analyses by gender, obesity status, and physical activity. Furthermore, a subgroup analysis stratified by these factors was performed to examine the associations between handgrip strength and gait speed with the risk of developing dementia.

All significance testing was two-tailed and unpaired. The overall primary significance level was set at 0.05, with corrected thresholds implemented to account for multiple testing [38]. All statistical analyses were performed using R version 4.4.1.

3. Results

3.1. Baseline characteristics

This study included 18335 participants for handgrip strength analysis (mean [SD] age at baseline, 71.0 [7.0] years; 10985 women [59.9 %]; 9931 below upper secondary education [55.2 %]; 17160 white [93.6 %]) and 11690 participants for gait speed analysis (mean [SD] age at baseline, 71.2 [7.2] years; 7020 women [60.1 %]; 6344 upper

secondary education [55.9 %]; 10515 white [89.9 %]), respectively. The median duration of follow-up was 10 years (interquartile range: 6-14 years) for the total sample and 8 years (interquartile range: 4-10 years) for dementia cases. At baseline (Table 1), participants who developed dementia were older, had lower wealth accumulation, a higher prevalence of cardiometabolic diseases, and engaged in less physical activity and social interaction. They also demonstrated weaker handgrip strength and slower gait speed compared to controls.

3.2. Trajectories of handgrip strength and gait speed before dementia or censor

Fig. 1 illustrated the trajectories of handgrip strength and gait speed for both cases and controls on a retrospective timescale. Globally, both handgrip strength and gait speed declined significantly over time (both $P < .001$). Handgrip strength declined more steadily in controls (year -14: 24.45 kg [95 % CI, 24.15 to 24.73]; year 0: 23.64 kg [95 % CI, 23.32 to 23.98]) compared to cases (year -14: 24.18 kg [95 % CI, 23.58 to 24.81]; year 0: 20.52 kg [95 % CI, 20.11 to 20.93]) over time. For gait speed, the control group showed no apparent decline (year -14: 0.87 m/s [95 % CI, 0.85 to 0.88]; year 0: 0.85 m/s [95 % CI, 0.84 to 0.87]), whereas cases exhibited a significant decline over time (Table S1).

Trajectories of handgrip strength began to differ significantly between dementia cases and controls 12 years before diagnosis (coefficient [SE], -0.23 [0.05], $P < 0.001$) (Table S2). At this time point, the marginal estimate for handgrip strength was 23.43 kg (95 % CI, 23.04 to 23.80) in dementia cases and 24.31 kg (95 % CI, 24.08 to 24.54) in controls. Similarly, the trajectory of gait speed showed a marked divergence 13 years prior to dementia diagnosis (coefficient [SE], -0.24 [0.08], $P = 0.003$). The marginal estimate of gait speed 12 years before diagnosis was 0.81 m/s (95 % CI, 0.79 to 0.83) in dementia cases and 0.86 m/s (95 % CI, 0.84 to 0.87) in controls.

The onset of accelerated decline in muscle function was marked by distinct time points: handgrip strength began to diverge at year -6, and gait speed at year -8. At these points, the second derivative of the annual differences in predicted values between cases and controls first turned significantly negative and remained so thereafter (Fig. S2). At year -6, handgrip strength averaged 23.79 kg (95 % CI, 23.58 to 24.01) in controls, compared with 22.14 kg (95 % CI, 21.85 to 22.43) in cases. Similarly, at year -8, gait speed averaged 0.85 m/s (95 % CI, 0.84 to 0.86) in controls versus 0.80 m/s (95 % CI, 0.78 to 0.81) in cases.

3.3. Association of handgrip strength, gait speed, and dementia

We initially examined the relationships between handgrip strength, gait speed, and dementia risk using raw data. Only the subgroups before the acceleration period satisfied the proportional hazards assumption (Table S3). Each 1 kg increment in handgrip strength was associated with a reduced dementia risk (hazard ratio [HR] 0.98, 95 % CI 0.97-0.99; Fig. 2A). Similarly, each 1 m/s increase in gait speed corresponded to a lower dementia risk (HR 0.35, 95 % CI 0.23-0.53; Fig. 2C). To facilitate direct comparisons of effect sizes, we conducted Cox proportional hazards regressions with standardized values of handgrip strength and gait speed (Fig. S3). A 1 standard deviation (SD) increase in handgrip strength conferred a 20 % lower risk of dementia (HR 0.80, 95 % CI 0.73-0.88), while a 1 SD increase in gait speed was associated with a 27 % lower risk (HR 0.73, 95 % CI 0.65-0.83). Dose-response relationships were evident for both handgrip strength and gait speed with incident dementia ($P < 0.001$ for both), with no significant non-linear effects ($P = 0.06$ for handgrip strength; $P = 0.08$ for gait speed; Fig. 2B, D). Critical thresholds for null dementia risk (HR = 1) were established at 29.07 kg for handgrip strength and 0.85 m/s for gait speed.

3.4. Sensitivity analyses and subgroup analyses

Findings were robust in the sensitivity analyses using non-imputed data (Fig. S2-5, Tables S3-5). Heterogeneity in the muscle function

Table 1
Characteristics of analytical samples at baseline.

	Handgrip Strength			Gait Speed		
Characteristic	Controls	Cases	P value	Controls	Cases	P value
N	14668	3667		9352	2338	
Age (mean (SD))	70.37 (6.81)	73.33 (7.12)	<0.001	70.64 (7.13)	73.17 (7.31)	<0.001
Female (%)	8788 (59.9)	2197 (59.9)	1	5616 (60.1)	1404 (60.1)	1
Ethnicity (%)			1			1
White	13728 (93.6)	3432 (93.6)		8412 (89.9)	2103 (89.9)	
Non-white	940 (6.4)	235 (6.4)		940 (10.1)	235 (10.1)	
Education (%)			0.999			0.979
Below upper secondary	7938 (55.2)	1993 (55.2)		2622 (28.9)	664 (29.1)	
Upper secondary	5073 (35.3)	1271 (35.2)		5073 (55.9)	1271 (55.7)	
Tertiary	1376 (9.6)	345 (9.6)		1376 (15.2)	345 (15.1)	
Total wealth (%)			<0.001			<0.001
Lowest quintile	3038 (20.9)	969 (26.8)		1925 (20.7)	648 (27.7)	
Second quintile	3517 (24.2)	918 (25.4)		2231 (23.9)	557 (23.8)	
Third quintile	3154 (21.7)	703 (19.4)		1989 (21.3)	440 (18.8)	
Fourth Quintile	2647 (18.2)	581 (16.1)		1717 (18.4)	384 (16.4)	
Highest quintile	2184 (15.0)	444 (12.3)		1458 (15.6)	308 (13.2)	
Hypertension (%)	6802 (46.4)	1817 (49.6)	0.001	4804 (51.4)	1248 (53.4)	0.086
Diabetes (%)	1825 (12.4)	615 (16.8)	<0.001	1291 (13.8)	393 (16.8)	<0.001
Cancer (%)	1400 (9.5)	362 (9.9)	0.569	1135 (12.1)	294 (12.6)	0.587
Pulmonary diseases (%)	925 (6.3)	266 (7.3)	0.041	688 (7.4)	179 (7.7)	0.653
Heart diseases (%)	2721 (18.6)	826 (22.5)	<0.001	1998 (21.4)	575 (24.6)	0.001
Stroke (%)	664 (4.5)	330 (9.0)	<0.001	492 (5.3)	240 (10.3)	<0.001
CESD (mean (SD))	1.28 (1.81)	1.69 (2.00)	<0.001	1.28 (1.81)	1.69 (2.00)	<0.001
BMI (mean (SD))	26.95 (4.26)	26.95 (4.59)	0.996	27.82 (4.64)	28.14 (4.96)	0.135
Smoke (%)	1656 (11.3)	380 (10.4)	0.12	1065 (11.5)	242 (10.4)	0.171
Alcohol (%)	701 (10.2)	145 (8.3)	0.022	701 (10.2)	145 (8.3)	0.022
MVPA (%)	4130 (28.2)	751 (20.6)	<0.001	1694 (18.2)	320 (13.8)	<0.001
Social contact (%)	3161 (44.3)	602 (35.1)	<0.001	880 (47.5)	184 (45.3)	0.46
Handgrip strength (mean (SD))	30.34 (11.08)	26.97 (10.76)	<0.001	29.33 (10.83)	26.81 (10.33)	<0.001
Gait speed (mean (SD))	1.23 (6.19)	1.12 (4.77)	0.553	0.97 (3.12)	0.76 (0.27)	0.043

Abbreviations: CES-D, the Center for Epidemiologic Studies Depression Scale; BMI, body mass index; MVPA, weekly moderate-to-vigorous activity.

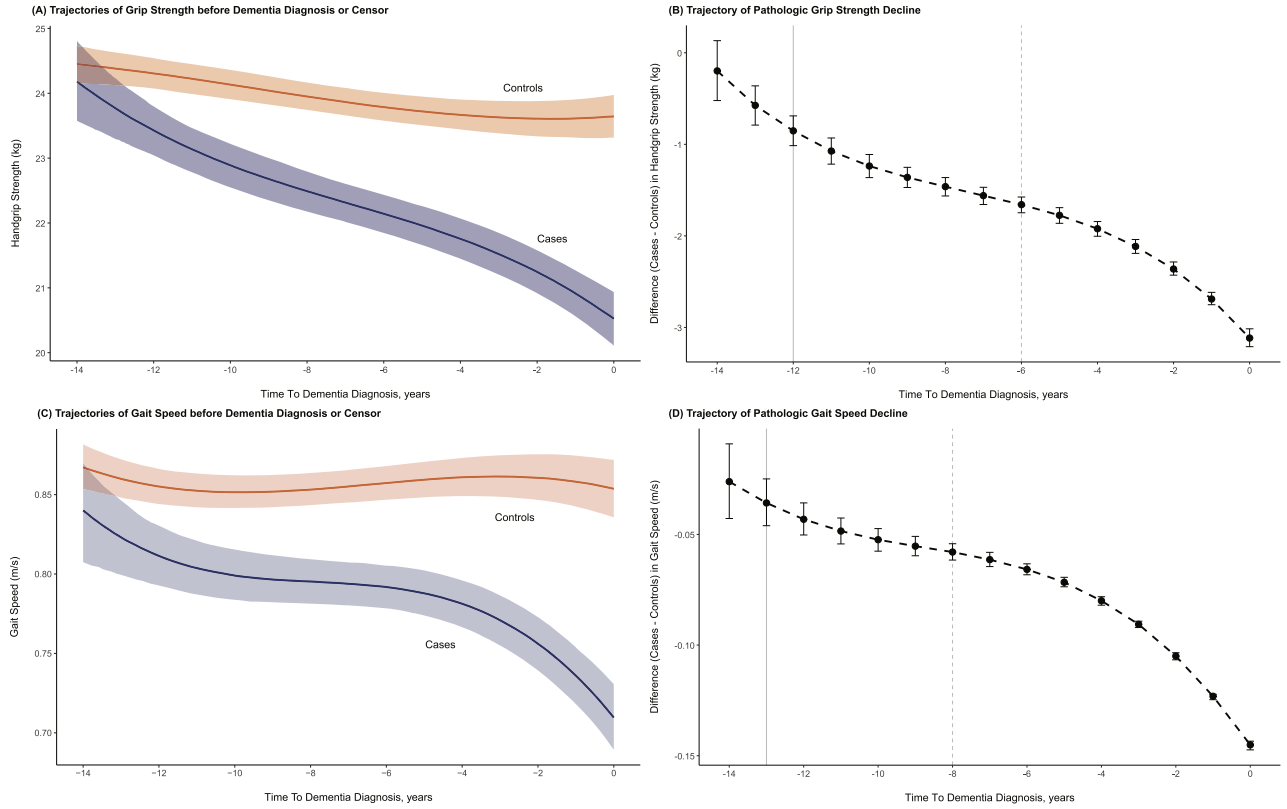

Fig. 1. Trajectories of Handgrip Strength and Gait Speed Before Dementia Diagnosis or Censoring

Trajectories were modeled using latent-process mixed models on a backward timescale, with the fixed effects including dementia status, time, time^2, time^3, and their interactions, adjusted for baseline age, gender, ethnicity, education, and study cohort. Trajectories for handgrip strength were estimated for a prototypical study participant: a white woman aged 65 years at baseline, enrolled at SHARE cohort, with an educational attainment below upper secondary. Trajectories for gait speed were estimated for a participant: a white woman aged 65 years at baseline, enrolled at HRS cohort, with an educational attainment upper secondary. Notably, the choice of profile affects only the trajectory levels, leaving differences between cases and controls and statistical test significance unchanged. The thresholds corrected for multiple testing were 1.02 % for handgrip strength and 0.95 % for gait speed.

Panels (A) and (C): Solid lines represent estimated mean trajectories, with shaded areas indicating 95 % confidence intervals (CIs). Trajectories were derived from latent-process mixed models using a backward timescale, incorporating dementia status, time, time^2, time^3, and their interactions, adjusted for baseline age, gender, ethnicity, education, and study cohort.

Panels (B) and (D): Dashed curves show the difference in estimated mean values between cases and controls. Solid gray lines mark the onset of divergence, and dashed gray lines indicate the start of accelerated decline. The interval between these lines represents the optimal time window for targeted intervention.

trajectories was evident among participants diagnosed with dementia during follow-up, with distinct patterns across subgroups (Fig. 3, Tables S6-8). Women consistently exhibited lower handgrip strength and gait speed than men throughout the study period. In men, both handgrip strength and gait speed declined significantly over time, whereas women showed no notable decline in handgrip strength. At baseline, obese participants had higher handgrip strength than their non-obese counterparts but experienced a steeper decline, resulting in lower values by dementia diagnosis. In contrast, non-obese participants sustained swifter gait speeds over time, marked by a plateau, while obese participants experienced a continuous decline in gait speed. Participants engaging in regular MVPA consistently displayed superior handgrip strength and gait speed. Notably, gait speed in MVPA participants remained stable until approximately 5 years prior to dementia diagnosis, followed by an accelerated decline. Additionally, associations between handgrip strength, gait speed, and dementia risk in subgroup analyses remained aligned with those from the main analyses (Fig. 4).

4. Discussion

To our knowledge, this is the first study to illustrate the non-linear trajectories of both handgrip strength and gait speed in the years prior to dementia onset, using data from three large and geographically diverse cohorts. By embedding muscle function within a temporal framework, our study offers novel insights into its dynamic role in dementia development—as a potential risk factor and later emerging as a preclinical manifestation. This longitudinal perspective helps disentangle temporal associations and mitigates concerns of reverse causality. Our key findings are: first, divergence in handgrip strength and gait speed trajectories between individuals who developed dementia and those who did not emerge at least 12 and 13 years prior to diagnosis, respectively; second, we identified that handgrip strength decline accelerated approximately 6 years before diagnosis, while the acceleration of gait speed decline began 8 years prior, which may indicate a critical point for muscle function as a precursor to pre-diagnostic dementia; third, both handgrip strength and gait speed were robust risk factors for dementia, even after minimizing the possibility of reverse causality by accounting for pre-diagnostic acceleration; finally, among individuals later diagnosed with dementia, those who maintained a healthy weight and exercised regularly preserved better physical function.

Our observation that declining handgrip strength and gait speed may function as early biomarkers of dementia is consistent with prior findings from the UK Biobank, which identified a significant association between reduced handgrip strength and subsequent dementia diagnosis up to 15 years in advance [10]. However, prior studies did not explore

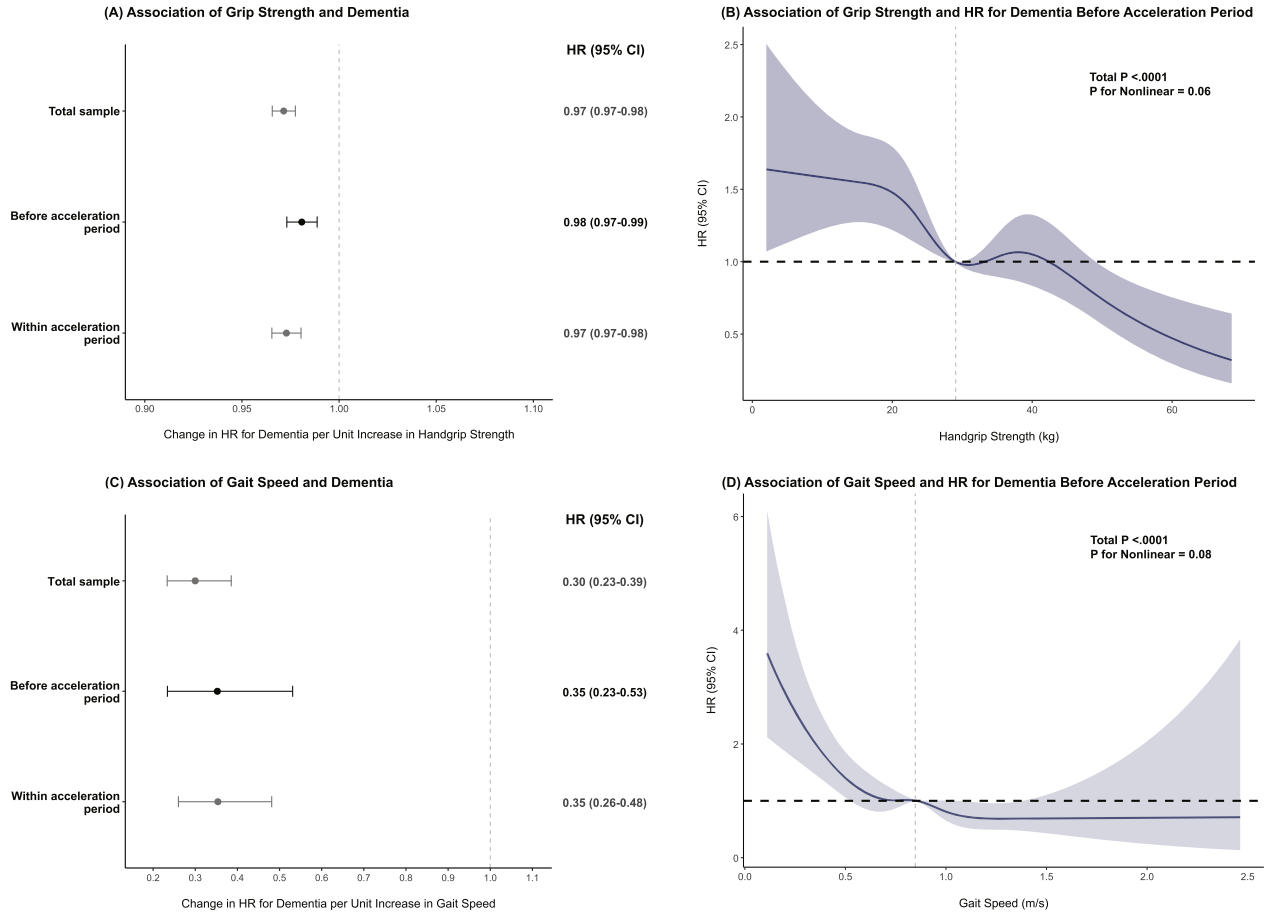

Fig. 2. Association of grip strength and gait speed with dementia risk.
Cox proportional hazards models were used to assess associations between muscle function (handgrip strength and gait speed) and dementia risk, adjusted for age, gender, ethnicity, education, wealth, hypertension, diabetes, cancer, pulmonary disease, cardiovascular disease, stroke, CES-D scores, BMI, smoking status, alcohol consumption, moderate-to-vigorous physical activity (MVPA), and social contact. Panels (A) and (C) show the hazard ratio (HR) for dementia risk per unit increase in handgrip strength (kg) and gait speed (m/s), respectively. Black lines indicate results where the proportional hazards assumption was met; grey lines indicate unreliable results where the assumption was violated. Panels (B) and (D) depict non-linear associations in subgroups before the acceleration period, with solid blue lines representing HRs, blue shaded areas indicating confidence intervals, and dashed grey lines marking the reference (HR = 1). The proportional hazards assumption held only for the subgroup before the acceleration period, with cut-off points at 29.07 kg for handgrip strength and 0.85 m/s for gait speed.

gender-specific differences in trajectories of handgrip strength together with those of gait speed. Our subgroup analyses revealed the importance of dynamically monitoring both handgrip strength and gait speed in women, as handgrip strength alone tended to plateau in women who later developed dementia.

A key limitation of existing research lies in the use of linear trajectory models of muscle function, which may overestimate the perceived duration of manifestation and obscure the temporal association between muscle function and dementia, particularly in the context of reverse causality [9,10]. To address this, the present study employed non-linear modeling to capture more nuanced changes in muscle function over time, allowing for the identification of an acceleration phase. This analytical approach aligns closely with a previous study that modeled non-linear trajectories of the frailty index preceding dementia [16]. However, unlike the frailty index—which depends on dozens of self-reported symptoms, disabilities, and chronic conditions—our study relies on objective, performance-based measures of handgrip strength and gait speed.

By excluding the impact of pre-dementia acceleration, hazard ratio estimates (HR = 0.98 per 1 kg increase in handgrip strength; HR = 0.35 per 1 m/s increase in gait speed) suggest clinically relevant reductions in dementia risk, which is consistent with previous research [6,8,39]. Drawing on prior intervention studies, an average of 2.4 kg increase in handgrip strength can be achieved through physical and nutritional intervention, even in prefrail or frail older adults, corresponding to an estimated 5 % reduction in dementia risk [40]. Similarly, a 0.13 m/s increase in gait speed via resistance training aligns with an estimated 8 % risk reduction [41]. Additionally, results from subgroup analyses emphasize that regular exercise and weight control may help maintain physical function in older adults even in the context of subsequent dementia. These findings reinforce the well-established role of physical activity in mitigating muscle decline and reducing dementia risk. However, weight control warrants greater attention—particularly in dementia-prone individuals at risk of sarcopenic obesity, a condition defined by the coexistence of obesity and muscle loss and increasingly prevalent in aging populations. Obesity promotes fat infiltration into muscle, accelerates physical deterioration, and is independently associated with elevated dementia risk [4,42]. Addressing both physical inactivity and excess weight may therefore reduce the burden of disability related to dementia in late life. Taken together, these findings highlight muscle function as a modifiable risk factor before prodromal dementia, suggesting a potential target for early intervention and dementia prevention.

A major strength of our study is the use of three large, prospective cohorts from two continents, combined with longitudinal trajectory modeling to examine the temporal relationship between muscle function

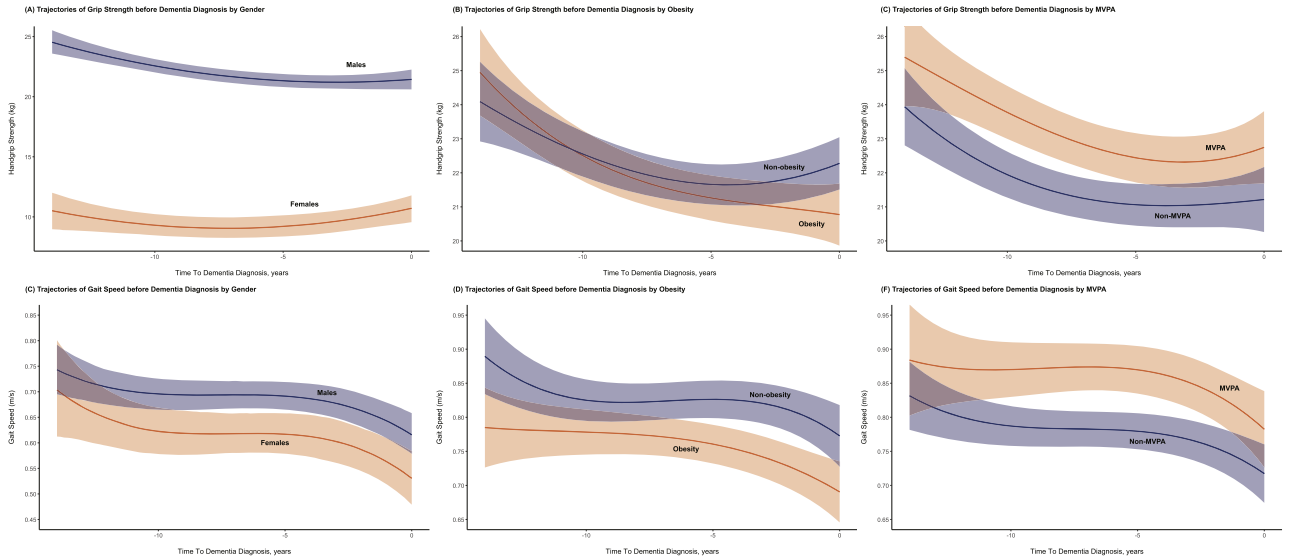

Fig. 3. Trajectories of grip strength and gait speed before dementia by subgroups.
Solid lines represent estimated mean trajectories, with shaded areas indicating 95 % confidence intervals (CIs). Solid lines depict estimated mean trajectories, with shaded regions representing 95 % confidence intervals (CIs). Trajectories were modeled using latent-process mixed models on a backward timescale, incorporating subgroup status (gender, obesity, and moderate-to-vigorous physical activity [MVPA]), time, time^2, time^3, and their interactions. Models were adjusted for baseline age, gender, ethnicity, education, and study cohort in participants diagnosed with dementia during follow-up.

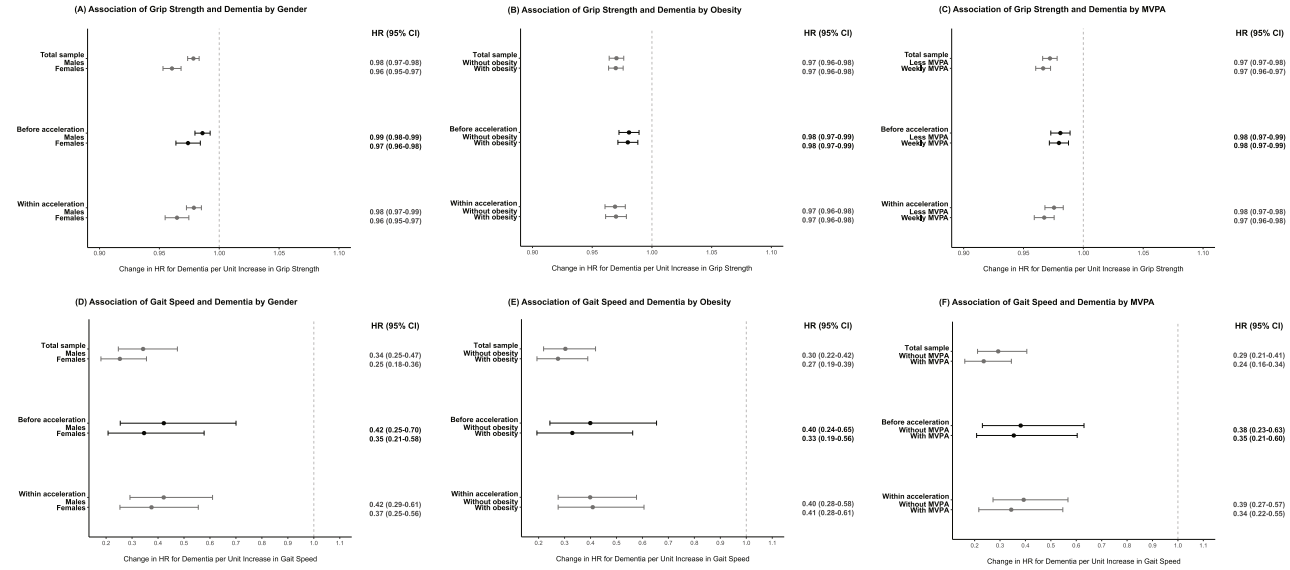

Fig. 4. Association of grip strength and gait speed with dementia risk across subgroups.
Cox proportional hazards models evaluated the associations between muscle function (handgrip strength and gait speed) and dementia risk, incorporating subgroup interaction terms. Models were adjusted for age, gender, ethnicity, education, wealth, hypertension, diabetes, cancer, pulmonary disease, cardiovascular disease, stroke, CES-D scores, body mass index (BMI), smoking status, alcohol consumption, moderate-to-vigorous physical activity (MVPA), and social contact. Black lines denote results satisfying the proportional hazards assumption; grey lines indicate results where the assumption was violated.

and dementia, while minimizing the potential for reverse causation. However, this study has limitations. First, we did not analyze muscle mass as it was not assessed across the three cohorts. However, the definition of sarcopenia has been revised in the 2019 European Working Group on Sarcopenia in Older People (EWGSOP2) guidelines, shifting emphasis from muscle mass to muscle strength as the primary diagnostic criteria [4]. Previous studies have suggested that decline of muscle function is more strongly associated with dementia than reduced muscle mass [5]. Second, the ability to draw definitive causal conclusions is constrained, as our modeled trajectories relied on observational data and baseline covariates were collected substantially before dementia onsets. Nevertheless, this large-scale prospective cohort study provides robust evidence, particularly given the ethical barriers to conducting randomized controlled trials (RCTs) in this context. Third, the exclusion of participants under 60 years of age may limit the generalizability of the study's findings to younger populations. Fourth, SHARE was excluded from the gait speed analyses due to limited data availability, as gait speed was only assessed in waves 1 and 2. Fifth, although cognitive assessments were generally harmonized across cohorts, differences in instruments and scoring criteria between HRS and the European cohorts (ELSA and SHARE) may have introduced measurement variability.

5. Conclusions

Utilizing three large prospective cohorts from two continents, this study illustrated the pathologic trajectories of muscle strength and physical performance in the years preceding dementia. By incorporating the acceleration period into the analysis, we mitigated potential reverse causality and strengthened evidence linking muscle strength and physical performance as modifiable risk factors for dementia. These findings highlight muscle function as a cost-effective tool for early detection and dynamic monitoring of dementia risk, and it may also assist in identifying high-risk groups for preferential enrollment into clinical trials for dementia prevention and treatment.

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Ethics approval and consent to participate

The English Longitudinal Study of Ageing (ELSA) was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91). The Health and Retirement Study (HRS) received approval from the Institutional Review Board at the University of Michigan and the National Institute on Aging (HUM00061128). The Survey of Health, Ageing and Retirement in Europe (SHARE) had its ethical approval process managed by the Ethics Committee of the Max Planck Society for the Advancement of Science. Ethical approvals were secured from relevant local committees for both cohorts, and participants provided written informed consent at each interview stage.

Consent for publication

Not applicable.

Availability of data and materials

The original the ELSA dataset is available at https://www.elsa-project.ac.uk/. The HRS dataset is accessible at https://hrs.isr.umich.edu/. The SHARE dataset is accessible at https://share-eric.eu/data/data-access. The complete dataset analyzed herein can be obtained from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Youjin Jiang: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Yi Ding:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Qiuyu Cao:** Writing – review & editing, Validation, Supervision. **Xianglin Wu:** Writing – review & editing, Validation, Supervision. **Xiaoran Li:** Validation. **Yu Xu:** Validation, Supervision. **Zhiyun Zhao:** Validation, Supervision. **Min Xu:** Validation, Supervision. **Jieli Lu:** Validation, Supervision. **Tiange Wang:** Validation, Supervision. **Guang Ning:** Validation, Supervision. **Weiqing Wang:** Validation, Supervision. **Yufang Bi:** Validation, Supervision, Funding acquisition, Data curation, Conceptualization. **Yuchen Xu:** Validation, Supervision, Data curation, Conceptualization. **Mian Li:** Validation, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100296.

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