Received: 24 May 2022 | Revised: 8 October 2022 | Accepted: 22 November 2022

DOI: 10.1002/dad2.12388

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Grip strength, gait speed, and trajectories of cognitive function in community-dwelling older adults: A prospective study

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Funding information
National Institute on Aging and the National Cancer Institute, Grant/Award Numbers: U01AG029824, U19AG062682; National Health and Medical Research Council (NHMRC), Grant/Award Numbers: 334047, 1127060; NHMRC Dementia Research Leader Fellowship, Grant/Award Number: APP1135727; Monash University; Victorian Cancer Agency; Zimu Wu received an Australian Research Training Program Scholarship

Abstract

Introduction: This study investigated whether grip strength and gait speed predict cognitive aging trajectories and examined potential sex-specific associations.

Methods: Community-dwelling older adults (n = 19,114) were followed for up to 7 years, with regular assessment of global function, episodic memory, psychomotor speed, and executive function. Group-based multi-trajectory modeling identified joint cognitive trajectories. Multinomial logistic regression examined the association of grip strength and gait speed at baseline with cognitive trajectories.

Results: High performers (14.3%, n = 2298) and low performers (4.0%, n = 642) were compared to the average performers (21.8%, n = 3492). Grip strength and gait speed were positively associated with high performance and negatively with low performance (P-values < 0.01). The association between grip strength and high performance was stronger in women (interaction P < 0.001), while gait speed was a stronger predictor of low performance in men (interaction P < 0.05).

Discussion: Grip strength and gait speed are associated with cognitive trajectories in older age, but with sex differences.

KEYWORDS
cognitive function, gait speed, grip strength, older adults, prospective

Highlights

- There is inter-individual variability in late-life cognitive trajectories.
- Grip strength and gait speed predicted cognitive trajectories in older age.
- However, sex-specific associations were identified.
- In women, grip strength strongly predicted high, compared to average, trajectory.
- In men, gait speed was a stronger predictor of low cognitive performance trajectory.

1 | INTRODUCTION

The preservation of mobility through adequate physical function is critical for the maintenance of independence with aging.[1] Physical function and mobility share biological processes with cognitive activities, such as neurological and musculoskeletal functioning.[2] Decline in physical and cognitive function may co-occur in older individuals and be risk factors for one another.[3,4]

Grip strength and gait speed are key components of common frailty assessments[5] and important determinants in maintaining mobility into older age.[6–8] Grip strength reflects upper limb strength,[9] while gait speed indexes the movements using lower limbs, along with balance.[10] Although there are studies suggesting that grip strength and gait speed are predictive of incident dementia,[11–14] it remains unclear to what extent these two physical function measures are associated with cognitive aging trajectories, and importantly, whether better physical function is associated with higher cognitive performance.

Cognitive aging is not a uniform process with some individuals demonstrating decline in their cognitive trajectories with age, while others can remain stable.[15] However, there is a clear knowledge gap regarding the association of grip strength and gait speed with individual variance in these trajectories. Moreover, body composition and physical function intrinsically vary by sex. For example, men have higher muscle mass than women, with the difference being most remarkable in the upper body.[16] Considering the recognized sex differences in performance of individual cognitive tasks,[17] the role of physical function in the process of cognitive aging may be different between men and women. Therefore, further investigation into whether sex modifies the association between physical function measures and cognitive trajectories is needed.

Using a large cohort of community-dwelling older adults recruited in Australia and the United States without major cognitive impairments or any other severe illness at enrolment, this study aimed to investigate the associations of grip strength and gait speed with cognitive trajectories in later life, as well as the potential for effect modification by sex.

RESEARCH IN CONTEXT

1. **Systematic Review**: A systematic review of the literature was conducted via MEDLINE and Embase. Findings indicate the need for further investigation into the association of physical function with cognitive trajectories with aging, specifically cognitive decline and the maintenance of high cognitive performance.
2. **Interpretation**: Results indicate that in older community-dwelling individuals, grip strength and gait speed were positively associated with the likelihood of high cognitive trajectories, and negatively with the risk of low cognitive trajectories. However, grip strength was a stronger predictor of high cognitive trajectories in women, while the association of gait speed with low cognitive trajectories was stronger in men.
3. **Future Directions**: The role of grip strength and gait speed as potentially modifiable factors of cognitive aging in older adult vary by sex. Further research with more diverse cohorts is needed to validate these findings and to understand the mechanisms underlying these sex differences.

2 | METHODS

2.1 | Study sample

The sample of this study was participants of the ASPREE (Aspirin in Reducing Events in the Elderly) clinical trial.[18,19] In brief, ASPREE was a randomized placebo-controlled clinical trial that aimed to investigate the effects of daily low-dose aspirin on community-dwelling older adults. Recruited were 19,114 participants aged 65 years or above (Hispanics/Latino and Black) and 70 years or above (all other ethno-racial groups) from Australia and the United States. At baseline, all participants were without dementia (and with a score >77 in the Modified Mini-Mental State Examination [3MS]), major cardiovascular disease, severe difficulty in any basic activity of daily living (physical disability), or any life-threatening illness.

2.2 | Cognitive assessment

Cognitive assessment was conducted at baseline and annually over follow-up. The cognitive battery included four tests: (1) 3MS (global cognitive function),[20] (2) single-letter Controlled Oral Word Association Test (COWAT, phonemic fluency),[21] (3) Hopkins Verbal Learning Test-Revised (HVLT-R) delayed recall task (episodic memory),[22] and (4) Symbol-Digit Modalities Test (SDMT, psychomotor speed).[23]

2.3 | Measurements of grip strength and gait speed

Grip strength and gait speed were measured at baseline and every 2 years over follow-up. Using a hand-held isometric dynamometer (Jaymar; JLW Instruments), grip strength was measured in kilograms on both hands. Participants were required to be in a seated position with their elbows vertically flexed to 90 degrees while being tested. The test was conducted only after confirming the complete functionality of each hand, and thus was not performed in the case of injury or pain. Grip strength was measured with three trials for each participant; the mean value from the self-reported dominant hand[24] was used for the analysis.

Gait speed was measured as the time spent in seconds to walk 3 meters (8 feet) on a flat level surface, at the speed of natural walking pace from a standing start. A minimum of 1 meter spare space at the end of the course was preserved for deceleration, so that the usual gait speed could be fully measured over the 3 meter distance. Gait speed was measured in two trials and the mean was used in the analysis.

2.4 | Statistical analysis

Cognitive performance was defined by the trajectories of cognitive function. We used group-based multi-trajectory modeling to identify the joint trajectories across the four cognitive tests. Group-based trajectory modeling is a semi-parametric approach that clusters those with similar developmental trajectories of a variable, assigning individuals into the most likely latent subgroups that produced the highest posterior probabilities.[25] Group-based multi-trajectory modeling, as an extension of this approach, identifies these latent subgroups based on trajectories of multiple indicators.[26] Cognitive data collected at up to seven waves (baseline and years 1, 3, 4, 5, 6, 7 or closeout visit) were used.[27] Eligible participants for trajectory modeling were required to have participated in the cognitive assessments at baseline and at least one subsequent wave. As reported previously,[28] we aimed a priori to compare three subgroups of participants with hierarchical cognitive performance based on trajectory parameters for interpretable comparisons. This includes a subgroup of high performers with the highest baseline levels and minimum decline across the four tests, and low performers with the lowest trajectories across the tests, as well as the subgroup of average performers with medium intercepts and rates of decline as the reference group. If more than three subgroups were identified by the trajectory models as the optimal statistical solution, the highest and lowest subgroups were compared to the medium subgroup, preventing compromise on the fit and precision of the model. Fitted curves of grip strength and gait speed measured biannually for up to 6 years were generated by cognitive trajectory subgroup.

Multinomial logistic regression was used to analyze the associations of grip strength and gait speed at baseline with cognitive performance. The subgroup of average performers was selected as the reference group. Grip strength and gait speed were analyzed as continuous variables in the primary analysis. However, given that grip strength and gait speed are also important components of the Fried frailty phenotype and the potential clinical utility of cut-offs,[5] secondary analyses were performed using quintiles of grip strength and gait speed, accounting for sex and body mass index (BMI) or height, respectively (following the standard procedure of Fried frailty;[5] Table S1 in supporting information).

Two regression models that sequentially adjusted for a number of potential confounders were performed. Model 1 adjusted for basic sociodemographic characteristics including age (continuous), sex (men, women), ethnicity (Australian White, US White, Black, Hispanic/Latino, Other), and years of education (≤12, 13–15, ≥16). Model 2 further adjusted for living at home alone (yes, no), smoking status (never, former, current), alcohol intake (never, former, current), hypertension (yes, no), diabetes mellitus (yes, no), depression (yes, no), BMI (continuous), and height (continuous). Aspirin use was not adjusted for in the models, as it was associated neither with dementia risk in the main trial[22] nor with cognitive trajectory subgroups in the current study. Participants with incomplete data in any of the exposures or covariates were excluded from the analyses.

Subgroup analyses by sex were performed by testing the interaction terms between sex and each of grip strength and gait speed. We also conducted a sensitivity analysis including all the seven cognitive trajectory subgroups in the analysis. All statistical analyses were conducted using Stata version 16.0 (Stata Corp. A) and its "Proc traj" package. A two-sided *P*-value < 0.05 was considered statistical significance. The ethics review board at each participating institution approved the ASPREE study, and all participants offered written informed consent. The current secondary analysis was approved by the Monash University Human Research Ethics Committee.

3 | RESULTS

A total of 17,724 participants were included in the trajectory modeling and seven cognitive trajectory subgroups were identified (Figure S1 in supporting information). The process of model selection and the assessment of model adequacy are summarized in Table S2 in supporting information. After excluding individuals with incomplete data related to grip strength, gait speed, or covariates ($n = 1706$), a total of 16,018 participants remained. Individuals excluded were older, more likely to be female, and with fewer years of education. They were also more likely to be a current smoker, live alone at home, and have depression, but less likely to be current alcohol drinkers. In terms of physical measurement, individuals excluded had weaker grip strength, slower gait speed, and lower body height at baseline (Table S3 in supporting information).

Based on the trajectory parameters, we selected a subgroup of high performers with the highest intercepts and least decline in all the tests (class 1, $n = 2298$, 14.3%), low performers with the lowest intercepts and steepest slopes across the four tests (class 7, $n = 642$, 4.1%), as well as a subgroup of average performers with medium trajectories (class 4, $n = 3835$, 21.8%; Figures S1 and S2 in supporting information). For a solid comparison, classes 2, 3, 5, and 6 were not included in subsequent analyses, as the cognitive performance of these subgroups was not hierarchical and thus not entirely comparable. For example, compared to class 3, class 2 has a higher trajectory in 3MS, COWAT, and HVLT-R but a lower trajectory in SDMT. Likewise, class 5 performed better in 3MS, COWAT, and SDMT, but worse in HVLT-R compared to class 6.

Table 1 summarizes the sociodemographic characteristics and anthropometry as well as grip strength and gait speed at baseline, according to these three cognitive performance subgroups. In general, participants who were higher cognitive performers were younger, more likely to be female, US White, and better educated. Faster gait speed was seen in the high performers, and the strongest grip strength in the average performers. In terms of lifestyle factors and chronic conditions (Table S4 in supporting information), the high performers were more likely to be current alcohol drinkers and less likely to live alone at home or be a current smoker, and had a lower prevalence of hypertension, diabetes, and depression.

TABLE 1 Baseline characteristics of the participants included in the study ($N = 16{,}018$)

	Overall (16,018, 100%) N (%)	High performers[a] (2298, 14.3%)	Average performers[a] (3492, 21.8%)	Low performers[a] (642, 4.0%)	P-value[b]
Sociodemographic characteristics					
Age, years					<0.001
65–69[c]	459 (2.9)	64 (2.8)	109 (3.1)	12 (1.9)	
65–74	8962 (56.0)	1725 (75.1)	1690 (48.4)	208 (32.4)	
75–84	6031 (37.6)	498 (21.7)	1551 (44.4)	327 (50.9)	
85+	566 (3.5)	11 (0.5)	142 (4.1)	95 (14.8)	
Sex					<0.001
Men	7042 (44.0)	680 (29.6)	1685 (48.3)	354 (55.1)	
Women	8976 (56.0)	1618 (70.4)	1807 (51.8)	288 (44.9)	
Ethnicity					<0.001
AU White	13,697 (85.5)	1925 (83.8)	3031 (86.8)	538 (83.8)	
US White	979 (6.1)	252 (11.0)	134 (3.8)	28 (4.3)	
Black	718 (4.5)	60 (2.6)	173 (4.9)	41 (6.4)	
Hispanic/Latino	397 (2.5)	33 (1.4)	115 (3.3)	22 (3.4)	
Other	227 (1.4)	28 (1.2)	39 (1.1)	13 (2.0)	
Education, years					<0.001
≤12	7146 (44.6)	540 (23.5)	1906 (54.6)	387 (60.3)	
13–15	4666 (29.1)	697 (30.3)	956 (27.4)	172 (26.8)	
≥16	4206 (26.3)	1061 (46.2)	630 (18.0)	83 (12.9)	
	Mean (standard deviation)				
Physical function					
Grip strength, kg	26.2 (9.8)	25.6 (9.1)	26.3 (9.9)	24.8 (9.5)	<0.001
Gait speed, m/s	1.02 (0.23)	1.10 (0.21)	0.99 (0.22)	0.91 (0.24)	<0.001
Anthropometry					
Height, m	1.65 (0.09)	1.65 (0.09)	1.65 (0.10)	1.64 (0.10)	0.06
BMI, kg/m^2	28.1 (4.7)	27.8 (4.6)	28.4 (4.8)	27.6 (4.8)	<0.001

[a]High performers refer to the participants with the highest intercepts and lowest rates of decline across the four cognitive tests, whereas low performers are those with the lowest intercepts and fastest decline across the tests. The average performers are the participants of the central class with medium intercepts and slopes.

[b]*P*-value for the comparison among the three groups (high, average, and low performers), chi-squared test for categorical variables and analysis of variance for continuous variables.

[c]Only includes Black or Hispanic/Latino participants from the United States, who were eligible if they were 65+ years (other participants had to be 70 years or above to be eligible).

Table 2 shows the association between grip strength and gait speed at baseline and cognitive trajectory subgroups. Compared to the average performers, higher grip strength and faster gait speed were associated with an increased likelihood of being high performers; and likewise, a lower risk of being low performers (all *P*-values < 0.01). When they were analyzed as categorical variables, all associations with high performers remained; however, only the lowest quintile of grip strength and gait speed was significantly associated with low cognitive performance (odds ratio [OR]: 1.73, 95% confidence interval [CI]: 1.29–2.31; OR: 1.59, 95% CI: 1.18–2.15, respectively).

In the subgroup analysis by sex shown in Table 3, differences were observed between men and women for the association of grip strength with high compared to average performers (interaction $P < 0.001$). Specifically, in women, grip strength (both as a continuous measure and when categorized), was significantly associated with the likelihood of being high performers, but no significant association was observed in men. Gait speed was associated with high and low cognitive performance in both sexes, but the association with the risk of being low performers was stronger in men than women (interaction $P = 0.04$). The results from the sensitivity analysis that considered all seven

TABLE 2 Associations of grip strength and gait speed at baseline with cognitive trajectory subgroups ($N = 6432$)

	Relative risk ratio (95% CI)			
	High performers ($n = 2298$)[a]		Low performers ($n = 642$)[a]	
	Model 1[d]	Model 2[e]	Model 1[d]	Model 2[e]
Grip strength				
Continuous, per 10 kg	1.34 (1.21–1.48)**	1.32 (1.19–1.46)**	0.73 (0.63–0.83)**	0.75 (0.65–0.86)**
Quintiles[b] (*N*, %)				
Q1 (highest)	Reference		Reference	
Q2	0.81 (0.68–0.96)*	0.83 (0.69–0.99)*	0.93 (0.67–1.29)	0.87 (0.62–1.23)
Q3	0.79 (0.66–0.94)**	0.78 (0.65–0.94)**	1.15 (0.84–1.57)	1.13 (0.82–1.55)
Q4	0.60 (0.50–0.72)**	0.61 (0.51–0.74)**	1.26 (0.93–1.70)	1.16 (0.85–1.59)
Q5 (lowest)	0.56 (0.46–0.68)**	0.56 (0.46–0.69)**	1.73 (1.29–2.31)**	1.59 (1.18–2.15)**
P-trend[f]	<0.001	<0.001	<0.001	<0.001
Gait speed				
Continuous, per m/5s	1.49 (1.40–1.59)**	1.44 (1.35–1.53)**	0.77 (0.70–0.84)**	0.79 (0.72–0.86)**
Quintiles[c] (*N*, %)				
Q1 (highest)	Reference		Reference	
Q2	0.72 (0.61–0.85)**	0.74 (0.62–0.89)**	1.24 (0.89–1.72)	1.14 (0.81–1.61)
Q3	0.56 (0.47–0.67)**	0.55 (0.46–0.66)**	1.25 (0.91–1.71)	1.10 (0.79–1.54)
Q4	0.49 (0.41–0.58)**	0.51 (0.42–0.62)**	1.19 (0.86–1.62)	1.10 (0.79–1.52)
Q5 (lowest)	0.25 (0.20–0.30)**	0.26 (0.21–0.33)**	2.04 (1.52–2.75)**	1.85 (1.36–2.53)**
P-trend[f]	<0.001	<0.001	<0.001	<0.001

[a]High performers refer to the participants with the highest intercepts and lowest rates of decline across the four cognitive tests, whereas low performers are those with the lowest intercepts and fastest decline across the tests. The units of continuous variables of gait speed and grip strength were adjusted to 1 standard deviation.
[b]Stratified by sex and BMI.
[c]Stratified by sex and height.
[d]Model 1 adjusted for age (continuous), sex (men; women, only for continuous grip strength and gait speed), ethnicity (Australian White; US White; Black; Hispanic/Latino; Other), education (≤12; 13–15; ≥16).
[e]Model 2 adjusted all the variables in model 1 and further adjusted for living at home alone (no; yes), smoking status (never; former; current), alcohol intake (never; former; current), body mass index (continuous, only for continuous grip strength), height (continuous, only for continuous gait speed), hypertension (no; yes), diabetes (no; yes), depression (no; yes).
[f]P-trend, test for linear trend.
*P-value between 0.01 and 0.05; **P-value < 0.01.
Abbreviations: BMI, body mass index; CI, confidence interval.

cognitive trajectory subgroups were largely consistent with the main findings (Table 4).

Figure 1 presents the fitted curves of grip strength and gait speed across four time points, by the subgroup of cognitive trajectory. Men had higher grip strength than women at each time point, but in both sexes, decline in grip strength was consistently observed across all three cognitive trajectory subgroups. The low performers had the lowest baseline performance and the steepest slope, and the high performers had the highest baseline and the lowest rate of decline. Likewise, gait speed was higher in men than women at each time point, but still declined over time in both sexes and in all three subgroups of cognitive performance. Meanwhile, the baseline level also decreased, and the rate of decline increased progressively from the high to low cognitive performers.

4 | DISCUSSION

The results of this study showed that, compared to average cognitive performers, higher baseline levels of grip strength and gait speed were associated with an increased likelihood of being high performers, and a decreased risk of being low cognitive performers ("cognitive decliners"). This indicates that grip strength and gait speed are not only predictors of the risk of cognitive decline, and thus likely early indicators of the risk of dementia, but also potential markers of healthy cognitive aging. In particular, the association appeared to be stronger in gait speed for both the continuous and categorical measures, with larger effect sizes compared to grip strength. Also, echoing the Fried phenotype that suggested the lowest quintile of grip strength and gait speed as the cut-off in defining frailty (weakness and slowness),[5] both

TABLE 3 Adjusted[a] associations of grip strength and gait speed with cognitive trajectory subgroups by sex ($N = 6432$)

	Relative risk ratio (95% CI)					
	High performers ($n = 2298$)[b]			Low performers ($n = 642$)[b]		
	Men ($N = 680$)	Women ($N = 1618$)	Interaction *P*-value[c]	Men ($N = 354$)	Women ($N = 288$)	Interaction *P*-value[c]
Grip strength						
Continuous per 10 kg	1.14 (0.99–1.31)	1.59 (1.36–1.84)**	<0.001	0.76 (0.64–0.90)**	0.78 (0.61–0.99)*	0.63
Quintiles[d] (*N*, %)						
Q1 (highest)	Reference		0.10	Reference		0.20
Q2	1.13 (0.83–1.55)	0.70 (0.55–0.89)**		0.88 (0.55–1.41)	0.85 (0.51–1.39)	
Q3	0.98 (0.71–1.34)	0.70 (0.55–0.89)**		1.15 (0.74–1.80)	1.06 (0.66–1.70)	
Q4	0.80 (0.58–1.11)	0.52 (0.41–0.67)**		0.99 (0.63–1.55)	1.30 (0.83–2.03)	
Q5 (lowest)	0.77 (0.54–1.10)	0.49 (0.38–0.64)**		1.69 (1.11–2.58)*	1.27 (0.81–1.99)	
P-trend[d]	0.04	<0.001		0.003	0.057	
Gait speed						
Continuous per m/5s	1.52 (1.36–1.70)**	1.38 (1.28–1.49)**	0.25	0.73 (0.64–0.84)**	0.84 (0.74–0.96)*	0.04
Quintiles[e] (*N*, %)						
Q1 (highest)	Reference		0.83	Reference		0.35
Q2	0.74 (0.55–0.99)*	0.79 (0.62–0.99)*		1.42 (0.87–2.32)	0.92 (0.56–1.51)	
Q3	0.50 (0.37–0.69)**	0.58 (0.46–0.74)**		1.45 (0.90–2.34)	0.84 (0.52–1.36)	
Q4	0.52 (0.37–0.73)**	0.49 (0.38–0.62)**		1.43 (0.89–2.30)	0.83 (0.52–1.33)	
Q5 (lowest)	0.23 (0.15–0.34)**	0.29 (0.22–0.39)**		2.21 (1.40–3.49)**	1.61 (1.05–2.49)*	
P-trend[f]	<0.001	<0.001		0.001	0.009	

[a]The models adjusted for age (continuous), ethnicity (AU White; US White; Black; Hispanic/Latino; Others), education (≤12; 13–15; ≥16), living at home alone (no; yes), smoking status (never; former; current), alcohol intake (never; former; current), body mass index (continuous, only for continuous grip strength), height (continuous, only for continuous gait speed), hypertension (no; yes), diabetes (no; yes), depression (no; yes).
[b]High performers refer to the participants with the highest intercepts and lowest rates of decline across the four cognitive tests, whereas low performers are those with the lowest intercepts and fastest decline across the tests. The units of continuous variables of gait speed and grip strength were adjusted to 1 standard deviation.
[c]*P*-value for the interaction term between sex and grip strength/gait speed.
[d]Stratified by sex and BMI.
[e]Stratified by sex and height.
[f]P-trend, test for linear trend.
*P-value between 0.01 and 0.05; **P-value < 0.01.
Abbreviations: BMI, body mass index; CI, confidence interval.

markers showed a linear association with cognitive trajectories in our study, with the participants whose grip strength and gait speed in the lowest quintile having the highest risk of low cognitive performance. In addition, the findings provide evidence of sex differences in the impact of grip strength on cognitive trajectories. The association between higher grip strength and high cognitive performance was seen only in women. This suggests the potential benefit of sex-specific strategies to help maintain good cognitive function with aging.

Consistent with our prior findings regarding the trajectories of individual cognitive tests,[27] most participants did not experience substantial decline in their scores, with the exception being psychomotor speed where decline across all subgroups was observed. Instead, improvements in verbal fluency and episodic memory were shown in those showing higher-functioning trajectories. This is possibly a limitation of the cognitive tests used for these two domains (COWAT and HVLT-R delayed recall), which arises from practice after repetitive assessments. Indeed, learning effects have been previously observed in both tests.[29–31] This suggests that it may be necessary to regularly change the letter used for COWAT or the word list of HVLT-R to mitigate against learning effects, especially for a cohort of relatively healthy individuals. On the other hand, it is also plausible that individuals with high cognitive function were able to accumulate vocabulary over time or familiarize a certain list of words, and subsequently generate personalized strategies to retrieve words from their vocabulary storage and memory. In this case, healthy cognitive aging may be characterized by improvements in certain cognitive domains, beyond maintenance at stable levels.

As the first study investigating the concurrent trajectories of multiple cognitive scores, our findings showed that cognitive performance may be consistent across cognitive domains. Participants with good

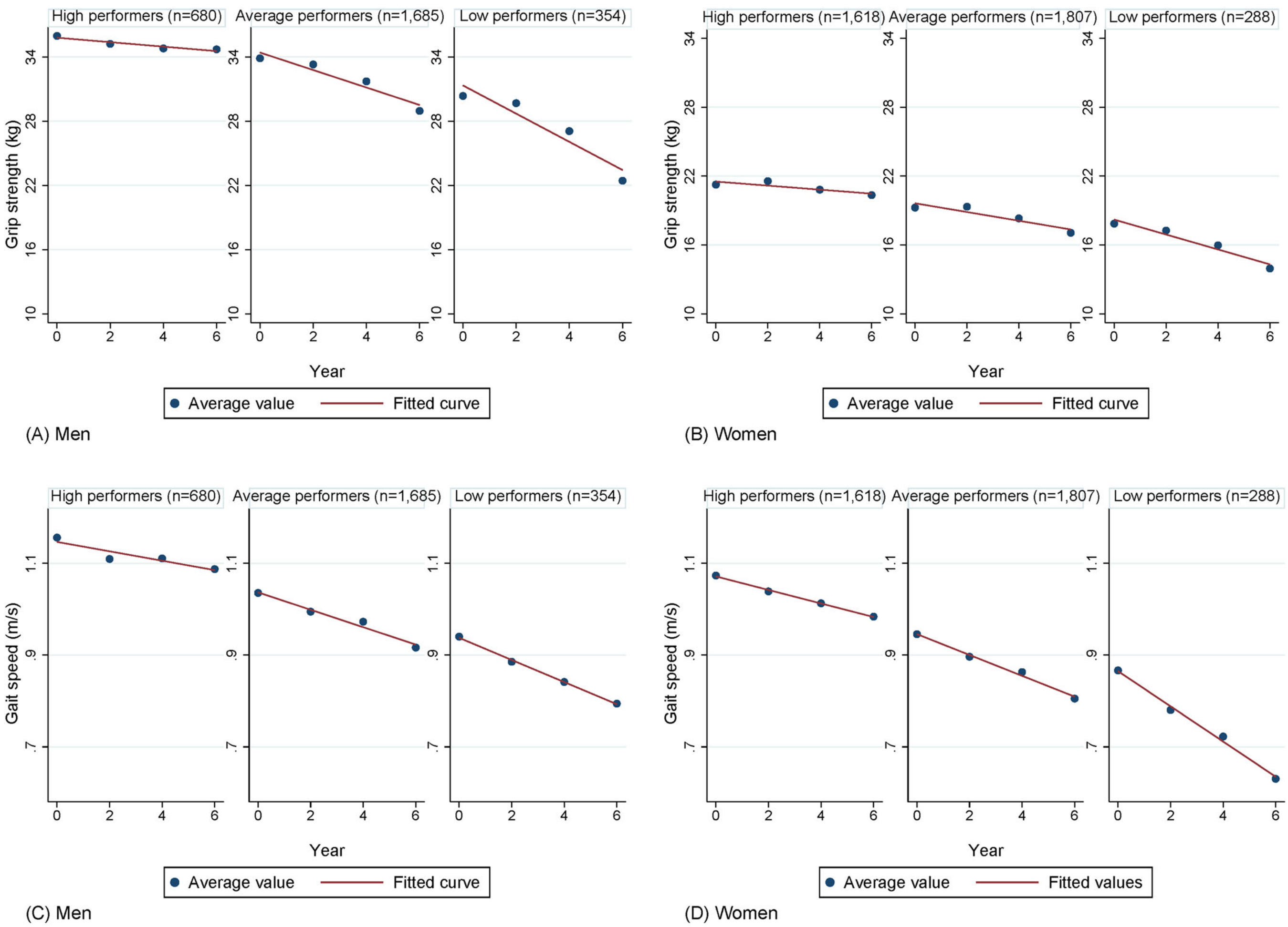

FIGURE 1 Fit curves of grip strength and gait speed over baseline, years 2, 4, and 6 by cognitive trajectory group for (A) grip strength of men, (B) grip strength of women, (C) gait speed of men, and (D) gait speed of women ($n = 6432$)

performance in the global cognitive assessment also showed high-functioning trajectories in the other three tests, suggesting that cognitive functioning is an integrated mental process. However, there was still variability in the aging patterns across cognitive domains. For example, in line with prior literature,[32] verbal fluency appeared to be resilient to aging. Although performance in this domain improved more significantly in higher-functioning classes, it remained relatively stable over time even in those with substantial decline in global cognitive function and episodic memory. In contrast, moderate decline in psychomotor speed was shown in all classes at a similar pace, regardless of the performance in other cognitive domains.

Our findings are in alignment with previous evidence regarding the association between physical activity and brain aging,[33] where all forms of physical activity (i.e., aerobic exercise, resistance training) were associated with better cognitive function in older individuals.[34] For older adults, grip strength and gait speed have been found to be predictive of disability[6] and they are also used as components of the Fried frailty phenotype.[5] Both are therefore important items in geriatric assessment. Grip strength primarily reflects the level of muscle strength and bone mineral density that facilitate the physical actions involving upper limbs and hands.[9] It is not directly related to the actions that require the use of lower limb muscles, such as walking, and thus does not necessarily reflect overall muscle strength or mobility.[9] Gait speed, on the other hand, reflects walking ability and mobility that primarily involves the actions of lower limbs. These two measures are thus complementary aspects of an individual's physical function.

These markers of physical function might also reflect overall health status, as physical movements require the cooperation and integration of multiple organs including the brain regions that control cognitive and motor function.[35] This is supported by previous studies that consistently found that grip strength and gait speed predicted the risk of many geriatric outcomes, including cognitive decline and dementia.[13,14,36-38] To our knowledge, the Victoria Longitudinal Study has been the only prior study that examined the associations of grip strength and gait speed with cognitive aging trajectories using a similar approach to ours, but in a smaller sample of 882 adults aged 53 to 95 years.[38] They identified three trajectories of episodic memory, a high and low trajectory group, and an average trajectory that included nearly half of the participants. Aligning with our findings, both grip strength and gait speed predicted low performance, but neither was associated with the high trajectory subgroup. This may relate to the limited power of that analysis (the current study had almost 10-fold

TABLE 4 Adjusted[a] associations of grip strength and gait speed with cognitive trajectory subgroups, with reference to class 4 (N = 16,018)

Trajectory subgroup	Grip strength, per 10 kg (OR, 95% CI) Overall (n = 16,018, 100%)	Grip strength Men (n = 7042, 44.0%)	Grip strength Women (n = 8976, 56%)	Gait speed, per m/5s (OR, 95% CI) Overall (n = 16,018, 100%)	Gait speed Men (n = 7042, 44.0%)	Gait speed Women (n = 8976, 56%)
Class 1[b]	1.36 (1.24–1.50)**	1.18 (1.04–1.35)*	1.60 (1.39–1.84)**	1.44 (1.37–1.52)**	1.49 (1.36–1.64)**	1.41 (1.32–1.52)**
Class 2	1.22 (1.12–1.33)**	1.18 (1.06–1.32)**	1.31 (1.15–1.49)**	1.24 (1.18–1.30)**	1.27 (1.17–1.38)**	1.22 (1.14–1.30)**
Class 3	1.17 (1.08–1.27)**	1.16 (1.05–1.28)**	1.23 (1.08–1.40)**	1.23 (1.18–1.29)**	1.24 (1.15–1.33)**	1.22 (1.15–1.30)**
Class 4[c]	Reference	Reference	Reference	Reference	Reference	Reference
Class 5	1.00 (0.92–1.09)	1.07 (0.97–1.19)	0.88 (0.75–1.03)	1.06 (1.00–1.12)*	1.02 (0.95–1.11)	1.09 (1.01–1.18)*
Class 6	0.86 (0.79–0.94)*	0.88 (0.79–0.98)*	0.80 (0.68–0.95)**	0.82 (0.78–0.87)**	0.84 (0.77–0.91)**	0.80 (0.74–0.87)**
Class 7[d]	0.73 (0.64–0.84)**	0.74 (0.63–0.87)**	0.80 (0.63–1.02)	0.78 (0.72–0.86)**	0.75 (0.66–0.84)**	0.81 (0.72–0.92)**

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]The model adjusted for age (continuous), ethnicity (AU White; US White; Black; Hispanic/Latino; Other), education (≤12; 13–15; ≥16), living at home alone (no; yes), smoking status (never; former; current), alcohol intake (never; former; current), body mass index (continuous), height (continuous), hypertension (no; yes), diabetes (no; yes), depression (no; yes).
[b]High performers: the participants with the highest intercepts and lowest rates of decline across the four cognitive tests.
[c]Average performers: the participants of the central trajectory class with medium intercepts and slopes.
[d]Low performers: the participants with the lowest intercepts and fastest decline across the four tests.
*P-value between 0.01 and 0.05; **P-value < 0.01.

more participants with high performance), as well as their wider age range and their focus on only a specific cognitive domain (episodic memory). Therefore, the findings from our analyses still require further validation in a large independent longitudinal cohort.

A well-established hypothesis was proposed by Christensen et al. that there is a set of "common causes" of physical frailty or disability and cognitive impairment.[39] They concluded that the decline in physical and cognitive function share similar underlying pathophysiologic mechanisms, including changes in the central nervous system (i.e., atrophy of white matter, gray matter, and hippocampus),[2,40–42] degeneration in the functioning of relevant organs (i.e., bones, muscles, tendons, lung, and heart), and expression of specific genetic architecture.[2,43] This hypothesis might also help explain the sex-specific findings of our study: stronger grip strength predicted a higher likelihood of being high cognitive performers in women but to a lesser extent in men. The reason for these results remains unknown, but it is plausible that the physiologic mechanisms underpinning the relationship between grip strength and cognitive function differ between men and women. Interestingly, it was observed that grip strength was more strongly associated with some major geriatric outcomes in women, such as depression and mortality.[44,45] Although there seems to be no current evidence suggesting any sex difference in the association between grip strength and dementia risk or cognitive function,[12,13] one study involving more than 15,000 individuals observed stronger associations of grip strength in women with fluid intelligence as well as hippocampal volume and white matter hyperintensities.[46] These findings suggest that grip strength is a more sensitive marker/indicator of cognitive function in females, which could also indicate greater importance of maintaining muscle strength for older women.

On the other hand, men are known to have higher grip strength than women across the lifespan,[47,48] possibly due to intrinsically higher levels of male hormones and stronger muscle strength.[49] In addition to intrinsic biological mechanisms, some sex-specific social factors might also be involved. For example, lifetime occupation has been found to be associated with both grip strength and cognitive function in older adults,[15,50–52] and historically there have been high levels of sex segregation across industries and occupations. As such, muscle mass and upper-body strength are generally high in men throughout their lifetime. This may make it harder for grip strength to differentiate varying levels of cognitive performance in older men, unless the underlying degeneration is severe enough to cause observable physical weakness and cognitive decline. However, individuals with lower cognitive performance still experienced a greater decline in grip strength over time, regardless of sex. Therefore, further studies are needed to explore the sex differences in the longitudinal associations of physical and cognitive function.

There are a few limitations to be acknowledged. First, the ASPREE study had a number of inclusion criteria based on the health status of participants at recruitment, including no previous cardiovascular events and life expectancy of more than 5 years, and the current secondary analysis further excluded approximately 9% of participants due to missing values. The study sample used may be thus healthier than the broader population, and with higher levels of grip strength and gait speed. Therefore, the results might not be generalizable to all community-dwelling older individuals. Second, some common risk factors of decline in physical and cognitive function, such as physical inactivity, were not included in the analysis. Therefore, residual confounding may help explain, at least in part, the findings reported here.

5 | CONCLUSION

Grip strength and gait speed are associated with cognitive trajectories in later life; not only negatively associated with low cognitive performance, but also positively associated with high performance. It remains possible that personalized sex-specific strategies could be beneficial for helping to maintain good cognitive function with aging, but further work is needed to determine whether there are casual associations. Further studies of diverse cohorts followed over long periods of time with regular assessment of cognitive and physical function are needed, to validate these findings and explore the possible reasons for these sex differences.

ACKNOWLEDGMENTS

The authors acknowledge the significant contribution of the dedicated and skilled staff in Australia and the United States to the ASPREE clinical trial. The authors are also most grateful to the ASPREE participants, who so willingly volunteered for this study, and the medical staff and clinics who cared for the participants. The ASPREE clinical trial was supported by the National Institute on Aging and the National Cancer Institute at the National Institutes of Health (U01AG029824 and U19AG062682); the National Health and Medical Research Council (NHMRC) of Australia (334047 and 1127060); Monash University (Australia) and the Victorian Cancer Agency (Australia). Joanne Ryan is funded by an NHMRC Dementia Research Leader Fellowship (APP1135727). Zimu Wu is funded by a Research Training Program scholarship, awarded by Monash University and the Australian government. The funding bodies were not involved in study design; collection, analysis, and interpretation of the data; the writing of the manuscript; or in the decision to submit the article for publication.

CONFLICTS OF INTEREST

Anne M. Murray reports receiving consulting fees from Alkahest, Inc., grants from the National Institute on Aging, as well as consulting fees and travel fees from Bayer AG to present the primary results of the ASPREE clinical trial. Raj C. Shah reports grants for clinical research regarding dementia and Alzheimer's disease from the National Institutes of Health, the Centers for Medicare and Medicaid Services, the Department of Defense, and the Illinois Department of Public Health; being a non-compensated member of the Board of Directors of the Alzheimer's Association–Illinois Chapter; and being a site principal investigator or sub-investigator for clinical trials and research studies for which his institution (Rush University Medical Center) is sponsored (Amylyx Pharmaceuticals, Inc., Athira Pharma, Eli Lilly & Co., Inc., Genentech, Inc., Lundbeck, Inc., Merck & Co, Inc., Navidea Biopharmaceuticals, Novartis Pharmaceuticals, Inc., Roche Holdings AG, and Takeda Development Center Americas, Inc.). Zimu Wu, Robyn L. Woods, Rory Wolfe, Elsdon Storey, Trevor T. J. Chong, John J. McNeil, Kerry M. Sheets, Suzanne G. Orchard, and Joanne Ryan report no competing interest. Author disclosures are available in the supporting information.

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REFERENCES

1. World Health Organization. Ageing: Healthy ageing and functional ability. 2020.
2. Christensen H, Mackinnon AJ, Korten A, Jorm AF. The "common cause hypothesis" of cognitive aging: evidence for not only a common factor but also specific associations of age with vision and grip strength in a cross-sectional analysis. *Psychol Aging*. 2001;16:588-599.
3. Grande G, Haaksma ML, Rizzuto D, et al. Co-occurrence of cognitive impairment and physical frailty, and incidence of dementia: systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2019;107:96-103.
4. Gray SL, Anderson ML, Hubbard RA, et al. Frailty and incident dementia. *J Gerontol A Biol Sci Med Sci*. 2013;68:1083-1090.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-156.
6. den Ouden ME, Schuurmans MJ. Arts IE, van der Schouw YT. Physical performance characteristics related to disability in older persons: a systematic review. *Maturitas*. 2011;69:208-219.
7. Vermeulen J, Neyens JC, van Rossum E, Spreeuwenberg MD, de Witte LP. Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: a systematic review. *BMC Geriatr*. 2011;11:33.
8. Miller ME, Magaziner J, Marsh AP, et al. Gait speed and mobility disability: revisiting meaningful levels in diverse clinical populations. *J Am Geriatr Soc*. 2018;66:954-961.
9. Bohannon RW. Grip strength: an indispensable biomarker for older adults. *Clin Interv Aging*. 2019;14:1681-1691.
10. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. *J Gerontol A Biol Sci Med Sci*. 2013;68:39-46.
11. Kobayashi-Cuya KE, Sakurai R, Suzuki H, Ogawa S, Takebayashi T, Fujiwara Y. Observational evidence of the association between handgrip strength, hand dexterity, and cognitive performance in community-dwelling older adults: a systematic review. *J Epidemiol*. 2018;28:373-381.
12. Zammit AR, Robitaille A, Piccinin AM, Muniz-Terrera G, Hofer SM. Associations between aging-related changes in grip strength and cognitive function in older adults: a systematic review. *J Gerontol A Biol Sci Med Sci*. 2019;74:519-527.
13. Cui M, Zhang S, Liu Y, Gang X, Wang G. Grip strength and the risk of cognitive decline and dementia: a systematic review and meta-analysis of longitudinal cohort studies. *Front Aging Neurosci*. 2021;13:625551.
14. Peel NM, Alapatt LJ, Jones LV, Hubbard RE. The association between gait speed and cognitive status in community-dwelling older people: a systematic review and meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2019;74:943-948.
15. Wu Z, Phyo AZZ, Al-Harbi T, Woods RL, Ryan J. Distinct cognitive trajectories in late life and associated predictors and outcomes: a systematic review. *J Alzheimers Dis Rep*. 2020;4:459-478.
16. Mauvais-Jarvis F. *Sex and Gender Factors Affecting Metabolic Homeostasis, Diabetes and Obesity*. Springer; 2017.
17. Hyde JS. Sex and cognition: gender and cognitive functions. *Curr Opin Neurobiol*. 2016;38:53-56.

18. McNeil JJ, Woods RL, Nelson MR, et al. Baseline characteristics of participants in the ASPREE (aspirin in reducing events in the elderly) study. *J Gerontol A Biol Sci Med Sci*. 2019;74:748.
19. Aspree Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. *Contemp Clin Trials*. 2013;36:555-564.
20. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48:314-318.
21. Ross TP. The reliability of cluster and switch scores for the Controlled Oral Word Association Test. *Arch Clin Neuropsychol*. 2003;18:153-164.
22. Ryan J, Woods RL, Murray AM, et al. Normative performance of older individuals on the Hopkins Verbal Learning Test-Revised (HVLT-R) according to ethno-racial group, gender, age and education level. *Clin Neuropsychol*. 2021:35(6):1174-1190.
23. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative Symbol Digit Modalities Test performance in a community-based sample. *Arch Clin Neuropsychol*. 2006;21:23-28.
24. Merriam-Webster. Handedness. Merriam-Webstercom dictionary; 2021.
25. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab*. 2014;65:205-210.
26. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27:2015-2023.
27. Wu Z, Woods RL, Wolfe R, et al. Trajectories of cognitive function in community-dwelling older adults: a longitudinal study of population heterogeneity. *Alzheimers Dement (Amst)*. 2021;13:e12180.
28. Wu Z, Woods RL, Chong TT, et al. Potential modifiable factors associated with late-life cognitive trajectories. *Front Neurol*. 2022;13:950644.
29. Duff K, Atkinson TJ, Suhrie KR, Dalley BC, Schaefer SY, Hammers DB. Short-term practice effects in mild cognitive impairment: evaluating different methods of change. *J Clin Exp Neuropsychol*. 2017;39:396-407.
30. Beglinger LJ, Gaydos B, Tangphao-Daniels O, et al. Practice effects and the use of alternate forms in serial neuropsychological testing. *Arch Clin Neuropsychol*. 2005;20:517-529.
31. Glisky EL, Woolverton CB, McVeigh KS, Grilli MD. Episodic memory and executive function are differentially affected by retests but similarly affected by age in a longitudinal study of normally-aging older adults. *Front Aging Neurosci*. 2022;14:863942.
32. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013;29:737-752.
33. Barha CK, Liu-Ambrose T. Exercise and the aging brain: considerations for sex differences. *Brain Plast*. 2018;4:53-63.
34. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med*. 2018;52:154-160.
35. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305:50-58.
36. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. *J Geriatr Phys Ther*. 2008;31:3-10.
37. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging*. 2009;13:881-889.
38. McFall GP, McDermott KL, Dixon RA. Modifiable risk factors discriminate memory trajectories in non-demented aging: precision factors and targets for promoting healthier brain aging and preventing dementia. *J Alzheimers Dis*. 2019;70:S101.
39. Christensen H, Korten AE, Mackinnon AJ, Jorm AF, Henderson AS, Rodgers B. Are changes in sensory disability, reaction time, and grip strength associated with changes in memory and crystallized Intelligence? A longitudinal analysis in an elderly community sample. *Gerontology*. 2000;46:276-292.
40. Murray ME, Senjem ML, Petersen RC, et al. Functional impact of white matter hyperintensities in cognitively normal elderly subjects. *Arch Neurol*. 2010;67:1379-1385.
41. Callisaya ML, Beare R, Phan TG, et al. Brain structural change and gait decline: a longitudinal population-based study. *J Am Geriatr Soc*. 2013;61:1074-1079.
42. Callisaya ML, Beare R, Phan TG, Chen J, Srikanth VK. Global and regional associations of smaller cerebral gray and white matter volumes with gait in older people. *PLoS One*. 2014;9:e84909.
43. Johnson W, Deary IJ, McGue M, Christensen K. Genetic and environmental links between cognitive and physical functions in old age. *J Gerontol B Psychol Sci Soc Sci*. 2009;64:65-72.
44. McDowell CP, Gordon BR, Herring MP. Sex-related differences in the association between grip strength and depression: results from the Irish Longitudinal Study on Ageing. *Exp Gerontol*. 2018;104:147-152.
45. Arvandi M, Strasser B, Meisinger C, et al. Gender differences in the association between grip strength and mortality in older adults: results from the KORA-age study. *BMC Geriatr*. 2016;16:201.
46. Duchowny KA, Ackley SF, Brenowitz WD, et al. Associations between handgrip strength and dementia risk, cognition, and neuroimaging outcomes in the UK biobank cohort study. *JAMA Netw Open*. 2022;5:e2218314.
47. Ahrenfeldt LJ, Scheel-Hincke LL, Kjaergaard S, Moller S, Christensen K, Lindahl-Jacobsen R. Gender differences in cognitive function and grip strength: a cross-national comparison of four European regions. *Eur J Public Health*. 2019;29:667-674.
48. Oksuzyan A, Maier H, McGue M, Vaupel JW, Christensen K. Sex differences in the level and rate of change of physical function and grip strength in the Danish 1905-cohort study. *J Aging Health*. 2010;22:589-610.
49. Schaap LA, Pluijm SM, Smit JH, et al. The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. *Clin Endocrinol (Oxf)*. 2005;63:152-160.
50. Russo A, Onder G, Cesari M, et al. Lifetime occupation and physical function: a prospective cohort study on persons aged 80 years and older living in a community. *Occup Environ Med*. 2006;63:438-442.
51. Liu KP, Chu MM. Grip strength and physical demand of previous occupation in a well-functioning cohort of Chinese older adults. *Percept Mot Skills*. 2006;103:14-20.
52. Mohd Hairi F, Mackenbach JP, Andersen-Ranberg K, Avendano M. Does socio-economic status predict grip strength in older Europeans? Results from the SHARE study in non-institutionalised men and women aged 50+. *J Epidemiol Community Health*. 2010;64:829-837.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wu Z, Woods RL, Chong TT-J, et al. Grip strength, gait speed, and trajectories of cognitive function in community-dwelling older adults: A prospective study. *Alzheimer's Dement*. 2023;15:e12388. https://doi.org/10.1002/dad2.12388