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Handgrip Strength Asymmetry as a Dynamic Functional Phenotype Distinct from Weakness and Associated with Incident Dementia: A Population-Based Cohort and Multi- State Analysis

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Abstract

Background

Handgrip strength asymmetry (HGSA) may represent a distinct hand motor imbalance phenotype beyond handgrip strength weakness (HGSW). However, whether HGSA reflects a distinct dynamic phenotype from overt weakness, and whether these phenotypes differ in their associations with dementia, cognition, and structural brain markers, remain unclear.

Methods

We analyzed 363,867 UK Biobank participants without pre-existing dementia or musculoskeletal disease, who had baseline handgrip strength (HGS) measurements and up to 13.7 years of follow-up. HGS phenotypes were classified as normal HGS, HGSA, HGSW, and HGSAW (combined HGSA and HGSW). Multi-state Markov models characterized transitions between phenotypes among participants with repeated assessments; Cox models estimated dementia risk; linear regression assessed cognitive performance and structural brain outcomes.

Results

Among participants with repeated assessments, transitions from normal HGS to HGSA was more frequent (intensity: 0.137 vs. 0.004) than transitions to HGSW, and HGSA showed greater reversibility (intensity: 0.118 vs. 0.015). In fully adjusted models, HGSA was associated with increased risk of all-cause dementia (hazard ratio [HR] = 1.17, 95% confidence interval [CI]: 1.11 to 1.24), although associations were stronger for HGSW (HR = 1.60, 95% CI: 1.39 to 1.84) and HGSAW (HR = 1.69, 95% CI: 1.50 to 1.90). HGSA was associated with Alzheimer's disease but not vascular dementia, whereas HGSW and HGSAW were associated with both subtypes. Cognitive analyses demonstrated that HGSW and HGSAW were associated with poorer general cognitive ability and multiple cognitive domains, whereas HGSA showed no association with general cognition. Neuroimaging analyses showed no significant associations with total brain volume or hippocampal volume; however, HGS phenotypes were all associated with greater white matter hyperintensity volume.

Conclusions

HGSA is a common, dynamic and partially reversible handgrip phenotype that is frequently observed before overt weakness in repeated assessments. HGSA and HGSW show partly different associations with dementia, cognition, and structural brain markers, suggesting that they capture overlapping but distinct dimensions of functional impairment. HGSA may provide additional context for characterizing functional heterogeneity, although its clinical utility requires further investigation.

1 Background

Dementia is a major and growing public health challenge, affecting more than 55 million people worldwide, with its prevalence projected to almost triple by 2050(1, 2). It is often preceded by a prolonged preclinical phase. Although disease-modifying treatments are now available for selected patients with early Alzheimer's disease, they do not reverse established neurodegeneration(3). Identifying accessible markers of early functional vulnerability therefore remains an important research priority.

Handgrip strength (HGS) is a simple, widely available measure of physical function and has been consistently associated with aging-related outcomes, including frailty, cardiovascular disease, cognitive decline, and dementia(4, 5). Beyond reflecting muscle force generation, HGS performance also integrates neuromuscular coordination, motor control, and systemic health, making it a potential marker of broader biological aging(6, 7).

However, conventional assessments of HGS primarily focus on maximal strength and may overlook other clinically relevant aspects of hand motor dysfunction. Handgrip strength asymmetry (HGSA), defined as a meaningful difference in strength between the dominant and non-dominant hands, represents a distinct form of hand muscle dysfunction, specifically termed strength imbalance(8, 9). Prior studies have linked HGSA to functional decline, cognitive impairment, and neurodegenerative outcomes(10–12). Yet several important questions remain unresolved. First, it remains unclear whether HGSA represents a distinct dynamic phenotype that may occur before overt weakness in population-level observations, or merely reflects concurrent manifestation of generalized strength impairment. Second, whether HGSA carries independent prognostic information beyond established weakness remains uncertain. Finally, the extent to which HGSA and HGSW differ in their associations with dementia subtypes, cognitive performance, and structural brain abnormalities has not been comprehensively characterized.

To address these gaps, we analyzed data from the UK Biobank cohort using complementary longitudinal and cross-sectional approaches. We applied multi-state Markov models to characterize transitions between handgrip phenotypes, Cox proportional hazards models to examine incident dementia risk, and linear regression models to explore associations with cognitive performance and structural brain MRI markers. We aimed to determine whether HGSA represents a common and dynamic phenotype distinct from overt weakness and whether its clinical correlates differ from those of overt weakness.

2 Methods

2.1 Study population

This study utilized data from the UK Biobank, a nationwide prospective cohort of approximately 500,000 individuals aged 40–69 recruited between 2006–2010(13, 14). Details of study design, recruitment, and quality-control procedures have been reported elsewhere(15).

We included participants with complete baseline handgrip strength (HGS) measurements and excluded those with a baseline diagnosis of dementia (International Classification of Diseases, Tenth Revision, ICD-10 codes F00–F03 and G30–G31)(16). To avoid confounding of handgrip asymmetry by unilateral weakness or neurological disorders, we further excluded participants with baseline stroke or cerebrovascular events (ICD-10 codes I60–I64), major nervous system disorders (ICD-10 codes G00-G99), or musculoskeletal/connective tissue diseases (ICD-10 codes M00-M25 and M60-M68) that could affect grip strength. For the multi-state transition analysis, we included only participants with at least two HGS assessments. A detailed participant flowchart is shown in **Figure S1**.

2.2 Handgrip strength assessment and phenotype definition

Handgrip strength (HGS) was measured using a Jamar J00105 hydraulic hand dynamometer(17). Participants held the elbow at approximately 90° with the forearm supported and squeezed the handle maximally. Measurements below 4 kg were treated as implausible and excluded(18). Following prior studies(14, 19), we defined two dimensions of hand muscle dysfunction: handgrip strength asymmetry (HGSA) and handgrip strength weakness (HGSW). Handedness was determined by self-report. HGSA was defined using the commonly applied 10% rule, based on an inter-hand ratio (dominant/non-dominant maximal HGS) of < 0.90 or > 1.10(13). This threshold was used as a pragmatic operational definition of inter-hand strength imbalance, consistent with previous studies of handgrip asymmetry(20). Because the clinical meaning of higher asymmetry thresholds remains uncertain, alternative cut-points of 15% and 20%, as well as continuous asymmetry measures, were examined in sensitivity analyses. HGSW was defined according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus criteria(21), using sex-specific low-grip strength thresholds. Specifically, low grip strength was defined as maximal handgrip strength < 27 kg for men and < 16 kg for women. Participants meeting these sex-specific thresholds were categorized as having HGSW. Based on HGSA and HGSW status, participants were classified into four mutually exclusive baseline phenotypes: (1) normal HGS (neither weakness nor asymmetry), (2) asymmetry alone (HGSA), (3) weakness alone (HGSW), and (4) combined asymmetry and weakness (HGSAW).

2.3 Ascertainment of outcomes

Incident dementia cases were identified through linkage to national health records. The primary outcome was incident all-cause dementia (ICD-10 codes: F00–F03 and G30–G31). Dementia subtypes included Alzheimer's disease (ICD-10 codes G30) and vascular dementia (ICD-10 codes F01)(16). Follow-up time was calculated from the date of baseline assessment to the date of dementia diagnosis, date of death, or the administrative censoring date (February 28, 2018, for Wales, and March 31, 2021, for Scotland and England), whichever occurred first.

2.4 Assessment of covariates

Covariates were selected based on prior evidence and their potential associations with handgrip function, dementia risk, or both. Demographic and socioeconomic covariates included age at

recruitment, sex, area of residence (urban or rural), ethnicity (white or non-white), Townsend deprivation index (derived from postcode)(22) and education (any school degree, college education, vocational qualification, or other). Anthropometric and lifestyle factors included body mass index (BMI), smoking status (never, former, or current), drinking status (never, moderate, or heavy), sleep duration (short: ≤6 h; normal: >6 and < 8 h; long: ≥8 h), healthy diet status (yes or no), and physical activity level (low: <800 MET-min/week; moderate: 800–2400 MET-min/week; high: ≥2400 MET-min/week)(23). Clinical covariates included hypertension and diabetes (yes or no), defined using self-reported diagnoses and hospital inpatient records. Healthy diet status was defined based on the recommended consumption levels of fruits, vegetables, fish, processed meats, and red meats(24). Further details on covariate assessments are available in the UK Biobank protocol and previous studies(25, 26).

2.5 Cognitive Outcomes

Cognitive function was assessed at baseline using five UK Biobank touchscreen tests: Pairs Matching, Reaction Time, Prospective Memory, Fluid Intelligence, and Numeric Memory. Following the method described by Fawns-Ritchie and Deary(26), scores from non-normally distributed tests were transformed (Pairs Matching: log(x + 1); Reaction Time: log-transformed). All five cognitive measures were entered into Principal Components Analysis (PCA). The scores from the first unrotated principal component were saved as a standardized measure of general cognitive ability, with higher values indicating better cognitive performance. Details of the PCA results were extracted and saved in **Tables S1-S2**. Individual cognitive tests were also analyzed separately to explore domain-specific associations.

2.6 Neuroimaging outcomes

Brain magnetic resonance imaging (MRI) data were acquired using Siemens Skyra 3T scanners with a 32-channel head coil. The UK Biobank team processed and quality-controlled the imaging data, providing researchers with pre-computed imaging-derived phenotypes. Detailed acquisition parameters and processing methods have been reported previously(27, 28).

We examined structural MRI markers relevant to dementia risk: total brain volume (TBV), hippocampal volume (HV), and white matter hyperintensity volume (WMHV). TBV and HV were normalized for intracranial volume (ICV). WMHV was transformed as log(WMHV + 1). Each processed measure was then standardized to a z score. TBV and HV were interpreted as markers of global and hippocampal atrophy, whereas WMHV was interpreted as a marker of cerebral small vessel disease burden, both of which are established correlates of dementia risk(29).

2.7 Statistical analysis

Baseline characteristics were summarized across the four handgrip phenotypes. Continuous variables were reported as means with standard deviations or medians with interquartile ranges, and categorical variables as frequencies and percentages.

To characterize dynamic transitions among handgrip phenotypes, we fitted a continuous-time multi-state Markov model in participants with repeated HGS assessments. Four mutually exclusive handgrip states

were defined: normal HGS, HGSA, HGSW, and HGSAW. All four states were treated as transient states, allowing participants to move bidirectionally between handgrip phenotypes over follow-up. Time since the first HGS assessment was used as the time scale. The prespecified transition matrix specified the allowable transitions among the four handgrip states **(Table S3)**. Transition intensities, mean sojourn times, and state occupation probabilities were estimated using the msm package in R. To assess whether mortality materially influenced the estimated handgrip transition dynamics, we additionally performed a sensitivity analysis using a five-state model in which death was included as an absorbing state and transitions from each of the four handgrip states to death were permitted.

Cox proportional hazards models were employed to estimate the associations between baseline HGS phenotypes and incident dementia. Participants with normal HGS served as the reference group. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated across sequentially adjusted models. Model 1 was unadjusted (crude model). Model 2 adjusted for age, sex, ethnicity, area of residence, Townsend deprivation index and education. Model 3 further adjusted for body mass index, smoking status, drinking status, physical activity level, sleep duration, healthy diet status, hypertension, and diabetes. The proportional hazards assumption was assessed using Schoenfeld residuals. Separate Cox models were fitted for Alzheimer's disease and vascular dementia.

Associations of HGS phenotypes with cognitive outcomes and neuroimaging markers were evaluated using multivariable linear regression, whereas prospective memory, treated as a three-categorical variable, was analyzed using multivariable ordinal logistic regression. All models followed the same sequential adjustment strategy. Results were presented as β coefficients for linear regression models and odds ratios (ORs) for logistic regression models, with corresponding 95% confidence intervals (CIs).

Stratified analyses were conducted to examine potential effect modification by key demographic and lifestyle factors. Multiplicative interactions were tested by including cross-product terms between handgrip phenotype and stratification variables.

Several sensitivity analyses were performed to assess robustness. First, to reduce potential reverse causality, we excluded participants diagnosed with dementia within the first 2, 5, and 10 years of follow-up. Second, HGSA was redefined using alternative thresholds of 15% and 20%. Third, maximal HGS and the inter-hand ratio were treated as continuous exposures. Fourth, a handedness-agnostic definition of asymmetry was applied. Fifth, participants with extreme HGS values were excluded (maximal HGS < 8 kg or > 60 kg). Sixth, Fine-Gray competing-risk models were fitted with death treated as a competing event.

All analyses were conducted using R. Statistical tests were two-sided, and P values < 0.05 were considered statistically significant.

3 Results

3.1 Transitions Between Handgrip Strength Phenotypes

Among 72,761 participants with repeated HGS assessments, 48.8% had normal HGS, 48.8% HGSA, 1.0% HGSW, and 1.4% HGSAW at the first assessment (**Table S4**). The estimated mean sojourn times were 7.08 years for the normal HGS, 7.42 years for HGSA, 3.01 years for HGSW and 4.81 years for HGSAW **(Table S5)**. The transition intensity from normal HGS to HGSA was markedly higher than that from normal HGS to HGSW (0.137, 95% CI 0.131 to 0.143 vs. 0.004, 95% CI 0.003 to 0.006), while the recovery intensity, transition back to normal HGS, was approximately 7.6-fold higher from HGSA than from HGSW (0.118 vs. 0.015; Fig. 1A). Consistently, among participants starting with normal HGS, the 5-year probability of occupying the HGSA state was 0.37 compared with 0.01 for HGSW; among those starting with HGSA, the probability of returning to normal HGS was 0.32 (Fig. 1B-E). Model-estimated 1- and 5-year transition probabilities are shown in **Figure S2**. In sensitivity analyses incorporating death as an absorbing state, the key transition patterns were largely unchanged, the HGSW-to-normal estimate was less stable but remained directionally consistent (**Table S6**).

3.2 Associations Between Handgrip Strength Phenotypes and Incident Dementia

The analytical sample comprised 363,867 adults, with a mean (SD) age of 56.2 (8.1) years; 174,187 (47.9%) participants were male. Baseline characteristics varied across HGS phenotype groups **(**Table 1**)**. During 4,979,721 person-years of follow-up (mean 13.7 ± 1.0 years), 5,717 (1.6%) participants developed incident dementia. In the fully adjusted Cox model, compared with normal HGS, HGSA was associated with higher dementia risk (HR = 1.17, 95% CI 1.11 to 1.24). Stronger associations were observed for HGSW (HR = 1.60, 95% CI 1.39 to 1.84) and HGSAW (HR = 1.69, 95% CI 1.50 to 1.90) **(**Fig. 2A, **Table S7)**. In direct comparisons, the association with dementia risk was stronger for HGSW than for HGSA (HR = 1.36, 95% CI: 1.19 to 1.56; P < 0.001, **Table S8**).

Table 1
Baseline characteristics of participants by handgrip strength phenotype

Variable, n (%)	Overall	normal HGS	HGSA	HGSW	HGSAW	p[b]
	N = 363867	N = 169232	N = 179788	N = 6113	N = 8734	
Age (years), mean (SD)	56.20 (8.10)	55.75 (8.13)	56.33 (8.06)	59.78 (7.33)	59.81 (7.19)	< 0.001
Sex (Female)	189680 (52.1)	79773 (47.1)	101591 (56.5)	3007 (49.2)	5309 (60.8)	< 0.001
Area of residence (Urban)	336716 (92.5)	156123 (92.3)	166485 (92.6)	5821 (95.2)	8287 (94.9)	< 0.001
Ethnicity (White)	347456 (95.5)	162152 (95.8)	171822 (95.6)	5533 (90.5)	7949 (91.0)	< 0.001
Townsend Deprivation Index, mean (SD)	-1.48 (2.99)	-1.56 (2.95)	-1.46 (3.00)	-0.79 (3.26)	-0.71 (3.33)	< 0.001
Education						
Any school degree	163773 (45.0)	76629 (45.3)	80805 (44.9)	2551 (41.7)	3788 (43.4)	< 0.001
College education	132319 (36.4)	62680 (37.0)	65510 (36.4)	1812 (29.6)	2317 (26.5)	
Vocational qualification	18606 (5.1)	8472 (5.0)	9266 (5.2)	370 (6.1)	498 (5.7)	
Other	49169 (13.5)	21451 (12.7)	24207 (13.5)	1380 (22.6)	2131 (24.4)	
Body mass index[a]						
Underweight	5238 (1.4)	2264 (1.3)	2665 (1.5)	136 (2.2)	173 (2.0)	< 0.001
Normal weight	115158 (31.6)	53295 (31.5)	57646 (32.1)	1755 (28.7)	2462 (28.2)	

Abbreviations: HGS, handgrip strength; HGSA, handgrip strength asymmetry; HGSW, handgrip strength weakness; HGSAW, handgrip strength asymmetry and weakness.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Continuous variables are presented as mean (SD) and compared using one-way analysis of variance (or the Kruskal–Wallis test). Categorical variables are presented as n (%) and compared using the chi-square test (or Fisher's exact test when expected cell counts were small).

Variable, n (%)	Overall	normal HGS	HGSA	HGSW	HGSAW	p[b]
	N = 363867	N = 169232	N = 179788	N = 6113	N = 8734	
Overweight	157909 (43.4)	74917 (44.3)	76847 (42.7)	2530 (41.4)	3615 (41.4)	
Obesity	85562 (23.5)	38756 (22.9)	42630 (23.7)	1692 (27.7)	2484 (28.4)	
Physical activity level						
Low	157772 (43.4)	70960 (41.9)	79265 (44.1)	3005 (49.2)	4542 (52.0)	< 0.001
Moderate	93644 (25.7)	43842 (25.9)	46365 (25.8)	1471 (24.1)	1966 (22.5)	
High	112451 (30.9)	54430 (32.2)	54158 (30.1)	1637 (26.8)	2226 (25.5)	
Smoking status						
Never	200327 (55.1)	92096 (54.4)	100107 (55.7)	3363 (55.0)	4761 (54.5)	< 0.001
Previous	127647 (35.1)	60004 (35.5)	62371 (34.7)	2161 (35.4)	3111 (35.6)	
Current	35893 (9.9)	17132 (10.1)	17310 (9.6)	589 (9.6)	862 (9.9)	
Sleep duration						
Less	85768 (23.6)	39106 (23.1)	42636 (23.7)	1618 (26.5)	2408 (27.6)	< 0.001
Normal	251445 (69.1)	118407 (70.0)	123912 (68.9)	3823 (62.5)	5303 (60.7)	
More	26654 (7.3)	11719 (6.9)	13240 (7.4)	672 (11.0)	1023 (11.7)	
Drinking status						

Abbreviations: HGS, handgrip strength; HGSA, handgrip strength asymmetry; HGSW, handgrip strength weakness; HGSAW, handgrip strength asymmetry and weakness.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Continuous variables are presented as mean (SD) and compared using one-way analysis of variance (or the Kruskal–Wallis test). Categorical variables are presented as n (%) and compared using the chi-square test (or Fisher's exact test when expected cell counts were small).

Variable, n (%)	Overall	normal HGS	HGSA	HGSW	HGSAW	p[b]
	N = 363867	N = 169232	N = 179788	N = 6113	N = 8734	
Never	13288 (3.7)	5428 (3.2)	6694 (3.7)	457 (7.5)	709 (8.1)	< 0.001
Previous	11821 (3.2)	5033 (3.0)	5897 (3.3)	338 (5.5)	553 (6.3)	
Current	338758 (93.1)	158771 (93.8)	167197 (93.0)	5318 (87.0)	7472 (85.6)	
Hypertension (yes)	7036 (1.9)	2764 (1.6)	3582 (2.0)	259 (4.2)	431 (4.9)	< 0.001
Diabetes (yes)	2647 (0.7)	943 (0.6)	1339 (0.7)	136 (2.2)	229 (2.6)	< 0.001
Healthy diet status (yes)	147444 (40.5)	69891 (41.3)	71455 (39.7)	2530 (41.4)	3568 (40.9)	< 0.001

Abbreviations: HGS, handgrip strength; HGSA, handgrip strength asymmetry; HGSW, handgrip strength weakness; HGSAW, handgrip strength asymmetry and weakness.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Continuous variables are presented as mean (SD) and compared using one-way analysis of variance (or the Kruskal–Wallis test). Categorical variables are presented as n (%) and compared using the chi-square test (or Fisher's exact test when expected cell counts were small).

Regarding dementia subtypes, all abnormal HGS phenotypes were associated with higher risk of Alzheimer's disease. For vascular dementia, significant associations were observed for HGSW and HGSAW, but not for HGSA (HR = 1.08, 95% CI: 0.96 to 1.21; Fig. 2B-C, **Table S7**). Kaplan–Meier curves showed divergence in dementia-free survival between the normal HGS and HGSA groups beginning approximately 8 years after baseline (**Figure S3**).

Stratified analyses showed generally consistent associations across demographic and lifestyle subgroups, with most interaction tests showing no significant evidence of effect modification (**Table S9-11**). Sensitivity analyses excluding dementia cases occurring within the first 2 or 5 years showed results comparable with the primary analyses. After excluding cases within the first 10 years, associations of HGSA and HGSAW remained unchanged, whereas the association between HGSW and Alzheimer's disease was attenuated and no longer statistically significant (**Table S12**). Additional sensitivity analyses using alternative HGSA thresholds, continuous HGS measures, a handedness-agnostic HGSA definition, exclusion of extreme HGS values, and competing-risk models produced similar findings (**Tables S13–S17**).

3.3 Cognitive Performance Across Handgrip Strength Phenotypes

Among 31,219 participants with cognitive assessments, the mean general cognitive ability score (z-score) differed across handgrip phenotypes (P < 0.001, **Table S18**). In fully adjusted linear regression models, HGSW (β = -0.22, 95% CI: -0.32 to -0.12) and HGSAW (β = -0.27, 95% CI: -0.36 to -0.19) were associated with poorer general cognitive ability compared with normal HGS, whereas HGSA showed no significant association (β = 0.01, 95% CI: -0.01 to 0.04). Across individual cognitive domains, HGSA showed a positive association with fluid intelligence, while HGSW and HGSAW were consistently associated with poorer performance in general cognition, reaction time, numeric memory, and prospective memory. HGSAW was additionally associated with poorer pairs memory and fluid intelligence, whereas HGSW showed no significant association with these two domains (Fig. 3, **Table S19**). No significant interactions were observed across demographic and lifestyle subgroups for general cognitive ability (all P-interaction > 0.05; **Table S20**).

3.4 Neuroimaging Outcomes

The neuroimaging analysis included 34,581 participants with available MRI data **(Table S21)**. In fully adjusted models, none of the HGS phenotypes was significantly associated with total brain volume and hippocampal volume. In contrast, higher white matter hyperintensity volume was consistently observed among participants with HGSA (β = 0.04, 95% CI: 0.03 to 0.06), HGSW (β = 0.07, 95% CI: 0.01 to 0.13), and HGSAW (β = 0.08, 95% CI: 0.03 to 0.13) compared with normal HGS **(**Fig. 4, **Table S22)**. Stratified analyses identified significant sex interactions for total brain volume and hippocampal volume (both P-interaction < 0.001), while no other significant subgroup interactions were observed (**Table S23**).

4 Discussion

In this large prospective UK Biobank cohort, we found that handgrip strength asymmetry (HGSA) was a common, dynamic, and partially reversible phenotype that was frequently observed prior to overt handgrip weakness (HGSW) in repeated assessments. HGSA was independently associated with incident dementia, although the magnitude of association was smaller than that observed for HGSW and combined asymmetry and weakness (HGSAW). Cognitive and neuroimaging analyses further demonstrated different association patterns across handgrip phenotypes, with weakness-related phenotypes showing more consistent associations with poorer cognitive performance, whereas HGSA showed a partially different profile. Together, these findings suggest that HGSA and HGSW capture partly distinct dimensions of functional impairment and that asymmetry may provide additional context when characterizing handgrip-related functional profiles.

The multi-state Markov analysis provides insight into the longitudinal organization of handgrip phenotypes. Transitions from normal HGS to HGSA were substantially more frequent than transitions to HGSW, and HGSA showed greater apparent reversibility. These findings indicate that inter-hand

imbalance represents a dynamic state of altered hand function that may be detectable earlier than overt weakness in population-level observations. However, the multi-state model does not establish a deterministic sequence in which HGSA inevitably progresses to HGSW. The observed reversibility of HGSA may reflect variation in motor coordination, habitual hand use, transient musculoskeletal factors, measurement variability, or regression toward the mean(30, 31). Therefore, HGSA should be interpreted as a dynamic phenotype of altered hand function rather than a definitive intermediate stage leading to weakness.

The dementia analyses further highlight differences between asymmetry and weakness-related phenotypes. HGSA was associated with a modestly increased risk of all-cause dementia after adjustment for established risk factors, indicating that inter-hand imbalance captures information that is not fully represented by maximal strength alone. However, direct comparison showed that HGSW carried a higher dementia risk than HGSA, suggesting that overt weakness represents a more pronounced functional impairment phenotype associated with dementia vulnerability. The comparable risk estimates between HGSW and HGSAW indicate that once overt weakness is present, concurrent asymmetry may provide limited additional information. Associations with dementia subtypes also differed across phenotypes: HGSA was associated with Alzheimer's disease (AD) but not with vascular dementia (VaD), whereas HGSW and HGSAW were associated with both dementia subtypes. Although the underlying explanations remain uncertain, these findings suggest that asymmetry and weakness may represent different aspects of handgrip dysfunction and may capture heterogeneous relationships with dementia outcomes(32).

The cognitive and neuroimaging analyses provided further evidence for phenotypic differences. HGSW and HGSAW were consistently associated with poorer general cognitive ability and multiple cognitive domains, whereas HGSA was not associated with impaired general cognition and showed a distinct pattern, including a positive association with fluid intelligence. These findings suggest that weakness-related phenotypes are more closely linked to broad cognitive vulnerability, whereas asymmetry may reflect a different aspect of functional variation(33). In neuroimaging analyses, none of the phenotypes was associated with total brain volume or hippocampal volume; however, HGSA, HGSW, and HGSAW were all associated with greater white matter hyperintensity volume. This pattern suggests that asymmetry may share some structural brain correlates with weakness while differing in its cognitive manifestations. Together, the cognitive and MRI findings support the interpretation that handgrip asymmetry and weakness represent related but distinct aspects of functional aging.

From a public health perspective, bilateral handgrip measurement is inexpensive, non-invasive, and already available in many epidemiological settings. Because asymmetry can be derived from the same measurements used to assess maximal strength, it requires minimal additional assessment burden. However, the modest dementia association of HGSA and the absence of consistent cognitive impairment indicate that HGSA should not be considered a standalone clinical screening marker. Instead, it may complement conventional strength assessment by providing additional information about heterogeneity in functional aging profiles. Because dementia prevention and early risk characterization

are global public health priorities, bilateral handgrip measures may warrant evaluation as a low-cost component of population-based functional assessment. However, this UK Biobank analysis does not establish screening benefit or clinical utility; validation in more ethnically, socioeconomically, and geographically diverse cohorts, including lower-resource settings, is needed before broader application.

Several limitations should be acknowledged. First, residual confounding by unmeasured or imperfectly measured factors remains possible. Second, reverse causality cannot be fully excluded given the long prodromal phase of dementia. Although analyses excluding dementia cases within the first 2 and 5 years supported the main findings, some associations involving HGSW were attenuated after 10-year exclusion, which may reflect reduced statistical power and differences in the relationship between weakness and long-term dementia risk. Third, the 10% HGSA threshold is pragmatic, and the optimal definition of clinically meaningful asymmetry remains uncertain. Fourth, the healthier and less socioeconomically diverse UK Biobank population may limit generalizability. The predominantly UK-based evidence also requires validation in other health systems and population settings before informing global policy or practice. Fifth, cognitive and MRI data were available only in subsets, and cross-sectional MRI measures limited causal inference regarding brain structural changes. Finally, HGSW was defined using EWGSOP2 sex-specific thresholds, and further validation is needed to determine the most appropriate cut-points across diverse populations.

5 Conclusions

In this large population-based cohort, handgrip strength asymmetry was a common, dynamic, and partially reversible handgrip phenotype that was more frequently observed before overt weakness in repeated assessments. HGSA was independently associated with incident dementia, although its association was weaker than that of HGSW and HGSAW. Cognitive and neuroimaging analyses further demonstrated that asymmetry and weakness were associated with partly different patterns of cognitive and structural brain outcomes. These findings suggest that asymmetry and weakness capture partly different functional profiles; whether HGSA improves risk prediction or has clinical utility requires further evaluation.

Abbreviations

AD
Alzheimer’s disease
BMI
body mass index
CI
confidence interval
HGS
handgrip strength
HGSA

handgrip strength asymmetry
HGSAW
handgrip strength asymmetry and weakness
HGSW
handgrip strength weakness
HR
Hazard ratio
HV
hippocampal volume
ICV
intracranial volume
MRI
magnetic resonance imaging
OR
odds ratio
PCA
principal components analysis
SD
standard deviation
TBV
total brain volume
VaD
Vascular dementia
WMHV
White matter hyperintensity volume

Declarations

Ethics approval and consent to participate

The UKB was reviewed and approved by the National Information Governance Board for Health and Social Care and the National Health Service Northwest Multicenter Research Ethics Committee (11/NW/0382). This study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants.

Consent for publication

Not applicable. This article does not contain any individual participant's data in any form.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

B-Z designed the research; PP-M and B-Z performed the statistical analyses; XJ-L, ZC-C, DN-G and B-Z helped visualize the results and interpreted the data; XJ-L, Y-H, LM-R, DN-G, PP-M and B-Z drafted the manuscript; All authors revised the manuscript; B-Z, YL-Y and ZC-C supervised the data analysis and interpretation; B-Z had the primary responsibility for the final content; and all authors read and approved the final manuscript.

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Data Availability

The data used in this study were obtained from UK Biobank under application number 109828. Researchers may apply for access to UK Biobank data through the UK Biobank Access Management System. The authors do not have permission to redistribute individual-level UK Biobank data. The summary results supporting this article are provided in the article and its supplementary information.

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Figures

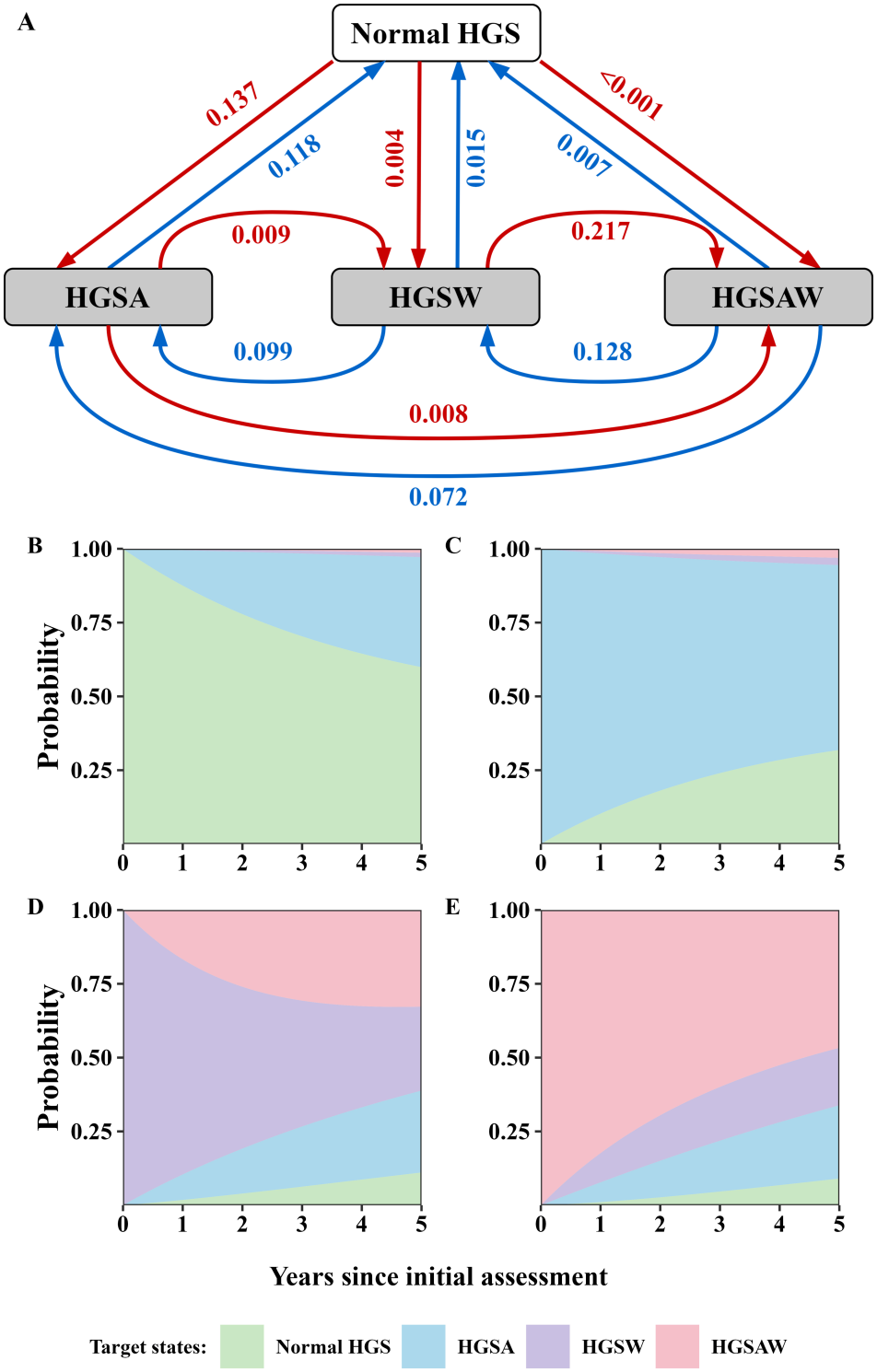


Figure 1

Transition dynamics of handgrip strength (HGS) phenotypes in a multi-state Markov model.

(A) Estimated transition intensities between HGS phenotypes. Arrows indicate the direction and intensity of transitions, with red arrows representing transitions toward impaired HGS states, blue arrows representing transitions toward normal HGS, and arrow labels show estimated transition intensities. (B–E) Estimated probabilities of occupying each HGS state over 5 years among participants initially classified as (B) normal HGS, (C) HGSA, (D) HGSW, and (E) HGSAW. Normal HGS was defined as absence of weakness and asymmetry; HGSA as asymmetry alone; HGSW as weakness alone; and HGSAW as concurrent asymmetry and weakness.

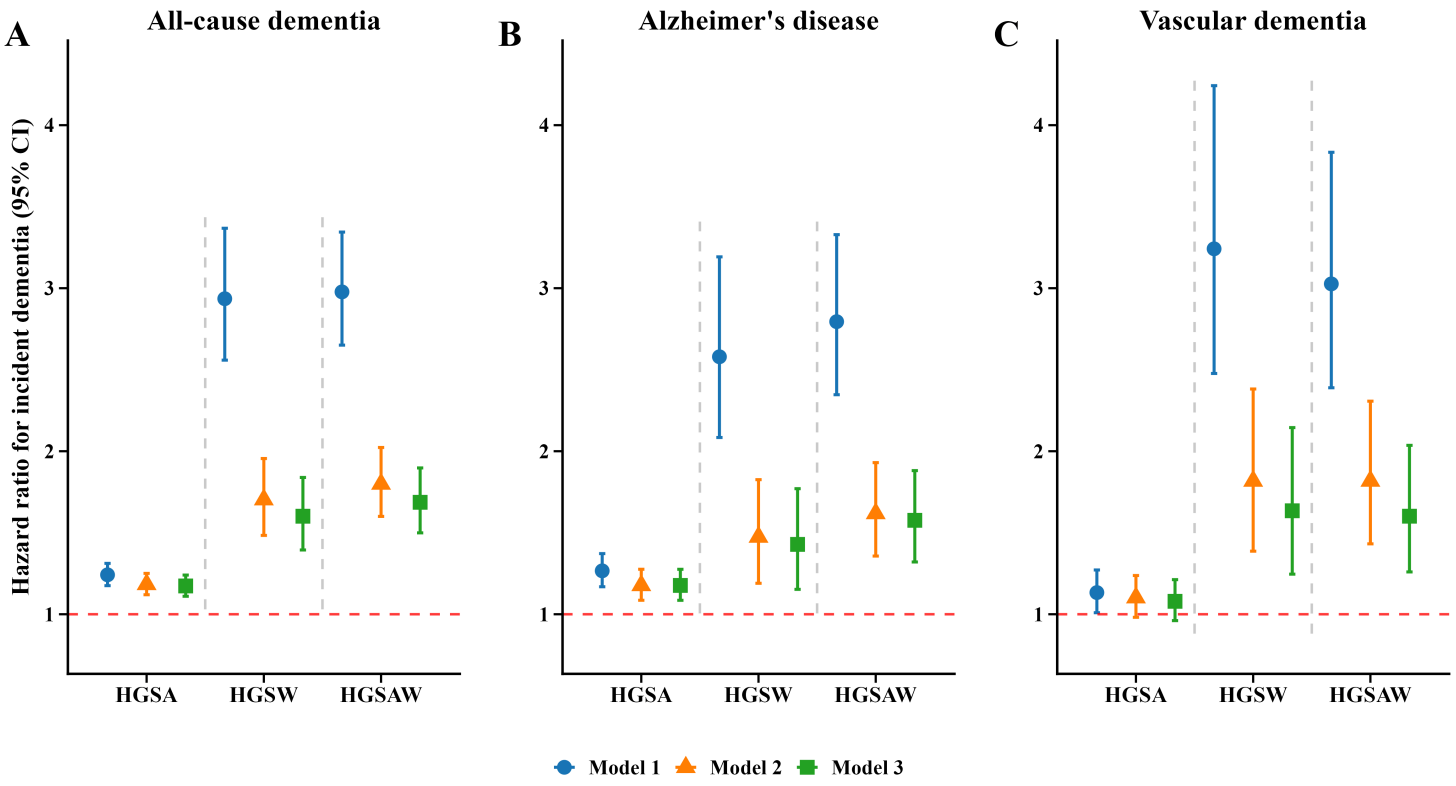


Figure 2

Associations between baseline handgrip strength (HGS) phenotypes and dementia risk.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for (A) all-cause dementia, (B) Alzheimer's disease, and (C) vascular dementia. The normal HGS group served as the reference. Model 1 was unadjusted, Model 2 adjusted for demographic factors, and Model 3 additionally adjusted for anthropometric, clinical, and lifestyle factors. Blue circles, orange triangles, and green squares indicate Model 1, Model 2, and Model 3 estimates, respectively. The red dashed line represents HR = 1.

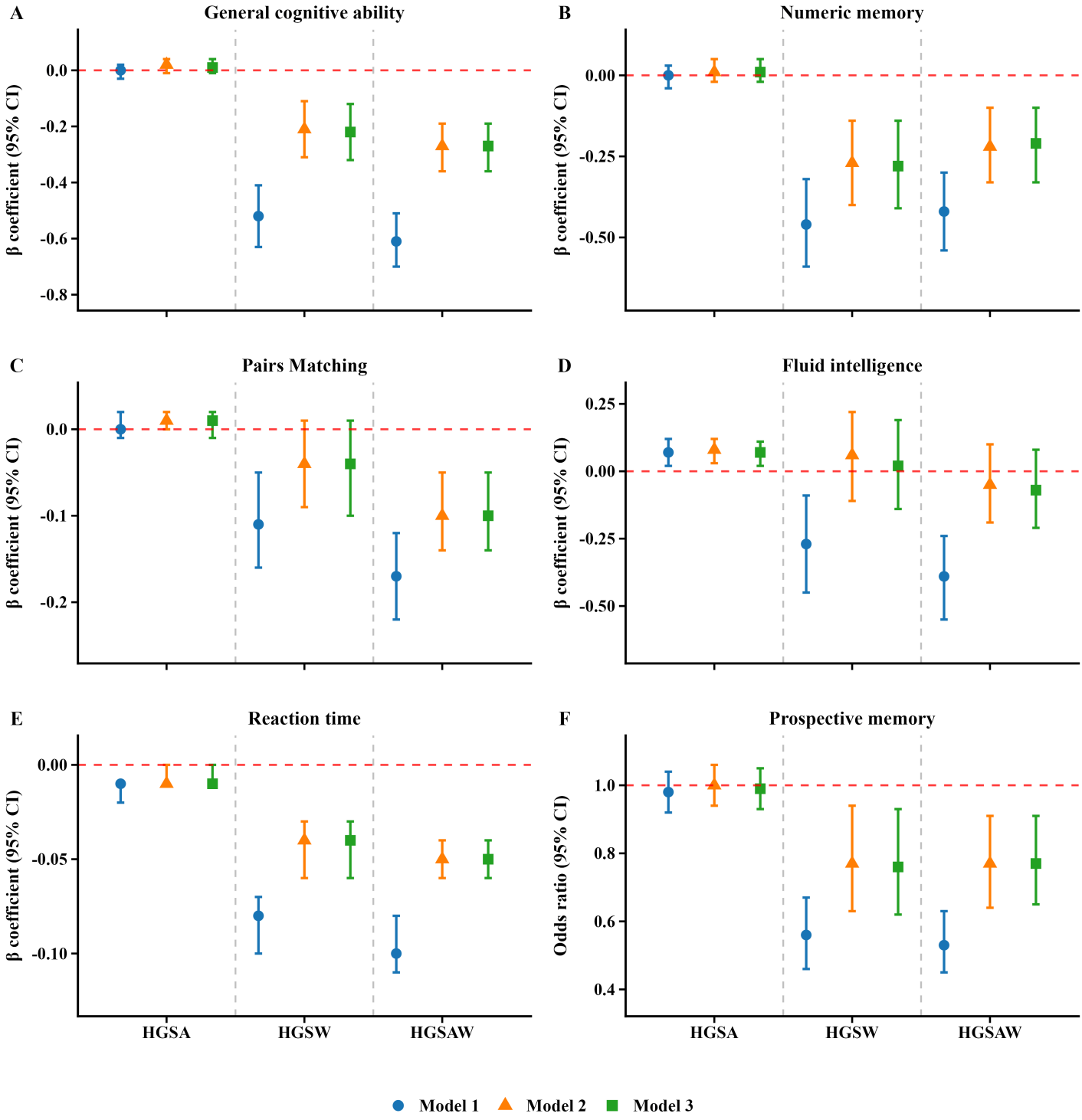


Figure 3

Associations between baseline handgrip strength (HGS) phenotypes and cognitive outcomes.

(A–E) show β coefficients and 95% confidence intervals (CIs) from linear regression models for (A) general cognitive ability, (B) Numeric Memory, (C) Pairs Matching, (D) Fluid Intelligence, and (E) Reaction Time. (F) shows odds ratios (ORs) and 95% CIs from ordinal logistic regression for Prospective Memory.

Normal HGS was the reference group. Model 1 was unadjusted, Model 2 adjusted for demographic factors, and Model 3 additionally adjusted for anthropometric, clinical, and lifestyle factors. The red dashed line represents no association (β = 0 or OR=1).

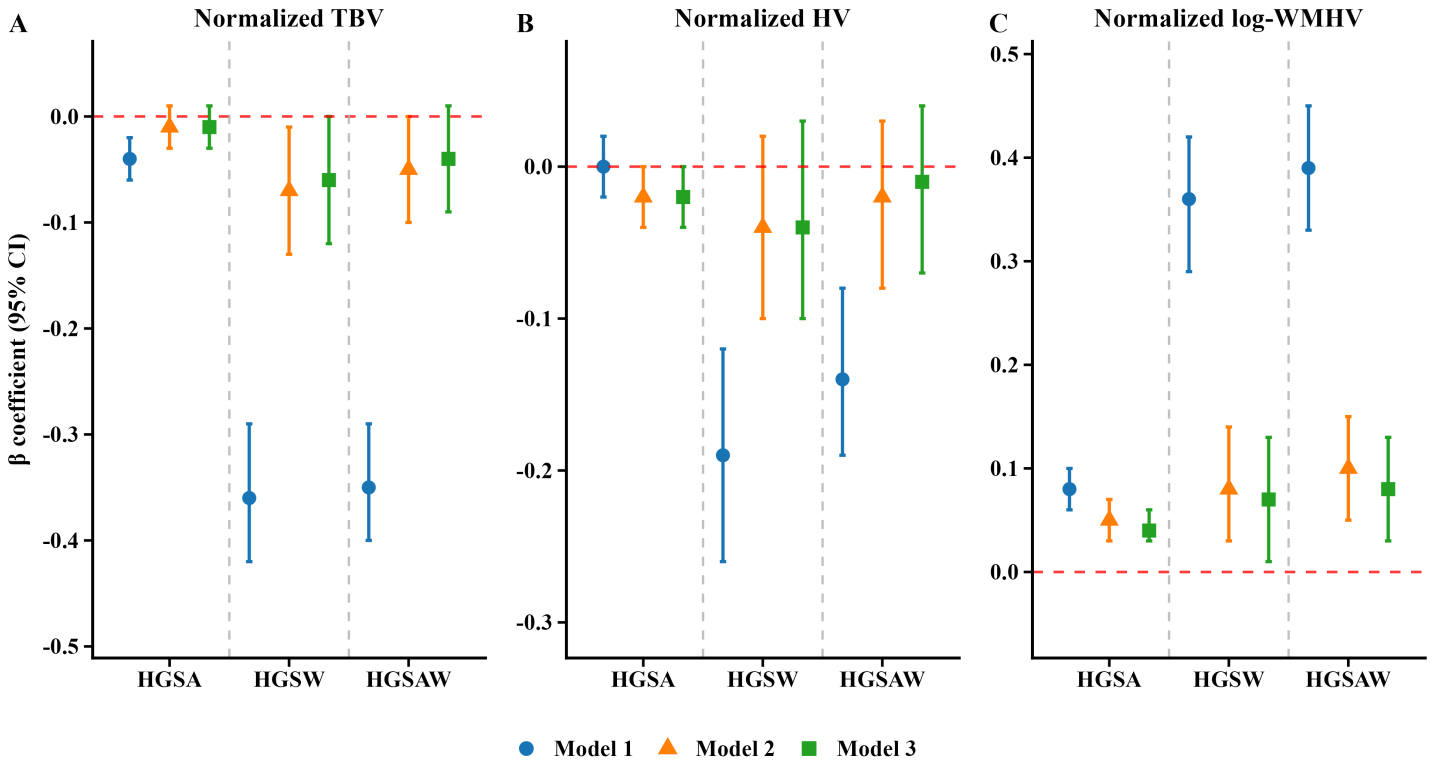


Figure 4

Associations between baseline handgrip strength (HGS) phenotypes and neuroimaging outcomes.

β coefficients and 95% confidence intervals (CIs) from linear regression models are shown, with the normal HGS group as the reference. Model 1 was unadjusted, Model 2 adjusted for demographic factors, and Model 3 additionally adjusted for anthropometric, clinical, and lifestyle factors. The red dashed line represents no association (β = 0). Panels display results for (A) normalized total brain volume (TBV), (B) normalized hippocampal volume (HV), and (C) normalized log white matter hyperintensity volume (WMHV).

Supplementary Files

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