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Research Article

Physical Function, An Adjunct to Brain Health Score for Phenotyping Cognitive Function Trajectories in Older Age: Findings From The Irish Longitudinal Study on Ageing (TILDA)

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Abstract

Background: Evidence is limited regarding the cumulative effect of risk factors on cognitive decline and the added value of physical function for cognitive function trajectory stratification. We operationalize 13 modifiable dementia risk factors in a scoring system and investigate the relationship between this brain health score, combined with simple measures of physical function, and risk of cognitive decline.

Methods: Population-based cohort study of persons aged 50 and older from the Irish Longitudinal Study on Ageing without a history of dementia at baseline who underwent repeated neuropsychological tests (8.08 ± 0.3-year follow-up) were included in the analyses. Exposures were the number of brain health metrics (defined by the *Lancet* Commission on Dementia Prevention, Intervention, and Care report) at recommended optimal levels. Physical function exposures included Timed Up and Go, dual-task walking speed, and grip strength. Each health metric and physical function measure at the recommended level was assigned a value of 1 and combined to generate brain health scores. Relationship with group-based trajectories of global cognitive function (multidomains composite score), estimated using *K*-means for longitudinal data, was assessed via ordinal logistic regressions.

Results: Among 2 327 participants (mean age, 61 years; 54% women), each additional optimal metric on the brain health score (odds 0.67 [0.62, 0.73]) was associated with reduced odds of cognitive decline. Adding Timed Up and Go (odds 0.71 [0.59, 0.84]) and dual-task walking speed (odds 0.74 [0.63, 0.89]) further improved model fit (ΔAIC = 14.8).

Conclusion: These findings support the promotion and maintenance of physical function in addition to brain health strategies to reduce the risk of cognitive decline.

Keywords: Cognitive decline, Dual-task walking speed, Heart–brain axis, Risk factors, Timed Up and Go

The American Heart Association (AHA) has emphasized the importance of promoting optimal health across the heart–brain axis (1). Several studies now report that scoring higher on the AHA's ideal cardiovascular health score, also referred to as Life's Simple 7, which is composed of modifiable health indices (body mass index, blood pressure, cholesterol, blood sugars) and modifiable behaviors

(physical activity, diet, smoking), is associated with lower risk of cardiometabolic disease, stroke, cognitive decline, and dementia (2–5). These studies support the hypothesis that risk factors and disease mechanisms are shared across the heart–brain axis (1).

Since the introduction of Life's Simple 7, there has been an increased appreciation of wider health indices (depression, hearing loss, concussion), health behaviors (alcohol intake), environmental risk exposures (household air pollutants), and life-course exposures (education, social isolation) that may predict heart–brain trajectories (5–8). New life-course models highlight the importance of taking a wider approach when considering strategies for promoting brain health and primordial prevention of cognitive decline (8). To date, few studies have investigated the cumulative effects of these risk factors on cognitive aging and the focus has been on using static or resting measures (eg, seated blood pressure) in risk scores. The reliance on resting measures, however, ignores the established evidence that using dynamic physiological stressors (or stress tests) that increase metabolic demands across the neuromuscular system and increase cardiac output and vascular stress can illicit abnormal or suboptimal physiological performance and therefore identify cardiovascular risk populations (9). In sedentary populations, stress testing may not even require cardiopulmonary exercise testing. There is growing evidence that simple functional measures such as Timed Up and Go (TUG) are associated with cardiovascular disease and dementia (10–12). Furthermore, midlife decline in physical function may be an early indicator of the start of the prodrome of cognitive decline and future risk of dementia and identify a potentially important period to deliver intensive strategies to optimize brain and cardiovascular health (13,14). To this extent, using simple functional measures such as TUG, dual-task walking speed, and grip strength may complement brain and cardiovascular health scores (15,16).

It is understood that there is a complex interplay and bidirectionality in the relationships between the central nervous system, peripheral nervous system, perceptual system, muscles, bones, and joints and that dysfunction in one of these systems may lead to executive and functional motor decline (17). Advances in brain imaging demonstrate distinctive cortical and subcortical networks including autonomic, sympathetic, and allostatic networks that regulate function across the heart–brain axis. Similar cortical and subcortical network activation patterns can also be observed during motor tasks. TUG and dual-task walking speed have been demonstrated to be sensitive indicators of cortical injury and atrophy associated with disease states such as stroke and multiple sclerosis (18,19). Therefore, in otherwise healthy individuals, suboptimal performance in simple tests of physical function may be an indicator of declining integrity in neural networks and risk of subsequent decline in executive function. This hypothesis is supported by previous longitudinal studies investigating the associations between measures of brain health across the life course and midlife gait speed (16). Slow midlife walking speed was independently associated with lower cognitive function in childhood and accelerated brain atrophy in midlife. The same study also demonstrated cross-sectional associations between slow walking speed and cognitive function in midlife.

In this study, we examine a new, novel 13-item brain health score (defined using 13 resting measures or risk factors identified by the *Lancet* Commission on Dementia Prevention, Intervention, and Care report) and expand this score further with the inclusion of functional measures derived from dynamic physiological stressors such as TUG, dual-task walking speed, and grip strength to investigate relationships with trajectories of cognitive decline in a large Irish cohort of individuals aged 50 and older from The Irish Longitudinal Study on Ageing (TILDA). Supplementary analyses examine the well-established AHA Life's Simple 7 tool, a 7-item cardiovascular health score, in relation to cognitive function trajectories, to quantify the added value of a wider brain health score and the inclusion of functional measures to cardiovascular resting measure-based scores for risk stratification of cognitive function trajectory. Supplementary analyses also explore the independent contribution of each of the resting and functional measures on cognitive function trajectories to identify the potent risk factors of cognitive decline or specific clustering of factors that may be associated with accelerated decline.

Method

Ethical approval was granted by the Trinity College Faculty of Health Sciences Research Ethics Committee, Dublin, Ireland. Protocols conformed with the 1964 Declaration of Helsinki and its later amendments. Signed informed consent was obtained from all respondents prior to participation.

Population

TILDA is a large population-based study of a nationally representative sample of community-dwelling older adults aged 50 years and older. TILDA's random sampling procedure and study design are available elsewhere (20). Participants have been followed biennially from Wave 1 (2009–2011), and this analysis includes data up to Wave 5 (2018). At each wave, participants completed a Computer-Assisted Personal Interview that collected information on their social, health, and financial situations. At baseline, participants were also offered to take part in an extensive nurse-administered health assessment in a dedicated health center or a modified version in the participant's home. Among the 8 173 participants aged 50 and older at baseline, 5 034 took part in the center-based health assessment and 2 132 had baseline resting and functional measures and cognitive data available from Wave 1 to 5 for a complete case analysis (see Supplementary Figure 1 for a detailed breakdown).

Brain Health Score

Data from Wave 1 collected during the personal interview were used to calculate participants' brain health score. The brain health score was generated using 13 resting measures or risk factors identified by the *Lancet* Commission on Dementia Prevention, Intervention and Care report (2020) (8). Brain health metrics included smoking, alcohol consumption, physical activity, body mass index, blood pressure, cholesterol, glycated hemoglobin (HbA1c), diet, education, hearing loss, depression, social connectedness, and indoor air pollution. The Food Frequency Questionnaire completed at Wave 3 and information on open fire usage collected at Wave 2 were included as retrospective indexes of baseline diet and indoor air pollution, respectively. Each measure was categorized into 2 levels (poor vs optimal) according to established criteria (2–5). Table 1 details the health metrics and cutoffs used to generate the brain health score. One point was assigned to each optimal measure and these measures were then summed to calculate the brain health score, ranging from 0 to 13. A higher score corresponds to better brain health.

Physical Function Measures

Data from Wave 1 collected during the health assessment were used to extract baseline functional measures derived from dynamic physiological stressors. The maximal isometric handgrip strength test was used to assess muscular strength (32). Hand grip strength

Table 1. Resting Measures and Cutoffs Used for the Generation of the Brain Health Score (Defined Using 13-Item Lancet Commission Dementia Report) and Cardiovascular Health Score (Defined Using 7-Item American Heart Association Tool)

Resting Measures	Data Collection	Optimal vs Poor Cutoffs (1)	Brain Health Score	Cardiovascular Health Score
Smoking	Self-reported smoking status (current, past, never) and years of smoking.	Optimal: never smoked or past (stopped >5 years ago).	x	x
Physical activity	Short-form version of the International Physical Activity Questionnaire (21). Respondents were asked to indicate the number of days and how much time per day they spent walking and doing physical activities of moderate and vigorous intensity during the past 7 days. The total time spent in each activity was weighted based on the energy requirements of the activity giving a score in MET-minutes/week for each respondent.	Optimal: vigorous-intensity activity of at least 20 minutes on 3 or more days per week; or moderate-intensity activity of at least 30 minutes on 5 or more days per week; or any combination of walking, moderate- or vigorous-intensity activities on 5 or more days per week accumulating at least 600 MET-minutes/week.	x	x
Body mass index (BMI)	BMI was calculated by dividing the participants' weight in kilograms by height in meters squared. Participants' height was measured to the nearest 0.01 m (Seca 240 Stadiometer, Seca Ltd, Birmingham, UK), weight to the nearest 0.1 kg (Seca 861 Electronic Scales, Seca Ltd, Birmingham, UK).	Optimal: <25.	x	x
Blood pressure	Two-seated systolic (SBP) and diastolic (DBP) blood pressure measurements were obtained separated by 1 minute using an OMRON digital automatic blood pressure monitor (Model M10-IT).	Optimal: averaged SBP <120 mm Hg and DBP <80 mm Hg, untreated.	x	x
Cholesterol	Nonfasting venous blood was drawn during the health assessment. The TILDA protocol for blood sample collection, processing, and storage has been described previously (22). Total cholesterol was measured using a single reagent, endpoint reaction method that is specific for cholesterol. The assay is optimized against the Centers for Disease Control and Prevention and the National Institute of Standards and Technology reference methods (23).	Optimal: ≤200 mg/dL (≤5.0 mmol/L), untreated.	x	x
HbA1c	HbA1c concentration was analyzed by reversed-phase action exchange chromatography using an ADAMS A1c HA-8180V analyzer, which is traceable to the internationally agreed standard developed by the International Federation of Clinical Chemistry (24).	Optimal: <39 mmol/mol (<5.7%), untreated.	x	x
Diet	The Food Frequency Questionnaire (FFQ) completed at Wave 3 was included as a retrospective index of diet. The FFQ was adapted from a questionnaire used in SLAN 2007 (25) and the European Prospective Investigation of Cancer study (26). Description and administration of the FFQ are available elsewhere (27).	Optimal: consumption of fruits and vegetables twice a day or more and consumption of high-fiber bread once a day.	x	x
Education	Self-reported education levels: none or primary (0–8 years); secondary (12–14 years); tertiary level or higher (16–21 years).	Optimal: tertiary or higher level of education.	x	
Alcohol	CAGE alcohol screening test (28).	Optimal: CAGE score <2; poor: CAGE ≥2.	x	
Hearing loss	Self-reported hearing (1 = excellent to 5 = poor).	Optimal: 1 (excellent), 2 (very good), or 3 (good).	x	
Depression	Center for Epidemiological Studies—Depression scale (29). Scores ranged 0–24.	Optimal: ≤4 was used to index optimal mental health.	x	
Social isolation/ connectedness (the size of an individual's social networks)	Berkman-Syme Social Network Index (30). Scores range 0–4 (0–1 = "most isolated" to 4 = "most integrated").	Optimal: 4 (most integrated).	x	

Table 1. Continued

Resting Measures	Data Collection	Optimal vs Poor Cutoffs (1)	Brain Health Score	Cardiovascular Health Score
Indoor air pollution	Not available at baseline. Self-reported residential heating at Wave 2 was used as a retrospective index of indoor air pollution. Indoor air pollution was reported unchanged across Waves in the TILDA data set (31). Respondents were asked how they heated their home during winter from the following options: central heating only, portable heaters only, closed solid fuel appliance only, a combination of closed solid fuel appliances and portable heaters, open fire only, and a combination of open fires and portable heaters.	Optimal: no usage of open fire or a combination of open fire and portable heater (31).	x	

was measured using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., White Plains, NY). The mean value from 2 trials on each hand was used in the analysis and indexed optimal if >16 for women and >27 for men (ie, values above the 25th percentile of grip strength distribution per sex). Functional mobility was assessed with the TUG test (33), where participants were asked to stand from a seated position, walk 3 m at their usual pace, turn around, walk back to the chair, and sit down. The time from the command "GO" to when the participant's back rested against the back of the chair was recorded. Gait was assessed using a 4.88 m (16 ft) computerized walkway with embedded pressure sensors (GAITRite; CIR Systems Inc., Franklin, NJ). There was a 2.5 m zone at the start and 2 m at the end of the mat to allow for acceleration and deceleration. Participants performed 2 walks under cognitive dual-task condition, which required to recite alternate letters of the alphabet (A-C-E, etc.) while walking. Mean dual-task gait speed was obtained from the 2 walks. Optimal TUG and dual-walking speed were defined for values below 8 sec and 120 cm/sec (ie, values below the 75th percentile), respectively. This high-risk quartile approach has been used elsewhere (34). One point was assigned to each optimal functional measure and these measures were then added separately and in combination to the brain health score to create expanded brain health scores. These scores ranged from 0 to 14 (when the functional measures were added separately) and 0 to 16 (when added in combination).

Outcomes

Analysis of cognitive decline used composite scores of global cognition extracted at Waves 1–5 (8.08 ± 0.3-year follow-up). Cognitive function collected during the personal interviews at each wave was assessed using a battery of neuropsychological tests, including 10-word immediate recall (2 trials), 10-word delayed recall, semantic verbal fluency (animal naming), and orientation (date, day, month, year). Details on the individual tests are published elsewhere (35). A composite score per participant was derived by combining individual test scores to broadly reflect global cognitive function across 3 domains: verbal memory, executive function, and orientation. Composite scores were generated based on an equally unit-weighted approach using standardized scores (z scores). The higher the composite score, the better the cognitive function.

Trajectories of global cognitive function (based on the composite scores) were estimated using K-means cluster modeling for longitudinal data (kml package in R version 4.0.3 with RStudio Version 1.4.1103) (36). Kml is a nonparametric, hill-climbing algorithm that does not impose assumptions regarding the shape of the trajectories. The kml analysis was specified to allow between 2 and 5 clusters (group-based trajectories), each obtained by running 1 000 permutations. The optimum number of clusters (groups) was determined using the Calinski and Harabasz criteria (described in detail elsewhere (36)), along with consideration of clinical relevance. Three trajectory groups of global cognitive function were identified: the high-increasing (36.8%), the mid-stable (43.2%), and the low-declining (20%). Examining trajectories of global cognitive function enables the longitudinal investigation of the pace of change in cognitive function, building upon and beyond cross-sectional investigations. Supplementary Table 1 provides the composite score means and standard deviations (SDs) per wave and cognitive function trajectory group. Supplementary Figure 2 illustrates the cognitive function trajectories per group from Wave 1 (2009–2011) to Wave 5 (2018).

Covariates

Covariates included baseline age, sex, and preexisting self-reported physician-diagnosed cardiovascular diseases and events (CVDEs), self-reported long-term diseases, and chronic conditions. CVDEs included history of angina, heart attack, congestive heart failure, stroke, transient ischemic attack, and atrial fibrillation. Self-reported long-term diseases corresponded to any health problem, illness, disability, or infirmity that troubled the respondent over a period of time. Self-reported chronic conditions included lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, stomach ulcer, varicose ulcer, liver disease, thyroid disease, or kidney disease. Data were pooled to create 3 separate dichotomous CVDEs, long-term and chronic disease measures, for absence (disease-free) or presence (≥1) of CVDEs, long-term diseases, and chronic conditions, respectively.

Statistical Analyses

All statistical analyses were performed using R version 4.0.3 with RStudio Version 1.4.1103 (37).

The observed sample was first characterized by baseline demographics, resting, functional measures, and brain health score. Continuous variables were described as unadjusted means with SDs; categorical variables were given as percentage (%). To estimate selection bias, differences between individuals included and excluded from these analyses (due to missing data) were investigated.

Bivariate tests of differences were carried out using Mann–Whitney *U* tests and chi-square tests as appropriate.

The relationship between standardized (*z*-score transformed) brain health score (predictor) and cognitive function trajectory groups (outcome; 3 groups) was first quantified by using ordinal logistic regressions (ie, odds ratios [ORs]) or the following form:

$$\log\frac{P\left(Y \le j|x_1 \ \ldots x_p\right)}{P\left(Y > j|x_1 \ \ldots x_p\right)} = \alpha_j - \beta_1 \ x_1 \ldots - \beta_p x_p$$

where Y is the ordinal outcome of cognitive function groups with $J = 3$ categories, $P(Y \le j)$ is the cumulative probability of Y less than or equal to category $j = 1,2$. α_j refers to the intercept/cut-points for the log odds of being at or below group j and $\beta_1 \ \ldots \beta_p$ are the log-odd coefficients for covariates $x_1 \ldots x_p$, respectively. This model hence assumes proportional odds or in other words that the log-odds coefficient for any given explanatory variable is independent of the response groups (ie, that the log OR across cut-points in the response is constant).

To assess the benefit of adding functional measures to the brain health score, cognitive function trajectory groups were then regressed separately on the standardized expanded brain health scores combining resting and functional measures, by using ordered logistic regression. All models were adjusted for age, sex, CVDEs, long-term diseases, and chronic conditions. Model fit was assessed using the Akaike information criterion (AIC). Lower values of AIC indicate better model fit. The extent to which the expanded brain health models are believed to better predict cognitive outcome depends on the magnitude of the difference between the information measures. An AIC difference >3 between the brain health model and the expanded brain health models indicates considerable improvement; a difference >10 suggests substantial improvement (38).

Supplementary Analyses

The above analyses were repeated using as predictors a standardized (*z*-score transformed) cardiovascular health score, defined using 7-item AHA Life's Simple 7 tool (2–5) and, in separate models, expanded cardiovascular health scores, combining resting and functional measures. As per the brain health score, each measure of the cardiovascular health score was categorized into 2 levels (poor vs optimal) following established criteria (Table 1). One point was assigned to each optimal measure and these measures were then summed to calculate the cardiovascular health score, ranging from 0 to 7. As per the expanded brain health scores, the expanded cardiovascular health scores were generated adding the dichotomized functional measures separately and in combination to the cardiovascular health score. These scores ranged from 0 to 8 (when the functional measures were added separately) and 0 to 10 (when added in combination). The AIC difference between the brain health model and the cardiovascular health model was used to quantify the added value of a wider brain health score compared to a cardiovascular health-focused score. The AIC difference between the cardiovascular health model and the expanded cardiovascular health models was used to assess the benefit of including functional measures to cardiovascular resting measure-based scores.

To identify the potent factors or clustering of specific factors associated with accelerated decline, additional supplementary analyses were conducted. All resting and functional dichotomous measures were entered as independent predictors in one ordered logistic regression model, adjusted for age, sex, CVDEs, long-term diseases, and chronic conditions.

Sensitivity Analyses

In sensitivity analyses, we tested for effect modification by fitting separate age (3 levels: 50–59, 60–69, 70+) × brain health score and sex × brain health score interaction terms. The significance of interaction terms was assessed through likelihood ratio tests comparing additive models with models with an interaction term.

Additional sensitivity analyses were conducted to assess the robustness of our findings when examining the joint effect of the functional measures and brain health score on cognitive function trajectory by using additive and interaction terms between the functional measures and brain health score instead of including the resting and functional measures into single expanded brain health scores. In these analyses, nested ordered logistic regression models, adjusted for age, sex, CVDEs, long-term diseases, and chronic conditions, were compared. The baseline model included as predictor the brain health score; the additive models included the brain health score plus TUG, grip strength, and dual-task walking speed, entered (as continuous variables) in separate models; the interaction models included the brain health score and the functional measures with an interaction term. The significance of additive and interaction terms was assessed through likelihood ratio tests comparing the baseline model with additive models and comparing the additive models with models with an interaction term, respectively.

A final set of analyses were carried out to assess the robustness of our findings when not using a dichotomized based brain health score. In these analyses, each resting and functional measure, as originally collected (ie, not dichotomized as optimal or poor), was entered as an independent predictor in ordered logistic regression models. The brain health model included 13 resting measures as predictors. The expanded brain health models included the 13 predictors of the brain health model plus TUG, grip strength, and dual-task walking speed entered (as continuous variables) in separate models and included together in one single model. All models were adjusted for age, sex, CVDEs, long-term diseases, and chronic conditions. Likelihood ratio tests comparing the brain health model with the expanded brain health models were used to assess the benefit of adding functional measures.

Results

Table 2 describes the characteristics of the sample. The mean age was 60.8 ± 7.5; 54% of the participants were women; 11% had one or more cardiovascular conditions. The mean brain health score was 8.3 ± 1.7. Compared to the individuals who were excluded from the analyses (Supplementary Table 2), those included were more likely to be younger (60.8% vs 64.9%), have a higher level of education (42% vs 25%), have less cardiovascular (11% vs 16%), chronic (73% vs 79%) and long-term diseases (34% vs 40%), be more physically active (74% vs 66%), have lower levels of depressive symptoms (3.9% vs 5.1%), be less isolated (67% vs 78%), and have lower open fire usage to heat their home (7.1% vs 11%). Cognitive function was also higher at baseline in the included participants (Wave 1: 0.27 vs −0.06).

Brain Health Scores and Cognitive Function Trajectories

In this Irish longitudinal cohort study, the probability of being in the low-declining group reduced with every additional health metric scored as optimal. Using the brain health score as predictor, each additional health metric score was associated with 32%

Table 2. Sample Characteristics (n = 2 132)

	Mean (*SD*)/ Frequency (%)
Demographics	
Age, mean (*SD*)	60.8 (7.5)
Sex (female), *n* (%)	986 (54)
Resting measures	
Education (0–14 years: none/primary or secondary), *n* (%)	1 243 (58)
Cardiovascular conditions (yes), *n* (%)	238 (11)
Chronic diseases (yes), *n* (%)	1 558 (73)
Long-term diseases (yes), *n*(%)	733 (34)
BMI, mean (*SD*)	28.4 (4.8)
Physical activity (Vig <20 min on less than 3 days/week or mod <30 min on less than 5 days/week or <600 MET-minutes/week based on walk + mod + vig), *n* (%)	559 (26)
Smoking (current or past <5 years), *n* (%)	310 (14)
Alcohol (problematic), *n* (%)	296 (14)
Blood pressure (systolic|diastolic), mean (*SD*), mmHg	133 (19) | 81 (11)
Antihypertensive treatment, *n* (%)	526 (24)
Cholesterol, mean (*SD*), mg/dL	200 (41)
Cholesterol medications (yes), *n* (%)	419 (19)
HbA1c, mean (*SD*), mmol/mol	32.7 (4.9)
Diabetes treatment (yes), *n* (%)	86 (4)
Diet (fruits and vegetables), mean (*SD*)	3.9 (2.8)
Diet (high-fiber bread), mean (*SD*)	2.1 (1.7)
Hearing loss (fair or poor), *n* (%)	253 (12)
Depression, mean (*SD*)	3.9 (3.6)
Social isolation (BSNI <4), *n* (%)	1 438 (67)
Indoor air pollution (open fire), *n* (%)	151 (7.1)
Functional measures	
Hand grip strength (men | women), mean (*SD*)	34.2 (7.5) | 20.1 (4.9)
Timed Up and Go, mean (*SD*)	8.3 (1.5)
Walking speed, mean (*SD*)	138.2 (18.7)
Dual-task walking speed, mean (*SD*)	113.7 (25.5)
Health scores	
Brain health score, mean (*SD*) [min, max]	8.3 (1.7) [0, 7]
Cardiovascular health score, mean (*SD*) [min, max]	4.2 (1.2) [2, 13]

Note: *n* = number; *SD* = standard deviation; mod = moderate activities; vig = vigorous activities; walk + mod + vig = combination of walking, moderate, and vigorous activities; BSNI = Berkman-Syme Social Network Index.

reduced odds of cognitive decline over 8 years (odds 0.68, 95% CI: 0.62–0.74). Using the expanded brain health scores as predictors showed that the separate addition of TUG (ΔAIC 9.3) and dual-task walking speed (ΔAIC 8.1) improved models fit for the association between brain health level and cognitive trajectory. The addition of both TUG and dual-task walking speed into a single expanded brain health score further improved model fit (ΔAIC = 13.7; Table 3). Figure 1 shows the probability of being in the high-stable, mid-stable, and low-declining group as a function of the brain health score and the TUG and dual-task walking speed expanded brain health score. As can be seen, the probability of belonging to the low-declining group (green dotted line) decreases as the brain and expanded brain health scores increase.

Supplementary Analyses

Using the cardiovascular health score as predictor, each additional health metric score as optimal was associated with a 16% reduced odds of cognitive decline (odds 0.84, 95% CI: 0.77–0.91). When comparing the cardiovascular and brain health models, the brain health model had the best model fit (ΔAIC = 61.3). Using the expanded cardiovascular health scores as predictors showed that the separate addition of grip strength (ΔAIC 2.9), TUG (ΔAIC 10.2), and dual-task walking speed (ΔAIC 8.6) improved models fit for the association of cardiovascular health with cognitive function trajectories. Including both TUG and dual-task walking speed into a single expanded cardiovascular health score substantially improved model fit (ΔAIC = 17.1; Supplementary Table 3).

The inclusion of the 13 resting risk factors and the 3 physical function measures as independent predictors in one single model revealed that education, physical activity, hbA1c, alcohol consumption, diet, hearing, depression, air quality, TUG, and dual-task walking speed were the strongest independent predictors of cognitive trajectories (Supplementary Table 4). Higher educational attainment was associated with the lowest odds of cognitive decline (67%).

Sensitivity Analyses

In sensitivity analyses, there were no significant interactions between the brain health score and age or the brain health score and sex ($p > .05$). Assessing the joint effect of the functional measures and brain health score on cognitive function trajectory by using additive and interaction terms between functional measures and brain health score instead of using expanded brain health scores as predictors corroborate our findings. Adding TUG (χ^2 (1) = 17.6, $p < .0001$) and dual-task walking speed (χ^2 (1) = 10.7, $p = .001$) as independent predictors significantly improved models fit. The interactions functional measures × brain health score were never significant ($p > .05$). Our analyses using nondichotomous variables as predictors of cognitive function trajectories showed similar trends. Adding TUG (χ^2 (1) = 19.5, $p < .0001$) and dual-task walking speed (χ^2 (1) = 13.0, $p < .001$) as additional independent predictors to the 13 resting measures of the brain health model significantly improved models fit. When both measures were added to the same model, only TUG remained significant ($p = .002$); dual-task walking speed was borderline significant ($p = .08$).

Discussion

This longitudinal cohort of older persons has 2 main findings. First, we demonstrate that a new, novel brain health score is associated with cognitive function trajectories over 2 132 participants with an average mean age of 61 at study entry and that this score improves cognitive trajectory stratification compared to the AHA's Life's Simple 7 tool. Second, we show that including assessment of TUG and dual-task cognitive walking speed significantly compliments both brain and cardiovascular health scores. In addition, the observed associations were consistent across different methodological approaches.

Higher cardiovascular health as indicated by the number of optimal metrics on the AHA's Life's Simple 7 tool has been demonstrated to be associated with better cognitive health in young and middle-age adults and lower rates of cognitive decline across the life course (5,39). Furthermore, higher cardiovascular health is associated with favorable white matter integrity, brain vascular indices, subcortical and cortical brain volume, and higher metabolic function in a number of brain imaging studies (2,4,40,41). The recent studies in middle life and older adults that demonstrate the association between the Life's Simple 7 tool and risk of dementia in later life support the hypothesis for shared vascular origins for later-life dementia. The current study supports the growing argument to

Table 3. Adjusted Odds Ratios (ORs), 95% Confidence Intervals (CIs), and Model Fit Statistics Derived From Ordered Logistic Regression Analyses for the Brain Health and Expanded Brain Health Scores Predicting Cognitive Function Trajectories

Models	ORs	AIC	ΔAIC
Brain health score	0.68*** (0.62, 0.74)	4 056.03	REF
Expanded brain health score with grip strength	0.68*** (0.62, 0.74)	4 055.31	0.7
Expanded brain health score with dual-walk	0.66*** (0.61, 0.73)	4 048.02	8.1
Expanded brain health score with TUG	0.66*** (0.61, 0.72)	4 046.65	9.3
Expanded brain health score with TUG and dual-walk	0.65*** (0.60, 0.71)	4 042.25	13.7

Notes: TUG = Timed Up and Go; dual-walk = dual-task walking speed; AIC = Akaike information criterion; ΔAIC = difference in AIC between the brain health model (REF) and the model that includes an additional functional measure. ORs and 95% CIs are given for standardized (*z*-score transformed) scores. Models were adjusted for age, sex, cardiovascular diseases and/or events, chronic diseases, and long-term diseases.

***$p < .001$.

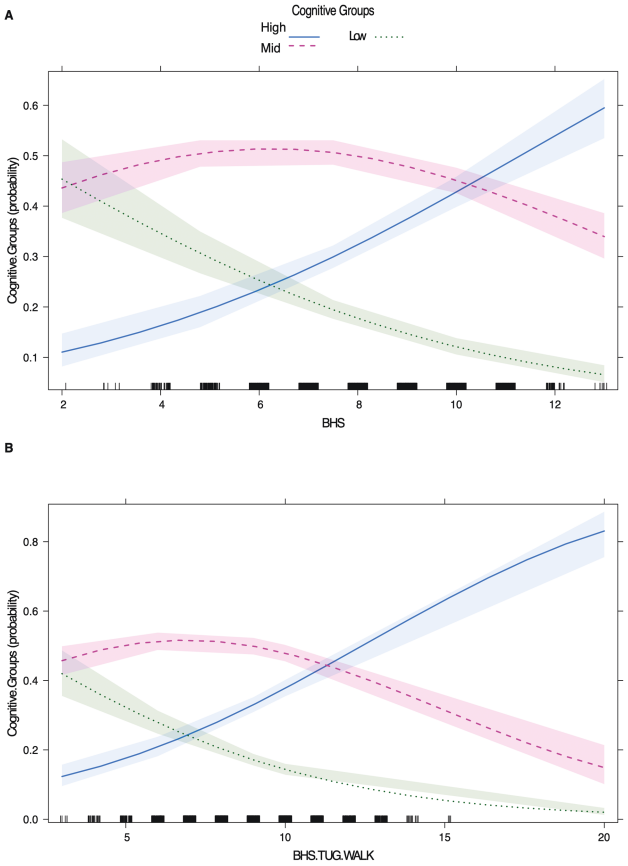

Figure 1. Probability of being in the groups of low-declining (green/dot line), mid-stable (pink/dash line), or high-increasing (blue/plain line) cognitive function trajectories as a function of the brain health score (**A**). Panel **B** presents the brain health score expanded with addition of optimal score for Timed Up and Go and dual-task walking speed. The models were adjusted for age, sex, cardiovascular diseases and events, long-term diseases, and chronic conditions. BHS = brain health score; BHS.TUG.WALK = TUG and dual-task walking speed expanded brain health score. The *y*-axis represents the probability (min = 0; max = 1) of being in the cognitive function trajectory groups. The *x*-axis connects the probabilities per one-point increment in the brain and expanded brain health scores for each group. Full color version is available within the online issue.

combine approaches for cardiovascular health screening with brain health initiatives for primordial prevention of cognitive decline.

The current study goes beyond using the simple risk stratification offered by the AHA tool to explore combined cardiovascular metrics with a broader spectrum of risk factors recently identified by the *Lancet* Commission on Dementia Prevention, Intervention, and Care (6,8). To our knowledge, our study is the first to operationalize these risk factors in a scoring system. The brain health score includes years of education, social isolation, alcohol consumption, household air pollution, hearing loss, and depression which have previously been independently associated with dementia.

The challenges which accompany risk stratification for cognitive decline and the proposed need to intervene earlier to reduce neuropathological damage are the incentive for using more comprehensive scoring tools to help identify at-risk cohorts. Accuracy of brain and cardiovascular health scores are further improved by incorporating simple physical functional tests of TUG and dual-task (cognitive) walking speed. The sensitivity of physical function measures for predicting cognitive outcomes and dementia risk such as gait has been demonstrated in a multicohort meta-analysis of 6 prospective population studies of older adults aged 60 and older (42). We hypothesized that using simple function tests derived from dynamic physiological stressors may help identify individuals with impaired cognitive reserve or even early neuropathology which would not otherwise be elucidated in resting measures. To our knowledge, our study is the first to incorporate simple functional measures in combination with brain and cardiovascular health risk scores to investigate the association with cognitive decline. TUG as a single measure of physical function was the strongest measure to improve the fit of the brain and cardiovascular health models. This test is widely used in clinical practice for the screening and diagnostics of older patients. The brain and cardiovascular health scores in addition to dynamic health measures may therefore enhance comprehensive geriatric assessments. Dual-task walking speed as adds-on testing may be particularly relevant within the context of cognitive health, given the observed decrease in executive functions in older age.

Our supplementary analyses identified that education, HbA1c, diet, physical activity, hearing, alcohol, depression, household air quality, TUG, and dual-task walking speed, clustered as the main predictors of cognitive trajectories in this cohort. With exception of educational attainment, which offered the greatest protection against cognitive decline, all the other factors are potentially modifiable in middle age and older adults. The mechanisms linking the identified cluster of risk factors are not clearly understood and likely multifactorial (1). The recent imaging studies suggest that there may be an interplay between (a) structural reserve and connectivity which may develop early in life and elevate peak capacity and neuroplasticity (43), (b) preservation of cerebral blood flow, autoregulation, and brain metabolism across midlife and older age which maintain the ability for localized flux to meet metabolic demands (44), and (c) innate or acquired resilience to injury and localized neuropathological degradation of structure and function (45). Encouragingly,

there may be potential to affect these pathways and attenuate decline in cognitive trajectories demonstrated by the success of diabetic and hypertension intervention studies (46–50). Multidomain interventions that could mitigate the cluster of risk factors identified in the current study are challenging to deliver and sustain (51–53). However, recent multidomain studies that are potentially scalable observed larger effects in younger ages (65–70 years), those with lowest level of education and higher baseline risk suggesting benefit for targeting early intervention in the highest risk groups (54). Therein, the observation in the supplementary analyses that TUG and dual-task walking speed are associated with cognitive function trajectories suggests that these dynamic tests could be utilized after the use of simple scoring systems to further stratify populations for intensive intervention. Further research is required to establish if these strategies would be effective in a trial setting and pragmatic for clinical translation. The potential of this approach needs to be caveated with the understanding that observed decline in physical function can be challenging to separate from causation versus prodromal patterns that may be the consequence of neurodegeneration.

Limitations and Strengths

This study has several limitations. First, is the inclusion of self-reported behavioral measures, although this is not specific to this study. Second, both self-reported diet and air pollution were not measured at baseline and air pollution did not account for the frequency and intensity of exposure and did not include other sources of exposure (eg, outdoor air pollution), which have also proved important. Third, dichotomizing continuous functional measures using the high-risk quartile approach imposes the arbitrary grouping of the participants based on the study sample which may pose the issue of generalizability to other populations. Our sensitivity analyses, however, show that our findings are robust to different methodological approaches. Fourth, changes in exposures over the 9-year follow-up were not controlled for in our models, whereas they could have an effect on cognitive function trajectories. Fifth, the cognitive trajectories group already differed in global cognition at baseline; however, these participants will be invited to participate in follow-up waves, which will ease the interpretation of cognitive decline and will allow for testing whether the models developed herein can predict incidence of brain health too. Sixth, loss to follow-up and missing data mean that the study sample was overall healthier than those excluded; therefore, the generalizability of our findings remains questionable. This does not however necessarily preclude the observed associations. As such, this study should be considered preliminary and exploratory but does support a need for future work, with the goal of expanding the current analyses by examining these relationships in other longitudinal studies of aging. Key strengths of this study include the operationalization of a 13 brain health score tested in comparison with the well-established AHA cardiovascular health score (the Life's Simple 7) using a relatively large cohort, the incorporation, for the first time, of simple functional measures of TUG (dual-task), walking speed and grip strength, and the ability to control for confounders.

Conclusion

In this cohort of Irish older adults, optimal physical function in addition to an increased number of optimal cardiovascular and brain health metrics was associated with a lower risk of cognitive decline. These findings may support the promotion and maintenance of physical function in addition to cardiovascular and brain health strategies to prevent risk factors associated with cognitive decline and dementia.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

C.D.L. and W.W. conceived, designed, and performed the analyses and wrote the article; N.D. and D.O.C. contributed to data analysis codes; B.H. provided feedback on statistical analyses; R.A.K. provided feedback on the manuscript.

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