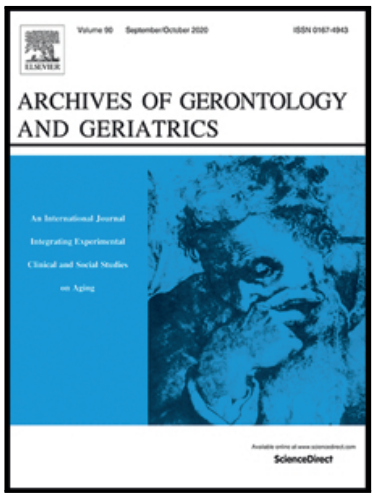


Exploring bi-directional temporal associations between timed-up-and-go and cognitive domains in The Irish Longitudinal Study on Ageing (TILDA)

Peter Hartley , Ann Monaghan , Orna A. Donoghue , Rose Anne Kenny , Roman Romero-Ortuno

PII: S0167-4943(21)00274-0
DOI: https://doi.org/10.1016/j.archger.2021.104611
Reference: AGG 104611

To appear in: *Archives of Gerontology and Geriatrics*

Received date: 26 August 2021
Revised date: 9 December 2021
Accepted date: 13 December 2021

Please cite this article as: Peter Hartley , Ann Monaghan , Orna A. Donoghue , Rose Anne Kenny , Roman Romero-Ortuno , Exploring bi-directional temporal associations between timed-up-and-go and cognitive domains in The Irish Longitudinal Study on Ageing (TILDA), *Archives of Gerontology and Geriatrics* (2021), doi: https://doi.org/10.1016/j.archger.2021.104611

Exploring bi-directional temporal associations between timed-up-and-go and cognitive domains in The Irish Longitudinal Study on Ageing (TILDA)

Peter Hartley[1,2,3*], Ann Monaghan[1,2], Orna A. Donoghue[1,2], Rose Anne Kenny[1,2,4], Roman Romero-Ortuno[1,2,4,5]

[1] The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Ireland.

[2] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland.

[3] Department of Public Health and Primary Care, University of Cambridge, United Kingdom.

[4] Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland.

[5] Global Brain Health Institute, Trinity College Dublin, Ireland.

* Corresponding author

Peter Hartley

hartleyp@tcd.ie

+ 44 1223 331841

Funding

Roman Romero-Ortuno is funded by a grant from Science Foundation Ireland under grant number 18/FRL/6188. TILDA is funded by Atlantic Philanthropies, Irish Life and the Irish Department of Health. Peter Hartley is funded by a fellowship from the Cambridge Biomedical Research Centre and the Addenbrooke's Charitable Trust [grant reference: 03/20 A]. The funders had no role in the conduct of the research or preparation of the article, study design, the collection, analysis and interpretation of data, writing of the report, or the decision to submit the paper for publication.

Highlights

- We explored bidirectional temporal relationships between timed-up-and-go (TUG) and five cognitive function domains: global cognition, processing speed, verbal fluency, executive function, and sustained attention.
- The effect sizes in both directions (i.e., cognitive function predicting future changes in TUG, and TUG predicting future changes in cognitive function) were found to be small.
- The ability for TUG to predict future cognitive function may have less clinical value than *vice-versa*.
- Global cognition, processing speed and sustained attention had the greatest clinical significance as predictors of future mobility.

Abstract

Introduction

The bi-directional longitudinal associations between mobility and cognition in older adults are poorly understood. Our objective was to study the temporal associations between timed-up-and-go (TUG) and five cognitive function domains: global cognition, processing speed, verbal fluency, executive function, and sustained attention.

Methods

We designed two longitudinal samples: A (for cognition as predictor of mobility), and B (for mobility as predictor of cognition). To examine the associations between the five cognitive domains at wave 1 and change in TUG times up to wave 5 (eight years), five linear mixed-effect models were fitted. To examine the associations between TUG times at wave 1 and change in the five cognitive domains between waves 1 and 3 (four years), five linear-regression models were fitted.

Results

After removing participants with missing data, sample A numbered 4913 participants (mean age 62), and sample B 3675 (mean age 61). Baseline cognitive domains were all significant predictors of future change in TUG times. Baseline TUG time was also a significant predictor of future change in all five cognitive domains. In both cases, poorer performance at baseline predicted greater future loss of function.

Conclusion

There was evidence of bi-directional temporal relationships between cognition and mobility. In both directions, the effect of the explanatory variable was small, though cognition as predictor of future mobility may have greater clinical relevance than *vice versa*. Our findings underscore the importance for clinicians of considering the bi-directional associations between cognition and mobility when observing subtle changes in either, especially as impairments emerge.

Key Words:

Mobility, Cognition, Ageing, Longitudinal

Abbreviations

Body mass index (BMI)

Choice Reaction Time (CRT)

Colour Trails Test (CTT)

Instrumental activities of daily living (IADL)

Interquartile range (IQR)

Montreal Cognitive Assessment (MOCA)

Timed-up-and-go (TUG)

The Irish Longitudinal Study on Ageing (TILDA)

Standard deviation (SD)

Sustained Attention to Response Task (SART)

1. Introduction

Mobility and physical performance are recognised as key markers of successful ageing and overall health [1, 2]. At a population level, mobility is observed to decline from midlife onwards, with the rate of decline accelerating in older age [2]. Cognitive decline is associated with ageing and in some cases, it can lead to loss of independence and dementia [3, 4]. However, as with most aspects of ageing, individual mobility and cognitive trajectories are extremely heterogeneous [2, 5, 6], dependent on the aspect of mobility or cognition being measured [6], and a product of multiple behavioural factors and biological mechanisms that occur and accumulate over a lifetime [1, 7, 8].

There is evidence of cross-sectional associations between mobility and cognition [9], including between slower performance in the timed-up-and-go (TUG) and poorer performance in global cognition, executive function, and processing speed tests [10]. This would suggest that there is a common underlying pathophysiological process affecting both cognition and mobility trajectories [11] such as white matter lesions [12], or that one precedes and contributes to the other's decline. For example, reduced processing speed may contribute to falls [13] and fear of falling, which could subsequently lead to reduced gait speed and/or altered gait [14]; or reduced mobility may contribute to reduced social interactions [15], which may in turn accelerate cognitive decline [16].

There is evidence that measures of mobility can predict future change in cognitive function [17-20]; in the reverse direction, some studies have reported baseline cognitive function as a significant predictor of change in measures of mobility [17, 18], but others have reported non-significant [20, 21], inconsistent findings [19], or association with certain cognitive domains only (e.g., executive function) [22]. In both directions, poorer performance at baseline predicted greater loss of function over time.

To contribute to the still poorly understood research field of longitudinal associations between mobility and cognition in older adults, the objective of this study was to utilise The Irish Longitudinal Study on Ageing (TILDA) datasets to assess the bidirectional temporal associations between TUG and five cognitive function domains: global cognition, processing speed, verbal fluency, executive function, and sustained attention.

2. Methods

2.1. Setting

We analysed data from TILDA, a population-based longitudinal study that collects information on the health, economic and social circumstances of community-dwelling adults aged 50 years and over in Ireland. Wave 1 of the study (baseline) took place between October 2009 and July 2011, and subsequent data was collected approximately 2-yearly over four additional waves (wave 2: February 2012 to March 2013; wave 3: March 2014 to October 2015; wave 4: January to December 2016; and wave 5: January to December 2018). At each wave, participants completed a computer-assisted personal interview conducted by trained social interviewers in the participants' own home, and a self-completion questionnaire, which they completed in their own time. Waves 1 and 3 also included a detailed health assessment conducted by trained research nurses at a dedicated health-centre or in the participant's own home. Health centre-based assessment data at waves 1 and 3 included four of the five cognitive measures of interest in this study (global cognition, processing speed, sustained attention, and executive function). All waves included assessment of verbal fluency and a TUG assessment. The full cohort profile has been described elsewhere [23, 24].

2.2. Design

To bidirectionally investigate the longitudinal relationships between TUG and cognitive domains, we designed two samples: sample A (for cognition as predictor of mobility) and B (for mobility as predictor of cognition).

2.2.1. Sample A

To investigate whether the cognitive domains (global cognition, processing speed, sustained attention, executive function and verbal fluency) predicted future TUG times, the sample consisted of all participants with: TUG times at wave 1 and at least one other wave, all wave 1 cognitive scores, and complete baseline covariate data (age, sex, body mass index [BMI], grip strength, instrumental activities of daily living [IADL], fear of falling, number of medications, number of chronic conditions, and level of education).

2.2.2. Sample B

To investigate whether TUG times at wave 1 predicted future changes in cognitive scores, the sample consisted of all participants with wave 1 and 3 cognitive scores, wave 1 TUG times, and complete baseline covariate data.

2.3.Measurements

The TUG test [25] is a well-validated measure of mobility [26]. Normative values for the TUG by age in older adults have previously been reported [27]. A time of over 12s to complete the TUG is a cut-off that is considered clinically significant for the identification of impaired mobility in community-dwelling older adults [28]. At the wave 1 and 3 health assessments that took place in the health centre, the TUG was measured using a chair with armrests and a seat of height of 46 cm. At all other waves, the TUG was measured in the participants' own homes using an available chair, which varied in height and design (assessors were instructed to find a chair that matched the centre chair as closely as possible). Participants were asked to rise from the chair, walk 3 metres at normal pace to a line clearly marked on the floor, turn around, walk back to the chair, and sit down again. Walking aids were allowed if required, and no instructions were given about the use of participants' arms. The time taken from the command "Go" to when the participant was sitting again with his/her back resting against the back of the chair was recorded using a stopwatch.

Cognitive function was separated into five domains: global cognition, processing speed, verbal fluency, executive function, and sustained attention. Global cognition was measured by the Montreal Cognitive Assessment (MOCA) [29]. The MOCA is widely used in clinical practice, scored out of 30 points, and tests several cognitive domains. Processing speed was measured by the Choice Reaction Time (CRT) test [30]. The CRT test used a computer-based program where participants were asked to depress a central button until a stimulus appeared on-screen: either the word YES or the word NO. In response to the on-screen stimulus, participants were required to lift their finger from the depressed central button and depress a target yes/no button. The CRT cognitive response time is measured from when the stimulus appears to when the participant lifts their finger from the button that is depressed. The CRT motor response time is measured from when the finger is lifted from the central button to when the target button is pressed. A return to the central button is necessary after each response for the next word to appear on-screen. There were approximately 100 repetitions [31] and we utilised the mean total response time (cognitive + motor). Verbal fluency was measured by asking participants to name as many animals as they could in one minute. Executive function was measured using the Colour Trails Test (CTT). The CTT is formed of two tests; for the first (CTT1), the participant is asked to draw a connecting line through consecutive circled numbers from 1 to 25. In the second test (CTT2) the task is repeated, but the participant is required to alternate between pink and yellow numbers whilst maintaining the ordered sequence of 1 to 25 [10]. Executive function was scored as a composite of the time taken to complete CTT2, and the difference in time between CTT2 and CTT1. A measure of sustained attention was constructed using the Sustained Attention to Response Task (SART) test [32]. The SART is a computer-based test where the participant is shown digits 1-9 in consecutive order

23 times. The participant is instructed to press a key in response to every digit other than '3'. A measure of sustained attention was constructed using the mean and standard deviation (SD) of the SART response time with intra-individual (single trial) outliers and errors of omission and commission removed. To aid comparison across the five cognitive domains, a standardised z-score of each of the domains was calculated by subtracting the sample mean from the individual scores and dividing by the sample SD. Each score was standardised so that a lower score represents better cognitive function (i.e., a standardised score of -1 at baseline represents a score of 1 SD better than the sample mean). For executive function and sustained attention, the measures used to construct the scores were first standardised and an average of the standardised measures was then used to represent the two cognitive domains.

Other covariates were age, sex, BMI in kg/m^2, level of education (up to primary school level, secondary school level or tertiary/higher level), number of self-reported chronic diseases (counted from the following list: heart attack or heart failure or angina, cataracts, hypertension, high cholesterol, stroke, diabetes, lung disease, asthma, arthritis, osteoporosis, cancer, Parkinson's disease, peptic ulcer and hip fracture), number of regular prescribed medications, fear of falling (not afraid, somewhat afraid, very afraid), handgrip strength (maximum grip strength was measured from four tests [2 on each hand] using a hydraulic hand dynamometer [Baseline, Fabrication Enterprises, Inc., White Plains, NY] [27]), and number of self-reported difficulties in IADL (counted from the following list: preparing a hot meal; doing household chores [laundry, cleaning]; shopping for groceries; making telephone calls; taking medications; and managing money such as paying bills and keeping track of expenses) [33].

2.4. Analysis

Data was analysed with R software [34]. Descriptive statistics were presented as mean with standard deviation (± SD), median with interquartile range (IQR), or count with percentage (%). To examine the association between the five cognitive domains at wave 1 and change in TUG times over the five waves, five linear mixed effect models (one for each domain) were fitted using the R packages lme4 [35] and lmerTest [36]. The marginal R^2 values were calculated using the MuMIn package [37] using methods based on Nakagawa, Johnson [38]. These models used a random intercept to account for repeated measures of the same individual. The effect of the cognitive domain on TUG at subsequent waves was of interest, therefore the interactions between cognition at wave 1 and time (in waves) were analysed. The resulting estimate for the interaction term can be interpreted as the estimated number of seconds change in the TUG from one wave to the next for 1 SD of change in the standardised cognitive score. All covariates listed above were measured at wave 1 and were fixed. In

addition to the covariates listed, TUG time at wave 1 and each standardised cognitive measure were included as independent variables in the models.

To estimate the association between TUG times at wave 1 and change in the five cognitive domains between wave 1 and wave 3, five linear regression models (one for each domain) were fitted. The dependent variable was the standardised cognitive variable value at wave 3. All covariates listed above were measured at wave 1 and were fixed. In addition to the covariates listed, the wave 1 value of the dependent variable was entered as a covariate to model change in said value.

Marginal effects plots were created for all models using the ggeffects [39]and ggplot2 [40] packages.

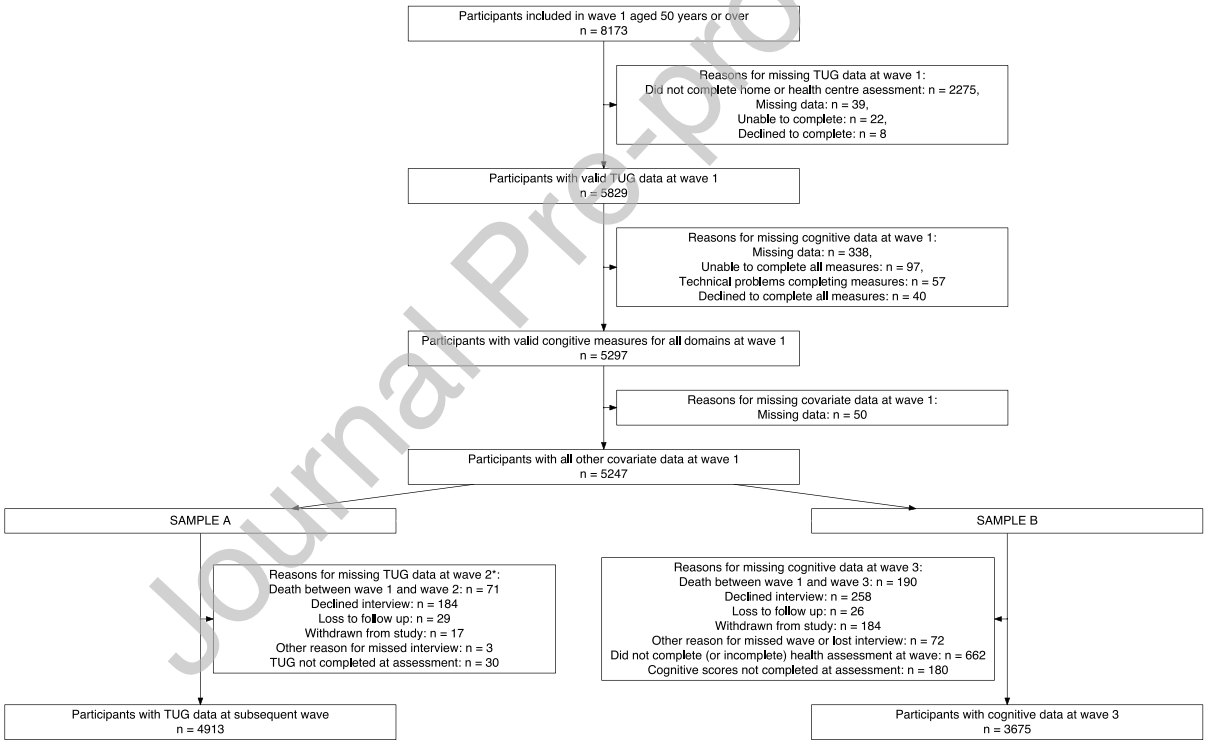
2.5. Ethics

Ethical approval for each wave was obtained from the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, Ireland: Wave 1: "The Irish Longitudinal Study on Ageing (granted 2 May 2008)"; Wave 2: "The Irish Longitudinal Study on Ageing (granted 19 October 2011)"; Wave 3: “Main Wave 3 Tilda Study (granted 9 June 2014)”; Wave 4: "Ref: 150506"; and Wave 5: "Ref: 170304". All participants provided written informed consent prior to inclusion in the study.

3. Results

TILDA wave 1 recruited a total of 8173 participants aged 50 years or older. After removing participants with missing data, Sample A (used to investigate the predictive ability of baseline cognitive domains on change in TUG times) consisted of 4913 participants, and Sample B (used to investigate the predictive ability of baseline TUG time on change in cognitive domain scores) consisted of 3675 participants (Figure 1). Both samples are described in Table 1. The majority of both samples received secondary or tertiary level education (sample A = 78%, sample B = 81%); 41% of sample A and 44% of sample B were in employment; and 18% of sample A and 17% of sample B lived on their own.

Fig. 1. Number of participants included in each sample and reasons for missing data.



*reasons for missing TUG values at subsequent waves may differ

Table 1. Description of the samples at wave 1.

Variables	Sample A (n = 4913)	Sample B (n = 3675)
Age	62.1 (±8.6)	61.4 (±8.1)
Female	2684 (54.6%)	1986 (54.0%)
BMI (kg/m²)	28.7 (±5.1)	28.5 (±4.9)
Education up to primary school level	1102 (22.4%)	697 (19.0%)
Education to secondary school level	2053 (41.8%)	1550 (42.2%)
Education to tertiary/higher level	1758 (35.8%)	1428 (38.9%)
Number of chronic conditions	1.0 (1.0—3.0)	1.0 (1.0—2.0)
Number of medications	2.0 (0.0—4.0)	2.0 (0.0—3.0)
Fear of falling - Not afraid	3879 (79.0%)	2977 (81.0%)
Fear of falling - somewhat afraid	824 (16.8%)	569 (15.5%)
Fear of falling - Very afraid	210 (4.3%)	129 (3.5%)
Grip strength (kg)	27.5 (±9.8)	27.9 (±9.8)
IADL score	0.0 (0.0—0.0)	0.0 (0.0—0.0)
TUG time (seconds)	8.8 (±2.8)	8.6 (±1.9)
MOCA	26.0 (23.0—28.0)	26.0 (24.0—28.0)
Mean total CRT (milliseconds)	818.9 (±281.4)	790.6 (±237.2)
Animal naming score	21.5 (±6.9)	22.1 (±6.9)
CTT 2 time (seconds)	109.3 (±40.2)	104.0 (±35.1)
CTT 2 time – CTT 1 time (seconds)	54.6 (±27.8)	52.2 (±25.6)
Mean SART response time (milliseconds)	379.3 (±98.8)	375.0 (±97.3)

Data presented as mean (± SD) or count (%) or median and (IQR).
TUG = timed up and go; BMI = body mass index; IADL = instrumental activities of daily living; MOCA = Montreal Cognitive Assessment, CRT = Choice Reaction Time; CTT = Colour Trails Test; SART = Sustained Attention to Response Task.

As shown in Table 2, baseline cognitive domains were all found to be significant independent predictors of future change in TUG times, with similar estimated marginal R^2 values of 0.36. The effect varied across domains, with verbal fluency (Model 3) showing the weakest relationship, with a very small 0.06-second reduction in TUG time per wave being associated with a verbal fluency score of 1 SD above the sample mean at baseline (higher cognitive scores represent poorer performance). Sustained attention (Model 5) had the largest estimated effect of a 0.30-second higher TUG time per wave being associated with a sustained attention score of 1 SD above the sample mean at baseline.

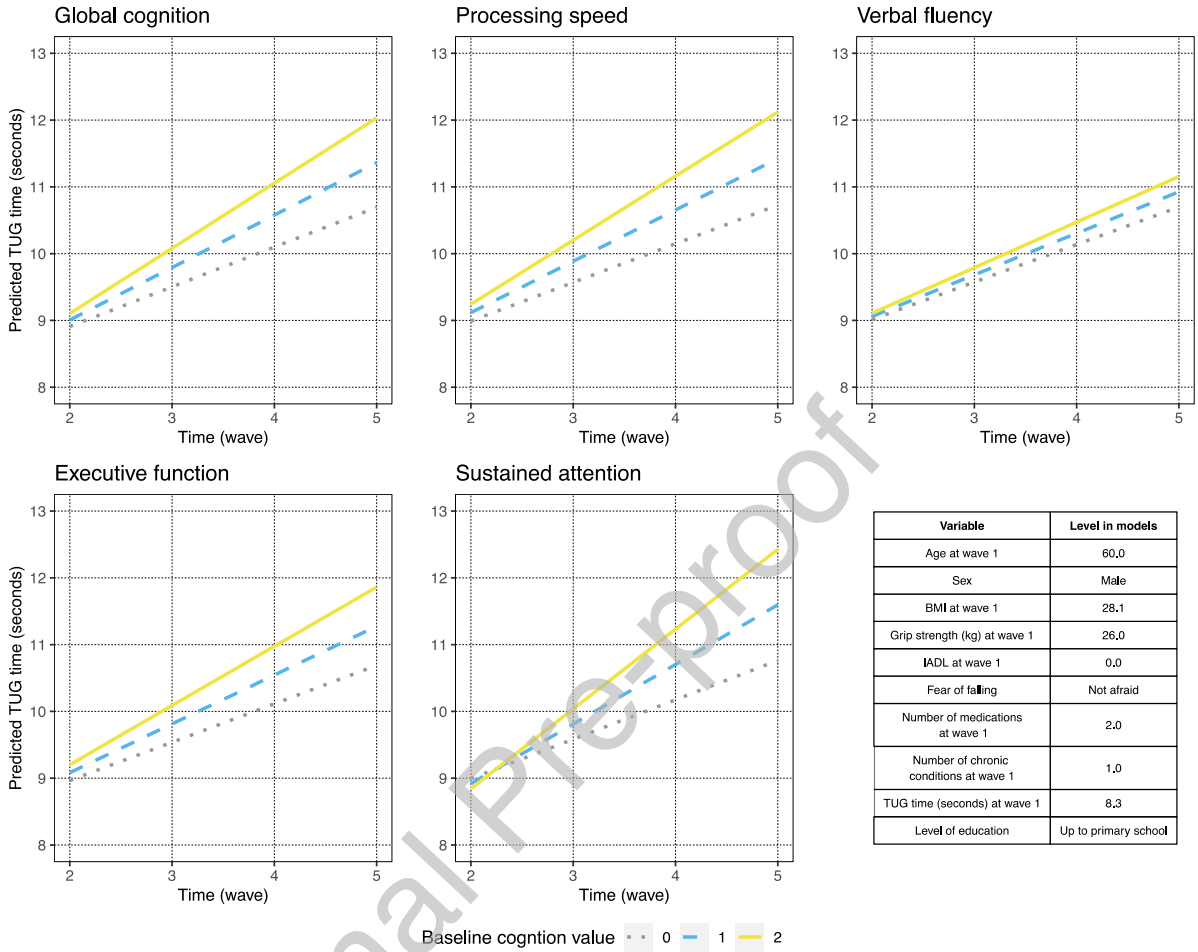
Table 2. Results of the repeated-measures mixed models for the prediction of change in timed up and go times (seconds) over five waves in Sample A (n=4913).

	Model 1	Model 2	Model 3	Model 4	Model 5
	Global cognition	Processing speed	Verbal fluency	Executive function	Sustained attention
	Marginal R^2 = 0.36	Marginal R^2 = 0.36	Marginal R^2 = 0.36	Marginal R^2 = 0.36	Marginal R^2 = 0.36
	Estimate (seconds) [95% CI]	Estimate (seconds) [95% CI]	Estimate (seconds) [95% CI]	Estimate (seconds) [95% CI]	Estimate (seconds) [95% CI]
Age at wave 1	0.06 [0.05 to 0.07]*	0.06 [0.05 to 0.07]*	0.06 [0.05 to 0.08]*	0.06 [0.05 to 0.07]*	0.06 [0.05 to 0.07]*
Female	-0.26 [-0.49 to -0.03]*	-0.26 [-0.50 to -0.03]*	-0.30 [-0.53 to -0.06]*	-0.28 [-0.51 to -0.04]*	-0.33 [-0.56 to -0.09]*
BMI (kg/m²) at wave 1	0.03 [0.01 to 0.04]*	0.03 [0.01 to 0.04]*	0.03 [0.01 to 0.04]*	0.03 [0.01 to 0.04]*	0.03 [0.01 to 0.04]*
Grip strength (kg) at wave 1	-0.04 [-0.05 to -0.02]*	-0.03 [-0.05 to -0.02]*	-0.04 [-0.05 to -0.02]*	-0.04 [-0.05 to -0.03]*	-0.04 [-0.05 to -0.02]*
IADL at wave 1	0.44 [0.24 to 0.65]*	0.42 [0.21 to 0.63]*	0.45 [0.24 to 0.65]*	0.44 [0.24 to 0.65]*	0.45 [0.24 to 0.66]*
Fear of falling at wave 1					
not afraid	reference	reference	reference	reference	reference
somewhat afraid	0.45 [0.25 to 0.66]*	0.45 [0.24 to 0.66]*	0.44 [0.24 to 0.65]*	0.44 [0.23 to 0.64]*	0.46 [0.25 to 0.67]*
very afraid	1.11 [0.73 to 1.50]*	1.18 [0.79 to 1.56]*	1.14 [0.75 to 1.52]*	1.11 [0.72 to 1.50]*	1.15 [0.76 to 1.53]*
Number of medications at wave 1	0.07 [0.03 to 0.11]*	0.07 [0.04 to 0.11]*	0.07 [0.04 to 0.11]*	0.07 [0.04 to 0.11]*	0.07 [0.04 to 0.11]*
Number of chronic conditions at wave 1	0.12 [0.05 to 0.19]*	0.12 [0.05 to 0.19]*	0.12 [0.05 to 0.19]*	0.13 [0.06 to 0.20]*	0.12 [0.05 to 0.19]*
Education					
To primary school level	reference	reference	reference	reference	reference
To secondary school level	0.08 [-0.12 to 0.28]	0.00 [-0.19 to 0.20]*	-0.02 [-0.22 to 0.18]*	0.05 [-0.15 to 0.25]*	0.03 [-0.17 to 0.23]*
To tertiary/higher level	0.12 [-0.10 to 0.34]	-0.02 [-0.23 to 0.19]*	-0.04 [-0.25 to 0.18]*	0.03 [-0.18 to 0.24]*	-0.02 [-0.23 to 0.19]*
TUG (sec) at wave 1	0.76 [0.73 to 0.79]*	0.75 [0.72 to 0.78]*	0.77 [0.73 to 0.80]*	0.76 [0.72 to 0.79]*	0.76 [0.73 to 0.79]*
Standardised cognitive score	-0.28 [-0.45 to -0.11]*	-0.25 [-0.43 to -0.08]*	-0.07 [-0.22 to 0.07]	-0.19 [-0.36 to -0.02]*	-0.68 [-0.88 to -0.48]*
Time (waves)	0.60 [0.56 to 0.63]*	0.58 [0.54 to 0.61]*	0.56 [0.53 to 0.60]*	0.58 [0.54 to 0.61]*	0.59 [0.55 to 0.63]*
Standardised cognitive score * Time (waves)	0.19 [0.15 to 0.23]*	0.19 [0.14 to 0.24]*	0.06 [0.02 to 0.10]*	0.16 [0.11 to 0.20]*	0.30 [0.25 to 0.35]*

TUG = timed up and go; BMI = body mass
* p < 0.05

Figure 2 shows the marginal effect plots of models 1-5 showing the effect of cognitive domain scores on TUG times, where baseline cognition value 0 represents sample mean at baseline; 1 represents 1 SD above the sample mean at baseline (poorer cognitive function); and 2 represents 2 SD above the sample mean at baseline (standardised scores). Echoing the results in Table 2, the most apparent divergence of trajectories was for sustained attention, and the least apparent for verbal fluency. For sustained attention, for baseline cognitive values 2 SD above the sample mean, the adjusted marginal estimated mean of TUG was below 9 seconds at baseline, and above 12 seconds at 8 years. At 2 SD above the cognitive mean at baseline, estimated TUG means had also reached 12 seconds at 8 years for MOCA and CRT, and almost reached 12 seconds for executive function.

Fig. 2. Marginal effect plots of models 1-5 showing the effect of cognitive domain scores on TUG times.



Variable	Level in models
Age at wave 1	60.0
Sex	Male
BMI at wave 1	28.1
Grip strength (kg) at wave 1	26.0
IADL at wave 1	0.0
Fear of falling	Not afraid
Number of medications at wave 1	2.0
Number of chronic conditions at wave 1	1.0
TUG time (seconds) at wave 1	8.3
Level of education	Up to primary school

Baseline cognition value 0 = sample mean at baseline (standardised score)
Baseline cognition value 1 = 1 SD above the sample mean at baseline (standardised score)
Baseline cognition value 2 = 2 SD above the sample mean at baseline (standardised score)

As Table 3 shows, baseline TUG times predicted change in all five cognitive domains from wave 1 to wave 3. Processing speed had the largest estimated effect, a baseline increase in TUG of 1 second predicted an increase of 0.05 units (1 unit is equal to the standard deviation of the cognitive score at wave 1, higher score representing poorer cognitive performance). However, the model had the lowest R^2 value of 0.20, significantly lower than global cognition ($R^2 = 0.45$), executive function ($R^2 = 0.41$) and sustained attention ($R^2 = 0.45$).

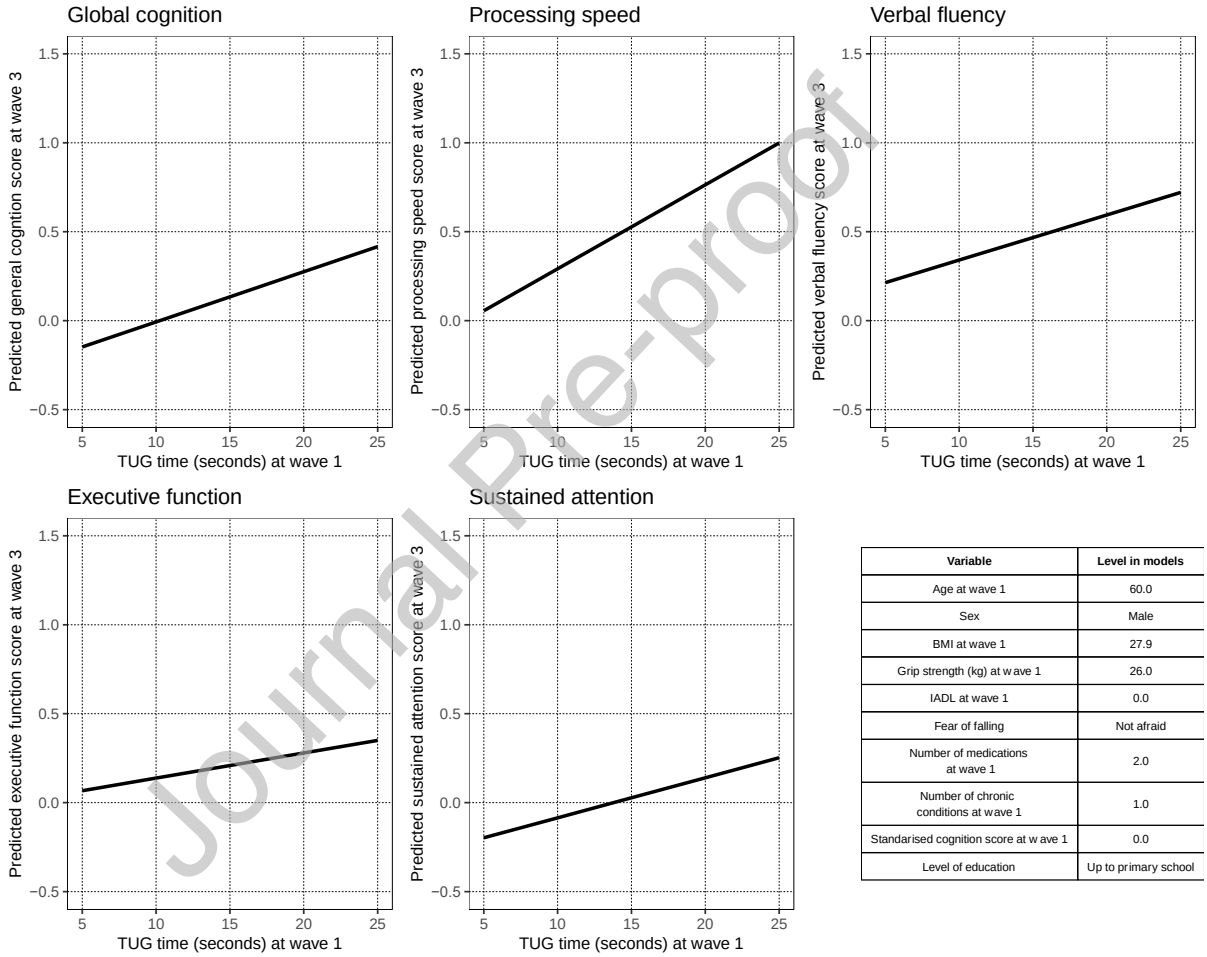
Table 3. Results of the linear models for the prediction of change in standardised cognitive scores from wave 1 to wave 3 in Sample B (n=3675).

	Model A	Model B	Model C	Model D	Model E
Dependent variable	**Global cognition**	**Processing speed**	**Verbal fluency**	**Executive function**	**Sustained attention**
	$R^2 = 0.45$	$R^2 = 0.20$	$R^2 = 0.26$	$R^2 = 0.41$	$R^2 = 0.41$
	Estimate [95% CI]	**Estimate [95% CI]**	**Estimate [95% CI]**	**Estimate [95% CI]**	**Estimate [95% CI]**
Age at wave 1	**0.01 [0.01 to 0.02]***	**0.02 [0.01 to 0.02]***	**0.01 [0.01 to 0.02]***	**0.02 [0.01 to 0.02]***	**0.01 [0.01 to 0.02]***
Female	0.01 [-0.05 to 0.07]	-0.06 [-0.18 to 0.06]	-0.05 [-0.12 to 0.02]	-0.02 [-0.09 to 0.05]	0.03 [-0.03 to 0.08]
BMI (kg/m²) at wave 1	0.00 [-0.01 to 0.00]	-0.01 [-0.01 to 0.00]	**0.01 [0.00 to 0.01]***	0.00 [-0.01 to 0.00]	0.00 [0.00 to 0.01]
Grip strength (kg) at wave 1	0.00 [0.00 to 0.00]	**-0.01 [-0.02 to 0.00]***	**-0.01 [-0.01 to 0.00]***	0.00 [0.00 to 0.00]	0.00 [0.00 to 0.00]
IADL at wave 1	0.04 [-0.03 to 0.11]	0.00 [-0.14 to 0.14]	0.00 [-0.08 to 0.08]	0.06 [-0.02 to 0.14]	0.01 [-0.05 to 0.08]
Fear of falling at wave 1					
not afraid	reference	reference	reference	reference	reference
somewhat afraid	0.02 [-0.04 to 0.07]	**0.18 [0.07 to 0.29]***	-0.01 [-0.07 to 0.06]	0.00 [-0.06 to 0.07]	0.05 [0.00 to 0.10]
very afraid	0.02 [-0.09 to 0.13]	**0.23 [0.01 to 0.45]***	0.05 [-0.07 to 0.18]	-0.02 [-0.15 to 0.10]	0.09 [-0.01 to 0.19]
Number of medications at wave 1	0.00 [-0.01 to 0.01]	0.00 [-0.02 to 0.02]	-0.01 [-0.02 to 0.01]	0.01 [-0.01 to 0.02]	**0.01 [0.00 to 0.02]**
Number of chronic conditions at wave 1	0.00 [-0.02 to 0.02]	0.02 [-0.02 to 0.06]	0.00 [-0.02 to 0.03]	0.01 [-0.01 to 0.03]	0.00 [-0.02 to 0.02]
Education					
To primary school level	reference	reference	reference	reference	reference
To secondary school level	**-0.16 [-0.21 to -0.10]***	-0.08 [-0.19 to 0.03]	-0.05 [-0.12 to 0.01]	**-0.15 [-0.21 to -0.09]***	-0.05 [-0.10 to 0.01]
To tertiary/higher level	**-0.23 [-0.29 to -0.17]***	-0.10 [-0.22 to 0.01]	**-0.27 [-0.34 to -0.20]***	**-0.21 [-0.27 to -0.14]***	**-0.10 [-0.15 to -0.04]***
Standardised cognitive score at wave 1	**0.59 [0.57 to 0.62]***	**0.64 [0.58 to 0.69]***	**0.32 [0.29 to 0.34]***	**0.60 [0.57 to 0.63]***	**0.55 [0.52 to 0.58]***
TUG (sec) at wave 1	**0.03 [0.02 to 0.04]***	**0.05 [0.02 to 0.07]***	**0.03 [0.01 to 0.04]***	**0.01 [0.00 to 0.03]***	**0.02 [0.01 to 0.03]***

TUG = timed up and go; BMI = body mass index; IADL = instrumental activities of daily living
* $p < 0.05$

Figure 3 shows the marginal effect plots of models A-E showing the effect of TUG times at wave 1 on cognitive domain scores at wave 3. One unit in each standardised cognitive score is equal to the standard deviation of the cognitive score at wave 1 and higher cognitive scores represent poorer cognitive function. A change in wave 1 TUG time from 5 (very fast) to 25 (very slow) seconds was associated with very modest increases in cognitive scores, below 1 SD of the cognitive score at wave 1 except for processing speed, which reached 1 SD at baseline TUG of 25 seconds.

Fig. 3. Marginal effect plots of models A-E showing the effect of TUG times at wave 1 on cognitive domain scores at wave 3. Higher cognitive scores represent poorer cognitive function.



Variable	Level in models
Age at wave 1	60.0
Sex	Male
BMI at wave 1	27.9
Grip strength (kg) at wave 1	26.0
IADL at wave 1	0.0
Fear of falling	Not afraid
Number of medications at wave 1	2.0
Number of chronic conditions at wave 1	1.0
Standarised cognition score at wave 1	0.0
Level of education	Up to primary school

Predicted cognition value 0 = sample mean at baseline (standardised score)
Predicted cognition value 1 = 1 SD above the sample mean at baseline (standardised score)
Predicted cognition value 2 = 2 SD above the sample mean at baseline (standardised score)

Discussion

The aim of the study was to contribute to the still poorly understood research field of bidirectional longitudinal associations between mobility and cognition in older adults, we utilised the TILDA dataset to assess the temporal associations between TUG and five cognitive function domains: global cognition (MOCA), processing speed (CRT), verbal fluency (animal naming), executive function (CTT), and sustained attention (SART). Findings suggest that associations were statistically significant in both directions i.e., cognition predicting mobility and mobility predicting cognition. Not all cognitive domains seemed equally predictive of mobility decline. The cognitive domain that seemed to have the greatest predictive effect for TUG decline was sustained attention, followed by processing speed, global cognition, executive function, and verbal fluency. On the other hand, baseline TUG was weakly associated with change in cognitive parameters. The effect of TUG on change in processing speed seemed to be the strongest, though the overall model had the poorest fit. The effect of TUG on change in sustained attention was smaller, but TUG explained much more of the variance in sustained attention values at wave 3. However, all effects were of very small clinical significance.

On the direction of cognition predicting mobility, our findings suggest that the mechanisms through which lower cognition may lead to progressive mobility decline are very slow acting, with the mobility impairment being more likely to become clinically significant as more years go by. Minimal clinically important differences in TUG have been suggested as being between 0.8 and 1.4 seconds in patients with hip osteoarthritis [41], and 0.9 – 1.4 seconds in patients with COPD [42]. Based on the more conservative estimate of 1.4 seconds, after 8 years, those above 2 SD of the standardised baseline cognitive scores for sustained attention, processing speed and general cognition would be classified as having a clinically important reduction in mobility compared to those with average cognitive scores at baseline. Thus, our findings highlight that cognitive impairment in the absence of clinically apparent mobility impairment may herald an accelerated pattern of mobility decline in subsequent years. Our findings are consistent with previous research that reported that TUG is often normal in those with mild cognitive impairment [43]. Our findings also mirror those from the Women's Health and Aging Study II, in which both impairments in and declines in executive functioning were associated with risk of physical frailty onset, which includes slowness in its definition [44].

Whilst we cannot provide mechanistic explanations for the effects of baseline cognition on mobility decline, early neurodegeneration may be a possible reason. However, our study has the limitation in that none of the cognitive tests employed are *per se* diagnostic of underlying neurodegeneration (e.g., Alzheimer's disease), in the absence of other clinical findings including neuropsychology, neuroimaging, or biomarkers. In our study, we cannot differentiate between non-neurodegenerative

and neuro-degenerative cognitive impairment. Indeed, access to neuroimaging and data-driven approaches are necessary to further understand mobility-cognition phenotypes [45-47].

On the direction of mobility predicting cognition, our results agree with a previous analysis of the same cohort that baseline mobility was not significantly associated with decline in cognitive function [21]; however, the previous analysis only included baseline participants aged 65 years or more, while the present analysis included those aged 50 or more. In the present study, a larger cohort may have been responsible for the detection of statistically significant associations of low clinical relevance.

As regards mobility predicting future cognition, the clinical meaningfulness of the models is more difficult to interpret due to the dependent variable (cognition) being on a standardised scale. However, except for processing speed, even a 20-second difference in TUG times at baseline did not predict over 1 unit (1 unit is equal to 1 SD in cognition at baseline) of difference in the cognitive domains at wave 3 (approximately 4 years later). For example, based on the baseline SD in MOCA of 3.2 in sample A, a difference of 11 seconds in the TUG would predict an approximate 1-point change in the MOCA score at wave 3. The predictive value of mobility on future cognition is therefore considered to be weak, despite the statistical significance, and may be of less clinical value than using cognitive function to predict future mobility. However, direct comparison between Models 1-5 and Models A-E needs to be cautious as TUG is not on a standardised scale as the cognitive domain variables are, and in Models 1-5, the coefficient estimates refer to change over 1 wave (approximately 2 years) compared to Models A-E where the coefficient estimates refer to change from wave 1 to 3 (approximately 4 years).

The ability of the TUG to predict future cognitive function may depend on the population studied. This study used a relatively healthy and independent-living population-based cohort. In more clinical cohorts where mobility impairments are more significant and advanced, the predictive value of mobility on future cognition may have greater clinical significance. Nevertheless, worse TUG performance has been related to poor performance on cognitive tests of executive function and independently associated with severe medial temporal area atrophy in community-dwelling older adults [48], suggesting that not all cognitive domains are equally associated with mobility [49]. Interestingly, in Alzheimer's disease it was found that motor performance was affected already at its mild stages [50], and even at the subjective cognitive decline stage [51]. Another study showed that the trajectory pattern of greater decline in amyloid positive subjects was predicted by greater baseline impairment of cognition and function [52]. While mobility within a functional independence range may not predict decline in cognition, more severe mobility impairments (such as those associated with

a state of frailty) may herald subsequent cognitive impairment [53, 54]. Interestingly, in a previous study, only the mobility subtype of the frailty phenotype was associated with cognitive impairments [55]. In the National Health and Aging Trends Study, incident dementia was associated with greater likelihood of cognitive impairment onset first, and frailty-cognitive impairment co-occurrence, but lower likelihood of frailty onset first [56]. Overall, it is possible that cognition may be more predictive of mobility in a population-based cohort where the prevalence of significant cognitive impairment is very low (and not included at baseline), while in more frail, clinical cohorts, mobility impairment may well follow cognitive decline as patients become more disabled during their progression to dementia.

The multiple significant associations between other covariates and mobility in the repeated-measures mixed models investigating cognitive functions as predictors, suggest that there may be scope for interventions to slow down adverse trajectories of mobility decline even in the presence of baseline cognitive impairment, by acting on potentially modifiable factors (e.g., improving muscle strength, addressing fear of falling, optimising medications). Intervention approaches including physical exercise may also be appropriate [57-59], although not necessarily effective in improving cognition [60]. Indeed, in community-based samples, comprehensive geriatric assessment and individually-tailored interventions may contribute to improvements in the health and functional status of older persons with multimorbidity [61]. A comprehensive approach assessing mobility and cognition simultaneously may be better because previous research has suggested that the combination of slow gait and cognitive impairment posed the highest risk for progression to dementia [62]. Indeed, considering both physical frailty and cognition as a single complex phenotype may be crucial in the prevention of dementia [63]. This is termed by others as motoric cognitive risk syndrome (MCR) [64]. TILDA previously showed that MCR is characterised by strong negative associations with global cognition, attention, and memory [65]. Identifying these complex mobility-cognition phenotypes is important; indeed, a previous study showed that a multidomain community group-based intervention among community-dwelling older adults with physio-cognitive decline syndrome can be effective to improve both cognition and mobility in some participants [66].

A general limitation of a longitudinal study of older adults is attrition, which can be due to refusal to participate at a particular wave, complete withdrawal from the study, loss to follow-up or death. Whilst TILDA wave 1 recruited a total of 8173 participants aged 50 years or older, there were only 4913 participants in sample A and 3675 in sample B. Even with a multiple imputation analysis replicating the same findings, we would not be confident that our findings are truly population representative. Further, only participants who participated in health centre assessments were included in both sample A and B, and previous analysis has demonstrated that participants were

generally fitter than the entire TILDA cohort [67], limiting generalisability further. Finally, three covariates were obtained by self-report: level of education, number of chronic diseases and number of medications. They are therefore considered open to information bias.

In conclusion, our results support that cognitive processes play an important role in the control of motor functions, and therefore it is important to incorporate examination of cognitive functions as early as possible in older people [68], even if their mobility is independent. Our findings underscore the importance for clinicians to take subtle changes in cognition seriously, especially when subtle mobility impairments start to emerge over time, as this may provide an opportunity to offer disability-slowing interventions when they could be most effective. Greater understanding of these relationships may aid clinicians in their choice of cognitive assessments and support management plans for individuals demonstrating decline in particular cognitive domains. Further, results may stimulate further research into common cause mechanisms of functional and cognitive decline.

Author Contributions:

All authors meet all 4 of the following authorship criteria: Criterion 1

- Study conception and design (PH, RRO, OAD) and/or
- Acquisition of data (RAK, OAD) and/or
- Analysis and interpretation of data (PH, AM, OAD, RAK, RRO)

Criterion 2

- Drafting of manuscript (PH, RRO) and/or
- Critical revision for important intellectual content (AM, OAD, RAK)

Criterion 3

• Final approval of the version to be submitted and any revision (PH, AM, OAD, RAK, RRO)

Criterion 4

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors accept public responsibility for the report.

Sponsor's Role:

This study is funded by a Grant from Science Foundation Ireland under Grant number 18/FRL/6188. TILDA is funded by Atlantic Philanthropies, the Irish Department of Health and Irish Life. Peter Hartley is funded by a fellowship from the Cambridge Biomedical Research Centre and the Addenbrooke's Charitable Trust [grant reference: 03/20 A]. The funders had no role in the conduct of the research or preparation of the article, study design, the collection, analysis and interpretation of data, writing of the report, or the decision to submit the paper for publication.

Conflicts of Interest

None

References

1. Anton SD, Woods AJ, Ashizawa T, Barb D, Buford TW, Carter CS, et al. Successful aging: Advancing the science of physical independence in older adults. Ageing Res Rev. 2015 Nov;24(Pt B):304-27.
2. Ferrucci L, Cooper R, Shardell M, Simonsick EM, Schrack JA, Kuh D. Age-Related Change in Mobility: Perspectives From Life Course Epidemiology and Geroscience. 2016(1758-535X (Electronic)).
3. Amieva H, Jacqmin-Gadda H, Orgogozo JM, Le Carret N, Helmer C, Letenneur L, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. Brain. 2005 May;128(Pt 5):1093-101.
4. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014 Aug;30(3):421-42.
5. Zaninotto P, Batty GD, Allerhand M, Deary IJ. Cognitive function trajectories and their determinants in older people: 8 years of follow-up in the English Longitudinal Study of Ageing. J Epidemiol Community Health. 2018 Aug;72(8):685-94.
6. van der Willik KD, Licher S, Vinke EJ, Knol MJ, Darweesh SKL, van der Geest JN, et al. Trajectories of Cognitive and Motor Function Between Ages 45 and 90 Years: A Population-Based Study. J Gerontol A Biol Sci Med Sci. 2021 Jan 18;76(2):297-306.
7. Plassman BL, Williams JW, Jr., Burke JR, Holsinger T, Benjamin S. Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. Ann Intern Med. 2010 Aug 3;153(3):182-93.
8. Yang CP, Yang WS, Wong YH, Wang KH, Teng YC, Chang MH, et al. Muscle atrophy-related myotube-derived exosomal microRNA in neuronal dysfunction: Targeting both coding and long noncoding RNAs. Aging Cell. 2020 May;19(5):e13107.
9. Demnitz N, Esser P, Dawes H, Valkanova V, Johansen-Berg H, Ebmeier KP, et al. A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. Gait Posture. 2016 Oct;50:164-74.
10. Donoghue OA, Horgan NF, Savva GM, Cronin H, O'Regan C, Kenny RA. Association between timed up-and-go and memory, executive function, and processing speed. Journal of the American Geriatrics Society. 2012 Sep;60(9):1681-6.
11. Chen LK, Arai H. Physio-cognitive decline as the accelerated aging phenotype. Arch Gerontol Geriatr. 2020 May - Jun;88:104051.

12. Soumare A, Tavernier B, Alperovitch A, Tzourio C, Elbaz A. A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci. 2009 Oct;64(10):1058-65.
13. Chen TY, Peronto CL, Edwards JD. Cognitive function as a prospective predictor of falls. J Gerontol B Psychol Sci Soc Sci. 2012 Nov;67(6):720-8.
14. Bueno GAS, Gervasio FM, Ribeiro DM, Martins AC, Lemos TV, de Menezes RL. Fear of Falling Contributing to Cautious Gait Pattern in Women Exposed to a Fictional Disturbing Factor: A Non-randomized Clinical Trial. Front Neurol. 2019;10:283.
15. Philip KEJ, Polkey MI, Hopkinson NS, Steptoe A, Fancourt D. Social isolation, loneliness and physical performance in older-adults: fixed effects analyses of a cohort study. Sci Rep. 2020 Aug 17;10(1):13908.
16. Lara E, Caballero FF, Rico-Uribe LA, Olaya B, Haro JM, Ayuso-Mateos JL, et al. Are loneliness and social isolation associated with cognitive decline? Int J Geriatr Psychiatry. 2019 Nov;34(11):1613-22.
17. Tian Q, An Y, Resnick SM, Studenski S. The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults: Results from the Baltimore Longitudinal Study of Aging. Age Ageing. 2017 May 1;46(3):445-51.
18. Gale CR, Allerhand M, Sayer AA, Cooper C, Deary IJ. The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing. Age (Dordr). 2014;36(4):9682.
19. Best JR, Liu-Ambrose T, Boudreau RM, Ayonayon HN, Satterfield S, Simonsick EM, et al. An Evaluation of the Longitudinal, Bidirectional Associations Between Gait Speed and Cognition in Older Women and Men. J Gerontol A Biol Sci Med Sci. 2016 Dec;71(12):1616-23.
20. Mielke MM, Roberts RO, Savica R, Cha R, Drubach DI, Christianson T, et al. Assessing the temporal relationship between cognition and gait: slow gait predicts cognitive decline in the Mayo Clinic Study of Aging. J Gerontol A Biol Sci Med Sci. 2013 Aug;68(8):929-37.
21. Donoghue O, Feeney J, O'Leary N, Kenny RA. Baseline Mobility is Not Associated with Decline in Cognitive Function in Healthy Community-Dwelling Older Adults: Findings From The Irish Longitudinal Study on Ageing (TILDA). Am J Geriatr Psychiatry. 2018 Apr;26(4):438-48.
22. Callisaya ML, Blizzard CL, Wood AG, Thrift AG, Wardill T, Srikanth VK. Longitudinal Relationships Between Cognitive Decline and Gait Slowing: The Tasmanian Study of Cognition and Gait. J Gerontol A Biol Sci Med Sci. 2015 Oct;70(10):1226-32.
23. Donoghue OA, McGarrigle CA, Foley M, Fagan A, Meaney J, Kenny RA. Cohort Profile Update: The Irish Longitudinal Study on Ageing (TILDA). International journal of epidemiology. 2018 Oct 1;47(5):1398-l.
24. Kearney PM, Cronin H, O'Regan C, Kamiya Y, Savva GM, Whelan B, et al. Cohort profile: the Irish Longitudinal Study on Ageing. Int J Epidemiol. 2011 Aug;40(4):877-84.
25. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991 Feb;39(2):142-8.
26. Schoene D, Wu SM, Mikolaizak AS, Menant JC, Smith ST, Delbaere K, et al. Discriminative ability and predictive validity of the timed up and go test in identifying older people who fall: systematic review and meta-analysis. J Am Geriatr Soc. 2013 Feb;61(2):202-8.

27. Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. J Am Geriatr Soc. 2013 May;61 Suppl 2:S279-90.
28. Bischoff HA, Stahelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, et al. Identifying a cut-off point for normal mobility: a comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. Age Ageing. 2003 May;32(3):315-20.
29. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9.
30. D'Elia LF SP LUC, White T. Colour Trails Test: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1996.
31. Chintapalli R, Romero-Ortuno R. Choice reaction time and subsequent mobility decline: Prospective observational findings from The Irish Longitudinal Study on Ageing (TILDA). EClinicalMedicine. 2021 Jan;31:100676.
32. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia. 1997 Jun;35(6):747-58.
33. Romero-Ortuno R, Scarlett S, O'Halloran AM, Kenny RA. Is phenotypical prefrailty all the same? A longitudinal investigation of two prefrailty subtypes in TILDA. Age Ageing. 2019 Dec 1;49(1):39-45.
34. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria2020.
35. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. 2015. [sparse matrix methods; linear mixed models; penalized least squares; Cholesky decomposition]. 2015 2015-10-07;67(1):48.
36. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. 2017. [denominator degree of freedom, Satterthwaite's approximation, ANOVA, R, linear mixed effects models, lme4]. 2017 2017-12-06;82(13):26.
37. Barton´ K. MuMIn: Multi-Model Inference. 1.43.17 ed2020.
38. Nakagawa S, Johnson PCD, Schielzeth H. The coefficient of determination R2 and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. Journal of The Royal Society Interface. 2017;14(134):20170213.
39. Lüdecke D. ggeffects: Tidy Data Frames of Marginal Effects from Regression Models. Journal of Open Source Software. 2018;3(26):772.
40. Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag 2016.
41. Wright AA, Cook CE, Baxter GD, Dockerty JD, Abbott JH. A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. J Orthop Sports Phys Ther. 2011 May;41(5):319-27.
42. Mesquita R, Wilke S, Smid DE, Janssen DJ, Franssen FM, Probst VS, et al. Measurement properties of the Timed Up & Go test in patients with COPD. Chron Respir Dis. 2016 Nov;13(4):344-52.
43. Harper KJ, Riley V, Petta A, Jacques A, Spendier N, Ingram K. Occupational therapist use of the 'Timed Up and Go' test in a Memory Clinic to compare performance between cognitive diagnoses and screen for falls risk. Aust Occup Ther J. 2020 Feb;67(1):13-21.

44. Gross AL, Xue QL, Bandeen-Roche K, Fried LP, Varadhan R, McAdams-DeMarco MA, et al. Declines and Impairment in Executive Function Predict Onset of Physical Frailty. J Gerontol A Biol Sci Med Sci. 2016 Dec;71(12):1624-30.
45. Kuo CY, Tai TM, Lee PL, Tseng CW, Chen CY, Chen LK, et al. Improving Individual Brain Age Prediction Using an Ensemble Deep Learning Framework. Front Psychiatry. 2021;12:626677.
46. Kuo CY, Lee PL, Hung SC, Liu LK, Lee WJ, Chung CP, et al. Large-Scale Structural Covariance Networks Predict Age in Middle-to-Late Adulthood: A Novel Brain Aging Biomarker. Cereb Cortex. 2020 Oct 1;30(11):5844-62.
47. Liu LK, Chou KH, Hsu CH, Peng LN, Lee WJ, Chen WT, et al. Cerebellar-limbic neurocircuit is the novel biosignature of physio-cognitive decline syndrome. Aging (Albany NY). 2020 Nov 25;12(24):25319-36.
48. Kose Y, Ikenaga M, Yamada Y, Morimura K, Takeda N, Ouma S, et al. Timed Up and Go test, atrophy of medial temporal areas and cognitive functions in community-dwelling older adults with normal cognition and mild cognitive impairment. Exp Gerontol. 2016 Dec 1;85:81-7.
49. Rajtar-Zembaty A, Rajtar-Zembaty J, Salkowski A, Starowicz-Filip A, Skalska A. Global cognitive functioning and physical mobility in older adults with and without mild cognitive impairment: evidence and implications. Folia Med Cracov. 2019;59(1):75-88.
50. Pettersson AF, Engardt M, Wahlund LO. Activity level and balance in subjects with mild Alzheimer's disease. Dement Geriatr Cogn Disord. 2002;13(4):213-6.
51. Yoon B, Choi SH, Jeong JH, Park KW, Kim EJ, Hwang J, et al. Balance and Mobility Performance Along the Alzheimer's Disease Spectrum. J Alzheimers Dis. 2020;73(2):633-44.
52. Trzepacz PT, Hochstetler H, Wang S, Yu P, Case M, Henley DB, et al. Longitudinal Trajectories of Clinical Decline in Amyloid Positive and Negative Populations. J Prev Alzheimers Dis. 2016;3(2):92-100.
53. Hsu HC. Relationship between Frailty and Cognitive Function among Older Adults in Taiwan. J Frailty Aging. 2014;3(3):153-7.
54. Wu YH, Liu LK, Chen WT, Lee WJ, Peng LN, Wang PN, et al. Cognitive Function in Individuals With Physical Frailty but Without Dementia or Cognitive Complaints: Results From the I-Lan Longitudinal Aging Study. J Am Med Dir Assoc. 2015 Oct 1;16(10):899 e9-16.
55. Liu LK, Guo CY, Lee WJ, Chen LY, Hwang AC, Lin MH, et al. Subtypes of physical frailty: Latent class analysis and associations with clinical characteristics and outcomes. Sci Rep. 2017 Apr 11;7:46417.
56. Chu NM, Bandeen-Roche K, Tian J, Kasper JD, Gross AL, Carlson MC, et al. Hierarchical Development of Frailty and Cognitive Impairment: Clues Into Etiological Pathways. J Gerontol A Biol Sci Med Sci. 2019 Oct 4;74(11):1761-70.
57. Lee G. Impaired Cognitive Function is Associated with Motor Function and Activities of Daily Living in Mild to Moderate Alzheimer's Dementia. Curr Alzheimer Res. 2020;17(7):680-6.
58. Wilke J, Giesche F, Klier K, Vogt L, Herrmann E, Banzer W. Acute Effects of Resistance Exercise on Cognitive Function in Healthy Adults: A Systematic Review with Multilevel Meta-Analysis. Sports Med. 2019 Jun;49(6):905-16.
59. Herold F, Torpel A, Schega L, Muller NG. Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements - a systematic review. Eur Rev Aging Phys Act. 2019;16:10.

60. Stuckenschneider T, Sanders ML, Devenney KE, Aaronson JA, Abeln V, Claassen J, et al. NeuroExercise: The Effect of a 12-Month Exercise Intervention on Cognition in Mild Cognitive Impairment-A Multicenter Randomized Controlled Trial. Front Aging Neurosci. 2020;12:621947.
61. Mazya AL, Garvin P, Ekdahl AW. Outpatient comprehensive geriatric assessment: effects on frailty and mortality in old people with multimorbidity and high health care utilization. Aging Clin Exp Res. 2019 Apr;31(4):519-25.
62. Montero-Odasso MM, Barnes B, Speechley M, Muir Hunter SW, Doherty TJ, Duque G, et al. Disentangling Cognitive-Frailty: Results From the Gait and Brain Study. J Gerontol A Biol Sci Med Sci. 2016 Nov;71(11):1476-82.
63. Panza F, Seripa D, Solfrizzi V, Tortelli R, Greco A, Pilotto A, et al. Targeting Cognitive Frailty: Clinical and Neurobiological Roadmap for a Single Complex Phenotype. J Alzheimers Dis. 2015;47(4):793-813.
64. Verghese J, Ayers E, Barzilai N, Bennett DA, Buchman AS, Holtzer R, et al. Motoric cognitive risk syndrome: Multicenter incidence study. Neurology. 2014 Dec 9;83(24):2278-84.
65. Maguire FJ, Killane I, Creagh AP, Donoghue O, Kenny RA, Reilly RB. Baseline Association of Motoric Cognitive Risk Syndrome With Sustained Attention, Memory, and Global Cognition. J Am Med Dir Assoc. 2018 Jan;19(1):53-8.
66. Liang CK, Lee WJ, Hwang AC, Lin CS, Chou MY, Peng LN, et al. Efficacy of Multidomain Intervention Against Physio-cognitive Decline Syndrome: A Cluster-randomized Trial. Arch Gerontol Geriatr. 2021 Jul-Aug;95:104392.
67. Cronin H, O'Regan C, Finucane C, Kearney P, Kenny RA. Health and aging: development of the Irish Longitudinal Study on Ageing health assessment. J Am Geriatr Soc. 2013 May;61 Suppl 2:S269-78.
68. Rajtar-Zembaty A, Salakowski A, Rajtar-Zembaty J. [The relationship between executive functions, physical and functional capability in people over 60 years old]. Przegl Lek. 2016;73(9):627-31.