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

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier B.V.
Exploring bi-directional temporal associations between timed-up-and-go and cognitive domains in The Irish Longitudinal Study on Ageing (TILDA)

Peter Hartley\textsuperscript{1,2,3*}, Ann Monaghan\textsuperscript{1,2}, Orna A. Donoghue\textsuperscript{1,2}, Rose Anne Kenny\textsuperscript{1,2,4}, Roman Romero-Ortuno\textsuperscript{1,2,4,5}

\textsuperscript{1} The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin, Ireland.
\textsuperscript{2} Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland.
\textsuperscript{3} Department of Public Health and Primary Care, University of Cambridge, United Kingdom.
\textsuperscript{4} Mercer’s Institute for Successful Ageing, St James's Hospital, Dublin, Ireland.
\textsuperscript{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/m², 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), hand grip 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 R² 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.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sample A (n = 4913)</th>
<th>Sample B (n = 3675)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.1 (±8.6)</td>
<td>61.4 (±8.1)</td>
</tr>
<tr>
<td>Female</td>
<td>2684 (54.6%)</td>
<td>1986 (54.0%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7 (±5.1)</td>
<td>28.5 (±4.9)</td>
</tr>
<tr>
<td>Education up to primary school level</td>
<td>1102 (22.4%)</td>
<td>697 (19.0%)</td>
</tr>
<tr>
<td>Education to secondary school level</td>
<td>2053 (41.8%)</td>
<td>1550 (42.2%)</td>
</tr>
<tr>
<td>Education to tertiary/higher level</td>
<td>1758 (35.8%)</td>
<td>1428 (38.9%)</td>
</tr>
<tr>
<td>Number of chronic conditions</td>
<td>1.0 (1.0—3.0)</td>
<td>1.0 (1.0—2.0)</td>
</tr>
<tr>
<td>Number of medications</td>
<td>2.0 (0.0—4.0)</td>
<td>2.0 (0.0—3.0)</td>
</tr>
<tr>
<td>Fear of falling - Not afraid</td>
<td>3879 (79.0%)</td>
<td>2977 (81.0%)</td>
</tr>
<tr>
<td>Fear of falling - Somewhat afraid</td>
<td>824 (16.8%)</td>
<td>569 (15.5%)</td>
</tr>
<tr>
<td>Fear of falling - Very afraid</td>
<td>210 (4.3%)</td>
<td>129 (3.5%)</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>27.5 (±9.8)</td>
<td>27.9 (±9.8)</td>
</tr>
<tr>
<td>IADL score</td>
<td>7.0 (0.0—0.0)</td>
<td>0.0 (0.0—0.0)</td>
</tr>
<tr>
<td>TUG time (seconds)</td>
<td>8.8 (±2.8)</td>
<td>8.6 (±1.9)</td>
</tr>
<tr>
<td>MOCA</td>
<td>26.0 (23.0—28.0)</td>
<td>26.0 (24.0—28.0)</td>
</tr>
<tr>
<td>Mean total CRT (milliseconds)</td>
<td>818.9 (±281.4)</td>
<td>790.6 (±237.2)</td>
</tr>
<tr>
<td>Animal naming score</td>
<td>21.5 (±6.9)</td>
<td>22.1 (±6.9)</td>
</tr>
<tr>
<td>CTT 2 time (seconds)</td>
<td>109.3 (±40.2)</td>
<td>104.0 (±35.1)</td>
</tr>
<tr>
<td>CTT 2 time – CTT 1 time (seconds)</td>
<td>54.6 (±27.8)</td>
<td>52.2 (±25.6)</td>
</tr>
<tr>
<td>Mean SART response time (milliseconds)</td>
<td>379.3 (±98.8)</td>
<td>375.0 (±97.3)</td>
</tr>
</tbody>
</table>

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 R² 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).

<table>
<thead>
<tr>
<th>Model</th>
<th>Global cognition</th>
<th>Processing speed</th>
<th>Verbal fluency</th>
<th>Executive function</th>
<th>Sustained attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marginal R² = 0.36</td>
<td>Marginal R² = 0.36</td>
<td>Marginal R² = 0.36</td>
<td>Marginal R² = 0.36</td>
<td>Marginal R² = 0.36</td>
</tr>
<tr>
<td></td>
<td>Estimate (seconds) [95% CI]</td>
<td>Estimate (seconds) [95% CI]</td>
<td>Estimate (seconds) [95% CI]</td>
<td>Estimate (seconds) [95% CI]</td>
<td>Estimate (seconds) [95% CI]</td>
</tr>
<tr>
<td>Age at wave 1</td>
<td>0.06 [0.05 to 0.07]</td>
<td>0.06 [0.05 to 0.07]</td>
<td>0.06 [0.05 to 0.08]</td>
<td>0.06 [0.05 to 0.07]</td>
<td>0.06 [0.05 to 0.07]</td>
</tr>
<tr>
<td>Female</td>
<td>-0.26 [-0.49 to -0.03]</td>
<td>-0.26 [-0.50 to -0.03]</td>
<td>-0.30 [-0.53 to -0.06]</td>
<td>-0.28 [-0.51 to -0.04]</td>
<td>-0.33 [-0.56 to -0.09]</td>
</tr>
<tr>
<td>BMI (kg/m²) at wave 1</td>
<td>0.03 [0.01 to 0.04]</td>
<td>0.03 [0.01 to 0.04]</td>
<td>0.03 [0.01 to 0.04]</td>
<td>0.03 [0.01 to 0.04]</td>
<td>0.03 [0.01 to 0.04]</td>
</tr>
<tr>
<td>Grip strength (kg) at wave 1</td>
<td>-0.04 [-0.05 to -0.02]</td>
<td>-0.03 [-0.05 to -0.02]</td>
<td>-0.04 [-0.05 to -0.02]</td>
<td>-0.04 [-0.05 to -0.03]</td>
<td>-0.04 [-0.05 to -0.02]</td>
</tr>
<tr>
<td>IADL at wave 1</td>
<td>0.44 [0.24 to 0.65]</td>
<td>0.42 [0.21 to 0.63]</td>
<td>0.45 [0.24 to 0.65]</td>
<td>0.44 [0.24 to 0.65]</td>
<td>0.45 [0.24 to 0.66]</td>
</tr>
<tr>
<td>Fear of falling at wave 1</td>
<td>not afraid</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td></td>
<td>somewhat afraid</td>
<td>0.45 [0.25 to 0.66]</td>
<td>0.45 [0.24 to 0.66]</td>
<td>0.44 [0.24 to 0.65]</td>
<td>0.44 [0.23 to 0.64]</td>
</tr>
<tr>
<td></td>
<td>very afraid</td>
<td>1.11 [0.73 to 1.50]</td>
<td>1.18 [0.79 to 1.56]</td>
<td>1.14 [0.75 to 1.52]</td>
<td>1.11 [0.72 to 1.50]</td>
</tr>
<tr>
<td>Number of medications at wave 1</td>
<td>0.07 [0.03 to 0.11]</td>
<td>0.07 [0.04 to 0.11]</td>
<td>0.07 [0.04 to 0.11]</td>
<td>0.07 [0.04 to 0.11]</td>
<td>0.07 [0.04 to 0.11]</td>
</tr>
<tr>
<td>Number of chronic conditions at wave 1</td>
<td>0.12 [0.05 to 0.19]</td>
<td>0.12 [0.05 to 0.19]</td>
<td>0.12 [0.05 to 0.19]</td>
<td>0.13 [0.06 to 0.20]</td>
<td>0.12 [0.05 to 0.19]</td>
</tr>
<tr>
<td>Education</td>
<td>To primary school level</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td></td>
<td>To secondary school level</td>
<td>0.08 [-0.12 to 0.28]</td>
<td>0.00 [-0.19 to 0.20]</td>
<td>-0.02 [-0.22 to 0.18]</td>
<td>0.05 [-0.15 to 0.25]</td>
</tr>
<tr>
<td></td>
<td>To tertiary/higher level</td>
<td>0.12 [-0.10 to 0.34]</td>
<td>-0.02 [-0.23 to 0.19]</td>
<td>-0.04 [-0.25 to 0.18]</td>
<td>0.03 [-0.18 to 0.24]</td>
</tr>
<tr>
<td>TUG (sec) at wave 1</td>
<td>0.75 [0.73 to 0.77]</td>
<td>0.75 [0.72 to 0.78]</td>
<td>0.75 [0.72 to 0.79]</td>
<td>0.75 [0.73 to 0.79]</td>
<td>0.75 [0.73 to 0.79]</td>
</tr>
<tr>
<td>Standardised cognitive score</td>
<td>-0.28 [-0.45 to -0.11]</td>
<td>-0.25 [-0.43 to -0.08]</td>
<td>-0.07 [-0.22 to 0.07]</td>
<td>-0.19 [-0.36 to -0.02]</td>
<td>-0.68 [-0.88 to -0.48]</td>
</tr>
<tr>
<td>Time (waves)</td>
<td>0.60 [0.55 to 0.65]</td>
<td>0.58 [0.54 to 0.61]</td>
<td>0.56 [0.53 to 0.60]</td>
<td>0.58 [0.54 to 0.61]</td>
<td>0.59 [0.55 to 0.63]</td>
</tr>
<tr>
<td>Standardised cognitive score * Time (waves)</td>
<td>0.19 [0.15 to 0.23]</td>
<td>0.19 [0.14 to 0.24]</td>
<td>0.06 [0.02 to 0.10]</td>
<td>0.16 [0.11 to 0.20]</td>
<td>0.30 [0.25 to 0.35]</td>
</tr>
</tbody>
</table>

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.

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).

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

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level in models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at wave 1</td>
<td>60.0</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>BMI at wave 1</td>
<td>27.9</td>
</tr>
<tr>
<td>Grip strength (kg) at wave 1</td>
<td>26.0</td>
</tr>
<tr>
<td>IADL at wave 1</td>
<td>0.0</td>
</tr>
<tr>
<td>Fear of falling</td>
<td>Not afraid</td>
</tr>
<tr>
<td>Number of medications at wave 1</td>
<td>2.0</td>
</tr>
<tr>
<td>Number of chronic conditions at wave 1</td>
<td>1.0</td>
</tr>
<tr>
<td>Standardised cognition score at wave 1</td>
<td>0.0</td>
</tr>
<tr>
<td>Level of education</td>
<td>Up to primary school</td>
</tr>
</tbody>
</table>
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

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)).


