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TITLE PAGE

Title: Orientation and verbal fluency in the English Longitudinal Study of Ageing: modifiable risk factors for falls?

Running Title: Cognitive function and falls

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DECLARATIONS (Non-Anonymised)

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ABSTRACT

OBJECTIVES: To determine the relationship between falls and deficits in specific cognitive domains in older adults.

DESIGN: An analysis of the English Longitudinal Study of Ageing (ELSA) cohort

SETTING: United Kingdom Community-Based

PARTICIPANTS: 5197 community-dwelling older adults recruited to a prospective longitudinal cohort study.

MEASUREMENTS: Data on the occurrence of falls and number of falls which occurred during a 12-month follow-up period were assessed against the specific cognitive domains of memory, numeracy skills, and executive function. Binomial logistic regression was performed to evaluate the association between each cognitive domain and the dichotomous outcome of falls in the preceding 12 months using unadjusted and adjusted models.

RESULTS: Of the 5197 participants included in the analysis, 1308 (25%) reported a fall in the preceding 12 months. There was no significant association between the occurrence of a fall and specific forms of cognitive dysfunction after adjusting for self-reported hearing, self-reported eyesight and functional performance. After adjustment, only orientation (odds ratio (OR): 0.80; 95% confidence intervals (CI): 0.65-0.98, p=0.03) and verbal fluency (adjusted OR: 0.98; 95% CI: 0.96-1.00; p=0.05) remained significant for predicting recurrent falls.

CONCLUSIONS: The cognitive phenotype rather than cognitive impairment *per se* may predict future falls in those presenting with more than one fall.

Keywords: memory; executive function; cognitive skills; fall; injury; aged

Word Count: 2604

INTRODUCTION

Falls are the leading cause of fatal and nonfatal injuries among older adults (Bergen et al., 2016). Falls in older adults are associated with multiple extrinsic and intrinsic risk factors. Extrinsic factors include environmental factors whilst intrinsic factors can include muscle strength, motor function and postural control (Gale et al., 2016; Muir et al., 2012). Early detection of risk factors, preferably before a fall has occurred, would enable earlier intervention to reduce falls and subsequent mortality and morbidity (Best et al., 2015).

It has been widely reported that people with impaired global cognitive function are at greater risk of falls (Hsu et al., 2012). However, the cognitive phenotype relating to this risk remains unclear (Passarino et al., 2007). More recent studies reported associations between specific cognitive domains and falls risk in older adults (Muir et al., 2012; Hsu et al., 2012). These studies report associations between executive function, dual-task ability and falls risk in older adults (Muir et al., 2012; Hsu et al., 2012). The evidence for an association between other cognitive domains including memory and falls risk in older adults is less clear with studies reporting a positive or no association (Hausdorff et al., 2003; Herman et al., 2010).

Focusing on specific cognitive domains may enable more tailored falls prevention interventions. Previous studies have suggested an inability to adapt gait in response to perturbations as being an underlying mechanism for the association between executive function/dual-task activities and falls (Amboni et al., 2013). To investigate this, several studies have explored the relationship between executive function and gait in older adults (Herman et al., 2010; Amboni et al., 2013; Savica et al., 2017). These studies show promise for a more tailored approach to falls prevention among patients with executive functional and dual-task activity impairment (Hausdorff, 2005).

While there is robust evidence linking global cognitive deficits and falls in older adults, the relationship between specific cognitive domains and falls in older adults remains limited. The purpose of this paper was therefore to advance knowledge over the previous literature and to understand the relationship between specific deficits in the cognitive domains of memory, numeracy skills and executive function with falls in older adults.

METHODS

The English Longitudinal Study of Ageing (ELSA) is a prospective, population-based cohort of 11,391 individuals born on or before 29th February 1952 (Steptoe et al., 2013). The cohort was established in 2002 with data gathered every two years. Ethical approval was provided by the London Multi-Centre Research Ethics Service (MREC/01/2/91). Anonymised unlinked data were obtained from the UK Data Service. Data which formed this cross-sectional analysis were extracted from Wave 4 (2008-2009) of the cohort.

Outcomes

The primary study outcome was a dichotomous indicator of self-reported falls in the 12 months preceding Wave 4. The secondary outcome was self-reported recurrent falls (two or more falls) in the 12 months preceding Wave 4.

Cognitive Parameters

The primary predictors were three domains of cognitive function: memory, executive function and numeracy skills. This approach to assess cognitive function has been previously reported (Llewellyn et al., 2008).

Memory was assessed through three tasks:

(1) Orientation in time was assessed through standard questions on the date (day, month and year) and the day of the week. Answers were combined to derive a 'total orientation score' (Shankar et al., 2011).

(2) Verbal learning, recall and working memory were assessed using a word recall test, where a recording of 10 common words was first played to the participants. Participants were asked to remember these words, recall them immediately (immediate word recall) and after approximately five minutes (delayed word recall).

(3) Prospective memory was tested by evaluating a participant's ability to 'remember to remember' (i.e. memory for future actions). At the start of the interview, participants were asked to write their initials in the top left-hand corner of the page attached to a clipboard when the interviewer handed the clipboard to them later in the interview. If, when the clipboard was handed to the participant, they wrote their initials in the top left-hand corner of the page within five seconds and without a prompt, this was deemed a correct response to this task.

Executive function was assessed through two tasks:

(1) Verbal fluency, which evaluates self-initiated activity, organisation and abstraction/mental flexibility. For this task, participants were given one minute to name as many animals as possible. The number of animals named was recorded.

(2) Letter cancellation, which assesses attention, visual searching and mental speed. Participants were provided with a page of random letters arranged in rows and columns and asked to cross out as many target letters (‘P’ and ‘W’) within one minute.

Numeracy skills were assessed by providing participants with six problems requiring simple mental calculations based on real-life situations. The first three questions were moderately easy. Participants who failed to answer these questions correctly were given an easier question. Participants who successfully answered the first three questions were then asked two progressively harder questions (and also given credit for an assumed correct response to the easier question). A score of one was given for each correct answer, except for the final question, where a score of two was awarded for a correct answer. Thus, numeracy scores range from zero to six.

Potential Confounding Factors

We extracted data on the following potential confounding factors relevant to falls and physical functioning. These were: age, sex, ethnicity, the five-item National Statistics Socio-Economic Classification scheme (NS-SEC) category, body mass index (BMI), self-reported hearing (rated excellent, very good, good, fair or poor) and self-reported eyesight (rated excellent, very good, good, fair, poor or registered blind). Physical function was assessed using the measures of timed balance (side by side stance, semi-tandem stance and tandem stance), gait speed and time to complete 10 chair raises. These measures were aggregated to calculate an overall score for physical functioning using the validated Short Physical Performance Battery (SPPB) (Guralnik et al., 1995).

Statistical Analysis

Only those participants with falls data available were included in the analysis. Of these, participants with missing cognitive or covariate data were excluded. Participant characteristics were compared using the Chi-squared test and independent samples t-test between non-fallers and fallers for categorical and continuous variables, respectively.

For our primary study outcome, binomial logistic regression was performed to evaluate the association between each cognitive domain and the dichotomous outcome of falls in the preceding 12 months. Three models were performed. Model A was unadjusted. Model B adjusted for age, sex, ethnicity, BMI and NS-SEC class. Model C additionally adjusted for self-reported hearing, self-reported eyesight and SPPB score.

For those participants who reported the number of falls, further binomial logistic regression analyses was performed to evaluate the association between each cognitive domain and the dichotomous outcome of recurrent falls (two or more falls) in the preceding 12 months, using the same regression models as above.

For all hypothesis tests, a two-sided p-value of $\leq$0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics (version 23.0).

RESULTS

Cohort

Of the 11,050 participants included in the Wave 4 ELSA cohort, falls data were available for 7014 participants. Of these, 788 participants were excluded due to missing cognition data and a further 1029 participants were excluded due to missing covariate data. The remaining 5197 participants were included in the analysis.

A summary of the characteristics of participants included in the analysis, stratified into fallers and non-fallers, are shown in **Table 1**. The mean age (SD) of the cohort was 69.9 (7.8) years and 2784 (54%) were female. Of the 5197 participants, 1308 (25%) reported a fall in the past 12 months. Participants who reported falls were more likely to be older (71.3 years vs. 69.4 years), female (59.1% vs. 51.7%) and have a higher BMI (28.6 kg/m^2 vs. 28.1 kg/m^2). They were also more likely to report poorer hearing (6.4% vs. 4.3%) and eyesight (4.3% vs. 1.8%), as well as having poorer physical functioning (5.5 points vs. 6.6 points in SPPB score). However, there appeared to be no difference in ethnicity (p=0.54) or NS-SEC class (p=0.28) between fallers and non-fallers. The crude outcome rates show that fallers were more likely to score worse on all cognitive function tasks (p$\leq$0.03), except orientation in time (p=0.07).

Cognitive Function and Falls

Table 2 shows the results of the logistic regression analyses examining the association between each cognitive function parameter and reported falls in the preceding 12 months. All cognitive function parameters except orientation were significantly associated with reported falls in the past 12 months in the unadjusted model (Model A). However, after adjustment for participant demographics and comorbidities, none of these associations remained significant (Model C).

Cognitive function and recurrent falls

Table 3 shows the results of the logistic regression analyses examining the association between each cognitive function parameter and reported recurrent falls (two or more falls) in the preceding 12 months. The number of falls was recorded for 1301 participants. All cognitive function parameters except immediate word recall (OR: 0.94; 95% CI: 0.89 to 1.00; p=0.07) were significantly associated with reported recurrent falls in the past 12 months in the univariate model (Model A). However, after adjustment for participant demographics and comorbidities. Two domains remained significant. Orientation remained significant where individuals with better orientation were 20% less likely to experience recurrent falls compared to those with poorer orientation scores (Model C, adjusted OR: 0.80; 95% CI: 0.65-0.98, p=0.03). Verbal fluency was significant where individuals with better verbal fluency were 2% less likely to experience recurrent falls compared to those with poorer verbal fluency scores (Model C, adjusted OR: 0.98; 95% CI: 0.96 to 1.00; p=0.05).

DISCUSSION

The specific aspects of cognitive dysfunction, when assessing memory, executive function and numeracy skills, do not appear to be associated to the occurrence of a fall in community-dwelling individuals. However, there is an indication that individuals who were better orientated in time and have better verbal fluency are less likely to experience a subsequent fall among the population who had at least one fall in the preceding 12 months. These provide a signal that not all measures of cognitive function have a similar association with recurrent falls risk and, therefore, assessment of specific cognitive phenotypes as opposed to 'overall' function may be more useful in risk assessment.

The significant relationship between falls and the specific domains of executive function or immediate, delayed or prospective memory identified in our unadjusted analyses were fully accounted by baseline demographic differences, hearing, vision and physical impairment. However, as both falls and cognitive impairment are considered multifactorial conditions that are both linked to increased age, female gender, visual impairment, hearing impairment and poorer physical performance, it is not possible to clearly differentiate whether in our analyses these were true confounders, or actual mediators of this effect. Previous literature has reported an association between executive function and memory with physical performance. Blumen et al (2018) reported the relationship between gait speed and executive function when assessed using the Trail Making Test (Reitan, 1978). This has been mirrored elsewhere (Herman et al., 2010; Montero-Odasso et al., 2012) where an association between gait performance and executive function and memory has been reported. Accordingly fluency in both processing and its manifestation to physical performance may be plausible, where individuals with greater cognitive agility may have greater capability for functional adaptation to negotiate falls hazards and perturbations (Senden et al., 2014). This also explains why, when the analyses were adjusted for SPPB, the relationship between falls and cognitive performance became non-significant.

A link exists between executive function and numeracy cognitive skills, which form dual-tasking activities. Dual tasking may be particularly valuable as it can assess attention, particularly alternating attending, which, when disrupted, may increase falls risk (Segev-Jacubovski et al., 2011). The finding that verbal fluency may also be associated with lower risk of recurrent falls also provides further support the importance of higher-level or dual-tasking cognitive skills and falls risk.

Improved orientation in time was significantly associated with a lower odds of recurrent falls. Preliminary data from a previous study suggesting a relationship between working memory impairment and falls (Herman et al., 2010). The assessments included in this analysis reflect temporal orientation which involves semantic information (dates/months/years) and episodic information (recall of current information) (Apolinario et al., 2016). This has also been attributed to a relationship between memory and muscle function, integrating cognitive and physical performance (Lauretani et al., 2017). Whilst the direction of causation remains unclear, there may be a bidirectional relationship between loss of cerebral volume and physical activity where increasing physical activity may protect against loss of both grey and white matter regions and memory loss (Fleischman et al., 2015; Gow et al., 2012). These provide plausible explanations for these findings.

Based on our findings, assessing orientation and verbal fluency may be valuable to identify older people who live in the community, who are at greater risk of experiencing recurrent falls. This approach may be a useful addition to falls risk screening in community settings which currently is limited to the identification of recurrent falls (Eckstrom et al., 2016). Given the number of older people expected to increase in the population, a more precision-medicine approach to identify those at greater risk to target with interventions would appear clinically advantageous (Eckstrom et al., 2016). This approach will allow us to identify high risk fallers earlier, reducing the physical, psychological, social and economic burden associated with the second and subsequent falls.

This study presented with four key limitations. The occurrence of falls was self-reported. Accordingly, there is a risk of variability in reporting of falls based on recall, social desirability bias, stigma associated with falls and a variability in an individual's definition of a fall (Hunter et al., 2017). This remains a continued challenge when collecting falls event data and re-ignites the discussion on how to best measure falls events. Current recommendations on falls diaries and assistive or wearable technologies are suggested as the gold-standard (Hunter et al., 2017; Pang et al., 2018), and may be considered in future studies to better record this important measure. Secondly, none of the cognitive tests included in this analysis specifically evaluated an individual’s capabilities in sequencing, cognitive reaction time, language comprehension or processing. Cognitive reaction time in particular has some evidence of an association with falls where slower reaction time (a cognitive indicator of speed of information processing) can be used as a predictor of risk of falling (Lord et al., 2003). Measuring these domains may provide further insights into falls risk and cognitive phenotype in different cohorts. Thirdly, there was insufficient data on concomitant medication use. Accordingly, it was not possible to adjust for this potential confounding factor in the analysis. Further prospective cohort study should consider this to explore the potential importance of this factor on outcome. Finally, this analysis was hypothesis-generating where the analysis was cross-sectional with data gathered to explore potential relationships. Given that we have identified a relationship between a cognitive phenotype and falls risk, further validation work using different cohort would be valuable.

CONCLUSION

The cognitive phenotype rather than cognitive impairment *per se* may predict future falls in those presenting with more than one fall. This analysis identified that orientation and verbal fluency as opposed to other forms of cognitive function are associated with an increased probability of recurrent fall events in older people living within the community. Given this variability in risk across older people, further stratification tools should be developed, based on these findings, to identify with greater certainty individuals who are at greater risk of fall recurrence. Through this, individuals could then be provided with appropriate interventions to reduce the risks of experiencing the associated injuries and trauma which come with these events in older adults.

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DECLARATIONS

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Conflicts of Interest: None. No author declares a conflict of interest in relation to this paper.

Ethical approval: Ethical approval for the ELSA cohort was obtained from London Multi-Centre Research Ethics Service (MREC/01/2/91).

Description of Author's Roles: TO Smith co-designed the study, collected the data from the ELSA cohort database, co-designed the statistical analysis, and co-wrote and approved the paper. SR Neal co-designed the study and the statistical analysis, performed the statistical analysis, and co-wrote and approved the paper. G Peryer co-designed the study and co-wrote and approved the paper. KJ Sheehan co-designed the study and co-wrote and approved the paper. MP Tan co-designed the study and co-wrote and approved the paper, PK Myint co-designed the study and the statistical analysis and co-wrote and approved the paper.

FIGURE AND TABLE LEGENDS

Table 1. Summary of characteristics between fallers and non-fallers.

Table 2. Results of logistic regression for cognitive function parameters predicting falls in the preceding 12 months in 5197 participants of the ELSA study wave 4 cohort.

Table 3. Results of logistic regression for cognitive function parameters predicting recurrent falls (two or more falls) in the preceding 12 months in 1301 participants of the ELSA study wave 4 cohort.

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Table 1. Summary of characteristics between fallers and non-fallers.

Characteristic	All	Non-Fallers	Fallers	*P*-value*
N (%)	5197 (100%)	3889 (74.8%)	1308 (25.2%)	
Demographics				
Age (years)[a]	69.9 (7.8)	69.4 (7.5)	71.3 (8.5)	**<0.001**
Sex (female)[b]	2784 (53.6)	2011 (51.7)	773 (59.1)	**<0.001**
BMI (kg/m^2)[a]	28.2 (5.1)	28.1 (5.0)	28.6 (5.3)	**0.001**
Ethnicity (white)[b]	5095 (98.0)	3810 (98.0)	1285 (98.2)	0.54
NS-SEC class[b]				0.28
Class 1	1680 (32.3)	1261 (32.4)	419 (32.0)	
Class 2	711 (13.7)	533 (13.7)	178 (13.6)	
Class 3	639 (12.3)	478 (12.3)	161 (12.3)	
Class 4	538 (10.4)	421 (10.8)	117 (8.9)	
Class 5	1629 (31.3)	1196 (30.8)	433 (33.1)	
Self-reported hearing[b]				**0.005**
Excellent	859 (16.5)	652 (16.8)	207 (15.8)	
Very good	1381 (26.6)	1044 (26.8)	337 (25.8)	
Good	1801 (34.7)	1372 (35.3)	429 (32.8)	
Fair	904 (17.4)	653 (16.8)	251 (19.2)	
Poor	252 (4.8)	168 (4.3)	84 (6.4)	
Self-reported eyesight[b]				**<0.001**
Excellent	752 (14.5)	585 (15.0)	167 (12.8)	
Very good	1827 (35.2)	1430 (36.8)	397 (30.4)	
Good	1967 (37.8)	1462 (37.6)	505 (38.6)	
Fair	521 (10.0)	339 (8.7)	182 (13.9)	
Poor	126 (2.4)	70 (1.8)	56 (4.3)	
Registered blind	4 (0.1)	3 (0.1)	1 (0.1)	
SPPB score[a]	6.4 (1.9)	6.6 (1.8)	5.8 (2.2)	**<0.001**
Cognitive Function Parameters				
Memory				
Immediate word recall[a]	5.7 (1.7)	5.8 (1.6)	5.5 (1.8)	**<0.001**
Delayed word recall[a]	4.3 (2.0)	4.4 (2.0)	4.1 (2.1)	**<0.001**
Prospective memory (correct response to task)[b]	3280 (63.1)	2487 (63.9)	793 (60.6)	**0.031**
Orientation[a]	3.8 (0.5)	3.8 (0.5)	3.7 (0.6)	0.07
Executive function				
Verbal fluency[a]	20.3 (6.5)	20.5 (6.5)	19.7 (6.5)	**<0.001**
Letter cancellation[a]	18.4 (5.3)	18.6 (5.2)	18.0 (5.5)	**0.001**
Numeracy skills				
Numeracy score[a]	4.1 (1.2)	4.2 (1.2)	4.0 (1.3)	**<0.001**

BMI – Body Mass Index; NS-SEC - National Statistics Socio-Economic Classification scheme ; SPPB – Short Performance Physical Battery

Values are reported as [a]mean (standard deviation) or [b]number of participants (% within group).

*Two-sided *P*-value for Chi-squared test and independent samples t-test between non-fallers and fallers groups for categorical and continuous variables, respectively.

Table 2. Results of logistic regression for cognitive function parameters predicting falls in the preceding 12 months in 5197 participants of the ELSA study wave 4 cohort.

Cognitive function parameters	**Model A**			**Model B**			**Model C**		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Memory									
Immediate word recall	0.91	0.88-0.95	<0.001	0.95	0.91-0.99	0.010	0.98	0.94-1.02	0.24
Delayed word recall	0.93	0.90-0.96	<0.001	0.96	0.93-0.99	0.016	0.98	0.95-1.02	0.32
Prospective memory	0.87	0.76-0.99	0.031	0.93	0.82-1.06	0.30	1.01	0.88-1.16	0.91
Orientation	0.90	0.81-1.01	0.07	0.95	0.85-1.07	0.40	1.01	0.90-1.14	0.86
Executive function									
Verbal fluency	0.98	0.97-0.99	<0.001	0.99	0.98-1.00	0.12	1.00	0.99-1.01	0.92
Letter cancellation	0.98	0.97-0.99	0.001	0.99	0.97-1.00	0.026	1.00	0.98-1.01	0.60
Numeracy skills									
Numeracy score	0.90	0.86-0.95	<0.001	0.96	0.90-1.01	0.12	1.00	0.95-1.06	0.93

BMI – Body Mass Index; NS-SEC - National Statistics Socio-Economic Classification scheme ; SPPB – Short Performance Physical Battery

- Model A = unadjusted
- Model B = adjusted for age, sex, ethnicity, BMI and NS-SEC class
- Model C = model B, additionally adjusted for self-reported hearing, self-reported eyesight and SPPB score

Table 3. Results of logistic regression for cognitive function parameters predicting recurrent falls (two or more falls) in the preceding 12 months in 1301 participants of the ELSA study wave 4 cohort.

Cognitive function parameters	**Model A**			**Model B**			**Model C**		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Memory									
Immediate word recall	0.94	0.89-1.00	0.07	0.95	0.89-1.02	0.17	1.01	0.94-1.08	0.86
Delayed word recall	0.93	0.88-0.98	0.004	0.93	0.87-0.98	0.011	0.97	0.91-1.03	0.34
Prospective memory	0.78	0.62-0.97	0.027	0.78	0.62-0.99	0.038	0.87	0.68-1.10	0.25
Orientation	0.70	0.58-0.85	<0.001	0.72	0.59-0.89	0.002	0.80	0.65-0.98	0.030
Executive function									
Verbal fluency	0.97	0.95-0.99	<0.001	0.97	0.95-0.99	0.001	0.98	0.96-1.00	0.05
Letter cancellation	0.96	0.94-0.98	<0.001	0.96	0.94-0.99	0.002	0.98	0.96-1.01	0.14
Numeracy skills									
Numeracy score	0.89	0.82-0.97	0.010	0.86	0.78-0.95	0.003	0.93	0.84-1.04	0.20

BMI – Body Mass Index; NS-SEC - National Statistics Socio-Economic Classification scheme ; SPPB – Short Performance Physical Battery

- Model A = unadjusted
- Model B = adjusted for age, sex, ethnicity, BMI and NS-SEC class
- Model C = model B, additionally adjusted for self-reported hearing, self-reported eyesight and SPPB score