Recent syncope and unexplained falls are associated with poor cognitive performance

JOHN FREWEN1, BELLINDA KING-KALLIMANIS1, GERARD BOYLE2, ROSE ANNE KENNY1

1Department of Gerontology, Trinity College, Dublin, Ireland
2Department of Medical Physics, St James Hospital, Dublin, Ireland

Address correspondence to: J. Frewen. Tel: (+353) 1 896 4120; Fax (+353) 1 896 2451. Email: frewenj@tcd.ie

Abstract

Objective: to compare cognitive performance in participants with and without syncope and unexplained falls in a large population representative sample aged 50 years or older.

Methods: participants of the Irish longitudinal study on ageing (TILDA) were studied. Participants with a history of syncope and/or unexplained falls in the past 12 months were compared with those with no reported events. Cognitive performance was measured using the Montreal cognitive assessment (MoCA) score. Multivariate linear regression analysis controlling for potential confounders was performed to compare cognitive function by syncope and falls status.

Results: five thousand eight hundred and forty-six participants were analysed, median age 62 years (inter-quartile range = 14), and 54% were female. Five hundred and forty-nine (9.4%) had a syncopal event and/or an unexplained fall in past 12 months. One hundred and two (1.8%) subjects had two-plus syncopal events in the same period. There was a significant association between syncope/falls history and lower MoCA score, following adjustment for all confounders (β = −0.4; −0.69, −0.11; P = 0.006). Higher syncope burden was also associated with lower performance; however, this was largely explained by confounders. There was no age interaction with these findings.

Conclusion: participants who experienced syncope and/or non-accidental falls in the previous year have poor global cognitive performance compared with case–controls. There was no effect of age on our results. Further investigation of the association between syncope burden, unexplained falls and cognitive decline is required to establish a relationship between these disorders.

Keywords: syncope, neurocardiovascular instability, cognition, epidemiology, older people

Introduction

The role of vascular risk factors in the pathogenesis of cognitive disorders has gained research momentum in recent years [1]. This is partially driven by the projected increase in the burden of cognitive disorders, secondary to dramatic changes in ageing demographics worldwide [2]. Late-life hypotension and orthostatic hypotension are both reported to be associated with reduced cognitive function from cross-sectional and longitudinal studies [3, 4].

Syncope is defined as a sudden loss of consciousness due to transient global cerebral hypoperfusion characterised by rapid
onset, short duration and spontaneous complete recovery [5]. Syncope is a common symptom—up to 40% of persons report at least one episode over the course of their lifetime [6]. The prevalence peaks in youth and in older age. The majority of syncopal episodes in youth (>99%) are due to vasovagal syncope [6], which is generally considered to be a benign disorder [7]. With advancing age, cardiac causes of syncope and medication-related syncope become much more common [6].

Up to 30% of older persons for whom syncopal episodes are unwitnessed present with non-accidental falls rather than syncope [8]. Syncope and falls are frequently unwitnessed, and often individuals are unable to recall a blackout, hence may cases of syncope may be misdiagnosed as falls. Amnesia for loss of consciousness (A-LOC) has been reproduced in experimental studies in these patients [9].

Cardiac disease, cerebral vascular pathology and neurodegeneration often co-exist and share common pathophysiological substrates, such as atherosclerosis and inflammation [1]. It has been hypothesised that repeated symptomatic hypotension in older persons with poor cerebrovascular autoregulation could cause cerebral damage manifesting as cognitive impairment [10]. Conversely, neurodegeneration may lead to autonomic dysfunction causing syncope due to hypotension or arrhythmias; thus, syncope and non-accidental falls might parallel the progression of cognitive decline.

To the best of our knowledge, no previous studies have investigated the association between syncope and cognition in healthy populations. The objective of our study was to examine the association between syncope, unexplained falls and cognitive performance, with data from a large nationally representative sample of community-dwelling adults aged 50 and older.

Methods

Study population

Data from the first wave of The Irish Longitudinal Study on Ageing (TILDA) were analysed (collected June 2009–June 2011). TILDA is a large, prospective cohort study on ageing, comprising healthy community-dwelling adults aged 50 and older resident in the Republic of Ireland, who did not have dementia. A statistically robust nationally representative sample was selected using the regularly updated RANSAM sampling technique, from a listing of all residential addresses in the Republic of Ireland (The Irish Geodirectory). Details of the study design are published elsewhere [11]. Data collected within TILDA comprised (i) computer-assisted personal interviewing (CAPI), carried out in the participant’s home, (ii) self-completion questionnaire and (iii) physical health assessment carried out by trained study nurses in one of two dedicated health centres. Participants unwilling or unable to undergo centre-based assessment were offered a nurse delivered in-home health assessment (where all measures for this study were also recorded). Ethical approval was obtained, and all respondents provided signed informed consent prior to participation. All experimental procedures adhered to the Declaration of Helsinki.

Classification of syncope, syncope burden and unexplained falls

Participants were asked whether they had fainted at any point during their lifetime during the CAPI interview. Those who responded positively were further asked ‘have you fainted in the past 12 months?’ and ‘how many times have you fainted in the past 12 months?’ Number of syncopal events in the past 12 months was a count variable (mean = 0.6, SD = 3.3). Participants were also asked whether they had fallen in the past 12 months, the number of falls and whether any of these falls were unexplained, i.e. ‘a fall with no apparent or obvious reason’. Subjects were subsequently grouped according to 12-month syncope/non-accidental falls history and 12-month syncope burden.

Assessment of cognitive function

Cognitive function was assessed during the health assessment, using the Montreal Cognitive Assessment (MoCA) [12]. MoCA is a measure of global cognitive function (score range: 0–30), assessing the subdomains: (i) memory, (ii) visuospatial function, (iii) executive function, (iv) sustained attention, (v) language and (vi) orientation.

Co-variates

Other variables that were considered potential confounders and/or modifiers of the association between syncope and cognition were also collected and their effects estimated by multivariate analyses. These included age, sex, educational attainment (primary, secondary or tertiary), smoking status (never smoked, former or current), physical activity (using the International Physical Activity Questionnaire (IPAQ) short form, classified as low, medium or high) [13], height (cm), body mass index (BMI) (kg/m²), systolic blood pressure (BP), total blood cholesterol (mmol/l), depression (The Centre for Epidemiological Studies Depression (CES-D) scale was used with a cut-off score of 16 or above, to define subjects as depressed [14]), history of angina, myocardial infarction, heart failure, diabetes mellitus, stroke, transient ischaemic attack (TIA) and cardiac arrhythmias (self-report).

Medication use was recorded during the home interview (CAPI) and confirmed by cross-checking with medication labels. Anatomical Therapeutic Classification (ATC) codes were subsequently recorded for categorisation [15]. BP-modifying medications were anti-adrenergic agents (‘C02*’), diuretics (‘C03*’), beta-blockers (‘C07*’), calcium channel blockers (‘C08*’), angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (‘C09*’), benzodiazepines (N03AE, N05B, N05C) and combinations of the above (‘C02+’). Anti-psychotic medications (‘N05A’) were also controlled for in analysis.

Statistical analyses

Statistical analysis was performed using Stata version 12 (StataCorp, College Station, TX, USA).
continuous variables was assessed using Q–Q plots and histograms. Normally distributed variables were described as means and standard deviations (SD) and were compared across groups using independent t-tests. Non-normally distributed variables were described as medians and percentiles and compared using Mann–Whitney tests, and categorical variables were compared using $\chi^2$ tests.

Linear regressions were fitted to assess the association between syncope, unexplained falls and MoCA score. Models in a two-stage order were fitted, the first adjusting for age, sex and educational attainment and the second adjusting additionally for health behaviours, clinical profile, cardiovascular disease (CVD), mental health and medications, as described above. To investigate the individual associations between syncope and unexplained falls, and cognition, linear regression analysis with syncope entered as the independent variable was adjusted for falls history and vice versa. Missing data for any single co-variate were ≤0.1% and hence excluded on a case-wise basis. Statistical significance was taken as $P \leq 0.05$.

Results

The study sample consisted of 5,846 subjects, median age 62 years (inter-quartile range = 14); 54% were female ($n = 3,163$). Prevalence of syncope and/or unexplained falls in the past 12 months was 9.4% ($n = 549$). Five per cent ($n = 305$) experienced a single syncopal event in the past 12 months, while a further 4.1% ($n = 238$) experienced two or more events. Demographic and clinical characteristics according to syncope group are presented in Table 1. Individuals with a syncope/falls history were older, had lower educational attainment, MoCA score, physical activity level, cholesterol level and prevalence of depression. They also had higher former smoking rates, prevalence of CVD, and antihypertensive and antipsychotic medication use. There was no difference in gender, BMI, BP and prevalence of myocardial infarction and heart failure between groups. The prevalence of syncope/non-accidental falls and syncope burden is presented in Table 2, according to age group. The overall prevalence increased significantly with age, from 7.6% among subjects aged 50–64 to 9.8% among those aged 65–79 and 12.6% among the oldest old (>80 years).

The overall association between syncope/falls history and MoCA score is summarised in Table 2. In Model 1 (adjusted for age, sex and education), subjects reporting a syncopal event and/or an unexplained fall within the past 12 months scored significantly lower, compared with those without any events in the same period ($B = −0.58; −0.87, −0.29; P < 0.0001$). Further adjustment was applied in Model 2 for smoking status, exercise, height, BMI, total cholesterol level, resting systolic BP, angina, myocardial infarction, heart failure, stroke, TIA, heart arrhythmias, depression, and

Table 1. Clinical characteristics of the study cohort, comparing subjects with and without a history of syncope/unexplained falls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Any 12-month syncope/unexplained falls history</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ($n = 5,297$)</td>
<td>Yes ($n = 549$)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>63 ± 9</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Male, % ($n$)</td>
<td>91.4 (2,451)</td>
<td>8.6 (232)</td>
</tr>
<tr>
<td>Female, % ($n$)</td>
<td>90 (2,846)</td>
<td>10 (317)</td>
</tr>
<tr>
<td>Education, % ($n$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>25.5 (1,352)</td>
<td>41.2 (229)</td>
</tr>
<tr>
<td>Smoking status, % ($n$) (Ref = Never)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>38.8 (2,056)</td>
<td>43 (236)</td>
</tr>
<tr>
<td>Current</td>
<td>16 (845)</td>
<td>16.4 (90)</td>
</tr>
<tr>
<td>MOCA score, median (25th, 75th percentile)</td>
<td>25 (23, 27)</td>
<td>25 (22, 27)</td>
</tr>
<tr>
<td>Level of physical activity (IPAQ), % ($n$) (Ref = Low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>35 (1,839)</td>
<td>36.3 (198)</td>
</tr>
<tr>
<td>High</td>
<td>35.8 (1,881)</td>
<td>23.6 (129)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD</td>
<td>28.7 ± 5</td>
<td>28.6 ± 5</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l), mean ± SD</td>
<td>5.1 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Mental health, % ($n$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression (CES-D ≥16)</td>
<td>11.1 (389)</td>
<td>9.3 (218)</td>
</tr>
<tr>
<td>Disease prevalence, % ($n$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>4.9 (260)</td>
<td>8.2 (45)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4.5 (238)</td>
<td>5.5 (30)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.9 (48)</td>
<td>1.5 (8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (369)</td>
<td>10.4 (57)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>3.1 (164)</td>
<td>7.3 (40)</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>7.2 (383)</td>
<td>11.1 (61)</td>
</tr>
<tr>
<td>Systolic BP, mean ± SD</td>
<td>136 ± 20</td>
<td>135 ± 20</td>
</tr>
<tr>
<td>Diastolic BP, mean ± SD</td>
<td>82 ± 11</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Anti-hypertensive medications, % ($n$)</td>
<td>35.9 (1,901)</td>
<td>45.2 (248)</td>
</tr>
<tr>
<td>Anti-psychotic medications, % ($n$)</td>
<td>1.1 (60)</td>
<td>3.1 (17)</td>
</tr>
</tbody>
</table>

SD, standard deviation; TIA, transient ischaemic attack; BP, blood pressure.
antihypertensive and antipsychotic medications. This association with a lower MoCA score remained significant ($B = -0.4; -0.69, -0.11; P = 0.006$).

Next, the effect of syncope burden was assessed. In Model 1, subjects reporting two-plus syncope events in the past 12 months scored significantly lower in MoCA, than subjects with no syncope history ($B = -1.23; -1.6, -0.81; P < 0.0001$). Further adjustment in Model 2 attenuated the association and was no longer significant ($B = -1.0; -1.43, 0.57; P < 0.0001$). Subjects reporting a single syncope event in the same period did not score significantly better or worse than those without a syncope history, in Models 1 or 2.

Further analysis was performed to determine the effects of age. The interaction effect of age on (i) 12-month syncope/unexplained falls history ($B = -0.02; -0.05, 0.01; P = 0.2$) and (ii) syncope burden ($B = -0.01; -0.07, 0.06; P = 0.9$) was not significant. The effect of sex was also studied. The significant association between 12-month syncope/unexplained falls history and lower MoCA was confined only to men. However, the interaction effects between sex and syncope group were also estimated and did not reach significance (data not shown). Data were reanalysed using logistic regressions, with outcomes of scoring below various used MoCA cut-off scores ($\leq 25$, $\leq 23$, $\leq 22$). There was a trend in each analysis consistent with the directions of effects observed in the main analysis (data not shown). However, significant associations between syncope and lower MoCA score were limited to men and for cut-off scores of $\leq 22$ and $\leq 23$.

**Discussion**

Syncope and unexplained falls in the past year are independently associated with poorer cognitive performance among individuals aged 50 and older. No age effect was observed on this association. Higher burden of syncope was also associated with poorer performance; however, this was explained by confounding factors of smoking status and exercise level (Table 3). The association was more evident among men; however, there was no effect of gender on the interaction between syncope and cognitive score. This may be explained by the increased power of the data on analysis in men. Further studies are required to investigate the effect of sex on this association. Although comprehensive adjustment for medication categories was undertaken in analysis, with a significant association remaining following adjustment, we cannot out rule the possibility that such medications have a role to play in the aetiology of syncopal cases.

A number of pathophysiological mechanisms may explain the findings of this study. Lower cognitive performance may be caused by neurodegenerative processes triggered by hypoperfusion and hypoxia in the brain. Hypoperfusion can occur during syncope events.

Neurodegeneration secondary to numerous pathophysiological processes may result in both cognitive and autonomic dysfunction. Syncope is a clinical manifestation of autonomic dysfunction. Hence, cognitive decline and syncope may occur in parallel without being causally linked.

There are a number of consequences to the findings of this study. It is important to ascertain the directionality of this association, as intervention strategies for managing syncope may have a role in preventing cognitive decline. Older adults with syncope should undergo cognitive assessment to monitor their performance over time, which may detect subtle decline otherwise missed. The relationship between syncope and lower cognition may have implications for management of patients with syncope, for example driving advice. Concurrent syncope and cognitive impairment may serve to prolong the period during which driving is prohibited.

The cross-sectional design is a limitation of this study. Future follow-up of the TILDA cohort will allow for...
Unexplained falls in the past 12 months are also independently associated with lower global cognitive performance. This study is the first to describe an association between syncope and cognition. All potential participants of the TILDA study were screened for signs of obvious cognitive impairment by the interviewer prior to recruitment and excluded on a case-wise basis.

Previous research from the TILDA study and elsewhere indicates a relationship between lower cognitive function and other indicators of autonomic dysfunction, namely orthostatic hypotension [16] and reduced heart rate variability [17]. This study is the first to describe an association between syncope and cognitive function, and serves to highlight the need for further research in this area. Syncope is a treatable condition, and the burden of cognitive disorders is increasing worldwide, alongside pressure to identify modifiable factors to reduce the risk of developing symptomatic disease.

Key points

• Studies indicate an association between autonomic dysfunction and lower cognition, but few have studied the role of syncope.
• We report that higher recent burden of syncope is independently associated with lower global cognitive performance.
• Unexplained falls in the past 12 months are also independently associated with lower global cognitive performance.

Acknowledgements

Financial contributions from the following entities were acknowledged: The Atlantic Philanthropies (research grant to the Irish Longitudinal Study of Ageing); Irish Life plc and the Irish Government (grant to the Irish Longitudinal Study of Ageing). The funding sources had no role in the design, methodology, data analysis, or preparation of this manuscript. We acknowledge the participants in the study, and the study’s nurses and administrators.

Conflicts of interest

None declared.

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