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RESEARCH PAPER

Longitudinal associations between falls and future risk of cognitive decline, the Motoric Cognitive Risk syndrome and dementia: the Einstein Ageing Study

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Abstract

Background: falls share risk factors with cognitive decline but whether falls predict cognitive decline, pre-dementia syndromes and dementia is poorly understood.
Objectives: this study aimed to examine if falls are associated with cognitive decline in specific domains and the risk of Motoric Cognitive Risk (MCR) syndrome and dementia.
Design: cross-sectional study.
Methods: in older people (age 80.6 ± 5.3 years) free of dementia at baseline, the number of falls (none, one or multiple) during the year before enrolment and the first year of follow-up (exposure) were recorded. Decline in specific cognitive functions (global cognition, episodic verbal memory, verbal fluency, working memory, response inhibition and processing speed-attention), incident MCR and incident dementia were outcome measures. Linear mixed effects models were used to examine the associations between falls and cognitive decline, adjusting for confounders. Cox proportional hazards models were used to determine if falls predicted risk of incident MCR or dementia.
Results: of 522 eligible participants, 140 had a single fall and 70 had multiple falls. Multiple falls were associated with a greater decline in global cognition, episodic memory, verbal fluency and processing speed-attention compared to those with no falls ($P < 0.05$). Over a median follow-up of 1.0 years 36 participants developed MCR and 43 participants developed dementia. Those with multiple falls had a two-fold increased risk of MCR compared to those with no falls, but no increased risk of developing dementia.
Conclusions: multiple falls may be an important marker to identify older people at greater risk of future cognitive decline and incident MCR.

Keywords: falls, multiple falls, cognitive decline, the Motoric Cognitive Risk syndrome, dementia, older people

Key Points

- Falls share risk factors with cognitive decline.
- Whether falls predict cognitive decline, pre-dementia syndromes and dementia is poorly understood.

- We examined if falls predict cognitive decline, onset of the Motoric Cognitive Risk (MCR) syndrome and dementia.
- Multiple falls were associated with faster decline in memory and non-memory related cognitive functions.
- Multiple falls were associated with increased risk of developing Motoric Cognitive Risk (MCR) but not dementia.

Introduction

Dementia develops over many years where subtle decline in cognitive functions occur without obvious clinically detectable changes, followed by pre-dementia stages such as Mild Cognitive Impairment (MCI; [1]) or the Motoric Cognitive Risk (MCR) syndrome (a pre-dementia syndrome characterized with slow gait speed and subjective cognitive complaints; [2]). Simple and informative clinical markers that facilitate early identification of those who may go on to develop cognitive decline or dementia may offer means to target individuals for timely prevention. Falls may be one such clinical marker.

Falls and dementia may be linked by common risk factors (i.e. poor executive function or changes in brain structure such as white matter hyperintensities on imaging; [3–7]) or through the consequences of falls (i.e. social isolation, limited physical activity due to concern about falling [8, 9] or brain injury [10, 11]). Therefore, older adults who fall may represent a group at increased risk for cognitive decline, dementia or conditions that precede to dementia such as MCR. Previously, the occurrence of two or more falls has been associated with a faster decline in global cognition measured by Mini Mental Status Examination (MMSE; [12]). No studies, to the best of our knowledge, have examined if falls in older age are associated with decline in specific domains of cognitive functions, the onset of the MCR syndrome or incident dementia.

Therefore, the aims of this study were to determine if falls are associated with: (i) accelerated decline in global cognition and in specific cognitive domains, (ii) increased risk of onset of the MCR syndrome and (iii) incident dementia. We hypothesized that older people with falls, particularly multiple falls, may have accelerated decline in cognition, and be at increased risk of the MCR syndrome and dementia. Older people are likely to present to primary care after falls. Hence, examining these associations is important to determine if falls may offer a useful screener, whereby incidence of falls suggest the need for a detailed dementia risk assessment.

Methods

Study participants

The Einstein Ageing Study (EAS) is a population-based longitudinal study that primarily aims to identify risk factors for dementia [13]. Older adults aged 70 years or over, and who were able to ambulate independently, were randomly selected from Medicare eligible lists (between 1993 and 2004) and registered voter lists of Bronx County, New York, USA (from 2004 onwards). Those who were institutionalized or who had severe auditory or visual loss were excluded from the larger study. For the current analyses, those with a diagnosis of probable or definite Alzheimer's disease or dementia at baseline were also excluded. EAS baseline assessments started in 1993 and, participants were followed up annually for medical, cognitive and mobility assessments. Ethical clearance was obtained from the Einstein Institutional Review Board. Informed written consent was obtained from all participants.

Falls

Falls assessments were incorporated into EAS in September 2004. At baseline participants were asked 'have you had any falls in the last year?', where a fall was defined as an unexpected event in which a person unintentionally comes to rest on the ground, floor or other lower level [14]. In addition, between annual follow-up visits, participants were contacted by trained research assistants via telephone every 2–3 months to ascertain any falls. In the current study, for each participant, the total number of falls during the year prior to the baseline assessment was combined with the number of falls during the first year of follow-up to obtain a substantial number of people with falls. Participants were classified based on the number of falls during this 2-year window into three groups of fall types: (i) those with no falls (ii) those with a single fall and (iii) those with multiple (two or more) falls. We separated single and multiple falls because multiple, but not single, falls have been associated with slower reaction time, poorer balance and executive dysfunction [4, 15].

Cognitive functions

Global cognition was assessed with the Blessed Information Memory Concentration test [16]. Cognitive functions in specific domains were assessed in EAS with the following validated neuropsychological battery; (i) *Executive function*: Digit Span subsets of the Wechsler Adult Intelligence Scale-III (WAIS-III) and Trail Making Test (TMT) interference (TMT B-A) to assess working memory [17], the Controlled Word Association Test (FAS and category fluency subsets) to assess verbal fluency [18, 19] and the Victoria Stroop test interference [20] to assess response inhibition; (ii) *Processing speed-attention*: Digit Symbol Substitution test of the WAIS-III [17] and TMT-A [19] and (iii) *Memory*: Free Recall on the Free and Cued Selective Reminding Test [21, 22]. Since the exposure variable of this study includes falls that occurred during the first year of follow-up, data from the cognitive assessments at the baseline visit were excluded from the analyses.

Diagnosis of MCR

The criteria for the MCR syndrome are the presence of slow gait speed and subjective cognitive complaints without a diagnosis of dementia or mobility disability (inability or required assistance with ambulation) [23]. Criteria scores for MCR diagnosis in EAS and other cohorts have previously been published [24, 25]. Cognitive complaints were assessed with an item of memory complaint on the 15-item Geriatric Depression Scale (GDS) and a standard self-health assessment questionnaire (and verified by an informant or a clinician; [26]). Gait speed was assessed while participants traversed an 8.5-m computerized GAITRite walkway at their usual walking pace [13]. Slow gait speed was defined as one standard deviation (SD) below age and sex adjusted means (<101.9 cm/s for men and <97.4 cm/s for women under 75 years, and <85.3 cm/s for men and <76.7 cm/s for women age ≥ 75 years; [24]).

Diagnosis of dementia

During annual follow-up visits, participants received neurocognitive assessments outlined above as an evaluation by a study neuropsychologist. All the clinical and neuropsychological information for each participant was reviewed by the study neurologists, neuropsychologist and a social worker to reach consensus on dementia diagnosis using the Diagnostic and Statistical Manual, 4th edition (DSM-IV; [13]).

Data analysis

The descriptive characteristics of those with no falls, single falls and multiple falls were examined. Longitudinal mixed effect models were used to examine associations between falls and cognitive decline in specific cognitive domains, in separate models. An interaction between falls and time was used as the independent variable. Cox proportional hazard models were used to examine the associations between falls and risk of the MCR syndrome and dementia. For these time to event analyses, individuals with a diagnosis of MCR ($n = 57$) or dementia ($n = 21$) in the first year of follow-up were additionally excluded as these events may have occurred before a fall that determines group membership. In both models, time to event was calculated as the difference in years between the date of the first follow-up visit to the date of diagnosis of the MCR syndrome or dementia or final study contact. Proportional hazard assumptions were examined using visual inspection.

In addition, we performed two sensitivity analyses to examine; (i) the association between falls obtained only during the first year of follow-up (excluding the falls ascertained at baseline asking the participant to recall prior 12 months which are more susceptible to recall bias) and risk of the MCR syndrome and (ii) the association between falls and the MCR syndrome excluding individuals who had events during the first 2 years of follow-up. This was done to reduce any effects of reserve causation that may have arisen due to undiagnosed MCR in this period. All models were adjusted for age at the first follow-up visit, sex and level of education. STATA (StataCorp LLC, College Station, TX, United States) version 16.1 was used in all the analyses.

Results

From the initial sample of EAS participants with falls data ($n = 854$), those with only one wave of data ($n = 332$) were excluded, leaving a final eligible sample of 522 participants with complete data for the analysis of aim 1. The mean age of the whole sample was 80.6 (SD5.3) and 61.5% ($n = 321$) were female. Participant characteristics of those with no falls, single falls and multiple falls at the first-year follow-up are summarized in Table 1. Compared to those with no falls, people with multiple falls were mostly women, slightly older and had slower gait speed, but there were no meaningful differences in cognitive tests.

Association between falls and cognitive decline in specific domains

Table 2 shows the associations between falls and longitudinal change in the different cognitive functions. Compared to those with no falls, people with any falls showed faster decline in the Blessed Information Memory Concentration test (global cognition) and TMT-A (processing speed-attention). When falls were categorized into no falls, single and multiple falls, compared to no falls, multiple falls were associated with an additional 0.12 faster annual decline in the Blessed, 0.49 decline in Free Recall, 0.83 decline in FAS fluency, 0.47 decline in CAT fluency and 1.74 increase in TMT-A, whereas single falls were only associated with an additional 1.08 faster increase in TMT-A, compared to those with no falls (Table 3).

Associations between falls and the MCR syndrome and dementia

Over a median follow-up of 1.0 survival years, 36 participants developed the MCR syndrome. Compared to those with no falls, people with any falls were at increased risk of developing the MCR syndrome (HR 2.06, 95% CI 1.02, 4.17, $P = 0.04$). When falls were separated into single and multiple falls, only people with multiple falls, not single falls, were at greater risk of MCR (HR 2.62, 95%CI 1.10, 6.24 $P = 0.03$; Table 4). Over a median follow-up of 1.1 survival years, 43 participants developed dementia ($n = 40/43$ without an intermediate MCR stage on follow-up). Compared to those with no falls, people with any falls (HR 0.68 95%CI 0.35, 1.33 $P = 0.26$), single (HR 0.45 95%CI 0.18, 1.11 $P = 0.08$) or multiple falls (HR 1.07 95%CI 0.48, 2.40 $P = 0.86$) were not found to be at risk of developing dementia during the follow-up.

Sensitivity analyses

When the number of falls was limited to the first year of follow-up, 123 people had at least one fall and, 40/123 had

Table 1. Participant characteristics at the first year of follow up ($n = 522$)

	Participants with no falls $n = 312$		Participants with single falls $n = 140$		Participants with multiple falls $n = 70$	
Age, mean, SD	80.2	5.2	81.0	5.4	81.8	5.2
Female, *n*, %	179	57.4	86	61.4	56	80.0
Education (years), mean, SD	14.2	3.4	14.4	3.5	14.7	3.2
BMI (kg/cm^2), mean, SD	27.6	4.8	28.2	5.0	27.5	4.4
MCR, *n*, %	16	44.4	10	27.8	10	27.8
Incident dementia, *n*, %	27	62.8	6	14.0	10	23.3
Medical conditions						
Hypertension, *n*, %	146	45.9	72	51.1	3	50.0
Diabetes, *n*, %	40	12.6	22	15.6	11	15.3
Cardiac arrhythmia, *n*, %	4	1.3	2	1.4	0	0
Gait speed (cm/s), mean, SD	95.1	21.6	91.7	22.6	88.1	22.3
Cognitive function						
Blessed information test, mean, SD	26.8	1.4	26.6	1.4	26.6	1.5
Free recall, mean, SD	32.1	6.3	32.0	5.8	31.7	6.1
TMT-A, mean, SD	52.7	21.5	53.9	21.1	53.2	22.3
TMT interference, mean, SD	81.3	61.2	85.6	62.0	78.9	62.7
Stroop interference, mean, SD	28.3	9.7	27.5	9.4	27.0	10.8
Digit span test, mean, SD	15.3	3.6	14.6	3.2	15.3	3.8
Digit symbol substitution test, mean, SD	47.2	13.8	46.7	13.3	47.0	13.9
CAT fluency, mean, SD	38.1	9.3	37.0	8.4	38.4	9.8
Category fluency, mean, SD	37.8	12.5	37.0	12.1	38.9	14.5

Abbreviations: BMI, body mass index; cm, centimetre; kg, kilograms; s, seconds; SD, standard deviation; TMT, Trail Making Test.

Table 2. Longitudinal associations between falls (at least 1 versus none) and decline in cognition ($n = 522$)

Cognitive functions	*b*	95%CI	*P*-value
Global cognition			
Blessed information memory concentration test	−0.067	−0.133, −0.001	0.047
Memory			
Free recall	−0.150	−0.403, 0.103	0.244
Executive function			
Working memory			
Digit span test	−0.008	−0.122, 0.107	0.898
TMT interference	0.134	−2.543, 2.812	0.922
Verbal fluency			
FAS fluency	−0.273	−0.640, 0.094	0.145
Category fluency test	−0.041	−0.385, 0.304	0.817
Response inhibition			
Stroop interference	−0.029	−0.411, 0.353	0.881
Processing speed-attention			
Digit symbol substitution test	−0.190	−0.595, 0.215	0.358
TMT-A	1.369	0.485, 2.252	0.002

Note: TMT, Trail Making Test; For TMT-A, TMT interference and Stroop interference higher scores indicate poorer function. Coefficients represent the interactions between falls and time.

multiple falls. Having a fall, single or multiple falls were not associated with the risk of MCR syndrome (Appendix 1, Supplementary data are available in *Age and Ageing* online). After additionally excluding $n = 12$ people who developed the MCR syndrome during the second year of follow-up, falls were not associated with risk of developing MCR (Appendix 2, Supplementary data are available in *Age and Ageing* online).

Discussion

Falls may be a marker of declining health in older people. In this study of community dwelling older people without dementia, multiple falls were associated with faster decline in global cognition, episodic verbal memory, verbal fluency and processing speed-attention. Those with multiple falls also showed a two-fold increased risk of developing the MCR syndrome, compared to those with no falls. These findings suggest that having multiple falls could potentially be used as a simple marker in primary care to identify those at risk of cognitive decline and a prevalent pre-dementia syndrome.

Association between falls and cognitive decline

There has been only one prior study that has examined if falls are associated with subsequent cognitive decline [12].

Table 3. Longitudinal associations between single and multiple falls and decline in different cognitive functions ($n = 522$)

	Falls during the first 2 years of follow up (exposure)					
	Single falls ($n = 140$) versus None			Multiple falls ($n = 70$) versus None		
	b	95%CI	*P*-value	b	95%CI	*P*-value
Cognitive functions (outcome measures)						
Global cognition						
Blessed Memory Concentration test	−0.028	−0.108, 0.052	0.489	−0.117	−0.205, −0.029	0.009
Memory						
Free recall	0.111	−0.193, 0.416	0.473	−0.486	−0.822, −0.150	0.005
Executive function						
Working memory						
Digit Span	0.085	−0.053, 0.223	0.228	−0.130	−0.282, 0.023	0.096
TMT interference	−1.260	−4.497, 1.977	0.446	1.983	−1.591, 5.557	0.277
Verbal fluency						
FAS fluency	0.150	−0.292, 0.592	0.507	−0.826	−1.314, −0.337	0.001
Category fluency	0.286	−0.129, 0.701	0.177	−0.469	−0.927, −0.010	0.045
Response inhibition						
Stroop interference	0.032	−0.431, 0.496	0.891	−0.109	−0.620, 0.402	0.676
Processing speed-attention						
Digit symbol substitution test	−0.224	−0.714, 0.267	0.372	−0.147	−0.689, 0.395	0.594
TMT-A	1.083	0.015, 2.152	0.047	1.740	0.561, 2.921	0.004

Note: The coefficients reported are those for people with single and multiple falls, compared to people with no falls. TMT, Trail Making Test; For TMT-A, TMT interference and Stroop interference higher scores indicate poorer function. Coefficients represent the interactions between falls and time.

Table 4. Hazard ratios with 95% CI for developing the MCR syndrome and dementia as a function of having falls and having single and multiple falls adjusted for age at the first year of follow up, sex and years of education

	Hazard ratio (95%CI)			
	MCR syndrome ($n = 36$)		Dementia ($n = 43$)	
Any falls versus no falls	2.07	1.02, 4.17	0.68	0.35, 1.33
A single fall versus no falls	1.75	0.77, 3.98	0.45	0.18, 1.11
Multiple falls versus no falls	2.62	1.10, 6.24	1.07	0.48, 2.40

Abbreviation: MCR, The Motoric Cognitive Risk syndrome.

In a large sample ($n = 1,119$) of initially cognitively healthy older people, having two or more falls at baseline were associated with a greater decline in MMSE. Supporting this, we observed faster decline in global cognition assessed with Blessed Information Memory Concentration test, a test that is highly correlated with the MMSE [16]. Furthermore, we add to this knowledge, by showing that falls are also associated with decline in specific cognitive functions including episodic verbal memory, verbal fluency and processing speed-attention. Importantly, the associations between falls and decline in cognitive function appear to be driven mainly by the occurrence of at least two falls. This is in line with the knowledge that multiple falls are usually the result of more intrinsic impairments such as poorer sensorimotor and cognitive functions [4, 15] whereas single falls can occur even in healthy older people who face difficult environments (i.e. slippery floor and curbs) or who take unnecessary risks [27]. These findings suggest that falls (particularly multiple falls) may not just represent poor cognition at the time of a fall but may also be a marker of future decline in cognitive health and could be useful in identifying older people at risk of decline in both memory and non-memory related cognitive functions.

Associations between falls, the MCR syndrome and dementia

Falls were also associated with risk of developing the MCR syndrome, with multiple falls being associated with a greater than two-fold increase in risk. The MCR syndrome is characterized with slow gait and subjective cognitive complaints [2]. Our results suggest that falls, mainly multiple falls, may be indicative of people who are at a greater risk of the MCR syndrome and thereby at risk of dementia (as MCR is a strong predictor of both Alzheimer's disease and vascular dementia [2, 25]). In this study, however, falls were not associated with incident dementia. This is potentially explained by the smaller sample of participants who developed dementia ($n = 43$) or the short follow-up time (median 1.1 survival years). Our MCR findings support the previous cross-sectional findings in community dwelling older people where falls were associated with the MCR syndrome [28],

and a multicentre prospective study, where MCR was associated with increased falls risk [29]. Ours is the first study to report that falls are a prospective risk factor for the MCR syndrome. We attempted to reduce any effects of reverse causation that may have occurred due to undiagnosed MCR, by excluding people who developed MCR during the first 2 years of follow-up. With a lower number of people with MCR ($n = 24$, only four of them had multiple falls), there was reduced power to detect a significant association between falls and MCR. We cannot rule out, however, the possibility of reverse causation with our findings.

Potential mechanisms

Falls may occur as a result of decline in ability to cope with multiple central and peripheral impairments [15, 30, 31]. Our findings may be explained by a few potential and, likely combined mechanisms. Firstly, a number of risk factors associated with MCR and dementia such as older age, poor cognition (i.e. executive function), changes in brain structure (i.e. higher burden of white matter hyperintensities) and cardiovascular risk factors (i.e. diabetes and obesity) are also risk factors for falls [3, 6, 28]. Also, other geriatric conditions such as frailty and sarcopenia are associated different stages of cognitive impairment and falls [32, 33]. Therefore, shared risk factors and conditions could be an antecedent to, or on the causal pathway between falls and cognitive decline. Secondly, it is possible that falls result in changes to behaviour and thereby indirectly result in cognitive decline. For example, an older person who experienced multiple falls may reduce physical activity and become socially isolated, due to concern regarding future falls [8]. Lastly, traumatic brain injury due to falls may eventually lead to cognitive decline in older people, particularly if damage is in the frontal lobe [34]. Finally, there is also the issue of reverse causality. That is, subtle cognitive impairment may lead to poor judgement (walking on ice for example), resulting in a higher rate of falls. The purpose of this study was to establish the association between falls, cognitive decline and MCR. Examining multiple potential mechanisms of this association is an interesting step for future studies but was beyond the scope of current study.

Clinical implications

Dementia is one of the most significant causes of loss of functional independence in older age. Identifying those at risk as early as possible and initiating timely preventive measures to combat accumulating pathology is key to reducing the healthcare burden of dementia. Although multiple falls did not show an association with incident dementia over the follow-up, the findings from this study suggest that incidence of multiple falls may be used as a simple screener to identify those at risk of cognitive decline and the MCR syndrome. For primary care, asking patients a simple question regarding multiple falls may provide means of a simple, quick trigger for a more detailed dementia risk assessment. Asking about falls does not require much time, personnel, additional equipment or space. From a research perspective, questions regarding falls may assist in distinguishing higher risk populations to target in interventions that are designed to maintain or improve cognitive health into older age.

Strengths and limitations

To the best of our knowledge, this is the first study to examine if falls are associated with future decline in specific cognitive domains and the risk of developing the MCR syndrome and dementia. Our sample was comprised of a large number of community dwelling older people, increasing the generalizability of findings. However, there are a few limitations to this study. Our exposure variable was created using the number of falls prior to baseline combined with falls during the first year of follow-up, to include a substantial number of people with falls. Limiting the number of falls only to the first year of follow-up, resulted in lower number of people with falls, particularly multiple falls (results of the sensitivity analysis). Falls assessment for the year prior to enrolment was based on self-report at the time of enrolment, which may have created a recall bias that may lead to under ascertainment of falls ($n = 123$ people reported falls during the first year of follow-up versus $n = 100$ people reporting falls at baseline) [35]. Furthermore, the number of participants who developed dementia was low, therefore limiting the ability to detect an association between falls and incident dementia within our follow-up time. Future studies with a longer follow ups are needed to determine this.

Conclusions

Multiple falls were associated with faster decline in specific cognitive functions and an increased risk of developing the MCR syndrome. Hence, multiple falls may be an important marker to identify older people at greater risk of future cognitive decline and in need of a comprehensive dementia risk assessment.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Declaration of Conflicts of Interest: None.

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