**Title:** Mild cognitive impairment is associated with fall-related injury among adults aged ≥65 years in low- and middle-income countries

**Running Title:** Mild cognitive impairment & fall-related injury

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## ABSTRACT

**Objectives:** There is a scarcity of data on the association between mild cognitive impairment (MCI) and falls, especially from low- and middle-income countries (LMICs) where 70% of all older adults reside. Thus, we investigated the association between MCI and fall-related injury among older adults residing in six LMICs (China, Ghana, India, Mexico, Russia, South Africa).

**Design:** Cross-sectional, community-based data from the WHO Study on global AGEing and adult health (SAGE) were analyzed.

**Methods:** The definition of MCI was based on the National Institute on Ageing-Alzheimer's Association criteria, and information on past 12-month fall-related injury was also collected. Multivariable logistic regression analysis was conducted to assess associations.

**Results:** The analytical sample consisted of 13,623 individuals aged ≥65 years [mean (SD) age 72.3 (10.9) years; 45.6% males]. The prevalence of fall-related injury was higher among those with MCI (6.3%) vs. no MCI (4.1%). After adjustment for potential confounders, MCI was associated with a 1.53 (95%CI=1.12-2.07) times higher odds for fall-related injury.

**Conclusions:** MCI was associated with higher odds for fall-related injury among older adults in LMICs. Future studies are warranted to investigate the mechanisms underlying this association and to elucidate whether targeting those with MCI can lead to reduced risk for falls among older adults.

**Key Words:** Fall-related injury, mild cognitive impairment, older adults, low-and-middle-income countries.

## INTRODUCTION

Every year, one-third of community-dwelling older adults fall, while approximately 10–15% subsequently endure an injury (Karlsson, Magnusson, von Schewelov, & Rosengren, 2013; Masud & Morris, 2001; Rubenstein, 2006). Indeed, in 2010, falls were responsible for approximately 80% of disability from unintentional injuries excluding traffic accidents in adults aged 50 years and over (Institute for Health Metrics and Evaluation (IHME), 2020). Moreover, falls are the major cause of injury-related fatalities in older adults (Majdan & Mauritz, 2015). Given that older adults are at the greatest risk of falling, and that there is a growing number of older people in all parts of the world, it is plausible to assume that the incidence of falls and fall-related injury will also rise. It is thus important to identify risk factors of falls and fall-related injuries to inform targeted interventions to reduce these events.

To date, many risk factors of falls have been identified. Some of the key identified risk factors include fear of falling (Pena et al., 2019), a history of falls, older age, female sex (among the oldest old), living alone, Caucasian ethnicity, specific medication and polypharmacy, chronic disease, impaired mobility and gait, sedentary behavior, and nutrition deficiencies (Grundstrom, Guse, & Layde, 2012; Li et al., 2016; Ravindran & Kutty, 2016; Todd & Skelton, 2004; Tzeng & Yin, 2013). More recently, there has been growing interest in the association between cognitive function and falls (Hsu, Nagamatsu, Davis, & Liu-Ambrose, 2012), and it has been suggested that early prevention of cognitive decline may play a role in fall and injury prevention (Montero-Odasso et al., 2009). It has been hypothesized that cognitive function may lead to a greater risk of falls via impairment in processing speed, attention, and executive functions (Holtzer et al., 2007). For example, one study found that speed/executive attention had the strongest and most consistent associations with falls in healthy older adults who reside in the community. A one-point increase (i.e., one standard deviation) on the speed/executive attention factor scores in the studied sample was associated with an approximately 50% reduction in the risk of falls (Holtzer et al., 2007). However, most previous studies have focused on cognitive decline in general and not mild cognitive impairment (MCI), a pre-clinical state of dementia (Morris, 2005), which is increasingly being considered as an important “target” for the prevention of cognitive decline and ultimately dementia. The few previous studies on MCI and falls (all conducted in high-income countries) have found that MCI is related with higher rates of falls (Borges, Radanovic, & Forlenza, 2015; Liu-Ambrose, Ashe, Graf, Beattie, & Khan, 2008; Tyrovolas, Koyanagi, Lara, Santini, & Haro, 2016). However, clearly, more studies from diverse settings are necessary to elucidate whether this association is context-specific. In particular, focusing on low- and middle-income countries (LMICs) is of importance as over 70 % of the world’s older population live in this setting, and this will increase in the coming decades (United Nations, 2019). Indeed, one of the consequences of this demographic change is that a greater share of the burden of morbidity and mortality due to falls and other chronic conditions including dementia will occur in LMICs. Furthermore, older people in LMICs may be particularly susceptible to falls due to factors such as lack of barrier-free facilities, poor nutrition, and limited availability of treatment for chronic conditions which may heighten risk for falls (e.g., stroke). Therefore, the aim of the present study was to investigate the association between MCI and fall-related injury in a large sample of older adults residing in LMICs.

## METHODS

***The survey***

Data from the Study on Global Ageing and Adult Health (SAGE) were analyzed. These data are publically available through http://www.who.int/healthinfo/sage/en/. This survey was undertaken in China, Ghana, India, Mexico, Russia, and South Africa between 2007 and 2010. Based on the World Bank classification at the time of the survey, all countries were LMICs.

Details of the survey methodology have been published elsewhere (Kowal et al., 2012). Briefly, in order to obtain nationally representative samples, a multistage clustered sampling design method was used. The sample consisted of adults aged ≥18 years with oversampling of those aged ≥50 years. Trained interviewers conducted face-to-face interviews using a standard questionnaire. Standard translation procedures were undertaken to ensure comparability between countries. The survey response rates were: China 93%; Ghana 81%; India 68%; Mexico 53%; Russia 83%; and South Africa 75%. Sampling weights were constructed to adjust for the population structure as reported by the United Nations Statistical Division (He, Muenchrath, & Kowal, 2012). Ethical approval was obtained from the WHO Ethical Review Committee and local ethics research review boards. Written informed consent was obtained from all participants.

***Mild cognitive impairment (MCI)***

MCI was ascertained based on the recommendations of the National Institute on Aging-Alzheimer's Association (Albert et al., 2011). We applied the identical algorithms used in previous SAGE publications to identify MCI (Koyanagi et al., 2018; Koyanagi et al., 2019). Briefly, individuals fulfilling all of the following conditions were considered to have MCI: (a) Concern about a change in cognition: Individuals who replied 'bad' or 'very bad' to the question "How would you best describe your memory at present?" and/or those who answered ‘worse’ to the question “Compared to 12 months ago, would you say your memory is now better, the same or worse than it was then?” were considered to have this condition.

(b) Objective evidence of impairment in one or more cognitive domains: was based on a <-1 SD cut-off after adjustment for level of education and age. Cognitive function was assessed through the following performance tests: word list immediate and delayed verbal recall from the Consortium to Establish a Registry for Alzheimer's Disease,(Morris et al., 1989) which assessed learning and episodic memory; digit span forward and backwards from the Weschler Adult Intelligence Scale (Tulsky & Ledbetter, 2000), that evaluated attention and working memory; and the animal naming task (Morris et al., 1989), which assessed verbal fluency.

(c) Preservation of independence in functional abilities: was assessed by questions on self-reported difficulties with basic activities of daily living (ADL) in the past 30 days (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). Specific questions were: “How much difficulty did you have in getting dressed?” and “How much difficulty did you have with eating (including cutting up your food)?” The answer options were none, mild, moderate, severe, and extreme (cannot do). Those who answered either none, mild, or moderate to both of these questions were considered to have preservation of independence in functional activities. All other individuals were deleted from the analysis (666 individuals aged ≥65 years).

(d) No dementia: Individuals with a level of cognitive impairment severe enough to preclude the possibility to undertake the survey were not included in the current study.

***Fall-related injury***

The variable on fall-related injury of the SAGE was derived from questions of the WHO guidelines on injuries (Williams et al., 2015). First, the participant was asked “In the past 12 months, have you had any other event (other than a road traffic accident) where you suffered from bodily injury?” Those who answered affirmatively were prompted to the next question

"What was the cause of the injury?" If there were multiple injuries, the respondent was instructed to refer to the most recent injury. If the respondent answered "Fall", then he or she was considered to have had a fall-related injury in the past year.

***Control variables***

The selection of the control variables included in this study was based on past literature (Tyrovolas et al., 2016) and included age, sex, years of education, wealth quintiles based on income, living arrangement (alone or not), physical activity, alcohol use in the past 30 days, low handgrip strength, obesity [body mass index (BMI) ≥30 kg/m$^2$ based on measured weight and height], arthritis, stroke, diabetes, angina, and depression. Levels of physical activity were assessed with the Global Physical Activity Questionnaire and were classified as low, moderate, and high based on conventional cut-offs (Bull, Maslin, & Armstrong, 2009). Weak handgrip strength was defined as <30kg for men and <20kg for women using the average value of the two handgrip measurements of the dominant hand (Cruz-Jentoft et al., 2010). Arthritis, stroke, and diabetes were based solely on self-reported lifetime diagnosis. An angina diagnosis referred to self-reported diagnosis or diagnosis based on the the validated Rose questionnaire (Rose, 1962). Questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview (Kessler & Üstün, 2004) were used for the endorsement of past 12-month DSM-IV depression (American Psychiatric Association, 2013).

***Statistical analysis***

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥65 years as MCI is an age-related condition. Difference in sample characteristics by the presence of fall-related injury was tested by Chi-squared tests and Student's *t*-tests for categorical and continuous variables, respectively. Multivariable logistic regression analysis with MCI as the exposure and fall-related injury as the outcome was conducted. Three models were constructed to assess the influence of inclusion of different blocks of variables in the association between MCI and fall-related injury. Specifically, model 1 was adjusted for sociodemographic factors (age, sex, education, wealth, living arrangement, and country), model 2 was adjusted for all variables in model 1 and behavioral factors (physical activity and alcohol consumption), and model 3 was adjusted for all variables in model 2 and health conditions (handgrip strength, obesity, arthritis, stroke, diabetes, angina, depression). In order to assess whether there is interaction by sex in the association between MCI and fall-related injury, we also conducted additional analysis including a product term (MCI X sex) in the fully adjusted model (model 3).

We did not use multilevel models as such analyses can produce biased estimates when used with complex study designs (Rabe-Hesketh & Skrondal, 2006). Adjustment for country was done by including dummy variables for each country as fixed effects in the model as in previous SAGE publications (Koyanagi et al., 2014; Koyanagi et al., 2018). All variables were included in the models as categorical variables with the exception of age and years of education (continuous variables). The sample weighting and the complex study design were taken into account in the analyses with the use of the Stata *svy* command which uses Taylor linearization methods. Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The level of statistical significance was set at $P<0.05$.

## RESULTS

The final analytical sample consisted of 13623 (China 5094; Ghana 1904; India 2211; Mexico 1179; Russia 1820; South Africa 1415) individuals aged ≥65 years with preservation in functional abilities. The overall prevalence of MCI and fall-related injury was 18.5% and 4.5%, respectively. The sample characteristics are shown in **Table 1**. The mean (SD) age was 72.3 (10.9) years while 45.6% were males. Those who had a fall-related injury were more likely to be females, have lower levels of education, not be living alone, have low handgrip strength, and have stroke and depression. The prevalence of fall-related injury was higher among those with MCI than in those without MCI in the overall sample (6.3% vs. 4.1%), and sex-stratified samples [female 7.2% vs. 4.9%; male 5.1% vs. 3.1%] (**Figure 1**). **Table 2** illustrates the association between MCI and fall-related injury estimated by multivariable logistic regression. In the model adjusted only for sociodemographic factors, MCI was associated with a 1.60 (95%CI=1.18-2.16) times higher odds for fall-related injury (model 1). The addition of physical activity and alcohol consumption in the model had almost no influence in the association between MCI and fall-related injury (model 2). After additional adjustment for factors related with health status, the OR was attenuated slightly (OR=1.53; 95%CI=1.12-2.07) (model 3). There was no significant interaction by sex in the association between MCI and falls.

## DISCUSSION

### *Main findings*

In the present sample of 13,623 individuals aged ≥65 years from six LMICs, it was found that in the overall sample, and in males and females separately, the prevalence of fall-related injury was higher in those with MCI than those without. Moreover, in the final adjusted model, MCI was associated with a significant 1.53 higher odds of falling compared to those without MCI.

***Interpretation of the findings***

These findings are in line with previous studies on MCI and falls conducted in high-income countries. For example, Liu-Ambrose et al. (2008), in a sample of 158 older Canadians, reported that females with MCI had higher physiological risk of falling and increased postural sway compared to females without MCI (Liu-Ambrose et al., 2008). Additionally, Delbaere et al. (2012) analyzed a sample of 419 non-demented community-dwelling adults in Sydney and reported that MCI was associated with a 1.72 (95%CI 1.03–2.89) times greater risk for falls (Delbaere et al., 2012). Our findings add to the literature by showing for the first time that MCI is related with higher odds for (*injury-related*) falls also in LMICs.

There are several plausible pathways that may lead to higher odds of fall-related injury in those with MCI. First, those with cognitive impairment per se are at a higher risk of falls via impairment in processing speed, attention, and executive functions (Holtzer et al., 2007) and the more times one falls increases the odds of sustaining an injury (Alzheimer Society of Manitoba - Dementia Care & Brain Health, 2014). Second, those with MCI are more likely to be malnourished compared to those with normal cognition (Orsitto et al., 2009), and malnourished individuals may be more likely to fall (Kueper, Beyth, Liebergall, Kaplan, & Schroeder, 2015) because malnutrition symptoms include fatigue, dizziness, irritability, loss of muscle mass, impulsivity, and the potential for poor judgment (Julius, Kresevic, Turcoliveri, Cialdella-Kam, & Burant, 2017). Finally, those who sustain an injury related to a fall may subsequently develop MCI. It is possible that a serious fall-related injury, such as a hip fracture, reduces daily activities that one can engage in, consequently resulting in reduced brain stimulation and thus MCI. Furthermore, a head injury, for example, can potentially increase risk for cognitive decline. The observed association between MCI and fall-related injury observed in the present sample is likely to be bi-directional and as a consequence of a combination of the above hypothesized pathways.

***Clinical, public, and global health implication and areas for future research***

Collectively, findings from the present study and other literature support the implementation of interventions to reduce falls in those with MCI. Importantly, intervention strategies to reduce the risk of falls in those with MCI are being trialed and developed. One trial set out to determine the efficacy of donepezil, a cognitive enhancer that improves cholinergic neurotransmission, on gait performance in those with MCI. Donepezil treatment improved dual-task gait speed and dual-task gait cost, as well as a non-significant reduction in falls, in older patients with MCI (Montero-Odasso et al., 2019). Other trials are underway to reduce falls in those with MCI focusing on home-based therapy interventions (Harwood et al., 2018), and exercise and cognitive training (Lipardo & Tsang, 2018), for which outcomes are eagerly awaited. However, these trials are being carried out in high-income countries and their efficacy may not be transferable to LMICs. Trials to reduce falls in those with MCI in LMICs are required.

Although interventions to prevent falls is limited in LMICs, given rapid population ageing in this setting, the development and implementation of interventions to prevent falls is a priority. In contrast to high-income countries, interventions in LMICs must be carefully planned within financial constraints. Several potential interventions (e.g., education, vitamin D and calcium supplementation) have been proposed in countries such as China (Ye et al., 2020), but one relatively cost-effective intervention that can be implemented in LMICs is promotion of physical activity. This can potentially prevent falls by improving balance, flexibility, and strength (Gámez de la Hoz, Padilla-Fortes, & Padilla-Ruiz, 2019), while it can also potentially improve cognitive function (Nuzum et al., 2020). In LMICs, community health workers may be utilized to deliver fall prevention interventions. The use of community health workers has been shown to be a successful intervention component in LMICs in relation to disease prevention and behavioral interventions (Khetan et al., 2017; Mwai et al., 2013). To identify appropriate interventions in each country, further work of a qualitative nature and involving key stakeholders is required.

***Strengths and limitations***

The use of large nationally representative datasets from six LMICs which collectively comprise nearly half of the worldwide population (Kowal et al., 2012), and the fact that this is the first study on MCI and falls from LMICs are the strength of the present study. However, findings must be interpreted in light of the study limitations. First, the study was cross-sectional in nature and thus causality or temporal associations cannot be determined. Second, data on clinical diagnoses of dementia were not available, and there is the possibility that some individuals with mild dementia were included but it is reassuring that the prevalence of MCI in our study was within previously reported estimates (Petersen, 2016). Third, there is no consensus regarding how much functional impairment an individual with MCI can present. Our conservative definition of independence in functional abilities has been used in previous publications (Koyanagi et al., 2019; Wimo et al., 2017) but it is worth bearing in mind that results may differ slightly with the use of a different definition. Next, most of the data used in our study were based on self-report. Thus, this may have introduced some level of bias (e.g., recall bias, social desirability bias) in the analysis. Finally, due to the small sample size in each country and the consequent lack of statistical power, we were unable to conduct analyses stratified by country as meaningful results could not be obtained.

Future multicountry studies with larger sample size may wish to investigate whether there are notable between-country differences in the association between MCI and falls in order to understand whether country-specific approaches are necessary.

### *Conclusion*

In conclusion, in this large representative sample of older adults from six LMICs, it was found that those with MCI were at a significantly increased odds of experiencing fall-related injuries. Future studies are necessary to shed light on the mechanisms underlying this association, while interventional studies from LMICs to reduce falls among those with MCI are warranted.

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**Table 1** Sample characteristics (overall and by fall-related injury)

| Characteristic | | Overall | Fall-related injury No | Yes | P-value[a] |
|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 72.3 (10.9) | 72.3 (11.0) | 72.1 (9.2) | 0.767 |
| Sex | Female | 54.4 | 53.9 | 64.6 | 0.004 |
| | Male | 45.6 | 46.1 | 35.4 | |
| Education (years) | Mean (SD) | 5.3 (9.4) | 5.3 (9.4) | 3.8 (8.0) | <0.001 |
| Wealth | Poorest | 21.3 | 21.2 | 21.8 | 0.959 |
| | Poorer | 21.0 | 21.0 | 20.8 | |
| | Middle | 20.5 | 20.4 | 20.9 | |
| | Richer | 17.5 | 17.4 | 18.6 | |
| | Richest | 19.8 | 19.9 | 17.9 | |
| Living arrangement | Not alone | 83.6 | 83.3 | 89.5 | 0.008 |
| | Alone | 16.4 | 16.7 | 10.5 | |
| Physical activity | High | 36.6 | 36.5 | 38.1 | 0.879 |
| | Moderate | 25.9 | 25.9 | 25.9 | |
| | Low | 37.5 | 37.6 | 36.0 | |
| Current drinker | No | 85.5 | 85.4 | 86.4 | 0.668 |
| | Yes | 14.5 | 14.6 | 13.6 | |
| Low handgrip strength | No | 39.3 | 39.9 | 26.7 | <0.001 |
| | Yes | 60.7 | 60.1 | 73.3 | |
| Obesity | No | 89.6 | 89.6 | 90.7 | 0.626 |
| | Yes | 10.4 | 10.4 | 9.3 | |
| Arthritis | No | 73.1 | 73.3 | 70.4 | 0.328 |
| | Yes | 26.9 | 26.7 | 29.6 | |
| Stroke | No | 95.8 | 95.9 | 93.6 | 0.046 |
| | Yes | 4.2 | 4.1 | 6.4 | |
| Diabetes | No | 91.6 | 91.7 | 89.9 | 0.283 |
| | Yes | 8.4 | 8.3 | 10.1 | |
| Angina | No | 76.2 | 76.3 | 75.9 | 0.925 |
| | Yes | 23.8 | 23.7 | 24.1 | |
| Depression | No | 94.5 | 94.8 | 88.0 | <0.001 |
| | Yes | 5.5 | 5.2 | 12.0 | |

Abbreviation: SD Standard deviation
Data are % unless otherwise stated.
[a] P-values were calculated by Chi-squared tests for categorical variables and Student's *t*-tests for continuous variables.

**Table 2** Association between mild cognitive impairment or covariates and fall-related injury (outcome) estimated by multivariable logistic regression

| | | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|
| Characteristic | | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| Mild cognitive impairment | Yes vs. No | 1.60** | [1.18,2.16] | 1.60** | [1.19,2.15] | 1.53** | [1.12,2.07] |
| Age (years) | | 1.00 | [0.98,1.02] | 1.01 | [0.98,1.03] | 1.00 | [0.98,1.03] |
| Sex | Male vs. Female | 0.57*** | [0.40,0.79] | 0.52*** | [0.36,0.75] | 0.54*** | [0.37,0.77] |
| Education (years) | | 0.99 | [0.95,1.03] | 0.99 | [0.95,1.03] | 0.99 | [0.95,1.03] |
| Wealth | Poorest | 1.00 | | 1.00 | | 1.00 | |
| | Poorer | 0.98 | [0.66,1.45] | 0.98 | [0.66,1.46] | 0.99 | [0.67,1.46] |
| | Middle | 1.03 | [0.64,1.66] | 1.04 | [0.65,1.67] | 1.05 | [0.65,1.69] |
| | Richer | 1.12 | [0.71,1.77] | 1.14 | [0.72,1.80] | 1.17 | [0.74,1.84] |
| | Richest | 0.90 | [0.57,1.43] | 0.92 | [0.58,1.46] | 0.91 | [0.57,1.45] |
| Lving arrangement | Alone vs. other | 0.69 | [0.46,1.03] | 0.69 | [0.46,1.04] | 0.67 | [0.45,1.00] |
| Physical activity | High | | | 1.00 | | 1.00 | |
| | Moderate | | | 0.90 | [0.62,1.30] | 0.84 | [0.58,1.22] |
| | Low | | | 0.89 | [0.60,1.31] | 0.82 | [0.56,1.20] |
| Current drinker | Yes vs. No | | | 1.40 | [0.95,2.07] | 1.47 | [1.00,2.16] |
| Low handgrip strength | Yes vs. No | | | | | 1.35* | [1.03,1.78] |
| Obesity | Yes vs. No | | | | | 1.60 | [0.97,2.61] |
| Arthritis | Yes vs. No | | | | | 1.18 | [0.86,1.62] |
| Stroke | Yes vs. No | | | | | 1.95** | [1.19,3.20] |
| Diabetes | Yes vs. No | | | | | 1.23 | [0.81,1.86] |
| Angina | Yes vs. No | | | | | 1.11 | [0.73,1.69] |
| Depression | Yes vs. No | | | | | 1.91* | [1.12,3.26] |

Abbreviation: OR Odds ratio; CI Confidence interval
Models are adjusted for all variables in the respective columns and country.
* p<0.05, ** p<0.01, *** p<0.001

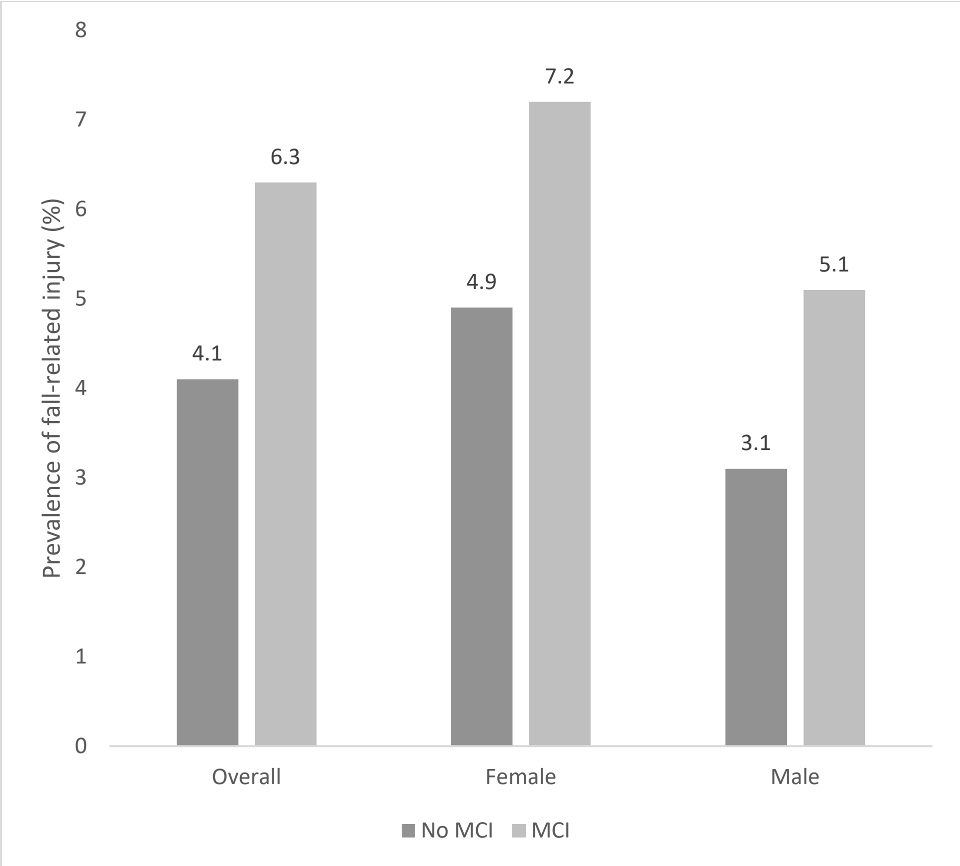


**Figure 1** Prevalence of fall-related injury by mild cognitive impairment status (overall and by sex)

Abbreviation: MCI Mild cognitive impairment