Gender differences in the association of cognitive impairment with the risk of hip fracture in the older population

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Abstract

Objectives

To test the hypothesis that differences by gender will be observed in the association of hip fracture risk with stages of cognitive impairment; and to explore the association between Petersen's "mild cognitive impairment" (MCI) and DSM-5 "mild neurocognitive disorder" (MND).

Study design

A community sample of 4803 individuals aged 55+ years was assessed in a two-phase case-finding enquiry in Zaragoza, Spain, and was followed up for 16 years. Medical and psychiatric history was collected with standardized instruments, including the Mini-Mental Status Examination (MMSE), Geriatric Mental State (GMS), History and Aetiology Schedule, and a Risk Factors Questionnaire.

The statistical analysis included calculations of Hazard Ratios (HR) in multivariate Cox proportional hazards regression models.

Main outcome measures

Identified cases of hip fracture, validated by blind researchers.

Results

In men, hip fracture risk was increased at the "mild" (HR = 4.99 (1.39–17.91)) and at the "severe" (HR = 9.31 (1.35–64.06)) stages of cognitive impairment, indicated by MMSE performance. In contrast, in women no association could be documented at the "mild stage" (power = 89%), and the association disappeared altogether at the "severe stage" in the final multivariate statistical model (power 100%). No association observed between hip fracture and mild cognitive impairment in both men (power = 28% for P-MCI) and women (power = 44% and 19% for Petersen's MCI and DSM-5 MND, respectively).

Conclusions

Increased hip fracture risk was associated with "mild" stages of cognitive impairment in men, but not in women. To explore the potential association with the construct MCI or MND, studies with greater statistical power would be required.

1. Introduction

Hip fractures are recognized to be an important public health problem in the elderly, as they are one of the main causes of morbidity, mortality and related health-care expenditures in the geriatric population of the western world [1]. The incidence of hip fracture is higher among women [1] and osteoporosis is considered to be the fundamental risk factor [2]. In relation to hip fracture, focused research on gender differences has been recommended to clarify the significance of epidemiological differences observed between men and women [3], and we have recently reported differences in risk factors: illiteracy and depression increased the risk of fractures in women, while tobacco and disability increased the risk in men [4].

Related to hip fracture and gender differences, conditions with important clinical implications in the elderly, such as cognitive impairment and dementia may also be of great interest, since epidemiological differences between men and women are also apparent: the incidence of dementia [5] and the rate of cognitive impairment [6], have been reported to be both higher in women. Cognitive difficulties increase the risk of falls [7] and the highest proportion of fractures in those aged 65 years or over result from a fall [8]. Furthermore, cognitive loss may play a role in the fragility of the bone in indirect ways [9], [10]. However, there is paucity of evidence on the association of hip fractures with cognitive difficulties [11], and the association with stages of cognitive impairment, and specifically with "mild" stages has not been studied. Staging models have been very successful in different medical diseases [12], and we have recently shown that the model may be applicable to cognitive impairment [13]. In case "mild" stages of cognitive impairment are associated with hip fracture risk the interest for early prevention or treatment would be apparent. Similarly, it is also timely to explore to what extent the construct "mild cognitive impairment" (MCI), which is widely considered to be a prodromal sign of neurodegeneration [14] but also a frailty sign [15], is associated with hip fracture risk.

In view of gender differences observed in the incidence of both hip fracture and cognitive impairment; in the risk factors of hip fracture; and in the rate of cognitive impairment, the aims of the present study are, first, to test the hypothesis that differences by gender will be observed in the association between stages of cognitive impairment, even in the "mild" stage, and an increased risk of hip fracture; and, second, to explore to what extent the construct MCI is also associated with an increased risk of hip fractures.

2. Methods

2.1. General design and study population

This study was designed during the Zaragoza Dementia and Depression (ZARADEMP) Project, and the general methods have previously been reported [5]. This Project was intended to document the incidence and risk factors of somatic and psychiatric diseases in the adult population aged ≥55 years, in a longitudinal, five-wave epidemiological enquiry. The sample was drawn from the eligible individuals in the Spanish official census lists, and included the institutionalized individuals. It was stratified with proportional allocation by age and sex. The refusal rate was 20.5%, and 4803 individuals were ultimately interviewed at baseline (wave I, starting in 1994). The Helsinki convention principles of written informed consent, privacy, and confidentiality have been maintained throughout the Project, and the Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved the study, according to Spanish Law.

The design of the study included a two-phase case finding. Validated, Spanish versions of international instruments were used, including the Mini-Mental Status Examination (MMSE) [16] (cognitive performance) and the Geriatric Mental State B (GMS-B), with its cognitive section and its Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) [17]. Other instruments were the History and Aetiology Schedule(HAS) (medical and psychiatric history data), disability scales (Katz's Index for basic activities of daily living (bADL's) and Lawton and Brody scale for instrumental (iADL's)), and the European Studies of Dementia (EURODEM) Risk Factors Questionnaire (medical conditions) [5]. In phase 2, the research psychiatrists reassessed all 'probable cases' of dementia identified in phase 1. They administered the same assessment instruments and performed a neurological examination and medical reports were also used to help in the diagnostic process, which was completed at the end of this phase. Dementia was diagnosed by the panel of research psychiatrists according to DSM-IV criteria. Clinically significant depression was defined as GMS-AGECAT level 3 or higher [5].

The main outcome for the present report was incident hip fractures in the study period (1994–2010).

2.2. Assessment of hip fracture

All incident hip fracture cases occurring during the study period were identified through the computerized inpatient register system in the hospitals of the health care area of Zaragoza. This register system was contrasted with the database, baseline sample of ZARADEMP Project. Two experienced, blinded and independent researchers (a general surgeon and an orthopedic/trauma surgeon) reviewed the medical records of all identified patients with hip fracture, and validated the hip fracture diagnosis, defined as follows: any fracture of the proximal femur, from the femoral head to 7 cm down the lesser trochanter. The assessment included the study of X-rays at the time of admission and discharge from hospital, and when necessary the discharge reports recorded in the medical history. Lower fractures, considered to be diaphyseal fractures, as well as pelvic, pubic or acetabular fracture cases were all excluded in this study. Other exclusion criteria were presence of high energy trauma, open fractures, non-osteoporotic pathologic fractures as malignancies or metastases, and a second hip fracture in the same patient. Non-osteoporotic fractures due to high energy trauma were identified through the computerized inpatient register by the "cause of admission", and those due to malignancies required a more systematic assessment. The participating researchers had been trained to identify four radiologic patterns suggesting malignancies: osteolytic lesions, cortical disruption, atypical fracture patterns (like reverted sub-throcanteric) and lesser trochanter avulsions.

2.3. Assessment of stages of cognitive decline

The validated, staging system of MMSE scores [13], was used to classify the subjects as: 'normal' (scores 30); 'questionable' (scores 26–29); 'mild' (scores 21–25); 'moderate' (scores 11–20) and 'severe' (scores 0–10).

The researchers reviewed all the information coming from the instruments used before individuals were classified as 'cases' or 'non-cases' of cognitive impairment. For this construct, both Petersen et al. [14] (MCI) and DSM-5 "mild neurocognitive disorder" (MND) criteria were used in view that they identify different populations of individuals with cognitive difficulties (see Fig. 1) [18]. The assessment and diagnosis of both was done blind to the results of the field work by a panel of research psychiatrists (and a psychologist), following a method previously reported [18]. The cognitive and ADL's items in the instrument used had been operationalized before to

conform to the criteria in both categories of impairment. Subjective cognitive impairment was assessed by the specific questions in the GMS.

2.4. Covariates

The following covariates, assessed at baseline and defined in a previous report [4] were included in the analysis: civil status; illiterate; smoking; alcohol intake; disability; body mass index (BMI), and clinically significant depression [19].

2.5. Data analysis

Baseline cognitive measures of the sample were described as frequencies and percentages except for MMSE score, presented as mean and standard deviation (SD). Analysis was done separately for men and women. The follow-up period was considered from baseline enrollment to the first one of the following events: first incident hip fracture (day of hospitalization) for cases; and time of death, last contact, or closing date for this study (December 31st, 2010) for non-cases.

Cox proportional hazards regression models were used to analyze associations between baseline cognitive measures and time to hip fracture during follow-up. All models were age-adjusted [20], and hazard Ratios (HR) with 95% confidence intervals (CI) were estimated. Subjects with no incident hip fracture were considered as censored at the last date when information on follow-up was assessed, or at their date of death, or loss to follow-up, whichever occurred first.

SPSS software v.22 (IBM Corp., 2013) was used for all the analysis; and Stata v.12 for power calculations.

3. Results

The sample inclusion procedure has been described previously [4]. A total of 4660 participants (1976 men and 2684 women) participated in this study, with a mean age of 73.4 years. In the 16-year follow-up, 50 men (2.5%) and 225 women (8.4%) suffered a hip fracture. Both men and women with hip fractures were significantly older and lived without a couple than their counterparts. No other significant differences were observed in the subgroup of men, but women having hip fractures, compared with those without, were more frequently illiterate, drinkers, had disability for iADL' and early menopause [4].

Cognitive measures at baseline showed that, compared with men, women had lower MMSE scores, were more frequently classified in the "mild", "moderate" and "severe" categories of MMSE, and had more frequently DSM-5 MND (Table 1).

Compared with their counterparts, both men and women having hip fractures had at baseline significantly lower scores in the MMSE (27.7 vs. 29.9, and 26.8 vs. 27.9, respectively) and were more frequently classified in the "mild" category of impairment in the staging model of the MMSE (34% vs. 15.2%, and 35.6% vs. 22%, respectively) (Table 2). Moreover, among women, the proportions in the "questionable" staging category (scores close to normality) were significantly lower for those with hip fracture compared with those without.

Referring to P-MCI in men, no statistically significant differences were found between those with hip fracture and those without (Table 2); and no cases of DSM-5 MND were observed in those with hip fracture. In women, no statistically significant differences in the proportions of P-MCI

cases were seen among those having hip fracture compared with their counterparts and a higher proportion of DSM-5 MND were detected in those with hip fracture (6.2% vs 3.9%), although the trend did not reach statistical significance (p = 0.105).

In the Cox proportional hazards regression analyses in men, after controlling for potential confounders, MMSE scores were associated with hip fracture (HR = 0.93 95%CI (0.89–0.97); p = 0.001). Similarly, associations were observed in those in the "mild stage" and in the "severe stage" categories of MMSE, the individuals being at 4.99 and 9.31 times higher risk of suffering a hip fracture, respectively. No association was observed in the 'moderate' category (power 88%) (Table 3).

On the contrary, in women, while MMSE score was associated with hip fracture in the age-adjusted model (HR = 0.96 95%CI (0.95–0.99); p = 0.002), it no longer remained associated when other confounders were included in the model (HR = 0.98 95%CI (0.95–1.01); p = 0.115, power = 3%). No associations were observed in the 'mild' or in the 'moderate' MMSE categories of staging (power 89% and 51% respectively), and the association in the severe staging category in the analysis adjusted only for age (HR = 3.02 (1.35–6.75, p = 0.007)), no longer remained significant in the multivariate regression analysis (power = 100%) (Table 4).

In relation to MCI, no association with hip fracture was observed in men nor in women in the Cox proportional hazards regression analyses (power = 28% for P-MCI in men; 44% and 19% for P-MCI and DSM-5 MND in women) (Table 3, Table 4).

4. Discussion

In support of the working hypothesis, this study documents differences by gender in the association between stages of cognitive impairment and an increased risk of hip fracture. Specifically, the association of both "mild" and "severe" stages of impairment in the MMSE system was confirmed in men, but not in women. Therefore, this study adds to the documentation of gender differences in the risk of hip fracture, as shown in a previous study [4], although the small number of men with hip fractures and the wide confidence intervals observed may limit the strength of the conclusion.

To our knowledge, Guo et al. [11] were the first authors to report the association of cognitive impairment and hip fracture risk, but their population was aged 75+ years. Moreover, our study is the first one to analyze independently the results in men and women, and the first one to utilize a validated staging system of cognitive impairment. Comparisons with other studies assessing hip fracture risk associated with cognitive impairment are also difficult. Explicitly, two studies reported the increased risk of hip fracture associated with specific cognitive areas rather than global performance, namely delayed recall [21] or time orientation and visual construction subdomains [22].

It is remarkable that men in the "mild" stage of cognitive impairment, compared with those with no impairment, had almost 5 times increased risk of hip fracture, and more than 9 times the ones in the "severe" stage of impairment. However, no significant increment in risk was observed in the "moderate" stage of impairment and, therefore, the gradient documented in this same sample in relation to dementia risk [13] was not observed here. Implicit in staging models of disease is the assumption that a gradual progression of the biological process underlies the progression of clinical symptoms of the disease [12]. While this model may be

applicable in relation to dementia risk [13], it may find more difficulties in pathologies such as hip fracture, where non-biological factors such as the individuals' behavior or the carers' supervision to avoid the individuals' falls may importantly influence the risk and accompany the underlying biological process, such as a progressive osteoporosis.

In relation to the second objective, the constructs MCI or MND, contrary to the "mild" stages of cognitive impairment, were not associated with an increased risk of hip fracture, even when using the DSM-5 category, which has been shown to capture more severe cases [18]. One potential explanation may be that the definition of the MCI construct implies criteria wider than the strict cognitive impairment (Table 1). However, no firm conclusions can be reached, since the study has very limited power to detect the association of either category with hip fracture risk. New studies with larger statistical power might be conducted to explore this association, because MCI is also thought to be a frailty sign [15]. Frailty states have been reported to be associated with falls [23], which often result in hip fractures [8]. Nevertheless, we have previously argued that there is still some way to go before the MCI is redefined in such a way as to better predict a negative outcome [24]. Several international initiatives are now trying to better characterize MCI [25].

Among the hypothesis to explain the association between cognitive impairment and hip fracture risk, aside from the most obvious one concerning the falls, a second, potential explanation relates to osteoporosis, characterized by low bone mineral density (BMD), which increases dramatically with age [2]. Both osteoporosis and cognitive impairment are highly prevalent conditions in elderly populations, and a bidirectional association could be conjectured: low BMD has been suggested to increase the risk of cognitive impairment [26]; and some studies have shown that cognitive impairment may affect bone density in indirect ways, by compromising feeding behavior and intake or by reducing the absorption of calcium [9], [10].

To explain the gender differences in risk documented in this study, some conjectures relate to the association between hip areal BMD and fracture risk, which may be stronger in men [27]. Moreover, the greater propensity among men to engage in risky behavior, which has also been suggested in older adults with fractures [28] might be an explanation for the difference with women. Finally, some studies show that women with MCI have greater longitudinal rates of cognitive and functional progression than men [6], the conjecture being that this might induce changes in the carers' attitudes to protect the women.

The results in this study add to the relevance of detecting mild stages of cognitive impairment, at least in men. Cognitive impairment as an index of ill-health [29] and of frailty [15] is receiving increasing attention in the medical and the public health literature. This study suggests the utility of a simple staging method of assessment based on the MMSE for the early prediction of the increased risk of hip fracture. Since cognitive impairment might have different sources [24], the detection is only the first step to initiate an adequate diagnostic and eventually a preventive or therapeutic intervention.

Among the advantages of this study is the 16-year follow-up of a large, representative population sample, including the institutionalized individuals. Xie et al. have recently underlined the relevance of this inclusion from the public health perspective [30]. Limitations in the sampling methods have been discussed in previous papers [4], including the fact that the diagnosis of both MCI and MND were applied retrospectively, using an algorithmic diagnostic method; and low power of some calculations impeded now to reach some firm conclusions.

Moreover, we cannot discard the possibility that factors uncontrolled in this study, such as the use of psychotropic medication might modify the results. Specifically, we did not have an adequate register of osteoporosis treatment, but antiresorptive medication was not widely used in our region at the time of the cross-sectional study.

In conclusion, this study supports the hypothesis that differences by gender are observed in the association between stages of cognitive impairment and hip fracture risk. No gradient of increased risk could be documented in parallel with the severity stages of impairment, but particular interest has the association documented in 'mild' stages, because of the potential implications for prevention or early treatment. The construct MCI was not associated with hip fracture risk, but new studies are needed before firm conclusions may be reached.

Contributors

Elena Lobo participated in the study design, analysis and interpretation of data and drafting the article. Guillermo Marcos participated in the study conception and design, acquisition, analysis and interpretation of data and revising critically the article for important intellectual content. Javier Santabárbara participated in the interpretation of data and revising critically the article for important intellectual content. Luis Lobo-Escolar participated in the acquisition of data and revising the article. Helena Salvador-Rosés participated in the acquisition of data and revising the article. Concepción De la Cámara participated in the study conception, in the acquisition and interpretation of data and critically revising the article. Raúl López-Antón participated in the interpretation of data and revising the article. Patricia Gracia-García participated in the interpretation of data and revising the article. Antonio Lobo-Escolar participated in the study conception and design, acquisition of data and critically revising the article for important intellectual content. The following members of the ZARADEMP Workgroup contributed to this paper: Pedro Saz, Tirso Ventura, Miguel Angel Quintanilla, José Luis Día, Antonio Campayo, Francisco Roy, José Angel Montañés, Sergio Aznar, Antonio Lobo. All authors saw and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The Helsinki Convention principles of written informed consent, privacy, and confidentiality have been maintained throughout the Project, and the Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved this study, according to Spanish law.

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Fig. 1. Diagnostic criteria for mild cognitive impairment (MCI) used in the study.

Petersen's MCI criteria (2)	DSM-5 MND criteria (5)
(A) Subjective complaint of decline in memory on self- or informant report	(A.1) Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and (A.2) A modest impairment in cognitive performance, documented by standardized cognitive assessment
(B) Isolated memory impairment on neuropsychological testing (below the standard threshold point)	(B) The cognitive deficits do not interfere with capacity for independence in everyday activities (as measured by ADL scales), but greater effort, compensatory strategies, or accommodation may be required
(C) Intact daily functioning in ADL scales	(C) The cognitive deficits do not occur exclusively in the context of a delirium
(D) Not meeting criteria for a diagnosis of dementia	(D) The cognitive deficits are not better explained by another mental disorder (specifically: psychosis and severe depression)

MCI: Mild cognitive impairment; MND: Mild neurocognitive disorder. ADL: activities of daily living

Table 1. Baseline characteristics and cognitive measures for the total sample and for men and women participants.

	Global (N = 4660) n (%)	**Men (N = 1976) n (%)**	**Women (N = 2684) n (%)**	***p-value***
MMSE, mean (SD)	29.6 (4.6)	29.9 (5.6)	27.9 (6.9)	<0.001*
Staging MMSE:				
Normal (score 30)	594 (12.7)	301 (15.2)	293 (10.9)	*<0.001*
Questionable (scores 26–29)	2629 (56.4)	1230 (62.2)	1399 (52.1)	*<0.001*
Mild (scores 21–25)	931 (20)	309 (15.6)	622 (23.2)	*<0.001*
Moderate (scores 11–20)	355 (7.6)	92 (4.7)	263 (9.8)	*<0.001*
Severe (scores 0–10)	151 (3.2)	44 (2.2)	107 (4)	*0.001*
MCI-P	316 (7.1)	122 (6.4)	194 (7.7)	*0.090*
DSM-5 MND	149 (3.3)	46 (2.4)	103 (4.1)	*0.002*

MMSE: Mini-mental Status Examination. MCI-P: Petersen's Mild Cognitive Impairment. DSM-5 MND: DSM-5 mild neurocognitive disorder. *U-Mann-Whitney.

Table 2. Cognitive measures in men and women with and without hip fracture during follow-up.

Men			**Women**			
	No hip fracture (n = 1926)	**Hip fracture (n = 50)**	***p-value***	**No hip fracture (n = 2459)**	**Hip Fracture (n = 225)**	***p-value***
MMSE mean(SD)	29.9 (5.6)	27.7 (5.6)	<0.001*	27.9 (6.9)	26.8 (6.7)	0.001*
Staging MMSE						
Normal (score 30)	298 (15.5)	3 (6)	*0.066*	275 (11.2)	18 (8)	*0.143*
Questionable (scores 26–29)	1204 (62.5)	26 (52)	*0.130*	1308 (53.2)	91 (40.4)	*<0.001*
Mild (scores 21–25)	292 (15.2)	17 (34)	*<0.001*	542 (22)	80 (35.6)	*<0.001*
Moderate (scores 11–20)	90 (4.7)	2 (4)	*0.824*	238 (9.7)	25 (11.1)	*0. 489*
Severe (scores 0–10)	42 (2.2)	2 (4)	*0.389*	96 (3.9)	11 (4.9)	*0.470*
MCI-P	120 (6.4)	2 (4.2)	*0.530*	175 (7.5)	19 (9)	*0.433*
DSM-5 MND	46 (2.5)	0	*0.272*	90 (3.9)	13 (6.2)	*0.105*

MMSE: Mini-mental Status Examination. MCI-P: Petersen's Mild Cognitive Impairment. DSM-5 MND: DSM-5 mild neurocognitive disorder. *U-Mann Whitney.

Table 3. Cognitive measures as risk factors for hip fracture in men.

	Model 1		**Model 2**	
	HR (95% CI)	***p-value***	**HR (95% CI)**	***p-value***
MMSE	0.93 (0.89–0.97)	*<0.001*	0.93 (0.89–0.97)	*0.001*
MMSE Staging:				
Normal (score 30)	1		1	
Questionable (scores 26–29)	1.87 (0.56–6.25)	*0.307*	1.88 (0.56–6.28)	*0.306*
Mild (scores 21–25)	5.18 (1.46–18.42)	*0.011*	4.99 (1.39–17.91)	*0.014*
Moderate (scores 11–20)	2.52 (0.4–15.81)	*0.323*	2.51 (0.39–16.43)	*0.336*
Severe (scores 0–10)	11.20 (1.74–71.9)	*0.011*	9.31 (1.35–64.06)	*0.023*
MCI-P	0.66 (0.16–2.71)	*0.561*	0.61 (0.15–2.56)	*0.500*
DSM-5 MND	–		–	

MMSE: Mini-mental Status Examination. MCI-P: Petersen's Mild Cognitive Impairment. DSM-5 MND: DSM-5 mild neurocognitive disorder. Model 1: age* adjusted. Model 2: adjusted for age*, illiterate, coupled♠◊, alcohol, tobacco$♠◊, under and overweight, obesity, bADL$♠◊, depression ($p < 0.05$: * in all models; $in MMSE; ♠ in Staging; ◊in MCI-P). HR: Hazard Ratio (95% Confidence Interval).

Table 4. Cognitive measures as risk factors for hip fracture in women.

	Model 1		**Model 2**	
	HR (95% CI)	***p-value***	**HR (95% CI)**	***p-value***
MMSE	0.96 (0.95–0.99)	*0.002*	0.98 (0.95–1.01)	*0.115*
MMSE Staging:				
Normal (score 30)	1		1	
Questionable (scores 26–29)	0.89 (0.53–1.47)	*0.639*	0.88 (0.52–1.48)	*0.625*
Mild (scores 21–25)	1.54 (0.9–2.62)	*0.114*	1.37 (0.79–2.4)	*0.263*
Moderate (scores 11–20)	1.31 (0.69–2.48)	*0.412*	1.03 (0.5–2.12)	*0.942*
Severe (scores 0–10)	3.02 (1.35–6.75)	*0.007*	2.81 (0.91–8.62)	*0.071*
P-MCI	1.30 (0.81–2.09)	*0.278*	1.19 (0.72–1.98)	*0.495*
DSM-5 MND	1.17 (0.66–2.07)	*0.593*	1.1 (0.6–2.02)”	*0.760*

MMSE: Mini-mental Status Examination. MCI-P: Petersen’s Mild Cognitive Impairment. DSM-5 MND: DSM-5 mild neurocognitive disorder. Model 1: age* adjusted. Model 2: adjusted for age*, illiterate◊†, coupled*, alcohol, tobacco, under and overweight, obesity, bADL, depression◊†, early menopause in women. ”:bADL excluded from the model ($p < 0.05$: * in all models; $in MMSE; ♠ in Staging; ◊in MCI-P; †in MCI-DSM-5 MND). HR: Hazard Ratio (95% Confidence Interval).