Highlights

- The incidence rate (IR) of hip fracture among women was three times higher than in men.
- In a population in which 10% of the women were illiterate, illiteracy independently increased the risk of hip fracture in women by 55%.
- Clinically significant, treatable depression independently increased the risk of hip fracture in women, smoking and disability increased the risk in men, and dementia did not increase the risk in either gender.

Gender differences in the incidence of and risk factors for hip fracture: a 16-year longitudinal study in a southern European population

Elena Lobo[a, b, c](corresponding), Guillermo Marcos[a,b, c, d], Javier Santabárbara[a, b, c], Helena Salvador-Rosés[e], Luis Lobo-Escolar[f], Concepción De la Cámara[b, c, g, h], Alberto Aso[i], Antonio Lobo-Escolar[j] and the ZARADEMP Workgroup*.

[a] Departamento de Medicina Preventiva y Salud Pública, Universidad de Zaragoza, C/Domingo Miral s/n, 50009 Zaragoza.

[b] Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Zaragoza, Spain.

[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, Spain.

[d] Servicio de Archivos. Hospital Clínico Universitario. Avda. San Juan Bosco 15. 50009 Zaragoza, Spain.

[e] Servicio de Cirugía Digestiva. Dr. Josep Trueta University Hospital. Avda. de França s/n. 17007 Girona, Spain.

[f] Servicio de Ortopedia y Traumatología. Asepeyo Sant Cugat Hospital. Av. Alcalde Barnils, 54-60, 08174 Sant Cugat del Vallés, Barcelona, Spain.

[g] Servicio de Psiquiatría. Hospital Clínico Universitario. Avda. San Juan Bosco 15. 50009 Zaragoza, Spain.

[h] Departamento de Psiquiatría. Universidad de Zaragoza, C/Domingo Miral s/n, 50009 Zaragoza, Spain.

[i] Servicio de Traumatología y Cirugía Ortopédica. Hospital General de la Defensa. Vía Ibérica, 1. 50009 Zaragoza. Spain.

[j] Servicio de Cirugía Ortopédica y Traumatológica. Hospital San Jorge. Avda. Martínez de Velasco 36. 22004, Huesca. Spain

*ZARADEMP Group (collaborators): Pedro Saz, Tirso Ventura, Miguel Angel Quintanilla, José Luis Día, Antonio Campayo, Raúl López-Antón, Patricia Gracia-García, Francisco Roy, José Angel Montañés, Sergio Aznar, Antonio Lobo.

Corresponding author: Elena Lobo. Preventive Medicine and Public Health Department. University of Zaragoza. C/Domingo Miral s/n, 50009 Zaragoza, Spain. Tel. +34976761761; email: elobo@unizar.es

ABSTRACT

Objectives

To analyze independently in men and women the incidence rate of and risk factors for hip fracture in a southern European population. Illiteracy, dementia, clinically significant depression and disability were factors to receive special emphasis.

Study design

A community sample of 4,803 individuals aged over 55 years was assessed in a two-phase case-finding study in Zaragoza, Spain, and was followed up for 16 years. Medical history and psychiatric history were collected with standardized instruments, including the History and Aetiology Schedule, the Geriatric Mental State (GMS) scale, and a Risk Factors Questionnaire. Operational criteria were used to define covariates, including diagnostic criteria for both dementia and depression.

The statistical analysis included calculations of *incidence rate, IR; women/men* incidence rate ratio (IRR); and Hazard Ratios (HR) in multivariate Cox proportional hazards regression models.

Main outcome measures

Cases of hip fracture (International Classification of Diseases, WHO) identified in the treating hospitals, validated by blinded researchers.

Results

Hip fractures were more frequent among women than men (IRR=3.1). Illiteracy (HR= 1.55) and depression (HR= 1.44) increased the risk in women, and smoking (HR= 2.13) and disability in basic activities of daily living (HR= 3.14) increased the risk in men. Dementia was associated with an increased risk in univariate analysis, but the association disappeared (power= 85% in men, 95% in women) when disability was included in the multivariate models.

Conclusions

The IR of hip fractures was three times higher among women. Illiteracy and clinically significant depression among women and active smoking and disability (HR= 3.14) among men independently increased the risk, but dementia did not.

Keywords: Hip fracture, risk factors, gender, disability, dementia, depression

Abbreviations: HAS: History and Aetiology Schedule; GMS: Geriatric Mental State; DSM-IV: Diagnostic and Statistical Manual, 4th edition; AGECAT: Automated Geriatric Examination for Computer Assisted Taxonomy; HR: Hazard Ratio; WHO: World Health Organization; IRR: Incidence Rate Ratio; bADL's: basic Activities of Daily Living; iADL's: instrumental Activities of Daily Living; ZARADEMP: Zaragoza Dementia and Depression Project.

1. Introduction

Hip fractures are a major public health concern, particularly among the older individuals, because of the high incidence and negative implications reported [1]. While recent studies suggest a rupture in the expected increase trend on the incidence of this pathology [2], hip fractures, similarly to other fractures continue to augment in absolute numbers due to the increased life expectancy and therefore some authors describe 'a worldwide epidemic'[3]. Nevertheless, wide differences in the incidence rate of hip fracture by sex and age have been reported in different countries [4], suggesting the need of new studies to document region-specific rates and to detect specific environmental risk factors to support clinical programs and preventive actions.

A considerable number of factors has been considered to increase the risk of hip fractures [5]. Still, controversies persist as to the specific weight of individual factors such as gender or low educational background [6]. Furthermore, while previous studies suggest that factors leading to a hip fracture might differ between men and women in an important way, only few studies have analysed the risks independently [7] . In relation to educational level, in a country such as Spain this might be "the last opportunity" to study the influence of illiteracy, which was very frequent in the older generations until recently, particularly among women [8]. Controversy also persists as to the role of potentially preventable risk factors with strong environmental influence, including life styles such as tobacco or alcohol use or diet-related disturbances[9][10]; or to the potential risk associated with conditions with important clinical implications in the elderly, such as dementia [11] and depression [12]. New methods seem now appropriate to clarify the potential risk associated with these conditions, such as the study of clinically significant, treatable depression, since previous studies only used questionnaires and scales to measure symptoms [12]. Moreover, most of these studies on dementia or depression did not control simultaneously for disability, which is strongly associated with both conditions in the elderly [13] and has also been reported to be an independent risk factor of hip fractures [5][14].

The present study aims to document separately in men and women the incidence rate and relevant risk factors of hip fracture in a Southern European population. Risks associated with illiteracy, dementia, clinically significant depression and dependency receive special emphasis.

2. Methods

2.1. General Design and Study Population

The sample for the present study was drawn from the Zaragoza Dementia and Depression (ZARADEMP) Project [15], a longitudinal, five-wave epidemiological enquiry, intended to document in this typical, large city in Spain the incidence and risk factors of somatic and psychiatric diseases in the adult population aged ≥55 years . A random sample of community dwelling people, stratified with proportional allocation by age and sex, was drawn from the eligible individuals in the Spanish official census lists. The refusal rate was 20.5%, and 4,803 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 this study, according to Spanish Law.

A two-phase, case finding design was implemented, the main outcome for this report being incident hip fractures in the study period (1994-2010). In phase 1, lay interviewers (trained, senior medical students) conducted interviews and assessments in the participants' homes, and institutionalized subjects were assessed in their place of residence. Standardized, Spanish versions of instruments were used throughout, including the following:

-History and Aetiology Schedule (HAS) [16], a standardized method to collect medical and psychiatric history data from a caregiver or directly from the respondent when he or she is judged to be reliable;

-Geriatric Mental State B (GMS-B) [17], a semi-structured standardized clinical interview incorporating Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT), a set of computer algorithms to analyze the GMS data resulting in a psychiatric diagnosis [18].

-Lawton and Brody scale [19] and Katz's Index [20], to assess instrumental (iADL's) and basic activities of daily living (bADL's), respectively.

-The European Studies of Dementia (EURODEM) Risk Factors Questionnaire, to collect information on medical conditions considered to be risk factors of dementia [21].

The individuals were nominated as "probable cases" of dementia or depression on the basis of threshold scores in the screening instruments, which we previously reported to have good validity coefficients [18]. The threshold points were decided on the bases of adequate negative predictive power.

In phase 2, the research psychiatrists reassessed all 'probable cases' 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. Additional details about the project's design and objectives have been published previously [15].

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 and were computed according to the norms in the International Classification of Diseases (Ninth Revision, ICD-9; code 820). This register covers all public hospitals in the area, three health sectors with 700.000 inhabitants. It was postulated that the number of residents living within the study area that had fractured and were treated outside the city was negligible. Two experienced, blinded and independent researchers reviewed the medical records and validated the hip fracture diagnosis. 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.

2.3. Covariates

Among potential risk factors assessed at baseline, the following variables were dichotomized: civil status (married/with couple or single/separated/widowed), Illiterate (able or unable to read and write), Smoking (currently smoking or not smoking), Alcohol intake (active drinkers or non-drinkers). Disability or no-disability (based on iADL's and bADL's scores). Body Mass Index (BMI, WHO International Classification) was categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and obesity (≥30.0 kg/m^2). 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, the confidence proven valid for detecting cases of depression that require clinical attention in community samples and are valid in concordance with DSM-IV diagnosis [22].

2.4 Data analysis

Baseline characteristics of the sample were described as frequencies and percentages except for age at recruitment, presented as mean and standard deviation (SD). Analysis was done separately for men and women. Age and sex-specific incidence was calculated per 5-year band. *Hip fracture incidence rate (IR)* was calculated as the number of incident hip fractures per 100,000 person-years at risk during the study period. The follow-up period was considered from baseline enrollment to the first 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. The incidence rate ratio (IRR) with 95% confidence intervals (CI) was used to compare IR'S in men and women, globally and for each age band.

Cox proportional hazards regression models were used to analyze associations between baseline characteristics and time to hip fracture during follow-up. 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 was used for power calculations.

3. Results

Out of the baseline participants, 143 (2.9%) were excluded because of incomplete information in the hospital's registry. No differences by gender, civil status, smoking habits, menopause, BMI or physical diseases were observed in dropouts compared with the 4,660 participants. However, the individuals excluded were 1.5 years older and more likely to be illiterate (12.9%), disabled (Instrumental iADL's = 29.8%; Basic bADL's = 21.8%) and to be diagnosed of dementia (9.8%).

Participants had a mean age of 73.4 years, and were more frequently women and married/with couple. There were 7.5% of illiterates; 13% of smokers; 12.4% of subjects drinking alcohol at the time of the interview; 40.4% had overweight and 23.2% had obesity. At baseline, 11.5% of subjects had been diagnosed of clinically relevant depression; 4.5% of dementia and 12.6% were dependent in basic and 20.8% in instrumental ADL's (Table 1).

Among the women, and compared with men, the proportion of illiterates (10.1% vs. 4.2%), individuals with disability for both bADL' (14.2% vs. 10.2%) and iADL's (24.9% vs. 15%) and those diagnosed of both depression (16.1% vs. 5.3%) and dementia (5.7% vs. 2.8%) were all significantly higher ($p<0.001$ for all). On the contrary, the proportion of active smokers (2.8% vs. 26.8%) or drinkers (4.6% vs. 23.2%) was significantly lower ($p<0.001$ for both)(Table 1).

During the 16-year follow-up, the proportion of women suffering a hip fracture (8.4%) was significantly higher than among men (2.5%) ($p<0.001$) (Table 2). An exponential increase in the incidence rate with age was observed in both genders, from 239.5 (women) and 0 (men) per 100,000 person-years in the ≥59 year age group to 3,247.6 (women) and 1,697.7 (men) per 100,000 person-years in the 90+ year age group (Fig. 1). An abrupt increase in the IR is observed in men starting at age 80 years, in contrast with women, where the curve is

smoother and the slope becomes steeper at age 70 (fig 1). The female:male hip fracture incidence rate ratio (IRR) also increased with age, peaking at the 80-84 years category (IRR: 3.9; 95%CI 1.6-1.2). The differences by gender were statistically significant in the age strata 75-89 years and in the global analysis (IRR =3.1 (95%CI 2.3-4.2).

Compared with their counterparts, both men and women having hip fractures were older, and were less frequently living with couple, the differences being statistically significant (table 2). Besides, compared with their counterparts, women having hip fractures were more frequently illiterate, drinkers, had disability for iADL' and early menopause, all the differences being similarly statistically significant. Depression and dementia were more frequently diagnosed in both men and women with hip fractures, but the differences did not reach statistical significance (table 2).

In the multivariate, Cox proportional hazards regression analyses, after controlling for potential confounders, the hip fracture risk in men increased significantly by age (HR= 1.13) , active smoking (HR= 2.13) and particularly by disability for bADL's (HR=3.15). A different profile was observed for women: age (HR= 1.12), but also illiteracy (HR=1.57); and depression (HR=1.45) all increased significantly the risk. On the contrary, in both men and women, being married/with couple significantly decreased the risk of hip fracture. Dementia was associated with an increased risk in univariate analysis, the association disappearing (power= 85% in men, 95% in women) when disability was included in the multivariate models (table 3).

4. Discussion

We have confirmed in a Southern European city the heavy burden posed by hip fractures in the older population, since 268 and 830 per 100,000 men and women (respectively) aged 55 or more years may suffer a hip fracture each year, the IR increasing by age in a linear way. In support of the emphasis given in this research to the analysis by gender, important differences were observed: first, compared with men, the IRR was more than three times higher in women (IRR=3.1), also indicating a statistically significant higher speed of having a hip fracture; and second, tobacco use and disability for bADL's increased the risk specifically in men, but illiteracy and depression increased the risk specifically in women.

Contrary to most previous reports in the population [11], dementia was not associated with risk fracture in this particular study. However, first, most previous studies are related to AD [23], but we studied global dementia, which includes a considerable proportion of vascular and other dementias. And second, previous studies did not control for clinically significant depression or disability for bADL's, as we did. It is also noticeable that disability for bADL's was

shown to increase more than three times (HR= 3.14) the risk of fractures in men, even after controlling for both dementia and clinically significant depression. Disability is common in both conditions [13], but this finding suggests that independent of the clinical diagnosis of either, disability for bADL's merits special clinical consideration in men in relation to the prevention of hip fracture.

The IR of hip fracture documented here is similar to rates recently observed in the same Zaragoza region [24]. This region was among the areas with intermediate IR rates in Spain. However between-region differences observed in this country might support the observation of Kanis et al [4] about important, between-country differences, that cannot be explained by the often multiple sources of error in the ascertainment of cases or the catchment population. Although different environmental factors have been considered to explain the geographical variation [25], methodological differences between-studies make comparisons difficult.

This study shows that the risk of hip fracture increases with age, more than 10% per year in both genders. This positive association was expected, since it has unanimously been reported [5], and previous studies have discussed in length potential mechanisms that may help in explaining causal mechanisms, such as the osteoporosis inevitably linked with the old age [26]. The increased risk of hip fractures in women in respect to men (IRR= 3.1) was likewise expected, since it has been reported in different cultures[27], and previous studies have analysed the relevance of non-environmental factors to explain this cross-cultural unanimity[27]. This female to male ratio is similar to rates recently reported in Spain (IRR= 3.2), but lower than those observed in previous years in the same study, suggesting a trend for a decreased IR of hip fracture in women [28].

We believe the finding that illiteracy increased the hip fracture risk specifically in women (by 55%) is quite relevant. We have previously shown in this same population that the life-time risk of Alzheimer's disease is more than twice higher among the illiterate, particularly among women [15]. Therefore, this report offers new evidence about the negative health outcome associated with low educational background. Illiterate individuals may be exposed to a number of derived risk factors [8]. Therefore, the preventive implications of these findings are apparent. Indeed, we show in this population born in the first half of the past century that illiteracy is more than double in women than in men. Fortunately, the educational level has improved dramatically in Spain in the last decades [29] and this study may be one of the "last opportunities" to study the influence of low educational level in this country, but the findings may stimulate similar research in other cultures.

In coincidence with some previous reports, being married/with couple decreased the risk of hip fracture in both genders, the decrease being approximately half in men, suggesting that

undetermined social factors may be at play [6]. In relation to life style factors, while some of them were associated with increased risk of fractures in the univariate analysis (alcohol consumption and underweight in women), in the final, multivariate model the association remained statistically significant only among men smokers. The literature about these factors remains also controversial and more detailed designs, considering elements such as the amount and duration of consumption or the differences between consumers and ex-consumers might be needed to gain insight in this subject, as suggested in a previous study [30].

More relevance may have the increased risk of hip fractures found in women with clinically significant depression. In a context of some disagreement about the association depression/hip fracture, a systematic review concluded that the association was positive [12]. However, out of the 14 studies reviewed, only three were specifically related to the association of depression and hip fracture risk and all of them used questionnaires or scales of depressive symptoms, rather than diagnostic categories. Our method to assess depression has been documented to identify cases that would be treated by clinical psychiatrists [22], the practical implications being obvious, particularly in view that a high proportion of the elderly depressed in the community go undetected/untreated [18].

Some statistical differences between participants and drop-outs were observed, but in view of the proportion of the latter (3%), we trust the influence in the main results would be minimal. We cannot discard the possibility that factors uncontrolled in this study, such as the use of antidepressants might modify the results. Similarly, the presence of physical morbidity could modify the results. However, a 'sensitivity analysis' shows that including in the multivariate models a general physical morbidity variable (HAS criteria), the main results are not modified substantially. Both in men and women the associations with risk factors (observed in table 3) were maintained. For men, the HR's for age, coupled, active smoking and basic ADL's were 1.12 (1.08-1.17); 0.51 (0.27-0.95); 2.11 (1.1-4.4); 3.34 (1.36-8.19), respectively. In women, the HR's for age, coupled, illiteracy and depression were 1.12 (1.09-1.14); 0.68 (0.48-0.96); 1.55 (1.02-2.35); 1.44 (1.01-2.06), respectively.

In conclusion, this study confirms the high incidence of hip fractures in the older population and the derived, potential burden for individuals and the society. The IR of hip fractures was three times higher among women and substantial differences by gender were observed: illiteracy and clinically significant depression among women and active smoking and disability among men independently increased the risk. These data have implications, both clinical and preventive.

Contributors

EL participated in the design, analysis and interpretation of data and drafting the article.

GM participated in the conception and design of the study, acquisition, analysis and interpretation of data and critically revising the article for important intellectual content.

JS participated in the analysis and interpretation of data and critically revising the article for important intellectual content.

HS-R participated in the acquisition of data and revising the article.

LL-E participated in the acquisition of data and revising the article.

CDIC participated in the conception of the study, in the acquisition and interpretation of data and critically revising the article.

AA participated in the acquisition of data and revising the article.

AL-E participated in the conception and design of the study, acquisition of data and critically revising the article for important intellectual content.

All authors saw and approved the final version of the manuscript.

The following members of the ZARADEMP Workgroup contributed to this paper: Pedro Saz, Tirso Ventura, Miguel Angel Quintanilla, José Luis Día, Antonio Campayo, Raúl López-Antón, Patricia Gracia-García, Francisco Roy, José Angel Montañés, Sergio Aznar, Antonio Lobo.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This work was supported by the Fondo de Investigación Sanitaria (FIS), Spanish Health Ministry [94-1562, 97-1321E, 98-0103; 01-0255 and PI10-01132] and by Gobierno de Aragón [B35-Grupo Consolidado Biomedicina] and Fondo Social Europeo. The funding sources had no involvement in the study or article preparation.

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 Investigacio´n Sanitaria (FIS) approved this study, according to Spanish Law.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

We are grateful to all subjects who took part in this study and to the medical students who administered the interviews in phase 1.

6. References

[1] C. Klop, P.M.J. Welsing, H.G.M. Leufkens, P.J.M. Elders, J.A. Overbeek, J.P. Van Den Bergh, J.W.J. Bijlsma, F. De Vries, The Epidemiology of Hip and Major Osteoporotic Fractures in a Dutch Population of Community-Dwelling Elderly: Implications for the Dutch FRAX ® Algorithm, PLoS One. 10 (2015). doi:10.1371/journal.pone.0143800.

[2] K. Briot, M. Maravic, C. Roux, Changes in number and incidence of hip fractures over 12years in France, Bone. 81 (2015) 131–137. doi:10.1016/j.bone.2015.07.009.

[3] A. Odén, E. V McCloskey, J.A. Kanis, N.C. Harvey, H. Johansson, Burden of high fracture probability worldwide: secular increases 2010-2040., Osteoporos. Int. 26 (2015) 2243–8. doi:10.1007/s00198-015-3154-6.

[4] J.A. Kanis, A. Odén, E. V. McCloskey, H. Johansson, D.A. Wahl, C. Cooper, A systematic review of hip fracture incidence and probability of fracture worldwide, Osteoporos. Int. 23 (2012) 2239–2256. doi:10.1007/s00198-012-1964-3.

[5] P. Pisani, M.D. Renna, F. Conversano, E. Casciaro, M. Di Paola, E. Quarta, M. Muratore, S. Casciaro, Major osteoporotic fragility fractures: Risk factor updates and societal impact., World J. Orthop. 7 (2016) 171–81. doi:10.5312/wjo.v7.i3.171.

[6] V. Benetou, P. Orfanos, D. Feskanich, K. Micha??lsson, U. Pettersson-Kymmer, L.A. Ahmed, A. Peasey, A. Wolk, H. Brenner, M. Bobak, T. Wilsgaard, B. Sch??ttker, K.U. Saum, A. Bellavia, F. Grodstein, E. Klinaki, E. Valanou, E.M. Papatesta, P. Boffetta, A. Trichopoulou, Education, marital status, and risk of hip fractures in older men and women: the CHANCES project, Osteoporos. Int. 26 (2015) 1733–1746. doi:10.1007/s00198-015-3054-9.

[7] J.C. Prior, L. Langsetmo, B.C. Lentle, C. Berger, D. Goltzman, C.S. Kovacs, S.M. Kaiser, J.D. Adachi, A. Papaioannou, T. Anastassiades, T. Towheed, R.G. Josse, J.P. Brown, W.D. Leslie, N. Kreiger, A. Tenenhouse, S. Poliquin, S. Godmaire, S. Dumont, B. Lentle, L. Mailloux, D. Bastien, L. Robertson, C. Joyce, C. Kovacs, E. Sheppard, S. Kirkland, S. Kaiser, B. Stanfield, L. Bessette, M. Gendreau, W. Hopman, K. Rees-Milton, R. Josse, S. Jamal, A.M. Cheung, B. Gardner-Bray, L. Pickard, P. Wojciech, Olszynski, K.S. Davison, J. Thingvold, D.A. Hanley, S. Boyd, J. Allan, M. Patel, Y.M. Vigna, N. Andjelic, ElhamRahme, B. Richards, S. Morin, S. Jackson, Ten-year incident osteoporosis-related fractures in the population-based Canadian Multicentre Osteoporosis Study - Comparing site and age-specific risks in women and men, Bone. 71 (2015) 237–243. doi:10.1016/j.bone.2014.10.026.

[8] A. Solé-Auró, M. Alcañiz, Educational attainment, gender and health inequalities among older adults in Catalonia (Spain), Int. J. Equity Health. 15 (2016) 126. doi:10.1186/s12939-016-0414-9.

[9] A.H. Pripp, O.E. Dahl, The population attributable risk of nutrition and lifestyle on hip fractures, HIP Int. 25 (2015) 277–281. doi:10.5301/hipint.5000229.

[10] A. Herrera, J. Mateo, J. Gil-Albarova, A. Lobo-Escolar, J.M. Artigas, F. L??pez-Prats, M. Mesa, E. Ibarz, L. Gracia, Prevalence of osteoporotic vertebral fracture in Spanish women over age 45, Maturitas. 80 (2015) 288–295. doi:10.1016/j.maturitas.2014.12.004.

[11] H.-K. Wang, C.-M. Hung, S.-H. Lin, Y.-C. Tai, K. Lu, P.-C. Liliang, C.-W. Lin, Y.-C. Lee, P.-H. Fang, L.-C. Chang, Y.-C. Li, Increased risk of hip fractures in patients with dementia: a nationwide population-based study., BMC Neurol. 14 (2014) 175. doi:10.1186/s12883-014-0175-2.

[12] Q. Wu, J. Liu, J.F. Gallegos-Orozco, J.G. Hentz, Depression, fracture risk, and bone loss: a meta-analysis of cohort studies., Osteoporos. Int. 21 (2010) 1627–35. doi:10.1007/s00198-010-1181-x.

[13] D.N. Kiosses, G.S. Alexopoulos, IADL functions, cognitive deficits, and severity of depression: a preliminary study., Am. J. Geriatr. Psychiatry. 13 (2005) 244–249. doi:10.1176/appi.ajgp.13.3.244.

[14] M. Kärkkäinen, T. Rikkonen, H. Kröger, J. Sirola, M. Tuppurainen, K. Salovaara, J. Arokoski, J. Jurvelin, R. Honkanen, E. Alhava, Association between functional capacity tests and fractures: an eight-year prospective population-based cohort study., Osteoporos. Int. 19 (2008) 1203–10. doi:10.1007/s00198-008-0561-y.

[15] A. Lobo, R. Lopez-Anton, J. Santab??rbara, C. de-la-C??mara, T. Ventura, M.A. Quintanilla, J.F. Roy, A.J. Campayo, E. Lobo, T. Palomo, R. Rodriguez-Jimenez, P. Saz, G. Marcos, Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population, Acta Psychiatr. Scand. 124 (2011) 372–383. doi:10.1111/j.1600-0447.2011.01754.x.

[16] M.E. Dewey, J.R.M. Copeland, Diagnosis of dementia from the history and aetiology schedule, Int. J. Geriatr. Psychiatry. 16 (2001) 912–917. doi:10.1002/gps.446.

[17] J.R. Copeland, M.E. Dewey, H.M. Griffiths-Jones, A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and

AGECAT., Psychol. Med. 16 (1986) 89–99. doi:10.1017/S0033291700057779.

[18] A. Lobo, P. Saz, G. Marcos, J.L. Día, C. De-la-Cámara, The prevalence of dementia and depression in the elderly community in a southern European population. The Zaragoza study., Arch. Gen. Psychiatry. 52 (1995) 497–506. http://www.ncbi.nlm.nih.gov/pubmed/7771920.

[19] M.P. Lawton, E.M. Brody, Assessment of older people: self-maintaining and instrumental activities of daily living, Gerontologist. 9 (1969) 179–186. doi:10.1093/geront/9.3_Part_1.179.

[20] S. Katz, A.B. Ford, R.W. Moskowitz, B. a Jackson, M.W. Jaffe, Studies of illness in the aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function, J. Am. Med. Assoc. 185 (1963) 914–919. doi:10.1001/jama.1963.03060120024016.

[21] L.J. Launer, C. Brayne, M.M. Breteler, Epidemiologic approach to the study of dementing diseases: a nested case-control study in European incidence studies of dementia, Neuroepidemiology. 11 (1992) 114–118.

[22] J.R.M. Copeland, A.T.F. Beekman, A.W. Braam, M.E. Dewey, P. Delespaul, R. Fuhrer, C. Hooijer, B.A. Lawlor, S.-L. Kivela, A. Lobo, H. Magnusson, A.H. Mann, I. Meller, M.J. Prince, F. Reischies, M. Roelands, I. Skoog, C. Turrina, M.W. deVries, K.C.M. Wilson, Depression among older people in Europe: the EURODEP studies., World Psychiatry. 3 (2004) 45–9. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1414664&tool=pmcentrez&rendertype=abstract.

[23] Y. Liang, L. Wang, Alzheimer's Disease is an Important Risk Factor of Fractures: a Meta-analysis of Cohort Studies, Mol Neurobiol. (2016). doi:10.1007/s12035-016-9841-2.

[24] R. Azagra, F. L??pez-Exp??sito, J.C. Martin-S??nchez, A. Aguy??-Batista, P. Gabriel-Escoda, M. Zwart, M.A. D??az-Herrera, J. Pujol-Salud, M. Iglesias-Mart??nez, N. Puchol-Ruiz, Incidencia de la fractura de f??mur en Espa??a (1997-2010), Med. Clin. (Barc). 145 (2015) 465–470. doi:10.1016/j.medcli.2015.02.023.

[25] J.M. Ten??as, M. Estarlich, E. Crespo, C. Rom??n-Ortiz, A. Arias-Arias, F. Ballester, Short-term relationship between hip fracture and weather conditions in two spanish health areas with different climates, J. Environ. Public Health. 2015 (2015). doi:10.1155/2015/395262.

[26] T. Rachner, S. Khosla, L. Hofbauer, A. Manuscript, New Horizons in Osteoporosis, Lancet. 377 (2011) 1276–1287. doi:10.1016/S0140-6736(10)62349-

5.New.

[27] O. Johnel, B. Gullberg, E. Allander, J.A. Kanis, The apparent incidence of hip fracture in Europe: A study of national register sources, Osteoporos. Int. 2 (1992) 298–302. doi:10.1007/BF01623186.

[28] R. Azagra, F. L??pez-Exp??sito, J.C. Martin-S??nchez, A. Aguy??, N. Moreno, C. Cooper, A. D??ez-P??rez, E.M. Dennison, Changing trends in the epidemiology of hip fracture in Spain, Osteoporos. Int. 25 (2014) 1267–1274. doi:10.1007/s00198-013-2586-0.

[29] C. Albert, Higher education demand in Spain: The influence of labour market signals and family background, High. Educ. 40 (2000) 147–162. doi:http://dx.doi.org/10.1023/A:1004070925581.

[30] E. Lobo, C. Dufouil, G. Marcos, B. Quetglas, P. Saz, E. Guallar, A. Lobo, Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline?, Am. J. Epidemiol. 172 (2010) 708–716. doi:10.1093/aje/kwq187.

Figure 1. Hip Fracture Incidence Rate (IR) (100,000person-year) in Men and Women

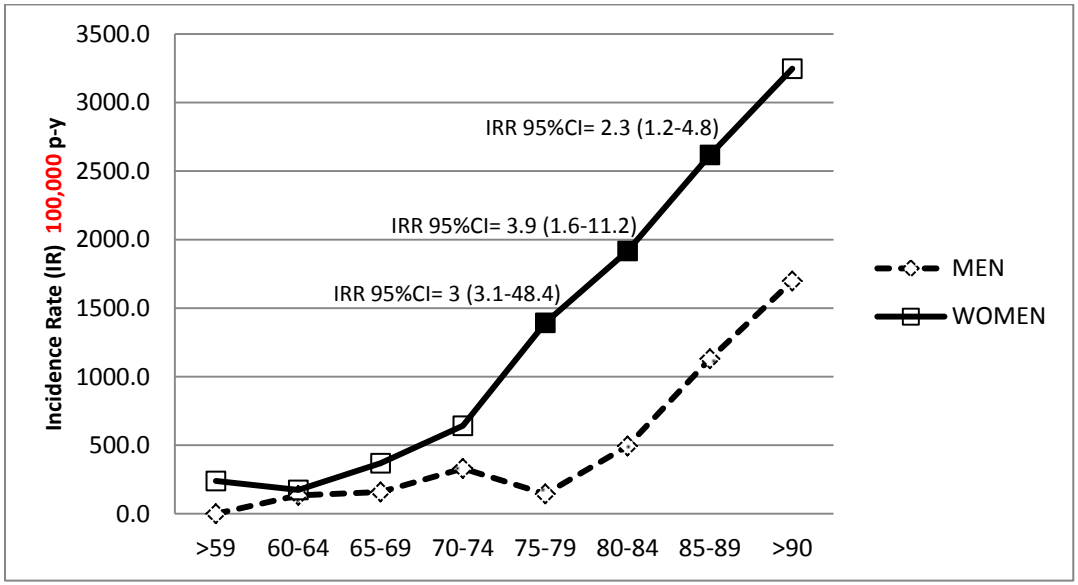

Table 1. Baseline characteristics for the total sample and for men and women participants

	GLOBAL (N=4660)	MEN (N=1976)	WOMEN (N=2684)	*p-value**
	N (%)	N (%)	N (%)	
Age, mean (SD)	73.4 (9.8)	72.5 (±9.5)	74 (±9.9)	<0.001
Female sex	2648 (57.6)			
Coupled	2719 (58.3)	1520 (77.2)	1199 (44.8)	<0.001
Missing	*14 (0.3)*			
Illiterate	351 (7.5)	82 (4.2)	269 (10.1)	<0.001
Missing	*55 (1.2)*			
Tobacco	604 (13)	528 (26.8)	76 (2.8)	<0.001
Missing tobacco	*13 (0.3)*			
Alcohol	580 (12.4)	457 (23.2)	123 (4.6)	<0.001
Missing alcohol	*18 (0.4)*			
BMI, mean (SD) (kg/m^2)	26.9 (5.1)	26.6 (±4.4)	27.2 (±5.5)	0.009
Underweight	164 (3.5)	58 (2.9)	106 (3.9)	0.063
Normoweight	1499 (32.2)	631 (31.9)	868 (32.3)	0.769
Overweight	1883 (40.4)	907 (45.9)	976 (36.4)	<0.001
Obesity	1083 (23.2)	374 (18.9)	709 (26.4)	<0.001
Missing	*31 (0.7)*			
Menopause <45y			566 (12.1)	
Missing			*260 (5.6)*	
bADL'	586 (12.6)	201 (10.2)	385 (14.4)	<0.001
Missing	*13 (0,3)*			
iADL'	986 (20.8)	293 (15)	662 (24.9)	<0.001
Missing	*47 (1)*			
Depression	537 (11.5)	104 (5.3)	433 (16.1)	<0.001
Dementia	209 (4.5)	55 (2.8)	154 (5.7)	<0.001

BMI: Body Mass Index; bADL': Basic Activities of Daily Living; iADL': Instrumental Activities of Daily Living. *Chi2 test for categorical data and the Mann-Whitney U test for continuous data

Table 2. Characteristics of men and women with and without hip fracture during follow-up

	MEN			WOMEN		
	No hip fracture (n=1926)	***Hip Fracture (n=50)***		***No hip fracture (n=2459)***	***Hip Fracture (n=225)***	
	N (%)	**N (%)**	***p-value****	**N (%)**	**N (%)**	***p-value****
Age, mean (SD)	72.4 (9.5)	76.9 (9.8)	0.002	73.6 (9.9)	78.5 (8.7)	<0.001
Female sex						
Coupled	1489 (77.6)	31 (62)	0.009	1135 (46.3)	64 (28.4)	<0.001
Illiterate	81 (4.2)	1 (2)	0.438	236 (9.6)	33 (14.8)	0.014
Tobacco	513 (26.7)	15 (30)	0.603	70 (2.9)	6 (2.7)	0.879
Alcohol	447 (23.3)	10 (20)	0.585	106 (4.3)	17 (7.6)	0.026
BMI, mean (SD) (kg/m^2)	26.6 (4.3)	25.7 (4.8)	0.188	27.2 (5.5)	26.7 (5.8)	0.187
Underweight	56 (2.9)	2 (4)	0.651	93 (3.8)	13 (5.8)	0.141
Normoweight	611 (31.7)	20 (40)	0.215	790 (32.1)	78 (34.7)	0.436
Overweight	887 (46.1)	20 (40)	0.396	902 (36.7)	74 (32.9)	0.278
Obesity	366 (19)	8 (16)	0.593	654 (26.6)	55 (24.4)	0.483
Menopause <45y				508 (22.8)	58 (29.3)	0.039
bADL'	193 (10)	8 (16)	0.170	345 (14.1)	40 (17.8)	0.130
iADL'	285 (14.9)	8 (17)	0.688	589 (24.2)	73 (32.6)	0.006
Depression	101 (5.2)	3 (6)	0.813	388 (15.8)	45 (20)	0.099
Dementia	53 (2.8)	2 (4)	0.596	139 (5.7)	15 (6.7)	0.531

BMI: Body Mass Index; bADL': Basic Activities of Daily Living; iADL': Instrumental Activities of Daily Living. *Chi2 test for categorical data and the Mann-Whitney U test for continuous data

Table 3. Risk factors for hip fracture in men and in women

	MEN				WOMEN			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p-value*	**HR (95% CI)**	*p-value*	**HR (95% CI)**	*p-value*	**HR (95% CI)**	*p-value*
Age	**1.14 (1.10-1.17)**	*<0.001*	**1.13 (1.08-1.17)**	*<0.001*	**1.13 (1.11-1.15)**	*<0.001*	**1.12 (1.09-1.14)**	*<0.001*
Coupled	**0.30 (0.17-0.53)**	*<0.001*	**0.51 (0.27-0.94)**	*0.032*	**0.31 (0.23-0.41)**	*<0.001*	**0.68 (0.48-0.96)**	*0.028*
Illiterate	0.75 (0.10-5.47)	*0.780*	0.35 (0.05-2.54)	*0.296*	**2.20 (1.52-3.19)**	*<0.001*	**1.57 (1.03-2.39)**	*0.035*
Alcohol	1.11 (0.55-2.19)	*0.796*	0.86 (0.42-1.78)	*0.691*	**2.02 (1.23-3.32)**	*0.005*	1.52 (0.88-2.64)	*0.135*
Tobacco	1.04 (0.57-1.91)	*0.894*	**2.13 (1.11-4.10)**	*0.024*	0.81 (0.36-1.81)	*0.602*	1.55 (0.68-3.56)	*0.301*
Underweigth	2.46 (0.59-10.15)	*0.213*	1.13 (0.26-4.95)	*0.874*	**2.28 (1.30-3.99)**	*0.004*	1.48 (0.79-2.75)	*0.221*
Overweight	0.66 (0.37-1.16)	*0.146*	0.77 (0.42-1.45)	*0.417*	0.81 (0.61-1.07)	*0.810*	0.95 (0.68-1.33)	*0.768*
Obesity	0.84 (0.40-1.79)	*0.66*	0.74 (0.32-1.69)	*0.477*	0.87 (0.64-1.17)	*0.349*	0.81 (0.56-1.18)	*0.271*
Depression	2.02 (0.63-6.5)	*0.240*	1.68 (0.51-5.55)	*0.396*	1.35 (0.97-1.87)	*0.075*	**1.45 (1.01-2.06)**	*0.042*
Dementia	**10.74 (2.51-45.9)**	*0.001*	2.34 (0.48-11.35)	*0.293*	**5.72 (3.32-9.84)**	*<0.001*	1.64 (0.69-3.90)	*0.265*
bADL'	**5.78 (2.68-12.49)**	*<0.001*	**3.15 (1.29-7.67)**	*0.011*	**3.42 (2.41-4.85)**	*<0.001*	1.23 (0.76-1.97)	*0.401*
Menopause <45y					1.34 (0.98-1.82)	*0.063*	1.27 (0.93-1.73)	0.127

bADL': Basic Activities of Daily Living. Cox regression models. HR: hazard ratios. CI: confidence interval.