Osteoporosis International (2019) 30:1157–1165
https://doi.org/10.1007/s00198-019-04951-6

REVIEW ARTICLE

Depression and risk of hip fracture: a systematic review and meta-analysis of cohort studies

T. T. Shi[1] · M. Min[1] · Y. Zhang[1] · C. Y. Sun[2] · M. M. Liang[1] · Y. H. Sun[1,3]

Received: 20 February 2019 / Accepted: 21 March 2019 / Published online: 11 April 2019

Abstract

Recently published studies on the association between depression and hip fracture (HF) are inconsistent. Therefore, we performed this meta-analysis with the main aim to clarify the association between depression and HF, and also to identify possible susceptible groups. Relevant literature published until February 2019 was obtained and screened according to established inclusion criteria. Two researchers independently processed quality assessment and data extraction prior to the meta-analysis. Pooled hazard ratios (HRs) with 95%CI (confidence intervals) were calculated. To explore the sources of heterogeneity, subgroup analyses were performed based on study design, study region, NOS scores, follow-up duration, diagnostic criteria, sex, national income level, and adjustments (bone mineral density (BMD), antidepressant, calcium intake, and smoking). Ten studies with 13 estimates, involving 375,438 participants and 4576 HFs, were included. It was found that patients with depression had a higher risk of HF than non-depressed patients (HR = 1.21; 95%CI 1.11–1.31). Sensitivity analysis results show that the association is relatively stable. The studies that were not adjusted for confounders (e.g., antidepressant, BMD, calcium intake, and smoking) had higher overall HR compared to the studies that adjusted for the corresponding confounding factors. HFs are more likely to occur in European and male depression patients. This meta-analysis provided evidence of a modest positive association between depression and the risk of HFs, and the association is stronger in European and male patients. Implementation of practical measures to prevent and treat depression is of great public health significance.

Keywords Depression · Depressive symptoms · Hip fracture · Meta-analysis

✉ Y. H. Sun
yhsun_ahmu_edu@yeah.net

T. T. Shi
shitingting199205@163.com

M. Min
419023179@qq.com

Y. Zhang
1476920440@qq.com

C. Y. Sun
centurysuncy@yahoo.com

M. M. Liang
840541969@qq.com

[1] Department of Epidemiology and Health Statistics, School of Public Health, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

[2] AMITA Health Saint Joseph Hospital Chicago, Chicago 60657, Illinois, USA

[3] Center for Evidence-Based Practice, Anhui Medical University, No. 81 Meishan Road, Hefei 230032, Anhui, China

Introduction

Hip fractures (HFs) are not only high in incidence but also associated with higher medical costs, poor functional recovery, high post-fracture mortality rate, and heavy social and economic burdens [1]. In addition, the worldwide population aging leads to a dramatic increase in the incidence of HFs in the past years [2]. Gullberg et al. anticipated a 3.5-fold increase in the incidence of HF by the year 2050 [3]. Reports of acute mortality rate and 1-year mortality rate were 5% and 15–25%, respectively [4]. Twenty percent of HF patients result in permanent disability and need long-term skilled nursing care [4].

Similarly, depression is a chronic, prevalent condition, and is a leading cause of disability, affecting at least 120 million people worldwide [5] and 18% of men and 26% of women in the USA [6]. The risk of HFs is reportedly high in elderly patients with neurological diseases, including Alzheimer's disease, Parkinson's disease, and stroke [7–10] and previous meta-analyses showed that people with depression are indeed more susceptible to all types of fractures [11–13], but no studies aimed specifically at the association between depression and HFs.

Recently, emerging studies [14–24] on the association between depression and HFs have been published, but with an inconsistent result. Due to the high disease burden of HF, if confirmed in future studies, the association between depression and HFs may open new avenues for HF prevention. Therefore, we set out to conduct the first formal meta-analysis to investigate the relationship between depression and HFs, to quantify the size of the effects, and to identify the vulnerable populations for prevention.

Methods and materials

Search strategy

Relevant studies were identified via a systematic search of the PubMed, Cochrane Library, Web of Science, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) Database, and Wanfang (Chinese) through February 10, 2019. A systematic search string of relevant terms was developed as follows: (depression OR depressive disorders OR depression symptoms) and (hip fracture OR HF OR hip injuries OR hip fractures OR fractures). We supplemented the computerized search by a manual search of the bibliographies of all retrieved articles for studies that not captured by electronic database searching. The search was limited to human studies and either English or Chinese language studies.

Selection criteria

Reviewers T Shi and M Min independently did the study selection and eligibility assessment, and studies were included when they met all of the following inclusion criteria: (1) focused on the association between depression and HFs, the term “depression” refers to clinical depression, depressive disorders, or depressive symptoms. Eligible exposures were unipolar depression, depressive disorders, or depressive symptoms confirmed by either clinical diagnosis or by a standardized psychometric tool. Bipolar depressive disorder and bipolar depression were not eligible; all HF cases must be diagnosed by the medical institution or verified by medical records and in accordance with International Classification of Diseases (ICD-9-CM, 820.0–820.9; ICD-10-CA, S720–722); (2) was an observational study (a cohort study or a case-control study); (3) was published in English or Chinese; (4) hazard ratio (HR) or risk ratios (RR) or odds ratios (OR) and corresponding 95%CI (confidence intervals) could be extracted directly (or allow recalculation). Studies were excluded if they only examined broader fractures but did not specifically consider HF, were reviews or commentaries, were animal based, or were intervention studies.

Data extraction and quality assessment

The following study characteristics were extracted: author(s), year of publication, study design, study population, distribution by age and sex, important factors such as duration of follow-up, cohort size, assessment of depression, assessment of HF, depression criterion, confounders that were adjusted by multivariate analysis, HR or RR or OR, and the corresponding 95%CI. Newcastle-Ottawa scale (NOS) was applied to assess the quality of the methodology in the original studies. The score ranged from 0 to 9, where a score of 9 indicates the strongest regarding methodology and scores of 0–3, 4–6, and 7–9 were rated as low, moderate, and high quality, respectively.

Two investigators (T Shi and M Min) independently conducted appraisal and data abstraction using a standard protocol and extraction form. Disagreement and uncertainty were discussed and adjudicated by a third reviewer (Y Zhang).

Statistical analysis

When original studies presented multiple adjusted estimates for the same outcome, the estimates that had been adjusted for the largest number of confounders was used. And for the concern of normalization and variance stabilization, natural logarithms of HR/RR/OR and their 95%CIs were used in the analysis instead of using HR/RR/OR directly. Heterogeneity among included studies was investigated using the I^2 statistics and Q test, and low statistical heterogeneity was defined as $I^2 \leq 50\%$ and $P > 0.1$, respectively. The existence of significant heterogeneity necessitated the use of a random-effects model; otherwise, a fixed-effects model was used [25]. To explore the sources of heterogeneity, subgroup analyses were performed according to study design, study region, NOS scores, follow-up duration, diagnostic criteria, sex, national income level, and adjustments (bone mineral density (BMD), antidepressant, calcium intake, and smoking). We identified the national income levels according to the World Bank classification of low-, middle-, and high-national income levels [26]. To weigh the influence of each eligible study on the pooled estimate and to assess the robustness of results from our meta-analysis, a sensitivity analysis was performed by omitting one study at each turn. Funnel plot asymmetry, Begg’s test [27], and Egger regression tests [28] were all used to explore the publication bias. All statistical analyses were implemented in Stata version 14.0 (Stata, version 14; Stata Corp, College Station, TX, USA). The difference was considered statistically significant when $P < 0.05$.

Results

Study selection and characteristics of eligible studies

The search was performed until February 2019. After initial systematical search and supplementary search, a total of 3746 individual publications were identified. After the removal of duplication and screening of titles, abstracts, and full-text, 11 (10 cohort studies and 1 case-control studies) [14–24] of them remained (Fig. 1). Characteristics of eligible studies on the association between depression and HFs were summarized in Table 1. There is only one case-control study, which is of a retrospective design, coupled with the consideration of the bidirectional relationship between depression and HFs [29]; thus, the only case-control study [24] was removed from our final meta-analysis.

Finally, 10 individual cohort studies (7 prospective cohort studies and 3 retrospective cohort study) with 13 effect estimates published from 1999 to 2018 were included. Of these, a total of 375,438 participants and 4576 HF events were investigated. Cheng et al. and Mussolion et al. reported effect estimates for the association between major depressive disorder-HF and less severe depressive disorder-HF, respectively [18, 21], Lobo et al. reported effect estimates for females and males, respectively [21], and were all incorporated separately in our analyses. For the geographical location, three in Taiwan of China, three in the USA, and one each in the UK, Norway, Canada, and Spain. The follow-up duration ranged from

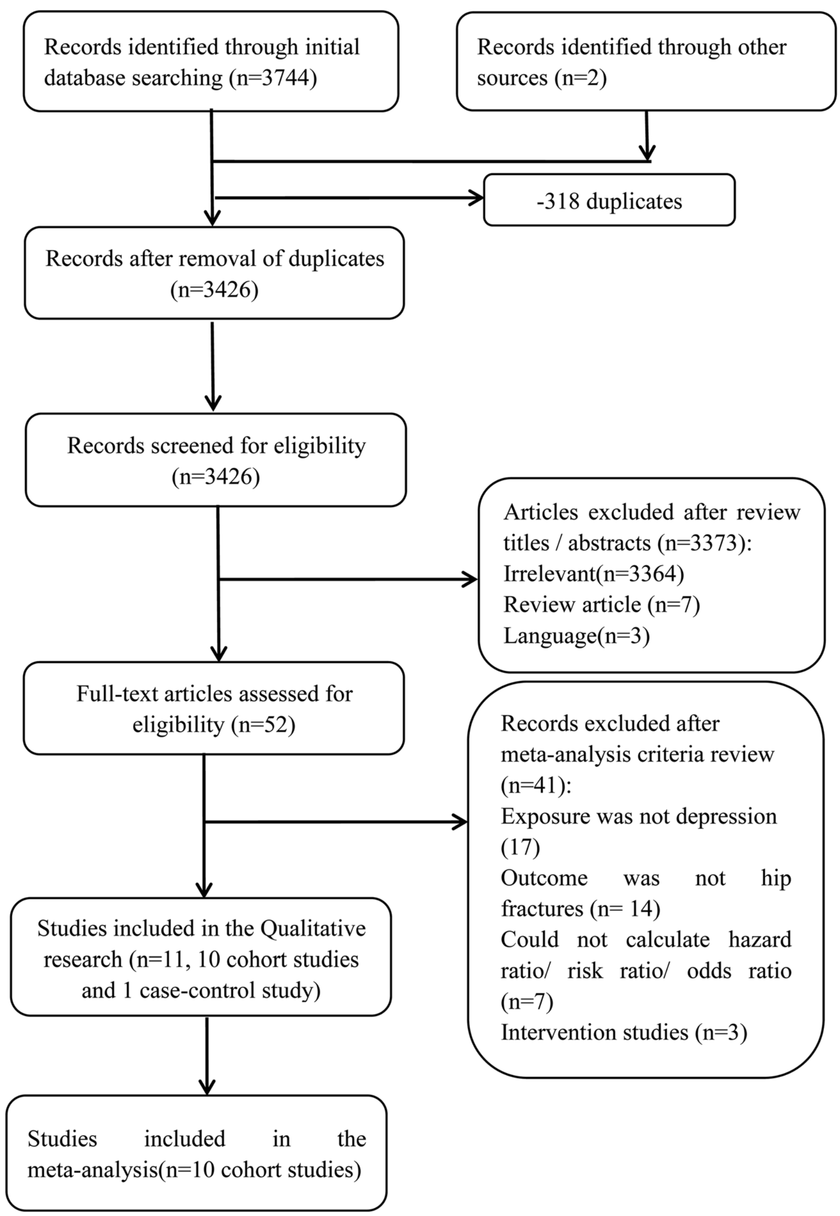

Fig. 1 Flow diagram of the study search and selection process

Table 1 Characteristics of studies included in the meta-analysis

First author (year)	Geographical region	Study design	Follow-up years	Measure of depression	Measure of HF	Age (range, mean)	Participants/male (%)	Variables adjusted	Sex	HR/OR (95%CI)	NOS scores
Whooley (1999)	USA	Pros. cohort	3.7	GDS	Verified radiological	≧ 65 Mean 73.37	7414/0	Age, marital status, education, BMD, history of vertebral fracture, history of falling, arthritis, DM, steroid use, estrogen use, calcium intake	Females	1.20 (0.80–1.90)	8
Forsen (1999)	Norway	Pros. cohort	3	MDI	Medical records	50–101 Mean 66	18,612/0	Age, medication use, VMI, smoking, physical inactivity, and impairment because of physical illness	Females	1.95 (1.18–3.23)	6
Mussolion (2005)	USA	Pros. cohort	22	GWB-D	ICD-9-CM, 820	25–74 Mean 49	6195/46	Age at baseline, sex, race, BMI, smoking status, alcohol consumption, and non-recreational physical activity level	Both	MDD, 1.70 (0.99–2.91) LDD, 1.01 (0.68–1.51)	9
Ojo (2007)	Mexico, UK	Pros. cohort	7	CES-D	Medical records	≧ 65 Mean 72.45	3050/41	Fracture at baseline, age, sex, marital status, smoking status, arthritis, DM, stroke, cancer, any ADL limitation, cognitive impairment, near and distant vision impairment, BMI, and performance score of lower body function	Both	1.46 (1.46–2.19)	8
Spangler (2008)	USA	Pros. cohort	7.4	CES-D	Medical records	50–79 Mean NA	82,410/0	Baseline BMD, age, years since menopause, ethnicity, physical function, height, log weight, oral hormone therapy, current smoker, and antidepressants	Females	0.87 (0.68–1.12)	7
Cheng (2016)	Taiwan of China	Retro. cohort	12	ICD-9-CM, 296.2, 296.3, 300.4, 311	ICD-9-CM, 820	≧ 65 Mean 46.5	139,110/37.8	Sex, age, Charlson comorbidity index, urbanization, osteoporosis, and antidepressants	Both	MDD, 1.61 (1.19–2.18) LDD, 1.10 (0.91–1.34)	7
Bolton (2017)	Manitoba, Canada	Pros. cohort	18	ICD-9-CM and ICD-10-CA codes	ICD-9-CM and ICD-10-CA codes	≧ 40 Mean 64.2	68,730/9	FRAX score computed with bone mineral density, prior use of osteoporosis medication and antidepressant	Both	1.06 (0.87–1.30)	9
Lobo (2017)	Zaragoza, Spain	Pros. cohort	16	GMS-B	ICD-9-CM, 820	≧ 55 Mean 73.4	4660/42	Age, civil status, illiterate, smoking/alcohol intake, disability or not, BMI, menopause	Females Males	Females, 1.45 (1.01–2.06) Males, 1.68 (0.51–5.55	7
Pan (2018)	Taiwan of China	Retro. cohort	13	ICD-9-CM, 296.2, 296.3, 300.4, 311	ICD-9-CM	28.6–50.9 Mean 38.6	22,414/40.2	Age, sex, comorbidities, degree of urbanization, and monthly income	Both	1.34 (1.08–1.66)	7
Yeh (2018)	Taiwan of China	Retro. cohort	15	ICD-9-CM	ICD-9-CM	All Mean 62.09	20,625/47.79	Age, comorbidity	Both	1.29 (0.99–1.67)	7
Huang (2014)	Japan	Case-control	/	ICD-10, S720–722	ICD-10-CM, S720–722	≧ 45 Mean NA	2218/0	Age, ocular diseases, stroke, musculoskeletal diseases, Parkinson's disease, cognitive, impairment	Females	2.09 (1.54–2.85)*	6

Abbreviations: *HF*, hip fracture; *HR*, hazard ration; *OR*, odds ratio; *CI*, confidence interval; *NOS*, Newcastle-Ottawa scale; *Pros. cohort*, prospective cohort study; *Retro. cohort*, retrospective cohort study; *ICD*, International Classification of Diseases; *GDS*, Geriatric Depression Scale; *MDI*, mental distress index; *GWB-D*, The General Well-Being Schedule; *CES-D*, Center for Epidemiologic Studies Depression Scale; *GMS*, Geriatric Mental State scale; *NA*, not available; *BMD*, bone mineral density; *MDD*, major depressive disorder; *LDD*, less severe depressive disorder; * OR was provided

3 years to 22 years (4 with a follow-up period of < 10 years and 6 with a follow-up period of ≧ 10 years). All included studies were classified either as moderate ($n = 1$) or as high quality ($n = 9$). The details were listed in Table 1.

Results of the meta-analysis

Overall estimates

The overall pooled results were presented in Fig. 2. The heterogeneity test I^2 was 44.7, which meant low heterogeneity across included studies and thus the fixed-effect model was adopted. The meta-analysis result from fixed-effect model indicated a 21% (95%CI 1.11–1.31) increase in the risk of hip fracture incidence (HFi) in individuals suffered from depression compared to those without depression.

Subgroup analyses

A number of pre-specified subgroup analyses were performed, including study design, study region, NOS scores, follow-up duration, diagnostic criteria, sex, national income level, and adjustments (BMD, antidepressant, calcium intake, and smoking) (Table 2). However, because all included studies were conducted in high-income regions and except for one study that is of medium quality, the rest are high-quality studies, corresponding analyses were not achieved. In the subgroup analysis of study design, we found a significant association between depression and HFs incidence both in prospective studies (HR = 1.15, 95%CI 1.02–1.29) and retrospective studies (HR = 1.27, 95%CI 1.13–1.43). Male depression patients (HR = 1.41, 95%CI 1.18–1.69) were more vulnerable to HFs than female patients (HR = 1.30, 95%CI 1.09–1.56). In terms of follow-up duration, studies that followed study participants for ≧ 10-year indicated a significant impact of depression on the risk of HFs (HR = 1.23, 95%CI 1.12–1.35); in the studies with a follow-up period of < 10 years, the association was not statistically significant (HR = 1.12, 95%CI 0.94–1.34). In subgroup analyses based on the study region, the association was stronger in individuals from European countries than those from North America and Asia. For diagnostic criteria, despite the different diagnostic criteria used in the included studies, the results of the two groups using the International Classification of Diseases (ICD) and other standardized tools all showed a significant positive relation between depression and HFs (ICD: HR = 1.22, 95%CI 1.10–1.34; other standardized tools: HR = 1.20, 95%CI 1.04–1.38). For subgroup analyses of adjustments, the estimated risk was higher in the studies without adjustments for antidepressant using or for smoking or for calcium intake or for BMD.

Sensitivity analyses and publication bias

There was no substantial change in the sensitivity analysis results, which proved that the association between depression

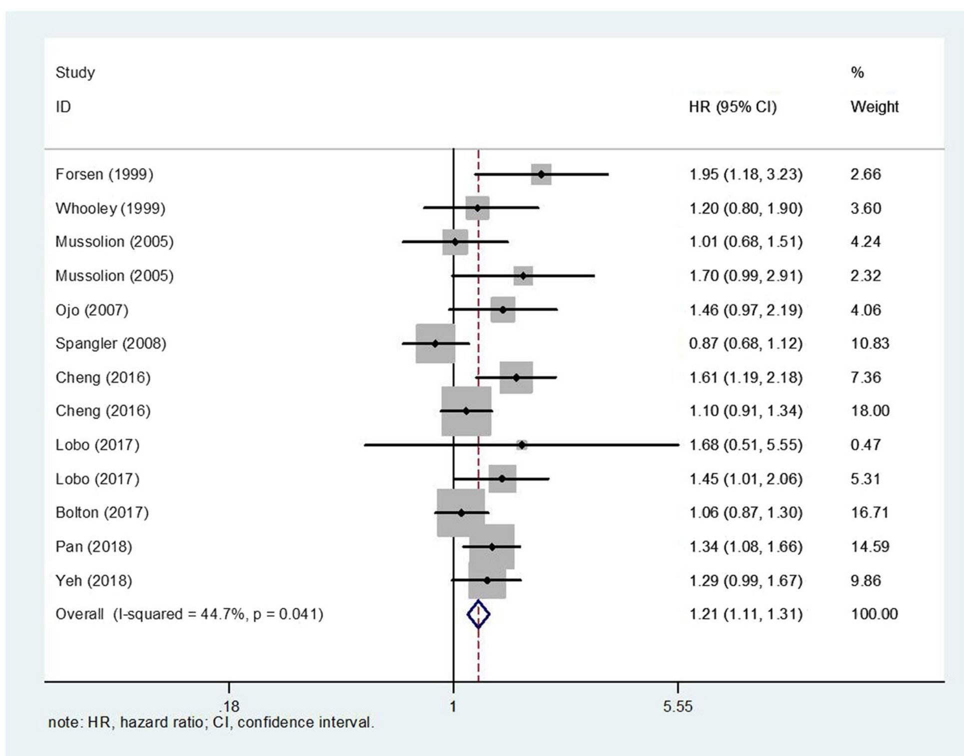

Fig. 2 Forest of the association between depression and hip fracture

Table 2 Subgroup analysis of the association between depression and hip fractures

Subgroups	Number of studies	Heterogeneity		Meta-analysis	
		I^2 (%)	*P*	HR (95%CI)	*P*
Study region					
North America	5	29.0	0.228	1.038 (0.908–1.186)	0.587
Europe	4	0.0	0.793	1.556 (1.234–1.963)	0.000
Asia	4	36.6	0.193	1.272 (1.133–1.429)	0.000
Study design					
Prospective	9	48.2	0.051	1.148 (1.022–1.289)	0.020
Retrospective	4	36.6	0.193	1.272 (1.133–1.429)	0.000
Sex					
Females	7	59.2	0.023	1.299 (1.086–1.555)	0.004
Males	4	0.0	0.800	1.411 (1.175–1.694)	0.004
Follow-up duration					
≧ 10	9	24.3	0.228	1.232 (1.123–1.352)	0.000
< 10	4	70.9	0.016	1.123 (0.940–1.343)	0.201
Diagnostic criteria					
ICD	5	43.7	0.13	1.215 (1.099–1.344)	0.000
Standardized tools	8	51.9	0.042	1.195 (1.037–1.377)	0.014
Adjusted for BMD					
Yes	2	78.1	0.033	1.050 (0.876–1.257)	0.597
No	11	29.5	0.165	1.254 (1.143–1.375)	0.000
Adjusted for antidepressant					
Yes	5	72.3	0.006	1.123 (1.006–1.254)	0.039
No	8	0.0	0.839	1.324 (1.170–1.497)	0.000
Adjusted for smoking					
Yes	7	58.8	0.024	1.194 (1.027–1.387)	0.021
No	6	29.7	0.212	1.215 (1.101–1.340)	0.000
Adjusted for calcium intake					
Yes	1	NA	NA	1.200 (0.779–1.849)	0.409
No	12	49.3	0.027	1.209 (1.112–1.314)	0.000

Abbreviations: *HR*, hazard ration; *CI*, confidence interval; *ICD*, International Classification of Diseases; *BMD*, bone mineral density; *NA*, not available

and HFs was relatively stable. Results were shown in Table 3. Publication bias was suspected by observing the funnel plots and Egger's test ($P = 0.018$), but the Begg rank correlation test showed that the publication bias was not significant ($P = 0.200$).

Discussion

To the best of our knowledge, this study was the first systematic review and meta-analysis aimed specifically at the association between depression and HFs. Our results establish that the risk of HF is increased among adults with depression (HR = 1.21; 95%CI 1.11–1.31) especially male patients. The increased risk associated with depression remained consistent and statistically significant in all sensitivity analyses (Table 3), such consistent findings suggest our results are robust and consistent. Subgroup analyses showed that the studies without adjustments for antidepressant using or for smoking or for calcium intake or for BMD had higher overall HR compared to the studies that adjusted for corresponding confounders. The association was stronger in individuals from European countries than those from North America and Asia. This means the results of our research should be cautiously generalized and more studies adjusted for the potential confounders are recommended to explore this topic in more detail.

The underlying mechanism of how depression contributes to HFs has not been fully elucidated. Among the hypotheses that attempt to explain the role of depression in hip fracture incidence (HFi), two have captured special attention in the past few years (decreased BMD and a higher propensity to fall). For the first hypothesis, the potential mechanisms are as follows. First, depression may alter concentrations of many hormones that affect bone formation and/or bone resorption.

Table 3 Sensitivity analysis of the association between depression and hip fractures

Study omitted	Heterogeneity		Meta-analysis	
	I^2 (%)	*P*	HR (95%CI)	*P*
Cheng (2016)a	38.8	0.082	1.181 (1.085–1.286)	0.000
Cheng (2016)b	46.6	0.038	1.234 (1.127–1.351)	0.000
Yeh (2018)	48.7	0.029	1.200 (1.100–1.308)	0.000
Whooley (1999)	49.3	0.027	1.209 (1.112–1.314)	0.000
Mussolion (2005)a	45.3	0.044	1.199 (1.103–1.302)	0.000
Mussolion (2005)b	47.3	0.035	1.218 (1.120–1.325)	0.000
Ojo (2007)	42.7	0.035	1.199 (1.102–1.303)	0.000
Spangler (2008)	22.7	0.221	1.258 (1.153–1.372)	0.000
Forsen (1999)	39.3	0.079	1.193 (1.097–1.296)	0.000
Pan (2018)	46.7	0.037	1.187 (1.086–1.297)	0.000
Bolton (2017)	44.3	0.049	1.241 (1.134–1.357)	0.000
Lobo (2017)a	46.7	0.037	1.196 (1.099–1.301)	0.000
Lobo (2017)b	48.6	0.029	1.206 (1.111–1.310)	0.000

Abbreviations: *HR*, hazard ration; *CI*, confidence interval

Depression resulted in hypercortisolemia [30] via the deregulation of the hypothalamic-pituitary-adrenocortical axis (HPA) [31], and depression also leads to decreased levels of key regulators of bone formation such as estrogen and growth hormone/insulin growth factor [32, 33], all these hormone changes can cause decreased bone formation and increased bone resorption [33]. Second, depression can also lead to chronic low-grade inflammatory response [34, 35]; it reported that levels of inflammatory cytokines such as interleukin-1β, interleukin-2, and interleukin-6 are elevated in depression, and elevated levels of these pro-inflammatory markers are linked to decreased BMD [30]. Third, many depression-related poor health behaviors (e.g., smoking, increased alcohol drinking, and decreased physical activity) have been found to impact bone metabolism [36]. Fourth, depression was associated with other major comorbidities, such as hypertension [37, 38] and diabetes [39]; these comorbidities were considered as risk factors for fracture [40, 41]. In addition, studies showed that antidepressants may have direct effects on bone metabolism and decreased bone strength [42, 43], thereby increasing the risk for fracture [44]. For the other hypothesis, the potential mechanisms are as follows. First, depression causes neuropathological damage in certain areas of the brain, affecting the balance, judgment, gait, and coordination of the patient, leading to an increased risk of falls [45–47]. In addition, depressed people are difficult to adapt to the environment and are unlikely to take the necessary safety precautions, which resulted in a higher fall risk [48].

As the first comprehensive analysis of the relationship between depression and HFs, this study has some advantages. First, this is the first comprehensive analysis of the relationship between depression and HFs. Second, only cohort studies which can minimize the selection and recall bias were included in our meta-analysis. Third, subgroup analyses were performed in order to explore the source of heterogeneity and discover susceptible populations. Relevant findings can be utilized for guiding effective prevention measures, lead to improved HF risk management and the development of appropriately targeted interventions. We have to admit that there are also notable limitations in the present study. First, heterogeneous assessment methods for depression in original reports may add to the multiple conceptual problems concerned with the definition of depression. Second, our pooled HR may underestimate the true risk because all the studies included in this meta-analysis were carried out in high-income countries. However, studies have reported that HF risk may be higher in poor areas [49]. Third, some original reports included in this meta-analysis lacked data on medication use and depression severity. The impact of medications and depression severity on the observed association between depression and risk of fracture and bone loss needs further investigation. Also, we were not able to conduct subgroup analysis on confounders (e.g., ethnicity, alcohol intake, and comorbidities) because the corresponding information was not provided in most original reports. Finally, our findings should be treated with caution because of limited numbers of included studies and potential publication bias.

Conclusion

In conclusion, our meta-analysis of cohort studies further confirmed that depression was significantly associated with an increased risk of HF. Because the current prevalence of depression and HFs is high worldwide, and the prevalence is anticipated to increase in the coming decades, the observed association between depression and HFs has important implications for public health globally. Thus, our research provided the basis for orthopedic psychological intervention, and strategies for reducing the risk of HFs should be established for patients with depression. Taking practical measures to prevent and treat depression will help reduce the risk of HFs. More studies conducted in various settings (different national income level, socioeconomic, and demographic features) with standardized assessment methods for depression, well-designed confounder adjustment, and subgroup analyses are needed to further confirm the association.

Acknowledgments We thank Dr. Guangbo Qu for his assistance with this project.

Funding This study received no funding.

Compliance with ethical standards

Conflicts of interest None.

References

1. Epstein S (2000) Postmenopausal osteoporosis: fracture consequences and treatment efficacy vary by skeletal site. Aging 12(5):330–341. https://doi.org/10.1007/BF03339858
2. Melton LJ (2003) Adverse outcomes of osteoporotic fractures in the general population. J Bone Miner Res 18(6):1139–1141. https://doi.org/10.1359/jbmr.2003.18.6.1139
3. Gullberg B, Johnell O, Kanis JA (1997) World-wide projections for hip fracture. Osteoporos Int 7(5):407–413. https://doi.org/10.1007/PL00004148
4. Rizzoli R, Bruyere O, Cannata-Andia JB, Devogelaer J, Lyritis G, Ringe JD, Vellas B, Reginster J (2009) Management of osteoporosis in the elderly. Curr Med Res Opin 25(10):2373–2387. https://doi.org/10.1185/03007990903169262
5. Lépine JP, Briley M (2011) The increasing burden of depression. Neuropsychiatr Dis Treat 7(suppl 1):3–7. https://doi.org/10.2147/NDT.S19617
6. Shim RS, Baltrus P, Ye J, Rust G (2011) Prevalence, treatment, and control of depressive symptoms in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2005-2008. J Am Board Fam Med 24(1):33–38. https://doi.org/10.3122/jabfm.2011.01.100121
7. Baker NL, Cook MN, Arrighi HM, Bullock R (2011) Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. Age Ageing 40(1):49–54. https://doi.org/10.1093/ageing/afq146
8. Grisso JA, Kelsey JL, Strom BL, Chiu GY, Maislin G, O'Brien LA, Hoffman S, Kaplan F (1991) Risk factors for falls as a cause of hip fracture in women. The Northeast Hip Fracture Study Group. N Engl J Med 324(19):1326–1331. https://doi.org/10.1056/NEJM199105093241905
9. Kang JH, Chung SD, Xirasagar S, Jaw FS, Lin HC (2011) Increased risk of stroke in the year after a hip fracture: a population-based follow-up study. Stroke 42(2):336–341. https://doi.org/10.1161/STROKEAHA.110.595538
10. Melton LJ, Leibson CL, Achenbach SJ, Bower JH, Maraganore DM, Oberg AL, Rocca WA (2006) Fracture risk after the diagnosis of Parkinson's disease: influence of concomitant dementia. Mov Disord 21(9):1361–1367. https://doi.org/10.1002/mds.20946
11. Wu Q, Liu B, Tonmoy S (2018) Depression and risk of fracture and bone loss: an updated meta-analysis of prospective studies. Osteoporos Int 29(6):1303–1312. https://doi.org/10.1007/s00198-018-4420-1
12. Qiu L, Yang Q, Sun N, Li D, Zhao YX, Li XT, Gong YH, Lv CZ, Yin XX (2018) Association between depression and the risk for fracture: a meta-analysis and systematic review. BMC Psychiatry 18(1):336–344. https://doi.org/10.1186/s12888-018-1909-2
13. Wu Q, Liu J, Gallegos-Orozco JF, Hentz JG (2010) Depression, fracture risk, and bone loss: a meta-analysis of cohort studies. Osteoporos Int 21(10):1627–1635. https://doi.org/10.1007/s00198-010-1181-x
14. Whooley MA , Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS (1999) Depression, falls, and risk of fracture in older women Study of Osteoporotic Fractures Research Group. Arch Intern Med 159(5): 484–490. https://doi.org/10.1097/00006842-199901000-00114
15. Forsén L, Meyer HE, Søgaard AJ, Naess S, Schei B, Edna TH (1999) Mental distress and risk of hip fracture. Do broken hearts lead to broken bones? J Epidemiol Community Health 53(6):343–347. https://doi.org/10.1136/jech.53.6.343
16. Mussolino ME (2005) Depression and hip fracture risk: the NHANES I epidemiologic follow-up study. Public Health Rep 120(1):71–75. https://doi.org/10.1177/003335490512000112
17. Ojo F, Al Snih S, Ray LA, Raji MA, Markides KS (2007) History of fractures as predictor of subsequent hip and non hip fractures among older Mexican Americans. J Natl Med Assoc 99(4):412–418. https://doi.org/10.1016/j.jpainsymman.2006.09.015
18. Spangler L, Scholes D, Brunner RL, Robbins J, Reed SD, Newton KM, Melville JL, Lacroix AZ (2008) Depressive symptoms, bone loss, and fractures in postmenopausal women. J Gen Intern Med 23(5):567–574. https://doi.org/10.1007/s11606-008-0525-0
19. Cheng BH, Chen PC, Yang YH, Lee CP, Huang KE, Chen VC (2016) Effects of depression and antidepressant medications on hip fracture: a population-based cohort study in Taiwan. Medicine 95(36):e4655. https://doi.org/10.1097/MD.0000000000004655
20. Bolton JM, Morin SN, Majumdar SR, Sareen J, Lix LM, Johansson H, Odén A, McCloskey EV, Kanis JA, Leslie WD (2017) Association of mental disorders and related medication use with risk for major osteoporotic fractures. JAMA Psychiatry 74(6):641–648. https://doi.org/10.1001/jamapsychiatry.2017.0449
21. Lobo E, Marcos G, Santabárbara J, Salvador-Rosés H, Lobo-Escolar L, De la Cámara C (2017) Gender differences in the incidence of and risk factors for hip fracture: a 16-year longitudinal study in a southern European population. Maturitas 97:38–43. https://doi.org/10.1016/j.maturitas.2016.12.009
22. Pan CC, Hu LY, Lu T, Tu MS, Shen CC, Chen ZJ (2018) Risk of hip fractures in patients with depressive disorders: a nationwide, population-based, retrospective, cohort study. PLoS One 13(4):e0194961. https://doi.org/10.1371/journal.pone.0194961
23. Yeh HF, Hsu YC, Clinciu DL, Tung HH, Yen YC, Kuo HC (2018) Depression and young age impact on hip fracture subsequent to stroke: a population-based cohort study. Int J Nurs Pract 24(5):e12665. https://doi.org/10.1111/ijn.12665
24. Huang HR, Ye ZJ, Aoyagi KS, Tazoe H (2014) Fall-related diseases and hip fractures among the elderly women: a case-control study in Nagasaki Prefecture in Japan. Chin J Osteoporos 20(7):839–843. https://doi.org/10.3969/j.issn.1006-7108.2014.07.025
25. Higgins JP, Green S (2011) Cochrane handbook for systematic reviews of interventions Version 5.1.0. Cochrane, London (Updated March 2011). https://doi.org/10.1002/jrsm.38.
26. World Bank (2017) 2017 world development indicators. World Bank, Washington, DC
27. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101. https://doi.org/10.2307/2533446
28. Egger M, Davey SG, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315(7109):629–634. https://doi.org/10.1136/bmj.315.7109.629
29. Yang P, Lu Q, Wang XD, Pang D, Jin SL, Wang SZ (2012) Study on depression and rehabilitation status in the old patients with hip fracture after operation. J Nurs Adm 12(3):175–177. https://doi.org/10.3969/j.issn.1671-315X.2012.03.010
30. Ganesan K, Teklehaimanot S, Tran T-H, Asuncion M, Norris K (2005) Relationship of C-reactive protein and bone mineral density in community-dwelling elderly females. J Natl Med Assoc 97(3):329–333. https://doi.org/10.1016/j.jpainsymman.2004.07.005
31. Atteritano M, Lasco A, Mazzaferro S, Macri I, Catalano A, Santangelo A, Bagnato G, Bagnato G, Frisina N (2013) Bone mineral density, quantitative ultrasound parameters and bone metabolism in postmenopausal women with depression. Intern Emerg Med 8(6):485–491. https://doi.org/10.1007/s11739-011-0628-1
32. Khosla S, Melton LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL (1998) Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key

role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266–2274. https://doi.org/10.1210/jcem.83.7.4924

33. Gkiatas I, Lykissas M, Kostas-Agnantis I, Korompilias A, Batistatou A, Beris A (2015) Factors affecting bone growth. Am J Orthop Belle Mead NJ 44: 61–67. [PMID: 25658073]
34. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M (2013) So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 11(1):200–215. https://doi.org/10.1186/1741-7015-11-200
35. Wu ZJ, He JL, Wei RQ, Liu B, Lin X, Guan J, Lan YB (2015) C-reactive protein and risk of fracture: a systematic review and dose-response meta-analysis of prospective cohort studies. Osteoporos Int 26(1):49–57. https://doi.org/10.1007/s00198-014-2826-y
36. Alghadir AH, Gabr SA, Al-Eisa E (2015) Physical activity and lifestyle effects on bone mineral density among young adults: sociodemographic and biochemical analysis. J Phys Ther Sci 27(7):2261–2270. https://doi.org/10.1589/jpts.27.2261
37. Patten SB, Williams JV, Lavorato DH, Campbell NR, Eliasziw M, Campbell TS (2009) Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. Psychosom Med 71(3):273–279. https://doi.org/10.1097/psy.0b013e3181988e5f
38. Ojike N, Sowers JR, Seixas A, Ravenell J, Rodriguez-Figueroa G, Awadallah M, Zizi F, Jean-Louis G, Ogedegbe O, McFarlane SI (2016) Psychological distress and hypertension: results from the National Health Interview Survey for 2004-2013. Cardiorenal Med 6(3):198–208. https://doi.org/10.1159/000443933
39. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Manson JE, Willett WC, Ascherio A, Hu FB (2010) Bidirectional association between depression and type 2 diabetes mellitus in women. Arch Intern Med 170(21):1884–1891. https://doi.org/10.1001/archinternmed.2010.356
40. Li C, Zeng Y, Tao L, Liu S, Ni Z, Huang Q, Wang Q (2017) Meta-analysis of hypertension and osteoporotic fracture risk in women and men. Osteoporos Int 28(8):2309–2318. https://doi.org/10.1007/s00198-017-4050-z
41. Wang J, You W, Jing Z, Wang R, Fu Z, Wang Y (2016) Increased risk of vertebral fracture in patients with diabetes: a meta-analysis of cohort studies. Int Orthop 40(6):1299–1307. https://doi.org/10.1007/s00264-016-3146-y
42. Rauma PH, Honkanen RJ, Williams LJ, Tuppurainen MT, Kroger HP, Koivumaa-Honkanen H (2016) Effects of antidepressants on postmenopausal bone loss—a 5-year longitudinal study from the OSTPRE cohort. Bone 89:25–31. https://doi.org/10.1016/j.bone.2016.05.003
43. Eom CS, Lee HK, Ye S, Park SM, Cho KH (2012) Use of selective serotonin reuptake inhibitors and risk of fracture: a systematic review and meta-analysis. J Bone Miner Res 27(5):1186–1195. https://doi.org/10.1002/jbmr.1554
44. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J (2011) Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 343:d4551. https://doi.org/10.1136/bmj.d4551
45. Lee SC, Hu LY, Huang MW, Shen CC, Huang WL, Lu T, Hsu CL, Pan CC (2017) Risk of vertebral fracture in patients diagnosed with a depressive disorder: a nationwide population-based cohort study. Clinics 72(1):44–50. https://doi.org/10.6061/clinics/2017(01)08
46. Andreescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC, Reynolds CF, Aizenstein H (2008) Gray matter changes in late life depression—a structural MRI analysis. Neuropsychopharmacology 33(11):2566–2572. https://doi.org/10.1038/sj.npp.1301655
47. Fossati P, Radtchenko A, Boyer P (2004) Neuroplasticity: from MRI to depressive symptoms. Eur Neuropsychopharmacol 14(Suppl 5):S503–S510. https://doi.org/10.1016/j.euroneuro.2004.09.001
48. Anstey KJ, Burns R, von Sanden C, Luszcz MA (2008) Psychological well-being is an independent predictor of falling in an 8-year follow-up of older adults. J Gerontol B Psychol Sci Soc Sci 63(4):249–257. https://doi.org/10.1093/geronb/63.4.p249
49. Hansen L, Judge A, Javaid MK, Cooper C, Vestergaard P, Abrahamsen B, Harvey NC (2018) Social inequality and fractures-secular trends in the Danish population: a case-control study. Osteoporos In 29(10):2243–2250. https://doi.org/10.1007/s00198-018-4603-9