Life Sciences 218 (2019) 213–223

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Proton pump inhibitors therapy and risk of bone diseases: An update meta-analysis

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ARTICLE INFO

Keywords:
Proton pump inhibitors
Fracture
Osteoporosis
Bone mineral density
Meta-analysis

ABSTRACT

Aims: Large observational studies have yielded conflicting results regarding whether the use of proton pump inhibitors (PPI) increases the risk of bone diseases. Here, we performed a meta-analysis to examine the link between PPI and risk of bone fractures, osteoporosis and bone mineral density (BMD) loss.

Materials and methods: We systematically performed a search for published reports on PubMed, EMBASE and the Cochrane Library. We considered articles published in English, and restricted the search to studies on human participants. Studies that reported adjusted Hazard ratio (HR) estimates with 95% confidence intervals (CI) for the associations of interest were included. Data from the articles which can be used to estimate standardized mean difference (SMD) were also obtained and utilized to assess the risk of BMD loss.

Key findings: Compared with patients not taking PPI, those taking PPI, had the increased risk of developing any-site fractures (HR: 1.30; 95%CI: 1.16 to 1.45), hip fracture (HR:1.22; 95%CI:1.15 to 1.31), spine fracture (HR:1.49; 95%CI:1.31 to 1.68), and osteoporosis (HR:1.23; 95%CI:1.06 to 1.42) based on a random model, but there was no correlation with developing BMD loss in the femoral (SMD: −0.27; 95%CI: −0.62 to 0.09), or in the spine (SMD: −0.06; 95%CI: −0.54 to 0.41).

Significance: Results of this meta-analysis suggest that PPI may moderately increase the risk of any-site, hip, spine fracture. Due to the widespread use of PPI and the impact of fractures on human health, clinicians should carefully evaluate the patient condition before prescribing PPI therapy.

1. Introduction

Proton pump inhibitors are among the most widely used acid-suppressive medicines with the capacity to treat a broad range of acid-related diseases, including heart-burn symptoms, dyspepsia, chronic cough, gastroesophageal reflux disease and peptic ulcers, or for the prevention of the gastric injuries induced by non-steroidal anti-inflammatory drugs (NSAIDs) and surgery, through a mechanism involving the inhibition of gastric acid secretion [1,2]. PPIs are generally well tolerated by the majority of patients and have traditionally been considered to be relatively safe. However, there have been reports linking PPI use to incidence of hypomagnesemia, pneumonia, Clostridium difficile-associated diarrhea, pancreatic cancer and dementia [3–7]. Particularly, there have been concerns related to the potential association between the use of PPI and the risk of bone events, such as bone fractures, osteoporosis, and BMD loss. This association was first reported by Yang et al. [8], where persons taking PPI suffered were 1.44 times more likely to develop hip fracture compared to controls. In 2011, the Food and Drug Administration (FDA) published a cautionary note on the increased risk of fractures with the use of high dose and/or long-term PPI [9]. Subsequently, several observational studies having been performed to determine the association of PPI use with osteoporosis or BMD loss. Although numerous observational studies supported this notion, some studies have reported conflicting results. These inconsistencies could be partly explained by different types of study designs, population characteristics, and different baseline levels. Furthermore, the association between bone diseases and PPI use may be over-estimated due to the existence of other confounders. Actually, the mechanism by which PPI increases the risk of fracture, osteoporosis, and BMD loss has yet to be elucidated.

Given this background, the use of PPI needs to be re-evaluated to guide clinical treatment decisions. Analysis of large numbers of cases may enhance the statistical power of meta-analysis to assess the relationship between exposure and outcome. To close this gap, we

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https://doi.org/10.1016/j.lfs.2018.12.058
Received 28 October 2018; Received in revised form 12 December 2018; Accepted 29 December 2018
Available online 31 December 2018

conducted an update meta-analysis to determine the link between PPI use and fractures, osteoporosis, and BMD loss.

2. Materials and methods

2.1. Search strategy

We searched for articles published on PubMed, EMBASE and the Cochrane Library from inception up to May 2018, using the following key words and text in combination, both as Mesh terms and text words: ("bone mineral density" OR "bone density" OR "osteoporosis" OR "osteoporoses" OR bone Loss" OR "fractures, Bone" OR "broken bones" OR "bone, broken" OR "bones, broken" OR "broken bone" OR "bone fractures" OR "bone fracture" OR "fracture, bone" OR "fractures" OR "fracture") and ("proton pump inhibitors" OR "inhibitors, proton pump" OR "proton pump inhibitor"). We searched for articles published in English and those involving human participants. At the same time, we hand-searched the reference lists of the retrieved articles, or meta-analysis to identify additional relevant studies.

2.2. Eligibility criteria

To minimize differences, studies were included if they met the following criteria:(1) those that were cohort studies, case-control studies, or cross-sectional studies, (2) the exposure of interest was PPI use, the outcomes were fractures, osteoporosis, and BMD loss or not, (3) the hazard ratio (HR), relative risk (RR) or odds ratio (OR) estimates with corresponding 95% CI were provided, or the data from the articles can estimate SMD, (4) the analysis had to be matched or adjusted for age, gender, or other confounders.

2.3. Data extraction

Two investigators (J.L, L.F) independently extracted the data, and if no agreement could be reached when discrepancies were observed, the two investigators discussed with a third investigator (Xq.L) to reach a consensus. For each study included, we extracted information including the first author's name, publication year, study design, country, study participants, mean age, gender, dosage and duration of PPI use, adjusted HR estimates with 95% CI, or the number (N), mean (M), standard deviation (SD) which can estimate SMD and covariates adjusted for in the multivariable analysis. The nine-star Newcastle-Ottawa quality assessment scale [10] was used to evaluate the quality of the cohort studies, and case-control studies, with a higher score indicating higher study quality.

The primary study endpoint was any-site fractures, hip fracture, and spine fracture as defined by International Classification of Disease 10th revision codes. The secondary endpoint was osteoporosis and BMD loss, in which osteoporosis was defined as T-score < -2.5 [11], T-score was calculated based on the number of standard deviations that BMD was above or below the mean for healthy young adults, and BMD loss was defined as the change in BMD among PPI users and nonusers between successive BMD assessments.

2.4. Statistical analysis

HR reflected the association between PPI use and fracture and osteoporosis risk. SMD was used to assess the association between PPI use and BMD. We assumed that RR approximated HR, and OR approximated RR since fracture, osteoporosis are rare events [12]. When crude HR and adjusted HR were available, we chose the adjusted risk estimates reported in the study. Among all the included studies, seven studies that provided HR for several categories, which were then combined by random-effects models and the combined HRs were used in the final analysis (S1 Table). We calculated the pooled HR, SMD, and 95% CI by using Stata version 12.0 software in a single study or all studies. We used random rather than fixed effects model to estimate pooled HR to account for heterogeneity, because the former is more conservative. I^2 statistic was calculated to assess heterogeneity among studies, and we classified it using the following interpretation: $I^2 < 50\%$, low heterogeneity; 50%–75%, moderate heterogeneity; and > 75%, high heterogeneity [13]. Publication bias was assessed using funnel plots and the Begg's adjusted rank correlation ($P < 0.05$ was considered significant). The tests for funnel plot asymmetry were not conducted when the number of included studies was less than five. Subgroup analyses were conducted according to various study characteristics and clinical factors, including the type of studies, location, mean age, female proportion, duration of PPI use, publication year, and whether adjusted for smoking or not. Since the duration of PPI use and the mean age of participants varied across studies, the short duration of PPI use, was defined as a duration of exposure of < 1 year, and the longer duration of PPI exposure, was defined as ≥ 1 year. The younger group was defined as mean age < 50 years, while the elderly group was defined as ≥ 50 years.

3. Results

3.1. Literature search

We initially retrieved 1313 articles, of which 147 articles were excluded after adjusting for duplicates. Of the remaining 1166 articles, 1112 were excluded after the initial title and abstract screening, because they were review articles, laboratory studies, or irrelevant to our study purpose. The full texts of the remaining 54 articles were examined in detail, of which 23 articles were excluded according to the eligibility criteria (Fig. 1). Among the included studies, one of them reported results from two independent cohorts [14], which were analyzed separately in the meta-analysis. Finally, one relevant conference abstract was identified and analyzed using data reported in the abstract only [15]. Hence, 31 articles involving 32 studies met the predefined inclusion criteria.

3.2. Study characteristics

A total of 2-181-546 individuals were included in 32 eligible studies. The primary characteristics of the studies are shown in Table 1. Thirteen studies were conducted in North America [14,16–27], 10 in Europe [8,15,28–35], 6 in Asia [11,36–40], and 2 in Oceania [41,42]. The studies included 17 cohort studies, 13 case-control studies, and 2 cross-sectional studies which were published between 2006 and 2018,

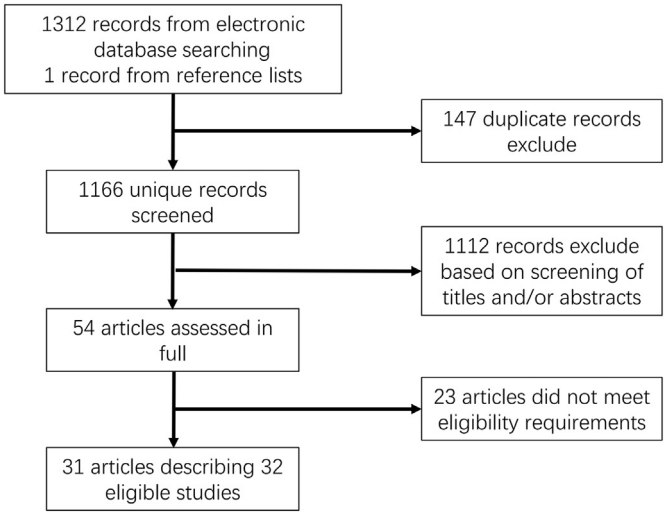

Fig. 1. Flowchart of the literature search.

Table 1
Characteristic of the included studies.

Study	Study design	Country	Study participants	Mean age (y)	Gender	Dosage	Duration	Fracture/ osteoporosis/BMD	HR (95% CI)/N M (SD)	Adjustments
Harding, 2018	Cohort	USA	408 PPI users and 4030 non-users	74	Female: 58.0%	light use: 31–540 SDD moderate use: 541–1080 SDD heavy use: ≥1081 SDD	1–19 months 19–36 months ≥ 36 months	Any-site	1.08 (0.90–1.30)	Age, sex, comorbidities
Lai, 2018	Case-control	Taiwan (China)	7208 cases and 7208 controls	79.8	Female: 60.3%	NA	< 3 months 3–6 months 6–12 months ≥ 12 months	Hip	1.16 (1.0.01–1.34)	Age, sex, comorbidities, medications
Lin, 2018	Cohort	Taiwan (China)	5298 PPI users and 5298 non-users	66.8	Female: 36.7%	1–90 cDDD 91–365 cDDD > 365 cDDD	< 3 months 3–12 months ≥ 12 months	Hip Spine Osteoporosis	1.18 (1.00–1.38) 1.33 (1.14–1.54) 1.26 (1.13–1.41)	Age, sex, comorbidities, medications, income level
Lenihan, 2017	Case-control	USA	231 cases and 15,575 controls	51.5	Female: 40.4%	Any use: covering < 80% of the 365 days Higher use: covering ≥ 80% of the 365 days	< 1 year	Hip	1.40 (1.13–1.73)	Age, sex, race, medications
Chen, 2016	Cohort	Taiwan(China)	10,620 PPI users and 20,738 non-users	46.9	Female: 43.8%	NA	NA	Hip Osteoporosis	0.79 (0.53–1.18) 1.50 (1.39–1.62)	Age, sex, comorbidities, index year
Wu, 2016	Cohort	Taiwan(China)	2247 PPI users and 24,885 non-users	54.4	Female: 50.0%	NA	NA	Osteoporosis	1.17 (1.03–1.34)	Age, sex
Jacob, 2016	Case-control	German	3092 cases and 3092 controls	72.3	Female: 100%	NA	≤1 year 1–5 years > 5 years	Osteoporosis	1.62 (1.43–2.06)	Age, health insurance, index year, physician
Freedberg, 2015	Case-control	UK	124,799 cases and 605,643 controls	4–29	Female: 34.6%	≥180 cumulative doses	NA	Any-site	1.28 (1.05–1.56)	Age, sex, medications
Van, 2015	Cohort	Australian	2328 PPI users and 2104 non-users	78.3	Female: 100%	< 400 DDD ≥400 DDD	NA	Any-site Osteoporosis	1.29 (1.08–1.55) 1.28 (1.13–1.44)	Age, comorbidities, medications, BMI, area
Lewis, 2014	Cohort	Australian	120 PPI users and 925 non-users	80	Female: 100%	27.1 ± 11.2 mg/d	≥1 year	Any-site	1.95 (1.20–3.16)	Medications, falls risk factor, hip BMD
Adams, 2014	Case-control	USA	6774 cases and 6774 controls	≥45	Female: 0%	NA	NA	Hip	1.12 (1.03–1.21)	Age, race, comorbidities, medical center
Ding, 2014	Cohort	USA	1064 PPI users and 23,672 non-users	78.6	Female: 82.1%	PDC < 0.40 PDC 0.40–0.79 PDC ≥0.80	≥6 months	Any-site Hip Spine	1.27 (1.12–1.43) 1.32 (1.01–1.71) 1.69 (1.26–2.27)	Age, sex, race, BMI, comorbidities, smoking status
Moberg, 2014	Cohort	Sweden	121 PPI users and 6130 non-users	56.4	Female: 100%	NA	NA	Any-site	2.01 (1.31–3.08)	Age, BMI, smoking status
Soriano, 2014	Case-control	UK	10,958 cases and 20,000 controls	40–89	Female: 74.8%	Low dose Medium dose High dose	< 1 month 1–3 months 3–12 months > 12 months	Hip	1.09 (1.01–1.17)	Age, sex, BMI, index date, Medications
Reyes, 2013	Case-control	Spain	358 cases and 698 controls	82	Female: 77%	NA	NA	Hip	1.24 (0.93–1.65)	Age, sex, comorbidities, medications
Fraser, 2013	Cohort	Canada	261 PPI users and 9162 non-users	64.8	Female: 73.7%	NA	0–10 years	Any-site Hip	1.33 (1.15–1.56) 1.52 (0.99–2.35)	Age, sex, BMI, medications, smoking status, activity level
Lee, 2013	Case-control	Korea	24,710 cases and 98,642 controls	77.7	Female: 73.4%	0 < DDD < 30 30 ≤ DDD < 90 90 ≤ DDD	< 1 month 1–3 months ≥3 months	Hip	1.34 (1.24–1.44)	Age, sex, osteoporosis
Mello, 2012	Cohort	USA	679 PPI users and 1894 non-users	49.7	Female: 0%	NA	> 1 year	Any-site	3.87 (2.46–6.08)	Age, race, BMI, medications, tobacco
Khalili, 2012	Cohort	USA	5341 PPI users and 74,558 non-users	66.8	Female: 100%	NA	> 2 years	Hip	1.36 (1.13–1.63)	BMI, medications, smoking history
Targownik, 2010	Cross-sectional	Canada	6149 cases and 15,784 controls	69.1	Female: 91.8%	Low < 750 doses Moderate 750–1500 doses High ≥1500 doses	> 5 years	Osteoporosis (hip) Osteoporosis (spine)	0.98 (0.83–1.16) 0.90 (0.78–1.04)	Age, sex
Gray, 2010	Cohort	USA		50–79		NA				

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Country	Study participants	Mean age (y)	Gender	Dosage	Duration	Fracture/ osteoporosis/BMD	HR (95% CI)/N M (SD)	Adjustments
			2731 PPI users and 119,804 non-users		Female: 100%		< 1 year 1–3 years > 3 years	Any-site Hip Spine	1.25 (1.15–1.36) 1.00 (0.71–1.40) 1.47 (1.18–1.82)	Age, race, BMI, comorbidities, medications, smoking
Corley, 2010	Case-control	USA	33,752 cases and 130,471 controls	≥18	Female: 65.7%	< 0.75 pills/day 0.75–1.49 pills/day ≥1.5 pills/day	> 1 year	Hip	1.30 (1.21–1.39)	Age, sex, race, smoking
Targownik, 2008	Case-control	Canada	15,792 cases and 47,289 controls	≥50	Female: 70.3%	≥0.70 standard doses	≥1 year	Any-site Hip	0.99 (0.90–1.11) 1.09 (0.88–1.34)	Age, sex, race, comorbidities, medications
Kaye, 2008	Case-control	UK	1098 cases and 10,923 controls	50–79	Female: 71.6%	NA	NA	Hip	0.90 (0.70–1.10)	Age, sex
Yu, 2008	Cohort	USA	MrOS: 5755 men SOF: 5339 women	≥65	Female: 0% Female: 100%	NA	NA	Any-site	0.62 (0.26–1.46) 1.16 (0.80–1.68)	Age, race, BMI, alcohol, medications
Roux, 2008	Cohort	France	61 users and 1150 non-users	65.9	Female: 100%	NA	< 1 year	Spine	3.10 (1.14–8.44)	Age, BMI, medications, smoking
Vestergaard, 2006	Case-control	Denmark	124,655 cases and 373,962 controls	43.4	Female: 51.8%	< 0.25 DDD 0.25–0.99 DDD ≥1 DDD	< 1 year	Any-site Hip Spine	1.18 (1.12–1.43) 1.45 (1.28–1.65) 1.60 (1.25–2.04	Age, sex, medications
Yang, 2006	Case-control	UK	13,556 cases and 135,386 controls	77	Female: 79.9%	NA	> 1 year	Hip	1.44 (1.30–1.59)	Age, sex, comorbidities, medications, smoking
Manickavasagan, 2017	Cohort	Netherland	30 PPI users and 30 non-users	69	Female: 90%	NA	≥5 years	Hip Femoral Spine	30–0.69 (1.24) 30–0.86 (0.92); 30–1.43 (0.84) 30–1.26 (0.89); 30–0.51 (1.56) 30–1.18 (1.24)	Age, sex
Targownik, 2016	Cohort	Canada	52 PPI users and 52 non-users	65	Female: 51.0%	NA	≥5 years	Hip Femoral Spine	52–0.32(1.01) 52–0.29(1.16); 52 0.13(0.89) 52 0.12(1.07); 52–0.73(1.30) 52–0.36(1.87)	Age, sex, BMI, smoking
Abbas,2016	Cross-sectional	Iran	40 PPI users and 40 non-users	40.7	Female: 61.3%	NA	≥2 years	Femoral Spine	40–0.44 (1.11) 40 0.19 (0.95); 40–0.94 (0.92) 40–0.53 (1.24)	Age, sex, BMI, serum vitamin D levels

SDD: standard daily doses; NA: non-available; cDDD: cumulative defined daily dose; BMI: body mass index; PDC: proportion of days covered.

Table 2
Methodological quality of included cohort studies and case-control studies based on the Newcastle-Ottawa Scale.

Cohort studies	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Yu, 2008	*	*	*	*	**	*	*		8
Roux, 2008	*	*		*	**	*	*	*	8
Gray, 2010	*	*		*	**	*	*	*	8
Mello, 2012	*	*		*	**	*	*		7
Khalili, 2012		*		*	**		*	*	6
Fraser, 2013	*	*	*	*	**	*	*	*	9
Lewis, 2014	*	*		*	**		*		7
Ding, 2014	*	*		*	**		*	*	7
Moberg, 2014	*	*		*	**	*	*		7
Van, 2015		*	*	*	**	*	*		7
Chen, 2016	*	*	*	*	**	*	*		8
Wu, 2016	*	*		*	**		*		6
Targownik, 2016	*	*	*	*	**		*	*	8
Lin, 2018	*	*	*	*	**	*	*	*	9
Harding, 2018	*	*	*	*	**		*		7

Case-control studies	Selection				Comparability	Exposure			Total score
	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Yang, 2006		*	*	*	**		*		6
Vestergaard, 2006		*	*	*	**		*		6
Kaye, 2008		*	*	*	**		*		6
Targownik, 2008	*	*	*	*	**		*		7
Corley, 2010	*	*	*	*	**		*		7
Reyes, 2013		*	*	*	**		*		6
Lee J, 2013	*	*	*	*	**	*	*		8
Adams, 2014	*	*	*	*	**		*		7
Soriano, 2014	*	*	*	*	**		*		7
Freedberg, 2015		*	*	*	**		*		6
Jacob, 2016		*	*	*	**		*		6
Lenihan, 2017	*	*	*	*	**		*		7
Lai, 2018		*	*	*	**		*		6

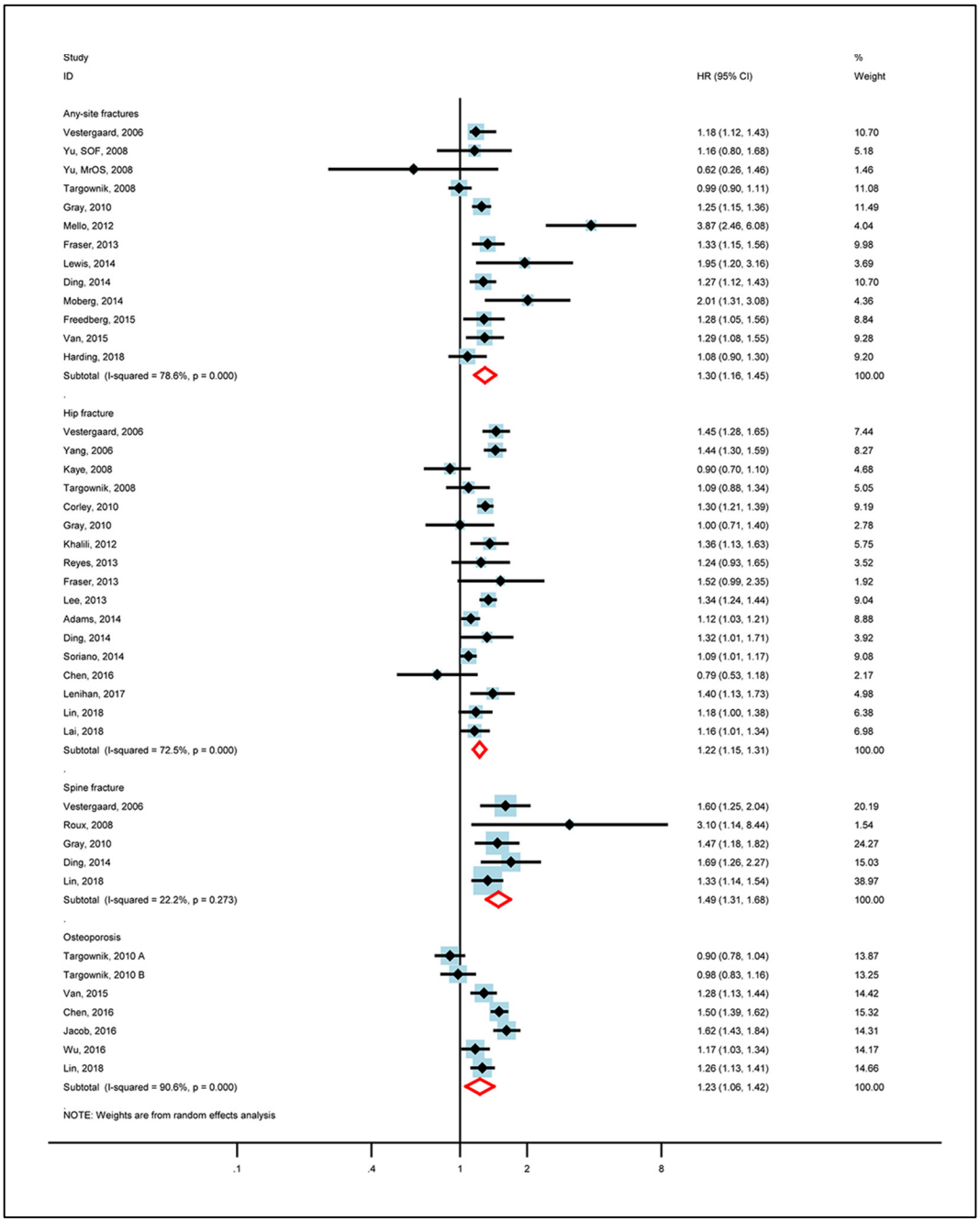

Fig. 2. Forest plots showing the association between PPI use and risk of any-site, hip, spine fracture, and osteoporosis. HR of any-site, hip, spine fracture and osteoporosis associated with PPI were compared to no PPI use cohorts. The size of each square is proportional to the study's weight (inverse of the variance); Horizontal lines indicate 95% CI; Diamonds indicate a summary risk estimate with its corresponding 95% CI.

and no randomized controlled trials were identified. Study size ranged from 60 to 730–442 subjects, with each of the 6 largest studies involving > 100–000 participants. The quality measured by Newcastle-Ottawa quality assessment scale ranged from 6 to 9, indicating a relatively good quality of these observational studies (Table 2). Almost all studies controlled for age and gender, and each study adjusted for other multiple potential confounders, such as body mass index (BMI), race, smoking status, alcohol use, medications, comorbidities and so on.

3.3. PPI use and risk of any-site, hip, and spine fracture

The analyses of PPI use and risk of any-site, hip, and spine fracture were based on individual 13, 17, and 5 studies. Fig. 2 shows multivariable-adjusted HRs of any-site, hip, and spine fractures in individual studies and all studies combined. Overall, patients taking PPI experienced a moderate increased risk for developing any-site fractures (HR: 1.30; 95% CI: 1.16 to 1.45), hip fracture (HR:1.22; 95% CI: 1.15 to 1.31), and spine fracture (HR: 1.49; 95% CI: 1.31 to 1.68) compared to those not on PPI therapy. Evidence of high heterogeneity of HRs was present among any-site fractures (I^2: 78.6%; $p < 0.001$) and moderate heterogeneity was observed among hip fracture (I^2: 72.5%; $p < 0.001$) studies, but not in the findings of spine fracture (I^2: 22.2%; $p = 0.273$). Neither funnel plots (Fig. 3) nor Begg test (Fig. 4) results showed any evidence of publication bias among any-site fractures (Begg test: $p = 0.54$), and hip fracture (Begg test: $p = 0.39$) studies. However, the evidence of publication bias was found in spine fracture studies (Begg

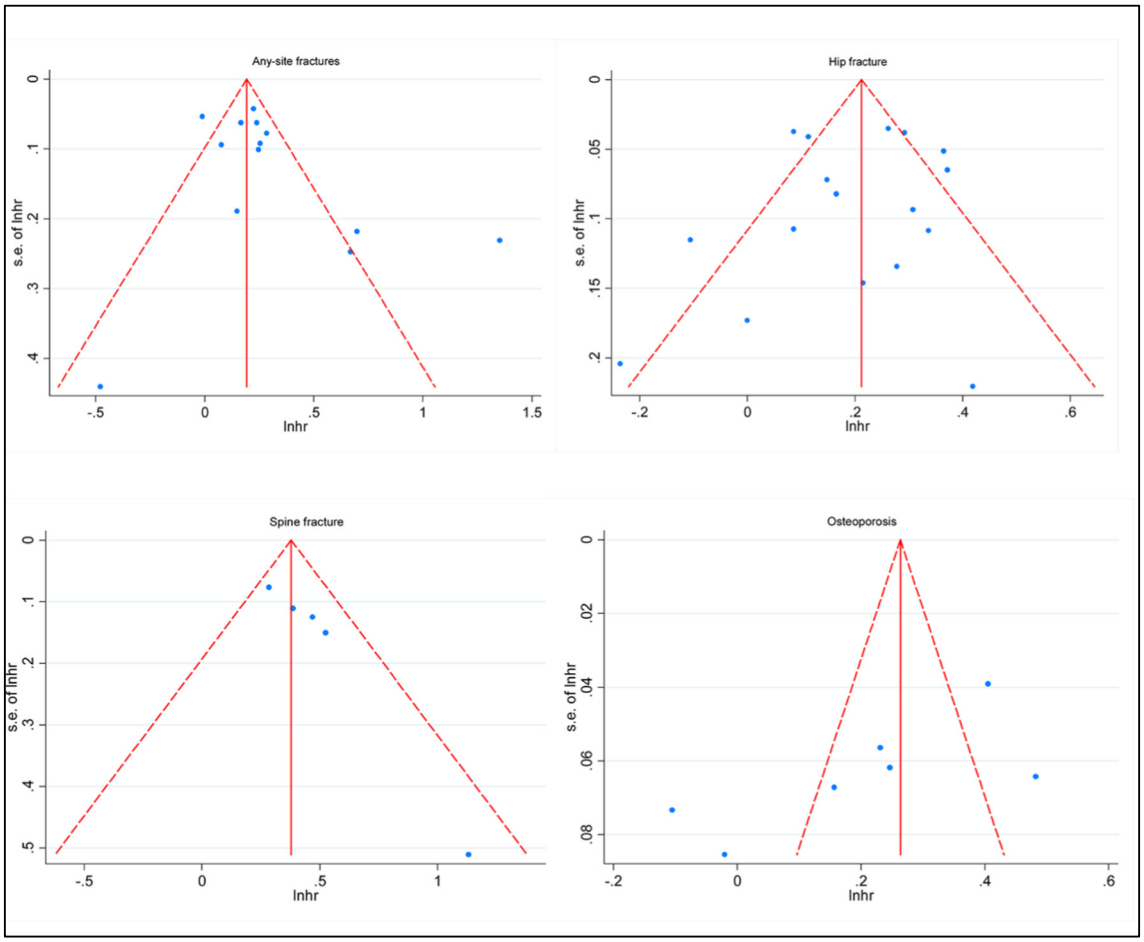

Fig. 3. Funnel plot to assess publication bias in studies among any-site, hip, spine fracture, and osteoporosis. Funnel plot with pseudo 95% CI. Each blue dot represents an identified study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

test: $p = 0.03$). Therefore, we further assessed the influence of publication bias on the final result in spine fracture studies using the trim and filling sensitivity analysis. As shown in Fig. 5, no significant effect was found among the results (HR: 1.49 and HR: 1.43), although the strength of the association was slightly attenuated, suggesting that the association is not an artifact of unpublished studies.

To further explore the heterogeneity among studies investigating the effects of PPI use on fracture risk, we performed stratified analysis across various study characteristics and clinical factors, including the type of studies, location, mean age, female proportion, duration of PPI use, publication year and whether adjusted for smoking or not (Table 3). Subgroup analysis to identify the source of heterogeneity of spine fracture was not performed due to the limited number of included studies, and all studies among spine fracture were positive results. As in any-site fractures, the increased risk obtained persisted when stratified by location, mean age and whether adjusted for smoking or not. However, when stratified by the type of study, analysis of three case-control studies showed that the associated risk was no longer statistically significant (HR: 1.13; 95%CI: 0.97 to 1.31) and lower heterogeneity was recorded (I^2: 72.9%; $p = 0.025$). In the subgroup analysis by female proportion, analysis of three studies on female proportion < 50% also found no significant result (HR: 1.53; 95%CI: 0.63 to 3.71), although heterogeneity was increased (I^2: 91.4%; $p < 0.001$). A similar result was also obtained when stratified by publication year, analysis of four studies with respect to publication year < 2010 showed that the subtotal result was no longer statistically significant (HR: 1.07; 95%CI: 0.93 to 1.24). As in hip fracture, we found that the associated risk was no longer statistically significant when stratified by mean age, based on the analysis of two studies with mean age < 50 years (HR: 1.10; 95%CI: 0.61 to 2.00), although higher heterogeneity was recorded (I^2: 87.6%; $p = 0.005$). (Table 3).

3.4. PPI use and risk of osteoporosis

Six articles with seven results provided data on the risk of PPI use and osteoporosis. As shown in Fig. 2, there was a moderate increase in the risk of osteoporosis (HR: 1.23; 95%CI: 1.06–1.42) among PPI users with high heterogeneity (I^2: 90.6%, $p < 0.001$). When the analysis was confined to the cohort and case-control studies, the overall combined HR (HR:1.36; 95%CI: 1.22–1.52) did not significantly change, and heterogeneity (I^2: 80.8%; $p < 0.001$) was observed among the remaining studies. Neither funnel plots (Fig. 3) nor Begg test (Fig. 4) results showed evidence of publication bias (Begg test: $p = 0.07$).

3.5. PPI use and risk of BMD loss

Only three articles provided data on the risk of PPI use and BMD. Fig. 6 shows SMD and 95%CI of femoral (SMD: −0.27; 95%CI: −0.62 to 0.09), spine (SMD: −0.06; 95%CI: −0.54 to 0.41) BMD in individual studies and all studies combined. Overall, we were unable to conclude a correlation between PPI use and BMD loss either in femoral or spine.

4. Discussion

This is an update meta-analysis of 32 observational studies involving 2-181-546 individuals which evaluated the effect of PPI use on the

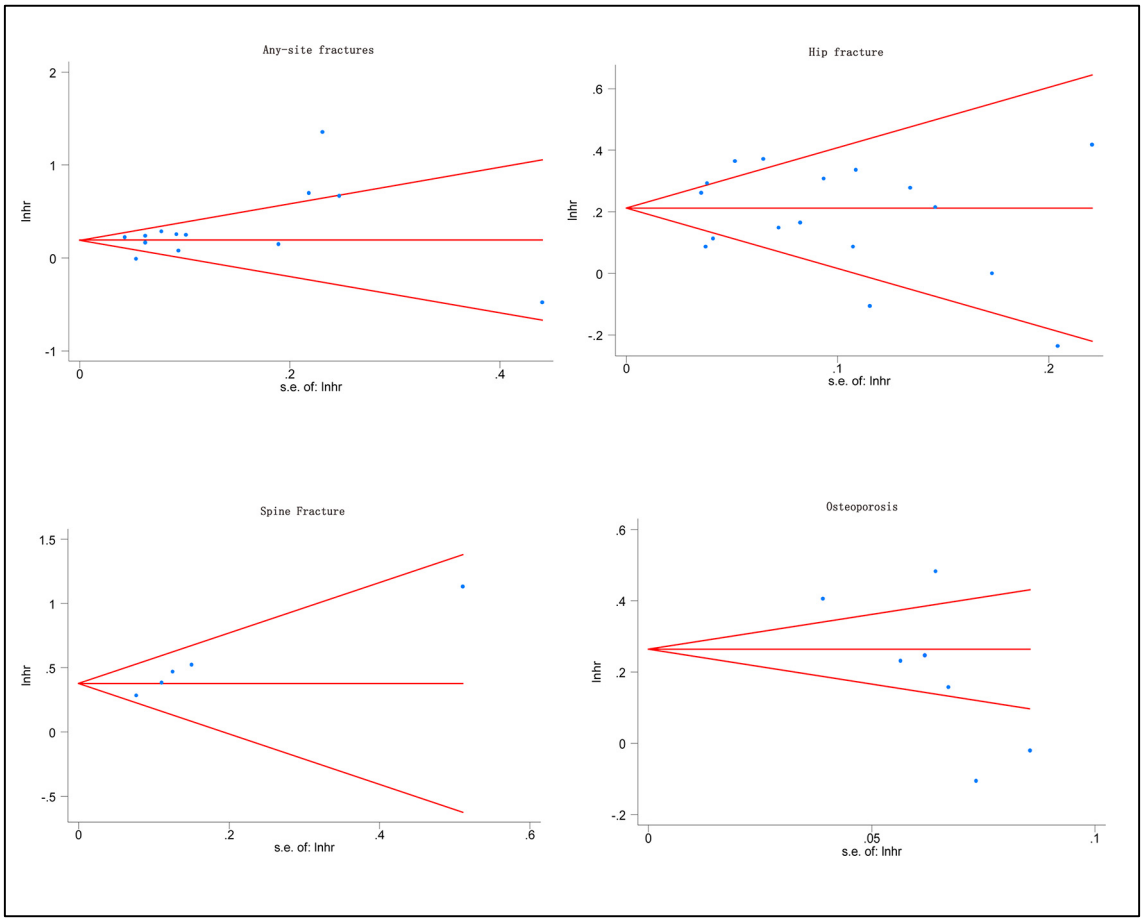

Fig. 4. Begg test to assess publication bias in studies among any-site, hip, spine fracture and osteoporosis. Begg funnel plot with pseudo 95% CI. Each blue dot represents an identified study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

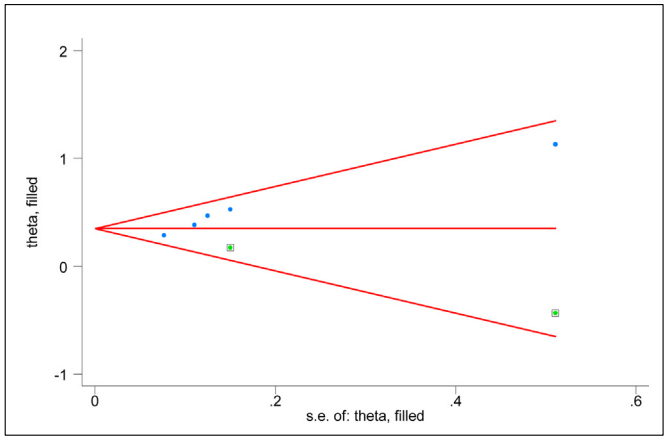

Fig. 5. Filled funnel plot showing the effect of publication bias. Filled funnel plot with pseudo 95% CI. The blue dots represent identified studies, the green dots with black box represent estimated missing studies after adjustment for publication bias. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

risk of bone diseases, such as bone fractures, osteoporosis and BMD loss. Our meta-analysis found that there was a moderate increased risk of any-site fractures, hip fracture, spine fracture and osteoporosis in people using PPI, but found no correlation between PPI use and BMD loss. In stratified analysis, the association of PPI use with any-site fractures or hip fracture was persisted when stratified by mostly study characteristics, and the strength of the association increased with the duration of PPI use among the studies on hip fracture, which showed a causal relationship between PPI use and any-site fracture, hip fracture. When stratified by whether adjusted for smoking or not, we found that the risk seemed to increase when adjusted for smoking, which indicated that smoking may not be a risk factor for bone fracture (Table 3). Our analysis included six studies [14,16,20,30,37,39] that were not included in previous meta-analyses [43] by Nassar et al. regarding the association of PPI use and fracture risk. Moreover, we analyzed the correlation between PPI use and osteoporosis.

Although the mechanism by which PPI use increases fracture and osteoporosis risk remains unknown, several plausible explanations have been suggested. First, PPI may reduce intestinal calcium absorption, thereby increasing bone resorption [44]. Yet, it should be recognized that but the ability of acid suppression to cause calcium malabsorption may be affected by dietary calcium intake, time of medication with meals, or many other factors [29]. Furthermore, the role of gastric pH in calcium absorption is controversial as it is based on limited data. Second, long-term PPI use may reduce serum vitamin B12 absorption [42]. Vitamin B12 is an essential co-factor for DNA synthesis and cellular energy production [45], and thus prolonged vitamin B12 deficiency can lead to gait disorders, muscle weakness, cognitive decline and visual disturbances which may result in increased falling rate. On this basis, it is known that many low trauma fractures, including hip fracture, which occur in patients without osteoporosis may be due to increased falling in elderly people. Third, some animal or human studies suggested that increased activity of the parathyroid gland induced by secondary hypergastrinemia could be a mechanistic link for PPI-induced bone loss [46,47]. However, it should be noted that PPI are mostly used by elderly people, some of whom are postmenopausal

Table 3
Stratified analysis of PPI therapy and risk of any-site, hip fracture.

Group	Subgroups	No. of studies	HR(95%CI)	*P* value	I2
Any-site fractures					
Type of studies	Cohort	10	1.38 (1.20–1.58)	< 0.001	75.70%
	Case-control	3	1.13 (0.97–1.31)	0.025	72.90%
Location	North America	6	1.33 (1.08–1.63)	< 0.001	82.80%
	Europe	5	1.24 (1.06–1.45)	0.001	79.20%
	Oceania	2	1.49 (1.01–2.19)	0.117	59.30%
Mean age	< 50 y	3	1.68 (1.08–2.61)	< 0.001	91.90%
	≥50 y	10	1.23 (1.11–1.37)	< 0.001	70.00%
Female proportion	< 50%	3	1.53 (0.63–3.71)	< 0.001	91.40%
	≥50%	10	1.23 (1.12–1.35)	0.001	67.70%
Publication year	< 2010	4	1.07 (0.93–1.24)	0.099	52.30%
	≥2010	9	1.40 (1.23–1.59)	< 0.001	76.40%
Adjusted for smoking	Yes	5	1.54 (1.26–1.88)	< 0.001	85.40%
	No	8	1.16 (1.04–1.31)	0.017	59.20%
Hip fracture					
Type of studies	Cohort	6	1.20 (1.04–1.38)	0.122	42.50%
	Case-control	11	1.23 (1.14–1.33)	< 0.001	79.80%
Location	North America	6	1.25 (1.14–1.37)	0.036	57.90%
	Europe	7	1.22 (1.06–1.41)	< 0.001	83.20%
	Asia	4	1.18 (1.03–1.36)	0.021	69.20%
Mean age	< 50 y	2	1.10 (0.61–2.00)	0.005	87.60%
	≥50 y	12	1.25 (1.15–1.35)	0.01	55.70%
Female proportion	< 50%	4	1.16 (1.01–1.32)	0.067	58.00%
	≥50%	13	1.25 (1.15–1.34)	< 0.001	73.20%
Publication year	< 2010	4	1.22 (1.01–1.48)	< 0.001	84.30%
	≥2010	13	1.22 (1.14–1.30)	0.001	64.10%
duration of PPI use	< 1	5	1.31 (1.13–1.53)	< 0.001	80.50%
	≥1	7	1.37 (1.26–1.49)	0.005	67.50%
Adjusted for smoking	Yes	6	1.34 (1.26–1.43)	0.315	15.40%
	No	11	1.18 (1.08–1.28)	< 0.001	74.80%

women, who suffer from multiple comorbidities that lead to partial immobility. Thus, the associations found between PPI use and bone disease could be a selection bias of elderly people with osteoporosis who happened to be treated with PPI. This is just one of the many confounding factors. It is worth mentioning that Kaye et al. [33]. found no correlation between PPI and hip fracture (HR:0.90; 95%CI: 0.70–1.10) when many major risk factors were excluded. Therefore, more rigorous experiments are needed to clarify the risk factors and additional mechanisms of PPI therapy.

Results of this study raise another question, why would PPI be associated with increased risk for bone fractures and osteoporosis but not BMD loss? First, we note that only three articles were included in the assessment of the relationship between PPI use and BMD change, which may lead to bias in the final result. Second, by definition, osteoporosis is

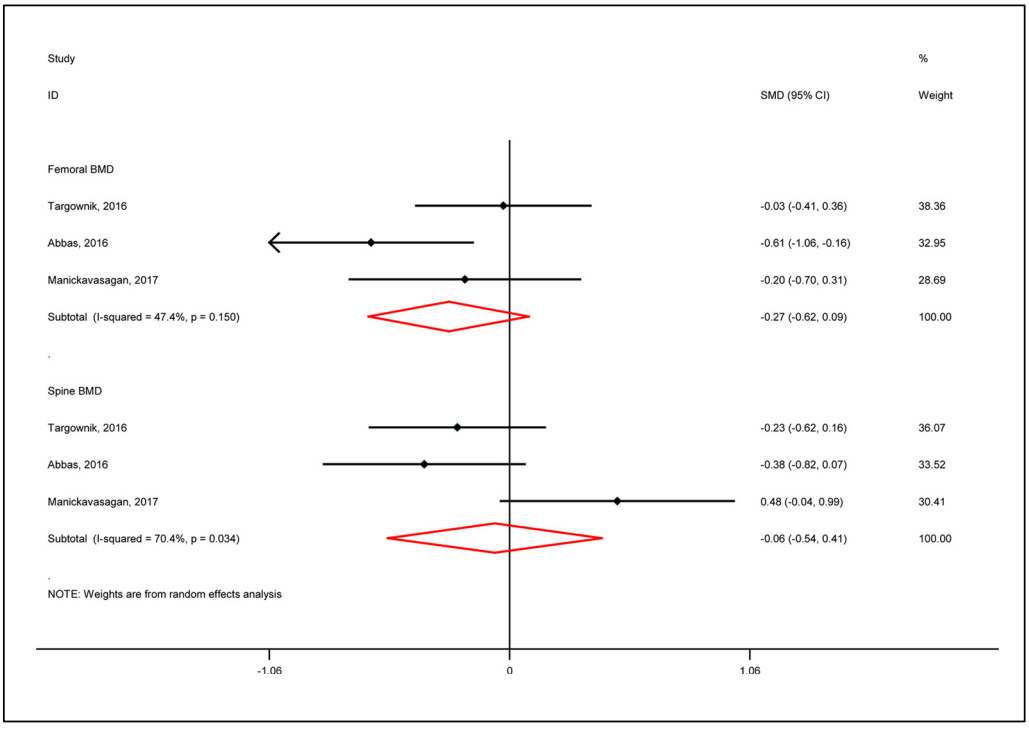

Fig. 6. Forest plots showing the association between PPI use and risk of BMD loss. SMD of bone mineral density (BMD) associated with PPI use cohorts was compared to no PPI users. The size of each square is proportional to the study's weight (inverse of variance); Horizontal lines indicate 95% CI; Diamonds indicate summary risk estimate with its corresponding 95% CI.

also part of BMD loss, thus the fundamental question is whether the use of PPI will lead to changes in BMD, implying that studying the relationship between PPI and osteoporosis is important. In fact, the relationship between PPI and osteoporosis can corroborate the correlation between PPI and BMD loss. Third, several previous studies suggested that PPI use caused increased fracture risk due to osteoporosis or decreased BMD [26,48], however, this conclusion is controversial. As indicated by Thaler et al. [49] and Fiona et al. [45], PPI use may increase the risk of falling, which increases the incidence of non-osteoporotic fracture. Thus, there may be no causal association between the two outcomes of fracture and BMD loss or osteoporosis caused by the PPI use.

This meta-analysis has several notable strengths including the strict inclusion criteria, the large number of patients included, the diversity of the study population, and the fact that all subgroup analyses were prespecified. Also, the absence of publication bias supports the robustness of the study findings. Moreover, we performed a more comprehensive analysis of the relationship between PPI use and bone diseases from three aspects, i.e. fracture, osteoporosis and BMD loss, compared with previous studies, which led to the conclusion that PPI use may actually increase the risk of bone fractures. But the relationship between PPI and BMD remains uncertain considering the contradictory results in this study among osteoporosis and BMD loss cohorts. Yet, there are some limitations to our study that are worth mentioning. First, we only included observational study published in English language, and hence useful data from the studies published in other languages may have been excluded. Second, moderate and even high heterogeneity were observed in the results from various studies and the subgroup analyses. Although differences in the types of studies, female proportion, publication year, and duration of PPI use may partially explain this observation, heterogeneity still existed in the outcome of any-site fractures and hip fracture. However, similar risk estimates were consistently observed in most stratified analyses which indicates that heterogeneity might not affect the results significantly. Third, subgroup analyses based on types of PPI used were not performed because only few studies have evaluated the associations between types of PPI and fracture and osteoporosis risk. Also, based on the study by van der Hoorn et al. [41], we observed that the use of esomeprazole and rabeprazole increased fracture and osteoporosis risk, but not any of the other PPI types. Therefore, we suggest that further studies are needed to evaluate the association between different types of PPI and fracture and osteoporosis risk in subjects while controlling for other confounders. Fourth, the presence of possible confounding factors e.g. underlying diseases such as gastrointestinal disorders, stroke, and kidney transplantation might influence the results, since those who receive PPI therapy often suffer from these conditions, which may also be risk factors for fractures and osteoporosis. Based on these limitations, long-term, well-designed randomized controlled trials (RCTs) are needed to explicitly assess the correlation between PPI use and fractures or osteoporosis. Finally, we were unable to pool the dose-response effects of PPI use due to inconsistent and incompatible definitions among studies.

5. Conclusion

Results of this meta-analysis suggest that PPI may moderately increase the risk of any-site, hip, spine fracture. However, the relationship between PPI and BMD remains uncertain. Due to the widespread use of PPI and the impact of fractures on human health, clinicians should carefully evaluate the patient condition before prescribing PPI therapy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2018.12.058.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

We thank Prof. Jiaming Sun for his assistance in structuring the search strings and linguistic advice. This work was supported by the National Natural Science Foundation of China (No. 81701922 to Zhenxing Wang, No. 81601701 to Jiecong Wang).

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