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Review Article

An updated meta-analysis: the effect of proton pump inhibitor on risk of osteoporosis and fracture

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Abstract: The aim of this study was to evaluate the association between proton pump inhibitor (PPI) use and risk of osteoporosis and fracture by performing an updated meta-analysis. We searched PubMed, EMBASE, and Web of Knowledge from inception to March 2017 for observational studies reporting the risk of osteoporosis and/or fracture with PPIs. Random-effects meta-analysis was used to obtain pooled estimates of effect due to heterogeneity. We identified 27 studies with a total of 1885507 subjects included. According to recent studies, use of PPIs was associated with an elevated risk of osteoporosis (OR 1.39, 95% CI 1.22-1.58). A meta-analysis of 20 observational studies showed that the overall risk of hip fracture was higher among people using PPIs (OR 1.22, 95% CI 1.15-1.30). Similar to hip fracture, high risk of any-site and spine fractures was observed in PPI users (OR 1.19 95% CI 1.12-1.27 and OR 1.53, 95% CI 1.36-1.73, respectively). Subgroup analyses by dose indicated that the high dose and the low dose group were consistent on the strength of the association between PPIs therapy and risk of hip fracture. In addition, no time response relationship was found in subgroup analysis. This meta-analysis demonstrates PPI therapy may be linked to an increased risk of both osteoporosis and fracture, but no evidence of dose-response and duration-response relationship was found in subgroup analysis. Considering the effect of unmeasured confounding, more rigorous experiments are needed to clarify whether PPI therapy or residual confounding lead to the increased risk of osteoporosis and fracture.

Keywords: Osteoporosis, fracture, meta-analysis, proton-pump inhibitors

Introduction

Osteoporosis is a very common medical condition and osteoporosis related fracture could lead to significant disability and poor quality of life, especially for elderly patients with cognitive obstacles and multiple comorbidities, with a mortality rate of 36.2% within 180 days of hip fracture [1].

Proton pump inhibitors (PPIs) are one of the most widely prescribed medications worldwide and their use is continuously increasing. Such drugs are among the most widely used antacids and have become a lynchpin in treatment for various gastrointestinal diseases, including H. pylori-negative peptic ulcers, gastroesophageal reflux disease (GERD), NSAID-induced gastropathy and acid hypersecretory conditions, such as Zollinger Ellison syndrome [2]. Moreover, they are an essential component of triple or quadruple therapies aimed at eradicating helicobacter pylori (Hp) infection, which has become the fundamental treatment to cure ulcer disease and its complications [3]. In recent years, a growing concern is the safety of PPIs. Several adverse effects of long-term PPI use have been reported, including decreased bone quality [4-27], pneumonia [28], enteric infections [29]. Some research suggests that use of PPIs may be linked to an increased incidence of fracture [4, 5, 7-10, 12, 16-19, 21, 23, 24, 26, 30, 31]. Others, however, have been unable to confirm this association [6, 11, 13, 15, 20, 22, 27]. Despite limited definitive evidence on the magnitude of risk associated with PPI use and widely varying results of the avail-

able data, warnings about PPIs and potentially increased fracture risk have been issued in Australia and in the US [32, 33].

Meta-analysis of the data suggests overall there is an association between PPI therapy and increased risk of fracture [34-38]. Use of PPIs has been associated with fracture in the elderly who are osteoporotic or at high risk for osteoporosis. Yet the relationship of chronic PPI use and the risk of osteoporosis is unclear. In addition, a number of epidemiologic studies typically compared all PPI users with non-users, while the effect may depend on the duration, interval time or dose of PPI use [4, 5, 9, 12, 13, 17, 19, 22]. Given the widespread use of PPIs, investigation of duration, interval time and dose of PPI use may not only give more insight into the reported adverse effects on bone health, but also have important implications for prescribing.

Recently, several new observational studies regarding the association of PPI use and Osteoporosis and/or fracture risk have been published [6, 12, 14, 23, 25, 30, 31, 39], which were not included by previous meta-analyses. We, therefore, performed an updated meta-analyses of existing observational studies to evaluate the effect of duration, interval time and dose of PPI use on osteoporosis and fracture.

Method

Search strategy

We searched PubMed, EMBASE and Web of Knowledge from inception up to March 2017. In addition, we signed up with PubMed to receive automated electronic notifications for any new articles. Recent review articles were examined for additional relevant studies. To identify observational studies, we used the following combinations of search terms: ("acid-suppressive therapy" OR "acid-suppressive drugs" OR "acid-suppressive medications" OR "gastric acid suppressants" OR "anti-ulcer agent*" OR "antacid" OR "proton pump inhibitors" OR "proton pumps" OR "PPI or PPIs" OR omeprazole OR nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole) AND ("fracture or fractures" OR "bone density" OR "osteoporosis"). We only included studies involving humans that were published in English.

Eligibility criteria

We included any study that met all of the following criteria: was a cohort study or a case-control study; evaluated the effect of PPI use on osteoporosis and/or fracture in general patient population; quantified the outcome with adjusted odds ratios (ORs), relative risks (RRs) or number of events, and corresponding 95% confidence intervals (CIs). We did not restrict studies by healthcare settings, duration, dose or type of PPI, but we aimed to look at subgroups of studies where such data were available.

Exclusion criteria

Exclusion criteria were as follows: cross-sectional study; no control group of patients; studies included patients who suffered from Acquired immune deficiency syndrome (AIDS) or Hepatitis C virus (HCV), along with transplanted patients; papers were commentaries, letters, editorials, duplicate publications and reviews.

Data collection and quality assessment

Two independent investigators extracted data independently from all eligible papers on the basis of the predetermined selection criteria. Disagreements between the two reviewers were resolved by discussion or by consultation with the corresponding author. Authors were contacted if the relevant information was not available for a particular study. We excluded studies that only reported bone density changes. If multiple updates of the same data were found, we used the most recent version for analysis. The data extracted included first author's name, year of report, publication type, study design, location, sample size of cohorts, number of cases and controls, age of participants, definition of PPI use, fracture site, adjusted OR or RR or HR estimates, the corresponding 95% CI for PPI use and adjusted confounding variables. The quality of cohort or case-control studies was evaluated using the Newcastle-Ottawa scale, as recommended by the Cochrane Non-Randomized Studies Methods [40], A total score of 6 or less was considered low quality and 7-9 was deemed high quality.

Data analysis

The endpoints included osteoporosis, hip/any-site and spine fractures. Osteoporosis was

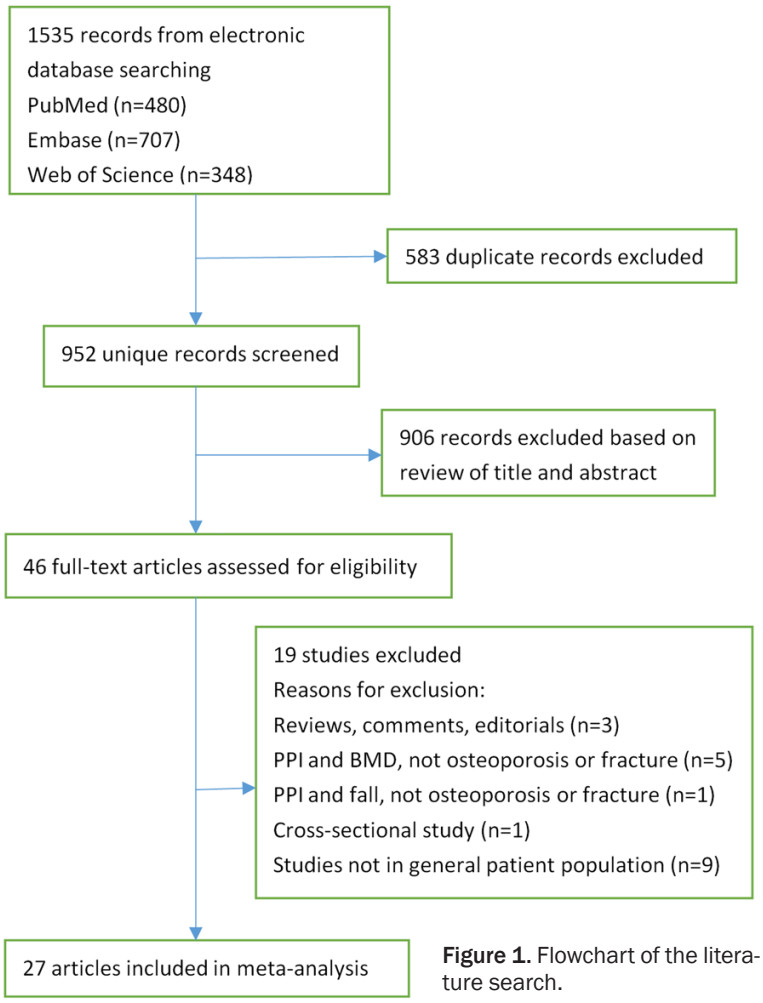

Figure 1. Flowchart of the literature search.

defined by either Imaging examinations or use of osteoporosis drugs. Meta-analysis was carried out to calculate pooled ORs with 95% CIs. We assumed similarity between the OR and other relative measures, such as RR, HR, because the rates of osteoporosis and fracture events were less than 20% [41]. We adopted adjusted ORs for our analysis, since they explained confounding variables. Random effects meta-analysis was conducted for pooled OR. Heterogeneity among studies was mainly assessed using I^2 statistic and Cochran chi-square (X^2). An I^2 value of >50% is suggestive of significant heterogeneity. For the chi-square test, P<0.10 was considered statistically significant for heterogeneity [42, 43]. Subgroup analyses were conducted according to different subtypes, such as study type, study quality, study region, duration, dose, and interval time of PPI use, and adjustment for several confounders (medications that might have affected the risk of osteoporosis or fracture, comorbidity, and other important variables associated with bone disease) in hip and any-site fractures studies. Since the duration of PPI use varied across studies, the shorter duration of PPI use, defined as a duration of exposure of <1 year, and the longer duration of PPI exposure, defined as a cumulative duration of exposure of ≥1 year. For studies that analyzed further stratification beyond 2 years of duration, we combined the separate ORs by random-effects models and used the combined ORs in our analysis (Table S1). The dose-related analysis of PPIs consumption was limited to studies that used the defined daily dose (DDD) as a unit for measuring a prescribed amount of PPIs. We had expected inconsistency among studies with regards to different average daily dose among low dose (<1.75 DDD) and high dose (>1.75 DDD) PPI, therefore, we had decided to use two groups of DDD, with the least overlap data in the analysis (Table S1). In the subgroup analysis stratified by interval time, current users of PPIs were defined as patients who had received PPIs treatment within the 30 days before the index date. Those who received their last dispensing exceeded 30 days before the index date were defined as the discontinuous users. For studies that provided OR for several categories of interval time, we combined the separate ORs by random-effects models and used the combined ORs in our analysis (Table S1). In order to compare effect in the subgroup analyses of duration, interval time, and dose of PPIs, interaction test was conducted. Sensitivity analyses were performed by the leave-one-out method [44]. Publication bias was evaluated using funnel plots and the Egger's correlation test (P<0.05 was considered significant) [45]. The tests for funnel plot asymmetry were not conducted when the included studies were less

Table 1. Characteristics of observational studies reporting the effects of PPI use on risk of osteoporosis and/or fracture

Study	Year	Country	Age, years	% Women	Study period	Design	PPI exposure	Control/ Total	Case	Fracture/ Osteoporosis	OR (95% CI)	Adjust-ments	Quality score*
Chen [6]	2016	China	≥20	44	2000-2011	Co	Ever use	31358	114	Hip	0.79 (0.53-1.18)	C, M	8
										Osteoporosis	1.5 (1.39-1.62)		
Jacob [14]	2016	Germany	60-90	100	2010-2014	Cc	Ever use	3092	3092	Osteoporosis	1.62 (1.43-1.84)	NR	6
Wu [25]	2016	Taiwan	≥18	35	1996-2010	Co	Ever use	54264	4794	Osteoporosis	1.17 (1.03-1.34)	NR	6
Van [23]	2015	Australia	76-81	100	2003-2012	Co	Ever use	4432	1377	Any	1.29 (1.08-1.55)	C, M	7
										Osteoporosis	1.28 (1.13-1.44)		
Freedberg [12]	2015	UK	<29	34	1994-2013	Cc	Ever use	605643	124799	Any	1.28 (1.05-1.56)	M	6
Moberg [18]	2014	Sweden	60-70	100	1995-2012	Co	Current use	6416	903	Any	2.53 (1.28-4.99)	S, F, C, M	6
Ding [10]	2014	USA	≥65	81	1999-2003	Co	Current use	25276	3861	Any	1.27 (1.12-1.43)	S, C, M	7
										Hip	1.32 (1.01-1.71)		
										Spine	1.69 (1.26-2.27)		
Soriano [5]	2014	UK	40-89	75	2000-2008	Cc	Current use	20000	10958	Hip	1.09 (1.01-1.17)	C,M	7
Lin [39]	2014	Taiwan	≥65	100	2008-2010	Co	Current use	365	101	Osteoporosis	1.32 (0.46-3.79)	NA	6
Adams [4]	2014	USA	≥45	0	1991-2006	Cc	Ever use	6774	6774	Hip	1.12 (1.03-1.21)	C	7
Lewis [17]	2014	Australia	≥70	100	1998-2008	Co	Current use	1025	110	Any	2.17 (1.25-3.77)	S, C, M	6
Abrahamsen [31]	2013	Denmark	NR	NR	2000	Cc	Current use	41551	124655	Any	1.08 (1.05-1.11)	F, C, M	7
										Hip	1.13 (1.05-1.21)		
Lee J [30]	2013	Korea	≥65	74	2005-2006	Cc	Ever use	98642	24710	Hip	1.34 (1.24-1.44)	C, M	8
Fraser [11]	2013	Canada	≥25	70	1995-2005	Co	Ever use	9423	1295	Any	1.4 (1.11-1.77)	S, C, M	9
Reyes [20]	2013	Spain	≥50	77	2007-2010	Cc	Ever use	698	358	Hip	1.24 (0.93-1.65)	S, F, C, M	6
Khalili [16]	2012	USA	54-79	100	2000-2008	Co	Current use	79899	896	Hip	1.36 (1.13-1.63)	Cal, S, C, M	6
Pouwels [19]	2011	Netherlands	≥18	73	1991-2002	Cc	Current use	26341	6763	Hip	1.2 (1.04-1.4)	M	6
Gray [13]	2010	USA	50-79	100	1993-2005	Co	Current use	130487	21247	Any	1.25 (1.15-1.36)	S, F, C, M	8
										Hip	1 (0.71-1.4)		
										Spine	1.47 (1.18-1.82)		
Corley [8]	2010	USA	≥18	65	1995-2007	Cc	Ever use	130471	33752	Hip	1.3 (1.21-1.39)	S	7
Chiu [7]	2010	Taiwan	≥50	58	2005-2006	Cc	Ever use	1241	1241	Hip	2.11 (1.45-3.07)	C, M	6
Roux [21]	2009	Europe	55-79	100	1999-2007	Co	Ever use	1211	49	Spine	3.1 (1.14-8.44)	Cal, S, F, C, M	8
De Vries [9]	2009	UK	≥40	56	1988-2007	Co	Ever use	234144	4399	Any	1.15 (1.1-1.2)	S, F, C, M	8
										Hip	1.22 (1.1-1.37)		
										Spine	1.4 (1.11-1.78)		
Yu-SOF [27]	2008	USA	>65	100	1986-2007	Co	Current use	5339	1410	Hip	1.16 (0.8-1.67)	C, M	8
Yu-MrOS [27]	2008	USA	>65	0	2000-2007	Co	Current use	5755	489	Hip	0.62 (0.26-1.44)	S, F, C, M	8
Targownik [22]	2008	Canada	>50	70	1996-2004	Cc	Current use	47289	15792	Any	0.99 (0.9-1.11)	C, M	7
										Hip	1.09 (0.88-1.34)		

Kaye [15]	2008	UK	50-79	72	1995-2005	Cc	Current use	1098	1098	Hip	0.9 (0.7-1.1)	NR	6
Yang [26]	2006	UK	>50	80	1987-2003	Cc	Ever use	135386	13556	Hip	1.44 (1.3-1.59)	S, F, C, M	6
Vestergaard [24]	2006	Denmark	43	51	2000	Cc	Ever use	373962	124655	Any	1.18 (1.12-1.43)	S, F, C, M	6
										Hip	1.45 (1.28-1.65)		
										Spine	1.6 (1.25-2.04)		

*The Newcastle-Ottawa scale was used to assess study quality. Cc: case-control study, Co: cohort, NR: not reported, C: comorbidities (diabetes, osteoporosis), M: medications (medications that might have affected the risk of osteoporosis or fracture), S: smoking status, F: prior fractures, Cal: calcium/vitamin D supplements.

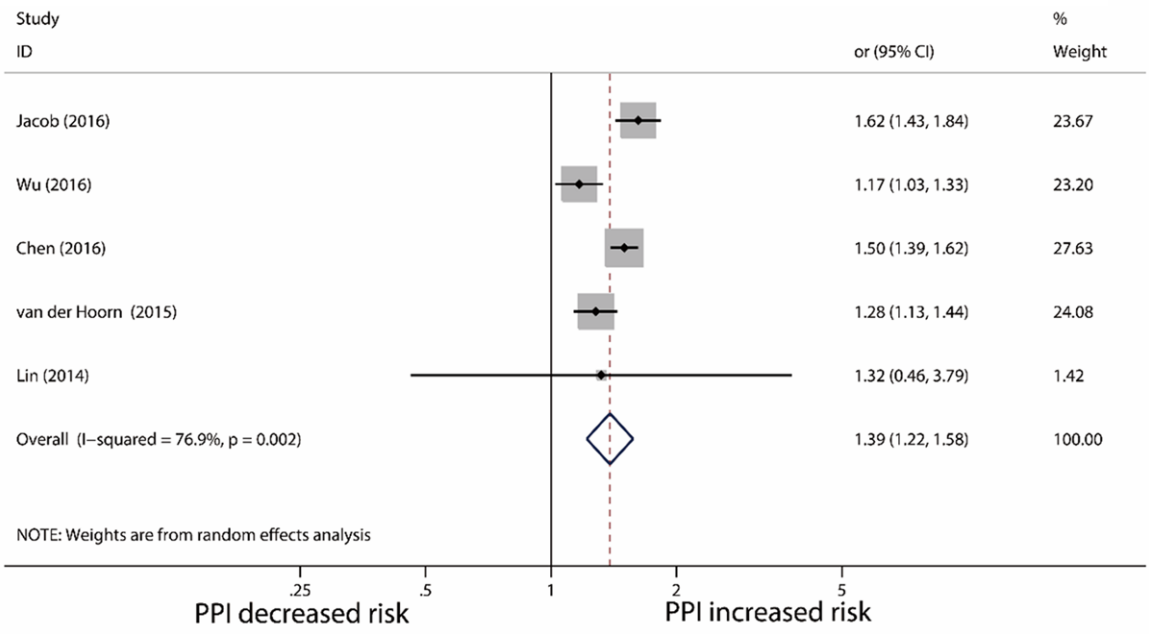

Figure 2. Forest plots for association between PPI use and risk of osteoporosis.

than 10. All analyses were performed using STATA 13 (StataCorp, College Station, Texas).

Result

Literature search

The systematic search of PubMed, EMBASE and Web of Knowledge provided a total of 952 citations, after adjusting for duplicates. Of these, 906 were excluded after initial abstract screening. Forty-six studies were reviewed as potentially relevant studies, of which 19 trials were excluded according to the exclusion criteria. Finally, 27 studies were pooled for meta-analysis. Among the included studies, one study reported results from 2 separate studies [27] (Yu-SOF2008, the Study of Osteoporotic Fractures; and Yu-MrOS2008, the Osteoporotic Fractures in Men) which were analyzed separately in the meta-analysis. The number of studies by reason for exclusion at each stage of the eligibility assessment is outlined in **Figure 1**. No additional abstracts were identified by hand searches of conference proceedings.

Study characteristics and quality

The remaining 27 articles [4-27] compared the risk of osteoporosis and/or fracture between PPI users and nonusers or between current and past PPI users, and the included articles consisted of 13 cohort studies [6, 9-11, 13, 16-18, 21, 23, 25, 27, 39] and 14 case-control studies [4, 5, 7, 8, 12, 14, 15, 19, 20, 22, 24, 26, 30, 31]. The detailed properties of included studies are exhibited in **Table 1**. A total of 1885507 patients were included in the meta-analysis. As shown in **Table 1**, 12 studies were conducted in Europe [5, 9, 12, 14, 15, 18-21, 24, 26, 31], 8 in North America [4, 8, 10, 11, 13, 16, 22, 27], 2 in Australia [17, 23], 5 in Asia [6, 7, 25, 30, 39].

Among the 27 studies, fracture risk was evaluated in the hip in 20 studies [4-9, 11, 13, 15, 16, 19, 20, 22-24, 26, 27, 30, 31], any-site in 11 studies [9-13, 17, 18, 22-24, 31], and spine in 5 studies [9, 10, 13, 21, 24]; the effect of PPI use on the risk of osteoporosis was evaluated in 5 studies [6, 14, 23, 25, 39]. Nine studies evaluated cumulative or continuous exposure of PPI for more than 1 year [4, 5, 8, 9, 13, 16, 19, 22, 26], providing data on prolonged PPI use, and the risk of fracture after the discontinuation of PPIs was evaluated in 4 studies [4, 5, 19, 30]. A dose-response relationship measured by average daily doses was demonstrated in 3 studies [9, 19, 24]. The quality measured through the NOS scale ranged from 6 to 9 points, suggesting a reasonable good quality of these observational studies (**Table 1**).

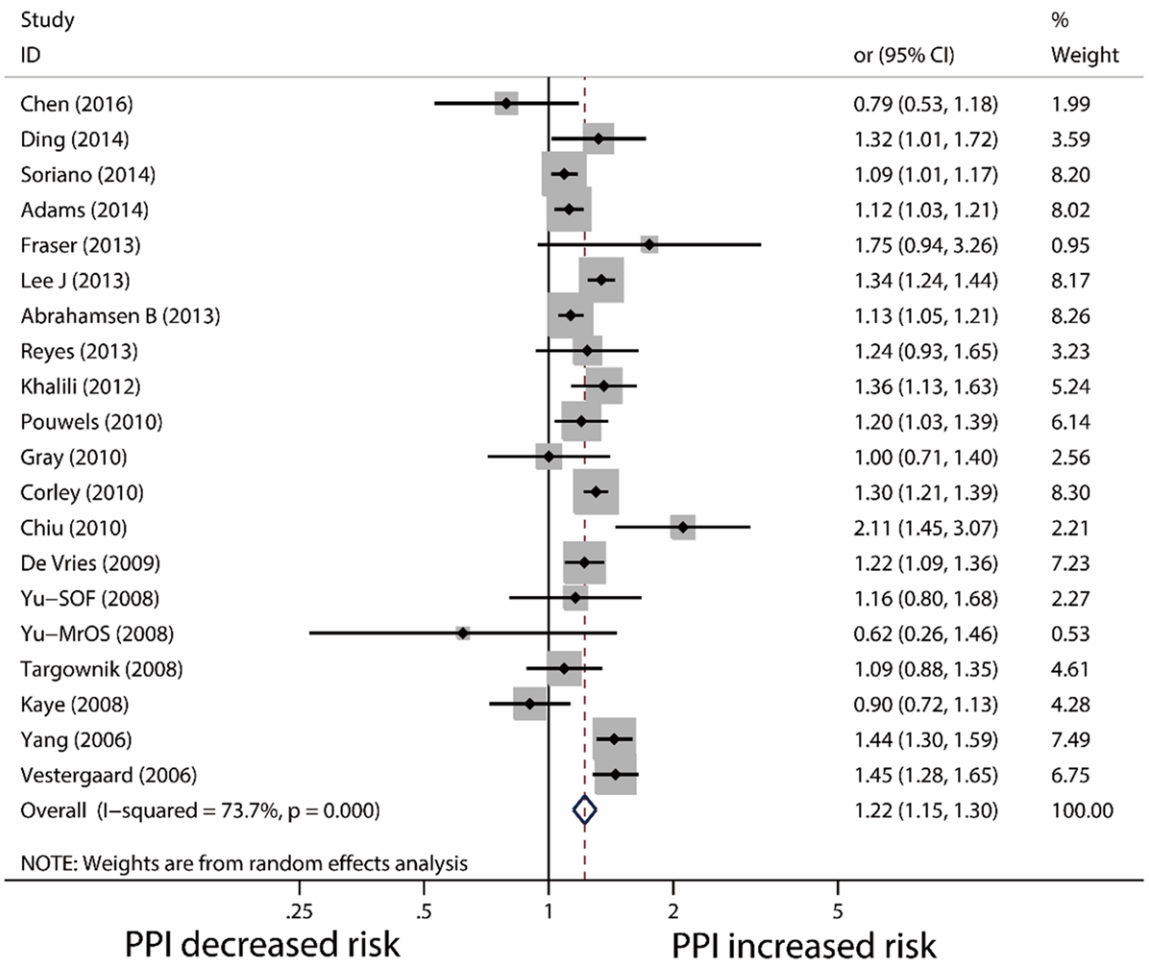

Figure 3. Forest plots for association between PPI use and risk of hip fracture.

Meta-analysis

PPI and risk of osteoporosis: Five studies provided data on risk of osteoporosis and PPI therapy; the pooled OR was 1.39 (95% CI = 1.22-1.58) with significant heterogeneity (P = 0.002, I^2 = 76.9%, **Figure 2**). Subgroup analysis to investigate the source of heterogeneity of osteoporosis was not performed due to the limited number of included studies.

PPI and risk of hip fracture: No evidence of publication bias was observed in the funnel plot (**Figure 7**) and the *p*-values for Egger's test of publication bias was 0.795. A meta-analysis of 20 studies showed a significantly higher risk of hip fracture with PPI therapy (OR 1.22, 95% CI 1.15-1.30, **Figure 3**). Significant heterogeneity of effects across studies was found (P<0.001, I^2 = 73.7%).

Subgroup analysis for hip fracture: To explore the heterogeneity among studies of PPI use and fracture risk, we performed stratified analyses.

We conducted a subgroup analysis by study design. Among the observational studies, we observed a significantly positive correlation for both case-control studies (OR 1.23, 95% CI 1.13-1.33) and cohort studies (OR 1.19, 95% CI 1.05-1.35). Although similar association of hip fracture was detected in both cohort and case-control studies, significant heterogeneity remained only for the case-control studies (P<0.001, I^2 = 88.7%, **Table 2**).

When stratified by study locations, the analysis of two studies location of Asia showed that the associated risk was no longer statistically significant (OR 1.32, 95% CI 0.87-1.98) while het-

Table 2. Stratified analysis of PPI treatment and risk of hip, and any-site Fracture

Group	Subgroups	No. of studies	OR (95% CI)	*P* value	I^2 (%)
Hip fracture					
Study design	Case-control	12	1.23 (1.13-1.33)	<0.001	88.7
	Cohort	8	1.19 (1.05-1.35)	0.126	38.1
Study quality	<7	7	1.32 (1.16-1.51)	0.001	74.3
	≥7	13	1.17 (1.08-1.25)	<0.001	79.1
Study region	Europen	8	1.20 (1.09-1.32)	<0.001	87.1
	North America	9	1.21 (1.10-1.32)	0.051	48.2
	Asia	3	1.32 (0.87-1.98)	0.002	83.8
Duration of PPI use	<1 year	6	1.18 (1.10-1.27)	0.057	53.5
	≥1 year	9	1.26 (1.15-1.38)	<0.001	80.5
Dosage of PPI use	Low dose	3	1.26 (1.12-1.41)	0.154	46.6
	High dose	2	1.39 (1.13-1.71)	0.738	0
Interval time of PPI use	<30 days	5	1.27 (1.12-1.43)	0.005	73.2
	≥30 days	4	1.15 (0.96-1.37)	0.006	76
Adjustment for calcium and vitamin D	Adjusted	7	1.24 (1.10-1.39)	0.001	74.2
	Unadjusted	13	1.21 (1.12-1.32)	<0.001	75.5
Adjustment for diabetes	Adjusted	9	1.20 (1.09-1.32)	0.001	68.7
	Unadjusted	11	1.24 (1.13-1.36)	<0.001	78.6
Adjustment for osteoporosis	Adjusted	4	1.17 (1.02-1.33)	0.125	47.7
	Unadjusted	16	1.23 (1.15-1.33)	<0.001	74.6
Adjustment for prior history of fracture	Adjusted	7	1.28 (1.14-1.43)	0.001	74.6
	Unadjusted	13	1.19 (1.10-1.29)	<0.001	74.6
Adjustment for smoking status	Adjusted	8	1.27 (1.21-1.35)	0.409	2.7
	Unadjusted	12	1.21 (1.11-1.31)	<0.001	82.1
Any-site fracture					
Duration of PPI use	<1 year	3	1.24 (1.18-1.30)	0.218	34.3
	≥1 year	5	1.19 (1.08-1.33)	0.003	75
Adjustment for prior history of fracture	Adjusted	6	1.18 (1.10-1.27)	<0.001	79.3
	Unadjusted	5	1.24 (1.05-1.46)	0.001	77.9
Adjustment for diabetes	Adjusted	6	1.21 (1.08-1.35)	<0.001	78.5
	Unadjusted	5	1.20 (1.09-1.33)	0.006	72.6
Adjustment for smoking status	Adjusted	6	1.28 (1.16-1.42)	0.007	68.6
	Unadjusted	5	1.12 (1.04-1.22)	0.026	63.8

The summary odds ratios (ORs) were estimated by the random effects model. Statistical heterogeneity was evaluated using the chi-square test and I^2 statistic. Abbreviations: OR, odds ratio; CI, confidence interval.

erogeneity further increased (P = 0.002, I^2 = 83.8%, **Table 2**).

In subgroup analyses by methodologic quality, similar association of hip fracture was detected in both low-quality (OR 1.32, 95% CI 1.16-1.51) and high-quality studies (OR 1.17, 95% CI 1.08-1.25), while heterogeneity was slightly higher in low-quality studies (P = 0.001, I^2 = 79.1%, **Table 2**).

We evaluated the treatment duration response and dose response in current PPI users. Subgroup analyses by dose indicated that the high dose of PPIs was more strongly associated with hip fracture (OR 1.39, 95% CI 1.13-1.71) than the low dose (OR 1.26, 95% CI 1.12-1.41). However, the difference between the pooled OR estimates was not significant (Z = 0.19, P = 0.85). The subgroup analyses of dose response were not performed for all studies due to discrepant definitions of dose and PPIs exposure across other studies. Fifteen studies examined the impact of duration of PPI therapy and risk of hip fracture. Subgroup analyses by duration of exposure showed that short-term (<1 year) and

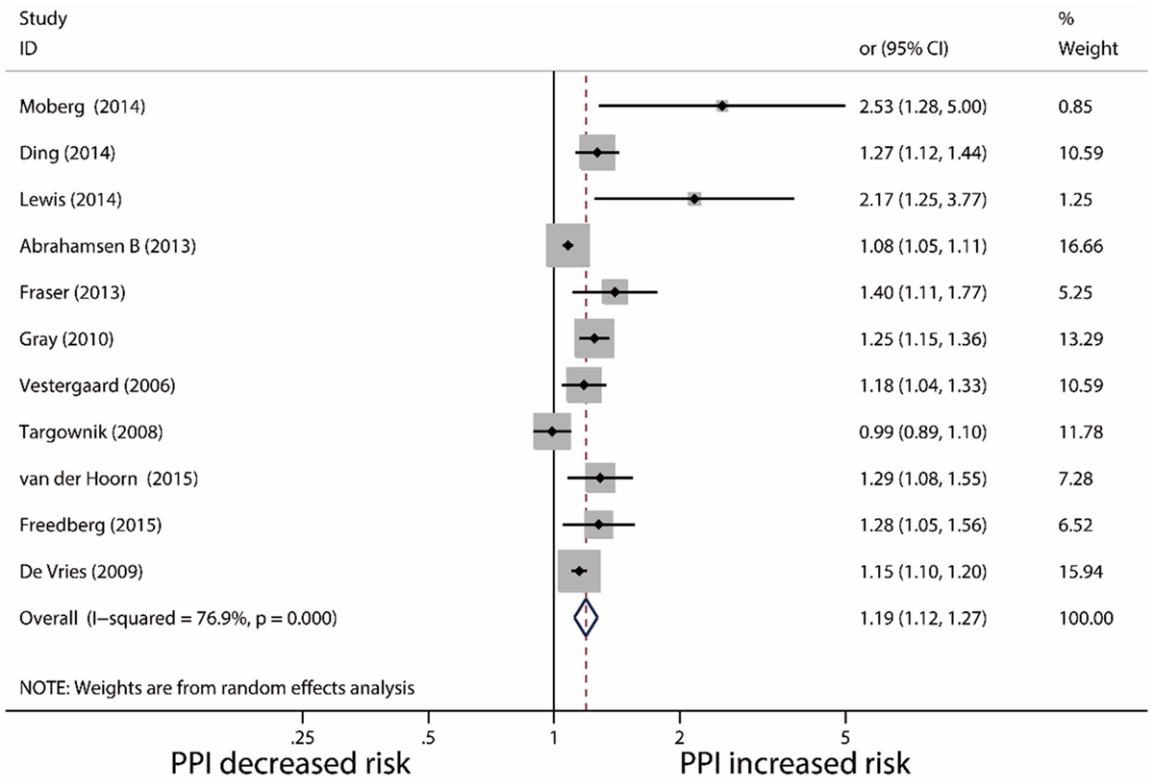

Figure 4. Forest plots for the association between PPI use and risk of any-site fracture.

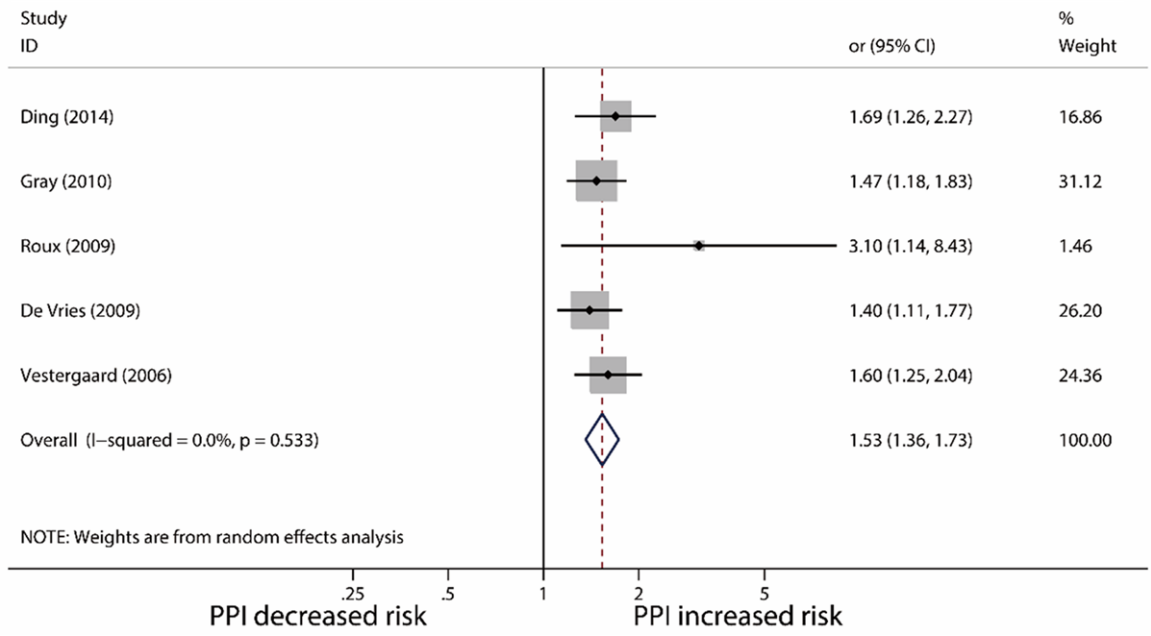

Figure 5. Forest plots for the association between PPI use and risk of spine fracture.

long-term (≥1 year) PPI use were consistent on the strength of the association between use of PPIs and risk of hip fracture (Z = 1.01, P = 0.27; **Table 2**).

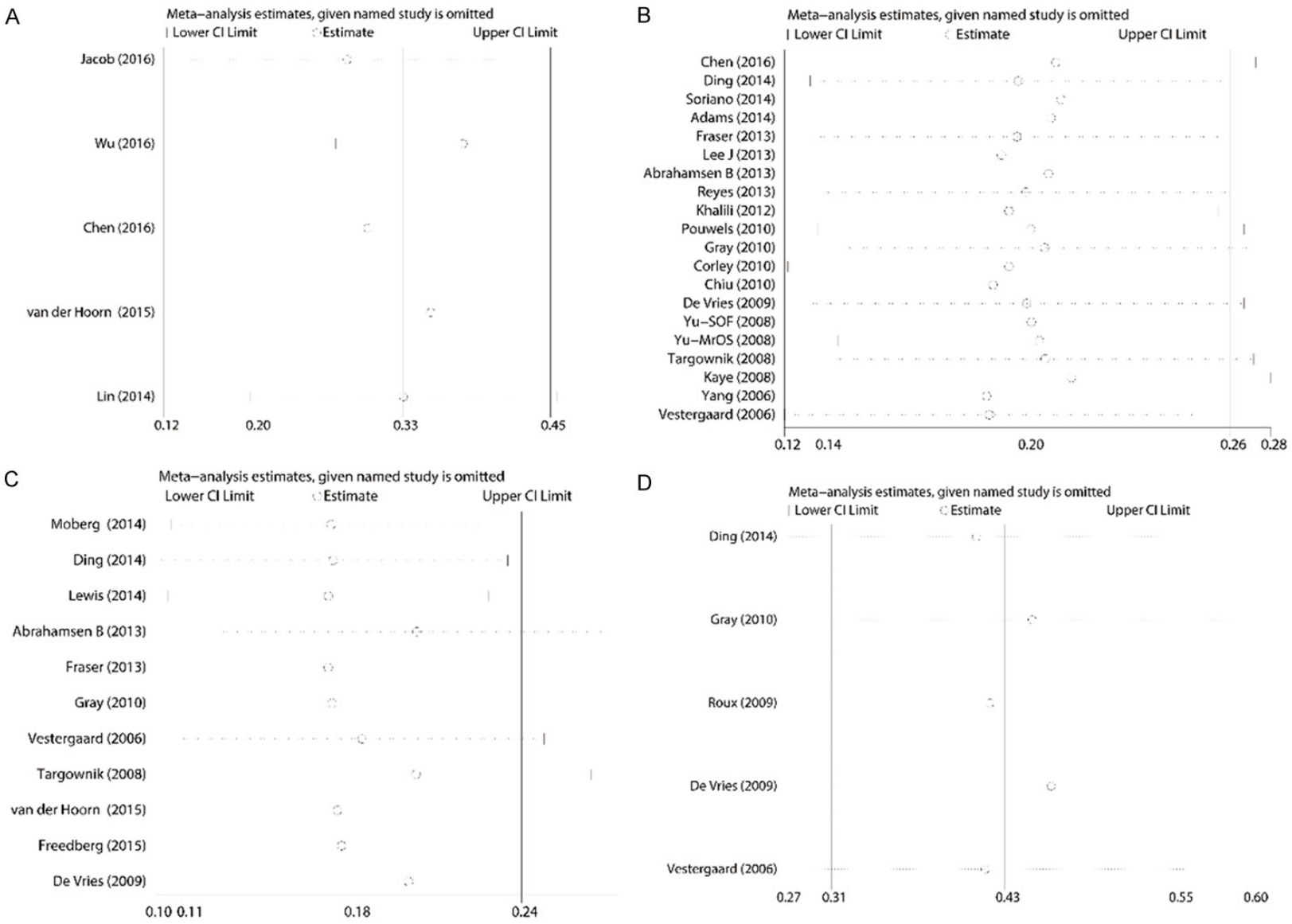

Figure 6. Sensitivity analysis for studies of PPI therapy and risk of osteoporosis (A), hip (B), any-site (C) and spine (D) fractures.

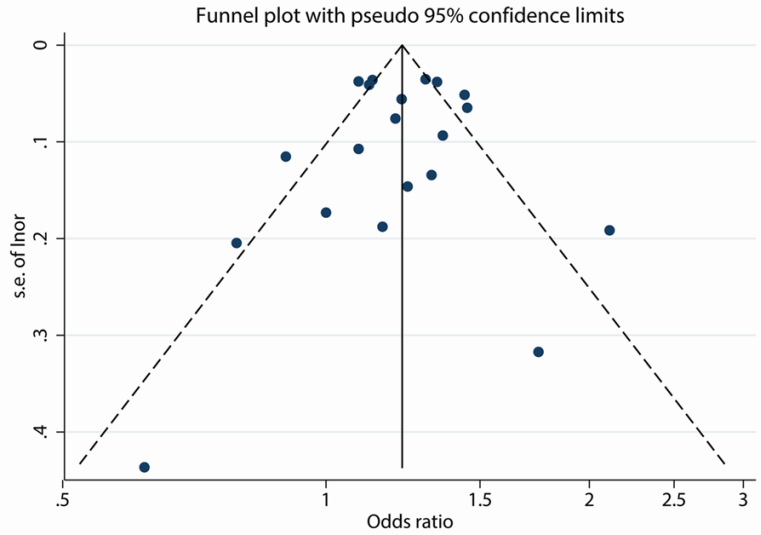

Figure 7. Funnel plot to assess publication bias in hip fracture study.

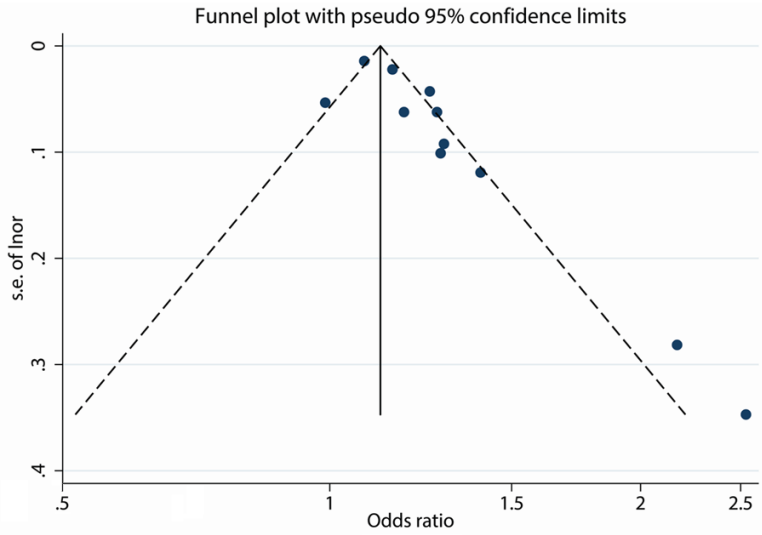

Figure 8. Funnel plot to assess publication bias in any-site fracture study.

From 9 studies, the strength of the association between PPI use and hip fracture was strongest among current users and diminished after discontinuation of PPI use. Based on the results from these studies, the risk appeared to be greater in the current users than the past users (**Table 2**). However, there was no statistical difference among two subgroups (Z = 0.91, P = 0.36).

The significant association between PPI use and risk of hip fracture was present in all the subgroup analyses, even when we restricted it to studies that provided adjusted data of ever use of medications that might have affected the risk of osteoporosis or fracture (calcium and vitamin D supplementation); comorbidity (diabetes, osteoporosis); and other important variables associated with fracture risk (prior history of fracture, smoking status, **Table 2**).

PPI and risk of any-site and spine fractures: PPI use was significantly associated with increased risk of any-site and spine fractures compared with non/past users. As shown in **Figures 4** and **5**, the pooled OR was 1.19 (1.12-1.27) for any-site fracture, and 1.53 (1.36-1.73) for spine fracture. Substantial heterogeneity was found in the stratified analysis by fracture sites, significant heterogeneity was observed for any-site fracture ($P<0.001$, $I^2 = 76.9\%$), but no heterogeneity was observed for spine fracture ($P = 0.533$, $I^2 = 0\%$). Evidence of publication bias was found among any-site fracture studies by the funnel plot (**Figure 8**) and the *p*-values for Egger's test of publication bias was 0.049. The increased risk of any-site fracture persisted after stratification by short-term (<1 year) and long-term (≥1 year) PPI use (**Table 2**). Statistically significant difference was not found in the test of interaction (Z = 0.70, P = 0.48). The associations of PPI use and any-site fracture risk did not differ by adjustment for different confounders (history of fracture, diabetes, and smoking status, **Table 2**).

Sensitivity analysis

To assess whether a single study had a substantial influence on the main results, we excluded each study and evaluated its effect on the summary estimates and heterogeneity of the main analysis. The positive association and heterogeneity were consistent when

excluding each study in turn. We did not find any major changes in direction or magnitude of the summary estimates and *P* values of heterogeneity in the other analyses (**Figure 6**).

Discussion

This is an update systematic review and meta-analysis of 27 observational studies to evaluate the effect of PPI therapy for the risk of osteoporosis and/or fracture. Our analysis included eight studies [6, 12, 14, 23, 25, 30, 31, 39] that were not included in the previous meta-analysis. Besides, the addition of five studies in our meta-analysis have for the first time identified evidence linking use of PPIs to osteoporosis [6, 14, 23, 25, 39]. Remarkably, a significantly higher risk of osteoporosis with PPI therapy was found in our study, which seems to contradict the previous systematic review conducted by Leontiadis, et al [46]. Different inclusion and exclusion criteria could explain the mixed results, we have adopted the strict control by limiting inclusion criteria that only included cohort studies or case-control studies.

The present meta-analysis shows that patients on PPI therapy have approximately 1.4 times the risk of developing osteoporosis compared with nonusers and PPI use is linked to a moderately increased risk of hip, spine, and any-site fractures. In our meta-analysis, dose-response or duration-effect relationship between the risk of hip fracture and PPI use was not found, which seems to consist with the previous meta-analysis conducted by Ngamruengphong, et al [37]. In addition, No significant statistical differences between the current users group and the past users group was found.

Osteoporosis is a very common medical condition while osteoporosis related fracture could lead to significant disability and poor quality of life [47]. Large studies and our meta-analysis continue to show a moderate connection between the risk of fracture and the use of PPIs [4-27, 34-38, 48], however, the mechanisms by which use of PPIs increases fracture risk remain unclear. Calcium absorption is the most important determinant of calcium balance. Decreased calcium absorption has previously been shown to lead directly to increased risk of greater bone resorption and osteoporotic fractures, particularly vertebral and hip fractures [49-51]. However, the meta-analysis conducted by Zhou et al [35], showed that calcium malabsorption would not be a major cause of the association between PPI use and an increased risk of fractures. Sugiyama suggested the impairment of collagen-related bone tissue properties and an increased risk of falling via PPI therapy could be the mechanisms of the PPI-related increased risk of fracture [52, 53]. Some data from animal and human studies also suggest that increased activity of the parathyroid gland induced by secondary hypergastrinemia could be an alternative or a supplementary mechanism for PPI-induced bone loss [54, 55]. Furthermore, Uzoigwe supported PPI-mediated inhibition of osteoclast bone resorption as an explanation of the increased risk of fracture caused by PPIs [56]. These physiologic and pharmacological effects of PPI therapy described above may have relevance to the mechanism by which PPIs predispose to fracture, but PPIs are mostly used in the elderly patients with multiple comorbidities that lead to partial immobility. Thus, the seeming associations between PPI and bone disease could be a selection bias of frail and elderly patients with osteoporosis and fracture who also happen to be frequently treated with acid inhibitors [57, 58]. The confounders-adjustment done by our meta-analysis may not be able to fully account for such confounding influence of comorbidities on the seeming link between PPI and bone disease. Therefore, more rigorous experiments are needed to clarify the potential mechanisms linking PPI therapy, gastrointestinal disorders and other possible comorbidities with osteoporosis and fracture risk.

The high heterogeneity among hip fracture studies was explored by subgroup analysis. Notably, the effect remained pronounced in the subgroup of the case-control study, but not in the subgroup of the cohort study. The study type may serve as a potential source of heterogeneity. When we stratified the studies based on adjustments, all studies with adjusted ORs yielded significant results. These consistent results imply that uncontrolled potential confounders may not be sources of heterogeneity. Our subgroup analysis found that neither study region nor study quality significantly affected outcomes.

Strengths and limitations

Our analysis incorporated all relevant studies that we could identify to March 2017. We have

included studies that reported on osteoporosis, as well as fracture, and for the first time identified evidence linking use of PPIs to osteoporosis by meta-analysis [6, 14, 23, 25, 39].

Despite these strengths, our study had some limitations. First, we included only English language publications for the selection of observational studies, so relevant studies published in non-English language journals may have been excluded. For a more comprehensive approach, we consulted several conference abstracts [59, 60]. However, the quality of these abstracts could not be assessed, and it is possible that important study information was not considered.

Second, the presence of gastrointestinal disorders might be confounders, as those who receive PPI therapy often experience these conditions, which in themselves could be risk factors for osteoporosis and fracture. However, the included studies adjusted for those factors were not enough to explain the observed effect.

Third, there was substantial heterogeneity across the studies in the analysis of osteoporosis, hip and any-site fractures. Although this could be partly explained by different study design, we were not able to identify other possible sources of heterogeneity due to the small number of included studies. However, we have attempted to account for heterogeneity using the random effects model, which contains study variability to generate the pooled estimate.

Fourth, subgroup analyses based on type of PPI use were not performed because of small number of studies. In such case, we explored other possible sources of variability by dose, interval time, and duration of PPI use. Differences in the dosage of PPI use could have potentially contributed to the significant heterogeneity.

Finally, evaluation of publication bias was found among any-site fracture studies. In such case, we searched for conference abstracts that were not published as full papers to minimize the possibility of publication bias.

Conclusion and clinical significance

Our meta-analysis of observational studies found that PPI use was associated with an approximately 1.4-fold increased risk of osteoporosis. PPI use was also associated with an increased overall risk of fracture. Although no evidence of dose-response and duration-response relation was found and more rigorous experiments are needed, for elderly patients with digestive disorders, whom antacids must be taken daily, the lowest effective dose combined with intermittent therapy will be the best approach.

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Disclosure of conflict of interest

None.

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References

[1] Neuman MD, Silber JH, Magaziner JS, Passarella MA, Mehta S and Werner RM. Survival and functional outcomes after hip fracture among nursing home residents. JAMA Intern Med 2014; 174: 1273-1280.

[2] Schubert ML and Peura DA. Control of gastric acid secretion in health and disease. Gastroenterology 2008; 134: 1842-1860.

[3] Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM and Kuipers EJ. Management of helicobacter pylori infection--the Maastricht IV/Florence consensus report. Gut 2012; 61: 646-664.

[4] Adams AL, Black MH, Zhang JL, Shi JM and Jacobsen SJ. Proton-pump inhibitor use and hip fractures in men: a population-based case-control study. Ann Epidemiol 2014; 24: 286-290.

[5] Cea Soriano L, Ruigomez A, Johansson S and Garcia Rodriguez LA. Study of the association between hip fracture and acid-suppressive drug use in a UK primary care setting. Pharmacotherapy 2014; 34: 570-581.

[6] Chen CH, Lin CL and Kao CH. Gastroesophageal reflux disease with proton pump inhibitor use is associated with an increased risk of osteoporosis: a nationwide population-based analysis. Osteoporos Int 2016; 27: 2117-2126.

[7] Chiu HF, Huang YW, Chang CC and Yang CY. Use of proton pump inhibitors increased the risk of hip fracture: a population-based case-control study. Pharmacoepidemiol Drug Saf 2010; 19: 1131-1136.
[8] Corley DA, Kubo A, Zhao W and Quesenberry C. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. Gastroenterology 2010; 139: 93-101.
[9] de Vries F, Cooper AL, Cockle SM, van Staa TP and Cooper C. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. Osteoporos Int 2009; 20: 1989-1998.
[10] Ding J, Heller DA, Ahern FM and Brown TV. The relationship between proton pump inhibitor adherence and fracture risk in the elderly. Calcif Tissue Int 2014; 94: 597-607.
[11] Fraser LA, Leslie WD, Targownik LE, Papaioannou A and Adachi JD. The effect of proton pump inhibitors on fracture risk: report from the Canadian multicenter osteoporosis study. Osteoporos Int 2013; 24: 1161-1168.
[12] Freedberg DE, Haynes K, Denburg MR, Zemel BS, Leonard MB, Abrams JA and Yang YX. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. Osteoporos Int 2015; 26: 2501-2507.
[13] Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE and Chen Z. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the women's health initiative. Arch Intern Med 2010; 170: 765-771.
[14] Jacob L, Hadji P and Kostev K. The use of proton pump inhibitors is positively associated with osteoporosis in postmenopausal women in Germany. Climacteric 2016; 19: 478-481.
[15] Kaye JA and Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy 2008; 28: 951-959.
[16] Khalili H, Huang ES, Jacobson BC, Camargo CA Jr, Feskanich D and Chan AT. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ 2012; 344: e372.
[17] Lewis JR, Barre D, Zhu K, Ivey KL, Lim EM, Hughes J and Prince RL. Long-term proton pump inhibitor therapy and falls and fractures in elderly women: a prospective cohort study. J Bone Miner Res 2014; 29: 2489-2497.
[18] Moberg LM, Nilsson PM, Samsioe G and Borgfeldt C. Use of proton pump inhibitors (PPI) and history of earlier fracture are independent risk factors for fracture in postmenopausal women. The WHILA study. Maturitas 2014; 78: 310-315.
[19] Pouwels S, Lalmohamed A, Souverein P, Cooper C, Veldt BJ, Leufkens HG, de Boer A, van Staa T and de Vries F. Use of proton pump inhibitors and risk of hip/femur fracture: a population-based case-control study. Osteoporos Int 2011; 22: 903-910.
[20] Reyes C, Formiga F, Coderch M, Hoyo J, Ferriz G, Casanovas J, Monteserin R, Brotons C, Rojas M and Moral I. Use of proton pump inhibitors and risk of fragility hip fracture in a Mediterranean region. Bone 2013; 52: 557-561.
[21] Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D, Reid DM, Eastell R and Gluer CC. Increase in vertebral fracture risk in postmenopausal women using omeprazole. Calcif Tissue Int 2009; 84: 13-19.
[22] Targownik LE, Lix LM, Metge CJ, Prior HJ, Leung S and Leslie WD. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008; 179: 319-326.
[23] van der Hoorn MM, Tett SE, de Vries OJ, Dobson AJ and Peeters GM. The effect of dose and type of proton pump inhibitor use on risk of fractures and osteoporosis treatment in older Australian women: a prospective cohort study. Bone 2015; 81: 675-682.
[24] Vestergaard P, Rejnmark L and Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. Calcif Tissue Int 2006; 79: 76-83.
[25] Wu CH, Tung YC, Chai CY, Lu YY, Su YF, Tsai TH, Kuo KL and Lin CL. Increased risk of osteoporosis in patients with peptic ulcer disease: a nationwide population-based study. Medicine (Baltimore) 2016; 95: e3309.
[26] Yang YX, Lewis JD, Epstein S and Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296: 2947-2953.
[27] Yu EW, Blackwell T, Ensrud KE, Hillier TA, Lane NE, Orwoll E and Bauer DC. Acid-suppressive medications and risk of bone loss and fracture in older adults. Calcif Tissue Int 2008; 83: 251-259.
[28] Eom CS, Jeon CY, Lim JW, Cho EG, Park SM and Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ 2011; 183: 310-319.
[29] Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R and Loke YK. Risk of clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol 2012; 107: 1011-1019.
[30] Lee J, Youn K, Choi NK, Lee JH, Kang D, Song HJ and Park BJ. A population-based case-control study: proton pump inhibition and risk of hip fracture by use of bisphosphonate. J Gastroenterol 2013; 48: 1016-1022.

[31] Abrahamsen B and Vestergaard P. Proton pump inhibitor use and fracture risk-effect modification by histamine H1 receptor blockade. Observational case-control study using national prescription data. Bone 2013; 57: 269-271.
[32] Release FN. FDA: Possible fracture risk with high dose, long-term use of proton pump inhibitors.
[33] Health AGDo and Administration ATG. Australian Adverse Drug Reactions Bulletin, Volume 28, Number 1, February 2009. Australian Government Department of Health & Ageing.
[34] Yang SD, Chen Q, Wei HK, Zhang F, Yang DL, Shen Y and Ding WY. Bone fracture and the interaction between bisphosphonates and proton pump inhibitors: a meta-analysis. Int J Clin Exp Med 2015; 8: 4899-4910.
[35] Zhou B, Huang Y, Li H, Sun W and Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016; 27: 339-347.
[36] Yu EW, Bauer SR, Bain PA and Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med 2011; 124: 519-526.
[37] Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A and Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol 2011; 106: 1209-1218; quiz 1219.
[38] Cai D, Feng W and Jiang Q. Acid-suppressive medications and risk of fracture: an updated meta-analysis. Int J Clin Exp Med 2015; 8: 8893-8904.
[39] Lin SC, Koo M and Tsai KW. Association between helicobacter pylori infection and risk of osteoporosis in elderly Taiwanese women with upper gastrointestinal diseases: a retrospective patient record review. Gastroenterol Res Pract 2014; 2014: 814756.
[40] Wells G. The Newcastle Ottawa 1 Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2014.
[41] Davies HT, Crombie IK and Tavakoli M. When can odds ratios mislead? BMJ 1998; 316: 989-991.
[42] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[43] Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
[44] Patsopoulos NA, Evangelou E and Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 2008; 37: 1148-1157.
[45] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[46] Leontiadis GI and Moayyedi P. Proton pump inhibitors and risk of bone fractures. Curr Treat Options Gastroenterol 2014; 12: 414-423.
[47] Si L, Winzenberg TM, Jiang Q, Chen M and Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010-2050. Osteoporos Int 2015; 26: 1929-1937.
[48] Yu EW, Bauer SR, Bain PA and Bauer DC. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. Am J Med 2011; 124: 519-526.
[49] O'Connell MB, Madden DM, Murray AM, Heaney RP and Kerzner LJ. Effects of proton pump inhibitors on calcium carbonate absorption in women: a randomized crossover trial. Am J Med 2005; 118: 778-781.
[50] Graziani G, Badalamenti S, Como G, Gallieni M, Finazzi S, Angelini C, Brancaccio D and Ponticelli C. Calcium and phosphate plasma levels in dialysis patients after dietary Ca-P overload. Role of gastric acid secretion. Nephron 2002; 91: 474-479.
[51] Hardy P, Sechet A, Hottelart C, Oprisiu R, Abighanem O, Said S, Rasombololona M, Brazier M, Moriniere P, Achard JM, Pruna A and Fournier A. Inhibition of gastric secretion by omeprazole and efficiency of calcium carbonate on the control of hyperphosphatemia in patients on chronic hemodialysis. Artif Organs 1998; 22: 569-573.
[52] Sugiyama T, Watarai K, Oda T, Kim YT and Oda H. Proton pump inhibitors and fracture: they impair bone quality and increase fall risk? Osteoporos Int 2016; 27: 1675-6.
[53] Sugiyama T, Torio T, Miyajima T, Kim YT and Oda H. Calcium, proton pump inhibitors, and fracture risk. Osteoporos Int 2016; 27: 349-350.
[54] Gagnemo-Persson R, Samuelsson A, Hakanson R and Persson P. Chicken parathyroid hormone gene expression in response to gastrin, omeprazole, ergocalciferol, and restricted food intake. Calcif Tissue Int 1997; 61: 210-215.
[55] Mizunashi K, Furukawa Y, Katano K and Abe K. Effect of omeprazole, an inhibitor of H+,K(+)-ATPase, on bone resorption in humans. Calcif Tissue Int 1993; 53: 21-25.
[56] Uzoigwe OF. Proton pump inhibitors and fracture: do they do what it says on the tin? Osteoporos Int 2016; 27: 1671-1672.
[57] Moayyedi P. Making sense of the adverse effects of PPIs. 2016.
[58] Moayyedi P, Yuan Y and Leontiadis G. Canadian association of gastroenterology position statement: hip fracture and proton pump in-

hibitor therapy-a 2013 update. Can J Gastroenterol 2013; 27: 593-595.

[59] Targownik L, Luo Y, Goertzen A, Slotboom A and Leslie WD. 781 comparing bone structure and bone metabolism between long-term proton pump inhibitor users and non-users. Gastroenterology 2015; 148: S-153.

[60] Rane PP, Guha S, Chatterjee S and Aparasu R. 497 prevalence and predictors of non-evidence based proton pump inhibitor use among elderly nursing home residents in the USA. Gastroenterology 2015; 148: S-95-S-96.

Table S1. A. Subgroup analysis of duration, dose, and interval time of PPI use in hip fracture studies

Duration of PPI use					
Study	Short-term PPI use		Study	Long-term PPI use	
	OR (95% CI)	Duration		OR (95% CI)	Duration
Soriano	1.11 (1.0-1.23)	Cumulative duration of <1 year	Soriano	1.10 (1.0-1.17)	Cumulative duration of ≥1 year
Adams	1.09 (1.0-1.20)	Cumulative duration of <1 year	Adams	1.24 (1.10-1.40)	Cumulative duration of ≥1 year
Pouwels	1.28 (1.04-1.58)	Cumulative duration of <1 year	Khalili	1.40 (1.20-1.63)	Cumulative duration of ≥1 year
Gray	1.0 (0.60-1.67)	Duration of Use <1 year	Pouwels	1.14 (0.94-1.38)	Cumulative duration of ≥1 year
Corley	1.25 (1.19-1.31)	Duration of Use <1 year	Gray	0.99 (0.64-1.53)	Cumulative duration of ≥1 year
De vries	1.31 (1.09-1.58)	Duration of Use <1 year	Corley	1.29 (1.22-1.37)	Cumulative duration of ≥1 year
			De vries	1.20 (1.06-1.36)	Cumulative duration of ≥1 year
			Targownik	1..47 (1.06-2.06)	Cumulative duration of ≥1 year
			Yang	1.50 (1.39-1.61)	Cumulative duration of ≥1 year

Dosage of PPI use				
Study	Low dose exposure		High dose exposure	
	OR (95% CI)	Dosage	OR (95% CI)	Dosage
Pouwels	1.16 (0.97-1.38)	<1.75 DDD	1,35 (1.02-1.77)	>1.75 DDD
De vries	1.20 (1.07-1.35)	<1.75 DDD	1.45 (1.06-1.99)	>1.75 DDD
Vestergaard	1.55 (1.39-1.73)	0.25-0.99 DDD		

Interval time of PPI use					
Study	Current use of PPI		Study	Past use of PPI	
	OR (95% CI)	Interval time		OR (95% CI)	Interval time
Soriano	1.09 (1.01-1.17)	Current use ended in the previous 30 days use	Soriano	1.29 (1.07-1.56)	Recent use ended 31-90 days before the index date
Adams	1.38 (1.12-1.71)	Recentness of use Most recent, 1-33 days	Adams	1.03 (0.84-1.27)	less recent, 34-532
Lee J	1.39 (1.21-1.59)	PPI prescription within the 30 days prior to the index date.	Lee J	1.37 (1.16-1.61)	Recent use ended 31-90 days before the index date
Khalili	1.39 (1.15-1.68)	Current use in past 30 days	Pouwels	0.96 (0.83-1.12)	Recent use 31-91 days before the index date
Pouwels	1.20 (1.04-1.40)	Current use in past 30 days			

Abbreviations: OR, odds ratio; CI, confidence interval; DDD, defined daily dosages.

B. Subgroup analysis of duration of PPI use in any-site fracture studies

Duration of PPI use					
Study	Short-term PPI use		Study	Long-term PPI use	
	OR (95% CI)	Duration		OR (95% CI)	Duration
Freedberg	1.27 (1.22-1.33)	Cumulative duration of <1 year	Freedberg	1.37 (1.19-1.57)	Cumulative duration of ≥1 year
Gray	1.27 (1.13-1.14)	Cumulative duration of <1 year	Lewis	2.17 (1.25-3,77)	Long-term use >1 year
De Vries	1.18 (1.10-1.27)	Duration of Use <1 year	Gray	1.21 (1.09-1.36)	Cumulative duration of ≥1 year
			De Vries	1.13 (1.08-1.19)	Cumulative duration of ≥1 year
			Targownik	0.99 (0.9-1.11)	Cumulative duration of ≥1 year

Abbreviations: OR, odds ratio; CI, confidence interval; DDD, defined daily dosages.