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ORIGINAL ARTICLE

Proton-pump inhibitors and risk of fractures: an update meta-analysis

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Abstract
Summary To identify the relationship between proton-pump inhibitors (PPIs) and the risk of fracture, we conducted an update meta-analysis of observational studies. Results showed that PPI use was associated with a modestly increased risk of hip, spine, and any-site fracture.
Introduction Many studies have investigated the association of proton-pump inhibitors (PPIs) with fracture risk, but the results have been inconsistent. To evaluate this question, we performed a meta-analysis of relevant observational studies.
Methods A systematic literature search up to February 2015 was performed in PubMed. We combined relative risks (RRs) for fractures using random-effects models and conducted subgroup and stratified analyses.
Results Eighteen studies involving a total of 244,109 fracture cases were included in this meta-analysis. Pooled analysis showed that PPI use could moderately increase the risk of hip fracture [RR=1.26, 95 % confidence intervals (CIs) 1.16–1.36]. There was statistically significant heterogeneity among studies ($p<0.001$; $I^2=71.9$ %). After limiting to cohort studies, there was also a moderate increase in hip fracture risk without evidence of study heterogeneity. Pooling revealed that short-term use (<1 year) and longer use (>1 year) were similarly associated with increased risk of hip fracture. Furthermore, a moderately increased risk of spine (RR=1.58, 95 % CI 1.38–1.82) and any-site fracture (RR=1.33, 95 % CI 1.15–1.54) was also found among PPI users.
Conclusion In this update meta-analysis of observational studies, PPI use modestly increased the risk of hip, spine, and any-site fracture, but no evidence of duration effect in subgroup analysis.

Keywords Fracture · Meta-analysis · Proton-pump inhibitors · Risk

Introduction

Osteoporosis is the most common type of bone disorder, and numbers are increasing as the population ages. More than 40 % of women and 13 % of men experience an osteoporotic fracture [1]. The most serious of these, hip fracture, is associated with high morbidity, mortality, and cost [2]. Thus, identifying modifiable risk factors for fractures would be of substantial benefit to public health.

Proton-pump inhibitors (PPIs) are a group of potent acid suppressive medication. Since introduced in 1989, they are used to treat several gastrointestinal disorders, including heartburn symptoms, gastroesophageal reflux, and peptic ulcer disease [3–5]. In clinical practice, PPIs are among the most widely prescribed therapies worldwide. Although PPIs are generally well tolerated by the majority of patients, concern has grown over potential association between its use and bone fracture risk. Indeed, many observational studies have reported on the association between PPI therapy and the risk of fracture. There is substantial variation between the results of each study. Meta-analyses of the data suggest overall there is an association between PPI therapy and increased risk of fracture [6–9]. And in May 2010, the Food and Drug Administration (FDA) issued a safety alert regarding a possible increased

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risk of fractures with PPI use and are recommending that no more than three 14-day treatment courses should be used in 1 year but acknowledged that more data were needed [10].

Subsequently, several observational including prospective studies have been performed regarding the association of PPI use and fracture risk. Large numbers of incident cases may enhance the statistical power of meta-analysis to assess the relationship between exposure and outcome risk. Therefore, we undertook this update meta-analysis to further clarify the association between PPI use and fracture risk.

Methods

Data sources and search

We performed a systematic literature search to February 2015 in PubMed without restrictions using the broad free-text and indexing search terms: proton pump inhibitor and fracture. Moreover, we also hand-searched reference lists from retrieved articles, reviews, and meta-analysis papers to identify additional relevant studies. This meta-analysis we conducted following the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [11]. The article search was performed independently by two investigators (BZ and YH). Differing decisions were resolved by consensus.

Eligibility criteria

Studies were included in our meta-analysis if they met the following criteria: (1) the study had a cohort and case-control design, (2) the exposure of interest was PPI use, (3) the outcome of interest was fracture, and (4) the relative risk (RR) estimates (approximated by the odds ratio [OR] estimates for case-control studies) with corresponding 95 % confidence interval (CI) were provided.

Data extraction

For each included study, we abstracted information on first author's name, country, study design, study period/duration of follow-up, number of subjects (cases, controls, or cohort size), age, definition of PPI use, fracture site, RR estimates, and the corresponding 95 % CI for PPI use. If available, information related to duration of PPI use was also retrieved. Whenever available, estimates adjusted for the greatest number of potentially confounding variables were used.

The quality of studies was assessed using the nine-star Newcastle-Ottawa scale (NOS) [12]. The NOS is a quality assessment tool for non-randomized study. This scale includes major three perspectives of evaluation: selection (0–4 stars), comparability (0–2 stars), and exposure between the case group and control group (0–3 stars). A total score of 3 or less was considered poor, 4–6 was considered moderate, and 7–9 was deemed high quality. The data extraction and quality assessments were conducted independently by two authors (BZ and YH). Any discrepancies were resolved by consensus.

Statistical analysis

The pre-defined primary endpoint was hip fracture, and secondary endpoints included any-site and spine fracture. Study-specific risk estimates were extracted from each article, and log risk estimates were weighted by the inverse of their variances to obtain a pooled risk estimate. We assumed that ORs approximated RRs since fracture is a sufficiently rare event (<5 % per year), and most case-control studies used an open-cohort sampling design. Studies were pooled by using the DerSimonian and Laird random-effects model, which considers both within- and between-study variations [13]. We also conducted analyses stratified by study location, study type, study quality, sex, adjustment for calcium intake, and duration of medication use to identify important subgroups or explain heterogeneity across studies. In addition, we conducted a sensitivity analysis in which one study at a time was removed and the rest analyzed to estimate whether the results could have been affected markedly by a single study.

The heterogeneity across studies was quantified using Cochrane's Q statistic and I^2 statistic [14]. For the Q statistic, $p<0.10$ was considered statistically significant for heterogeneity. The I^2 statistic ranges in value from 0 to 100 % (values of 25, 50, and 75 % corresponding to low, moderate, and high degrees of heterogeneity, respectively). Possible publication bias was assessed using funnel plot and Egger's regression asymmetry test ($p<0.05$ was considered significant) [15]. We used the Stata version 11 software package (StataCorp, College Station, Texas) for statistical analysis.

Results

Literature search

The search strategy identified a total of 195 articles, of which 174 articles were excluded after review of the title or abstract because they were laboratory studies, review articles, or irrelevant to the current study (Fig. 1). In the full-text stage, we narrowed the number of studies from 21 to 17 after applying our search criteria [16–32]. Two articles were excluded because they analyzed the same database (General Practice Research Database, GPRD) which were used in another publication [33, 34]; one article was also excluded because of data replication [35]. We further excluded one study that investigated the association of PPIs with fracture risk in chronic hepatitis C patients [36]. Hence, a total of 17 articles

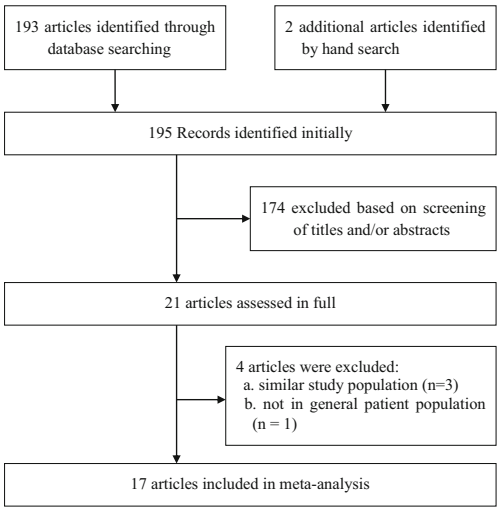

Fig. 1 Flow diagram of study identification

(including 18 studies because 1 article [19] reported results from two independent cohorts) met the predefined inclusion criteria.

Study characteristics

The study characteristics of these 18 studies are presented in Table 1. As shown in Table 1, seven studies were conducted in Europe [16, 17, 20, 24, 27–29], seven in USA [19, 21, 22, 25, 31, 32], two in Canada [18, 26], one in Australia [30], and one in Taiwan [23]. They were published between 2006 and 2014 including nine case-control studies [16–18, 21, 23, 24, 27, 29, 32] and nine prospective studies [19, 20, 22, 25, 26, 28, 30, 31]. Fifteen studies were used for analysis of hip fracture risk [16–19, 21–27, 29, 31, 32], ten studies for any-site facture risk [17–20, 22, 26, 28, 30, 31], and four studies for spine fracture risk [17, 20, 22, 31]. A total of 244,109 fracture cases were involved in these studies. The quality measured through the NOS scale ranged from 6 to 9 points, suggesting a reasonable good quality of these observational studies (Table 2). In all studies, relative risk estimates were adjusted for age and gender, and more than half of the study results were adjusted for body mass index (BMI) and smoking, close to half controlled for alcohol consumption and calcium intake. In some studies, the estimates were controlled for prior fracture, estrogen use, some medications, and comorbidities.

PPIs and hip fracture risk

The analyses of PPI use and hip fracture risk were based on 15 studies. Figure 2 shows multivariable-adjusted RRs of hip fracture in individual studies and all studies combined. All studies except one showed positive associations, which were statistically significant in eight studies. The pooled estimate showed that PPI use was statistically significantly associated with a moderately increased risk of hip fracture [RR=1.26, 95 % CI 1.16–1.36]. There was some indication of heterogeneity among studies ($p<0.001$; $I^2=71.9$ %). A sensitivity analysis omitting one study at a time was performed, and the result of analysis confirmed the stability of our results. In addition, Egger's test did not provide evidence of substantial publication bias ($p=0.607$).

To explore the heterogeneity among studies of PPI use and hip fracture risk, we performed stratified analyses. After limiting the meta-analysis to cohort studies, a moderate increase in hip fracture risk was still found without evidence of study heterogeneity [RR=1.24, 95 % CI 1.06–1.45; $p=0.263$, $I^2=22.7$ %] (Table 3). The associations of PPI use and hip fracture risk did not differ by study location, study type, study quality, sex, and adjustment for calcium intake (Table 3).

Further, several studies analyzed hip fracture risk in the context of PPI duration use (Table 3). Based on the results from these studies, the increase in hip fracture risk persisted after stratification by short-term (<1 year) and long-term (≥1 year) PPI use (Table 3).

PPIs and risk of any-site or spine fracture

As shown in Fig. 3, there was also a moderate increase in the risk of spine (RR=1.58, 95 % CI 1.38–1.82) and any-site fracture (RR=1.33, 95 % CI 1.15–1.54) among PPI users. Evidence of heterogeneity was present among any-site fracture studies ($p<0.001$; $I^2=66.07$ %), but not among the findings of spine fracture ($p=0.498$; $I^2=2.38$ %). Evidence of publication bias was not found among any-site fracture studies ($p=0.297$), but found among spine fracture studies ($p=0.038$).

Discussion

In this meta-analysis of observational studies, we found that PPI use was associated with a moderately increased risk of hip, spine, and any-site fracture. Furthermore, pooling revealed that short-term use (<1 year) and longer use (>1 year) were similarly associated with increased hip fracture risk. Rather than just reporting a similar finding as the previous meta-analysis, with the benefit of additional data, it would provide high statistical power to confirm this moderate, but consistently observed association with fracture risk.

The observed heterogeneity among studies of PPI use and hip fracture risk seemed to be explained by the study design. After limiting to cohort studies, there was also a moderate increase in hip fracture risk in PPI uses without evidence of study heterogeneity. In addition, cohort studies are generally considered to provide superior evidence compared with case-control studies because they are less susceptible to bias in the prospective design.

Table 1 Characteristics of observational studies included in the meta-analysis

Study (reference)	Country	Study population	Design	Study period	Age, years	Control/ participant	Cases	Definition of PPI	Fracture site	RR (95 % CI)	Adjustments
Yang, 2006 [16]	UK	GPRD	NCC	1987–2003	≥50	135,386	13,556	Cumulative use >1 year	Hip	1.44(1.30–1.59)	Age, gender, calendar, follow-up, BMI, medications, comorbidities, smoking, alcohol, prior fracture, calcium/vitamin D intake
Vestergaard, 2006 [17]	Denmark	NR	PCC	2000	43.4[a]	373,962	124,655	Any use in past 1 year	Any Hip Spine	1.18(1.12–1.43) 1.45(1.28–1.65) 1.60(1.25–2.04)	Age, gender, alcoholism, working status, Charlson index, medications, number of bed days, number of contacts with doctor, living with someone, prior fracture, education, income
Targownik, 2008 [18]	Canada	NR	PCC	1996–2004	≥50	47,289	15,792	Recent use and duration >1 year	Any Hip	0.99(0.90–1.11) 1.09(0.88–1.34)	Age, gender, comorbidities, ethnicity, income, region, comorbidities, home care, medications
Yu, 2008a [19]	USA	SOF	Co	1986–2007	>65	5339	1410	Current use	Hip	1.16(0.80–1.67)	Age, clinic, race, BMI, alcohol, exercise, medications, calcium supplements, self-reported health, caffeine use, estrogen use
Yu, 2008b [19]	USA	MrOS	Co	2000–2007	>65	5755	489	Current use	Hip	0.62(0.26–1.44)	Age, clinic, race, BMI, alcohol, exercise, medications, calcium supplements, self-reported health, smoking, history of stomach surgery
Roux, 2009 [20]	Europe	OPUS	Co	1999–2007	55–79	1211	49	Any use of omeprazole in past 1 year	Spine	3.10(1.14–8.44)	Age, BMI, history of fracture, medications, calcium/vitamin D supplements, smoking, alcohol, exercise, falls, self-reported health, bone density
Corley, 2010 [21]	USA	KPNC	NCC	1995–2007	>18	130,471	33,752	Cumulative use >2 years	Hip	1.30(1.21–1.39) 1.30(1.21–1.41)	Age, gender, duration of membership, first year of membership, race, smoking[b]
Gray, 2010 [22]	USA	WHI	Co	1993–2005	50–79	130,487	21,247	Current use	Any Hip Spine	1.25(1.15–1.36) 1.00(0.71–1.40) 1.47(1.18–1.82)	Age, race, BMI, enrollment in clinical trial, indicator for cohort, smoking, physical activity, self-reported health, parental history of fracture, history of fracture, osteoporosis, medications, comorbidities
Chiu, 2010 [23]	Taiwan	NR	PCC	2005–2006	≥50	1241	1241	Cumulative use >70 DDD since 1996	Hip	2.11(1.45–3.07)	Age, sex, index date, medications, comorbidities
Pouwels, 2011 [24]	Netherlands	NR	PCC	1991–2002	≥18	26,341	6763	Current use in past 30 days	Hip	1.20(1.04–1.40)	Age, gender, region, comorbidities, medications
Khalili, 2012 [25]	USA	NHS	Co	2000–2008	30–55	79,899	896	Regularly used for at least 2 years	Hip	1.36(1.13–1.63)	Age, BMI, alcohol, calcium intake, history of osteoporosis, physical activity, smoking, vitamin D intake, medications
Fraser, 2013 [26]	Canada	CaMos	Co	1995–2007	≥25	9423	1295	Ever use	Any Hip	1.40(1.11–1.76) 1.75(0.94–3.26)	Age, gender, BMI, prior fracture, femoral neck T-score, corticosteroid use, alcohol, smoking, physical activity, bisphosphonate use
Reyes, 2013 [27]	Spain	NR	PCC	2007–2010	≥50	698	358	Use ≥1 prescription in past 5 years	Hip	1.24 (0.93–1.65)	Age, gender, comorbidities, medications
Moberg, 2014 [28]	Sweden	WHILA	Co	1995–2012	60–70	6416	903	Ever use	Any	2.53(1.28–4.99)	Age, BMI, smoking, marital status, number of falls, facture after age of 40, family history of diabetes, selective

Table 1 (continued)

Study (reference)	Country	Study population	Design	Study period	Age, years	Control/ participant	Cases	Definition of PPI	Fracture site	RR (95 % CI)	Adjustments
											serotonin reuptake inhibitor use, corticosteroid use, oral contraceptive use, age at menopause, amenorrhea
Soriano, 2014 [29]	UK	THIN	NCC	2000–2008	40–89	20,000	10,958	Current single use	Hip	1.09(1.01–1.17)	Age, sex, year of hip fracture, primary care physician visits, specialist referrals, hospital admissions, BMI, vitamin D plus calcium, comorbidity, medications
Lewis, 2014 [30]	Australia	CAIFOS	Co	2003–2008	79.9[a]	1025	110	Continuous use >1 year before baseline	Any	2.17(1.25–3.77)	Age, BMI, physical activity, smoking, diabetes, CNS medication use, bisphosphonate use, corticosteroid use, total hip bone mineral density
Ding, 2014 [31]	USA	PACE	Co	1999–2003	≥65	25,276	3861	Ever use	Any Hip Spine	1.27(1.12–1.43) 1.32(1.01–1.71) 1.69(1.26–2.27)	Age, gender, race, BMI, comorbidity, smoking, medications
Adams, 2014 [32]	USA	KPSC	PCC	1997–2006	≥45	6774	6774	Ever use	Hip	1.12(1.03–1.21)	Age, race, medical center, index date, comorbidities

RR relative risk, *NCC* nested case-control, *PCC* population-based case-control, *Co* cohort, *NR* not reported, *DDD* defined daily doses, *GPRD* General Practice Research Database, *SOF* Study of Osteoporotic Fractures, *MrOS* Osteoporotic Fractures in Men Study, *OPUS* Osteoporosis and Ultrasound Study, *KPNC* Kaiser Permanente Northern California, *WHI* Women's Health Initiative, *NHS* Nurses' Health Study, *CaMos*, The Canadian Multicenter Osteoporosis Study, *PACE* Pennsylvania's Pharmaceutical Assistance Contract for the Elderly, *WHILA* Women's Health In the Lund Area, *THIN* The Health Improvement Network, *CAIFOS* Calcium Intake Fracture Outcome Study, *KPSC* Southern California region of Kaiser Permanente, *BMI* body mass index, *CNS* central nervous system

[a] Mean

[b] Comorbidities and medications not included in final model because did not meet criteria for significantly affecting the model

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

Cohort studies	Selection 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 control for important factor or additional factor	Outcome Assessment of outcome	Follow-up long enough for outcomes to occur[a]	Adequacy of follow-up of cohort	Total score
Yu, 2008 [19]	*[b]	*	*	*	**	*	*		8
Roux, 2009 [20]	*	*		*	**	*	*	*	8
Gray, 2010 [22]	*	*		*	**	*	*	*	8
Khalili, 2012 [25]		*		*	**		*	*	6
Fraser, 2013 [26]	*	*	*	*	**	*	*	*	9
Moberg, 2014 [28]	*	*		*	**	*	*		7
Lewis, 2014 [30]	*	*		*	**		*		6
Ding, 2014 [31]	*	*		*	**		*	*	7
Case-control studies	**Selection Adequate definition of cases**	**Representativeness of cases**	**Selection of controls**	**Definition of controls**	**Comparability control for important factor or additional factor**	**Exposure Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	**Total score**
Yang, 2006 [16]		*	*	*	**		*		6
Vestergaard, 2006 [17]		*	*	*	**		*		6
Targownik, 2008 [18]	*	*	*	*	**		*		7
Corley, 2010 [21]	*	*	*	*	**		*		7
Chiu, 2010 [23]		*	*	*	**		*		6
Pouwels, 2011 [24]		*	*	*	**		*		6
Reyes, 2013 [27]		*	*	*	**		*		6
Soriano, 2014 [29]	*	*	*	*	**		*		7
Adams, 2014 [32]	*	*	*	*	**		*		7

[a] Follow-up ≥4 years,

[b] means one star

[c] means two stars

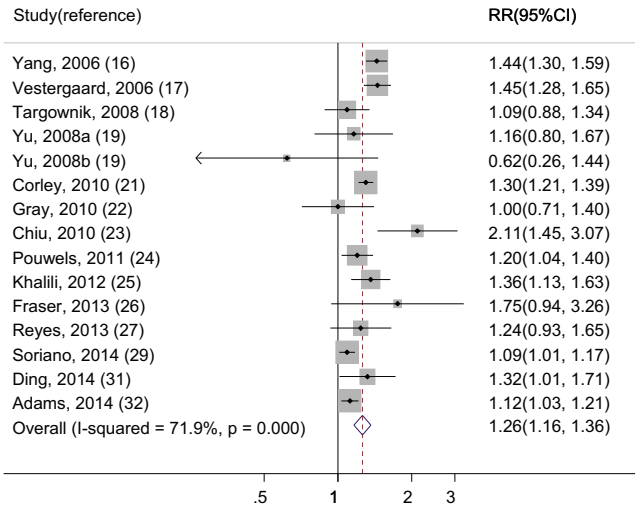

Fig. 2 Pooled risk estimate of hip fracture associated with PPI use. *Squares* indicate study-specific risk estimates (the size of the *square* reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals (CIs); *diamonds* indicate summary risk estimate with its corresponding 95 % confidence interval

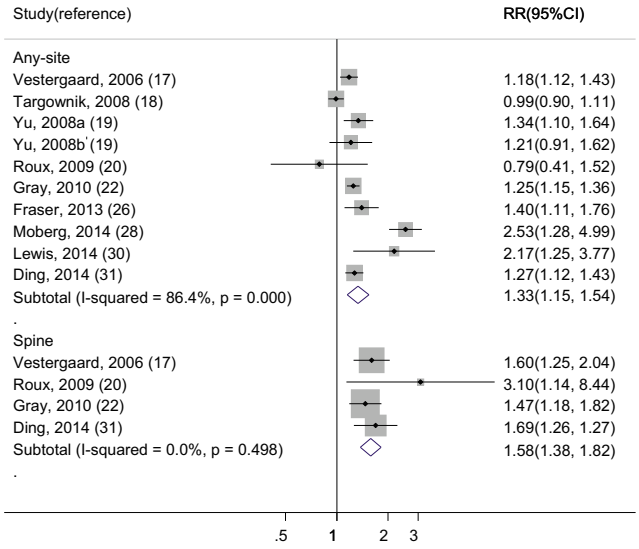

Fig. 3 Pooled risk estimate of spine and all-site fracture associated with PPI use. *Squares* indicate study-specific risk estimates (the size of the *square* reflects the study-specific statistical weight, i.e., the inverse of the variance); *horizontal lines* indicate 95 % confidence intervals (CIs); *diamonds* indicate summary risk estimate with its corresponding 95 % confidence interval

Table 3 Summary risk estimates

Stratification group	References	RR (95 % CI)		Heterogeneity test		
				Q	*P* value	I^2 (%)[a]
Hip	[16–19, 21–27, 29, 31, 32]	1.26	1.16 to 1.36	49.85	<0.001	71.9
Geographic region						
Europe	[16, 17, 24, 27, 29]	1.28	1.11 to 1.47	26.30	<0.001	84.8
USA	[19, 21, 22, 25, 31, 32]	1.21	1.10 to 1.34	13.03	0.043	53.9
Other	[18, 23, 26]	1.54	0.95 to 2.51	9.98	0.007	80.0
Study type						
Cohort	[19, 22, 25, 26, 31]	1.24	1.06 to 1.45	6.47	0.263	22.7
Case-control	[16–18, 21, 23, 24, 27, 29, 32]	1.27	1.15 to 1.39	43.22	<0.001	81.5
Study quality						
<7	[16, 17, 23–25, 27]	1.39	1.26 to 1.54	10.08	0.073	50.4
≥7	[18, 19, 21, 22, 26, 29, 31, 32]	1.16	1.06 to 1.27	19.35	0.013	58.7
Adjust for calcium intake						
No	[17, 18, 21, 23, 24, 26, 27, 31, 32]	1.28	1.17 to 1.41	24.32	0.002	67.1
Yes	[16, 19, 22, 25, 29]	1.20	1.01 to 1.41	24.37	<0.001	79.5
Sex						
Male	[19, 29, 32]	1.11	1.04 to 1.19	1.84	0.399	0
Female	[19, 22, 25, 29]	1.14	0.98 to 1.33	6.66	0.084	54.9
Duration of PPI use						
<1 year	[17, 21–25, 29, 32]	1.25	1.14 to 1.37	18.03	0.012	61.2
>1 year	[16–18, 21–25, 29, 32]	1.27	1.16 to 1.38	34.65	<0.001	74.0
Any site	[17–20, 22, 26, 28, 30, 31]	1.33	1.15 to 1.54	66.07	<0.001	86.4
Spine	[17, 20, 22, 31]	1.58	1.38 to 1.82	2.38	0.498	0

RR relative risk, *CI* confidence intervals

[a] I^2 is interpreted as the proportion of total variation across studies that are due to heterogeneity rather than chance

No evidence of publication bias was found from visual inspection of funnel plots and Egger's tests in the analyses conducted, except for PPIs and spine fracture risk where there was a suggestion of small studies with nonsignificant findings missing. Since the studies in the analysis have produced consistent results, it is unlikely for the missing studies to affect the association observed.

The biologic mechanisms through which PPIs may increase the risk of fracture are still unknown. Some potential mechanisms have been proposed in theory, including the hypothesis that PPI reduces intestinal calcium absorption, eventually leading to bone mineral density decreased. PPIs are potent blockers of gastric acid secretion, which is thought to be necessary for calcium absorption by increasing the solubility of insoluble calcium salts. However, the role of pH in calcium absorption is controversial and confounded by food effects. Clinical evidence is limited with regard to the effect of PPI use on calcium absorption and show conflicting results. O'Connell et al. conducted a randomized crossover trial in postmenopausal women found that a 7-day course of omeprazole can significantly reduce the absorption of calcium carbonate supplements when these are taken without meals [37]. In contrast, another randomized trial that assessed the absorption of ingested calcium under usual conditions did not find any reduction of calcium absorption when esomepazole was administered for 3 days in healthy adults [38]. Furthermore, PPI use may induce hypomagnesemia, which could increase the fracture risk, although this is also controversial [39].

If decreased calcium absorption is the mechanism by which PPIs increase fracture risk, calcium use may modify the effects of PPIs. Limited studies included in our meta-analysis examined this interaction [19, 25]. Yu et al. [19] found a possible interaction of PPI use and calcium supplement on the risk of non-spine fractures in men, but not in women. And Khalili et al. [25] used the study population of The Nurses' Health Study also found that the effect of PPIs was not modified by calcium intake in women. However, we cannot confirm this interaction in men based on the limited published information.

In present meta-analysis, we found that short-term PPI use (<1 year) was also associated with an increased risk of hip fracture, which may not support a link between PPI use and increased fracture risk through biochemical mechanisms (e.g., changes in calcium absorption or bone mineral density). There may exist other mechanisms that have direct effects upon bone mineralization or bone quality, which needs further studies to elucidate.

A major strength of our study is the large number of included participants and cases. With large numbers of incident cases, meta-analysis may provide high statistical power for estimating the association between exposure and outcome risk. In addition, we conducted a series of subgroup and stratified analyses to identify important subgroups or explain heterogeneity.

However, several limitations should be mentioned. First, as a meta-analysis of epidemiological studies, it is not able to solve problems with confounding factors. Inadequate control for confounders may bias the results. Most studies included in the meta-analyses adjusted results by smoking and BMI [16, 19, 20, 22, 25, 26, 28, 30, 31] in addition to age and sex; in several studies, the multivariate adjusted models also included calcium intake [16, 19, 22, 25, 29]. Several potential confounders were not included in the final statistical models in some studies because, as the authors reported, their inclusion in the model did not substantially modify the relative risk estimates. Second, observational studies are also susceptible to various biases. Prospective studies are less susceptible to bias than case-control studies because information on exposures is collected before the diagnosis of the disease in the prospective design. The positive association between PPIs and hip fracture risk is also supported by the prospective studies. Third, heterogeneity may be introduced because of methodologic differences among studies. We used appropriate well-motivated inclusion criteria to maximize homogeneity and performed sensitivity and subgroup analyses to find potential sources of heterogeneity. Fourth, we conducted stratified analysis by duration of PPI use; however, we were unable to pool the dose-response effects of PPI use due to incompatible definitions across studies. Finally, publication bias could be of concern because small studies with null results tend not to be published, though we found no evidence of publication bias in the meta-analysis of hip and any-site fracture.

This updated meta-analysis of observational studies showed that PPI use could modestly increase the risk of hip, spine, and any-site fracture. However, publication bias could also be of concern because small studies with null findings tend not to be published. Due to the high prevalence of PPI use and the impact of fractures on health and quality of life, even a moderate association would have important health implications. Thus, clinicians need carefully evaluate the risk factors for fracture in patients before prescribing PPI therapy.

Compliance with ethical standards

Conflicts of interest None.

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