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Review

Association between beta-blockers and fracture risk: A Bayesian meta-analysis

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ABSTRACT

Background: The association between beta-blockers (BB) and fracture risk is controversial, due largely to conflicting findings from previous studies. The present study sought to evaluate the effect of BB on fracture risk by using a Bayesian meta-analysis approach.
Methods and results: We systematically retrieved 13 observational studies on the association between BB use and fracture risk. This meta-analysis involved more than 907,000 men and women with mean/median age of individual studies ranging from 43 to 81 years. We used a hierarchical Bayesian random effects model to synthesize the results. BB use was associated with an average 17% reduction in the risk of any fracture (risk ratio [RR] 0.83; 95% credible interval [CrI]: 0.71–0.93), hip fracture (RR 0.83; 95% CrI: 0.70–0.92) and vertebral fracture (RR 0.81; 95% CrI: 0.61–0.99). The probability that BB use reduces fracture risk by at least 10% was 0.91.
Conclusions: Beta-blockers are associated with reduced risk of fracture in older adults, but the effect size is likely to be modest.

Contents

Introduction

Beta-blockers (BB), including selective and non-selective agents, are common medications for the treatment of hypertension and other cardiovascular diseases [1]. The prevalence of BB use in the general population is around 20% [2,3]. Recent findings from in vivo studies have suggested that these agents could have a beneficial effect on bone health. Indeed, mice treated with BB were found to have higher bone mass compared with controls [4]. As high bone mass is known to be associated with reduced fracture risk [5], it has been hypothesized that individuals on BB have lower fracture risk than non-users. However, observational studies have yielded conflicting findings, from "positive" [3,6] to null association [7,8]. Although the most appropriate approach to resolve these conflicting findings would be a randomized controlled trial (RCT) with BB use as the intervention and fracture the outcome,

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such a trial is not feasible at the present time. For a modest effect size and relatively low incidence of fracture, such a trial would require a prohibitively large sample size and long-term follow-up.

In the presence of inconsistent findings and unfeasibility of a randomized clinical trial, a quantitative approach such as meta-analysis may offer a sensible solution. Meta-analysis has a number of advantages over a single study, because it has greater statistical power than any single study, can control for between-study variation and estimate an overall effect size. A previous meta-analysis of 8 observational studies found that BB use was associated with a 12% reduction in fracture risk [9]. Since the publication of that meta-analysis, several additional studies have been published with yet again contradictory results [2,8,10]. Thus, the osteoporosis research community is still left with the unresolved question: is there an association between BB and fracture risk; and if there is, is the magnitude of the association clinically relevant?

There are two main approaches in meta-analysis: the classical or frequentist and the Bayesian approach. The frequentist approach is based on the philosophy of falsificationism, which aims at disproving the null hypothesis [of no association]. Results of the frequentist analysis are summarized by a *P*-value and confidence interval. Based on the *P*-value, an effect is categorically classified as either "significant" or "not significant". *P*-value is sensitive to sample size, such that a clinically trivial effect can be statistically significant when the sample size is large. As a result, *P*-value can mislead readers and researchers [11–13].

In the Bayesian approach, there is no *P*-value, and as a result, no arbitrary classification of significance or non significance. Instead, Bayesian analysis can "measure" the *certainty* (or uncertainty) of an effect size. Once a clinically relevant effect size is determined or agreed upon, it is possible to use the Bayesian analysis to make a direct inferential statement on the uncertainty of the effect size. For instance, if a risk reduction of 10% or more is considered clinically significant, Bayesian analysis allows us to make a statement such as "there is a 90% chance that the relative risk reduction is clinically significant". This statement, also referred to as "posterior probability", is considered more scientifically useful [14] than a *P*-value, because it directly addresses the clinically relevant question. Moreover, the Bayesian method approach to scientific evidence is a learning and updating process, which allows the incorporation of prior data into the present data to arrive at a better conclusion. An effect or an association is continuously updated when new data become available [15], which can be considered equivalent to a meta-analysis. Bayesian methods have gained prominence among clinical researchers, not only because it offers a logical and direct inference on an effect [16], it is also useful in cases where data collection is difficult or too expensive.

The aim of this paper is to use the Bayesian approach to update the association between BB use and fracture risk in light of new data from the literature, and to quantify the association in terms of clinical relevance.

Materials and methods

Identification of relevant studies

The studies included in this analysis were from two sources: previous meta-analysis and newly identified studies. The previously published meta-analysis identified 7 studies [2,3,6–8,17,18]. We then conducted further search for new studies that had published since the publication of the initial meta-analysis. The search was conducted using the Cochrane Central Register of Controlled Trials, Medline, Embase and PubMed up to November 2011. In addition, manual searches were made using the reference lists from the selected articles and conference abstracts to identify other papers that were not shown up in the systematic search. The papers were included in the analysis based on the following criteria: (a) written in the English language; (b) studies on human; (c) with BB users as exposure group and non-users control group; (d) original studies; (e) studies reported risk ratio (RR) including relative risks, odds ratios, hazard ratios, proportion ratio and its 95% confidence interval (CI); (f) studies with clearly defined fracture as an outcome; (g) adult men and women (aged 18+). In case of duplicate publications, data from the first paper were used in the analysis.

Quality assessment

Quality was assessed for each study, using criteria for observational studies [9]. Briefly, a 10-point scale was used to assess five methodological characteristics of case control or cohort studies. We assessed the case–control design by using the following characteristics: (a) response rate, (b) adjustment and matching, (c) control selection, (d) assessment of the exposure duration, and (e) whether the cases were prevalent or incident. For cohort studies, (c) and (e) were replaced with loss of follow-up and exposure maintenance respectively. Each item was scored from 0–2 based on previously defined criteria. A score of 6 or higher is considered "high quality".

Data synthesis

Two reviewers (S.Y., N.D.N.) independently examined papers or abstracts to extract basic data. A standardized form was used to collect basic data including first author, year of publication, type of study design, region, proportion of men and women, total sample size, type and number of fractures, mean age, RRs and 95% CIs of any fracture, hip fracture and vertebral fracture (e.g. odds ratio, hazard ratio), mean and standard deviation of BMD and associated risk factors. Any discordance between the two reviewers was resolved by verification of the third reviewer (T.V.N.).

We used the Bayesian hierarchical model to synthesize the data from individual studies, and then to evaluate the association between BB use and fracture risk. For each study, based on the observed RRs and 95% confidence interval, we calculated the logarithm of RR (denoted by λ_i) and variance of the logarithmic RR (denoted by V_i). The collection of λ_i across studies is assumed to follow a normal distribution with mean μ and variance σ^2. Here, μ is the estimate of overall log RR, and variance σ^2 is a measure of variation among studies. Our aim was therefore to estimate μ and σ^2. In the Bayesian analysis, it is necessary to quantify our belief on the μ and variance σ^2 through a probabilistic distribution (also referred to as "prior distribution"). In other words, the prior distribution is a mathematical representation of our best guess about the magnitude of RR as well as the uncertainty about the guess. In this study, we considered three types of prior distribution to reflect the equivocal, skeptical and optimistic views about the relationship between BB and fracture as follows:

- With the equivocal view, it is thought that the BB can exert positive as well as negative effect on fracture with equal chance. Thus, under this view, RRs can take any value with equal probability (i.e., equivocal, non-informative prior or vague prior). The equivocal prior distribution was therefore specified so that $\mu = 0$ (e.g., no association) and a very large variance (10,000).
- With the skeptical view, it was hypothesized that on average $\mu = 0$, but there is a little chance (i.e., 5%) that BB can reduce fracture risk by more than 50% ($RR \leq 0.5$), and also there is a little chance that BB can increase the risk by more than 50% ($RR \geq 1.5$). In logarithmic scale, this is equivalent to the statement $P(\mu \leq -0.693) = 0.05$, and by symmetry, $P(\mu \geq 0.693) = 0.05$. Under this skeptical prior, μ was set at 0, and the prior variance of $(0.693/1.645)^2 = 0.177$, in which 1.645 is a Z-score for the normal distribution probability of 0.05.
- With the optimistic view, it is assumed that BB can reduce fracture risk by 50% (i.e., $RR < 0.5$), with the same variance as in the skeptical prior. Thus, under this view, the prior distribution has a mean of -0.693 and variance of 0.177.

With the observed data and prior distribution, we derived the posterior distribution of RRs by using the well-known Bayes theorem [19].

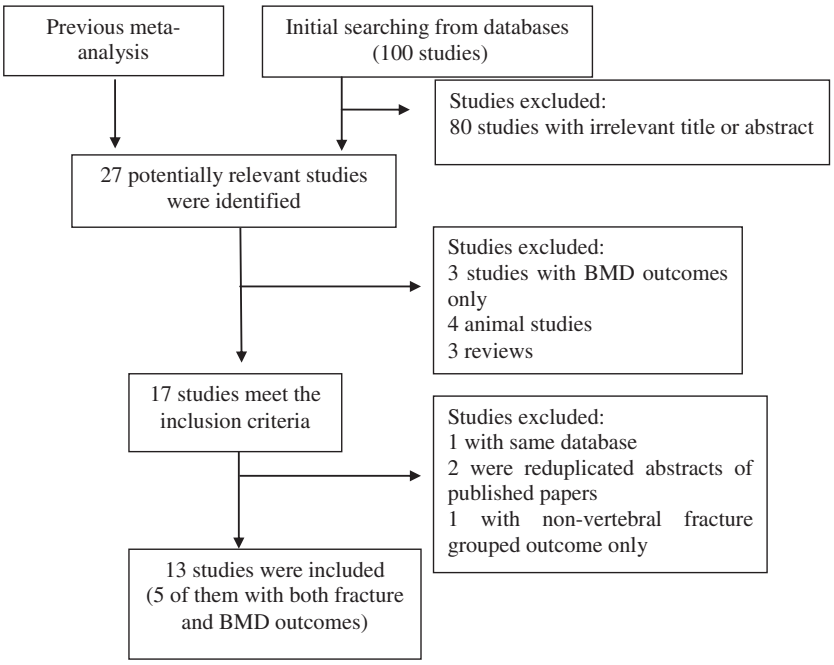

Fig. 1. Summary of search results.

With the posterior distribution parameters, we estimated the probability that RR is less than 1, 0.9 and 0.8. The estimation of model parameters was performed with the WinBUGS program (Version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). All other analyses were done with the R Statistical Environment (Version 2.1.1.1, R Foundation for statistical Computing, Vienna, Australia).

Sensitivity analyses

Estimates of effect size from observational studies are prone to bias. Usually, the bias is characterized by over-estimation of the true magnitude of association. In this analysis, it was assumed the observed RR in each study over-estimated the true RR by an average δ and variance ω. Therefore, we conducted a Bayesian sensitivity analysis [20] to assess the effect of potential bias on the overall RR by varying the value of δ. For instance, if the observed RR over-estimated the true RR by 50% in either direction, with $\delta = 0$, so that the variance ω is estimated as $[\log(1.5) / 1.96]^2 = 0.0427$. In subsequent analysis we assumed that the true RR was overestimated by $\delta = 10\%$ to 30%, and the variance ω was kept constant at 0.0427. The analysis was implemented in WinBUGS as previously described [20].

Results

Characteristics of studies

Thirteen original studies were included in this analysis (Fig. 1); of which, 6 studies were included in the previous meta-analysis [3,6–8,18] and an additional 7 newly identified studies [10,21–26]. All studies were based on Caucasian populations, with 9 studies including men and women. All studies were observational investigations, including 7 case–control and 6 prospective cohort studies. Five studies reported

Table 1
Characteristics of included studies.

Study (first author, year)	Design	Gender (% female)	Sample size	Fracture types	Mean age[a]	Quality score	Region
Jensen, 1991[b]	C-C	82	400	Hip	81/81	5	Denmark
Schlienger, 2004[b]	C-C	60	15,1420	Any/hip/vertebral	NA	9	UK
Reid, 2005[b]	Cohort	100	8098	Any/hip/nonvertebral	77/77	8	America
Pasco, 2004[b]	C-C	100	1344	Any/hip/vertebral/Colles	70/70	7	Australia
Rejnmark, 2004[b]	C-C	100	1141	Any	50/50[c]	4	Denmark
Schoof, 2005[b]	Cohort	NA	NA	Arm, hip and pelvis/vertebral	NA	4	Netherlands
Rejnmark, 2006	C-C	52	498,617	Any/hip/vertebral	43/43	8	Denmark
Gage, 2006	Cohort	53	13,381	Any	NA	2	America
Meisinger, 2007	Cohort	53	1793	Any	63/62	6	Germany
Bonnet, 2007	C-C	100	499	Any	66/64	4	France
Vries, 2007 (GPRD)	C-C	76	44,494	Hip	NA	9	UK
Vries, 2007 (PHARMO)	C-C	73	33,104	Hip	76/75	9	The Netherlands
Yang, 2011[d]	Cohort	0	1285	Any/hip/vertebral	69/69	6	Australia
Yang, 2011[e]	Cohort	100	2203	Any/hip/vertebral	69/69	6	Australia
Solomon, 2011	Cohort	80	150,164	Any/hip/wrist/humerus/pelvis	80/80	9	USA

Abbreviation: C-C: case control, NA: not available; fracture types separated with "/" were analyzed separately in original study.
[a] Mean age is case/control in case control study and beta-blocker users/non-users in cohort study.
[b] Studies have been used in previous meta-analysis.
[c] Values are medians.
[d] Study was results in men.
[e] Study was results in women.

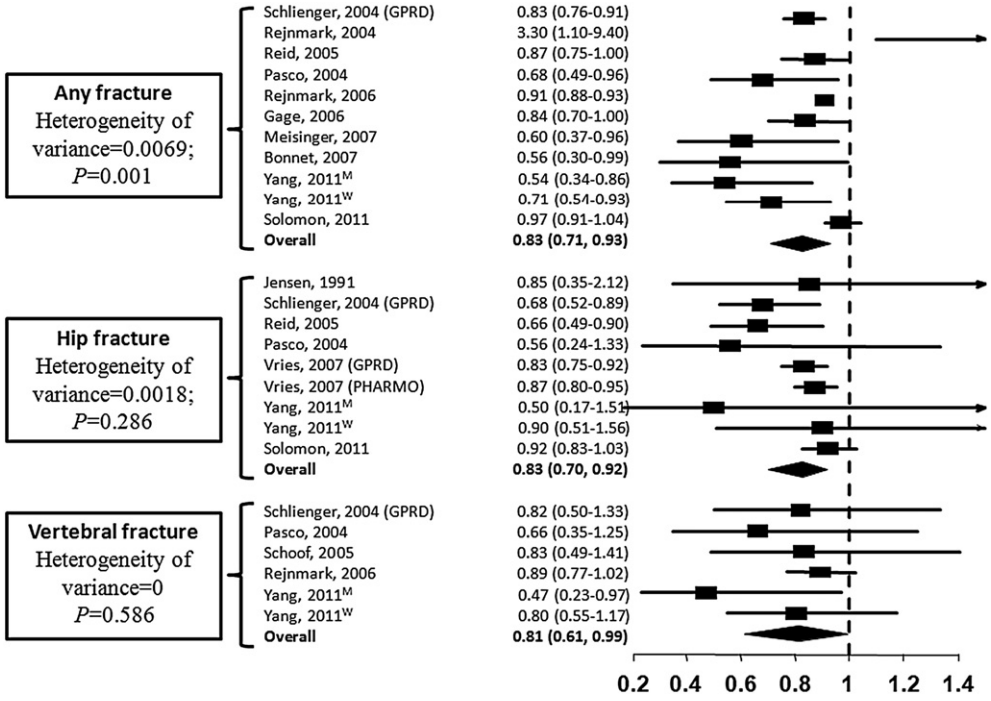

Fig. 2. Forest plots of risk ratio for beta-blocker and fracture risk under classical meta-analysis for individual studies.

both BMD and fracture outcomes and all others reported fracture risk only. A total of more than 907,000 participants were included in this meta-analysis. The per-study sample size ranged between 400 and 498,617 (median: 5,150). The average/median age of participants was 68 (range: 43–81 years). Seven studies had quality scores greater than 7, which was considered "high quality". Most of these high-quality studies also had large sample sizes (Table 1).

Association between BB and fracture risk

The observed RR and 95%CI for any fracture, hip fracture, and vertebral fracture for individual studies and summary RR are shown in Fig. 2. Almost all studies consistently showed that BB use was associated with lower risk of fracture, including hip and vertebral fractures. There was considerable variability in the magnitude of association between BB and any fracture risk. However, heterogeneity was not observed for hip fracture and vertebral fracture.

Under the equivocal prior, the overall RR for any fracture was 0.83 (95% CrI 0.71 to 0.93). The probability that BB reduces fracture risk was 100%. The probability that BB reduces fracture risk by at least 10% and 20% was 91% and 25%, respectively (Fig. 3). Similar effect size was also found for hip (RR 0.83; 95% CrI 0.70 to 0.92) and vertebral fracture (RR 0.81; 95% CrI 0.61 to 0.99).

Table 2 presents the estimates of RR, 95% CrI, and probability of effect size under the three prior distributions. It is clear from these results that the RRs for any fracture, hip and vertebral fractures remained

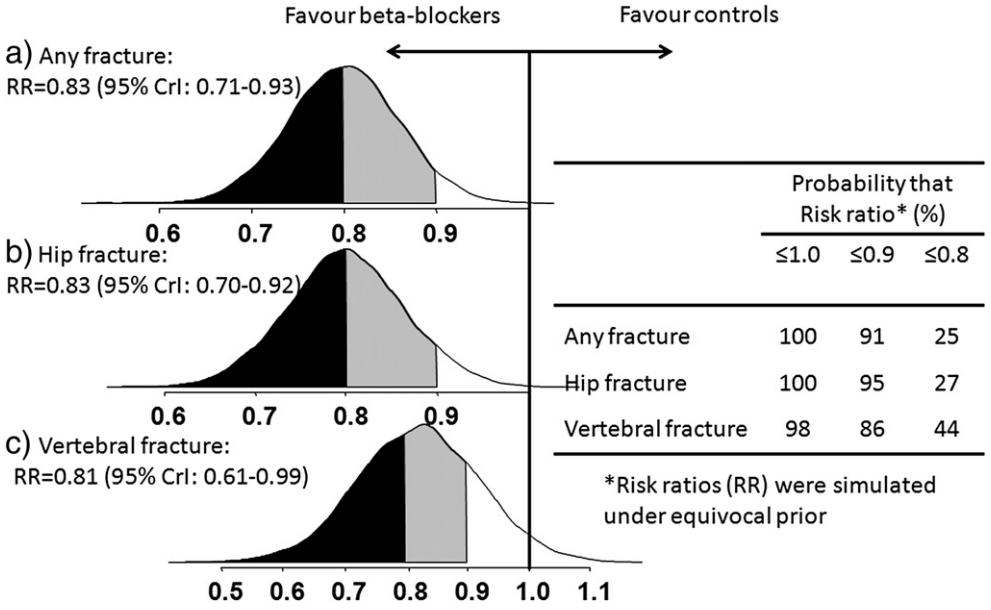

Fig. 3. Posterior distribution of risk ratios for beta-blocker and fracture risk (equivocal prior model).

Table 2
Overall risk ratio and 95% credible interval for fracture under 3 priors.

Fracture type	RR (95% CrI)	Probability (%) that risk ratio		
		≤1.0	≤0.9	≤0.8
Equivocal prior				
Any fracture	0.83 (0.71–0.93)	100	91	25
Hip fracture	0.83 (0.70–0.92)	100	95	27
Vertebral fracture	0.81 (0.61–0.99)	98	86	44
Skeptical prior				
Any fracture	0.84 (0.72–0.93)	100	90	22
Hip fracture	0.83 (0.71–0.92)	100	94	25
Vertebral fracture	0.82 (0.64–1.00)	97	82	39
Optimistic prior				
Any fracture	0.83 (0.69–0.92)	100	92	32
Hip fracture	0.82 (0.68–0.91)	100	97	36
Vertebral fracture	0.79 (0.57–0.95)	99	91	54

Table 3
A Bayesian analysis on the bias of beta-blockers and fracture risk under equivocal prior.

Type of fracture	Bias (%)	RR (95% CrI)	Probability that RR (%)		
			≤1.0	≤0.9	≤0.8
Any fracture	10%	0.91 (0.67, 1.26)	70	47	23
	20%	1.09 (0.62, 1.49)	34	19	11
	30%	1.14 (0.87, 1.55)	17	4	1
Hip fracture	10%	0.90 (0.58, 1.46)	71	50	29
	20%	1.01 (0.65, 1.64)	48	29	14
	30%	1.16 (0.74, 1.87)	25	13	5
Vertebral fracture	10%	0.91 (0.54, 1.50)	65	48	31
	20%	1.02 (0.61, 1.69)	46	31	18
	30%	1.17 (0.73, 1.83)	25	13	6

RR: risk ratio; 95% CrI: 95% credible interval.

virtually unchanged between the three priors, suggesting that the result was largely driven by observed data, and that prior distribution has little effect on the overall effect size.

Bayesian analysis of bias

Results of bias sensitivity analysis (under the equivocal prior) are shown in Table 3. If there was 10% bias in each study, then the probability of a beneficial effect (RR<1) of BB was reduced to 70% for any fracture, 71% for hip fracture, and 65% for vertebral fracture. A bias of 20% and 30% were associated with further reduced probability of an effect.

The funnel plot (Fig. 4) shows a symmetry for any fracture ($P=0.12$) and hip fracture ($P=0.08$), indicating no significant publication bias. However, we observed an asymmetric trend for vertebral fracture ($P<0.05$).

Discussion

The association of BB use with reduced fracture risk remains contentious. Results of the present analysis suggest that BB use is associated with a 17% reduction in osteoporotic fracture risk, including hip and vertebral fracture. Moreover, the analysis shows that there is a modest chance that BB use is associated with more than 20% reduction in fracture risk. Taken together, it seems clear that BB use has a beneficial effect on fracture, but the effect is likely to be modest.

The effect size of BB observed in this analysis is slightly greater than those observed in the previous meta-analysis [9] which reported a relative risk reduction of 12% associated with BB use. However, with accumulative data, the effect size for hip fracture in this study (RR 0.83) is somewhat lower than a previous estimate (RR 0.72). The present study included 7 new studies with a substantial increase in weight of evidence, indicating a greater statistical power in detecting a true relationship. The results were largely not affected by any prior distribution, suggesting that the effect is robust.

The underlying mechanism whereby BB exerts its beneficial effect on bone health is still not clear. However, results from animal studies suggested that the central nervous system might play a role in regulation of skeletal remodeling activity. There is evidence that BB stimulates bone formation via the same pathway [27], and that mice on BB have greater bone mass, bone formation rate and osteoblastic number possibly acting via beta-2 receptors on osteoblast of bone [4]. In addition, it has been shown that postmenopausal women on beta-blockers were associated with a greater cortical thickness [26], which could partly account for the reduction in fracture risk among beta-blocker users. Taken together, these basic and translational evidence suggest that the association between BB and reduced fracture risk has a biologic basis.

Regardless of mechanisms that might be involved, the association between BB and fracture risk has important clinical implications at the population level. Hypertension affects more than 65 million Americans [28] and is a major risk factor for myocardial infarction, stroke, heart failure, and renal failure. The control of blood pressure is crucial in the prevention of these adverse outcomes and mortality. BB use becomes commonly prescribed by doctors in hypertension treatment. Although the present study suggests that BB has a modest effect on fracture risk, with almost 20% of the population on BB (calculated from cohort studies included in our meta-analysis), the effect could translate into a significant reduction in fracture incidence in the general population. Apart from BB, thiazide diuretics could exert beneficial effect on bone density [29,30] and fractures [31,32]. Therefore, a combination of BB and thiazide diuretics would have extra benefits in protecting bone fragility and its consequent osteoporotic fractures beyond BB only.

Although our findings support the hypothesis that BB use reduced fracture risk, the findings must be considered within the context of strengths and weaknesses. The present analysis was based on the most comprehensive data to date, with more than 907,000 men and women,

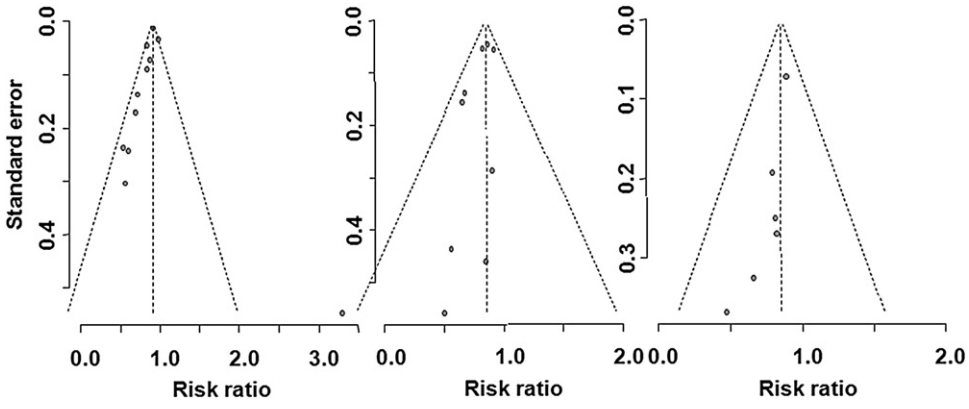

Fig. 4. Funnel plot of risk ratio versus standard error for any fracture (left panel), hip fracture (hip fracture), and vertebral fracture (right panel).

and the estimated effect size presented here is more reliable than estimates from individual studies. The Bayesian approach used in this study has considerable advantages over the classical analysis. In Bayesian analysis, it is possible to estimate the probability of a true association, a measure that is not possible in classical statistics. Moreover, bias can be easily taken into account in the Bayesian modeling, which is also superior to classical analysis. However, the quality of meta-analysis is highly dependent on the quality of individual studies [33]. A major weakness of this analysis is that it was based on observational studies, which may not be able to control for confounders. Unlike RCT, variation of fracture incidence could relate to different age groups, body weight, ethnicities [34], dietary calcium intakes, sun light exposure, physical activity and other risk factors. The present analysis could not control for these factors. In addition, uncontrolled and self-report of BB use may introduce a potential recall bias, which may misclassify intervention and control groups, and ultimately affect the magnitude of association. In the sensitivity analysis, we have shown that if the primary studies over-estimated the magnitude of association by just 10%, then the overall association no longer exists. Thus, any interpretation of the association between BB and fracture should be conditioned on the potential bias of individual studies.

In conclusion, these data show that BB use is associated with reduced fracture risk. Although the risk reduction is likely to be modest, given the high prevalence of BB use in elderly population, the association could be translated into a significant population health benefit.

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