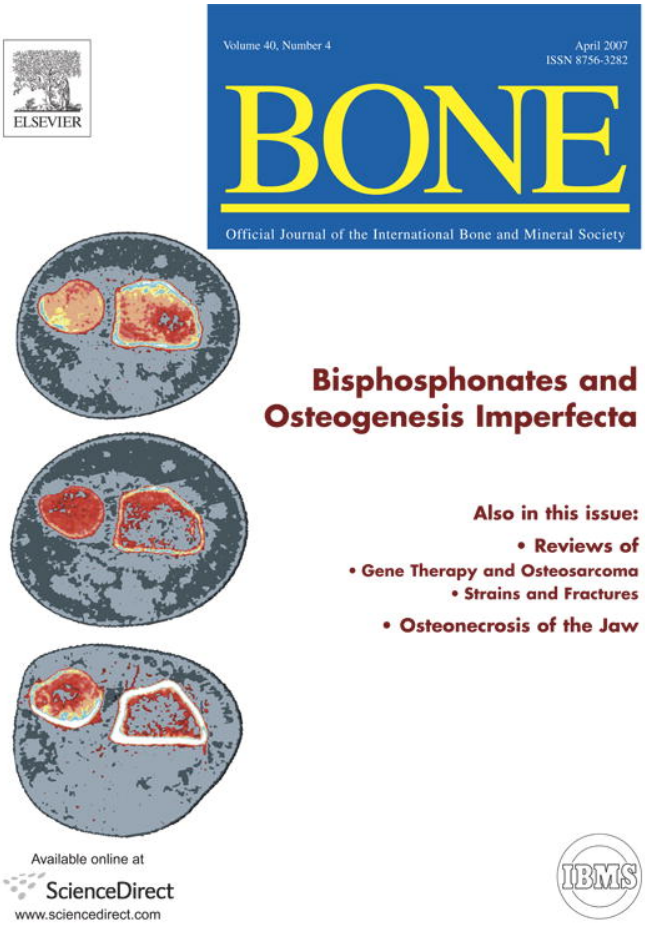

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Review

On the association between statin and fracture: A Bayesian consideration

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Abstract

Background: The association between statin use and fracture risk is controversial, due to conflicting findings from previous studies. This study utilized the Bayesian approach to combine existing evidence and update the association with consideration of potential bias.
Methods: Data on the association between statin use and fracture incidence from 11 observational studies and 4 RCTs were synthesized by both empirical Bayesian analysis and fully Bayesian random-effects meta-analysis models.
Results: Empirical Bayesian analysis showed that statin use was associated with a reduction in hip fracture risk (OR = 0.57, 95% credible interval (CrI): 0.46–0.71) and for non-vertebral (OR = 0.69, 95% CrI, 0.63–0.74). These results were comparable with results from the fully Bayesian random-effects meta-analysis only for hip fracture (OR 0.56, 95% CrI, 0.42–0.73), but not for non-vertebral fracture (OR 0.77, 95% CrI, 0.58–1.03). The probability that statin use reduces fracture risk by at least 20% was 0.995 for hip fracture and 0.61 for non-vertebral fracture. Under the assumption that bias over-estimates the true OR by 20%, there is still a probability of 0.97 that statin use reduces hip fracture risk by at least 20%; however, the effect on non-vertebral fracture was much less robust with a probability of 0.27.
Conclusions: Results of this Bayesian consideration are highly consistent with the hypothesis that statin use reduces hip fracture, but the association between statin use and non-vertebral fracture remains uncertain. The Bayesian approach presented here has the ability to help updating existing evidence as new data becomes available.

Keywords: Statins; Hip fracture non-vertebral fracture; Osteoporosis; Meta-analysis; Bayesian analysis

Contents

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Introduction

Of the association between statin use and fracture risk, several observational studies have found that the risk of fracture was significantly reduced in statin users [10,27,44] compared to non-statin users. Indeed, a recent meta-analysis of 6 observational studies and secondary data from 2 randomized controlled trials (RCTs) suggested that statin use was associated with an odds ratio (OR) of 0.43 (95% CI, 0.25–0.75) for hip fractures and 0.69 (95% CI, 0.75–0.88) for non-vertebral fractures [2].

There have been some further analyses since the publication of that meta-analysis [34,37]. For example, a recent secondary analysis of data from the "PROVE IT-TIMI 22" trial [9] concluded that "currently available statins do not impact on fracture risk" [34]. Still, the latest analysis of the New England Veterans Affairs health care system data suggested that statin users had a significantly reduced risk of fracture compared to individuals who did not use lipid-lowering therapy, and this association was statistically significant after adjusting for comorbidity [37].

It is perhaps not surprising that findings from observational studies are highly inconsistent, due to differences in study design, population characteristics, and distribution of confounders, which are hardly controlled for in the analysis. Initial findings of extremely large effect size are often contradicted by subsequent studies [22], which leads to the "Proteus phenomenon" [23]. In this scenario, it seems logical that a combination of data from all available studies to arrive at a more reliable estimate is preferable to any individual study.

Given that any single study is unlikely to unequivocally confirm or refute a hypothesis, analysis of multiple studies is currently accepted as the highest level of evidence. However, the latest evidence must be considered in addition to previously known data by a cumulative process. Traditionally, statistical methods for accumulating data from different studies are largely based on the fixed-effects and random-effects meta-analyses. In either analysis, the aim is to obtain an overall effect size as the weighted average of all individual effect sizes with the weight being the inverse variances of individual studies. The statistical significance of this overall effect size is traditionally assessed via the *p*-value or confidence interval (CI), such that *p*-values being greater than 0.05 or 95% CIs including unity are usually deemed to be "negative".

However, *p*-value has been reported to be widely misunderstood [19]. In the context of association hypothesis testing, it is a measure of the likelihood of having observed the data (or more extreme data) conditional on the hypothesis of no association. It does not address the more pertinent question: "given the observed data, what is the probability of the hypothesis of association being true." Similarly, the 95% confidence interval has an awkward interpretation: if the study is repeated infinite number of times, then 95% of the calculated "95% confidence intervals" would be expected to contain the true parameter value (e.g. odds ratio, mean difference, etc.); it does not mean that the probability of true parameter is 0.95. It has been commented that *p*-value and confidence interval are "two sides of the same unsatisfactory coin" [17], because they do not address the question of probable level of any apparent observed relationship.

Such questions can be addressed by the Bayesian approach. The Bayesian model of scientific evidence is a learning and updating process as new data or evidence becomes available [39]. It is possible to update from what is already known (i.e. previous data or prior information) based on Bayes' theorem, which states that the probability that a hypothesis is true, given some currently observed data (also called "posterior probability"), is a function of two pieces of information, namely, the prior probability of the hypothesis, and the probability that the data would occur if the hypothesis is true. The posterior probability is analogous to the positive predictive value in a diagnostic test (e.g. the probability of having a disease given a positive test result is a function of the prevalence of the disease and the sensitivity of the test). Thus, "posterior" probability, not *p*-value, is a more scientifically useful piece of information [8].

In the context of statin-fracture association hypothesis, it is much more relevant to address the question, "given what has been reported from observational studies and secondary analysis of RCTs, what is the likelihood that statin use does reduce fracture risk", rather than calculating the *p*-value. In the absence of a proper RCT examining the effect of statin on fracture risk, it is possible to combine these two sources of data along with other studies that were not included in the previous meta-analysis in a Bayesian approach. Therefore, the aim of the present study was to use the Bayesian approach to update the association between statin use and fracture risk in light of new data from secondary endpoints (fractures) in RCTs.

Methods

Identification of relevant studies

The present analysis was limited to hip fracture and other non-vertebral fractures, because most previous data on the association between statin and fracture risk were based on these two types of fracture. In addition to the studies identified and analyzed by Bauer et al. [2], to identify studies examining the relationship between statin use and fracture risk, an electronic search of PubMed was performed from January 1966 to September 2005. The language was limited to English. The keywords used for this search were "fracture* OR fracture risk OR hip fracture* OR non-vertebral fracture* OR nonvertebral fracture*" concatenated with "statin* OR statin use OR pravastatin OR atorvastatin OR fluvastatin OR lovastatin OR simvastatin OR cervistatin OR HMG-CoA reductase inhibitor". With this search, 4 additional studies were retrieved [29,32,35,37]. In total, 11 observational studies [7,10,13,25,27,29,32,35,37,43,44] and 4 RCTs (FIT, the Fracture

Intervention Trial [4]; HERS, the Heart and Estrogen/Progestin Replacement Study [21]; 4S, Scandinavian Simvastatin Survival Study [30] and The LIPID study [33]) were identified from the literature that have examined the association between statin use and either hip or non-vertebral fracture risk.

In each study, odds ratio (OR) and 95% confidence interval (95% CI) were extracted (Table 1), and converted to a logarithmic scale to facilitate the synthesis of data across studies. For any given study with OR and 95% CI ranging from L to U, the log OR (denoted by LOR) is defined as LOR = ln(OR), and the variance of *LOR* is estimated as $V = \ln(U/L)/3.92$. The synthesis of LOR was done by both empirical Bayesian and fully Bayesian methods.

Empirical Bayesian analysis

In the empirical Bayesian analysis, both prior and current data are expressed by a probability distribution. The synthesis of a posterior distribution is done via the Bayes' theorem, which takes the prior and the current data into consideration [31].

Prior information

Prior data were synthesized from the 11 observational studies with the classical random-effects model [14], incorporating the between-study and within-study heterogeneity and does not assume a common "treatment" effect across different studies. Estimates of the classical random-effects model parameters were based on the method of maximum likelihood. In this analysis, individual LOR_i ($i = 1, 2, \ldots, 11$) are assumed to be normally distributed with a "true" but unknown mean λ_i and a within-study variance σ_i^2. The collection of λ_i across the 11 studies is assumed to follow a normal distribution with mean λ_0 and between-study variance τ^2. The resulting estimates are an overall log OR (λ_0) and variance V_0. These two estimates were considered prior information for the subsequent analysis. Data from three RCTs were combined to obtain an average LOR (denoted by λ_d) and variance (V_d) as described above.

Posterior distribution

Given the prior information from the observational studies (λ_o and V_0) and the RCT data (λ_d and V_d), it was possible to derive the posterior estimate of log OR (denoted by λ_p) and its variance (V_p): $1/V_p = 1/V_0 + 1/V_d$, and $\lambda_p = V_p\,(\lambda_o/V_0 + \lambda_d/V_d)$. It follows that the posterior OR is $\exp(\lambda_p)$ and its 95% credible interval (95% CrI) is $\exp(\lambda_p \pm 1.96\sqrt{V_p})$. In Bayesian analysis, the *LOR* is considered a random variable (in the sense that its true value is uncertain), and the uncertainty is expressed by a probability density distribution. It is therefore possible to compute the probability of any effect size of interest. For example, if an effect with OR ≤ 0.8 (i.e. reduction of fracture risk by 20%) is considered clinically relevant, Bayesian analysis can provide the probability of such an effect size.

Fully Bayesian analysis

In this analysis, data from both observational studies and clinical trials were synthesized by a Bayesian random-effects meta-analysis model, with external prior information of the variance, instead of using previously published data as prior information as in the empirical Bayesian analysis. In contrast to the traditional random-effects model where the parameters λ, σ_i^2 and τ^2 are assumed to be fixed, in the Bayesian random-effects model, σ_i^2 and τ^2 are assumed to be random variables. Fully Bayesian analysis refers to the use of external prior information, which must be specified for λ_i and σ_i^2. The prior distribution for τ^2 was assumed to be uniformly distributed with parameters (0, 10). The prior

Table 1
Summary of odds ratios from individual studies and the fully Bayesian random-effects meta-analysis

Study	OR (95% CI) [a]	
	Hip fracture	Non-vertebral fracture
Observational		
1. Cummings et al. (SOF) [13]	0.19 (0.03, 1.38)	0.76 (0.50, 1.16)
2. Burger et al. [7]	0.31 (0.04, 2.25)	0.49 (0.15, 1.57)
3. Wang et al. (NJ Medicaid) [44]	0.50 (0.33, 0.76)	NA
4. Chan et al. (HMO) [10]	0.22 (0.03, 1.66)	NA
5. LaCroix et al. (WHI) [25]	0.98 (0.73, 1.62)	NA
6. Meier et al. (GPRD-1) [27]	0.12 (0.04, 0.41)	0.55 (0.44, 0.66)
7. Van Staa et al. (GPRD-2) [43]	0.59 (0.31, 1.13)	NA
8. Rejnmark et al. [35]	0.68 (0.50, 0.93)	NA
9. Ray et al. [32]	0.62 (0.45, 0.85)	NA
10. Pasco et al. [29]	0.45 (0.25, 0.80)	NA
11. Scranton et al. [37]	0.40 (0.28, 0.58)	0.59 (0.53, 0.67) [b]
Overall estimate [c]	0.53 (0.42, 0.68)	0.59 (0.53, 0.65)
RCTs		
12. Black et al. (FIT) [4]	0.53 (0.07, 3.82)	0.95 (0.59, 1.52)
13. Hulley et al. (HERS) [21]	0.62 (0.16, 2.35)	0.92 (0.64, 1.32)
14. Pedersen et al. (4S) [30]	1.00 (0.42, 2.40)	1.11 (0.81–1.52)
15. Reid (LIPID) [33]	0.77 (0.34, 1.75)	0.94 (0.77, 1.16)
Overall estimate [c]	0.79 (0.47, 1.35)	0.97 (0.84, 1.13)
Empirical Bayesian analysis [d, e]	0.57 (0.46, 0.71)	0.69 (0.63, 0.74)
Fully Bayesian random-effects meta-analysis [e, f]		
Reference prior	0.56 (0.42, 0.73)	0.77 (0.58, 1.03)
Skeptical prior	0.59 (0.46, 0.75)	0.79 (0.61, 1.02)
Positive prior	0.55 (0.43, 0.71)	0.74 (0.57, 0.96)

Non-vertebral fractures were defined as any non-vertebral fractures, otherwise specified.
NA, data not available.
[a] Obtained from the meta-analysis [2] or from original publications.
[b] Hip fractures were not included.
[c] Estimated from traditional random-effects model.
[d] Posterior (updated) information with overall estimate of observational data considered as prior information and overall estimate of RCT data as current likelihood.
[e] Values are OR(95% credible interval, CrI).
[f] Included all observational and RCT (secondary end-point) data, using external prior.

distribution for λ_I was given a vague prior normal distribution of mean 0 and variance of 10,000. This is considered a "referent prior", in the sense that it reflects statin effect that could be negative as well as positive equally. In subsequent analyses, the prior distribution of λ_i was specified in such a way that reflects both skepticism and positive about the effects of statin on fracture risk.

In the skeptical assumption, it was hypothesized that there is little chance (i.e. 5%) that statin can reduce fracture risk by more than 50% (OR ≤ 0.5). In the logarithmic scale, this is equivalent to the statement $P(\text{LOR} \leq -0.693) = 0.05$, and by symmetry, $P(\text{LOR} > 0.693) = 0.05$. With this skeptical assumption and by Normal distribution, it can be shown that the prior variance of LOR is $(1.645/0.693)^2 = 0.177$. Therefore the skeptical prior distribution was specified as mean 0 and variance of 0.177.

In the positive scenario, it was assumed that statin could reduce fracture risk by 50% (i.e. OR = 0.5), with the same variance of skeptical prior variance. Under this assumption, it can be shown that the prior distribution is characterized by a mean of −0.6932 and a variance of 0177. The estimation of model parameters was performed by the MCMC technique with the WinBUGS program [40].

Sensitivity analysis

Estimates of effect size from observational studies and analyses of secondary data are prone to bias, in the sense that the observed OR shows a systematic departure from the "true" OR. Since all studies considered in this analysis were either observational or secondary outcomes from RCTs, it is important to evaluate the potential effect of bias on the results. To ensure the rigor of estimation, the observed OR in each study from the fully Bayesian analysis was assumed to over-estimate the "true" effect size by an average δ and variance ω. Sensitivity analysis with various values of δ was conducted to assess the influence of bias on the observed OR. Details of the methods have been described by Spiegelhalter et al. [38]. Briefly, it was assumed that the true OR was over-estimated 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 the subsequent analysis, it was assumed that the true odds ratio was overestimated by $\delta = 5\%$ to 30%, and the variance ω was kept constant at 0.0427. The procedure was implemented in WinBUGS [40].

Testing for heterogeneity

The heterogeneity of effects across studies was assessed by computing the Cochran's Q statistic [11] and the coefficient of inconsistency (I^2) as an estimate of the proportion of total variation in study estimates that is due to heterogeneity [20]. Publication bias was examined by a funnel plot [41].

Results

Empirical Bayesian analysis

Hip fracture

Of the 11 observational studies, 6 studies reported a statistically significant association between the use of statin and reduced hip fracture incidence. When results of all studies were combined within the random-effects model, the OR of fracture associated with statin use was 0.53 (95% CI: 0.42–0.68). However, data from the 4 RCTs yielded a summary OR of 0.79 (95% CrI: 0.47–1.35) (Table 1). The large variance of this effect size is reflected by the wide spread of the distribution (Fig. 1). When the RCT data were considered in relation to the prior data from the observational studies by the Bayesian approach, the posterior OR was 0.56 (95% credible interval, CrI: 0.44–0.70) (short-dashed line Fig. 1, c.1).

Non-vertebral fracture

The distribution of odds ratio combined from 4 observational studies was 0.59 (95% CI: 0.53–0.65). The average odds ratio combined from 4 RCTs was 0.97 (95% CI: 0.84–1.113). The

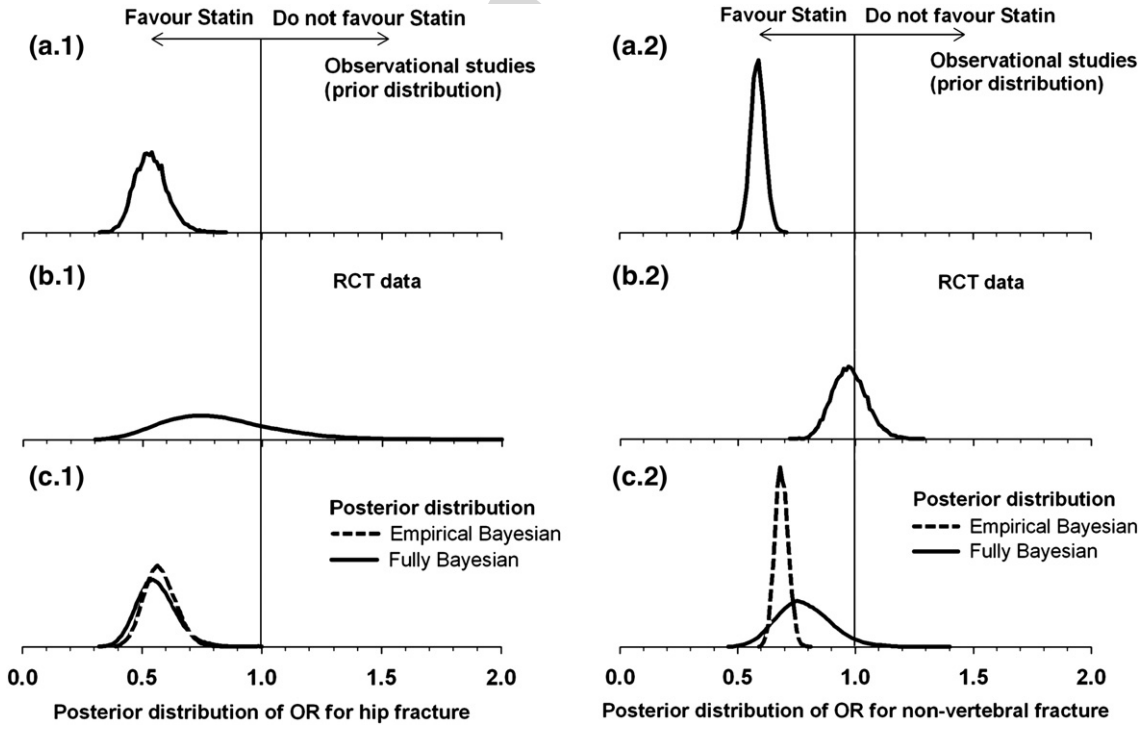

Fig. 1. Association between statin use and hip fracture risk (left) and non-vertebral fracture risk (right). In each panel, the top figure (a) displays the prior distribution of odds ratios from observational studies; the middle figure (b) shows the distribution of odds ratio from RCT studies; and the bottom figure (c) is the posterior distribution of odds ratios. Short-dashed lines are the distribution derived from the empirical Bayesian analysis, whereas solid lines are the distribution derived from the fully Bayesian analysis using vague prior.

Table 2
Effects of bias on the statin-fracture association: a sensitivity analysis (fully Bayesian analysis)

Bias (%)	OR	(95% CrI)	Probability (%) that OR			
			<1.0	≤0.9	≤0.8	≤0.7
Hip fracture						
No bias	0.56	(0.42, 0.73)	100.0	100.0	99.5	96.3
0±50	0.56	(0.42, 0.74)	100.0	99.9	99.4	95.1
5±50	0.59	(0.44, 0.78)	100.0	99.8	98.9	89.7
10±50	0.62	(0.47, 0.82)	99.9	99.5	96.9	82.0
15±50	0.66	(0.49, 0.87)	99.7	99.1	92.4	68.6
20±50	0.70	(0.52, 0.93)	99.4	96.9	84.6	49.9
25±50	0.74	(0.56, 0.99)	98.6	91.6	70.9	31.3
30±50	0.80	(0.60, 1.06)	95.1	82.0	49.9	16.7
Non-vertebral fracture						
No bias	0.77	(0.58, 1.03)	96.1	87.1	61.0	20.3
0±50	0.78	(0.59, 1.02)	96.6	86.4	58.8	20.6
5±50	0.81	(0.63, 1.05)	94.7	81.1	46.2	9.9
10±50	0.86	(0.66, 1.11)	89.2	66.8	27.1	5.2
15±50	0.91	(0.70, 1.18)	80.3	47.5	14.6	2.6
20±50	0.96	(0.74, 1.25)	62.6	27.1	6.6	1.2
25±50	1.03	(0.78, 1.34)	42.3	14.7	3.1	0.6
30±50	1.10	(0.83, 1.46)	22.4	6.9	1.6	0.4

OR, odds ratio; 95% CrI, 95% credible interval.

uncertainty in the RCT data (as indicated by its range, Fig. 1) resulted in lower weight of evidence and the posterior odds ratio tended to be closer to the prior data, with the average of 0.69 (95% CrI: 0.63–0.74) (short-dashed line Fig. 1, c.2).

Fully Bayesian meta-analysis of all studies

Meta-analyses of results from the 15 studies (11 observational studies and 4 RCTs combined) showed an overall OR of 0.56 (95% CrI, 0.43–0.73) for the association between statin use and reduction of hip fractures which was comparable to the OR derived from the empirical Bayesian analysis (0.56, 95% CrI, 0.44–0.70). The corresponding OR for the association between statin use and non-vertebral fractures was 0.77 (95% CrI, 0.58–1.03) (Table 1 and solid line Fig. 1, c.1). Under the assumption of no bias, the probability that statin use reduces hip fracture risk by at least 20% and 30% was 0.995 and 0.963, respectively. The corresponding probabilities for non-vertebral fractures were 0.61 and 0.203, respectively (Table 2 and solid line Fig. 1, c.2). This result remains virtually unchanged when the prior distribution was expressed as skeptical or positive.

Heterogeneity of studies

Although almost all studies updated showed a positive trend of reduction in fracture risk associated with statin use, there was statistically a significant heterogeneity with Cochran's Q statistic of 23.2 ($p=0.0571$) for hip fracture and 16.62 ($p=0.02$) for non-vertebral fracture. The coefficient of inconsistency (I^2) was estimated at 44% for hip fracture, and 70% for non-vertebral fracture. A funnel plot of log ORs versus the precisions showed that smaller studies (with large confidence intervals) tended to produce more pronounced effects than large trials (Fig. 2). Furthermore, for the hip fracture case, there were more "positive" studies than "negative" studies. This imbalance distinction raises the issue of publication bias which is considered in the sensitivity analysis.

Sensitivity analysis of bias

For the case of non-systematic bias ($\delta=0$) and assuming that the observed OR was deviated from the true OR by 50% in either direction, the 95% CrI was, as expected, wider than those obtained under the assumption of no bias (Table 2). However, the overall result did not substantially change for hip fracture: the probability that OR of hip fracture being less than 1 (any

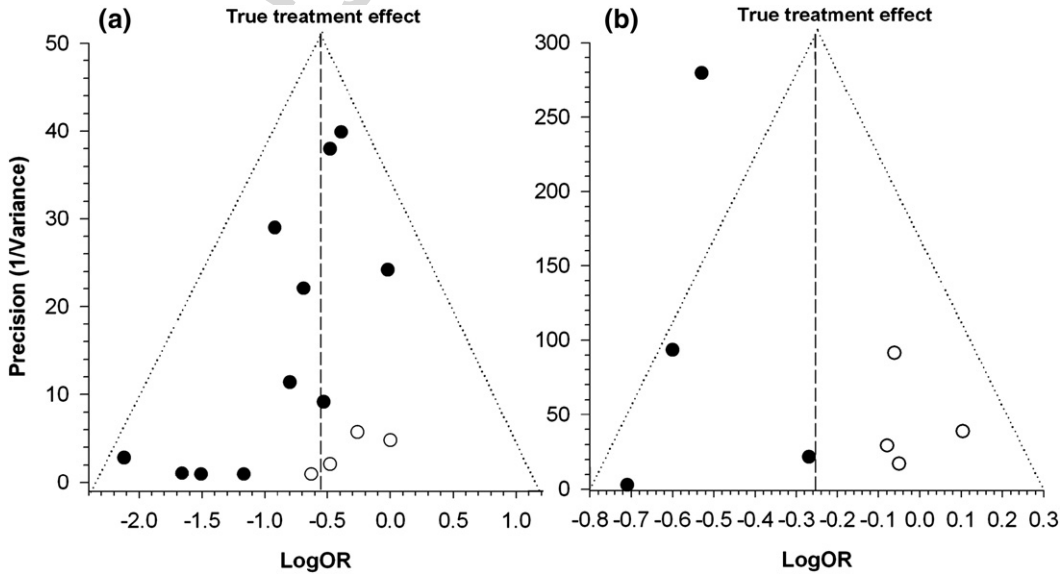

Fig. 2. Funnel plots of log odds ratio against precision (inverse variance) for statin and hip fracture risk (a) and statin and non-vertebral fracture risk (b). Observational studies and RCTs are denoted by the filled and hollow circles respectively. True treatment effects obtained from fully Bayesian analysis.

effect at all) was 1. Even with the bias of up to 30% (i.e. true odds ratio is over-estimated by a mean of up to 30%), there was still a probability of 0.95 that OR is less than 1.

For the case of non-vertebral fracture, the result was less robust than that for hip fracture. For example, if the true OR was over-estimated by 5%, the resulting posterior distribution of ORs suggested that there was a 0.95 probability that statin had beneficial effect on the reduction of fracture risk (e.g. OR < 1). However, if the bias effect was 15% up to 30%, the probability that statin reduces non-spine fracture risk was less than 0.80.

Discussion

Whether the use of statin, a lipid-lowering drug, is associated with reduced risk of fracture is a contentious issue, because of inconsistent findings and lack of a confirmatory randomized controlled trial. Results of the present analysis suggested that statin may confer beneficial effect on bone health. Indeed, by using the Bayesian approach and based on the data available so far from observational studies as well as secondary analyses of RCTs, it was estimated that there is a 0.95 probability that statin use reduces hip fracture risk by between 27% and 58%. Although there is little evidence that the reduction of fracture risk is more than 50%, the effect of statin on reducing fracture risk seems clinically significant, given the large number of people in the population who are on statin therapy.

In the present study, results of the empirical Bayesian and fully Bayesian analyses were highly comparable in terms of the effect of statin on hip fracture risk. However, for non-vertebral fractures, there was an uncertain association as the two analyses were not quite converged. The discrepancies could be explained by the use of prior information. Although Bayesian method allows making use of the current data with consideration of the existing knowledge (prior information) to derive the posterior distribution for the population, the posterior distribution substantially depends on the prior information when there is insufficient or inconsistent current data [24]. This is the case for non-vertebral fractures, where the overall estimate of observational studies strongly favors to statin, but such a trend was not observed in secondary analyses of clinical trials; therefore, results derived from the empirical Bayesian analysis were driven by the prior information of observational studies. On the other hand, for hip fracture, the current observational studies' data were relatively consistent, and the effect of prior information on the posterior estimate of association was negligible.

Hyperlipidemia is highly prevalent (28%) in the general population, particularly among post-menopausal women [26]. Approximately 63% individuals with hyperlipidemia use statin [42], making it one of the most commonly used drugs in the population. Furthermore, around 27% of patients with a history of coronary heart disease or myocardial infarction use statins [16]. The magnitude of association between statin use and reduced fracture risk observed in this analysis is comparable to that between bisphosphonate treatment and vertebral fracture [1,12] or hip fracture [28] in post-menopausal women with low bone mineral density, albeit randomized controlled trials. Therefore, given the common concomitant use of statin and its apparent anti-fracture effect size, the present finding raises the possibility that this lipid-lowering drug may have materially affected osteoporosis in many populations with high prevalence of hyperlipidemia such as in the US and the Europe.

As all studies considered in this analysis were either observational or secondary clinical trials, their results are, although consistent with the hypothesis that statin use can reduce fracture risk, the finding must be interpreted as an evidence of association, not cause-and-effect relationship. Moreover, there may be alternative non-causal explanations for the observed association between statin and fracture risk. In these observational studies, unknown biases or confounders could also be responsible for the observed association [5]. In this analysis, the potential effect of bias was explicitly considered in the Bayesian random-effects model. Under the assumption that bias results in an over-estimate of 30% of odds ratio, there was still a 95% chance that statin can reduce hip fracture risk. However, for the same magnitude of bias, the association between statin and non-spine fracture risk was less certain. These results suggest that the association between statin and hip fracture risk was more robust than that between statin and non-spine fracture risk.

One of the major threats to meta-analysis is the problem of publication bias. A funnel plot suggested that there is no presence of publication bias among the studies. However, there was evidence of significant heterogeneity, which could explain up to 44% variation in hip fractures and 54% of non-vertebral fractures. This implies that factors specific to individual studies could account for up to 50% of the variability in the effect sizes. In relation to this, an inherent limitation of meta-analysis is the inability to obtain the exact patient data from each individual trial, which would have permitted a detailed analysis of treatment effect according to pertinent clinical and demographic subgroups.

The Bayesian approach used in this analysis deserves some comments. Both observational and clinical trial data represent an important source of scientific knowledge, and should be updated when new data become available. The issue of how to formally update knowledge has received little attention of clinical researchers, as research results are often considered in isolation from previous studies. Indeed, when a study yields a p-value >0.05 or 95% confidence interval includes unity, the study is almost always viewed as a "negative" result, despite the availability of prior evidence. Yet, p-value is known to be a poor measure for evaluating evidence and making clinical decisions and is often misinterpreted [8,18,19]. The Bayesian approach, on the other hand, formally considers the latest evidence in relation to prior evidence to derive a posterior estimate, which is the weighted average between the two sources of evidence. As such, it is a useful method of updating knowledge and is considered to be the only formal coherent calculus of statistical inference [15]. Results from a Bayesian analysis are considered more informed for decision making than are frequentist statistics such as odds ratio [6]. In this study, the Bayesian analysis of accumulative evidence appears decisive enough to conclude that statins have beneficial effect on reducing hip and non-spine fracture risk.

While the traditional classical inference considers the parameter of interest (e.g. effect size, odds ratio, etc.) fixed, the Bayesian inference regards the parameter of interest as random, in the sense that its true values are uncertain, and this uncertainty is represented by a probability distribution. Therefore, a Bayesian analysis allows the reporting of direct probability statements about any differences that are of interest and processes.

A meta-analysis is not a substitution for a properly controlled randomized clinical trial. Indeed, the association between the use of statin and fracture risk reduction needs to be confirmed by a randomized controlled trial to establish the optimal formulations, doses and routes and schedules of administration even though statin use has been shown to be quite safe [36]. However, in the case of statin, such a placebo-controlled trial may not ethically be feasible. Nevertheless, with the recent advance in clinical trial methodology, particularly in relation to the Bayesian clinical trial [3], such a trial may be practically feasible.

In conclusion, the present analysis suggests that statins as a group could reduce the risk of hip fractures by between 27% and 58%. The probability that statin reduces hip fracture risk by at least 30% was estimated to be 0.963. However, these effect sizes are uncertain if bias was 30% or higher. The effect of statin on non-vertebral fractures remains uncertain due to small probability of the effect. The Bayesian approach presented here can help researchers to update evidence when new data become available, and can help informed judgments about treatment. It is hoped that this analysis will assist in resolving discrepancies in findings regarding statin use and fracture risk.

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