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Effect of vegetarian diets on bone mineral density: a Bayesian meta-analysis[1–3]

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ABSTRACT

Background: The association between vegetarian diets and bone mineral density (BMD) is controversial because of conflicting findings from previous studies.

Objective: The aim of this study was to estimate the effect of vegetarian diets on BMD by using a meta-analytic approach.

Design: A systematic electronic literature search was conducted to identify all relevant articles on the association between vegetarian diet and BMD. Nine studies of 2749 subjects (1880 women and 869 men) were included in the analysis. Traditional and Bayesian methods of meta-analysis were applied to synthesize the data.

Results: Overall, BMD was ≈4% lower in vegetarians than in omnivores (95% CI: 2%, 7%) at both the femoral neck and the lumbar spine. Compared with omnivores, vegans had a significantly lower lumbar spine BMD (6% lower; 95% CI: 2%, 9%), which was more pronounced than in lactoovovegetarians (2% lower; 95% CI: 1%, 4%). The probability that BMD was ≥5% lower in vegetarians than in omnivores (or ≈0.3 SD) was 42% for the femoral neck and 32% for the lumbar spine. There was no evidence of publication bias. There was a moderate degree of between-study heterogeneity; the coefficient of heterogeneity varied between 46% and 51%.

Conclusion: The results suggest that vegetarian diets, particularly vegan diets, are associated with lower BMD, but the magnitude of the association is clinically insignificant. *Am J Clin Nutr* 2009;90:943–50.

INTRODUCTION

Osteoporosis, with its consequence of fragility fracture, is increasingly becoming a public health problem in industrialized and developing countries, because it is highly prevalent in the general population and imposes a significant demand on medical care and health services. The prevalence of osteoporosis in Asian women aged ≥50 y ranged between 17% and 30% (1–4), which is comparable with that in white populations (5, 6). The residual lifetime risk of hip fracture, the most serious consequence of osteoporosis, is 10% (7), which is equivalent to that of invasive breast cancer. Moreover, fracture is associated with a series of adverse outcomes, such as an increased risk of morbidity and disability (8), excess risk of mortality (9, 10), and increased loss of productivity and ultimately incurs a significant health care cost (11).

Bone mineral density (BMD) is the most robust and consistent predictor of osteoporotic fracture (12, 13). The magnitude of the association between BMD and fracture risk is equivalent to, or stronger than, the association between blood pressure and stroke or cholesterol and cardiovascular disease (14). Of the many factors that affect BMD (15), nutrition is considered an important factor (16, 17). In Western countries, a sizeable proportion of the population has adopted a vegetarian diet. According to previous studies in the European Union, the proportion of self-reported vegetarians in the general population is ≈5% (18). Whether vegetarian diets confer benefit or harm to bone health is a contentious issue. Ecologic studies found an inverse association between the incidence of hip fracture and vegetarian protein intake, such that countries with a high intake of vegetable protein had a lower risk of hip fracture (19). Whereas some data suggest that a raw vegetarian diet is associated with lower bone mass (20), other studies have found no such association (21–23). A common feature of these studies is that they were based on relatively small sample sizes, which might have limited the statistical power to detect a small effect.

Because of conflicting results and the limited sample sizes in individual studies, a meta-analysis may be helpful to resolve the association between vegetarian diets and bone health. Therefore, this study sought to estimate the magnitude of effect of vegetarian diets on BMD by using a Bayesian meta-analysis.

METHODS

Search strategy and study inclusion

A systematic search of the literature was carried out by using PubMed, Ovid, and ISI Web of Knowledge resources (all-year time span). The keywords used for the search included "vegan*" OR "vegetarian*" OR "lacto-ovo*" concatenated with "osteoporo*" OR "bone mass" OR "bone health" OR "bone mineral density". Three reviewers (LTH-P, NDN, and TVN) independently identified eligible articles for which the abstracts

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were recorded. If the abstract was consistent with the inclusion criteria, the full article text was obtained.

The inclusion criteria were as follows: *1*) original studies and articles/abstracts reporting studies on humans, written in English, and published in peer-reviewed journals; *2*) observational studies, including vegetarian and nonvegetarian diets as factors and BMD as the outcome; and *3*) adult aged ≥18 y. The exclusion criteria were as follows: *1*) review articles, and *2*) studies conducted in children or adolescents. The term *vegetarian diet* used in this study included 4 types of diets: semivegetarian, which excludes meat intake; lactoovovegetarian, which excludes meat and seafood; lactovegetarian, which excludes meat, seafood, and eggs but not milk and dairy products; and vegan, which excludes all foods of animal origin.

Data extraction

For each study, relevant data, including details of study design, mean age, sex, dietary type (eg, vegetarian or nonvegetarian diet), BMD measurement, and the number of participants, were extracted. If more than one article with the same data was identified, only the article that contained definitive data was included in the analysis. All 3 authors independently checked the data for consistency. Because the diagnosis and management of osteoporosis are based on lumbar spine and femoral neck BMD (24), in this analysis we included studies that measured BMD at these 2 skeletal sites.

Data synthesis and analysis

The difference in mean BMD values between vegetarians and omnivores for each study was expressed as the ratio of the mean value in the vegetarian group to the mean value in the nonvegetarian group (25). Let m_0 and m_1 denote the mean BMD for vegetarians and nonvegetarians, respectively, then the ratio of means (RoM) is defined as RoM = m_0/m_1. Thus, a RoM = 1 indicates that there is no difference in BMD between the 2 groups, whereas a RoM < 1 indicates that BMD in vegetarians is lower than in omnivores. An analysis based on the RoM, therefore, allows pooling of results from studies that measured BMD by different instruments.

The synthesis of data was performed with both traditional (26, 27) and Bayesian (28, 29) random-effects models. Briefly, we calculated the natural logarithm of RoM (denoted as d_i) and its SE for individual studies. It is assumed that each d_i is normally distributed with a "true" but unknown mean θ_i and a within-study variance (σ_i^2). The collection of θ_i across studies is further assumed to follow a normal distribution with unknown mean δ_0 and between-study variance τ^2. The classic fixed-effects method of meta-analysis assumes that there is no between-study variance (ie, $\tau^2 = 0$), whereas the classic random-effects method recognizes the possibility of heterogeneity of between-study variation (ie, τ^2 could be difference from 0) but with a fixed value. In contrast with the traditional random-effects model, for which the parameters θ, σ^2 and τ^2 are assumed to be fixed, σ_i^2 and τ^2 are assumed to be random variables in Bayesian random-effects model, in the sense that they have a probability distribution. A full Bayesian analysis refers to the use of external prior distribution, which must be specified for θ_i and σ_i^2. In this analysis, the prior distribution for θ_i was given a vague prior normal distribution of a mean of 0 and a variance of 10,000 to reflect the presumption that vegetarianism could have negative or positive effect on BMD with equal probability. The prior distribution for τ^2 was assumed to be uniformly distributed with parameters (0, 10).

The heterogeneity of effects across studies was assessed by computing the Cochran's Q statistic (30), and the coefficient of inconsistency (I^2), which is the proportion of total variation among studies due to between-study heterogeneity (31). An I^2 >50% is regarded as evidence of substantial heterogeneity (32). Publication bias was examined with a funnel plot (33). Finally, recursive cumulative meta-analysis was also performed to examine whether the magnitude of effect changes markedly with time of study. All statistical analyses were performed by using the R language on the Window XP platform (34). The Bayesian analysis was performed with the WinBUGS program (35).

RESULTS

Characteristics of studies

An initial search yielded 922 articles written in English with contents relating to vegetarian diets and BMD, of which 35 were potentially relevant articles and were subsequently retrieved. After a close examination, 20 articles were excluded from the analysis because they were review articles, original articles with no BMD measurements, or studies in children. Of the remaining 15 studies (20, 22, 23, 36–47), 6 additional studies were excluded because they had no lumbar spine or femoral neck BMD data; 1 of these studies measured BMD at the calcaneum, 2 at the radius, 2 at the distal radius, and 1 at the proximal phalanx (36, 37, 40, 44–46). As a result, 9 studies were included in the analysis (20, 22, 23, 38, 39, 41–43, 47) (**Figure 1**).

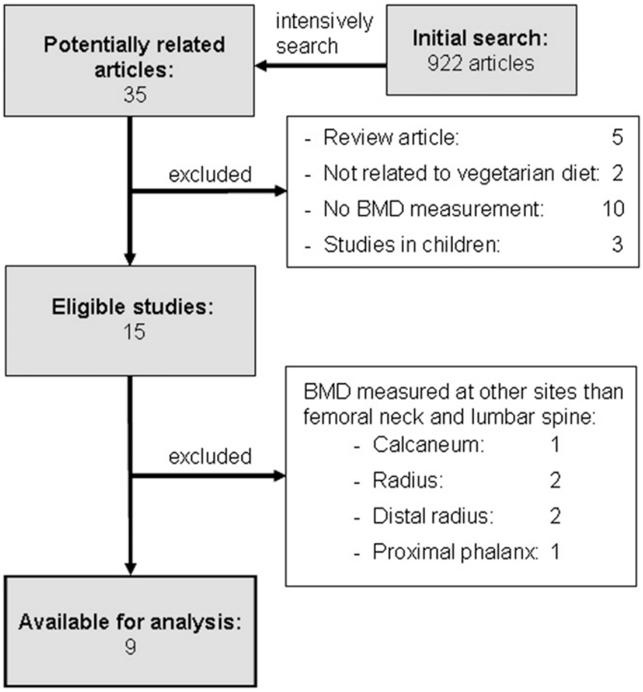

FIGURE 1. Summary of search strategy and results. BMD, bone mineral density.

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The 9 studies included 2749 individuals (1880 women and 869 men) with an average age ranging from 20 to 79 y. The median sample size of all studies was 152, split equally between omnivores and vegetarians. Of the 9 eligible studies, 6 studies were conducted in lactoovovegetarians, and only 3 were conducted in vegans. Five studies were conducted in Asian populations (22, 23, 39, 41, 47), and only 2 included men (20, 23). In the 2 studies that included both sexes, ≈50% of the sample was men for femoral neck BMD and 7% for lumbar spine BMD. Only one study had a prospective design (43), and the remainder were cross-sectional (**Table 1**).

Vegetarianism and BMD

The pooled analysis showed that vegetarians had a 4% lower femoral neck BMD than did the nonvegetarians (RoM = 0.96; 95% CI: 0.93, 0.98). A similar effect size was observed at the lumbar spine, and the RoM was 0.96 (95% CI: 0.93, 0.98) (**Figures 2** and **3**). Results from both fixed-effects and random-effects analyses were almost identical for the femoral neck and lumbar spine BMD. There was, however, a moderate between-study heterogeneity; the I^2 ranged from 46% (95% CI: 18, 64) for femoral neck BMD to 51% (95% CI: 29, 66) for lumbar spine BMD. The funnel plot for each outcome did not indicate any systematic trend of publication bias (**Figure 4**). One small study (n = 14) (20) yielded a strong effect, but did not have a significant effect on the publication bias.

Results of the subgroup analysis suggested that the effect of vegetarianism on femoral neck BMD was more pronounced among vegans (RoM = 0.94; 95% CI: 0.91, 0.98) than among lactoovovegetarians (RoM = 0.98; 95% CI: 0.96, 0.99). Moreover, the effect was more pronounced in whites (RoM = 0.90; 95% CI: 0.84, 0.96) than in Asians (RoM = 0.97, 95% CI: 0.95, 0.99) and was observed in women (RoM = 0.95; 95% CI: 0.92, 0.98) but not in men (RoM = 0.94; 95% CI: 0.83, 1.06). Similar differential effects were also observed in lumbar spine BMD, except in men, for whom data were not available. (**Table 2**).

Results of a cumulative meta-analysis by sample size are shown in **Figure 5**. Studies with smaller sample sizes tended to yield a larger effect size than did studies with larger sample sizes. The effect size exponentially decreased as the sample sizes were cumulatively increased, and the "stable" effect size was reached at a sample size of ≈800 individuals.

Bayesian analysis

We were specifically interested in the following question: what is the probability that vegetarians have a lower BMD (of ≥50%) than omnivores, a difference of potential clinically relevance. In other words, we wanted to estimate probability (RoM ≤ 0.95). The posterior distribution of RoM for the femoral neck and lumbar spine BMD is shown in **Figure 6**. The area under the curve between any 2 points on the x axis of the distribution is an estimate of the probability of the effect size of interest. Accordingly, the probability of RoM ≤ 0.95 was 42% for femoral neck BMD and 32% for lumbar spine BMD. These features were slightly different for subgroup analyses, but the magnitudes of the association were not clinically relevant (Table 2).

DISCUSSION

The association between vegetarianism and BMD has been a subject of contention primarily because of inconsistent findings from previous studies. All previous studies showed that vegetarians had a lower BMD than did omnivores; however, only 2 studies showed a statistically significant difference (20, 22). This suggests that a meta-analysis could be helpful in resolving the effect size. Results of this meta-analysis suggest that individuals consuming vegetarian diets, as a group, have a lower BMD than do nonvegetarians. However, the probability that vegetarians have a lower BMD (of ≥50%) than nonvegetarians (a level deemed to be clinically relevant) is <50%, which suggests that the effect is very modest.

Fragility fracture is an important outcome of osteoporosis, and each 1-SD lower BMD is associated with a 1.45-fold increase in the risk of fragility fracture (48). Therefore, given that BMD is lower in vegetarians than in nonvegetarians by 4% and that other risk factors of fracture are held constant, it can be inferred that the

TABLE 1
Characteristics of individual studies[1]

Reference	Study design	Sex	Ethnicity	Vegetarian diet	BMD site	DXA instrument	Vegetarians *n*	Vegetarians Mean age	Omnivores *n*	Omnivores Mean age
								y		*y*
Lloyd et al, 1991 (42)	CS	F	White	Lactoovovegetarian	LS	DPA[2]	27	35	37	36
Chiu et al, 1997 (47)	CS	F	Asian	Vegan	LS, FN	DPA[3]	77	61	87	61
Barr et al, 1998 (38)	CS	F	White	Lactoovovegetarian	LS	DXA[4]	23	27	22	28
Lau et al, 1998 (22)	CS	F	Asian	Vegan	LS, FN	DPA[2]	76	79	109	77
Outila et al, 2000 (43)	PS	F	White	Vegan	LS, FN	DXA[4]	12	35	16	33
Fontana et al, 2005 (20)	CS	F and M	White	Vegan	LS, FN	DXA[2]	18	53–57	18	52
Kim et al, 2007 (41)	CS	F	Asian	Lactoovovegetarian	LS, FN	DXA[3]	76	61	76	61
Wang et al, 2008 (23)	CS	F and M	Asian	Vegan	LS, FN	DXA[3]	872	≥20	993	≥20
Ho et al, 2008 (39)	CS	F	Asian	Vegan	LS, FN	DXA[2]	105	62	105	62

[1] DXA, dual-energy X-ray absorptiometry; DPA, dual photon absorptiometry; CS, cross-sectional; PS, prospective; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck.
[2] Hologic Inc, Waltham, MA.
[3] Norland Corp, Fort Atkinson, WI.
[4] GE-Lunar, Madison, WI.

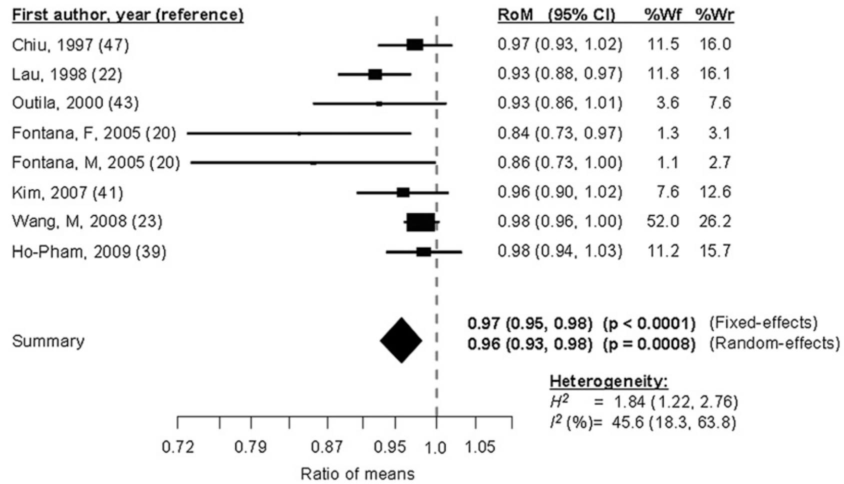

FIGURE 2. Ratio of the mean (RoM) femoral neck bone mineral density (FNBMD) in the vegetarian group to the mean FNBMD in the nonvegetarian group and 95% CIs. The symbol sizes are proportional to sample sizes. The overall effect size (♦) was derived from the random-effects model as described in Methods. An RoM <1 indicates that the mean FNBMD was lower in the vegetarian group than in the omnivorous group. For example, the overall RoM of 0.96 (random-effects model) indicates that the mean FNBMD in the vegetarian group was 4% lower than that in the nonvegetarian group. Wf, weighted for fixed-effects; Wr, weighted for random-effects; F, female; M, male.

relative risk of fracture in vegans is ≈10% higher than in nonvegetarians. In the European Prospective Investigation into Cancer and Nutrition (EPIC)–Oxford Study, the adjusted relative risk associated with veganism was 1.05, but the association was not significant (95% CI: 0.76, 1.44) (21). These data reinforce the fact that vegetarian diets have no clinically detrimental effect on bone health.

It is important to distinguish between vegan and lactoovovegetarian diets, because the latter includes dairy products and eggs in the diet. In this analysis, we found that much of the effect of vegetarian diets on bone density was mainly due to a vegan diet and that a lactoovovegetarian diet did not exert a markedly negative effect on bone density. Because vegetarians usually have lower intakes of dietary calcium and protein intakes than do omnivores (49, 50), the present study's finding raises the issue of the role of dietary calcium and protein intakes in bone health.

Dietary calcium is mainly found in dairy foods and vegetables. Several studies have found that higher intakes of dietary calcium were associated with higher bone density (6, 51) and reduced hip fracture risk (52). However, a meta-analysis of 33 studies found that the correlation between dietary calcium intakes and bone density was 0.13 (53), which suggests that the contribution of calcium to bone density is modest. This seems to suggest that differences in calcium intakes or sources of intake (ie, animal or plant) do not have a significant effect on the observed variance in BMD. The average dietary calcium intake in the 9 studies reviewed varied from 200 to 1200 mg/d, with little difference between vegetarians and nonvegetarians. Therefore, it is unlikely that the lower BMD in vegetarians observed in this analysis was due to differences in dietary calcium intake.

The relation between protein intake, particularly animal protein, and bone health has been controversial. It has long been

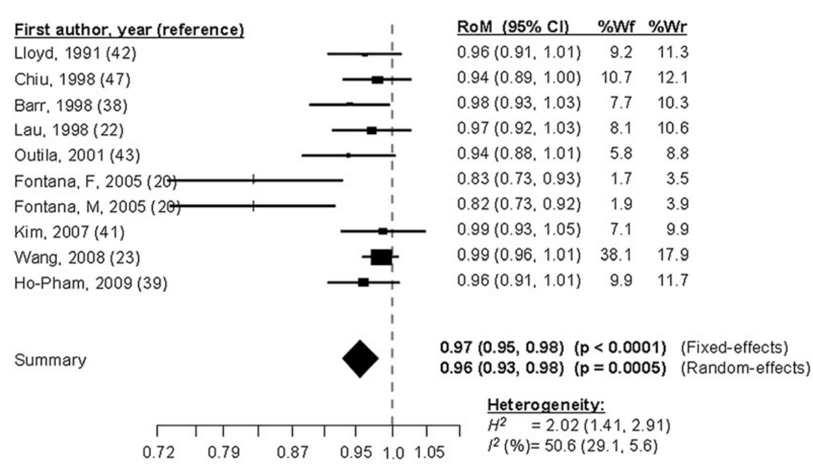

FIGURE 3. Ratio of the mean (RoM) lumbar spine bone mineral density (LSBMD) in the vegetarian group to the mean LSBMD in the nonvegetarian group and 95% CIs. The symbol sizes are proportional to sample sizes. The overall effect size (♦) was derived from the random-effects model as described in Methods. An RoM <1 indicates that the mean LSBMD was lower in the vegetarian group than in the omnivorous group. For example, the overall RoM of 0.96 (random-effects model) indicates that the mean LSBMD in the vegetarian group was 4% lower than that in the nonvegetarian group. Wf, weighted for fixed-effects; Wr, weighted for random-effects; F, female; M, male.

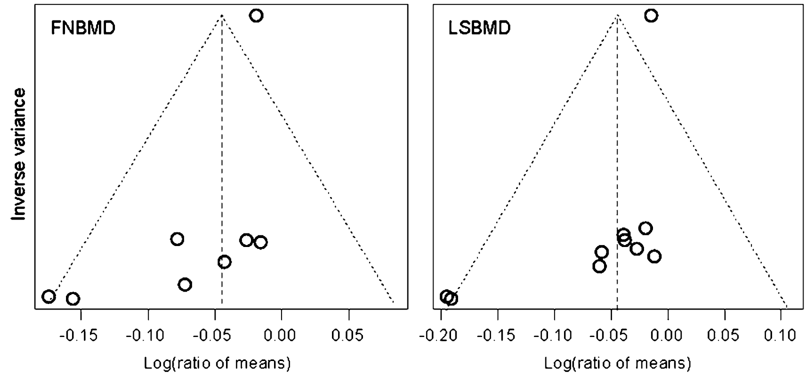

FIGURE 4. Funnel plot of the logarithmic ratio of means versus inverse variance (precision) for femoral neck bone mineral density (FNBMD) and lumbar spine bone mineral density (LSBMD). Studies with higher effect sizes tended to have larger variance.

hypothesized that a high animal protein diet exerts a negative effect on bone health, because it generated a high endogenous acid load that would require buffering from bone, thus increasing bone resorption (54). However, empirical data are not consistent. On the one hand, there are data suggesting that higher dietary protein intakes are associated with a lower risk of fragility fracture (55) and hip fracture (56). On the other hand, other studies showed that higher dietary protein intakes were associated with increases in bone loss (57) and with a greater risk of fragility fracture (57, 58). Of the 9 studies reviewed herein, only 5 reported dietary protein intakes (22, 39, 41, 42, 47), but only 2 studies (22, 39) found that dietary protein intakes in vegans were lower than in omnivores. In these 2 studies, there was no significant difference in BMD between vegans and omnivores. On the basis of these data, it seems that dietary protein intakes could not account for the lower BMD in vegetarians observed in this analysis.

BMD is a complex trait, in the sense that it is affected by multiple environmental and genetic factors. It is therefore unrealistic to expect that any single modification, including dietary change, can result in a significant change in the trait. The complexity and possible interaction between dietary calcium and protein makes it difficult to attribute the modest effect of vegetarianism on bone density to either dietary factor. Indeed, it has been suggested that protein and calcium act synergistically on bone if both are present in sufficient quantities in the diet; however, protein may exert detrimental effect on bone density when calcium is low (16). Moreover, vegetarian diets often contain more phytoestrogens than do nonvegetarian diets, particularly non-Western vegetarian diets. The average intake of isoflavones in vegans has been estimated at 75 mg/d (59), which is higher than that in Western consumers (average intake: <2 mg/d; 60) and in vegetarians (12 mg/d; 61). It has been suggested that these compounds can help prevent postmenopausal bone loss, although the case is not clear cut (62, 63) and there are less data as to how this might be relevant to vegetarians.

The present study's results are largely applicable to women, because only 2 original studies included data for men. In fact, a subgroup analysis for men showed that the effect of vegetarian diets on femoral neck BMD was not significant. All studies included in this analysis were observational; therefore, no cause-and-effect relation between vegetarian diets and BMD can be drawn from the finding. As with any meta-analysis, exclusion of pertinent unpublished studies represents a threat to the validity of the analysis. In this analysis, we found no evidence of publication bias. However, there was a modest degree of between-study heterogeneity in effect sizes. The heterogeneity could be due to study populations (eg, whites and Asians) and types of vegetarian diets (eg, lactoovovegetarian and vegan diets).

TABLE 2
Association between vegetarian diets and bone mineral density (BMD): subgroup analysis[1]

	Femoral neck BMD				Lumbar spine BMD			
	k	RoM	95% CI[2]	Prob 5%[3]	*k*	RoM	95% CI[2]	Prob 5%[3]
Female	6	0.95	(0.92, 0.98)	0.52	9	0.97	(0.95, 0.98)	0.09
Male[4]	2	0.94	(0.83, 1.06)	0.50	—	—	—	—
Age $\geq$ 50 y	6	0.95	(0.92, 0.98)	0.58	6	0.94	(0.90, 0.99)	0.61
Diet								
Vegan	6	0.94	(0.91, 0.98)	0.66	6	0.94	(0.89, 0.98)	0.64
Lactoovovegetarian	3	0.98	(0.96, 0.99)	0.49	3	0.98	(0.96, 0.99)	0.27
Ethnicity								
Asian	6	0.97	(0.95, 0.99)	0.22	6	0.98	(0.96, 0.99)	0.02
White	3	0.90	(0.84, 0.96)	0.56	3	0.92	(0.87, 0.97)	0.75

[1] *k*, number of studies included in the analysis; RoM, ratio of the mean BMD in the vegetarian group to the mean BMD in the nonvegetarian group; Prob 5%, probability of RoM $\leq$ 0.95.
[2] Results were obtained from classic random-effects models.
[3] Results were obtained from a Bayesian random-effects model (*see* Methods).
[4] Result was not available for the lumbar spine because only one study reported BMD at this site (20).

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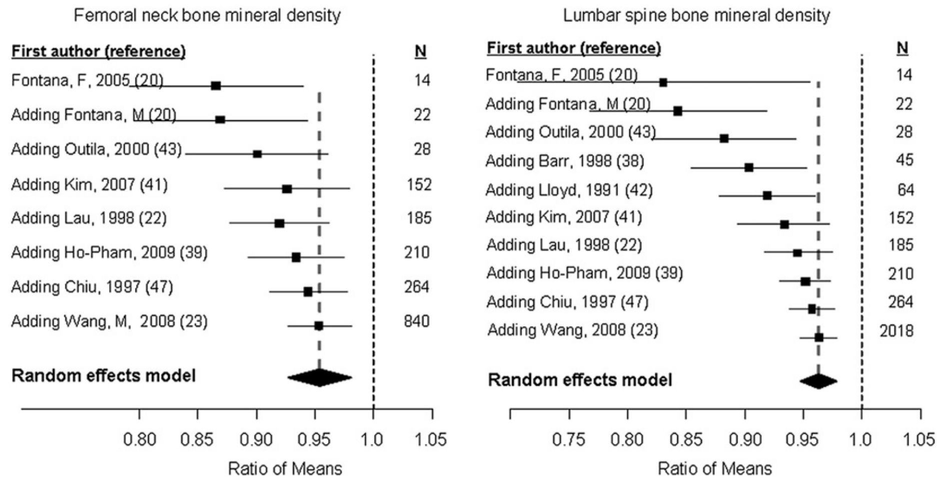

FIGURE 5. Cumulative meta-analysis by sample size for femoral neck and lumbar spine bone mineral density. In each additional study, the ratio of the mean bone mineral density in the vegetarian group to the mean bone mineral density in the nonvegetarian group was cumulatively estimated. F, female; M, male.

The Bayesian meta-analysis had several advantages. In contrast with a classic meta-analysis, which considers the probability (eg, *P* value) of observed data given the hypothesis of no treatment effect, the Bayesian analysis considers the probability of the hypothesis of treatment effect given the observed data. The *P* value is known to be a poor measure for evaluating evidence and making clinical decisions (64, 65) and is often misinterpreted. Even the CI, which has been advocated as a better measure than the *P* value, is not without its shortcomings (64). In contrast, the Bayesian method does not depend on, and bypasses the shortcomings associated with, *P* values for inference (66). The Bayesian analysis allows the reporting of direct probability statements about any differences that are of interest and processes. For instance, on the basis of the posterior

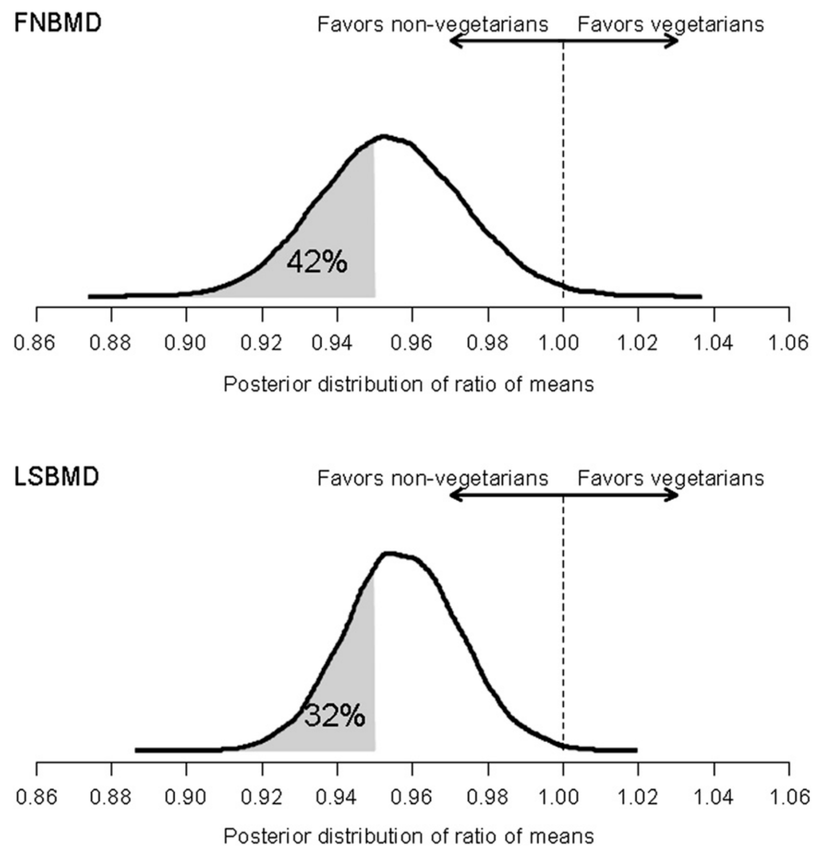

FIGURE 6. Posterior distribution of the ratio of the mean (RoM) for femoral neck bone mineral density (FNBMD) and lumbar spine bone mineral density (LSBMD). The shaded areas in the figures represent the probability of an RoM ≤ 0.95, or the probability that bone mineral density (BMD) in the vegetarians is $\geq 5\%$ lower than the BMD in the nonvegetarians. The probability was 42% for FNBMD and 32% for LSBMD.

distribution of effect size estimates, it is possible to state that the probability that vegetarians have a lower BMD (by ≥5%) than do omnivores is only 42%.

In conclusion, the results of this meta-analysis suggest that there is a modest effect of vegetarian diets, particularly a vegan diet, on BMD, but the effect size is unlikely to result in a clinically important increase in fracture risk.

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The authors' responsibilities were as follows—TVN, NDN, and LTH-P: study concept and design, analysis and interpretation of the data, and draft of the manuscript; LTH-P and NDN: acquisition of data; and NDN and TVN: critical revision of the manuscript and statistical expertise. All authors declared that they had no conflict of interests in relation to the present work.

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