Lead Article

Veganism, vegetarianism, bone mineral density, and fracture risk: a systematic review and meta-analysis

Isabel Iguacel*, María L. Miguel-Berges*, Alejandro Gómez-Bruton, Luis A. Moreno, and Cristina Julián

Context: *The numbers of vegans and vegetarians have increased in the last decades. However, the impact of these diets on bone health is still under debate.* ***Objective:*** *This systematic review and meta-analysis sought to study the impact of vegetarian and vegan diets on bone mineral density (BMD) and fracture risk.* ***Data Sources:*** *A systematic search was conducted of PubMed, Scopus, and Science Direct, covering the period from the respective start date of each database to November 2017.* ***Data Extraction:*** *Two investigators evaluated 275 studies against the inclusion criteria (original studies in humans, written in English or Spanish and including vegetarian or vegan diets and omnivorous diets as factors with BMD values for the whole body, lumbar spine, or femoral neck and/or the number of fractures as the outcome) and exclusion criteria (articles that did not include imaging or studies that included participants who had suffered a fracture before starting the vegetarian or vegan diet). The quality assessment tool for observational cohort and cross-sectional studies was used to assess the quality of the studies.* ***Results:*** *Twenty studies including 37 134 participants met the inclusion criteria. Compared with omnivores, vegetarians and vegans had lower BMD at the femoral neck and lumbar spine and vegans also had higher fracture rates.* ***Conclusions:*** *Vegetarian and vegan diets should be planned to avoid negative consequences on bone health.* ***Systematic Review Registration:*** *PROSPERO registration no. CRD42017055508.*

INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by thinning and deterioration of bone tissue with loss of calcification and density predisposing to an increased risk of fracture.[1] It has been estimated that this major health problem affects 200 million people worldwide.[2–4] Bone mass decreases as people age (particularly in postmenopausal women), leading in some cases to osteoporosis and fragility fractures.[5,6] As the elderly population has increased worldwide, osteoporosis and fracture prevalence have risen through the last decades.[7] Melton et al[8,9] estimated that approximately 1 in 3 women and 1 in 5 men would suffer a fracture after the age of 50 years. Fractures are related to increase morbidity and mortality,[10] and in the United States, they are responsible for an annual direct economic cost of 17 to 20 billion dollars.[11,12] It is therefore of critical

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importance to identify risk factors associated with poor bone health in order to reduce fracture rates and mortality and, consequently, healthcare-related costs.

Several genetic and lifestyle factors influence bone mineral density (BMD) and fracture risk. Among them, physical activity and diet are considered the most relevant for BMD.[13] Regarding diet, some nutrients, such as calcium and vitamin D, are essential for maintaining bone health.[13] Other nutrients such as protein, vitamin B12, zinc, and n-3 fatty acids, which are mainly found in animal products, may also be related to bone health, although their roles are less clear.[14–16] Consequently, vegetarians and vegans might be at greater risk of lower BMD and fractures than omnivores because of a deficiency of these nutrients in their diets.[14] Vegetarians are defined as individuals who do not consume meat, poultry, fish, seafood, and flesh from any animal but include dairy products and/or eggs in their diets. Vegans exclude all animal products from their diets and therefore do not consume dairy products and eggs.

Compared with nonvegetarian diets, vegetarian diets can provide protection against many chronic diseases, such as heart disease, hypertension, type 2 diabetes, obesity, and some cancers such as colorectal and prostate[17]; however, a 2009 meta-analysis of 9 studies found that vegetarians had 4% lower BMD than omnivores.[18]

In contrast, some studies that have assessed the risk of fractures in vegetarians, vegans, and omnivores did not show statistically significant differences among groups.[19,20] Because of these inconclusive results, it seems timely to perform a systematic review and meta-analysis that includes new studies with larger sample sizes and novel approaches to evaluate the risk of fractures. The aims of this systematic review and meta-analysis are 1) to quantify the effect that vegetarian and vegan diets may have on BMD and fracture risk and 2) to compare the impact of vegetarian and vegan diets versus omnivore diets on BMD and fracture risk. The research question this study sought to address was whether vegetarians and vegans have lower BMD and higher risk of fracture.

METHODS

Search strategy

The present systematic review and meta-analysis was registered in the PROSPERO database (ID: CRD42017055508) and followed the systematic review methodology proposed in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Table S1 in the Supporting Information online).[21,22] A specific question was constructed according to the PICO (Participants, Interventions, Control, Outcomes) principle (Table 1).[23]

A systematic search of the literature was carried out using PubMed, Scopus, and Science Direct databases (from the beginning of each respective database to November 2017). Two different searches were conducted in each database to ensure that all of the published studies were included in the meta-analysis. When possible, the search included Thesauros (MESH terms in PubMed). First, the diet terms were combined as follows: "Vegans" OR "Diet, Vegan" OR "Vegetarians" OR "Diet, Vegetarian." Second, the bone and fracture terms were combined as follows: "Bone and Bones" OR "Bone Density" OR "Fractures, Bone" OR "Osteoporosis, Postmenopausal" OR "Osteoporosis." Finally, both the diet and the bone and fracture terms were combined with "AND." In Scopus and Science Direct, these terms had to appear in the title, abstract, or keywords. The filters "humans," "articles," and "in English and Spanish" were applied when possible. Two reviewers independently examined each database to obtain the potential publications. Agreement between reviewers was found for 97% of the publications to be included. Inter-reviewer discrepancies were resolved by consensus. Arbitration by a third reviewer was used for unresolved discrepancies. Relevant articles were obtained in full and assessed against the inclusion and exclusion criteria described below.

Inclusion criteria

The inclusion criteria were as follows: 1) original studies; 2) studies performed in humans; 3) studies written in English or Spanish; 4) studies including vegetarian (lacto-ovo-vegetarian; ovo-vegetarian, or lacto-vegetarian) or vegan diets and omnivorous diets as factors; 5) studies including BMD measured with imaging techniques; and 6) studies including BMD values for the whole body (WB), lumbar spine (LS), or femoral neck (FN) and/or the number of fractures as the outcome. In the present study, vegetarians were defined as those who excluded meat, fish, and seafood but not milk and dairy products from their diet; vegans were defined as those who excluded any kind of animal product.

Exclusion criteria

The exclusion criteria were as follows: 1) articles that did not provide original data (eg, systematic reviews, meta-analysis, literature reviews); 2) case reports; 3) articles that did not include imaging techniques

Table 1 **PICO criteria for inclusion and exclusion of studies**

PICO	Inclusion criteria	Exclusion criteria
Participants	Children, adolescents, or adults; both sexes; all nationalities	Animals
Interventions	Vegetarianism or veganism	Pescetarians, macrobiotic diets
Control/comparator group	Omnivores	Not having an omnivore group
Outcome	Bone mineral density, fracture rate, bone mineral content, bone strength	Other outcomes not related with health status

(eg, only included bone biomarkers); and 4) studies that included participants who had suffered a fracture before starting the vegetarian or vegan diet.

Data extraction

For each study that included BMD as an outcome, relevant data, including number of participants, sex, mean age, ethnicity (Caucasian or Asian), diet (eg, vegetarian or omnivores diet), the period of time for which the vegetarian or vegan diet had been followed, quality assessment, and BMD measurements and instruments (dual-energy X-ray absorptiometry [DXA] or dual-photon absorptiometry [DPA]), were extracted (Table 2).[24–38] Number of fractures and body site of the fracture were also recorded (Table 3).[19,20,39–41] Bone mineral density values were extracted from the different studies, and only raw data (unadjusted) were used to perform the meta-analyses.

Dual-energy X-ray absorptiometry enables different types of scans that give information on several regions. Compared with alternative bone densitometry techniques, FN and LS DXA examinations have a number of advantages, including include a proven ability to predict fracture risk, a consensus for defining osteoporosis through BMD results according to the World Health Organization T-score definition, and the ability to monitor response to treatment.[42] Moreover, WB examinations provide extra body composition values that can be included for many other purposes.[43]

Finally, LS, FN and WB BMD and/or fracture rates were included as outcomes in the analysis. A total of 4 meta-analyses were carried out, with 3 bone site measurements (LS, FN, and WB) and fracture rates as the main outcomes. When >1 article with the same sample was identified, only the article with the larger sample was selected and included in the analysis.

Quality assessment

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies provided by the National Heart, Lung, and Blood Institute was used to assess the quality of the included studies.[44] Two reviewers independently assessed and thereafter discussed the quality of the studies. Agreement between reviewers was found for 90% of the publications. Inter-reviewer discrepancies were resolved by consensus. Arbitration by a third reviewer was used for unresolved discrepancies.

Search summary

A total of 486 articles were extracted from PubMed, Scopus, and Science Direct. After eliminating all of the duplicates, 275 manuscripts were evaluated. Review of titles and abstracts excluded 222 records, leaving 53 articles for full-text assessment. Five articles were discarded because they did not have another group (omnivorous group) with which bone status could be compared.[45–49] Six studies were excluded because they were literature reviews, systematic reviews, or meta-analyses.[18,50–53] One study was discarded because it included the same number of participants as another study from the same authors.[54] Bone mineral density measurements or fracture rates were not reported for 3 studies.[55–57] Seven studies did not follow a vegetarian or vegan diet.[58–64] One study was a case report.[65] Unadjusted BMD data were not reported for 1 study.[66] Nine additional studies were excluded from this systematic review and meta-analysis because LS, FN, or WB BMD data were not presented; 5 of these studies measured BMD at the calcaneum,[61,67–70] 3 measured it at the radius (mid and distal),[71–73] and 1 measured it at the proximal phalanx of the third finger.[74] Consequently, the final sample consisted of 20 articles (15 including BMD and 5 including fracture rate data) (Figure 1).

Statistical analyses

For continuous data (BMD in g/cm^2 comparing vegetarians and vegans with omnivores for LS, FN, and WB), the mean difference (MD) with a 95% confidence interval (95%CI) was used. Categorical data (fracture rates referred to as the incidence of any new fracture) were reported as relative risks (RRs) with a 95%CI. DerSimonian and Laird estimators using random

Table 2 **Descriptive characteristics of included studies on bone mineral density**

Reference	Participants[a]				BMD (g/cm^2)		Years following the diet[b]	Ethnicity	Quality Assessment	Instruments
	OMN no. (age in y)[c]	LOV no. (age in y)[c]	Vegan no. (age in y)[c]	Sex	BMD site	Mean ± SD				
Lloyd et al (1991)[24]	36 (36.1 ± 0.4)	23 (35 ± 0.7)		F	LS	LOV (1.020 ± 0.096)	≥5 y	Caucasian	43	DPA
						OMN (1.006 ± 0.120)				
Tesar et al (1992)[25]	28 (62.9 ± 5.6)	28 (62.9 ± 5.1)		F	LS	LOV (1.079 ± 0.203)	≥10 y	Caucasian	43	DPA
						OMN (1.066 ± 0.155)				
Chiu et al (1997)[26]		71 (64.0 ± 11.5)	187 (59.5 ± 8.0)	F	LS	Vegan (0.940 ± 0.190)	≥15 y	Asian	64	DPA
						OMN (0.990 ± 0.170)				
					FN	Vegan (0.690 ± 0.110)				
						OMN (0.750 ± 0.130)				
Barr et al (1998)[27]	22 (27.9 ± 5.9)	15 (25.8 ± 4.7)	8 (28.0 ± 3.2)	F	LS	Vegan (1.153 ± 0.100)	≥2 y	Caucasian	57	DXA
						LOV (1.145 ± 0.117)				
						OMN (1.216 ± 0.132)				
Lau et al (1998)[28]	109 (77.0 ± 3.8)	40 (79.9 ± 5.4)	36 (78.2 ± 4.9)	F	LS	Vegan (0.720 ± 0.150)	± 30 y	Asian	57	DPA
						LOV (0.680 ± 0.110)				
						OMN (0.720 ± 0.140)				
					FN	VEGAN (0.500 ± 0.080)				
						LOV (0.480 ± 0.080)				
						OMN (0.530 ± 0.082)				
Outila et al (2000)[29]	16 (34.0 ± 7.0)	6 (33.0 ± 9.0)	6 (37.0 ± 7.0)	F	LS	Vegan (1.034 ± 0.174)	≥2 y	Caucasian	64	DXA
						LOV (1.138 ± 0.060)				
						OMN (1.177 ± 0.099)				
					FN	Vegan (0.843 ± 0.116)				
						LOV (0.961 ± 0.059)				
						OMN (0.999 ± 0.138)				
Siani et al (2003)[30]	10 (38.4 ± 7.8)	20 (34.8 ± 15.1)		F/M	WB	LOV (1.190 ± 0.070)	Vegetarian their entire lives (≥30 y)	Caucasian	28	DXA
						OMN (1.190 ± 0.110)				
Fontana et al (2005)[31]	7 (53.2 ± 4.1)		7 (56.5 ± 13.1)	F	LS	Vegan (0.850 ± 0.080)	≥1.5 y	Caucasian	43	DXA
						OMN (1.030 ± 0.140)				
					FN	Vegan (0.630 ± 0.100)				
						OMN (0.750 ± 0.080)				
					WB	Vegan (0.990 ± 0.006)				
						OMN (1.100 ± 0.100)				
Fontana et al (2005)[31]	11 (52.3 ± 9.9)		11 (52.7 ± 10.7)	M	LS	Vegan (0.880 ± 0.120)	≥1.5 y	Caucasian	43	DXA
						OMN (1.070 ± 0.150)				
					FN	Vegan (0.710 ± 0.160)				
						OMN (0.830 ± 0.130)				
					WB	Vegan (1.070 ± 0.110)				
						OMN (1.210 ± 0.140)				
Kim et al (2007)[32]	76 (60.8 ± 6.7)	76 (60.7 ± 6.9)		F	LS	LOV (0.806 ± 0.140)	≥20 y	Asian	43	DXA
						OMN (0.809 ± 0.158)				

(continued)

Table 2 **Continued**

Reference	Participants[a]				BMD (g/cm^2)		Years following the diet[b]	Ethnicity	Quality Assessment	Instruments
	OMN no. (age in y)[c]	LOV no. (age in y)[c]	Vegan no. (age in y)[c]	Sex	BMD site	Mean ± SD				
					FN	LOV (0.684 ± 0.144) OMN (0.711 ± 0.112)				
Wang et al (2008)[33]	529 (21.0–89.0)	489 (21.0–89.0)		F	LS	LOV (0.953 ± 0.179) OMN (0.968 ± 0.183)	≥5 y	Asian	57	DXA
Wang et al (2008)[33]	463 (21.0–89.0)	383 (21.0–89.0)		M	FN	LOV (0.813 ± 0.127) OMN (0.829 ± 0.142)	≥5 y	Asian	57	DXA
Ho-Pham et al (2009)[34]	105 (62.0 ± 10.0)		105 (62.0 ± 10.0)	F	LS	Vegan (0.740 ± 0.140) OMN (0.770 ± 0.140)	≥10 y	Asian	28	DXA
					FN	Vegan (0.620 ± 0.110) OMN (0.630 ± 0.110)				
					WB	Vegan (0.880 ± 0.110) OMN (0.900 ± 0.120)				
Krivosíková et al (2010)[35]	131 (40.8 ± 19.8)	141 (41.9 ± 19.7)		F	LS	LOV (1.085 ± 0.192) OMN (1.102 ± 0.159)	Long-term vegetarian diet	Caucasian	43	DXA
					FN	LOV (0.918 ± 0.142) OMN (0.941 ± 0.136)				
Ying-Ming et al (2010)[36]	302 (50.0–≥70.0)	173 (50.0–≥70.0)		F	LS	LOV (0.795 ± 0.140) OMN (0.837 ± 0.140)	NA	Asian	50	DXA
Kaur (2013)[37]	46 (45.0–80.0)	204 (45.0–80.0)		F	LS	LOV (0.872 ± 0.118) OMN (0.888 ± 0.140)	NA	Asian	50	DXA
Knurick et al (2015)[38]	27 (27.2 ± 6.7)	27 (31.1 ± 9.1)	28 (33.9 ± 8.6)	F/M	WB	Vegan (1.130 ± 0.110) LOV (1.120 ± 0.100) OMN (1.180 ± 0.110)	>1 y	Caucasian		DXA

Abbreviations: BMD, bone mineral density; DPA, dual-photon absorptiometry; DXA, dual-energy X-ray absorptiometry; F, females; FN, femoral neck; LOV, lacto-ovo-vegetarians; LS, lumbar spine; M, males; NA, not available; OMN, omnivores; SD, standard deviation; WB, whole body.

[a]Control group in this study refers to omnivorous.

[b]Minimum years following the vegetarian or vegan diet.

[c]Age is given as mean ± standard deviation or range.

Table 3 **Descriptive characteristics of included studies on fracture risk**

Study	Participants				Fracture risk					
	OMN no. (age in y)[b]	LOV no. (age in y)[b]	Vegan no. (age in y)[b]	Sex	No. of fractures	Place of fracture	Years of follow-up	Years following the diet[a]	Ethnicity	Qulaity Assessment
Thorpe et al (2008)[39]	1139 (≥35)		718 (≥35)	F	Vegan 81 OMN 88	Wrist	25 y	NS	Caucasian	64
Appleby et al (2007)[19]	14 725 (50.5 ± 12.1)	7272 (41.0 ± 13.2)	700 (39.4 ± 13.3)	F	Vegan 47 LOV 368 OMN 913	All	5.2 y	NS	Caucasian	64
Appleby et al (2007)[19]	4524 (50.5 ± 12.1)	1968 (41.0 ± 13.2)	1126 (39.4 ± 13.3)	M	Vegan 27 LOV 103 OMN 179	All	5.2 y	NS	Caucasian	64
Ho-Pham et al (2012)[20]	93 (61.0 ± 9.0)		88 (62.0 ± 10.0)	F	Vegan 5 OMN 5	Vertebral	2 y	≥20 y	Asian	64
Dash and Kushwaha (2012)[40]	6439 (NS)	2131 (NS)		M	LOV 209 OMN 395	All	5 y	NS	Asian	43
Lousuebsakul-Matthews et al (2014)[41]	15831 (30–≥85)	13524 (30–≥85)	3776 (30–≥85)	F/M	Vegan 54 LOV 130 OMN 120	Hip	≥ 2 y	≥1y	Caucasian	64

Abbreviations: F, females; LOV, lacto-ovo-vegetarians; M, males; NS, non-specified; OMN, omnivores.
[a]Number of years following the vegetarian or vegan diet.
[b]Age is given as mean ± standard deviation or range.

effects models were applied for continuous and categorical data. Effect sizes were calculated for each outcome.

Sources of heterogeneity were investigated by subgroup analyses comparing results based on diet (vegetarians or vegans), sex (women or men), age (<50 y or >50 y), ethnicity (Asian or Caucasian), and quality assessment when information was available. For fracture rates, the number of years of follow-up was also included. All analyses were performed using Open Meta[Analyst] software.

The heterogeneity of the studies was tested using the I^2 statistic.[75] This statistic describes the variance among studies as a proportion of the total variance. A value of <25% indicated low heterogeneity, a value of 25% to 50% indicated moderate heterogeneity, a value of >50% to 75% indicated high heterogeneity, and a value of >75% indicated very high heterogeneity. The associated *P* value of the heterogeneity of the studies was also calculated, with a nonsignificant result indicating absence of heterogeneity.

Publication bias was assessed by Egger's linear regression test following the indications provided by Peters et al.[76] Additionally, the Begg and Mazumdar rank correlation test was applied to measure asymmetry in funnel plots.[77]

RESULTS

Description of the included studies

The 20 studies included 37 134 individuals (BMD data were available for 4003 individuals, and fracture rate data were available for 33 131 individuals).[19,20,24–41] The mean age of the participants varied from 25 to 80 years, and most of the studies equally sampled omnivores and vegetarians/vegans. One study only included men (5%; n = 1/20), most of the studies (65%; n = 13/20) only included women, and 6 studies included both women and men (30%; n = /20). Of the eligible studies, 45% (n = 9/20) included only vegetarians, 25% (n = 5/20) included only vegans, and 30% (6/20) included both vegetarians and vegans. Participants in 11 of the 20 studies (55%) were Caucasians; participants in the other 9 studies (45%) were Asians. Of the 20 studies included in the systematic review, 45% (n = 9/20) were conducted in Asia (3 in Taiwan, 2 Vietnam, 2 in India, 1 in Korea, and 1 in Hong-Kong), 35% (n = 7/20) were conducted in North America (6 in the United States and 1 in Canada), and 20% (n = 4/20) were conducted in Europe (1 in Italy, 1 in Finland, 1 in Slovakia, and 1 in the United Kingdom). Regarding BMD measurements, LS, FN and WB were reported for 13% (n = 2/15) of the included studies, LS and FN were reported for 40%

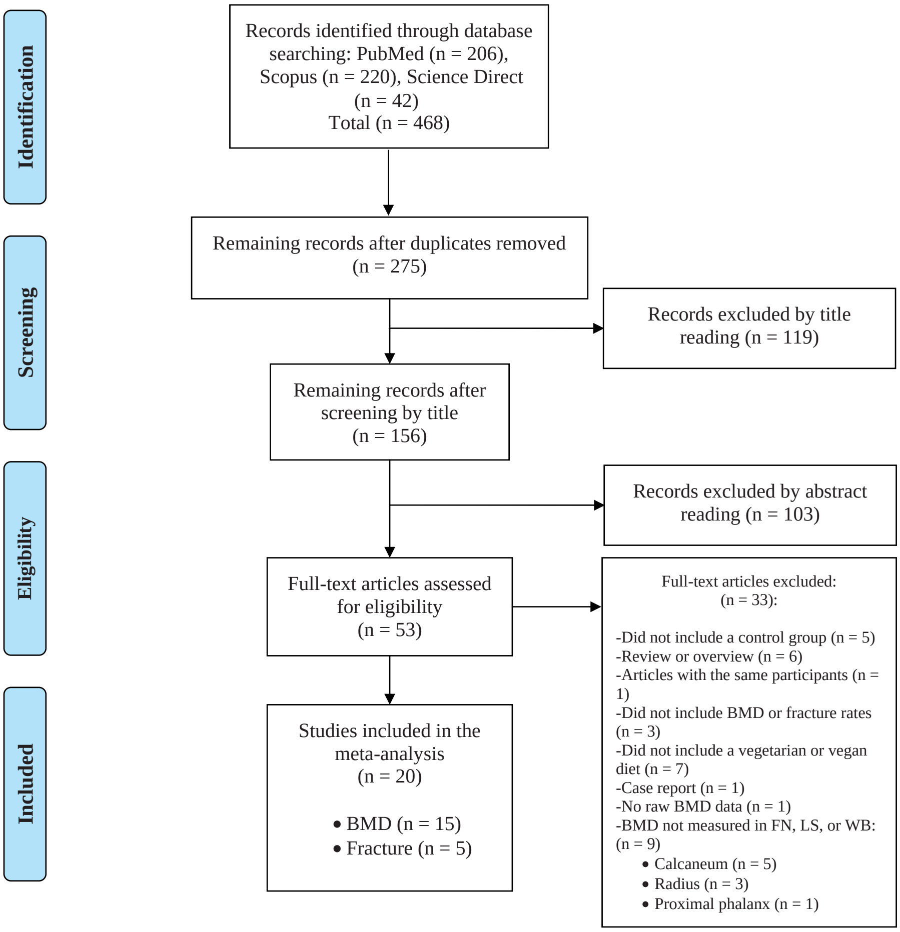


Figure 1 **Flow diagram of the literature search process.** *Abbreviations:* BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; WB, whole body.

(n = 6/15) of the studies, LS was reported for 33% (n = 5/15) of the studies, and WB was reported for 13% (n = 2/15) of the studies. All of the studies for which the number of fractures was reported as an outcome were prospective studies. All but one of the studies for which BMD was reported as an outcome were cross-sectional; the exception was a longitudinal study[29] (Tables 2 and 3).

Quality assessment

The obtained grade for each study is included in Table S2 in the Supporting Information online. Grades for the included studies ranged from 28 to 64 points out of a total 100 points. Most of the included studies in the present meta-analysis were of medium quality.

Bone mineral density differences between vegetarians/vegans and omnivores

Figures 2–4 show[24–38] the individual study results and plot the global effect of vegetarianism/veganism on BMD.

Lumbar spine. As shown in Figure 2a, vegetarians and vegans had lower LS BMD than omnivores (MD, −0.032; 95%CI, −0.048 to −0.015). Heterogeneity among studies for the lumbar spine BMD was moderate ($I^2 = 41.04$; $P = 0.04$).

Subgroup analysis. Results of the subgroup analysis suggested that the effect of diet on LS BMD was stronger among vegans (MD, −0.070; 95%CI, −0.116 to −0.025) than among vegetarians (MD, −0.023; 95%CI, −0.035 to −0.010) (Figure 2b). Additionally, the effect was stronger in Caucasian participants (MD, −0.058; 95%CI, −0.101 to −0.015) than in Asian participants (MD, −0.026; 95%CI, −0.038 to −0.013) (Figure 2c). In regard to age, the effect was statistically significant in those aged >50 years (MD, −0.032; 95%CI, −0.052 to −0.012; $P = 0.002$) but not in those aged <50 years (MD, −0.031; 95%CI, −0.063 to 0.001) (Figure 2d). Concerning the quality of the studies, the effect was higher in those studies determined to be of higher quality (grade of ≥50 points) (MD, −0.035; 95%CI, −0.048 to −0.015) than in those with a grade of <50 points (Figure 2e). Heterogeneity was more pronounced in vegans ($I^2 = 62.83$; $P = 0.013$), Caucasians

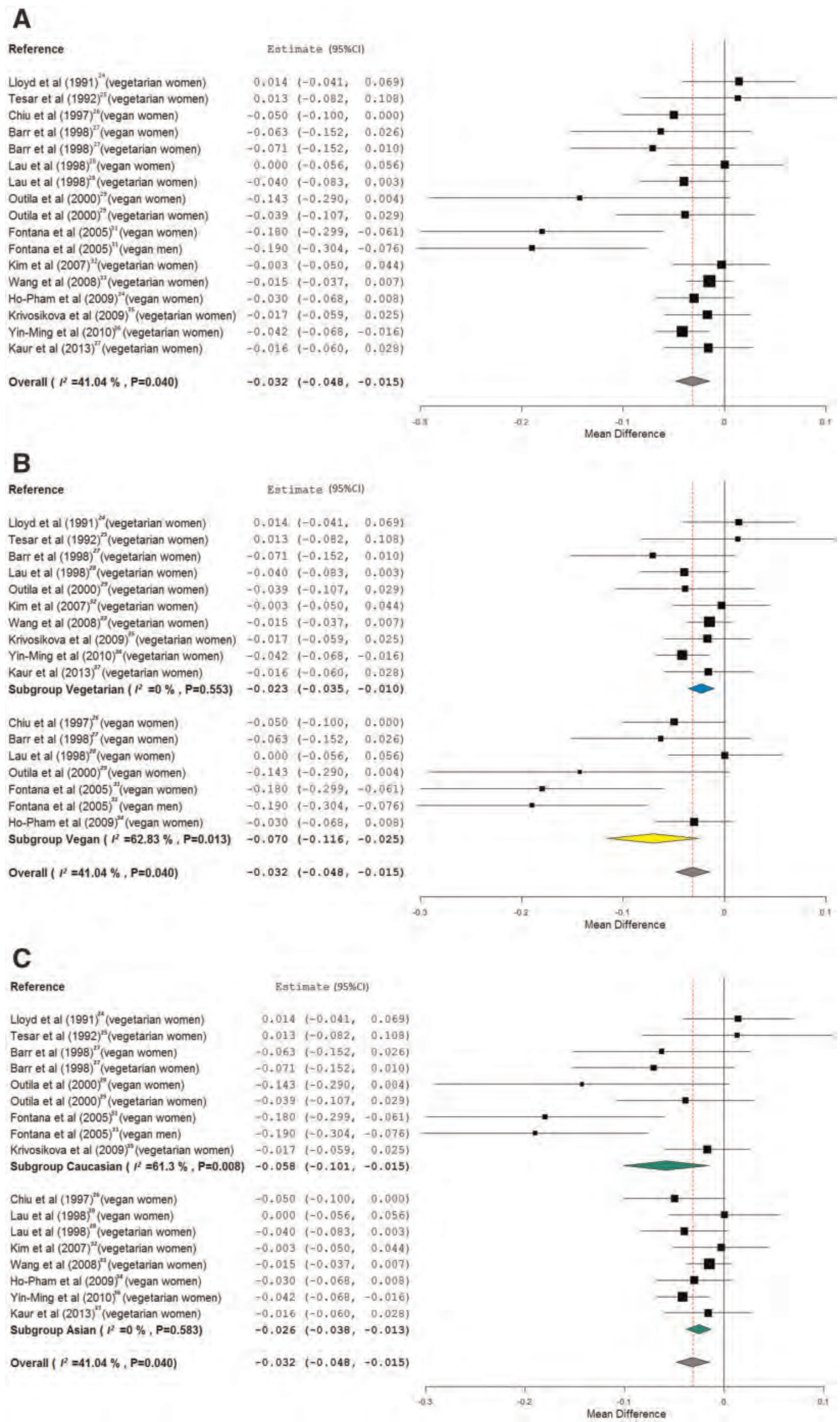
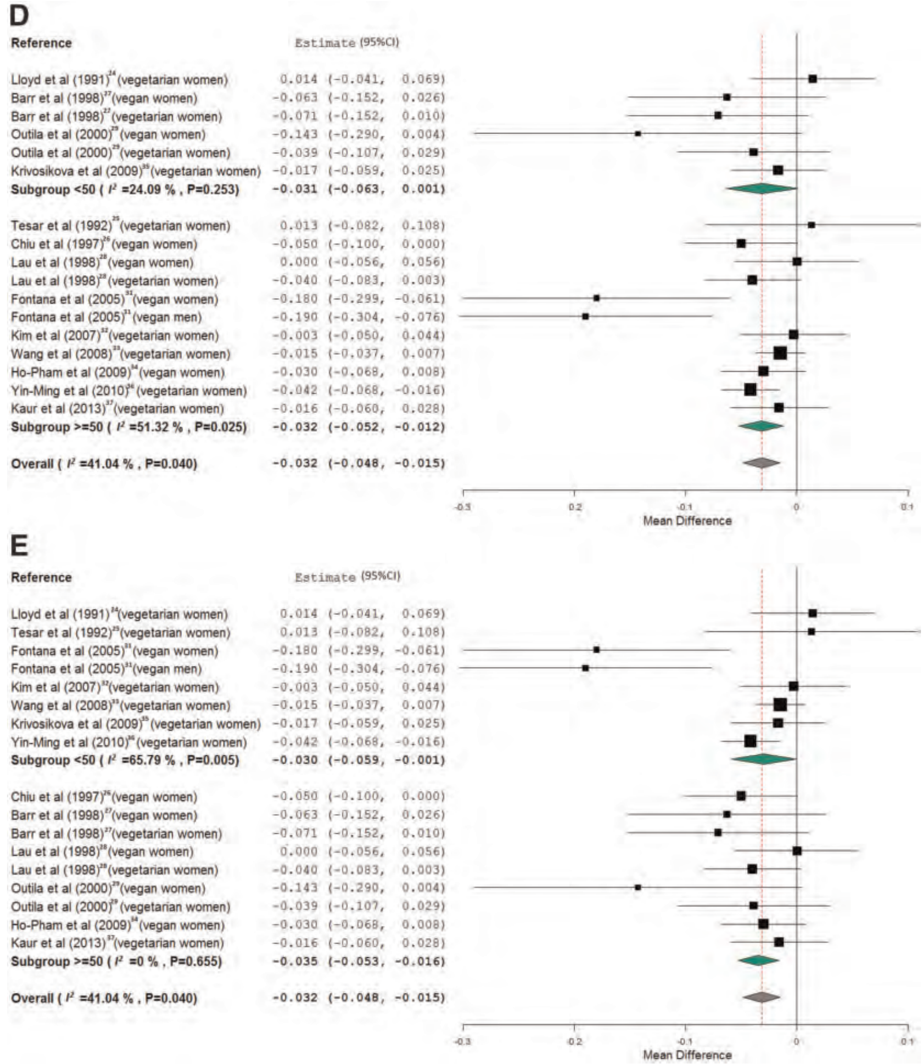


Figure 2 **Random-effects meta-analysis of the effects of vegetarian and vegan diets on bone mineral density (BMD) at the lumbar spine (LS).** (a) BMD differences between vegetarian/vegans and omnivores. (b) Subgroup analyses by diet (vegetarians vs vegans). (c) Subgroup analyses by ethnicity (Caucasians vs Asians). (d) Subgroup analyses by age (<50 y vs $\geq$50 y). (e) Subgroup analyses by quality assessment score (score of <50 vs $\geq$50). Abbreviations: BMD, bone mineral density; LS, lumbar spine.

◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.



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◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.

(I^2 = 61.30; P = 0.008), adults aged >50 years (I^2 = 51.32; P = 0.025), and in studies determined to be of a lower quality (I^2 = 65.70; P = 0.005). Heterogeneity among studies could not be compared by sex because only 1 study exclusively included men.[32]

Femoral neck. Figure 3a shows that vegetarians and vegans had lower FN BMD than omnivores (MD, −0.037; 95%CI, −0.054 to −0.020). Heterogeneity among studies for the FN BMD was moderate (I^2 = 48.92; P = 0.034).

Subgroup analysis. Similar to findings from the LS subgroup analyses, the effect of diet on FN BMD was found to be stronger among vegans (MD, −0.055; 95%CI, −0.090 to −0.021) than among vegetarians (MD, −0.025; 95%CI, −0.038 to −0.012) (Figure 3b). The effect was also more pronounced in Caucasian participants (MD, −0.082; 95%CI, −0.144 to −0.020) than in Asian participants (MD, −0.031; 95%CI, −0.047 to −0.015) (Figure 3c). The effect of vegetarianism and veganism was significant in those aged >50 years (MD, −0.036; 95%CI, −0.054 to −0.018; P < 0.001), but not in those aged <50 years (MD, −0.062; 95%CI, −0.145 to 0.021) (Figure 3d). Similarly, the effect of vegetarianism and veganism was significant in women (MD, −0.040; 95%CI, −0.058 to −0.021; P < 0.001) but not in men (MD, −0.050; 95%CI, −0.145 to 0.046) (Figure 3e). Concerning the quality of the studies, the effect was higher in those studies determined to be of higher quality (score of ≥50 points; MD, −0.042; 95%CI, −0.066 to −0.018) than in those deemed to be of lower quality (score of <50 points) (Figure 3f). Heterogeneity was more pronounced in vegans (I^2 = 64.41; P = 0.015), Caucasians (I^2 = 56.26; P = 0.058), adults aged <50

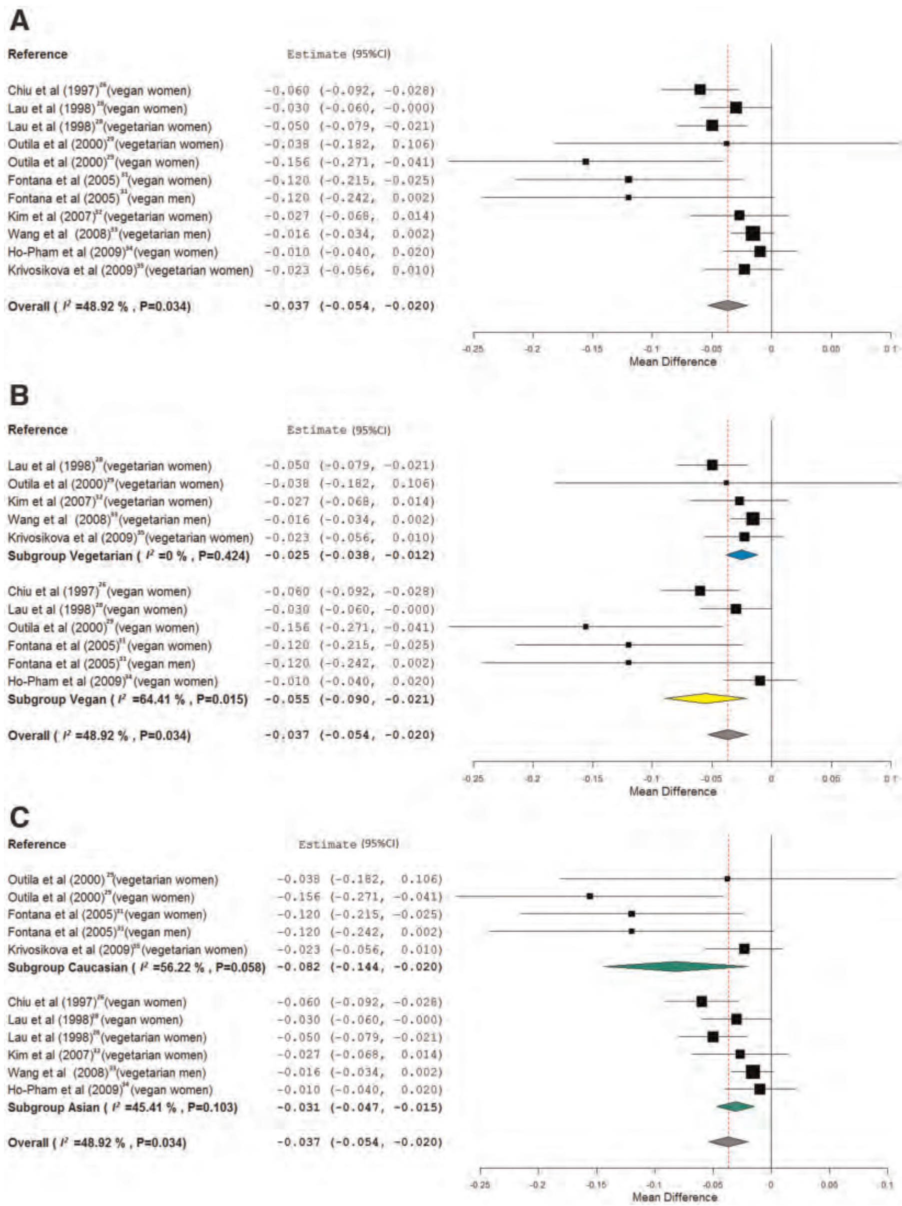

Figure 3 **Random0effects meta-analysis of the effects of vegetarian and vegan diets on bone mineral density (BMD) at the femoral neck (FN).** (a) BMD differences between vegetarians/vegans and omnivores. (b) Subgroup analyses by diet (vegetarians vs vegans). (c) Subgroup analyses by ethnicity (Caucasians vs Asians). (d) Subgroup analyses by age (<50 y vs ≥50 y). (e) Subgroup analyses by sex (women vs men). (f) Subgroup analyses by quality assessment score (score of <50 vs ≥50). Abbreviations: BMD, bone mineral density; FN, femoral neck.

◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.

years (I^2 = 57.91; P = 0.093), men (I^2 = 63.40; P = 0.098), and high-quality studies (I^2 = 51.04; P = 0.072).

Whole body. As shown in Figure 4a. Vegetarians and vegans had lower WB BMD than omnivores (MD, −0.048; 95%CI, −0.080 to −0.016). Heterogeneity among studies for the WB BMD was moderate (I^2 = 40.37; P = 0.136).

Subgroup analysis. When analyzing the impact of diet on WB BMD, this effect was statistically significant for vegans (MD, −0.059; 95%CI, −0.106 to −0.012; P = 0.013) but not for vegetarians (MD, −0.035; 95%CI, −0.093 to 0.023) (Figure 4b). The effect of vegetarianism and veganism was significant in those aged <50 years (MD, −0.043; 95%CI, −0.078 to −0.007; P = 0.018) but not in those aged >50 years (MD, −0.071; 95%CI, −0.145 to 0.003) (Figure 4c). Concerning the

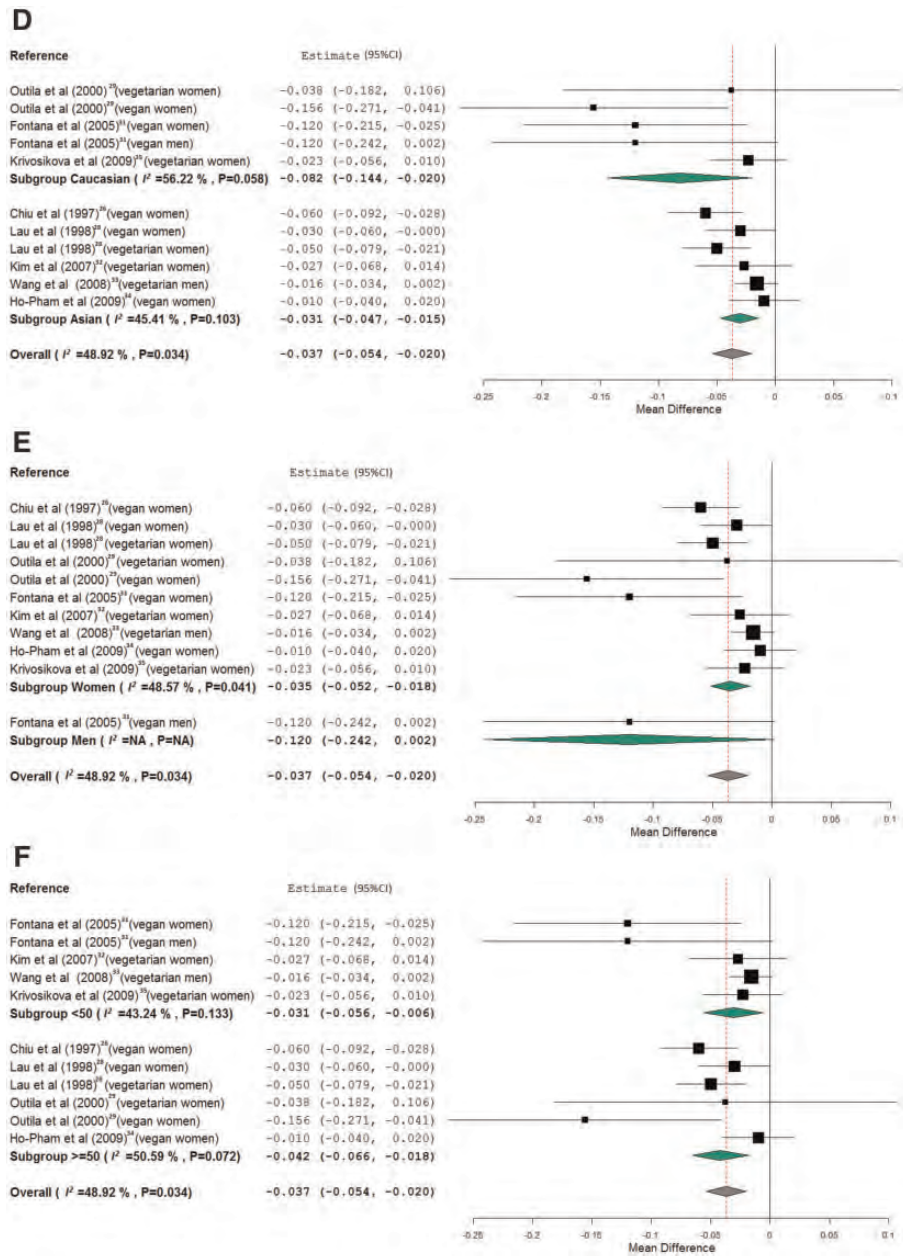

Figure 3 Continued.

◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.

quality of the studies, this effect was significant in those studies determined to be of higher quality (score of ≥50 points) (MD, −0.033; 95%CI, −0.058 to −0.008; $P = 0.008$) but not in those determined to be of lower quality (score of ≥50 points) (MD, −0.071; 95%CI, −0.152 to 0.010) (Figure 4d). Heterogeneity was more pronounced in vegans ($I^2 = 55.90$; $P = 0.078$), adults aged >50 years ($I^2 = 70.00$; $P = 0.036$), and lower-quality studies ($I^2 = 60.67$; $P = 0.079$). Heterogeneity among studies could not be compared by ethnicity and sex because only 1 study was conducted in Asian population[34] and only 1 study included men.[31]

Fracture risk differences between vegetarians/vegans and omnivores

Figure 5 presents the effects of vegetarian/vegan and omnivore diets on fracture rates. Vegetarians and vegans had a higher fracture risk than omnivores (relative risk [RR], 1.316; 95%CI, 1.038–1.668). Heterogeneity among studies was found to be very high ($I^2 = 87.80$; $P < 0.001$).

Subgroup analysis. A significantly higher fracture risk was found in vegans (RR 1.439; 95%CI, 1.047–1.977;

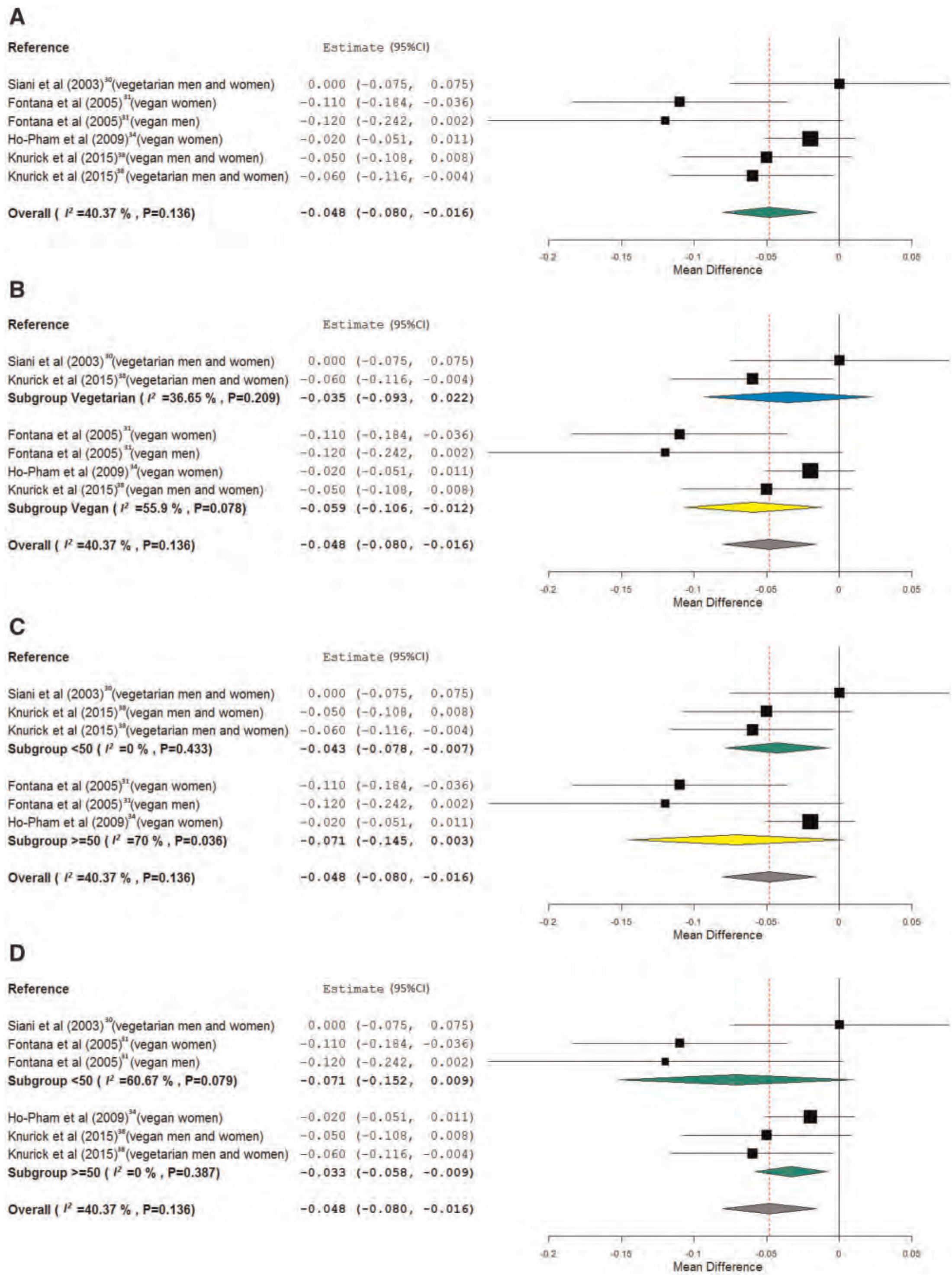

Figure 4 **Random-effects meta-analysis of the effects of vegetarian and vegan diets on bone mineral density (BMD) on the whole body (WB).** (a) BMD differences between vegetarians/vegans and omnivores. (b) Subgroup analyses by diet (vegetarians vs vegans). (c) Subgroup analyses by age (<50 y vs ≥50 y). (d) Subgroup analyses by quality assessment score (score of <50 vs ≥50). Abbreviations: BMD, bone mineral density; WB, whole body.

◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.

$P < 0.001$) in comparison with omnivores. However, this effect was not statistically significant for vegetarians (RR, 1.254; 95%CI, 0.917–1.714; $P = 0.067$) (Figure 5b). Asian participants (RR, 1.587; 95%CI, 1.354–1.861; $P < 0.001$) had a significantly higher fracture risk; this effect was not significant in Caucasians (RR, 1.285; 95%CI,

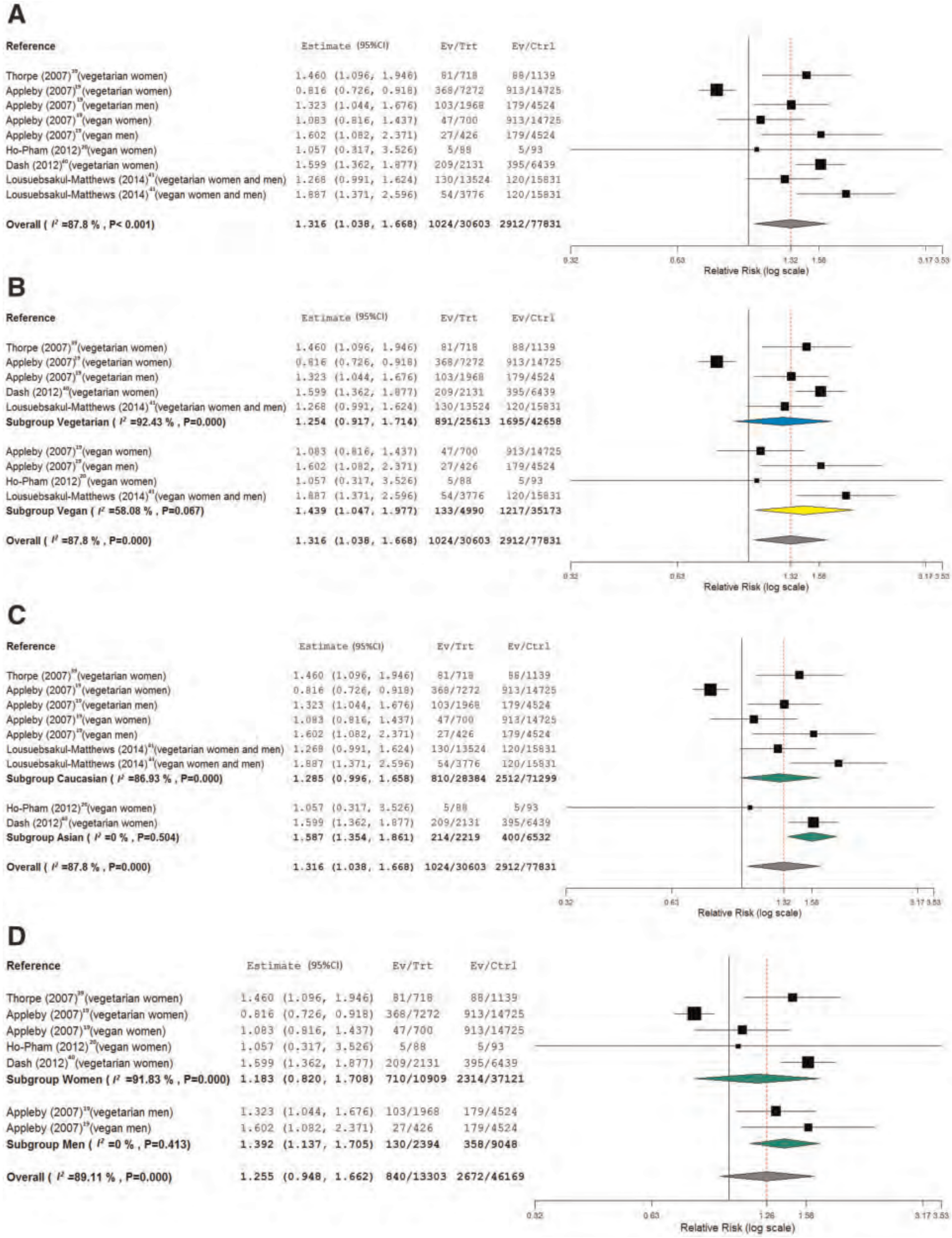

Figure 5 **Random effects meta-analysis of the effects of vegetarian and vegan diets on fracture rates.** (a) Fracture rate differences between vegetarians/vegans (treatment group) and omnivores (control group). (b) Subgroup analyses by diet (vegetarians vs vegans). (c) Subgroup analyses by ethnicity (Caucasians vs Asians). (d) Subgroup analyses by sex (women vs men). Vegetarians/vegans were the treatment group. Omnivores were the control group. Abbreviations: Ctrl, control group; Ev, event; Trt, treatment group.

◆-Vegetarians and vegans, ◆-Only vegetarians, ◆-Only vegans, ◆-Overall results.

0.996–1.658; $P = 0.054$) (Figure 5c). The impact of vegetarianism or veganism in fracture rates was significant in men (RR, 1.392; 95%CI, 1.137–1.705; $P = 0.001$) but not in women (RR, 1.183; 95%CI, 0.820–1.708) (Figure 5d). Heterogeneity was more pronounced in vegetarians ($I^2 = 92.43$; $P = 0.000$), Caucasians ($I^2 = 86.93$; $P = 0.000$) and women ($I^2 = 91.83$; $P = 0.000$) compared with vegans, Asians, and men, respectively.

Subgroup analyses by age, years of follow-up, and study quality were not possible because only 2 studies included the age of the participants,[19,20] only 1 included a long-term follow-up (>10 y),[39]and only 1 was determined to be of low quality (score of <50 points).[40]

Sensitivity analysis. A sensitivity analysis was developed excluding the Appleby et al study[19] as a possible outlier (see Figure 5). The effect size of both vegetarian and vegan diets on fracture risk increased (RR, 1.522; 95%CI, 1.338–1.731 vs RR, 1.316; 95%CI, 1.038–1.668), and the heterogeneity of the studies decreased (I^2 = 13.61; $P = 0.000$ vs $I^2 = 87.80$; $P < 0.001$). Results for the diet subgroup analyses were also modified. The effect of vegetarian diets on fracture risk became significant (RR, 1.475; 95%CI, 1.286–1.693; P <0.001 vs RR, 1.254; 95%CI, 0.917–1.714), whereas the heterogeneity of the studies decreased ($I^2 = 16.52$; $P = 0.302$ vs I^2 = 92.43; $P = 0.000$). Similar results were found for the ethnicity subgroup analysis, with the effect of vegetarianism and veganism on fracture risk in Caucasians becoming significant (RR, 1.491; 95%CI, 1.193–1.862; $P <$ 0.001 vs RR, 1.285; 95%CI, 0.996– to 1.658) and the heterogeneity decreasing ($I^2 = 46.28$; $P = 0.155$ vs I^2 = 86.93; $P < 0.001$). When applying the sensitivity analysis to the sex subgroup analysis, results were also modified, with the effect of vegetarian and vegan diets on fracture risk becoming significant not only in men but also in women (RR, 1.556; 95%CI, 1.354–1.789; $P <$ 0.001 vs RR, 1.183; 95%CI, 0.820–1.708; $P = 0.033$); additionally the heterogeneity decreased ($I^2 = 0$; P = 0.707 vs $I^2 = 91.83$; $P = 0.000$).

Publication bias

No indication for publication bias was found for studies that included LS measurements (Begg $P = 0.128$; Egger $P = 0.070$), WB measurements (Begg $P = 0.260$; Egger $P = 0.120$), and fracture risk (Begg $P = 0.755$; Egger $P = 0.169$). A modest publication bias was found for the studies that included FN measurements (Begg P = 0.043; Egger $P = 0.014$).

DISCUSSION

The present meta-analysis aimed to study the effect of vegetarian and vegan diets compared with omnivorous diets on BMD and fracture rates. Both vegetarians and vegans were found to have lower BMD at the LS and FN, and vegans had a higher risk of fracture than omnivores. The lower BMD and the higher risk of fracture were more pronounced in vegans than in vegetarians and in high-quality studies (≥50 points) versus lower-quality studies.

Previous studies have suggested that vegetarians may have higher BMD and bone mineral content than omnivores.[24,71,74,78,79] However, recent studies have not found any positive impact of vegetarian diets on bone health,[35,37] and some of them have found a negative impact.[28,31,35,36] In fact, most of the studies published in the last decades have found lower BMD in vegetarians and vegans compared with omnivores, although only 3 have found statistically significant associations.[28,31,35,36] The present results are in line with a previous meta-analysis that included 9 studies and found lower BMD at the LS and the FN for vegetarians compared with omnivores.[18] Ho-Pham et al concluded that vegetarians and vegans had approximately 4% lower BMD at the FN and LS than omnivores.[18] In contrast with the results of the present study, they stated that this difference was statistically significant but not clinically relevant. The present findings suggest that the lower BMD values found for vegetarians and vegans could be clinically relevant because fracture risk was found to be higher in vegans than in omnivores.

Four of 5 studies included in the present meta-analysis found higher fracture rates in vegetarians and vegans compared with omnivores.[20,75–77] The study from Appleby et al[19] was the only one that found a higher prevalence of fractures in female meat eaters than female vegetarians. This study compared fracture rates in meat eaters (defined as those who eat meat), fish eaters (defined as those who did not eat meat but did eat fish), vegetarians (defined as those who did not eat meat or fish but did eat either dairy products or eggs), and vegans (defined as those who did not eat meat, fish, dairy products, or eggs).[19] In fact, when the study by Appleby et al[19] was removed from the sensitivity analyses, it was observed that vegetarians had a higher fracture risk than omnivores.

The moderate heterogeneity observed among the studies on BMD was partly explained by the type of diet, age, sex, ethnicity, and quality of the studies. After conducting subgroup analysis, the heterogeneity of the studies performed in vegans, those aged <50 years, men, and Asians was considerably reduced and became no longer statistically significant. When a subgroup analysis was performed with the studies stratified by quality, heterogeneity was no longer statistically significant in high-quality studies. Heterogeneity among studies on fracture risk was very high and partly explained by the type of diet, ethnicity, and sex. Differences in heterogeneity were mainly due to the Appleby et al study.[19] This may be because meat eaters smoked more and had higher alcohol consumption, higher body mass index (BMI), lower physical activity levels, and similar calcium intakes than vegetarians.

Subgroup analysis showed that the effect of vegetarianism and veganism on fracture rates was only statistically significant for vegans, Asians, and men. When analyzing the effect on vegetarianism and veganism on LS and FN BMD, this effect was higher in Caucasians than in Asians, and it was only statistically significant in studies determined to be of a higher quality (score of ≥50 points) and in individuals aged >50 years.

Subgroup analyses showed that the increased fracture risk was only statistically significant for vegans. One could argue that specific nutrients found in higher amounts in animal food sources, such as dietary calcium, high biological value proteins, vitamin B12, vitamin D, and retinol, which are present in ovo-lacto-vegetarian diets but in lower quantities in vegan diets,[17] could exert an important impact on bone health. Similarly, in a previous large cohort study, Appleby et al[19] suggested that vegans were only at a higher risk of suffering a fracture when calcium intake was <525 mg/day. However, a recent meta-analysis concluded that calcium intake produced a small but nonprogressive increase in BMD, making it unlikely that calcium intake would lead to a clinically significant reduction in the risk of fractures.[80] Moreover, when a vegan or vegetarian diet is appropriately planned, these nutrients deficiencies should not occur.[17]

Others have hypothesized that proteins may have a positive impact on bone health.[15,81,82] In elderly people with osteoporosis, increased levels of protein intake (>0.8 g/kg body weight/day or 24% of total energy intake) are positively associated with BMD,[15] a slower rate of bone loss,[81] and a reduced risk of hip fracture.[82] Nevertheless, 2 meta-analyses suggested that there is only a small positive effect of protein on BMD.[15,16]

As shown by Roman-Garcia et al,[83] a deficiency in vitamin B12 can negatively affect bone development and maintenance. Vitamin B12 serves as a cofactor for methionine synthase,[83] which is involved in the metabolism of homocysteine. High homocysteine levels, caused by a deficiency of vitamin B12, may affect bone remodeling by increasing bone resorption and decreasing bone formation and bone blood flow.[84]

The effect of vegetarianism and veganism on BMD at the LS and FN was only statistically significant in the population aged >50 years. Bone mineral density decreases over time, and this population might have been exposed to the effects of these diets for a longer period.

When stratifying by sex, the effect of diet on fracture risk was only statistically significant in men. However, results were provided separately by sex for only 3 investigations, and therefore, results should be considered with caution.[19,31,33]

The effect of vegetarianism and veganism on BMD of the LS and FN was more pronounced in Caucasians than in Asians. In contrast, when studying fracture rates, the results of this study indicated that this effect was only statistically significant in Asians. However, it is necessary to highlight that only 2 studies included in the subgroup analysis assessed fracture rates in Asian populations,[20,40] and therefore results may be equivocal. In fact, as previously reported, Asian populations have showed a lower fracture risk than Caucasian populations, even if they have a lower areal bone mineral density, lower weight, and smaller bone sizes.[85,86] Asians may have smaller bones but thicker and denser cortices[85,87]; as a consequence, the authors hypothesized that the impact of vegetarianism and veganism could be higher in Caucasians than in Asians.

Moreover, the consumption of soy products is part of the regular diet of the Asian population but it is not so common in Western diets.[88] Thus, Asian vegetarians may have a higher intake of tofu and other soy products compared with Caucasian vegetarians. Soybeans are a rich source of calcium, proteins and isoflavones, a class of phytoestrogens found predominantly in legumes and beans. Because protein/isoflavones intakes have a modest but statistically significant association with BMD as well as with WB bone mineral content, the effect of vegetarianism and veganism could have a greater impact on Caucasians than in Asians.[89]

It is worth noting that lifestyle factors may have influenced the associations between diet and BMD. Vegetarians and vegans tend to show healthier behaviors, such as higher levels of physical activity, lower smoking rates, and lower alcohol and caffeine intakes, than omnivores.[90] Particularly, in the studies included in this systematic review and meta-analyses, vegans and vegetarians generally reported higher levels of physical activity, lower smoking rates, lower alcohol and caffeine intakes,[28,29] lower BMI[31,32] and lower energy[28] and calcium intakes[38] than omnivores, although some of these group differences were not statistically significant in several studies.[27,29,38]

In the relationship between vegetarian/vegan diets and bone health, it is important to consider the possible effect that overall dietary quality can have. Among the studies included in the present systematic review and meta-analysis, only 1 study considered overall dietary quality.[38] In this study, diet quality was superior for individuals adhering to a vegan diet as compared with the other diet groups, and there were no differences in BMD among vegans, vegetarians, and omnivores, which suggests that a high-quality vegan/vegetarian diets would look similar to that of an omnivore in relation to bone health.

This meta-analysis has several strengths. To the best of the authors' knowledge, this is the first meta-analysis to examine the association between vegetarianism and veganism and fracture rates. This analysis included not only fracture rates, but also BMD measurements at the FN, LS, and WB. This allowed us to estimate the total effect size of the vegan and vegetarian diets on BMD with a larger sample size and a higher statistical power than a previously published meta-analysis.[18]

The present study has a number of limitations. First, most of the studies in the present meta-analysis included only women, and hence results are mainly applicable to this population. Second, investigations included a very heterogeneous population (ie, some of the studies focused on Buddhist nuns or religious followers of Buddhism, whereas others focused on young adult vegetarians with very different characteristics). Third, some factors associated with BMD and fracture risk, such as the time that vegetarians and vegans had been following the diet, daily energy intake, number of hours engaged in physical activity, BMI, use of hormone replacement therapy, sunlight exposure, consumption of alcohol, and smoking behavior, could not be evaluated because this information was not reported for most of the studies. For the same reason, the present study could not evaluate differences in BMD and fracture rates between pre- and postmenopausal women. Additionally, publication bias was found for the FN measurements, and therefore results from this region should be interpreted with caution. Another limitation is the reliance on self-reported measurements, which are prone to errors, for such data as BMI,[91] physical activity, and fracture rates. The lack of dietary quality information for most studies could be considered another limitation. Furthermore, whether individuals had a low bone mass or osteoporosis prior to starting a vegetarian or vegan diet, which could influence the results, was not reported for any of the included studies. Moreover, for some of the studies, it was reported that the participants were mostly vegetarians or vegans or long-term vegetarians without specifying the duration of the diet, which make definitions sometimes ambiguous for interpretation. Finally, it was not possible to run moderator analyses for other important variables such as diet quality, energy intake, or physical activity because of the small number of studies for which this information was reported.

CONCLUSION

The findings of this study suggest that both vegetarian and vegan diets are associated with lower BMD compared with omnivorous diets and that vegans have a higher fracture risk than omnivores. The effect of vegan diets on BMD is more pronounced than the effect of vegetarian diets. Both vegetarian and vegan diets should be appropriately planned to avoid dietary deficiencies associated with bone health.

Acknowledgments

Author contributions. I.I. and M.L.M-B. contributed equally and share the first authorship. I.I., M.L.M-B., A.G.B., and C.J. searched for studies and agreed on inclusion and exclusion. I.I. extracted data and performed the meta-analysis. I.I. and M.L.M-B. drafted the manuscript. All authors revised and provided intellectual input into the final manuscript.

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Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **PRISMA checklist**

Table S2 **Quality assessment for observational cohort and cross-sectional studies. Studies of bone mineral density (BMD) and fracture rates.**

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