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A *posteriori* dietary patterns are related to risk of fracture and low bone mineral density: Findings from a systematic review and meta-analysis

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ABSTRACT

Background: Observational studies suggest that dietary pattern intake plays an important role in the development of fracture and low bone mineral density (BMD). However, the association remains unclear. This systematic review was performed to evaluate the relationship between dietary patterns and fracture and BMD by pooling available data from existing studies.
Methods: MEDLINE and EMBASE databases were searched up to January 2015 for eligible observational studies regarding the relationships between common dietary patterns and risk of fracture/ low BMD. Random-effects models were applied to pool the summary estimates for the highest versus the lowest category of dietary pattern. Sensitivity analyses were conducted and publication bias was assessed using Begg or Egger's tests.
Results: A total of thirteen cross-sectional studies were included in the meta-analysis. There was evidence of inverse associations between the Healthy/Prudent dietary pattern and the risk of low BMD (OR: 0.75; 95% CI: 0.21 to 1.30; p =0.007) and a positive association between Unhealthy/Western dietary pattern and low BMD risk (OR: 1.21; 95% CI: 0.58 to 1.90; p<0.001) for the highest versus the lowest category. Moreover, the association between highest compared with lowest categories of intake of the Healthy/Prudent dietary pattern and the risk of fracture showed a significant inverse association (OR = 0.63; 95% CI: 0.53, 0.73; p< 0.001) which was positive for Unhealthy/Western dietary patterns and fracture risk (OR = 1.08; 95% CI: 0.90, 1.26; p<0.001).
Conclusion: There appears to be a beneficial effect of healthy dietary pattern on fracture and low BMD risk and adding a new direction toward prevention of fracture and low BMD level on population level.

Introduction

The prevalence of osteoporosis and related fractures appears to be increasing [1]. Osteoporosis and related fractures are shown to be responsible for high health care costs related to hospitalizations, surgery, outpatient care, long-term care, disability, and premature death [2-3]. It has been estimated that about 70% of the 6.26 million cases of hip fracture in the year 2050 will occur worldwide [4].

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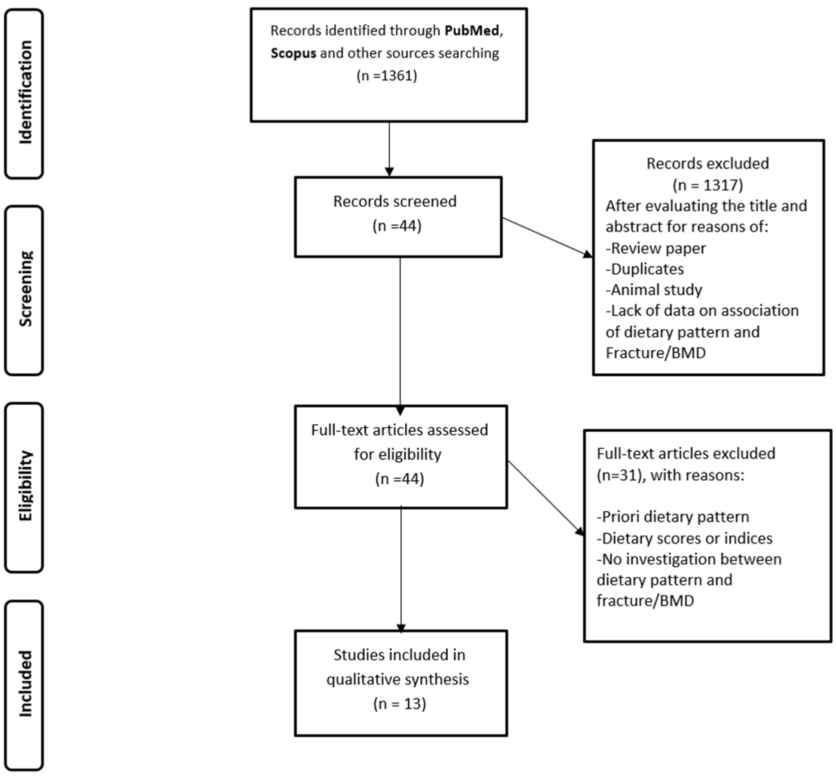

Figure 1. Flow chart of the study selection

The combination of vitamin D and calcium has long been a great deal of attention to reduce the risk of bone fracture, and many studies have been undertaken to test supplementation with these nutrients [5]. Studies suggest that dietary intakes other than calcium and vitamin D including such as potassium, magnesium, vitamin K, and fruit and vegetables, may also play an important role in bone health [6-7]. However, a clear relation with bone metabolism still remained unclear.

Traditionally, an important approach to assessing the potential influence of diet is to determine the relationship of a single nutrient to an exposure after controlling for other nutrients. To be noted, foods and nutrients are never eaten in isolation, and their effects are likely to be interacted. People consume diets consisting of a variety of foods with complex combinations of nutrients, rather than isolated nutrients, while the examination of only single nutrients or foods could lead to the identification of erroneous associations between dietary factors and disease. Recently another approach called dietary patterns gives complementary information to determine the relationship of a particular pattern to a given outcome [8].

The dietary patterns derived from the posteriori method, such as cluster analysis, factor analysis, and principal component analysis, aggregate variables into the factors representing broad eating patterns of specific population[9]. In the current study we use two common dietary patterns named Healthy/Prudent or Unhealthy/Western dietary pattern in our analysis due to large variation in the number and description of dietary patterns. These two patterns share most foods with similar factor loadings. Moreover, to minimize risk of bias using one analyses' approach like FA/PCA with long term reproducibility, stability and validity compared with other approaches [8] is recommended.

Accumulating evidence suggests that there is a relationship between dietary patterns and the risk of fracture or low BMD level. However, a consistent perspective has not been established across studies to date. There are no systematic reviews to have a pooled estimate of the size effect. Hence, this systematic review with meta-analysis was conducted, aiming at evaluating the association between dietary patterns and the risk of fracture.

Methods

We followed an a priori defined protocol (http://www.crd.york.ac.uk/PROSPERO;

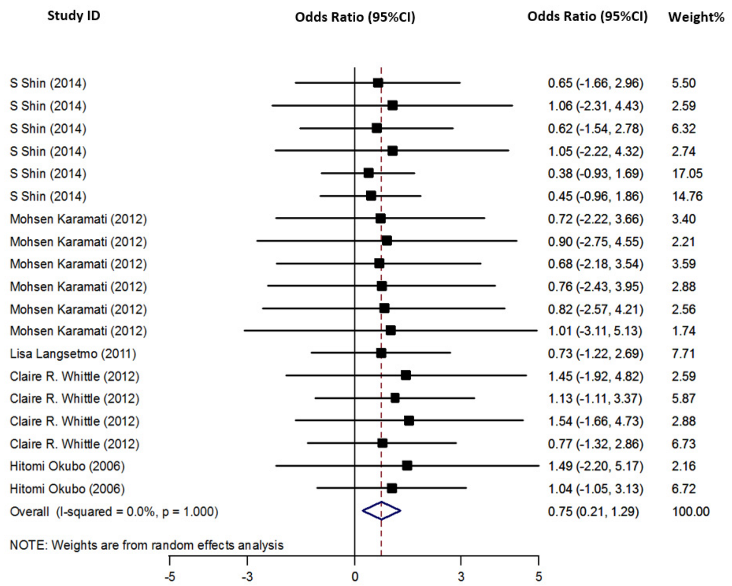

Figure 2. Forest plot of the highest compared with the lowest categories of intake of the healthy dietary pattern and low BMD

CRD42015016956).The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement was used for writing up this systematic review [9].

Review question(s)

What is the association between dietary patterns and bone mineral density and fracture?

Search strategy

An electronic search was conducted in the following electronic bibliographic databases: MEDLINE; EMBASE; SCOPUS up to January 2015. Only studies published in the English language included in the review. No date limits were set. The search strategy was include the following key search terms and relevant MeSH/keywords and Boolean operators

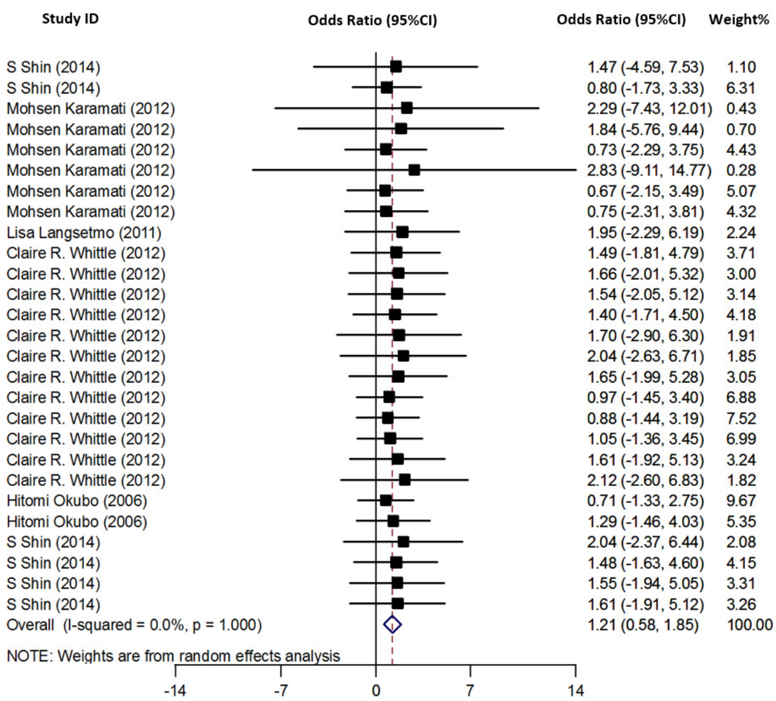

Figure 3. Forest plot of the highest compared with the lowest categories of intake of the unhealthy dietary pattern and low BMD

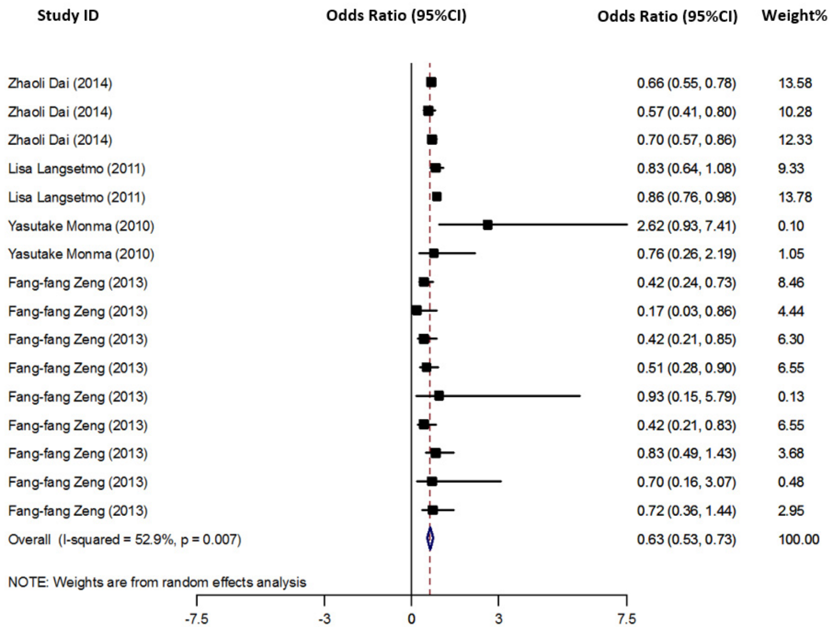

Figure 4. Forest plot of the highest compared with the lowest categories of intake of the healthy dietary pattern and fracture risk

("dietary pattern*" OR "eating pattern*" OR "food* pattern*" OR "dietary habit*" OR diet OR "dietary") AND ("factor analysis" OR "principal component analysis" OR "cluster analysis" OR clustering OR "reduced rank regression" OR "Mediterranean diet" OR "diet diversity" OR "diet variety" OR quality OR index* OR indices OR scores)' AND ("bone disease" OR "bone density" OR "bone mineral density" OR "osteoporosis" OR "osteopenia" OR "fracture" OR "bone fracture").

Study selection

Titles and abstracts of all articles retrieved in the initial search were evaluated independently by 2 reviewers (SM and SSH). Articles not

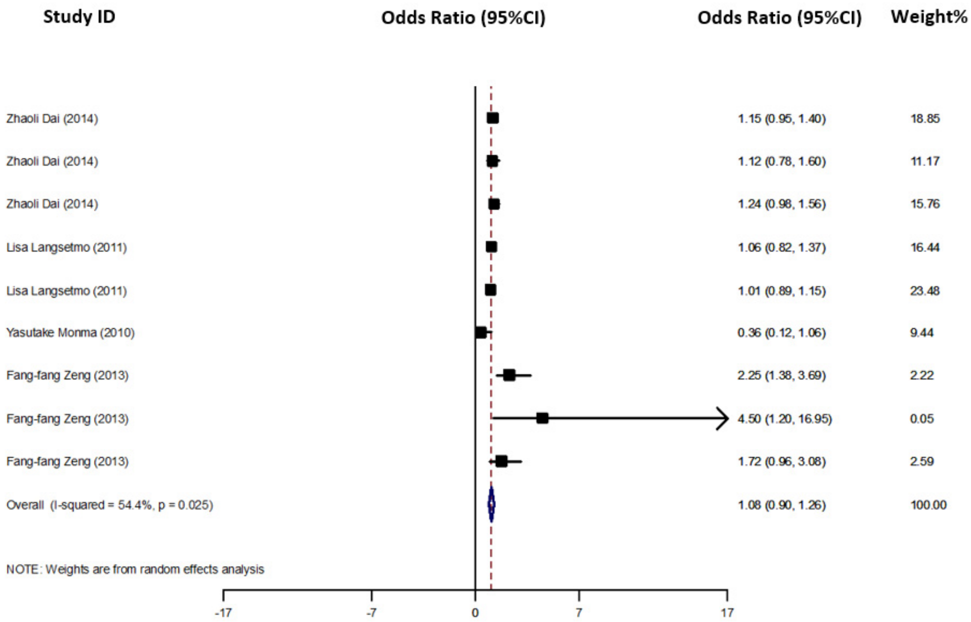

Figure 5. Forest plot of the highest compared with the lowest categories of intake of the unhealthy dietary pattern and fracture risk

meeting the eligibility criteria were excluded by using a screen form with a hierarchical approach based on study design, population or exposure, and outcome. The reference lists of relevant review articles identified during this process were also examined to include additional studies. Full-text articles were retrieved if the citation was considered eligible, and subjected to a second evaluation for relevance by the same reviewers. Any disagreements were discussed and resolved by consensus or by a third independent reviewer (T.N.) if necessary.

Eligibility criteria

Relevant articles obtained and included in this review if they 1) examine whole diet and include measurements of all dietary components by using a 24-h dietary recall, food record, food frequency questionnaire (FFQ), or similar instruments; 2) include BMD measures or odds ratio of fracture; and 3) enrolled adults,. Articles will be excluded if they 1) examine only individual nutrients or do not examine all dietary components, 2) do not report BMD measures or fracture OR, or 3) comprise study samples that are not population based or only focused on a subgroup of individuals with nutritional needs that are different from the general population.

Data extraction

The following information will be extract: first author, publication year and country, study design, sampling frame, sample size, number of cases and controls (if available), dietary assessment tool, method of identifying dietary patterns, dietary patterns identified, confounders adjusted for in analysis, and main findings, including the estimates of association. When a study provided several estimates with adjustment for different confounders, results were reported for the one adjusting for the largest number of factors.

Data synthesis

Only the most common patterns of dietary intake or dietary interventions were considered for meta-analysis. Because the labeling of dietary patterns varied across studies, the studies were grouped and analyzed jointly if the selected patterns were similar with regards to the most frequently consumed foods. For example, those dietary patterns with a high intake of fruit and vegetables, fish, and whole grains, and these studies were pooled and analyzed together and the corresponding dietary pattern was labeled "Healthy/Prudent."

Statistical analysis

A meta-analysis was conducted for the highest compared with lowest categories of dietary pattern to combine ORs, and 95% CIs. Random-effects models were used for the analysis. Heterogeneity was assessed by using the I^2 statistic [10]. Publication bias was examined through a contour-enhanced funnel plot to look for asymmetry Egger's tests [11]. All statistical analyses were conducted by using Stata version 11(StataCorp, College Station, Texas, USA).

Results

Search Strategy

The first search through electronic databases identified 1361 articles, of which 1317 were omitted because of duplication and not examining a given outcome: dietary pattern and fracture or bone mineral density. Of the 44 articles remained, that were reviewed in detail, 25 were excluded based on screening form items such as population and type of the study e [12-36]. An additional 6 articles were excluded as they did not report outcomes as odds ratio of fracture, osteoporosis or low BMD [37-42]. Finally 13 articles retrieved in our analyses which identified Healthy/Prudent and Unhealthy/Western dietary patterns [43-55].

Description of studies

Eight studies were conducted in Asia (2 in Japan, 3 in Korea, 1 in China, Singapore and Iran)[44-48, 51, 53-54], 3 in European countries (Greece, Scotland and Northern Ireland) [43, 52, 55], 1 in Canada [50] and 1 in Australia[49]. Sample sizes of the studies varied between 154 and 63154. Participant's ages ranged from 18 to 85 years at the time of study. Seven studies were restricted to female subjects [45-47,49,51-52, 55] and others were conducted on both sexes. All studies were observational and were consist of 6 cohorts [43-44,46,48,50,53], 6 cross-sectional [45,47,49,51-52,55] and 1 case control studies [54]. Dietary variables were measured by using a variety of instruments. Four studies used food records [43-44,49,55], one used 24-hour-recall [45], another used DHQ [47] and remaining studies used validated FFQs (n = 8]. We identified 2 dietary patterns across studies even in different countries and methods with similar characteristics. The Healthy/Prudent dietary pattern was characterized by high intakes of fruits, vegetables, fishes, and whole grains and the Un-Healthy/Western dietary pattern generally consisted of refined grains, processed meat foods or snacks, and high-sugar and high-fat products. Studies reported odds ratios of fractures, osteoporosis or low BMD only or in combination with median and standard deviation of BMD in different parts of the body. Just 3 studies reported regression coefficient as outcome [49,52,55].

Meta-analysis

Healthy /Prudent or Western/Unhealthy patterns and risk of low BMD

The results of all studies that examined the association between higher compared with lower consumption of the Healthy/Prudent pattern and risk of low BMD are shown in Figure 2. Subjects with higher consumption of the Healthy/Prudent pattern were shown to have a lower risk of BMD (OR: 0.75; 95% CI: 0.21 to 1.30; p =0.007). There was no evidence of heterogeneity (I^2: 0.0%, p=1.00). Results from the meta-analysis of the Western/Unhealthy diet are presented in Figure 3. A trend toward a positive association of higher consumption of the Western /Unhealthy pattern and the risk of having low BMD was observed, which was significant (OR: 1.21; 95% CI: 0.58 to 1.90; p<0.001) though it was associated with heterogeneity with I^2: 0.0%, p=1.000.

Publication bias of lower risk of BMD

Funnel plots revealed little evidence of asymmetry (not shown) and therefore little evidence of publication bias (highest compared with lowest categories: prudent/healthy Egger's test p= 0.14; Western/Unhealthy Egger's test p= 0.14).

Healthy/prudent or Western/Unhealthy patterns and risk of fracture

There was evidence of a decrease in risk of fracture in the highest compared with the lowest categories of the Healthy/Prudent DP (OR= 0.63; 95% CI: 0.53, 0.73; p< 0.001). The studies showed an evidence of heterogeneity (p = 0.007, I^2 = 52.9%) (Figure 4).

The association between highest compared with lowest categories of intake of Western/Unhealthy dietary patterns and fracture risk for studies is shown in Figure 5. There was an evidence of a difference in the risk of fracture for subjects in the highest category compared with lowest category (OR= 1.08; 95% CI: 0.90, 1.26; p<0.001). There was an evidence of a difference in the risk of fracture (p= 0.025, I^2 = 54.4%).

Sensitivity analysis

There were not much changes found in the risk estimates of fracture after we excluded Monma study as outlier [48] in Healthy/Prudent patterns (OR=0.63, 95% CI: 0.52, 0.73; p<0.001, I^2=52.9%; p=0.007). Excluding Zeng study[54] resulted in OR=0.62, 95% CI: 0.52, 0.72; p<0.00.1, I^2=52.9%; p=0.007 in risk of fracture. When we exclude [54] study as Outlier , subjects with higher consumption of the Unhealthy/Western diet were shown to have a lower risk of fracture (OR: 1.07; 95% CI: 0.89 to 1.26; p =0.001) and there was not any evidence of heterogeneity with I^2: 58.4% and p=0.019.

Publication bias of Fracture studies

The funnel plot for the 'Western/Unhealthy' DPs and 'Healthy/Prudent' patterns gave no evidence of asymmetry and small study effects (not shown), as confirmed by the corresponding statistical tests, Egger's test, p= 0.20 for Healthy/Prudent patterns and Egger's test, p= 0.17 for unhealthy/Western patterns.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis which evaluates the association between dietary patterns, BMD and fall-related fractures. Of the available literature, we found that a Healthy/Prudent dietary pattern may reduce the risk of having both low BMD and fracture. This dietary pattern in our analyses had high factor loading for fruits, vegetables, fishes and whole grains. Some studies suggest that fruits and vegetables provide base buffers against dietary metabolic acids which leads to increase osteoclast activity and decline the body's PH that helps bone resorption [44]. Acidosis may restrain osteoblast function and increase osteoclast activity which leads to bone loss. Furthermore, healthy dietary pattern is characterized by plenty of dietary antioxidants and low high-fat products specially saturated fat, which may cause the protective effects [53-54]. There is growing evidence of the negative role of oxidative stress in bone formation. Population-based and animal studies have suggested that oxidative stress may lead to have low BMD. Moreover, high intake of fishes rich in vitamins, minerals and omega 3 fatty acids have been shown to benefit bone health by increasing lean body mass and calcium absorption[54]. Data from the other studies suggested that people with healthy dietary pattern, also had healthier life style, for example more physical activity, which is known to increase BMD and reduce fracture risk[44].

On the other side, Western/Unhealthy dietary pattern showed an increase in the risk of having low BMD and fractures. The western dietary pattern in our analysis was characterized by high intakes of refined grains, processed meat foods or snacks, and high-sugar and high-fat products. The adverse effect of high-fat diet on bone health may be due to the abundant saturated fatty acids which could increase urinary excretions of calcium and limits osteoblast activity [47]. Saturated fat also may cause the production of inflammatory cytokines which increase bone resorption[54]. Moreover, there is the hypothesis that animal protein can provide a higher dietary acid load than vegetable protein, which may increase calcium excretion leading to bone loss [50].

Only Monma, et al., reported that a dietary pattern high in fruits and vegetables increased fracture risk in Japanese elderly and meat pattern reduced the risk of fracture inversely. The difference between results of Monma study and others can be explained by population characteristics. Studies have reported that the mean intake of meat in Japan was only 77.5g/day in 2002 whereas it was about 400g/day in USA in 2002. Moreover, in Monma et al., study, analysis of each food item, vegetables with light green leaves reduced fracture risk whereas root vegetables increased it, Although vegetable pattern showed adverse effect on fractures overall[48].

This systematic review was performed with an assumption of methodological homogeneity across articles in population characteristics, study design, and methods used for measuring exposure and for characterizing dietary patterns. All included articles adopted a cross-sectional design to explore the effects of potential dietary patterns. In addition, the two patterns under study were selected from the included articles with similar higher factor loadings in target components. However, the heterogenity observed in the association of dietary pattern and fracture risk may be partially explained by adjusting for different confounders in the analysis. To be noted, the heterogeneity of reported results may also explained by the number of confounders controlled for in the studies which could pose challenges for interpretation of the diet–disease relationship. However, the effect size in the most of articles was adjusted for all the major recognized confounding variables, including age, sex, body mass index (BMI), education, energy intake, and physical activity.

There were some limitations in this study. First, this systematic review was performed on cross-sectional studies which have inherent limitations in regards to determining causality. Whilst cross-sectional study designs do not provide information regarding the directionality of associations, this review is a reflection of the existing evidence base. Second, despite selecting same patterns with similarly higher factor loading of essential components, not all components in each of the patterns were identical which could lead to heterogeneity when data were pooled. Third, the principle component factor analysis used for deriving the dietary patterns in the included articles is a subjective technique and may increase variation at almost every step such as a variation in the number, type of dietary patterns derived within each study and categories of dietary patterns score[56]. Finally, a few articles from limited countries were included in this review, and the small number of articles might not be adequate to obtain conclusive evidence.

Conclusion

In conclusion our analysis suggests that a healthy dietary pattern may prevent osteoporotic fractures. This protective effect may be due to plenty of vitamins, minerals and phytochemicals enriched in such a diet. Inversely, an unhealthy dietary pattern high in red meat, saturated fat and refined sugar may increase the risk of fractures. Therefore, having a healthy diet rich in fruits, vegetables, fishes and whole grains could be a strategy to prevent bone loss and fall-related fractures.

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Conflict of interest

The authors declare that there is no conflicts of interest.

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Table 1. Descriptions (characteristics) of included studies

Author	Country	Type of study	Journal	Sex/ age	Sample size	DP assessment	DP method	Type-DP	DP component	OR	Mean ± SD BMD	β - BMD	Factors adjusted
Hitomi Okubo, 2006	Japan	Cross-sectional	Am J Clin Nutr	F (40-55)	291	DHQ	PCA	Healthy	Green and white vegetables, mushrooms, fish and shellfish, fruit, processed fish, seaweed, and soy products	_	Forearm,Q1:0.476±0.006 Forearm,Q5:0.498±0.006	_	Age, BMI, grasping power, current smoking, fracture history, use of HRT, age at menarche, parity and use of calcium and multivitamin supplements.
								Japanese traditional	Rice, miso soup and soy products	_	Forearm,Q1:0.493±0.007 Forearm,Q5:0.495±0.007	_	
								Western	fats and oils, meat, processed meats, and seasoning	_	Forearm,Q1:0.501±0.006 Forearm,Q5:0.482±0.007	_	
								Beverage and meat	Coffee, soft drinks, dairy products, sugary foods, and meats	_	Forearm,Q1:0.478±0.006 Forearm,Q5:0.492±0.006	_	
Meropi D. Kontogianni, 2009	Greece	Cross-sectional	Nutrition	F (36-60)	220	3-day food record	PCA	Food component 1	Dairy, cereals, red meat, and olive oil consumption	_	_	LS:0.094	BMI, smoking status, physical activity level, and low energy reporting
								Food component 2	Vegetables, fruits, and olive oil	_	_	LS:0.011	
								Food component 3	Fish and olive oil	_	_	LS:0.185	
								Food componen	Poultry and nuts	_	_	LS:0.054	

								t 4					
								Food component 5	Alcohol	_	_	LS:-0.041	
								Food component 6	Legume	_	_	LS:-0.061	
								Food component 7	Sweets	_	_	LS:-0.09	
								Food component 8	Fruit drink	_	_	LS:0.063	
								Food component 9	Coffee	_	_	LS:0.024	
								Food component 10	Soft drink	_	_	LS:0.227	
Yasutake Monma, 2010	Japan	Prospective cohort	BMC Geriatrics	M&F (≥70)	877	FFQ	PCA	Vegetable	Vegetable, seaweeds, mushrooms, soy products, salt	**Fracture** 2.62(0.93-7.41)	_	_	Age, gender, BMI, energy intake and experience of falls in previous 6 month.
								Meat	Meat and processed meat, seafood	0.36(0.12-1.06)	_	_	
								Traditional	Rice and Miso soup, Natto (fermented soybean)	0.76(0.26-2.19)	_	_	
Lisa Langsetmo, 2011	Canada	Retrospective cohort	Am J Clin Nutr	M&F (≥50)	5188	FFQ	PCA	Nutrient dense	Fruit, vegetables, and whole grains	**Fracture** M:0.83(0.64-1.08) F:0.86(0.76-0.98)	FN,T1:0.742±0.128 FN,T3:0.72±0.127	_	BMI, BMD, falls, prior fracture, comorbidities, smoking, milk consumption, supplements, for women: diagnosis of osteoporosis, anti-receptive use, education, alcohol use,

													physical activity and sedentary hours.
								Energy dense	Soft drinks, potato chips, French fries, meats, and desserts	M:1.06(0.82-1.37) F:1.01(0.89-1.15)	FN,T1:0.712±0.126 FN,T3:0.759±0.129		
Sarah A. McNaughton, 2011	Australia	Cross-sectional	The Journal of Nutrition	F (18-65)	527	4-day food diary	PCA	Pattern 1	Refined cereals, soft drinks, fried potatoes, sausages, processed meat, vegetable oils, beer, and take-away foods	_	_	Hip:0.0013 (-0.008-0.0033) LS:-0.001 (-0.0029-0.0009)	Age, height, energy intake, smoking, sport, walking, education and calcium intake
								Pattern 2	Vegetables (potatoes, carrot, peas, and beans, brassica vegetables, zucchini, and squash), red meat, butter, and cream	_	_	Hip:-0.0009 (-0.003-0.0012) LS: -0.001 (-0.0029-0.0009)	
								Pattern 3	Leafy vegetables, tomato and tomato products, milk and yogurt (<1% fat), fruit, cheese, eggs, and fish	_	_	Hip: -0.0006 (-0.0025-0.0013) LS:-0.0004 (-0.0022-0.0015)	
								Pattern 4	Legumes, seafood, seeds and nuts, wine, rice and rice dishes, and other vegetables	_	_	Hip:0.0022 (0.0001-0.0044) LS:0.0037 (0.0018-0.0056)	
								Pattern 5	Chocolate, confectionary, and added	_	_	Hip:0.0002 (-0.0019-	

									sugar, fruit drinks and cordials, and dairy milk and yogurt (>1% fat)			0.0022) LS:-0.0021 (-0.004—0.0002)	
AC Hardcastle, 2011	Scotland	Cross-sectional	European Journal of Clinical Nutrition	F (50-59)	3236	FFQ	PCA	processed food	Processed foods, with cakes and desserts	_	_	FN:-0.009 (-0.013—0.004) LS:-0.008 (-0.013—0.003)	Unadjusted
								snack food	Confectionery, crisps or nuts and sauces	_	_	FN:-0.007 (-0.013—0.003) LS:-0.008 (-0.013—0.003)	
								healthy diet	Fruit, vegetables and rice or pasta	_	_	No association	
								bread and butter	Bread and fats or oils	_	_	No association	
								fish and chips	Fish, fish dishes, potatoes, bread and fats or oils	_	_	No association	
Seon-Joo Park, 2012	Korea	cohort	Osong Public Health Res Perspect	F (40-69)	1725	FFQ	PCA	traditional	Rice, kimchi, vegetables	**Osteoporosis** Radius:1.46(1-2.13) Tibia:1.82(1.12-2.96)	_	_	Age, residual area, exercise, passive smoking.
								Dairy	Milk, dairy products, green tea	Radius:0.63(0.42-0.93) Tibia:0.56(0.35-0.9)	_	_	
								Western	Sugar, fat, bread	Radius:1.46(1.02-2.1) Tibia:1.46(0.91-2.33)	_	_	
Claire R. Whittle, 2012	Northern Ireland	cohort	British Journal of Nutrition	M& F (20-25)	489	7 day diet history	PCA	healthy	fruit, vegetables, brown bread, rice and pasta	_	M,LS,Q1:1.22±0.159 M,LS,Q5:1.251±0.132 M,FN,Q1:1.121±0.171 M,FN,Q5:1.132±0.152 F,LS,Q1:1.193±0.124 F,LS,Q5:1.219±0.09	_	Unadjusted

								Traditional	White bread, fats and hot drinks	_	F,FN,Q1:1.045±0.134 F,FN,Q5:1.026±0.126 M,LS,Q1:1.239±0.154 M,LS,Q5:1.27±0.133 M,FN,Q1:1.125±0.168 M,FN,Q5:1.171±0.16	_	
								Social	Alcohol	_	F,LS,Q1:1.179±0.112 F,LS,Q5:1.205±0.103 F,FN,Q1:1.057±0.18 F,FN,Q5:1.084±0.125 M,LS,Q1:1.235±0.147 M,LS,Q5:1.278±0.145 M,FN,Q1:1.124±0.168 M,FN,Q5:1.191±0.172	_	
								Refined (men)	Puddings, crisps, chips, confectionery, chocolate and soft drinks	_	F,LS,Q1:1.166±0.106 F,LS,Q5:1.199±0.125 F,FN,Q1:1.055±0.144 F,FN,Q5:1.053±0.136 M,LS,Q1:1.259±0.133 M,LS,Q5:1.249±0.145 M,FN,Q1:1.139±0.149 M,FN,Q5:1.143±0.163	_	
								Nuts and meat (women)	Nuts, chocolate, red meat, meat dishes and poultry	_	F,LS,Q1:1.178±0.132 F,LS,Q5:1.211±0.118 F,FN,Q1:1.009±0.148 F,FN,Q5:1.073±0.159	_	
Mohsen Karamati, 2012	Iran	Cross-sectional	Calcif Tissue Int	F (50-85)	154	FFQ	PCA	Factor 1	High-fat dairy products, organ meats, red or processed meats and non-refined cereals	**Low _ BMD** LS:2.29(1.05-4.96) FN:1.84(0.87-3.88)	LS,C1:0.86±0.14 LS,C2:0.88±0.2 FN,C1:0.67±0.1 FN,C2:0.86±0.11	_	age, BMI, physical activity and parity, smoking, education, fragility fracture history, history of HRT, supplement intake, anti-receptive drug use, age at menarche and relative accuracy of energy reporting.
								Factor 2	French fries,	LS:0.73(0.35-	LS,C1:0.89±0.2	_	

									mayonnaise, sweets and desserts, and vegetable oils	1.54) FN:2.83(1.31-6.09)	LS,C2:0.85±0.15 FN,C1:0.69±0.11 FN,C2:0.65±0.1		
								Factor 3	Hydrogenated fats, pickles, eggs and soft drinks	LS:0.67(0.33-1.44) FN:0.75(0.36-1.56)	LS,C1:0.87±0.2 LS,C2:0.87±0.15 FN,C1:0.65±0.1 FN,C2:0.69±0.11	_	
								Factor 4	Vegetables, low-fat dairy products, fruits and fruit juices, legumes and fish, and low intakes of salt	LS:0.72(0.35-1.5) FN:0.9(0.44-1.86)	LS,C1:0.85±0.14 LS,C2:0.88±0.2 FN,C1:0.67±0.1 FN,C2:0.68±0.11	_	
								Factor 5	Condiment and potatoes and low intake of refined cereals	LS:0.68(0.31-1.46) FN:0.76(0.35-1.63)	LS,C1:0.86±0.15 LS,C2:0.88±0.19 FN,C1:0.67±0.11 FN,C2:0.67±0.1	_	
								Factor 6	Snacks, tea and coffee, poultry and nuts	LS:0.82(0.39-1.73) FN:1.01(0.49-2.1)	LS,C1:0.86±0.16 LS,C2:0.88±0.19 FN,C1:0.69±0.11 FN,C2:0.66±0.1	_	
Fang-fang Zeng, 2013	China	Case- control	J Clin Endocrinol Metab	M&F (55-80)	1162	FFQ	PCA	Healthy	Fruit, vegetables, eggs, and freshwater fish	**Fracture** Overall:0.42(0.24-0.73) M:0.1790.03-0.86) F:0.42(0.21-0.85)	_	_	BMI, education, household income, house orientation, smoking, alcohol drinking, tea drinking, physical activity, daily energy intake, family history of fractures, calcium supplement use, and multivitamin use.
								Prudent	Nuts, mushrooms,	Overall:0.51(0.28-0.9)	_	_	

									algae, sea foods, and white vegetable	M:0.93(0.15-5.79) F:0.42(0.21-0.83)			
								Traditional	Chinese herbal tea, double-stewed soup, processed meat and fish,animal organ meat	Overall:0.83(0.49-1.83) M:0.7(0.16-3.07) F:0.72(0.36-1.44)	_	_	
								High fat	red meat, poultry with the skin, animal organ meat, and cooking oil	Overall: 2.25(1.38-3.69) M:4.5(1.2-16.95) F:1.72(0.96-3.08)	_	_	
S Shin, 2013	Korea	Cross-sectional	British Journal of Nutrition	F (≥50)	3735	24-h recall	PCA	Factor 1	Meat, alcohol and sugar	**Osteoporosis** LS:0.78(0.57-1.07) FN: 0.89(0.6-1.31)	_	_	BMI, energy intake, parathyroid hormone and serum 25-OH-D, alcohol intake, moderate physical activity, supplement use, oral contraceptive use.
								Factor 2	Vegetables and soya sauce	LS:1.22(0.86-1.74) FN:0.79(0.51-1.21)	_	_	
								Factor 3	White rice, kimchi and seaweed	LS:1.4(1.03-1.9) FN:1.14(0.8-1.64)	_	_	
								Factor 4	dairy and fruit	LS:0.47(0.34-0.65) FN:0.8(0.54-1.19)	_	_	
S Shin, 2014	Korea	cohort	European Journal of Clinical Nutrition	M&F (≥30)	1818	3-day food record	PCA	Factor 1	Rice and kimchi	**Low _ BMD** M:0.62(0.35-1.1) F:1.05(0.67-1.67)	Pelvis,Q1:1.091±0.154 Pelvis,Q4:1.112±0.148 LS,Q1:0.953±0.169 LS,Q4:0.968±0.16	_	Age, body size, energy intake, smoking, alcohol

													consumption, physical activity, for women: menopausal status.
								Factor 2	Eggs, meat and flour	M:0.65(0.36-1.18) F:1.06(0.65-1.72)	Pelvis,Q1:1.062±0.155 Pelvis,Q4:1.119±0.137 LS,Q1:0.927±0.18 LS,Q4:0.964±0.136	_	
								Factor 3	fruit, milk and whole grains	M:0.38(0.22-0.67) F:0.45(0.28-0.72)	Pelvis,Q1:1.079±0.146 Pelvis,Q4:1.12±0.148 LS,Q1:0.937±0.159 LS,Q4:0.989±0.174	_	
								Factor 4	Fast food and soda	M:1.47(0.81-3.09) F:0.8(0.5-1.29)	Pelvis,Q1:1.08±0.145 Pelvis,Q4:1.115±0.137 LS,Q1:0.933±0.154 LS,Q4:0.973±0.149	_	
Zhaoli Dai, 2014	Singapore	cohort	The Journal of Nutrition	M&F (45-74)	63154	FFQ	PCA	Vegetable-Fruit-Soy	Vegetable, Fruit, Soy foods	**Fracture** Overall:0.66(0.55-0.78) M:0.57(0.41-0.8) F:0.7(0.57-0.76)	_	_	Age at recruitment, year of recruitment, gender, dialect group, BMI, education, total energy intake, smoking, physical activity, history of diabetes and strok, for women: menopausal status and use of HRT.
								Meat-dim-sum	Meat and refined starchy foods	Overall:1.15(0.95-1.4) M:1.12(0.78-1.6) F:1.24(0.98-1.56)	_	_	