ORIGINAL ARTICLE

The reverse association of dietary antioxidant index with osteoporosis in postmenopausal iranian women: A case–control study

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Background: Osteoporosis, a prevalent bone malady, is prevalent in Iran. Several studies have represented the role of dietary antioxidants on osteoporosis. The dietary antioxidant index (DAI) is a valid and reliable index, which indicates a comprehensive view of dietary antioxidant capacity. This study aimed to survey the relationship of the DAI with the risk of osteoporosis in postmenopausal women in Iran. This research aimed to examine the association between the DAI and the risk of osteoporosis among postmenopausal women in Iran. **Materials and Methods:** In this case–control study, 440 postmenopausal women (220 cases and 220 controls) were enrolled. The dietary intake of contributors was evaluated using a 147-item food frequency questionnaire. To estimate the DAI, the amount of six antioxidant micronutrients such as Vitamins A, C, and E, selenium, manganese, and zinc was standardized. Then, the DAI was estimated by collecting the standardized consumption of these antioxidant micronutrients. **Results:** Our findings represented the participants in the first (crude odds ratio [OR] = 1.79, 95% confidence interval [CI]: 1.13–2.85, P = 0.013) and second (crude OR = 1.60, 95% CI: 1.01–2.55, P = 0.043) tertiles of the DAI scores had significantly higher odds of osteoporosis compared to those in the third one; while after modifying for confounding factors, this significant reverse relationship was observed just between women in the first and third tertiles of the DAI scores (adjusted OR = 1.90, 95% CI: 1.34–3.18, P = 0.015). **Conclusion:** The consequence of this study suggested that adherence to a diet rich in antioxidant compounds may have protective effects against osteoporosis.

Key words: Antioxidants, bone resorption, inflammation, osteoporosis, oxidative stress

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INTRODUCTION

Osteoporosis, which is recognized as a prevalent bone malady, is represented by reduced bone density.[1] Postmenopausal osteoporosis is a serious health-care issue that directly affects the life quality.[2] This disease and bone fractures are related to noticeable morbidity, mortality, and health-care cost worldwide.[2] Approximately, a quarter and a half percent of postmenopausal Iranian women suffer from lumbar spine osteoporosis and osteopenia, respectively.[3] According to the increasing prevalence of this disorder and its complex treatment,[2] finding new procedures that help sustain optimal bone mass through the postmenopausal period is significantly essential to prevent osteoporosis.

Osteoporosis is affected by a comprehensive interaction among genetic, environmental, and nutritional factors.[4] Based on previous studies, chronic inflammation could raise the risk of this bone disorder.[5] Pro-inflammatory cytokines are released from a variety of cells. Interleukin (IL)-1 and tumor necrosis factor-α (TNF-α) are known as the main triggers for osteoclast activation, and IL-6 cooperates with other bone-absorbing agents.[6] Moreover, reducing circulating estrogen levels during

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menopause may be associated with increased production of IL-1 and TNF-α levels.[7] According to previous evidence, dietary habits could influence an individual's inflammatory response; for example, increased consumption of dietary fiber could be correlated with lower plasma levels of some pro-inflammatory cytokines.[8] Hence, the dietary components could regulate inflammation by pre-inflammatory and anti-inflammatory mechanisms.[8]

It was reported that an enriched diet with antioxidants, like the Mediterranean diet, may have positive effects on the inflammatory processes and the bone mineral cycle, and also a reverse relation between following an enriched diet with antioxidants and pro-inflammatory cytokines has been indicated.[9] Based on the previous papers, adherence to a diet that is rich in antioxidant compounds might have a suitable influence on bone protection.[10,11]

The content of the antioxidant diet is estimated by the dietary antioxidant index (DAI).[12] In fact, the DAI can categorize dietary intakes into two main groups: antioxidative or oxidative diets.[12] Although, the determination of the sensitivity and specificity of this index requires more examination and validation.[12] Several literatures have reported their significant findings about this index.[12,13] The results of Wright *et al.*'s study[12] showed that dietary antioxidants decreased lung cancer among male smokers.

This study aimed to evaluate the relationship of the DAI with the risk of osteoporosis among postmenopausal Iranian women. Our hypothesis was that the DAI might have a reverse association with the risk of developing osteoporosis.

MATERIALS AND METHODS

Study population

This case–control study was performed during 2018–2019 in Tehran, Iran. In general, 440 postmenopausal women (220 cases and 220 controls) in the age of 45–85 years, who were referred to Shariati Hospital, some private clinics, and health-care centers, were enrolled in the current study. A convenience sample method, which is a nonprobability sampling technique, was utilized to select the participants. The purpose of the study was described to all individuals, and they signed written informed consent. Then, the participants' information was gathered by a qualified expert. Menopause was described as a lack of the menstrual period throughout at least 12 months. Osteoporosis in the patients was determined by dual-energy X-ray absorptiometry,[11] and it was based on the diagnosis of a rheumatology specialist. This study was accepted by the Ethics Committee of the Islamic Azad University, Science and Research Branch of Tehran, Iran (IR.IAU.SRB.REC.1396.119).

Inclusion and exclusion criteria

The inclusion criteria included: not following a specific diet during the past year; not taking supplements or drugs that influence the bone metabolisms such as anticoagulants, glucocorticoids, thyroxin, calcitonin, antacids, Vitamin D (15 IU/day), calcium (500 mg/day), multivitamins, glucosamine, omega-3, and bisphosphonate; not have been diagnosed with endocrine, rheumatoid, gastrointestinal, or renal diseases which effect on bone mineral density (BMD) status; and not using hormone therapy. Furthermore, the exclusion criteria were as follows: individuals who did not answer more than 20% of the questions of the Food Frequency Questionnaire (FFQ), and women with a total energy intake of <800 kcal/day or >4200 kcal/day.[14]

Data collection

All the participants completed the valid questionnaires through the interviews, and an expert nutritionist evaluated all measurements. The general questionnaire collected data about age, physical activity, education, alcohol drinking, breastfeeding, and taking contraceptive. Besides, a valid physical activity questionnaire was performed to estimate the physical activity status, that was prepared in Europe, and its validity was approved by Daily Activity Questionnaire and "CSA Accelerometer Ambulatory Monitor" system (Model 7164), that it was confirmed among 2500 Danish men and women (20–60 years).[15] The physical activity levels were assessed based on metabolic equivalent hours per week (metabolic equivalent minute-minute/week).[15] The validity and reliability of this questionnaire were confirmed in Iran.[16]

Body weight was calculated using digital scales (Tefal) after the participants were wearing lightweight clothing. Body weight was recorded within 0.1 kg of precision. The height was assessed by a tape meter and was reported within 0.1 cm of precision, while the contributors were standing and removing their shoes. The body mass index (BMI) was estimated for each participant using this formula: body weight (kg)/(height [m])^2.

Assessment of dietary intake

The dietary intake of the participants was obtained by a 147-item FFQ,[17] and its validity and reliability were proved in Iran.[17] The frequency consumption of each item was reported in the previous year regarding its portion size. The reported frequency for each food item in the FFQ was changed to a gram per day by household measures.[18]

Assessment of the dietary antioxidant index

According to FFQ data, the DAI was estimated for each contributor. We utilized the method that was created by Wright *et al.*[12] To estimate this index, the amount of six antioxidant micronutrients, such as Vitamin A, Vitamin C, Vitamin E, selenium, manganese, and zinc, was

standardized by deducting the total mean and divided by the total standard deviation (SD). Then, the DAI was estimated by collecting the standardized consumption of those, as indicated below:[12,13]

$$DAI = \sum_{i=1}^{n=6} \frac{\text{Individual Intake - Mean}}{SD}$$

Statistical analysis

To describe the qualitative data, we used the frequency distribution indices. Furthermore, the mean and SD were reported to describe the quantitative variables. To compare the mean of normally distributed variables between two groups, we used the independent samples *t*-test, and we used one-way ANOVA to compare the mean of normally distributed quantitative variables among more than two groups. In addition, the Mann–Whitney test was utilized to compare the differences between nonnormal variables between the two groups. Besides, the Chi-square test was performed to assess the association among categorical factors. The odds ratio (OR) and 95% confidence intervals (CI) were computed using the binary logistic regression for estimating the relation of the DAI with the risk of osteoporosis, adjusted for physical activity, BMI, and alcohol drinking. The SPSS software (version 26.0), IBM Corporation,Armonk,NY,USA) carried out all statistical analyses. The level of significance was set at 0.05.

RESULTS

The general characteristics of the individuals are represented in Table 1. The mean age was not significantly different between the two groups (55.80 ± 6.65 vs. 55.56 ± 6.01 years, P = 0.685). The mean DAI score, which represents adherence to an antioxidant diet, was reported to be significantly higher in the control group in comparison with cases (P < 0.001). The mean DAI score was 0.82 (SD = 5.86) and −0.81 (SD = 2.33), respectively, in controls and cases. Furthermore, controls had significantly higher physical activity than cases (P < 0.001). However, BMI (P = 0.011) and alcohol consumption (P < 0.001) were significantly higher in cases compared to controls.

Table 2 compares the mean dietary intake of nutrients between the two groups. The mean consumption of dietary carbohydrates (P = 0.217), cholesterol (P = 0.085), Vitamin D (P = 0.777), and Vitamin B12 (P = 0.110) was not significantly different in cases and controls. The reported findings in Table 2 indicate that the intake of total fat (crude OR = 1.018; 95% CI = 1.012–1.023), saturated fatty acid (crude OR = 1.019; 95% CI = 1.006–1.032), monounsaturated fatty acid (crude OR = 1.035; 95% CI = 1.021–1.048), polyunsaturated fatty acid (PUFA) (crude OR = 1.047; 95% CI = 1.027–1.067), and Vitamin E (crude OR = 1.062; 95% CI = 1.029–1.095) had a significantly negative association with the risk of osteoporosis.

Table 3 shows the dietary consumption of nutrients in different tertiles of the DAI scores. According to these results, individuals in the highest tertile had significantly more nutrient intake than those in the lowest tertile (P < 0.001).

The association between the DAI tertiles and osteoporosis was reported in Table 4 in both crude and adjusted models. The crude model shows that the odds of having osteoporosis for women in the second tertile of the DAI scores were about 1.6 times of the same odds for those in the third tertile of the DAI (crude OR = 1.60, 95% CI: 1.01–2.55, P = 0.043), and the women in the first tertile of the DAI scores had an odds of

Table 1: General characteristics of the sample in the case and control groups

Variables	Case (*n*=220)	Control (*n*=220)	*P*†,‡
Age (years)	55.80±6.65*	55.56±6.01	0.685††
Physical activity (METs h/day)	1531.86±830.59	2300.00±2043.76	<0.001‡‡
BMI (kg/m^2)	29.09±4.13	27.91±5.46	0.011††
DAI	−0.81±2.33	0.82±5.86	<0.001††
Education			
Less than undergraduate	180 (81.8)**	166 (75.5)	0.264††
Undergraduate	38 (17.3)	51 (23.2)	
Postgraduate	2 (0.9)	3 (1.4)	
Breastfeeding			
Yes	200 (90.9)	190 (86.4)	0.133††
No	20 (9.1)	30 (13.6)	
OCP			
Yes	76 (34.5)	71 (32.3)	0.542††
No	144 (65.5)	149 (67.7)	
Alcohol use			
Yes	29 (13.2)	5 (2.3)	<0.001††
No	191 (86.8)	215 (97.7)	

*Mean±SD; **_n_ (%); †Independent sample *t*-test was used for continuous variables, and Chi-square test was used for categorical variables; ‡*P*<0.05 was considered statistically significant; ††*t*-test; ‡‡Mann–Whitney test. METs=Metabolic equivalents; BMI=Body mass index; DAI=Dietary antioxidant index; OCP=Oral contraceptive pill; SD=Standard deviation

Table 2: Daily intake of nutrients in the case and control groups

Nutrients	Case	Control	Crude OR† (95% CI)	*P*‡
Energy intake (kcal/day)	2744.63±895.11*	2638.52±875.38	1.000 (1.000–1.000)	0.209
Protein (g/day)	83.95±22.65	91.81±32.02	0.991 (0.984–0.997)	0.005
Carbohydrate (g/day)	354.39±110.87	368.02±120.23	0.999 (0.997–1.001)	0.217
Total fat (g/day)	107.04±44.78	81.09±30.38	1.018 (1.012–1.023)	<0.001
Cholesterol (mg/day)	263.82±151.08	320.15±458.62	0.999 (0.998–1.000)	0.085
Saturate fatty acid (g/day)	32.66±15.02	28.19±16.55	1.019 (1.006–1.032)	0.003
MUFA (g/day)	37.49±16.22	29.12±16.70	1.035 (1.021–1.048)	<0.001
PUFA (g/day)	23.47±11.19	18.34±10.16	1.047 (1.027–1.067)	<0.001
Vitamin A (RAE/day)	697.78±439.03	851.59±830.67	1.000 (0.999–1.000)	0.016
Alpha-carotene (mg/day)	461.21±804.11	1101.27±1278.98	0.999 (0.999–1.000)	<0.001
Beta-cryptoxanthin (mg/day)	142.08±166.34	385.51±398.31	0.995 (0.994–0.996)	<0.001
Vitamin C (mg/day)	98.92±80.73	193.56±190.03	0.992 (0.989–0.994)	<0.001
Vitamin D (μg/day)	2.57±2.08	2.63±2.81	0.989 (0.917–1.067)	0.777
Vitamin E (mg/day)	15.87±5.94	13.45±6.99	1.062 (1.029–1.095)	<0.001
Vitamin K (μg/day)	149.75±159.19	263.79±327.84	0.997 (0.996–0.998)	<0.001
Thiamin (mg/day)	2.15±0.71	2.55±1.34	0.662 (0.533–0.821)	<0.001
Riboflavin (mg/day)	2.16±0.83	2.54±1.37	0.715 (0.588–0.870)	<0.001
Niacin (mg/day)	24.93±8.14	28.26±16.61	0.977 (0.960–0.995)	0.008
Vitamin B6 (mg/day)	1.62±0.53	2.34±1.26	0.245 (0.171–0.352)	<0.001
Total folate (μg/day)	536.44±152.39	665.85±363.43	0.997 (0.996–0.998)	<0.001
Vitamin B12 (μg/day)	6.02±4.47	5.14±6.86	1.032 (0.991–1.075)	0.110
Biotin (μg/day)	31.09±13.47	46.50±27.41	0.954 (0.941–0.966)	<0.001
Calcium (mg/day)	1040.53±415.37	1463.08±2201.93	0.999 (0.999–0.999)	0.006
Iron (mg/day)	18.67±5.95	24.27±29.03	0.953 (0.929–0.977)	0.005
Magnesium (mg/day)	404.25±137.98	575.79±345.56	0.996 (0.995–0.997)	<0.001
Zinc (mg/day)	12.07±3.87	16.22±12.32	0.897 (0.862–0.935)	<0.001
Manganese (mg/day)	6.66±2.66	9.77±10.35	0.859 (0.812–0.908)	<0.001
Selenium (mg/day)	136.03±54.66	162.18±107.02	0.996 (0.993–0.998)	0.001

*Mean±SD; †Based on logistic regression; ‡Independent sample *t*-test was used for continuous variables. MUFA=Monounsaturated fatty acid; PUFA=Polyunsaturated fatty acid; RAE=Retinol activity equivalent; OR=Odds ratio; CI=Confidence interval; SD=Standard deviation

about 1.8 times for osteoporosis compared to those in the third tertile (crude OR = 1.79, 95% CI: 1.13–2.85, *P* = 0.013). Besides, in the adjusted model, the odds of osteoporosis for participants in the first tertile of the DAI scores were about 1.9 times of the same odds for those in the third one (adjusted OR = 1.90, 95% CI: 1.13–3.18, *P* = 0.015); while there was not any significant association between the participants in the second and third tertiles of the DAI scores (adjusted OR = 1.33, 95% CI: 0.78–2.27, *P* = 0.283).

DISCUSSION

The present research showed a significant reverse relation of DAI with the risk of osteoporosis among postmenopausal women. Based on our findings, the mean consumption of antioxidant compounds, such as Vitamins A and C, selenium, zinc, manganese, and alpha-carotene, was significantly reported higher in controls compared to cases. The present article is the first one which surveys the relationship between the DAI and the risk of osteoporosis.

Multiple literatures have supported the useful effects of dietary antioxidants on bone health. Kim *et al*.[19] evaluated the correlation of dietary total antioxidant capacity (TAC) with the risk of osteoporosis within postmenopausal Korean women. According to their findings, the dietary TAC had a reverse link with the risk of osteoporosis. Furthermore, a positive relation was indicated between bone density and dietary TAC among both pre- and postmenopausal women. In one cohort study,[20] an opposite association was shown between higher dietary nonenzymatic antioxidant capacity intake and a lower risk of hip fracture among elderly men and women. De França *et al*.[21] did not observe any correlation between DAQs and BMD in postmenopausal women; although, a reverse association was reported between Vitamin A intake and BMD of the lumbar spine. However, when the other antioxidants were combined, this correlation did not remain significant. Moreover, they did not use any biomarker that may affect the reliability of participants' antioxidant intake. Hence, it seems that following an antioxidant diet could have a useful effect on the risk of osteoporosis.

According to previous evidence, oxidative stress may lead to osteoporosis due to chronic inflammation.[22] Increasing the level of free radicals leads to oxidative stress; hence,

Table 3: Dietary intake of nutrients in different tertiles of the dietary antioxidant index

Nutrients	Total (*n*=440), mean±SD	Tertiles of DAI			*P*†
		T1 (DAI ≤−1.77) (*n*=145)	T2 (−1.77 <DAI <0.52) (*n*=145)	T3 (DAI ≥0.52) (*n*=150)	
Energy intake (kcal/day)	2691.57±885.88	1832.50±535.78	2694.95±577.49	3518.75±552.71	<0.001
Protein (g/day)	87.88±29.51	62.97±16.64	91.19±18.64	108.75±30.15	<0.001
Carbohydrate (g/day)	361.20±115.72	256.18±72.65	363.35±72.23	460.65±92.82	<0.001
Total fat (g/day)	94.07±40.37	65.91±30.49	99.55±34.60	115.98±38.23	<0.001
Cholesterol (mg/day)	291.99±342.21	185.34±93.34	285.22±147.81	401.62±540.63	<0.001
Saturate fatty acid (g/day)	30.43±15.94	19.42±9.61	31.74±12.39	39.79±17.42	<0.001
MUFA (g/day)	33.31±16.97	21.64±10.16	33.83±12.76	44.07±18.48	<0.001
PUFA (g/day)	20.91±10.98	13.98±7.31	20.98±9.20	27.53±11.45	<0.001
Vitamin A (RAE/day)	774.68±668.06	395.69±200.63	726±344.61	1188.01±920.43	<0.001
Alpha-carotene (mg/day)	781.24±1114.11	425.65±511.62	729.14±974.32	1175.33±1484.80	<0.001
Beta-cryptoxanthin (mg/day)	263.80±328.32	162.70±144.73	213.51±214.39	410.14±467.93	<0.001
Vitamin C (mg/day)	146.24±153.33	84.44±45.68	124.38±81.25	227.22±223.79	<0.001
Vitamin D (μg/day)	2.60±2.47	1.47±1.31	2.61±1.79	3.68±3.28	<0.001
Vitamin E (mg/day)	14.66±6.60	10.11±4.44	14.48±4.74	19.23±6.80	<0.001
Vitamin K (μg/day)	206.77±263.66	112.52±72.25	189.81±165.90	314.28±390.67	<0.001
Thiamin (mg/day)	2.35±1.09	1.58±0.50	2.20±0.52	3.24±1.25	<0.001
Riboflavin (mg/day)	2.35±1.15	1.48±0.50	2.27±0.62	3.27±1.29	<0.001
Niacin (mg/day)	26.60±13.17	18.12±5.86	25.09±5.97	36.26±16.65	<0.001
Vitamin B6 (mg/day)	1.98±1.03	1.34±0.36	1.86±0.43	2.71±1.37	<0.001
Total folate (μg/day)	601.14±285.78	429.22±121.60	567.17±127.86	800.18±375.18	<0.001
Vitamin B12 (μg/day)	5.58±5.80	2.97±1.49	5.29±2.96	8.38±8.60	<0.001
Biotin (μg/day)	38.79±2291	23.91±9.09	35.54±11.70	56.33±28.26	<0.001
Calcium (mg/day)	1251.80±153.33	769.57±302.76	1164.54±397.04	1802.32±2594.60	<0.001
Iron (mg/day)	21.47±21.12	13.38±3.75	19.03±3.79	31.63±33.37	<0.001
Magnesium (mg/day)	490.02±276.48	300.40±75.02	447.08±95.58	714.83±351.12	<0.001
Zinc (mg/day)	14.14±9.35	8.74±2.40	13.09±2.70	20.39±13.28	<0.001
Manganese (mg/day)	8.21±7.71	5.02±1.85	7.03±2.26	12.45±11.72	<0.001
Selenium (mg/day)	149.11±85.88	91.00±29.16	135.41±39.39	218.51±105.32	<0.001

†One-way ANOVA was used for continuous variables. MUFA=Monounsaturated fatty acid; PUFA=Polyunsaturated fatty acid; RAE=Retinol activity equivalent; DAI=Dietary antioxidant index; SD=Standard deviation

Table 4: Logistic regression results for assessing the association between the dietary antioxidant index tertiles and risk of osteoporosis

Variable	Category	Crude OR† (95% CI)	*P*‡	Adjusted OR†† (95% CI)	*P*‡
DAI tertiles	1	1.79 (1.13–2.85)	0.013	1.90 (1.13–3.18)	0.015
	2	1.60 (1.01–2.55)	0.043	1.33 (0.78–2.27)	0.283
	3	Reference category			

†Based on logistic regression; ‡*P*<0.05 was considered statistically significant; ††Based on logistic regression adjusted for physical activity; BMI and alcohol consumption. BMI=Body mass index; DAI=Dietary antioxidant index; OR=Odds ratio; CI=Confidence interval

the antioxidant defense system is disabled to remove these oxidants.[23]

The extreme levels of reactive oxygen species created by various environmental factors or through normal cellular metabolisms can lead to oxidative stress.[24] Oxidative stress could have a key role in bone loss through different mechanisms, including elevation apoptosis in osteoblast and osteocyte,[25] and reducing the amount of bone growth by Wnt/β-catenin signaling.[26]

Oxidative stress may have an association with chronic inflammation.[22] According to previous studies, chronic inflammation may be one of the most important factors of osteoporosis.[5] Inflammatory cytokines may increase bone loss through direct and indirect processes. In the direct process, they exert their effects by inducing osteoclast formation and maturation; however, in the other process, they promote the ligand-receptor activator of nuclear factor kappa-B ligand release.[27] Apart from that, more consumption of total fat and saturated fatty acid could increase the levels of inflammatory cytokines; while PUFA, especially n-3 PUFAs, has an important role in decreasing them.[28] Therefore, it could be hypothesized that various fats might have different effects on the prevention and creation of osteoporosis.

Decreased estrogen levels after menopause might be an important factor to release inflammatory cytokines.[7] Previous

studies showed that inflammatory cytokines, as stimuli factors for producing C-reactive protein,[29] may contribute to reduced BMD through stimulating bone resorption.[6]

Based on previous evidence, increased adherence to an enriched antioxidant diet may contribute to greater BMD.[10] Some papers reported that consuming 240–400 g of fruits and vegetables per day is related to higher BMD and lower fracture risk.[10] Karamati *et al*.[11] showed that adherence to dietary patterns, which are rich in total fiber, folate, potassium, β-carotene, magnesium, copper, and Vitamins A, C, K, and B6, had a significant relationship with BMD in postmenopausal Iranian women. They suggested that more consumption of fruits and vegetables might have profitable impacts on bone health. Results of a cohort study[10] showed that the risk of hip fracture was significantly higher in the group with consumption of ≤1 serving/day of fruits and vegetables compared to the moderate consumption (>3 and ≤5 serving/day).[30]

Until now, no research has not investigated the correlation of the DAI with the risk of osteoporosis. However, the previous studies surveyed the association between the DAI and different diseases, like gastric cancer.[30]

Strengths and limitations

To the best of our knowledge, this article is the first study investigating the relationship between the DAI and the risk of osteoporosis. We calculated the antioxidant capacity of the diet using the DAI, which is a valid and reliable index. This indicator represents a comprehensive view of antioxidant status. The second strength of this study was using a validated FFQ for collecting dietary intake data, which could correctly describe previous long-term dietary intake.

Our study has some limitations. Recall bias and select bias are the inherent limitations of case–control studies. However, we used a validated FFQ to reduce the recall bias. As well, we tried to reduce interview bias by training the expert interviewer.

CONCLUSIONS

Our findings indicated a significant reverse relationship between the DAI and the risk of osteoporosis among postmenopausal women. This study's results suggested that adherence to a diet rich in antioxidant compounds may have protective effects against osteoporosis. More studies, especially prospective cohort studies, are essential to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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