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Association Between Circulating Antioxidant Concentrations and Bone Mineral Density in an Adult Population

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Running title: Carotenoids and bone mineral density

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Background: Evidence regarding the relationship between various circulating antioxidants and bone mineral density (BMD) remains controversial.

Objective: This study aimed to evaluate the associations between circulating antioxidant levels and BMD in an older adult population.

Methods: We included 398 participants from the midlife in the United States (MIDUS) study who underwent BMD measurements (g/cm²) of lumbar spine (L1-L4) and total femur, as well as circulating antioxidant concentrations (umol/L). The relationships between blood antioxidants (total lutein, zeaxanthin, alpha-carotene, 13-cis-beta-carotene, all trans-beta-carotene, gamma-tocopherol, alpha-tocopherol, total lycopene, beta-cryptoxanthin and retinol) and BMD value in lumbar spine and femur were examined.

Results: Univariate correlation analysis revealed positive associations between four blood antioxidants (total lutein, 13-cis-beta-carotene, alpha-carotene and all trans-beta-carotene) and BMD value at both sites (lumbar spine and femur). After adjusting for demographic characteristics and lifestyle factors, After adjusting for demographic characteristics and lifestyle factors, sensitivity analyses demonstrated significant associations of total lutein (P for linear trend = 0.038), 13-cis-beta-carotene (P for linear trend = 0.044), and alpha-carotene (P for linear trend = 0.019) with lumbar spine BMD. For femoral BMD, 13-cis-beta-carotene (P for linear trend = 0.010) and alpha-carotene (P for linear trend = 0.007) remained significantly associated. Trend tests suggested that these associations weakened as antioxidant levels increased.

Conclusions: Higher circulating levels of total lutein, 13-cis-beta-carotene, and alpha-carotene were strongly associated with increased BMD in the lumbar spine and femur. Further prospective studies are warranted to confirm these findings.

Keywords: antioxidants, carotenoids, vitamins, bone density, femur, lumbar spine

INTRODUCTION

Osteoporosis is a systemic bone disease caused by multiple factors, characterized by decreased in bone mineral density (BMD) and bone strength [1, 2], leading to an increased risk of fractures [3, 4]. Existing studies have reported that individuals over 40 years of age in Asia and other regions might suffer from osteoporosis, especially among postmenopausal women [5]. Common fractures, such as vertebral compression fractures and femoral fractures, occur most frequently and are attributed to high osteoporosis risk [6-8]. Therefore, identifying strategies to prevent osteoporosis and enhance bone density remains crucial for improving the quality of life in middle-aged and older populations.

Antioxidants, including carotenoids and vitamins, play an important role in bone health [9]. It is widely recognized that antioxidants are involved in osteoblast/osteoclast activity, oxidative stress, and adiposity-related metabolic inflammation, potentially influencing BMD and bone strength [10-13]. For instance, β-carotene can attenuate lipopolysaccharide-induced endoplasmic reticulum stress and mitochondrial oxidative damage [14]. Lycopene may help prevent bone loss in postmenopausal women by activating multiple signaling pathways [15]. A previous epidemiological study in the USA suggested that dietary vitamin B12 intake might benefit osteoporosis and fracture risk in elderly women [16, 17]. However, other studies have yielded inconsistent or even opposing conclusions [18-22]. A clinical study reported that elevated serum retinol levels were associated with an increased risk of low bone mass and osteoporotic fractures [23]. Some research indicated that dietary vitamin A intake could increase osteoclast proliferation and reduce BMD [18, 19]. Another randomized clinical trial involving nearly 3000 participants found that daily vitamin B intake did not significantly reduce fracture risk [20]. A recent study showed no correlation between plasma folate or vitamin B12 concentrations alone and bone loss in 447 participants [21]. A cross-sectional analysis of 6481 South Korean individuals reported that higher dietary vitamin A intake was associated with lower BMD and increased fracture risk [22]. These inconsistent conclusions share a common limitation: most studies focused on only one or two antioxidants. This narrow focus hinders our understanding of the

potential relationships between multiple blood antioxidants and BMD or fracture risk in real-world settings. Furthermore, most human or animal studies used oral supplementation or dietary intake, making it difficult to determine actual circulating antioxidant levels.

Given this background, our study aimed to evaluate the associations between ten blood antioxidants (total lutein, zeaxanthin, alpha-carotene, 13-cis-beta-carotene, all-trans-beta-carotene, gamma-tocopherol, alpha-tocopherol, total lycopene, beta-cryptoxanthin, and retinol) and BMD in the lumbar spine (L1–L4) and total femur in a middle-aged and elderly population. We hope to provide additional evidence to clarify this controversial topic.

Methods

Participants

The Midlife in the United States (MIDUS) study containing a total of 7,108 noninstitutionalized adults was performed on 1995, and 4,963 individuals of them participated in the first follow-up between 2004 and 2006 in MIDUS II [24, 25]. During the MIDUS II period, 1,255 adult individuals completed a biomarker project containing demographic characteristics, lifestyle, disease history, physical examinations, blood antioxidants and BMD measurement [26]. Of these participants in the biomarker project (N=1,225), 398 adult individuals with complete data including blood antioxidants and BMD in lumbar spine and femur were enrolled into our analysis after excluding samples with missing variables (N=857), as described as in Figure 1. We freely extracted the MIDUS II data from ICPSR (www.icpsr.umich.edu/web/pages/ICPSR/) where the raw data is stored for free and each researcher can obtain it. The institutional review board of the MIDUS II Biomarker Project approved this study in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Blood antioxidants

The specific method for detecing blood antioxidants in the biomarker project has been

previously described [24-26]. Briefly, fasting blood samples were obtained from each participant before breakfast, and were then detected in the MIDUS Biocore Lab. A multiplex based assay (Bio-Rad Laboratories, Munich, Germany) for blood antioxidants including total lutein, zeaxanthin, alpha-carotene, 13-cis-beta-carotene, all trans-beta-carotene, gamma-tocopherol, alpha-tocopherol, total lycopene, beta-cryptoxanthin and retinol were measured, according to manufacturer's instructions. Data analysis was performed using Bio-Plex Manager software version 6.0. The within-batch coefficient of variation (CV%) ranged from 7.15 to 13.89.

BMD in lumbar spine (L1-L4) and total femur

The measurement procedures have also been previously described [24-26]. In summary, the BMD levels in the femur and lumbar spine from each participant were measured using dual-energy X ray absorptiometry (DXA) scans with Hologic 4500 (Hologic, Inc., Bedford, Massachusetts, USA) technology or GE Healthcare Lunar Prodigy (GE Healthcare, Madison, Wisconsin, USA). Reading of all DXA scans was performed centrally by physicians at the University of Wisconsin DXA center. Three times per week, and on all days on which scans were obtained, instruments were calibrated and phantom scan data were acquired. No densitometer shift or drift occurred during the course of this study. For BMD cross-calibration across the three clinical sites, a phantom was scanned 10 times on the densitometers at each of the three study sites. The linear regression equation developed from these calibration scans was used to correct BMD values from two of the three sites to make the data comparable across study sites. The recalibrated BMD values at the lumbar spine and left hip were reported in units of grams per square centimeters(g/cm2) [24-26].

Femoral neck axis length (FNAL), the distance along the femoral neck axis from the lateral margin of the base of the greater trochanter to the apex of the femoral head, and femoral neck width (FNW), the smallest thickness of the femoral neck along any line perpendicular to the femoral neck axis, were measured from the hip scans using software provided by the scanner manufacturers. Composite indices of femoral neck strength relative to load were created using the following formulas[24-26]: 1)

CSI=BMD×FNW/Weight; 2) BSI=(BMD×FNW^2)/(FNAL×Weight); and 3) ISI=(BMD ×FNW×FNAL)/(Height×Weight). These three bone strength indices were recorded in grams per kilogram meter (g/kg-m). All three indices were recorded in units of grams per kilogram per meter (g/kg-m). Because BMD was measured in grams per square centimeter, FNW and FNAL in centimeters, weight in kilograms, and height in meters, we scaled CSI and BSI by 100 to obtain values in units of grams per kilogram per meter (g/kg-m). CSI reflects the ability of the femoral neck to withstand an axial compressive load, BSI reflects its ability to withstand bending forces, and ISI reflects the ability of the femoral neck to absorb the potential energy in a fall from standing height.

Covariates

Covariates included age, gender, body mass index (BMI), smoking, drinking, regular exercise and medical history (ever diagnosed with arthritis, depression, diabetes, stroke, or cancer). Smoking was classified as "whether or not ever smoked cigarettes regularly" (yes/no). Drinking was defined as "Number of years drank that much (years)". Regular exercise was classified as "whether or not engage in regular exercise, or activity, of any type for 20 minutes or more at least 3 times/week". BMI was calculated as weight (kg) divided by height squared (m^2).

Statistical analysis

Statistical analyses were performed using EmpowerStats 5.2 (www.empowerstats.com; X&Y solutions, Inc., Boston MA). Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and are presented as mean ± standard deviation (SD). Categorical variables are expressed as percentages (%). Each antioxidant was divided into tertiles (Q1–Q3). Univariate correlation analysis was first conducted to explore relationships between blood antioxidants and BMD. Adjusted linear regression models were then used to evaluate independent associations. Trend tests were performed to assess changes in associations across tertiles.

In the adjusted analyses, antioxidants were independent variables, and BMD values

were dependent variables. The crude model was unadjusted. Model 1 was adjusted for age and gender. Sensitivity analyses further adjusted for age, gender, smoking, alcohol consumption, and regular exercise. Additionally, we also added "BMI" into the above model for these potential associations. A P value < 0.05 was considered statistically significant.

RESULTS

Characteristics of these participants

A total of 398 individuals with complete data were analyzed. As shown in Table 1, the mean age was 52.3 ± 11.4 years, and 163 (41.0%) were male. Mean blood antioxidant levels were as follows: total lutein (0.2 μmol/L), zeaxanthin (0.1 μmol/L), beta-cryptoxanthin (0.2 μmol/L), 13-cis-beta-carotene (0.1 μmol/L), alpha-carotene (0.1 μmol/L), all-trans-beta-carotene (0.5 μmol/L), total lycopene (0.4 μmol/L), gamma-tocopherol (4.3 μmol/L), alpha-tocopherol (25.6 μmol/L), and retinol (1.6 μmol/L). Mean BMD was 1.3 ± 0.2 g/cm² in the lumbar spine and 1.0 ± 0.2 g/cm² in the total femur. Univariate correlation analysis showed approximate positive correlations between total lutein, 13-cis-beta-carotene, alpha-carotene, and all-trans-beta-carotene with BMD in both the lumbar spine (Figure 2A–2D) and femur (Figure 2E–2H). However, these relationships weakened as antioxidant levels increased.

Crude linear regression Models for associations between blood antioxidants and BMD

In crude models without adjusting for any covariate (Table 2), significant associations with lumbar spine BMD were observed for total lutein (P for trend = 0.012), 13-cis-beta-carotene (P for trend = 0.007), alpha-carotene (P for trend = 0.002), and all-trans-beta-carotene (P for trend = 0.050). No significant associations were found for zeaxanthin (*P* value for trend=0.117), beta-cryptoxanthin (*P* value for trend=0.336), total lycopene (*P* value for trend=0.134), gamma-tocopherol (*P* value for trend=0.908), alpha-tocopherol (*P* value for trend=0.972), or retinol (*P* value for trend=0.766).

Similar results were obtained for femoral BMD, with total lutein (P for trend = 0.009), 13-cis-beta-carotene (P for trend < 0.001), alpha-carotene (P for trend < 0.001), and all-trans-beta-carotene (P for trend < 0.001) showing significant associations. Also, these positive associations weakened with increasing antioxidant concentrations.

Sensitivity analyses for associations between blood antioxidants and BMD

After adjusting for age and gender (Model 1, Table 3), total lutein (P for trend = 0.027), 13-cis-beta-carotene (P for trend = 0.036), and alpha-carotene (P for trend = 0.015) remained significantly associated with lumbar spine BMD. For femoral BMD, 13-cis-beta-carotene (P for trend = 0.011) and alpha-carotene (P for trend = 0.008) remained significant.

Further sensitivity analysis with adjustment for age, gender, smoking, alcohol consumption, and regular exercise confirmed significant associations for total lutein (P for trend = 0.038), 13-cis-beta-carotene (P for trend = 0.044), and alpha-carotene (P for trend = 0.019) with lumbar spine BMD (Table 4). For femoral BMD, 13-cis-beta-carotene (P for trend = 0.010) and alpha-carotene (P for trend = 0.007) remained significant. However, when BMI was added to the models, no significant associations were observed for any antioxidant with BMD at either site (Supplementary Table 1).

Discussion

Using data from the MIDUS II biomarker project, we evaluated associations between various circulating antioxidants and BMD in the lumbar spine and femur. Our results revealed significant positive correlations for total lutein, alpha-carotene, 13-cis-beta-carotene, and all-trans-beta-carotene with BMD, whereas zeaxanthin, beta-cryptoxanthin, alpha-tocopherol, gamma-tocopherol, total lycopene, and retinol showed no significant associations. These independent associations persisted after adjusting for demographic and lifestyle factors but disappeared after further adjustment for BMI.

Beyond irreversible factors such as age, gender, genetics, and ethnicity [27-29], numerous studies have confirmed that antioxidants, including vitamins and carotenoids, can reduce oxidative stress damage, delay cellular aging, and promote bone health [9-13]. Dietary nutrients are essential for proper physiological function [9]. Vitamins A and D are involved in substance synthesis, enzymatic reactions, and molecular metabolism, while vitamin C exerts antioxidant effects to protect cellular structure and function [9]. However, the relationship between antioxidant intake and BMD remains controversial. For instance, a cross-sectional study found that dietary vitamin A intake did not alter BMD, consistent with our finding that blood retinol levels were unrelated to BMD [22]. Conversely, a recent meta-analysis indicated that varying levels of vitamin A intake or blood retinol were associated with total fracture risk [30]. That meta-analysis also suggested a U-shaped association between blood retinol and hip fracture risk [30]. Another study of 6,002 adolescents from National Health and Nutrition Examination Survey (NHANES) reported a strong positive association and saturation effect between serum vitamin A and BMD [19]. Vitamin D, another fat-soluble vitamin, is known to promote bone cell proliferation and regeneration. Daily vitamin D intake or sunlight exposure for osteoporosis prevention is supported by substantial evidence [31, 32]. Juhász et al. found that vitamin D use was associated with higher bone mass and better bone quality in young adults [33]. Falbová et al. reported that the COVID-19 pandemic period was associated with lower BMD, and vitamin D supplementation was an important predictor of bone parameters in women [34]. However, a high-quality meta-analysis including 51,145 participants from 33 randomized trials reported that calcium and/or vitamin D supplementation was not associated with fracture risk in older adults [35], challenging conventional beliefs. Vitamin E, another antioxidant, can inhibit chronic inflammatory responses and oxidative stress, potentially stimulating osteoblast proliferation and bone formation. However, this mechanism does not align with a previous study reporting a negative association between blood α-tocopherol concentrations and femoral neck BMD in older U.S. adults, suggesting adverse effects of α-tocopherol on bone health [36]. In our study,

we did not observe any significant association between vitamin E (gamma-tocopherol or alpha-tocopherol) and BMD at either site (spine L1-4 and total femur).

The impact of blood carotenoids on BMD is also debated. A community-based study of 1,898 women and 933 men measuring blood β-cryptoxanthin, α-carotene, lycopene, and zeaxanthin found dose-response associations between α-carotene, lycopene, and β-cryptoxanthin with BMD in women after covariate adjustment [37]. Another study in postmenopausal Korean women reported that β-carotene intake was positively associated with BMD [38]. Sugiura et al. conducted a 4-year prospective study in Japanese adults and found that higher baseline serum β-carotene and β-cryptoxanthin were associated with less radial BMD loss and a lower risk of incident osteoporosis in postmenopausal women [39]. Consistently, our findings showed positive associations for total lutein, alpha-carotene, 13-cis-beta-carotene, and all-trans-beta-carotene with BMD, but not for zeaxanthin, total lycopene, beta-cryptoxanthin, alpha-tocopherol, gamma-tocopherol, or retinol. A previous study reported that in men and premenopausal women, serum carotenoids including lutein, lycopene, β-cryptoxanthin, and zeaxanthin were not associated with radial BMD, whereas in postmenopausal women, serum beta-carotene levels were weakly correlated with radial BMD [40]. The reasons for these inconsistent findings remain unclear. Several factors may explain the discrepancies. First, heterogeneity may arise from the narrow concentration range within which antioxidants exert their physiological effects. Excessively high or low circulating levels could lead to adverse outcomes. Second, many previous studies relied on dietary intake or oral supplementation, which may not accurately reflect actual circulating antioxidant levels. Third, differences in analytical methods or sample selection may also contribute to variability. For example, BMI is well-known to be positively correlated with BMD and negatively correlated with serum carotenoid concentrations [41]. Although we adjusted for demographic and lifestyle factors, the associations between blood antioxidants and BMD remained significant. However, these relationships largely disappeared after further adjusting for BMI, suggesting that BMI may be the primary driver of the observed associations. Therefore, more multicenter clinical and basic research is needed to address these limitations.

To our knowledge, this is the first study to investigate the relationship between ten common fat-soluble circulating antioxidants and BMD in the lumbar spine and femur in an adult population. Our findings indicate that only blood carotenoids, specifically total lutein, alpha-carotene, 13-cis-beta-carotene, and all-trans-beta-carotene, were significantly associated with increased BMD. These associations remained robust after adjusting for demographic and lifestyle factors, offering a potential explanation for previous controversies. Several limitations should be acknowledged. First, the cross-sectional design precludes causal inferences. Second, although we adjusted for demographic and lifestyle factors, residual confounding from unmeasured variables such as disease history (cardiovascular and metabolic diseases), drug use (hormones and biologics) and others cannot be excluded. Third, only 398 participants had complete data, which may introduce selection bias. This study including antioxidants in 398 individuals explored coexposure patterns but required careful statistical control, although multicollinearity was excluded. Fourth, the study population was limited to US adults, limiting generalizability. Finally, the significant attenuation of associations after BMI adjustment suggests that BMI may be a key confounder, warranting further investigation in larger, prospective multicenter studies.

Conclusions

We found that blood carotenoids, including total lutein, alpha-carotene, 13-cis-beta-carotene, and all-trans-beta-carotene, were positively associated with BMD in the lumbar spine and femur. However, these associations disappeared after further adjustment for BMI, suggesting that BMI may be the primary driver of the observed relationship. Large-scale prospective studies are needed to confirm these findings.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the institutional review boards at the three sites of the MIDUS II Biomarker Project, and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the [ICPSR] repository, [www.icpsr.umich.edu/web/pages/ICPSR/].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Kongning Chen and Bin Zou wrote the main manuscript text. Chengzhao Liu, Chunjie Lin, Hengmei Chen, Xuemei Huang completed the validation; Bin Zou supervised and revised this the manuscrip. All authors reviewed the manuscript.

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References

[1] Walker MD, Shane E. Postmenopausal Osteoporosis. N Engl J Med. 2023 Nov 23;389(21):1979-1991. doi: 10.1056/NEJMcp2307353

[2]. Wong RH, Thaung Zaw JJ, Xian CJ, Howe PR. Regular Supplementation With Resveratrol Improves Bone Mineral Density in Postmenopausal Women: A Randomized, Placebo-Controlled Trial. J Bone Miner Res. 2020 Nov;35(11):2121-2131. doi: 10.1002/jbmr.4115.

[3] Adesina OO, Jenkins IC, Galvão F, de Moura AC, Fertrin KY, Zemel BS, Saad STO. Alendronate preserves bone mineral density in adults with sickle cell disease and osteoporosis. Osteoporos Int. 2025 Jan;36(1):93-102. doi: 10.1007/s00198-024-07268-1.

[4] Bolland MJ, Nisa Z, Mellar A, Gasteiger C, Pinel V, Mihov B, Bastin S, Grey A, Reid IR, Gamble G, Horne A. Fracture Prevention with Infrequent Zoledronate in Women 50 to 60 Years of Age. N Engl J Med. 2025 Jan 16;392(3):239-248. doi: 10.1056/NEJMoa2407031.

[5] Chandran M, Brind'Amour K, Fujiwara S, Ha YC, Tang H, Hwang JS, Tinker J, Eisman JA. Prevalence of osteoporosis and incidence of related fractures in developed economies in the Asia Pacific region: a systematic review. Osteoporos Int. 2023 Jun;34(6):1037-1053. doi: 10.1007/s00198-022-06657-8.

[6] Harvey NC, Odén A, Orwoll E, Lapidus J, Kwok T, Karlsson MK, Rosengren BE, Ljunggren Ö, Cooper C, McCloskey E, Kanis JA, Ohlsson C, Mellström D, Johansson H. Falls Predict Fractures Independently of FRAX Probability: A Meta-Analysis of the Osteoporotic Fractures in Men (MrOS) Study. J Bone Miner Res. 2018 Mar;33(3):510-516. doi: 10.1002/jbmr.3331. Epub 2017 Dec 8.

[7] Bailey S, Mhango G, Lin JJ. The impact of bone mineral density screening on incident fractures and healthcare resource utilization among postmenopausal breast cancer survivors treated with aromatase inhibitors. Osteoporos Int. 2022 Sep;33(9):1989-1997. doi: 10.1007/s00198-022-06458-z.

[8] Sarafrazi N, Wambogo EA, Shepherd JA. Osteoporosis or Low Bone Mass in Older Adults: United States, 2017-2018. NCHS Data Brief. 2021 Mar;(405):1-8.

[9] Liu J, Tang Y, Peng B, Tian C, Geng B. Bone mineral density is associated with composite dietary antioxidant index among US adults: results from NHANES. Osteoporos Int. 2023 Dec;34(12):2101-2110. doi: 10.1007/s00198-023-06901-9.

[10] Harahap IA, Suliburska J. Probiotics and Isoflavones as a Promising Therapeutic for Calcium Status and Bone Health: A Narrative Review. Foods. 2021 Nov 3;10(11):2685. doi: 10.3390/foods10112685.

[11] Harahap IA, Landrier JF, Suliburska J. Interrelationship between Vitamin D and Calcium in Obesity and Its Comorbid Conditions. Nutrients. 2022 Aug 3;14(15):3187. doi: 10.3390/nu14153187. **;**

[12] Wang M, Pan W, Xu Y, Zhang J, Wan J, Jiang H. Microglia-Mediated Neuroinflammation: A Potential Target for the Treatment of Cardiovascular Diseases. J Inflamm Res. 2022 May 25;15:3083-3094. doi: 10.2147/JIR.S350109.

[13] Harahap IA, Moszak M, Czlapka-Matyasik M, Skrypnik K, Bogdański P, Suliburska J. Effects of daily probiotic supplementation with *Lactobacillus acidophilus* on calcium status, bone metabolism biomarkers, and bone mineral density in postmenopausal women: a controlled and randomized clinical study. Front Nutr. 2024 Jul 1;11:1401920. doi: 10.3389/fnut.2024.1401920.

[14] Meng M, Jiang Y, Wang Y, Huo R, Ma N, Shen X, Chang G. β-carotene targets IP3R/GRP75/VDAC1-MCU axis to renovate LPS-induced mitochondrial oxidative damage by regulating STIM1. Free Radic Biol Med. 2023 Aug 20;205:25-46. doi: 10.1016/j.freeradbiomed.2023.05.021.

[15] Russo C, Ferro Y, Maurotti S, Salvati MA, Mazza E, Pujia R, Terracciano R, Maggisano G, Mare R, Giannini S, Romeo S, Pujia A, Montalcini T. Lycopene and bone: an in vitro investigation and a pilot prospective clinical study. J Transl Med. 2020 Jan 29;18(1):43. doi: 10.1186/s12967-020-02238-7.

[16] Bailey RL, Looker AC, Lu Z, Fan R, Eicher-Miller HA, Fakhouri TH, Gahche JJ, Weaver CM, Mills JL. B-vitamin status and bone mineral density and risk of lumbar osteoporosis in older females in the United States. Am J Clin Nutr. 2015 Sep;102(3):687-94. doi: 10.3945/ajcn.115.108787.

[17] Dhonukshe-Rutten RA, Lips M, de Jong N, Chin A Paw MJ, Hiddink GJ, van Dusseldorp M, De Groot LC, van Staveren WA. Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. J Nutr. 2003 Mar;133(3):801-7. doi: 10.1093/jn/133.3.801.

[18] Hu L, Lind T, Sundqvist A, Jacobson A, Melhus H. Retinoic acid increases proliferation of human osteoclast progenitors and inhibits RANKL-stimulated osteoclast differentiation by suppressing RANK. PLoS One. 2010 Oct 11;5(10):e13305. doi: 10.1371/journal.pone.0013305.

[19] Ling L. Association between serum vitamin A and bone mineral density in adolescents. Sci Rep. 2025 Feb 26;15(1):6892. doi: 10.1038/s41598-025-91367-4.

[20] van Wijngaarden JP, Swart KM, Enneman AW, Dhonukshe-Rutten RA, van Dijk SC, Ham AC, Brouwer-Brolsma EM, van der Zwaluw NL, Sohl E, van Meurs JB, Zillikens MC, van Schoor NM, van der Velde N, Brug J, Uitterlinden AG, Lips P, de Groot LC. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr. 2014 Dec;100(6):1578-86. doi: 10.3945/ajcn.114.090043.

[21] Hsieh RL, Huang YL, Chen WJ, Chen HH, Shiue HS, Lin YC, Hsueh YM. Associations between Plasma Folate and Vitamin B12, Blood Lead, and Bone Mineral Density among Adults and Elderly Who Received a Health Examination. Nutrients. 2022 Feb 21;14(4):911. doi: 10.3390/nu14040911.

[23] Joo NS, Yang SW, Song BC, Yeum KJ. Vitamin A intake, serum vitamin D and bone mineral density: analysis of the Korea National Health and Nutrition Examination Survey (KNHANES, 2008-2011). Nutrients. 2015 Mar 10;7(3):1716-27. doi: 10.3390/nu7031716.

[23] Navarro-Valverde C, Caballero-Villarraso J, Mata-Granados JM, Casado-Díaz A, Sosa-Henríquez M, Malouf-Sierra J, Nogués-Solán X, Rodríguez-Mañas L, Cortés-Gil X, Delgadillo-Duarte J, Quesada-Gómez JM. High Serum

Retinol as a Relevant Contributor to Low Bone Mineral Density in Postmenopausal Osteoporotic Women. Calcif Tissue Int. 2018 Jun;102(6):651-656. doi: 10.1007/s00223-017-0379-8.

[24] Brim OG, Baltes PB, Bumpass LL, Cleary PD, Featherman DL, Hazzard WR, Kessler RC, Lachman ME, Markus HR, Marmot MG, Rossi AS, Ryff CD, & Shweder RA (2019). Midlife in the United States (MIDUS 1), 1995–1996 (ICPSR 2760; Version V18) [Data set]. ICPSR. 10.3886/ ICPSR02760.v18

[25] Ryff CD, Seeman T, & Weinstein M (2019). Midlife in the United States (MIDUS 2): Biomarker Project, 2004–2009 (ICPSR 29282; Version V9) [Data set]. ICPSR. 10.3886/ICPSR29282.v9

[26] Ryff C, Almeida DM, Ayanian J, Carr DS, Cleary PD, Coe C, Davidson R, Krueger RF, Lachman ME, Marks NF, Mroczek DK, Seeman T, Seltzer MM, Singer BH, Sloan RP, Tun PA, Weinstein M, & Williams D (2017). Midlife in the United States (MIDUS 2), 2004–2006 (ICPSR 4652; Version V7) [Data set]. ICPSR. 10.3886/ICPSR04652.v7

[27] Falbová D, Kovalčíková V, Beňuš R, Sulis S, Vorobeľová L. Effect of COVID-19 pandemic on lifestyle and bone mineral density in young adults. Am J Hum Biol. 2024 Apr;36(4):e24009. doi: 10.1002/ajhb.24009.

[28] Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Yano M. High serum carotenoids associated with lower risk for bone loss and osteoporosis in post-menopausal Japanese female subjects: prospective cohort study. PLoS One. 2012;7(12):e52643. doi: 10.1371/journal.pone.0052643.

[29] Ng JS, Chin KY. Potential mechanisms linking psychological stress to bone health. Int J Med Sci. 2021 Jan 1;18(3):604-614. doi: 10.7150/ijms.50680.

[30] Wu AM, Huang CQ, Lin ZK, Tian NF, Ni WF, Wang XY, Xu HZ, Chi YL. The relationship between vitamin A and risk of fracture: meta-analysis of prospective studies. J Bone Miner Res. 2014 Sep;29(9):2032-9. doi: 10.1002/jbmr.2237.

[31] Brincat M, Gambin J, Brincat M, Calleja-Agius J. The role of vitamin D in osteoporosis. Maturitas. 2015 Mar;80(3):329-32. doi: 10.1016/j.maturitas.2014.12.018.; Yoo KO, Kim MJ, Ly SY.

[32] The association between vitamin D intake and BMD in Koreans aged ≥ 50 years: analysis of the 2009 Korea National Health and Nutrition Examination Survey using a newly established vitamin D database. Nutr Res Pract. 2019 Apr;13(2):115-125. doi: 10.4162/nrp.2019.13.2.115

[33] Juhász MF, Varannai O, Németh D, Szakács Z, Kiss S, Izsák VD, Martonosi ÁR, Hegyi P, Párniczky A. Vitamin D supplementation in patients with cystic fibrosis: A systematic review and meta-analysis. J Cyst Fibros. 2021 Sep;20(5):729-736. doi: 10.1016/j.jcf.2020.

[34] Falbová D, Kovalčíková V, Beňuš R, Sulis S, Vorobeľová L. Effect of COVID-19 pandemic on lifestyle and bone mineral density in young adults. Am J Hum Biol. 2024 Apr;36(4):e24009. doi: 10.1002/ajhb.24009.

[5] Zhao JG, Zeng XT, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017 Dec 26;318(24):2466-2482. doi: 10.1001/jama.2017.19344.

[36] Zhang J, Hu X, Zhang J. Associations between serum vitamin E concentration and bone mineral density in the US elderly population. Osteoporos Int. 2017 Apr;28(4):1245-1253. doi: 10.1007/s00198-016-3855-5.

[37] Zhang ZQ, Cao WT, Liu J, Cao Y, Su YX, Chen YM. Greater serum carotenoid concentration associated with higher bone mineral density in Chinese adults. Osteoporos Int. 2016 Apr;27(4):1593-1601. doi: 10.1007/s00198-015-3425-2.

[38]Kim DE, Cho SH, Park HM, Chang YK. Relationship between bone mineral density and dietary intake of β-carotene, vitamin C, zinc and vegetables in postmenopausal Korean women: a cross-sectional study. J Int Med Res. 2016 Oct;44(5):1103-1114. doi: 10.1177/0300060516662402.

[39] Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Matsumoto H, Ando F, Shimokata H, Yano M. Synergistic interaction of cigarette smoking and alcohol drinking with serum carotenoid concentrations: findings from a middle-aged Japanese population. Br J Nutr. 2009 Oct;102(8):1211-9. doi: 10.1017/S0007114509382124.

[40] Sugiura M, Nakamura M, Ogawa K, Ikoma Y, Ando F, Yano M. Bone mineral density in post-menopausal female subjects is associated with serum antioxidant carotenoids. Osteoporos Int. 2008 Feb;19(2):211-9. doi: 10.1007/s00198-007-0457-2.

[41] Zhang H, Li L, Wang Y, Xie Y, Chen B. Moderate carotenoid intakes protect against sarcopenic obesity among U.S. adults: A cross-sectional study. Nutr Res. 2025 Oct;142:46-62. doi: 10.1016/j.nutres.2025.09.002.

Figure legends

Figure 1. Flow chart of participant selection in this study.

Figure 2. Univariate correlation curves showing associations between circulating antioxidant concentrations and BMD in the lumbar spine (L1–L4) and total femur.