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ORIGINAL ARTICLE

# Dietary inflammatory index® and cortical bone outcomes in healthy adolescent children

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## Abstract

**Summary** Diet is thought to modulate inflammation. This study shows no relationships between the dietary inflammatory index (DII) and biomarkers of inflammation or bone after adjusting for covariates. Monocyte chemoattractant protein-1 was inversely associated with peripheral tibia cortical thickness and prospective childhood studies should be conducted to better understand this relationship and to determine if there are long-term consequences in adulthood.

**Introduction** Examine the relationships between the DII-scores and bone and biomarkers of inflammation in 290 adolescents, ages 9–13 years.

**Methods** DII-scores were calculated from 3-day diet records and categorized into tertiles, low (< − 1.34), medium (− 1.34 to 1.41), and high (> 1.41) inflammation. Radius and tibia bone were assessed via peripheral quantitative computed tomography (Stratec XCT 2000) at the 66% site relative to the distal growth plate. Fasting serum was measured for tumor necrosis factor alpha (TNF-$\alpha$), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1). The relationships between DII-scores and bone and biomarkers of inflammation were assessed using bivariate and partial correlations adjusting for sexual maturation, sex, race, muscle cross-sectional area, and height. ANOVA/ANCOVA models were used to compare DII-tertiles with dependent variables.

**Results** DII-scores were negatively associated with tibia trabecular area (TtAr; $r = -.141$, $P = .019$), periosteal perimeter (PsPM; $r = -.145$, $P = .016$), endosteal perimeter ($r = -.145$, $P = .016$), strength strain index (SSI; $r = -.129$, $P = .032$), and radius TtAr ($r = -.140$, $P = .020$), PsPM ($r = -.138$, $P = .027$) and SSI ($r = -.131$, $P = .036$) but nullified when adjusting for covariates. Tibia PsPM was higher in the low DII group compared to the medium ($P = .050$) and high ($P = .046$) groups but nullified after controlling for covariates. DII-scores were not associated with TNF-α, VEGF, or IL-6, but were associated with MCP-1 only in the unadjusted model ($r = .125$, $P = .042$). In the adjusted model, MCP-1 was inversely associated with tibia cortical thickness ($r = -.150$ $P = .030$).

**Conclusion** The DII-scores were not related to biomarkers of inflammation or bone; however, the biomarker of inflammation, MCP-1 was negatively associated with tibia CtTh. Future prospective pediatric studies should be conducted to better understand this relationship and determine if there are long-term implications in adulthood.

**Keywords** Adolescents · Diet · DII · Inflammation · pQCT

## Introduction

Systemic, low-grade inflammation is associated with several chronic diseases including cardiovascular disease [1, 2], type 2 diabetes mellitus [3], obesity [4], and osteoporosis [5, 6]. Once considered adult diseases, children and adolescents are increasingly being diagnosed with these chronic conditions [7]. Similar to adults, the relationships between inflammation and metabolic syndrome [8], obesity [8], and insulin resistance [9] are observed in youth. Low-grade, systemic inflammation in youth tracks into adulthood, putting these adolescents at increased risk for chronic diseases later in life [10].

Modifiable factors such as diet have been demonstrated to influence the inflammatory response process [11]. The primary research approaches to test whether nutrition modifies inflammation is to target individual nutrients [12, 13]. For

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example, consumption of omega-6 fatty acids and antioxidant vitamins (e.g., vitamin E, lutein, and vitamin C) have been associated with lower inflammation [13], while consuming saturated fatty acids and excessively refined grains have been correlated with higher inflammation [12].

There are published reports that dietary patterns or whole foods may be more robust than individual nutrients in producing pro- or anti-inflammatory affects [14]. The dietary inflammatory index (DII®) was developed by Cavicchia et al. [15] and updated by Shivappa et al. [16] to assess the overall quality of the diet on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. Utilizing the first version of the DII, Cavicchia et al. demonstrated that the DII scores correlate with the inflammatory biomarker C-reactive protein (CRP) in a longitudinal study of apparently healthy adults [15]. These analyses were repeated for the next generation DII [16]. Several cross-sectional studies have demonstrated significant relationships between the updated DII score and CRP in adults [17], as well as, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-$\alpha$), and a combined inflammatory biomarker score in postmenopausal women [18]. Among adolescents, pro-inflammatory diet (indicated by higher DII scores) was associated with increased levels of various inflammatory markers: TNF-$\alpha$, interleukin-1, interleukin-2, interferon gamma, and vascular cell adhesion molecule [19].

The heightened interest in the link between chronic inflammation and pediatric bone health is derived from observations of low bone mass in children with a wide range of inflammatory disease states, including ulcerative colitis, cystic fibrosis, systemic lupus erythematous, and rheumatoid arthritis [20–22]. In a review addressing the link between the skeleton and immune system in children with clinical disorders, Cheung et al. noted that independent of pharmacological interventions, a high percentage of patients with chronic inflammatory conditions, had low total body bone mineral density (BMD) and were at greater risk for fracture [23]. For example, Roth et al. demonstrated low trabecular volumetric BMD and cortical bone strength in children with juvenile arthritis [24].

Given that inflammation may negatively impact both cortical and trabecular bone density and volume, researchers have investigated the impact of the DII in relation to prospective changes in BMD and fracture. Orchard et al. found that a more anti-inflammatory diet, as measured by the DII, was associated with attenuated hip BMD loss in postmenopausal women, and consuming a higher inflammatory diet was associated with increased risk of hip fracture in younger women [25]. A pro-inflammatory diet, as indicated by a high DII score, also has been shown to be a risk factor for lower lumbar spine BMD in postmenopausal women [26]. Similarly, body mass index (BMI)-adjusted mean BMD at the total femur, femoral neck, trochanter, and intertrochanteric significantly decreased across increasing quartiles of DII score in US adults [27]. These studies offer some evidence that chronic inflammation is related to adverse skeletal outcomes in adults. To our knowledge, there are no published studies examining the effects of a pro-inflammatory diet, as measured by the DII, on bone outcomes in healthy children. This could have important ramifications for peak bone mass attainment because bone mass tracks from youth into adulthood [28]. Thus, the aim of this study is to assess the relationships between inflammatory diet patterns, as represented by DII scores, with cortical bone outcomes in otherwise healthy boys and girls.

## Subjects and methods

### Study design and participant characteristics

This study was a secondary analysis of baseline data obtained from a randomized controlled clinical trial previously described [29]. Healthy non-Hispanic Black and White participants were included if they were between the ages of 9–13 years, free from chronic diseases, and in the early stages of puberty with self-reported sexual maturation ratings of 2 or 3 for breast development for females and genital development for males as described by Tanner ($N = 323$) [30]. Participants were excluded from the parent study if they were menarcheal (for females), had growth disorders/chronic diseases (e.g., cerebral palsy), or used medications (e.g., corticosteroids) known to influence bone metabolism. Thirty-three participants were excluded from this ancillary analysis due to incomplete diet records. History of previous fracture and fracture site was assessed using a Health History Questionnaire and was not considered in the exclusion criteria. Specific details surrounding the fracture incident (i.e., high- vs. low-impact fractures,) were not recorded. The Institutional Review Boards for Human Subjects at all study sites approved the study procedures. Participant informed assent and parental informed consent were obtained prior to all testing procedures.

### Dietary assessment

Three-day diet records, a valid and reliable method for estimating energy and nutrient intakes in children [31, 32], were completed at home by participants, with assistance from their parents or guardians, for two weekdays and one weekend day. A registered dietitian nutritionist and one trained research assistant analyzed the diet records using Nutrition Data Systems for Research (NDSR®) software version 16 (Nutrition Coordinating Center [NCC], Minneapolis, MN). Test-retest coefficients of variation (CV) were determined for energy, protein, total fat, carbohydrates, vitamin D, and calcium (all $\geq 0.85$). Average measure (3-days) intra-class correlation coefficients (ICCs) were calculated in girls aged 6–10 years ($N = 10$), whose 3-day diet records were completed twice

during a 2-week period and calculated for vitamin D, calcium, and energy (all ≥ 0.86).

## DII score calculation

The details of developing the DII are described by Shivappa et al. elsewhere [16]. Briefly, high sensitivity CRP measurements were used to construct validity of the DII score in a longitudinal cohort using multiple (up to 15) 24-h dietary recall interviews and up to five 7-day dietary recalls. The DII was subsequently validated in four studies among different populations with a variety of inflammatory biomarkers (i.e., interleukin, IL-6, high sensitivity CRP, fibrinogen, homocysteine, and TNF-$\alpha$) [16, 18]. In this updated version of the DII, 1943 articles were reviewed and scored. Forty-five food parameters, including foods, nutrients, and other bioactive compounds, were identified based on their inflammatory effect on six specific inflammatory markers, including CRP, interleukin-1 beta, interleukin-4, IL-6, interleukin-10, and TNF-$\alpha$. A regionally representative world database representing diet surveys from 11 countries was used as a comparative standard for each of the 45 parameters (i.e., foods, nutrients, and other bioactive food components). Intake values from this database were used to calculate the DII scores. This is explained in more detail in the DII methods paper [16]. Briefly, a standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate Z-scores. These Z-scores were converted to proportions (thus minimizing effects of outliers/right-skewing). These values were then doubled, and one was subtracted to achieve symmetrical distribution with values centered on approximately zero. The resulting value was then multiplied by the corresponding inflammatory score for each food parameter and summed across all food parameters, to obtain the overall DII score. Using 3-day diet records, we calculated the DII based on 27 single food parameters of the 45 possible food parameters (Table 1).

## Anthropometry

Height (to the nearest 0.1 cm) and body mass (to the nearest 0.1 kg) were measured using a wall-mounted stadiometer and electronic scale, respectively. BMI (kg/m$^2$) was calculated, and BMI age-percentile scores were derived using the 2000 CDC growth charts [33]. BMI Z-scores were calculated using STATA® software (StataCorp. 2017. *Statistical Software: Release 15*. College Station, TX; StataCorp LLC). Single-measure ICCs and test-retest CVs were determined previously in our lab for standing height (0.99 and 0.4%) and body weight (0.99 and 1.4%) in females aged 6–10 years ($N$ = 10) who were measured twice over a 2-week period by the same researcher.

**Table 1** Mean, standard deviation (SD), RDAs, and typical intakes nutrients and food components included in the calculation of DII score

| DII food parameters | RDA | Mean | SD | Typical intakes* |
|---|---|---|---|---|
| Energy, kcal/day | | 1804 | 497 | 1813–2247 |
| Carbohydrate, g/day | | 227 | 71 | 233–282 |
| Protein, g/day | 34–52 | 69 | 20 | 63–85 |
| Total fat, g/day | | 70.8 | 21.8 | 72.1–88.5 |
| Alcohol, g/day | | 0.26 | 3.80 | |
| B-Carotene, μg/day | | 2019 | 2513 | 1086–1409 |
| Vitamin A, μg/day | 600 | 504 | 430 | 506–653 |
| Caffeine, g/day | | 9.98 | 3.63 | 11.5–50.0 |
| Cholesterol, mg/day | | 224.4 | 110.4 | 214–276 |
| MUFA, g/day | | 24.1 | 7.91 | 24.3–30.1 |
| n-3 Fatty acids, g/day | | 1.62 | 0.69 | |
| n-6 Fatty acids, g/day | | 15.0 | 5.56 | |
| PUFA, g/day | | 16.9 | 6.24 | 15.6–19.1 |
| Saturated fat, g/day | | 24.2 | 8.20 | 24.8–31.0 |
| Trans fat, g/day | | 2.37 | 1.52 | |
| Fiber, g/day | 25–30 | 14.0 | 5.11 | 13.9–16.0 |
| Iron, mg/day | | 14.1 | 5.18 | 13.2–16.7 |
| Magnesium, mg/day | | 211.5 | 70.2 | 223–276 |
| Niacin, mg/day | 12 | 21.4 | 6.61 | 19.9–27.8 |
| Riboflavin, mg/day | 0.9 | 1.95 | 0.66 | 1.70–2.26 |
| Selenium, mg/day | 40 | 102.7 | 31.5 | 91.9–122.8 |
| Thiamin, mg/day | 0.9 | 1.79 | 0.53 | 1.46–1.83 |
| Vitamin B6, mg/day | 1.0 | 1.64 | 0.60 | 1.56–2.11 |
| Vitamin C, mg/day | 45 | 64.2 | 50.2 | 63.5–67.9 |
| Vitamin D, μg/day | 15 | 5.52 | 3.06 | 4.2–5.7 |
| Vitamin E, mg/day | 11 | 6.72 | 3.07 | 7.1–8.5 |

*From *What We Eat in America, National Health and Nutrition Examination Survey 2015–2016, range for boys and girls ages 6–19* [51]. *RDA*, Recommended Dietary Allowances; *DII*, dietary inflammatory index; *kcal*, calories; *MUFA*, monosaturated fatty acids; *PUFA*, polyunsaturated fatty acids; *RE*, retinol equivalents; *SD*, standard deviation. $N$ = 290

## Body composition and whole body bone measurements

Fat mass, percent fat, fat-free soft tissue, whole body BMD, and whole body bone mineral content (BMC) were assessed using dual-energy X-ray absorptiometry (DXA; Delphi-A, Hologic Inc. [UGA]; Lunar iDXA, GE Medical Instruments [PU; Purdue University]; and Hologic Discovery-W [IU; Indiana University]) as previously described [29, 34, 35]. The same technician at each site conducted scans and performed analyses using instrument-specific software and protocols. ICCs were calculated for body composition in females, aged 5–8 years ($N$ = 10), and scanned twice over 7 days (all ≥ 0.98). Short- and long-term precision of DXA at IU was < 2%. The UGA/PU sites were cross-calibrated by scanning 26 children on the Delphi-A and an iDXA, whereas the

IU and PU sites were cross-calibrated by scanning 10 children on the Discovery-W and iDXA. Regression formulae between UGA/PU and IU/PU were derived and used to adjust data from UGA/IU to PU values.

## Cortical bone measurements

Peripheral quantitative computed tomography (pQCT) was used to assess cortical bone outcomes using Stratec XCT 2000 (Stratec Medizintechnik GmbH, Pforzheim, Germany), as previously reported [29]. To measure tibia length, subjects were asked to cross their non-dominant leg over their dominant leg. A pen mark was placed on the upper border of the medial condyle of the non-dominant tibia and at the tip of the medial malleolus. The distance between the two points was measured in millimeters (mm) with a spreading caliper. To measure radius length, participants were asked to place their non-dominant forearm on a table forming a 90° angle. A pen mark was placed at the end of the styloid process and the distance between the bottom of the forearm to the pen mark at the styloid process was measured in mm with a spreading caliper. All measurements were conducted by the same technician at all study sites. A single tomographic slice 66% relative to the distal growth plate was taken for the non-dominant tibia and radius. A cortical bone phantom specific to the pQCT with known properties has scanned a minimum of 20 times and the variation in phantom measures differed by < 1% [34].

Cort mode 1 (threshold, 710 mg/cm$^3$) was used to obtain cortical volumetric bone mineral density (CtvBMD, mg/cm$^3$), cortical bone mineral content (CtBMC, mg/mm), and cortical area (CtAr, cm$^2$) and to define the outermost edge of the bone. Peel mode 2 (threshold, 400 mg/cm$^3$) was used to separate the cancellous and cortical bone compartments. Total bone area (TtAr, mm$^2$), cortical thickness (CtTh, mm), periosteal perimeter (PsPM, mm), and endosteal perimeter (EsPM, mm) were also measured. This same threshold was used to calculate polar-strength strain index (pSSI, mm$^3$), which represents the density-weighted section modulus and has been validated as a non-invasive measure of bone strength [36]. The pSSI was determined in a separate analysis using cort mode 2 (threshold, 400 mg/cm$^3$) and was calculated as the section modulus multiplied by the ratio of CtBMD and normal physiologic density (i.e., 1200 mg/mm$^3$), as previously descripted [34]. Section modulus (mm$^3$) was calculated as $(a \times d^2)$/dmax, where "$a$" is the cross-sectional area of a voxel (mm$^2$), "$d$" is the distance of the voxel from the center of gravity (mm), and "dmax" is the maximum distance (eccentricity) of one voxel to the center of gravity (mm).

$$SSI_P = \Sigma\ [(a \times d^2)\ (\text{Cortical volumetric BMD}/\text{normal physiologic density BMD})]/\text{dmax}$$

Tibia and radius muscle cross-sectional areas (MCSA) were assessed using a F03F05 filter (contour mode 3 [threshold of − 100 mg/cm$^3$] and peel mode 2). All pQCT measures were performed and analyzed by a one trained operator and the pQCT operator scanned the phantom daily to maintain quality assurance. Five healthy females (ages 18–24 years) were scanned twice over 7 days to determine test-retest reliability [37]. One-way random effects model and single measure ICCs for all pQCT variables were $R \geq 0.97$. At the IU site, short-term precision for the pQCT scanning produce on 30 healthy individuals scanned six times with interim repositioning showed root mean square coefficients of variation of < 1% for bone density, mass, structure, and estimated strength measures [38].

## Biochemical analyses

Serum inflammation-related biomarkers, TNF-$\alpha$, vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein-1 (MCP-1) were quantified using the Luminex xMAP system, a high-throughput microsphere–based suspension array, with a MILLIPLEX MAP human cytokine/chemokine immunoassay (Millipore, St. Charles, MO). These biochemical measures were conducted in a single laboratory in the batch analysis. The assay was analyzed on a Luminex 200 instrument (Luminex Corporation, Austin, TX) using Luminex xPONENT 3.1 software. Additional analysis was performed using the MILLIPLEX analyst (Millipore). The intra- and inter-assay coefficients of variation were 2.6% and 13.0% for TNF-$\alpha$, 3.7% and 10.4% for VEGF, and 1.5% and 7.9% for MCP-1, respectively [39]. Serum IL-6 was quantified using a Meso Scale Discovery assay with a SECTOR Image plate reader. The intra- and inter-assay coefficients of variation were 4.4% and 12.3% for IL-6, respectively.

## Statistical analyses

Data were analyzed using SPSS® version 21 (SPSS, Inc.) for the Mac Os X. Histograms were visually inspected for outliers and normal distribution. Distributions were classified as skewed or kurtotic if > 2.0 standard deviations (SDs). Because serum IL-6 and TNF-$\alpha$ each had positively skewed distributions, they were log-transformed (i.e., IL-6) or square root transformed (i.e., TNF-$\alpha$) prior to analyses. Pearson's bivariate and partial correlations were conducted to determine the association between DII score and biomarkers of inflammation while adjusting for the covariates stage of sexual maturation, sex, and race. Additionally, Pearson's bivariate correlations were conducted to determine the associations between DII score and bone parameters and serum biomarkers of inflammation and bone outcomes. Because MCSA and height are considered key determinants of bone strength in children [40–42], these covariates were added to the Pearson's partial

correlations models to determine the association between DII score and bone parameters and serum biomarkers of inflammation and bone outcomes. The DII score groups were created using tertile categories (low [< − 1.34], medium [− 1.34 to 1.41], and high [> 1.41]) levels of inflammatory potential. Bone outcomes and biomarkers of inflammation were compared between groups using one-way analysis of variance and one-way analysis of covariance. Post hoc comparisons using the Bonferroni correction were utilized to compare DII ranking scores on serum inflammatory biomarkers and bone parameters. The Bonferroni correction was used to correct *P* values for multiple comparisons. A *P* value of < 0.05 was considered statistically significant for all analyses.

## Results

### Participant characteristics

Descriptive participant characteristics are presented in Table 2. Participants were evenly distributed by sex and race (i.e., non-Hispanic White and Black). Average BMI-age percentile and BMI Z-score fell within the normal range. Participants had a mean ± SD DII score of 0.59 ± 1.36 (pro-inflammatory) and the means ± SDs are reported for the individual 27 nutrients and food components used to calculate DII score (Table 2). Participants met at least two-thirds the recommended dietary intakes for vitamin A, vitamin C, vitamin B6, selenium, iron, riboflavin, niacin, omega-3 fatty acids, omega-6 fatty acids, magnesium, and thiamine. Participants met 49% of the recommended dietary allowances (RDA) for fiber, 37% of the RDA for vitamin D, and 61% of the RDA for vitamin E. Approximately 23% (*n* = 66) of participants had a history of a previous fracture (25 radius fractures, 8 tibia fractures, and 1 femur fracture).

**Table 2** Participant characteristics

| | Mean | SD |
|---|---|---|
| Age, years | 11.38 | 1.23 |
| SMR stage, 2 | 188 (65%) | |
| Race (Black), *n* | 137 (47%) | |
| Height, cm | 150.74 | 9.23 |
| Weight, kg | 47.7 | 12.44 |
| BMI | 20.8 | 4.52 |
| BMI-age-percentile | 68.1 | 29.3 |
| BMI Z-score | 0.68 | 1.08 |
| Fat Mass, kg | 15.15 | 7.3 |
| FFST mass, kg | 30.30 | 6.90 |
| DII score | 0.59 | 1.36 |
| TNF-α, pg/mL | 10.69 | 5.16 |
| IL-6, pg/mL | 0.73 | 0.89 |
| MCP-1, pg/mL | 481.41 | 228.82 |
| VEGF, pg/mL | 269.35 | 220.74 |

*DII*, dietary inflammatory index; *SMS*, sexual maturation rating; *BMI*, body mass index; *TNF-α*, tumor necrosis factor-alpha; *IL-6*, interleukin-6; *MCP-1*, monocyte chemoattractant protein-1; *VEGF*, vascular endothelial growth factor. *N* = 290

### Dietary inflammatory index and bone outcomes

DII score was negatively associated with tibia TbAr, PsPM, EsPM, and SSI and radius TtAr, PsPM, and SSI (Table 3). All relationships were non-significant when controlling for stage of sexual maturation, sex, race, MCSA (tibia and radius), and height. When comparing DII rank score categories, tibia PsPM was significantly higher in the low-inflammation group compared to both medium-($P = .050$) and high-($P = .046$) inflammation groups, $F(2,277) = 3.088$, $P = .047$. When controlling for the covariates, these group differences were non-significant.

### Dietary inflammatory index and biomarkers of inflammation

The DII score was not significantly associated with VEGF, IL-6, and TNF-α; however, it was positively associated with MCP-1 in the unadjusted model ($r = .125$, $P = .042$). When adjusting for the covariates stage of sexual maturation, sex, and race, the relationship between DII and MCP-1 was nullified ($r = .100$; $P = .166$). There were no significant differences between DII rank score groups on MCP-1, VEGF, IL-6, and TNF-α ($P = .120$, $P = .770$, $P = .250$, and $P = .637$, respectively).

### Biomarkers of inflammation and bone outcomes

In the unadjusted model, TNF-α was significantly negatively associated with tibia CtBMC, CtAr, and SSI; however, these relationships were nullified when adjusting for the covariates stage of sexual maturation, sex, race, tibia MCSA, and height (Table 4). In the unadjusted and adjusted models, there were no significant relationships between IL-6 and VEGF and any tibia bone outcomes. MCP-1 was significantly negatively correlated with tibia CtBMD, EsPM, and SSI in the unadjusted model. When adjusting for the covariates, there was a significant inverse relationship between MCP-1 and tibia CtTh.

Similar to the tibia, significant negative correlations were observed between TNF-α and radius CtBMC, CtAr, and SSI in the unadjusted model (Table 5). These relationships were nullified when controlling for the covariates, stage of sexual maturation, sex, race, radius MCSA, and height. In the unadjusted and adjusted models, there were no significant correlations between IL-6 and VEGF and radius bone outcomes. There were no significant correlations between MCP-1 and

**Table 3** Bivariate and partial correlations between DII score and cortical bone outcomes

| | Tibia unadjusted | | Tibia adjusted | | Radius unadjusted | | Radius adjusted | |
|---|---|---|---|---|---|---|---|---|
| | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* |
| CtBMD | − 0.07 | .27 | − 0.31 | .61 | − 0.01 | .99 | − 0.03 | .64 |
| CtBMC | − 0.11 | .06 | − 0.06 | .30 | − 0.07 | .30 | − 0.02 | .77 |
| TtAr | − 0.14 | .02 | − 0.03 | .97 | − 0.14 | .02 | − 0.09 | .15 |
| CtAr | − 0.10 | .10 | − 0.08 | .19 | − 0.09 | .14 | − 0.01 | .85 |
| CtTh | − 0.02 | .74 | − 0.09 | .14 | − 0.02 | .76 | − 0.04 | .54 |
| PsPM | -0.15 | .02 | − 0.01 | .94 | − 0.14 | .03 | − 0.09 | .18 |
| EsPM | − 0.15 | .02 | − 0.05 | .44 | − 0.11 | .07 | − 0.08 | .21 |
| SSI | − 0.13 | .03 | − 0.05 | .40 | − 0.13 | .04 | − 0.07 | .25 |

Statistically significant at $P < .05$; $N = 290$; adjusted stage of sexual maturation, sex, muscle cross-sectional area and height. *CtBMD*, cortical bone mineral density; *CtBMC*, cortical bone mineral content; *TtAr*, trabecular area; *CtAr*, cortical area; *CtTh*, cortical thickness; *PsPM*, periosteal perimeter; *EsPM*, endosteal perimeter; *SSI*, strength strain index

radius bone outcomes in the unadjusted model. When adjusting for the covariates, the relationship between MCP-1 and radius CtBMD approached significance ($P = .050$).

## Discussion

The aim of this cross-sectional study was to assess the relationships between dietary patterns reflective of varying degrees of inflammation, as represented by DII scores, and cortical bone outcomes in healthy children. A secondary aim of this study was to determine the relationships between baseline DII scores and serum biomarkers of inflammation. The primary finding was that DII scores were not related to cortical bone strength or serum biomarkers of inflammation. Importantly, the pro-inflammatory biomarker of inflammation, MCP-1, was negatively associated with tibia CtTh.

The present study is the first to assess the relationships between the DII and bone outcomes as measured by pQCT in children and adolescents. The fact that no significant relationships existed between DII scores and cortical bone could be due to several factors. The studies that have reported positive findings were conducted in older adults. For example, Orchard et al. found that in comparison to a pro-inflammatory diet, postmenopausal women consuming a more anti-inflammatory diet had less hip BMD loss over a 6-year period, despite lower baseline hip BMD measurements [26]. Additionally, a pro-inflammatory diet, as indicated by increasing DII scores, was associated with lower lumbar spine BMD in postmenopausal Iranian women [16]. Consistent with our null findings, a study in young adults ages 18–25 found no associations between increased DII scores and quantitative ultrasound of the right calcaneus [43]. It is possible that the significant associations between low DII scores and better bone outcomes in older adults, but not in children, adolescents, or young adults, could be due to more years of exposure to a pro-inflammatory diet in the older adults than shorter exposure intervals in children and adolescents, although this is unknown. One of the limitations of the current study and others [44, 45] is the cross-sectional nature of the study designs and that dietary assessment targeted current intakes and not historical dietary information. Hence, based on the study design in the current study and the dietary methodology employed, the authors cannot address the question regarding long-term dietary exposures.

The DII was validated in adults using the pro-inflammatory biomarkers, CRP, IL-6, and an overall inflammatory biomarker score. In the current study, CRP was not assessed, but TNF-$\alpha$, IL-6, VEGF, and MCP-1 were included as biomarkers of inflammation. We selected the biomarkers TNF-$\alpha$, IL-6, VEGF, and MCP-1 because of their potential detrimental effects on bone strength which was confirmed by the inverse relationships found between MCP-1 and tibia CtTh. To our knowledge, it is not known whether CRP is higher in apparently healthy children due to lifestyle factors such as adhering to specific dietary patterns. Several factors including social (e.g., socioeconomic status) and physical (e.g., body fat) have been associated with higher levels of CRP in children [46]. Because of the unavailability of additional serum samples, in the current study, CRP was not measured. It remains to be elucidated whether CRP is higher in apparently healthy children consuming pro-inflammatory diets; future studies of children should include assessment of CRP. The biomarkers IL-6, TNF-$\alpha$, and VEGF were not related to DII scores in the present study. MCP-1 was the only biomarker found to be positively associated with DII scores, but once race was added as a covariate to the adjusted model, the significant relationships did not persist. In adults, Blacks have significantly lower MCP-I concentrations than Whites, but no data are published in children and adolescents. Our

**Table 4** Bivariate and partial correlations between biomarkers of inflammation and tibia bone outcomes

| | TNF-$\alpha$ | | | | IL-6 | | | | MCP-1 | | | | VEGF | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | |
| | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* |
| CtBMD | − 0.12 | .06 | − 0.09 | .16 | − 0.06 | .36 | − 0.06 | .41 | − 0.20 | < .01 | − 0.02 | .82 | − 0.04 | .95 | − 0.05 | .44 |
| CtBMC | − 0.14 | .03 | − 0.09 | .19 | 0.05 | .46 | − 0.02 | .72 | − 0.07 | .24 | − 0.10 | .14 | 0.02 | .75 | − 0.09 | .18 |
| TtAr | − 0.10 | .11 | − 0.02 | .75 | 0.06 | .35 | − 0.04 | .50 | − 0.11 | .09 | − 0.02 | .82 | − 0.02 | .78 | − 0.01 | .89 |
| CtAr | − 0.12 | .05 | − 0.07 | .32 | 0.06 | .36 | − 0.04 | .54 | − 0.04 | .58 | − 0.11 | .09 | 0.03 | .69 | − 0.08 | .21 |
| CtTh | − 0.11 | .09 | − 0.06 | .36 | 0.04 | .54 | − 0.02 | .81 | − 0.06 | .34 | − 0.15 | .03 | 0.05 | .40 | 0.08 | .23 |
| PsPM | − 0.09 | .14 | − 0.01 | .89 | 0.07 | .31 | − 0.05 | .42 | − 0.10 | .11 | − 0.01 | .89 | − 0.02 | .77 | − 0.01 | .92 |
| EsPM | − 0.05 | .42 | − 0.02 | .73 | 0.05 | .43 | − 0.03 | .61 | − 0.14 | .03 | − 0.08 | .24 | − 0.04 | .49 | − 0.03 | .62 |
| SSI | − 0.12 | .05 | − 0.05 | .41 | 0.05 | .49 | − 0.02 | .80 | − 0.13 | .05 | − 0.02 | .82 | 0.04 | .96 | − 0.06 | .33 |

Statistically significant at $P < .05$; $N = 290$; adjusted for stage of sexual maturation, sex, race, tibia muscle cross-sectional area, and height. *CtBMD*, cortical bone mineral density; *CtBMC*, cortical bone mineral content; *TtAr*, trabecular area; *CtAr*, cortical area; *CtTh*, cortical thickness; *PsPM*, periosteal perimeter; *EsPM*, endosteal perimeter; *SSI*, strength strain index

findings of lower MCP-I levels in Black children and adolescents compared to Whites is consistent with studies in several adult populations [47].

The most noteworthy finding in the current study was the significant inverse relationship observed between the pro-inflammatory biomarker of inflammation, MCP-1, and tibia CtTh. This inverse relationship makes sense given the biomarkers of inflammation investigated in this study are pro-resorptive and there is evidence for inflammation having a negative effect on bone outcomes [23]. MCP-1 is a chemokine that regulates migration and infiltration of monocytes and macrophages into body tissues and has been implicated in multiple chronic inflammatory diseases. For example, it is well established that chronic inflammatory diseases such as rheumatoid arthritis and cystic fibrosis are associated with impairments in bone quality [20, 21]. During growth, cortical bone expands and thickens through periosteal apposition and the cortical density and structural strength of the growing bone are determined by bone dimension and thickness. Thus, the negative association seen between MCP-1 and tibia CtTh is relevant and should be addressed in prospective trials to better ascertain if this negative association persists through growth and is linked with bone fragility and greater childhood fractures.

This is the first study to our knowledge that demonstrates a negative relationship between the serum biomarker of inflammation, MCP-1, and tibia CtTh in healthy children. This is important because it is during these years that children are developing maximum bone strength; thus, if inflammation attenuates bone strength in children, this could have long-term fracture implications in adulthood. Future studies should consider prospective study designs to confirm these cross-sectional findings, investigate potential mechanisms, and explore potential strategies for intervention.

There were several strengths to this study including the large sample size, diverse population, and the use of advanced imaging technology (i.e., pQCT) for the assessment of bone indices. Despite these strengths, this study is not without limitations. We calculated the DII score using 27 out of a possible 45 food parameters because these were the only components present in our database. Additionally, the DII score considers nutrients from foods but does not account for other bioactive components of foods such as lycopene, zeaxanthin, and lutein, which are thought to play a role in both inflammation and bone health [48, 49]. A dietary measurement at one-time point may not be a true reflection of a child's typical current dietary intake as many factors can influence a child's diet over time such as stage of development, seasons of the year, and family preferences [50]. Another limitation when analyzing the biomarkers of inflammation is the high variability associated with the methodologies. It is possible that the high variability in the biomarkers could limit the ability to detect significant relationships between DII and the biomarkers. For quality control, to reduce assay variability, one individual conducted batch analyses in a single lab at the same time. Despite these limitations, our results provide valuable insight into the relationships between dietary patterns, biomarkers of inflammation, and bone outcomes in a cohort of diverse healthy adolescents.

In conclusion, this was the first study to examine DII scores and bone outcomes in children and adolescents. In contrast to studies in older adults, the DII score was found not to be related to biomarkers of inflammation or bone strength. Because of the finding that the biomarker of inflammation, MCP-1, was negatively associated with tibia CtTh,

**Table 5** Bivariate and partial correlations between biomarkers of inflammation and radius bone outcomes

| | TNF-$\alpha$ | | | | IL-6 | | | | MCP-1 | | | | VEGF | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | | Unadjusted | | Adjusted | |
| | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* | *R* | *P* |
| CtBMD | −0.06 | .35 | −0.03 | .62 | 0.09 | .17 | −0.12 | .07 | −0.02 | .73 | −0.13 | .05 | 0.051 | .43 | 0.08 | .23 |
| CtBMC | −0.14 | .04 | −0.05 | .47 | < −0.01 | .95 | −0.03 | .62 | −0.03 | .62 | −0.04 | .55 | −0.03 | .64 | −0.06 | .36 |
| TtAr | −0.12 | .06 | −0.03 | .64 | −0.02 | .79 | −0.09 | .21 | −0.10 | .13 | −0.07 | .31 | −0.06 | .39 | −0.03 | .71 |
| CtAr | −0.14 | .03 | −0.05 | .48 | 0.01 | .83 | −0.02 | .82 | −0.10 | .11 | −0.01 | .94 | −0.06 | .37 | −0.06 | .41 |
| CtTh | −0.10 | .12 | −0.02 | .76 | 0.03 | .71 | −0.04 | .57 | −0.06 | .33 | −0.08 | .27 | −0.05 | .41 | −0.02 | .79 |
| PsPM | −0.12 | .07 | −0.03 | .68 | −0.02 | .80 | −0.08 | .23 | −0.10 | .14 | −0.60 | .35 | −0.05 | .47 | −0.04 | .60 |
| EsPM | −0.05 | .49 | −0.01 | .91 | −0.03 | .63 | −0.08 | .24 | −0.05 | .46 | −0.09 | .20 | −0.01 | .89 | −0.02 | .82 |
| SSI | −0.14 | .03 | −0.05 | .46 | < 0.01 | .99 | −0.06 | .35 | −0.11 | .09 | −0.04 | .57 | −0.07 | .31 | −0.04 | .54 |

Statistically significant at $P < .05$; $N = 290$; adjusted for stage of sexual maturation, sex, race, muscle cross-sectional area, and height. *CtBMD*, cortical bone mineral density; *CtBMC*, cortical bone mineral content; *TtAr*, trabecular area; *CtAr*, cortical area; *CtTh*, cortical thickness; *PsPM*, periosteal perimeter; *EsPM*, endosteal perimeter; *SSI*, strength strain index

future prospective studies should be conducted to better understand the role of inflammation on bone quality in youth and to determine if there are long-term fracture implications in adulthood.

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## Compliance with ethical standards

The Institutional Review Boards for Human Subjects at all study sites approved the study procedures. Participant informed assent and parental informed permission were obtained prior to all testing procedures.

**Conflicts of interest** Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

## References

1. Libby P (2006) Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 83:456S–460S
2. Martinez BK, White CM (2018) The emerging role of inflammation in cardiovascular disease. Ann Pharmacother 1060028018765939
3. Donath MY, Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 11:98–107
4. Skalicky J, Muzakova V, Kandar R, Meloun M, Rousar T, Palicka V (2008) Evaluation of oxidative stress and inflammation in obese adults with metabolic syndrome. Clin Chem Lab Med 46:499–505
5. Ginaldi L, Di Benedetto MC, De Martinis M (2005) Osteoporosis, inflammation and ageing. Immun Ageing 2:14
6. Ganesan K, Teklehaimanot S, Tran TH, Asuncion M, Norris K (2005) Relationship of C-reactive protein and bone mineral density in community-dwelling elderly females. J Natl Med Assoc 97:329–333
7. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire D, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2014) Heart disease and stroke statistics–2014 update: a report from the American Heart Association. Circulation 129:e28–e292
8. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S (2004) Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 350:2362–2374
9. Rubin DA, McMurray RG, Harrell JS, Hackney AC, Thorpe DE, Haqq AM (2008) The association between insulin resistance and cytokines in adolescents: the role of weight status and exercise. Metabolism 57:683–690
10. Pirkola J, Vaarasmaki M, Ala-Korpela M et al (2010) Low-grade, systemic inflammation in adolescents: association with early-life factors, gender, and lifestyle. Am J Epidemiol 171: 72–82
11. Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, Holgate ST, Jönsson LS, Latulippe ME, Marcos A, Moreines J, M'Rini C, Müller M, Pawelec G, van Neerven RJJ, Watzl B, Zhao J (2013) A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr 109(Suppl 1):S1–S34
12. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, Teeling JL, Blaak EE, Fenech M, Vauzour D, McArdle HJ, Kremer BHA, Sterkman L, Vafeiadou K, Benedetti MM, Williams CM, Calder PC (2015) Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr 114:999–1012
13. Sears B, Ricordi C (2011) Anti-inflammatory nutrition as a pharmacological approach to treat obesity. J Obes 2011:1–14

14. Nicklas TA, Baranowski T, Cullen KW, Berenson G (2001) Eating patterns, dietary quality and obesity. J Am Coll Nutr 20:599–608
15. Cavicchia PP, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Hebert JR (2009) A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr 139:2365–2372
16. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR (2014) Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 17:1689–1696
17. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Tabung F, Hebert JR (2014) A population-based dietary inflammatory index predicts levels of C-reactive protein in the seasonal variation of blood cholesterol study (SEASONS). Public Health Nutr 17:1825–1833
18. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, Hingle M, Hou L, Hurley TG, Jiao L, Martin LW, Millen AE, Park HL, Rosal MC, Shikany JM, Shivappa N, Ockene JK, Hebert JR (2015) Construct validation of the dietary inflammatory index among postmenopausal women. Ann Epidemiol 25:398–405
19. Shivappa N, Hebert JR, Marcos A et al (2017) Association between dietary inflammatory index and inflammatory markers in the HELENA study. Mol Nutr Food Res 61
20. Cauley JA, Danielson ME, Boudreau RM, Forrest KY, Zmuda JM, Pahor M, Tylavsky FA, Cummings SR, Harris TB, Newman AB, Health ABC Study (2007) Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. J Bone Miner Res 22:1088–1095
21. Hardy R, Cooper MS (2009) Bone loss in inflammatory disorders. J Endocrinol 201:309–320
22. Lien G, Selvaag AM, Flato B, Haugen M, Vinje O, Sorskaar D, Dale K, Egeland T, Forre O (2005) A two-year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis. Arthritis Rheum 52:833–840
23. Cheung WW, Zhan JY, Paik KH, Mak RH (2011) The impact of inflammation on bone mass in children. Pediatr Nephrol 26:1937–1946
24. Roth J, Palm C, Scheunemann I, Ranke MB, Schweizer R, Dannecker GE (2004) Musculoskeletal abnormalities of the forearm in patients with juvenile idiopathic arthritis relate mainly to bone geometry. Arthritis Rheum 50:1277–1285
25. Haring B, Crandall CJ, Wu C, LeBlanc ES, Shikany JM, Carbone L, Orchard T, Thomas F, Wactawaski-Wende J, Li W, Cauley JA, Wassertheil-Smoller S (2016) Dietary patterns and fractures in postmenopausal women: results from the Women's Health Initiative. JAMA Intern Med 176:645–652
26. Shivappa N, Hebert JR, Karamati M, Shariati-Bafghi SE, Rashidkhani B (2016) Increased inflammatory potential of diet is associated with bone mineral density among postmenopausal women in Iran. Eur J Nutr 55:561–568
27. Mazidi M, Shivappa N, Wirth MD, Hebert JR, Vatanparast H, Kengne AP (2017) The association between dietary inflammatory properties and bone mineral density and risk of fracture in US adults. Eur J Clin Nutr 71:1273–1277
28. Gordon CM, Zemel BS, Wren TA, Leonard MB, Bachrach LK, Rauch F, Gilsanz V, Rosen CJ, Winer KK (2017) The determinants of peak bone mass. J Pediatr 180:261–269
29. Lewis RD, Laing EM, Hill Gallant KM, Hall DB, McCabe GP, Hausman DB, Martin BR, Warden SJ, Peacock M, Weaver CM (2013) A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. J Clin Endocrinol Metab 98:4816–4825
30. Tanner JM (1975) The measurement of maturity. Trans Eur Orthod Soc, pp 45–60
31. Crawford PB, Obarzanek E, Morrison J, Sabry ZI (1994) Comparative advantage of 3-day food records over 24-hour recall and 5-day food frequency validated by observation of 9- and 10-year-old girls. J Am Diet Assoc 94:626–630
32. Bergman EA, Boyungs JC, Erickson ML (1990) Comparison of a food frequency questionnaire and a 3-day diet record. J Am Diet Assoc 90:1431–1433
33. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL (2000) CDC growth charts: United States. Adv Data 1–27
34. Warden SJ, Hill KM, Ferira AJ, Laing EM, Martin BR, Hausman DB, Weaver CM, Peacock M, Lewis RD (2013) Racial differences in cortical bone and their relationship to biochemical variables in Black and White children in the early stages of puberty. Osteoporos Int 24:1869–1879
35. Ferira AJ, Laing EM, Hausman DB, Hall DB, McCabe GP, Martin BR, Hill Gallant KM, Warden SJ, Weaver CM, Peacock M, Lewis RD (2016) Vitamin D supplementation does not impact insulin resistance in Black and White children. J Clin Endocrinol Metab 101:1710–1718
36. Kontulainen SA, Johnston JD, Liu D, Leung C, Oxland TR, McKay HA (2008) Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. J Musculoskelet Neuronal Interact 8:401–409
37. Pollock NK, Laing EM, Baile CA, Hamrick MW, Hall DB, Lewis RD (2007) Is adiposity advantageous for bone strength? A peripheral quantitative computed tomography study in late adolescent females. Am J Clin Nutr 86:1530–1538
38. Swinford RR, Warden SJ (2010) Factors affecting short-term precision of musculoskeletal measures using peripheral quantitative computed tomography (pQCT). Osteoporos Int 21:1863–1870
39. Berger PK, Pollock NK, Laing EM, Warden SJ, Hill Gallant KM, Hausman DB, Tripp RA, McCabe LD, McCabe GP, Weaver CM, Peacock M, Lewis RD (2014) Association of adenovirus 36 infection with adiposity and inflammatory-related markers in children. J Clin Endocrinol Metab 99:3240–3246
40. Binkovitz LA, Henwood MJ (2007) Pediatric DXA: technique and interpretation. Pediatr Radiol 37:21–31
41. Wetzsteon RJ, Zemel BS, Shults J, Howard KM, Kibe LW, Leonard MB (2011) Mechanical loads and cortical bone geometry in healthy children and young adults. Bone 48:1103–1108
42. Cole ZA, Harvey NC, Kim M, Ntani G, Robinson SM, Inskip HM, Godfrey KM, Cooper C, Dennison EM, Southampton Women's Survey Study G (2012) Increased fat mass is associated with increased bone size but reduced volumetric density in pre pubertal children. Bone 50:562–567
43. Correa-Rodriguez M, Rueda-Medina B, Gonzalez-Jimenez E, Correa-Bautista JE, Ramirez-Velez R, Schmidt-RioValle J (2018) Dietary inflammatory index, bone health and body composition in a population of young adults: a cross-sectional study. Int J Food Sci Nutr 1–7
44. Berteus Forslund H, Torgerson JS, Sjostrom L, Lindroos AK (2005) Snacking frequency in relation to energy intake and food choices in obese men and women compared to a reference population. Int J Obes 29:711–719
45. Sjoberg A, Hallberg L, Hoglund D, Hulthen L (2003) Meal pattern, food choice, nutrient intake and lifestyle factors in The Goteborg Adolescence Study. Eur J Clin Nutr 57:1569–1578
46. Dowd JB, Zajacova A, Aiello AE (2010) Predictors of inflammation in U.S. children aged 3-16 years. Am J Prev Med 39:314–320
47. Deo R, Khera A, McGuire DK, Murphy SA, Meo Neto Jde P, Morrow DA, de Lemos JA (2004) Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. J Am Coll Cardiol 44:1812–1818
48. Palozza P, Parrone N, Catalano A, Simone R (2010) Tomato lycopene and inflammatory cascade: basic interactions and clinical implications. Curr Med Chem 17:2547–2563

49. Chung RWS, Leanderson P, Lundberg AK, Jonasson L (2017) Lutein exerts anti-inflammatory effects in patients with coronary artery disease. Atherosclerosis 262:87–93
50. Birch L, Savage JS, Ventura A (2007) Influences on the development of children's eating behaviours: from infancy to adolescence. Can J Diet Pract Res 68:s1–s56
51. DeSalvo KB, Olson R, Casavale KO (2016) Dietary guidelines for Americans. JAMA 315:457–458