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Clinical Research Article

Dietary Inflammatory Index and Fractures in Midlife Women: Study of Women's Health Across the Nation

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Abstract

Context: While evidence suggests that chronic, low-grade inflammation is a risk factor for bone loss and fractures, the potential relation between an inflammatory dietary profile and greater fracture risk is uncertain.

Objective: We examined whether a more inflammatory diet, consumed during pre- and early perimenopause, is associated with more incident fractures starting in the menopause transition (MT) and continuing into postmenopause.

Methods: Dietary inflammatory potential was quantified using 2 energy-adjusted dietary inflammatory index scores: one for diet only (E-DII), and one for diet plus supplements (E-DII-S). We included 1559 women from the Study of Women's Health Across the Nation, with E-DII and E-DII-S scores from the baseline visit (during pre- or early perimenopausal), and up to 20 years of follow-up. We excluded women using bone-beneficial medications at baseline; subsequent initiators were censored at first use. The associations of E-DII or E-DII-S (each tested as separate exposures) with incident fracture were examined using Cox proportional hazards regression.

Results: Adjusted for age, BMI, cigarette use, diabetes, MT stage, race/ethnicity, prior fracture, bone-detrimental medication use, aspirin or nonsteroidal anti-inflammatory drug use, and study site, greater E-DII and E-DII-S (tested separately) were associated with more future fractures. Each SD increment in E-DII and E-DII-S predicted 28% ($P = .005$) and 21% ($P = .02$) greater fracture hazard, respectively. Associations were essentially unchanged after controlling for bone mineral density.

Conclusion: A more pro-inflammatory diet in pre- and early perimenopause is a risk factor for incident fracture. Future studies should consider whether reducing dietary inflammation in midlife diminishes fracture risk.

Key Words: dietary inflammatory index, fractures, menopause, population-based studies

Abbreviations: BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; E-DII, Energy-adjusted Dietary Inflammatory Index (computed based on food only); E-DII-S, E-DII based on food plus supplements; FFQ, food frequency questionnaire; FN, femoral neck; FPIR, family-adjusted poverty-to-income ratio; HR, hazard ratio; IL, interleukin; LS, lumbar spine; MT, menopause transition; OAI, Osteoarthritis Initiative; SWAN, Study of Women's Health Across the Nation; TASOAC, Tasmanian Older Adult Cohort Study; TNF, tumor necrosis factor; WHI, Women's Health Initiative.

There is increasing recognition that chronic, low-grade inflammation is a risk factor for bone loss, osteoporosis, and fractures (1). In experimental studies, pro-inflammatory cytokines such as IL-1 (2), IL-6 (3), IL-17 (4), TNF-alpha (5), and RANKL (6), promote osteoclastogenesis and bone resorption. In human cohorts, higher levels of these cytokines and C-reactive protein (CRP [an inflammatory marker produced in response to IL-1, IL-6, and TNF]) are associated with lower bone mineral density (BMD) (7), faster BMD decline (8-11), and more fractures (12-17). The link between inflammation and fracture is further supported by studies showing that IL-1 and TNF blockade (eg, with etanercept) prevents hypogonadal increases in bone resorption (18).

A growing body of literature points to poor diet as a primary source of chronic inflammation (19). An individual's diet may be more or less pro-inflammatory, depending on nutrient composition. Certain foods (eg, fatty fish rich in omega-3 fatty acids) (20, 21) and nutrients (eg, vitamin C) (22) may have anti-inflammatory properties. In contrast, other foods (eg, red meat (23)) can be pro-inflammatory. The energy-adjusted dietary inflammatory index (E-DII^{TM}) is a comprehensive, internationally standardized score that ranks an individual's diet from maximally anti-inflammatory to maximally pro-inflammatory (higher values indicate greater inflammatory potential) (24). Greater DII or E-DII scores are associated with higher circulating levels of inflammatory markers (eg, IL-1, IL-4, IL-6, IL-10, TNF-alpha, and CRP) (25, 26) and greater risk of chronic inflammatory medical conditions (notably, myocardial infarction) (27), supporting criterion validity.

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At the present time, whether a more inflammatory dietary pattern (a higher E-DII score) is associated with greater fracture risk is uncertain: results from several studies of mostly older adults are inconsistent (28-33). Moreover, to our knowledge, there have been no investigations of the potential relation between an inflammatory dietary profile and incident fractures starting early in the menopause transition (MT) and continuing into postmenopause, specifically. Bone turnover and bone loss accelerate during the MT (34, 35), and predict a greater incidence of fractures during the fifth and sixth decades of life (36-38). If a diet's inflammatory potential contributes to fracture during midlife, a diet-based intervention could be a novel, low-risk avenue for early risk reduction.

Accordingly, we designed a study using data from the Study of Women's Health Across the Nation (SWAN), a longitudinal study of the MT in a diverse cohort of community-dwelling women. Specifically, we assessed whether higher E-DII scores, assessed in pre- or early perimenopause, predicted greater rates of incident fracture starting in the MT and continuing into postmenopause. If we observed such a relation, our planned secondary analysis was to examine whether the relation between E-DII and fractures was independent of femoral neck (FN) or lumbar spine (LS) BMD (measured at the same time as the diet). SWAN computed 2 separate E-DII scores: one based on diet only (E-DII) and one that included input from diet plus dietary supplements (E-DII-S).

Methods

SWAN is a multicenter, longitudinal study of 3302 community-dwelling women (39). At study inception, participants were from 42 to 52 years of age, and in premenopause (no change from usual menstrual bleeding) or early perimenopause (less predictable menstrual bleeding at least once every 3 months). Exclusion criteria were not having an intact uterus and at least one ovary, or use of sex steroid hormones. Seven clinical sites recruited study participants: Boston, Chicago, Detroit, Pittsburgh, Los Angeles, Newark, and Oakland. The SWAN Bone Cohort was composed of 2365 participants from 5 sites (Chicago and Newark did not perform BMDs) and included Black, Chinese, Japanese, and White women. Each SWAN clinical site obtained Institutional Review Board approval, and all participants provided written informed consent.

Study Sample Derivation

Our analysis sample included 1559 women. To derive this sample, we started with all 2365 SWAN Bone Cohort participants and excluded: (1) women taking bone-beneficial (hormone therapy, calcitonin, calcitriol, bisphosphonates, denosumab, parathyroid hormone) or bone-detrimental (oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin releasing hormone agonists, or anti-epileptics) medications at study baseline (N = 129); (2) those taking aspirin or nonsteroidal anti-inflammatory drugs at baseline (N = 596); and (3) women without ≥1 follow-up visit (to permit observation for incident fracture) (N = 81).

Outcome

Incident fractures after the SWAN baseline visit were outcomes in analyses. Self-reported fractures were ascertained with standardized questionnaires. Questionnaires were administered at the SWAN baseline visit (to identify occurrence and location of fractures prior to SWAN inception, as well as age at time of fracture) and at each follow-up visit (to ascertain occurrence and location of fractures since the previous visit). For on-study fractures, SWAN began collecting precise fracture date at follow-up visit 7. For fractures reported at the first 6 follow-up visits, the fracture date was imputed as the midpoint between the participant's previous and index visit. Also starting at visit 7, medical records were obtained to adjudicate fractures; since inauguration of adjudication, 95% of self-reported fractures were confirmed. Fractures were considered low trauma if they did not occur after a fall from a height of 6 inches or more, a motor vehicle accident, moving fast (eg, skating), playing sports, or from impact with heavy or fast-moving projectiles. This analysis excluded craniofacial and digital fractures, but included low- and high-trauma fractures, as both fracture types are associated with low BMD (40, 41).

Primary Exposure

The primary exposures were E-DII scores computed from dietary data acquired at baseline. E-DII is a literature-derived, population-based tool that quantifies an individual's diet on a continuum from maximally anti-inflammatory to maximally pro-inflammatory (range, −8.87 to 7.98; higher scores reflect greater inflammatory potential) (24). The scoring algorithm for E-DII considers up to 45 food parameters. The overall inflammatory effect score of each food parameter is calculated based on its relation (negative, positive, or null) with inflammatory markers (IL-1, IL-4, IL-6, IL-10, TNF-alpha, and CRP). The inflammatory effect for each food parameter is then multiplied by the amount consumed (standardized against the mean intake values from a global dataset representing diverse world regions and diets). Lastly, this product is summed for all foods reported. Greater DII scores are associated with higher levels of inflammatory markers (25, 26).

E-DII scores were calculated based on the SWAN food frequency questionnaire (FFQ), an adapted version of the Block FFQ (42). The SWAN FFQ assessed usual intake, over the prior 3 months, of 31 of the 45 food parameters that are E-DII components: alcohol, vitamin B12, vitamin B6, beta carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fiber, folic acid, iron, magnesium, monounsaturated fatty acid, niacin, omega 3, omega 6, onion, protein, polyunsaturated fatty acid, riboflavin, saturated fat, selenium, thiamin, trans fat, vitamin A, vitamin C, vitamin D, vitamin E, zinc, green or black tea, and isoflavones. The SWAN FFQ was missing 12 E-DII food parameters: ginger, turmeric, garlic, oregano, pepper, rosemary, eugenol, saffron, flavan-3-ol, flavones, flavonols, flavonones, and anthocyanidins. Energy was not included as E-DII was adjusted for energy. However, in other studies, foods absent from the SWAN FFQ were consumed in low amounts and did not substantially influence E-DII scores (24-26). To obtain an energy-standardized E-DII score, we quantified the intake of each food parameter per 1000 kcal of food energy intake, using an energy-standardized version of the global composite database. SWAN computed 2 separate E-DII scores: one based on diet only (E-DII) and one that included input from diet plus dietary supplements (E-DII-S).

Covariates

Models adjusted for risk factors for fracture. For the following covariates, we included values obtained at baseline: age, MT stage (pre- or early perimenopausal), race/ethnicity, fracture

prior to SWAN baseline (yes/no), body mass index (BMI, weight in kilograms/[height in meters]^2), current cigarette use (yes/no), diabetes mellitus diagnosis (yes/no), and FN or LS BMD. Models also accounted for use of bone-detrimental medications, and use of aspirin or nonsteroidal anti-inflammatory medications. We quantified use of these agents as cumulative exposure (ie, the percent of visits after the baseline visit until the final observation visit that a participant reported use). Diabetes was defined as a fasting blood glucose of ≥126 mg/dL or use of a diabetes medication (metformin, sulfonylurea, meglitinide, thiazolidinedione, dipeptidyl peptidase-IV inhibitor, glucagon-like peptide 1 agonist, insulin). At all study visits, SWAN measured FN and LS BMD by dual-energy x-ray absorptiometry using Hologic 4500A (Boston, Detroit, and Los Angeles) or Hologic 2000 instruments (Davis and Pittsburgh) (Hologic, Inc., Waltham, Massachusetts). A standard BMD quality-control program, conducted in collaboration with Synarc, Inc. (Newark, CA), included daily phantom measurements, SWAN site cross-calibration with a circulating anthropomorphic spine standard, local site review of all scans, and central review of scans that met problem-flagging criteria.

To assess whether models should be adjusted for rate of *change* in BMD during follow-up, rate of *change* in BMI during follow-up, or diabetes status during follow-up (ie, the proportion of all study visits that a participant had diabetes), we examined Spearman rank correlations between each of these variables and E-DII or E-DII-S. Correlations were very small ($r < 0.1$ for all pairs), suggesting that DII did not have substantial associations with BMD, BMI, or diabetes over time; therefore, these exposures were not included in models.

Women with less inflammatory diets may also have other healthy lifestyle habits and higher socioeconomic status that could benefit fracture risk. Thus, we conducted sensitivity analyses in which we re-ran the above models but added controls for lifestyle and socioeconomic status variables that also relate to fractures. These included calcium intake (dietary and supplemental) (43), leisure time physical activity (44), education level (45), and family-adjusted poverty-to-income ratio (FPIR) (45). Leisure time physical activity was recorded at the SWAN baseline visit using the sport/exercise domain of the Kaiser Physical Activity Survey and scored on a scale of 1 (lowest) to 5 (highest) (46). Socioeconomic status, including education, household income, and household composition, was also assessed at study baseline. We collapsed education level into 4 categories: high school or less, some college, baccalaureate, or at least some postgraduate education. FPIR was calculated from household income and composition to index total household income against the number of household members and the census-defined poverty level by geographic region. For example, a FPIR of 2 indicates that the total household income is 2 times greater than the census-specified poverty level, adjusted for number of household members.

Statistical Analysis

We generated descriptive statistics for all variables to assess their distribution.

For each E-DII exposure (E-DII or E-DII-S), we designed analyses to answer 2 questions: (Q1) Does baseline E-DII or E-DII-S predict incident fracture during follow-up; and (Q2) Is the hypothesized relationship between E-DII or E-DII-S with fracture independent of starting BMD?

To examine whether baseline E-DII or E-DII-S scores were associated with subsequent fracture, (Model 1), we used Cox proportional hazards regression with time to first fracture as the outcome (clock starting at SWAN baseline), and E-DII or E-DII-S as primary predictors in separate models. Model 1 covariates included: age (years), MT stage (pre- vs early perimenopause), diabetes mellitus (yes/no), cigarette use (yes/no), BMI (kg/m^2), race/ethnicity, fracture prior to SWAN baseline (yes/no), study site, cumulative exposure to bone-detrimental medications, and cumulative exposure to aspirin or nonsteroidal anti-inflammatory drugs. Participants were censored at first use of bone-beneficial medications.

Our second set of analyses examined whether the proposed relations of E-DII and E-DII-S with fracture were independent of BMD measured at the same time as the dietary assessment. Specifically, to Model 1, we added controls for FN (Model 2A) or LS (Model 2B) BMD.

In sensitivity analyses, we re-ran the above models but additionally adjusted for calcium intake, leisure time physical activity, education level, and FPIR.

Results

Sample Characteristics

Table 1 presents relevant characteristics of the 1559 participants. Twenty-six percent of the sample was Black, 15% Chinese, 17% Japanese, and the remaining White. At SWAN baseline, mean age and BMI were 45 years and 27.0 kg/m^2, respectively. Four percent of participants had diabetes mellitus. E-DII and E-DII-S scores were normally distributed; on average, women had E-DII and E-DII-S scores of 0.5 and −0.1, respectively. Mean E-DII and E-DII-S scores differed by race/ethnicity, but their distributions overlapped substantially.

E-DII and E-DII-S as Predictors of Incident Fracture

In total, 175 participants sustained an incident fracture during follow-up. Fractures occurred most commonly at the foot, ankle, arm (excluding wrist), wrist, and leg. Three women sustained clinical vertebral fractures and 2 women fractured their hips (Table 2). On average, the observation period for women who sustained a fracture (time to first fracture) spanned 7.8 years (range, 0.3 to 19.4 years), while observation time for those without fracture (time to last follow-up visit) was 10.3 years (range, 0.8 to 20.3 years).

Greater E-DII scores at SWAN study baseline predicted greater rates of incident fracture and these associations were independent of starting BMD (Table 3). Using Cox proportional hazards regression to adjust for age, MT stage, BMI, cigarette use, diabetes diagnosis, race/ethnicity, prior fracture, study site, use of bone-detrimental medications, and use of aspirin or nonsteroidal anti-inflammatory drugs (Model 1), the hazard ratio (HR) for subsequent fracture for each SD increment in baseline E-DII was 1.28 (95% CI 1.08, 1.52). The magnitude and statistical significance of this relation was essentially unchanged after accounting for baseline FN (Model 2A) or LS (Model 2B) BMD. Specifically, after adjustment for BMD, the standardized HRs in Models 2A and 2B were 1.26 (95% CI 1.06, 1.49) and 1.23 (95% CI 1.03, 1.46), respectively. Also, in BMD-adjusted models, greater BMI was associated with greater fracture hazard: HRs per SD increment in BMI were 1.31 (95% CI 1.10, 1.57) in Model 2A, and 1.19 (95% CI 1.01, 1.42) in Model 2B.

Table 1. Dietary Inflammatory Index and fractures in the Study of Women's Health Across the Nation: description of analytic sample N = 1559

Characteristics[a]	Mean value (SD) or count (%)
Age, years	45.8 (2.7)
Race/ethnicity	
Black	390 (25%)
Chinese	203 (13%)
Japanese	226 (15%)
White	740 (47%)
Dietary Inflammatory Index, food only (E-DII)[b]	
All participants	0.5 (2.3)
Black	1.6 (2.1)
Chinese	−0.9 (2.3)
Japanese	−0.1 (2.1)
White	0.5 (2.3)
Dietary Inflammatory Index, food + supplements (E-DII-S)[c]	−0.1 (2.4)
All participants	1.1 (2.3)
Black	−1.2 (2.2)
Chinese	−1.0 (2.2)
Japanese	−0.1 (2.4)
White	
Menopause transition stage	
Premenopause	894 (57%)
Early perimenopause	665 (43%)
Body mass index, kg/m^2	27.0 (6.7)
Bone mineral density, g/cm^2	
Lumbar spine	1.068 (0.136)
Femoral neck	0.836 (0.133)
Cigarette use	
Yes	211 (14%)
No	1348 (86%)
Diabetes mellitus diagnosis	
Yes	53 (4%)
No	1506 (96%)
Bone-detrimental medications, ever use[d,e]	
Yes	206 (13%)
No	1353 (87%)
Bone-detrimental medications, percent of visits	29 (6)
Aspirin or nonsteroidal anti-inflammatory drugs, ever use[d]	
Yes	430 (27%)
No	1129 (73%)
Aspirin or nonsteroidal anti-inflammatory drugs, percent of visits	26 (5)

[a]Values for age, E-DII, E-DII-S, menopause transition stage, body mass index, bone mineral density, cigarette use, and presence of diabetes mellitus were those obtained at the SWAN baseline visit. Use of bone-detrimental medications was quantified as the percent of visits (from baseline to final follow-up) at which bone-detrimental medications were used. Bone-detrimental medications were oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin releasing hormone agonists, or anti-epileptics. Use of aspirin or nonsteroidal anti-inflammatory drugs calculated the same way.
[b]Energy-adjusted dietary inflammatory index score (food only), computed from the SWAN food frequency questionnaire. Scale range was −6.0 to 6.1, with higher scores indicating more inflammatory dietary patterns.
[c]Energy-adjusted dietary inflammatory index score (food plus supplements), computed from the SWAN food frequency questionnaire. Scale range was −6.5 to 6.2, with higher scores indicating more pro-inflammatory dietary patterns.
[d]"Ever use" defined as reporting use of a bone-detrimental medications, aspirin or nonsteroidal anti-inflammatory drugs at ≥1 study visit after the SWAN baseline visit up to the final observation visit.
[e]Bone-detrimental medication use in the analysis sample (note, some participants used more than one): glucocorticoids (N = 181), aromatase inhibitors (N = 53), gonadotropin releasing hormone agonists (N = 4), anti-epileptics (N = 8).

Similar to E-DII, higher E-DII-S scores were also associated with more future fractures and these relations were independent of starting BMD at the FN and LS. In Model 1, before adjustment for BMD, each SD increment in E-DII-S was associated with a HR for incident fracture of 1.21 (95% CI 1.02, 1.42). The Model 1 relative hazard and CI were not substantially altered by adjustment for FN (Model 2A: 1.20 [95% CI 1.01, 1.41]) or LS (Model 2B: 1.19 [95% CI 1.00, 1.39])

BMD. Standardized HRs for BMI in Model 2A and Model 2B were 1.31 (95% CI 1.10, 1.58) and 1.20 (95% CI 1.01, 1.42), respectively.

Sensitivity Analyses

In sensitivity analyses that also adjusted for calcium intake, leisure time physical activity, education level, and FPIR, HRs for E-DII and E-DII-S were nearly identical to those in models without controls for lifestyle and socioeconomic status variables (data not shown).

Table 2. Dietary Inflammatory Index and fractures in the Study of Women's Health Across the Nation: incident fractures during the study observation period[a,b]

Fracture site	Number of fractures (%)
Foot	44 (25%)
Ankle	36 (21%)
Arm (above wrist)	24 (14%)
Wrist	22 (13%)
Leg	18 (10%)
Ribs	11 (6%)
Shoulder	5 (3%)
Hand	8 (5%)
Clinical Vertebral	3 (2%)
Hip	2 (1%)
Pelvis	2 (1%)
Total	175

[a]Includes low-trauma (N = 92) and high-trauma (N = 83) fractures. See "Methods" for definition of low- vs high-trauma. Vertebral fractures were clinically diagnosed; serial radiographs were not performed.
[b]Observation period for fracture, starting at the SWAN baseline visit and lasting until the first incident fracture or last SWAN study visit (whichever occurred first).

Discussion

This study examined whether pro-inflammatory dietary patterns consumed by pre- and early perimenopausal women were associated with greater incidence of fracture starting in the MT and continuing into postmenopause, before and after adjustment for BMD measured contemporaneously with diet. We report that both greater E-DII and E-DII-S scores predicted greater rates of future fractures, and this relation was independent of starting BMD.

Few studies have examined the relation between E-DII scores and fracture in women, and results of these investigations are inconsistent (28-33). Participants in prior studies range in age from 40 to 83 years and mean ages are in the early 60s (31). Three cross-sectional analyses from the Brazilian Osteoporosis Study (BRAZOS) (28), the National Health and Nutrition Examination Survey (NHANES) (29), and a sample of adults from Guangzhou, China (30) reported that women with higher DII or E-DII scores were more likely to have prevalent fractures, concordant with our findings. Three longitudinal studies of DII or E-DII predicting incident fractures presented discordant results from each other and from our study (31-33). The Osteoarthritis Initiative (OAI) reported that in a sample of 2071 women, each SD increment in DII score was related to a 14% greater hazard for incident forearm, hip, or vertebral fracture (31). Conversely, the primary analysis of 160 191 postmenopausal women from the Women's Health Initiative (WHI) Clinical Trials and

Table 3. Associations of energy-adjusted dietary inflammatory index score computed based on food only and based on food plus supplements with incident fracture, before and after adjustment for bone mineral density

	Hazard ratio for fracture (95% CI)					
	Model 1[b]		Model 2A[c]		Model 2B[d]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
E-DII[a]	1.28 (1.08, 1.52)	.005	1.26 (1.06, 1.49)	.009	1.23 (1.03, 1.46)	.01
Femoral neck BMD[a]	—	—	0.62 (0.50, 0.76)	<0.0001	—	—
Lumbar spine BMD[a]	—	—	—	—	0.75 (0.63, 0.89)	.001
	Hazard ratio for fracture (95% CI)					
	Model 1[b]		**Model 2A[c]**		**Model 2B[d]**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
E-DII-S[a]	1.21 (1.01, 1.42)	.02	1.20 (1.01, 1.42)	.03	1.18 (1.00, 1.39)	.04
Femoral neck BMD[a]	—	—	0.61 (0.50, 0.76)	<.0001	—	—
Lumbar spine BMD[a]	—	—	—	—	0.75 (0.64, 0.89)	.001

Abbreviations: BMD, bone mineral density; E-DII, energy-adjusted dietary inflammatory index (computed based on food only); E-DII-S, E-DII based on food plus supplements; HR, hazard ratio.
[a]All exposure variables are per SD.
[b]Model 1: Cox proportional hazards regression with time to first fracture (clock starting at SWAN baseline) as outcome, and E-DII or E-DII-S as primary predictor (each tested separately). Covariates include age (years), menopause transition stage (pre- vs early perimenopause), BMI (kg/m^2), diabetes mellitus (yes/no), cigarette use (yes/no), race/ethnicity, prior fracture (yes/no), exposure to bone-detrimental medications, exposure to aspirin or nonsteroidal anti-inflammatory drugs, and study site. Bone-detrimental medications were oral or injectable glucocorticoids, aromatase inhibitors, gonadotropin releasing hormone agonists, or anti-epileptic medications. Values for all covariates were obtained from the SWAN baseline visit, except for exposure to bone-detrimental medications, and exposure to aspirin or nonsteroidal anti-inflammatory drugs. Exposure to these agents were modeled as the percentage of visits at which women reported use during the observation period.
[c]Model 2A: Model 1 with additional adjustment for femoral neck bone mineral density measured at SWAN baseline.
[d]Model 2B: Model 1 with additional adjustment for lumbar spine bone mineral density measured at SWAN baseline.

Observational Study produced an unexpected result: DII scores in the highest quartile were associated with a 5% *lower* hazard of any subsequent fracture. Stratification of the sample by race/ethnicity and age revealed that White women younger than 63 years with dietary inflammation in the highest quartile had a 48% greater hip fracture hazard (32). In 562 European women, the Tasmanian Older Adult Cohort Study (TASOAC) found that, with a control for total hip BMD, each unit increment in E-DII score was associated with a 12% *lower* risk of any incident fracture. E-DII was not related to non-vertebral fracture (33).

Discrepancies in findings among the above longitudinal studies and with ours may stem from several methodological and analytic differences. First, the DII or E-DII exposure varied across analyses. The OAI, WHI, and TASOAC computed their DII or E-DII scores using 24, 32, and 19 (out of 45) food inputs, respectively (31-33). Mean scores ranged from a low of −3.4 in OAI to −0.7 in WHI and TASOAC; SWAN's average E-DII score was 0.5, more in line with the US average (47). Second, the effect of dietary inflammation on fracture may be modified by age, evidenced by WHI only finding a link between dietary inflammation and hip fracture in younger women (32). The positive relation between E-DII and E-DII-S with fracture in our analysis could be a function of the younger age of our cohort. Lastly, the analytic treatment of bone-beneficial medications may influence results. OAI and WHI both adjusted for baseline hormone therapy use, and OAI additionally adjusted for baseline bisphosphonate use. However, it may be more appropriate to exclude and subsequently censor those being treated with bone-beneficial medications. In WHI, women with more pro-inflammatory diets lost bone more rapidly during follow-up (32). They, therefore, may have been more likely to initiate bone-beneficial medications, making it appear that more dietary inflammation leads to fewer fractures. Excluding (and subsequently censoring) bone-beneficial medication could account for our ability to detect a positive E-DII-fracture relation.

Beyond methodological differences, our study differs from the previously published body of literature by being the first, to our knowledge, to specifically demonstrate that a more inflammatory diet assessed in midlife, when women are pre- or early perimenopausal (average age 45.8 years), predicts a greater rate of incident fracture beginning in the MT and continuing into postmenopause. Moreover, in our analysis, the fracture risk conferred by greater dietary inflammation was independent of BMD. Identifying risk factors for appendicular fractures that occur when women are in the fifth to seventh decades of life is important not only because they directly lead to morbidity (48-50), but because they double the risk of hip fractures in older age (51-55). Our results suggest that reducing the diet's inflammatory profile prior to or during middle age could be a novel approach for early fracture risk reduction, regardless of starting BMD.

We cannot discern, from this analysis, the mechanism(s) by which a more inflammatory diet contributes to fracture. Controlling for BMD did not substantively attenuate the associations of E-DII or E-DII-S with fracture, supporting that lower starting BMD does not explain this relation. Pro-inflammatory diets may also lead to fracture through non-BMD-related, muscular pathways that predispose to falls. In experimental studies, TNF-alpha causes muscle atrophy, and TNF-alpha positively relates to E-DII (56, 57). In humans, higher CRP is associated with more sarcopenia, diminished grip strength, and slower walking speed (58, 59). Greater E-DII also predicts more falls (33). Thus, women transitioning through menopause, when lean mass loss accelerates (60), may be especially vulnerable to insults to the musculature.

In fully adjusted models, greater BMI was associated with greater fracture hazard, which may appear paradoxical. However, it is consistent with emerging data that the relation between BMI and fracture is site-dependent: greater BMI is a risk factor for distal appendicular fractures (61-63). Although more fat mass and higher BMI relate to higher BMD (64), they are associated with more fractures at distal appendicular sites that have less fat cushion and greater vulnerability to impact forces (61-63).

Our analysis has a number of strengths. SWAN is the largest longitudinal study of the MT and is the ideal cohort in which to investigate the longitudinal relations of E-DII in midlife with incident fractures. After approximately 2 decades of follow-up, cohort retention remains high at nearly 80%. Also, at each follow-up visit, SWAN collected data on an expansive number of relevant covariates (including bone-active medications), permitting us to exclude or censor bone-beneficial medication users in analyses. SWAN measured 32 of the 45 DII foods, placing it at the high end of E-DII ascertainment in comparison to other fracture outcome studies. Moreover, prior work demonstrated that SWAN's 12 missing items do not alter E-DII scores substantially (25, 26). Starting a third of the way into SWAN, fractures were adjudicated, with 95% agreement between medical records and self-report. Our study's limitations also warrant consideration. To maximize the number of fracture events, we included both low- and high-trauma fractures in one composite outcome. We justify this approach because both fracture types are associated with lower BMD (40, 41). Because E-DII and E-DII-S scores were obtained from 1 single time point (SWAN baseline), our analysis did not account for possible changes in dietary patterns between the baseline visit and end of follow-up. We acknowledge that participant diets may have changed, but these changes would have introduced a conservative bias (32). Finally, inferring nutritional causality in observational studies can be constrained due to potential confounding by lifestyle and socioeconomic status. However, we do not believe that the observed relation between dietary inflammation and fracture was substantively confounded by these factors, as adjustment for calcium intake, leisure time physical activity, education level, and FPIR in sensitivity analyses did not substantially alter the HRs for E-DII or E-DII-S.

To conclude, this study demonstrates that more inflammatory diets, measured in pre- and early perimenopause, predict greater rates of incident fractures in the fifth to seventh decades of life, and this relation is independent of starting BMD. Future studies should investigate the mechanisms by which pro-inflammatory diets contribute to fracture, including the relation between dietary inflammation and change in body composition over time.

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Author Contributions

Participant recruitment for the parent SWAN study was contributed by G.A.G. Calculation of E-DII scores by M.H.H., N.S., M.D.W., J.R.H. Study conception by A.S., A.S.K., G.A.G. Analytic design by A.S., A.S.K., M.H.H., G.A.G. Data analysis by A.S., M.H.H. Primary manuscript drafting by A.S., G.A.G. Critical review and revision of manuscript by A.S., A.S.K., M.H.H., N.S., M.D.W., J.R.H., A.S.K.

Disclosures

A.S., A.S.K., M.H., and G.A.G. have nothing to disclose. 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 smart phone applications for patient counseling and dietary intervention in clinical settings. CHI owns exclusive right to the E-DII™. Drs. Nitin Shivappa and Michael Wirth are employees 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.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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