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# THE RELATIONSHIP BETWEEN THE DIETARY INFLAMMATORY INDEX AND PREVALENCE OF RADIOGRAPHIC SYMPTOMATIC OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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**Disclosure**: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

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## Abstract

**Purpose—**To investigate whether higher dietary inflammatory index (DII®) scores were associated with higher prevalence of radiographic symptomatic knee osteoarthritis in a large cohort of North American people from the Osteoarthritis Initiative database.

**Methods—**4,358 community-dwelling participants (2527 females; mean age: 61.2 years) from the Osteoarthritis Initiative were identified. DII was calculated using the validated Block Brief 2000 Food-Frequency Questionnaire and categorized into quartiles. Knee radiographic symptomatic osteoarthritis was diagnosed clinically and radiologically. The strength of association between DII (divided in quartiles) and knee osteoarthritis was investigated through a logistic regression analysis and reported as odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for potential confounders.

**Results—**Participants with a higher DII score, indicating a more pro-inflammatory diet, had a significantly higher prevalence of radiographic symptomatic knee osteoarthritis compared to those with lower DII score (Quartile 4: 35.4% vs. Quartile 1: 24.0%; $p<0.0001$). Using a logistic regression analysis, adjusting for 11 potential confounders, participants with the highest DII score (Quartile 4) had a significantly higher probability of experiencing radiographic symptomatic knee osteoarthritis (OR: 1.40; 95% CI: 1.14 to 1.72; $p=0.002$) compared to participants with the lowest DII score (Quartile 1).

**Conclusions—**Higher DII values are associated with higher prevalence of radiographic symptomatic knee osteoarthritis.

### Keywords

knee osteoarthritis; dietary inflammatory index; inflammation

## INTRODUCTION

Chronic inflammation is associated with an increased risk of developing several age-related diseases though a process commonly termed as “inflammaging”.[1, 2] Higher levels of inflammatory markers have been associated with negative clinical outcomes among older people including reduced physical performance[3, 4], cardiovascular disease,[5] and fractures.[6] Knee osteoarthritis (OA) is a musculoskeletal disease highly prevalent in older people. The prevalence of knee OA linearly increases with age, with a worldwide prevalence estimated to be 10% in men and 20% in women over the age of 60 years.[7] Osteoarthritis of the knee has been associated with reduced quality of life and increased mortality in this population[8]. It is the 11$^{th}$ highest contributor to global disability.[9]

Inflammation has been reported to play an important role in the development and progression of knee OA.[10] This has been acknowledged through a number of features. For example, synovitis (defined as inflammation of the synovial membrane) is an early and

common finding in individuals with knee OA.[10] Epidemiologic studies have showed that serum levels of C-reactive protein (CRP) are significantly associated with a higher incidence and progression of knee OA.[11] Other studies have confirmed a positive correlation between levels of serum CRP and histologic evidence of synovitis pre-joint replacement.[12] These observations strongly suggest that the systemic inflammation observed in knee OA is at least partially reflective of local synovial inflammation.[10]

The Dietary Inflammatory Index (DII) is literature derived dietary tool developed to assess the overall inflammatory potential of individual's diet.[13, 14] Higher DII values are associated with higher serum interleukin (IL)-6 and tumor necrosis factor (TNF)-R2 levels, thus suggesting a close relationship between this index and inflammatory parameters.[15] The DII has also been shown to be associated with metabolic syndrome, asthma, breast cancer, colorectal cancer and fractures.[16–19] However, to the best of our knowledge, no study has explored the association between DII and knee OA.

The purpose of this study was therefore to investigate whether increasing DII scores were associated with the increased prevalence of knee OA (diagnosed through radiological and clinical findings) using a large cohort of North American people from the Osteoarthritis Initiative database.

## MATERIALS AND METHODS

### Data source and subjects

Data were gathered from the Osteoarthritis Initiative (OAI) database. The OAI is freely available (http://www.oai.ucsf.edu/). Within the OAI, potential participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In this analysis, we identified people who either: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA[20] with data collected during baseline and screening evaluations. All participants provided informed written consent.

The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center, at University of California in San Francisco. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### Dietary data and Dietary inflammatory index (exposure)

Dietary pattern was analyzed using a validated tool, the Block Brief 2000 Food Frequency Questionnaire (FFQ) during the baseline visit.[21] Seventy items were assessed to determine an individual's typical food and beverage consumption over the past year. The frequency of consumption was reported at nine levels of intake from "never" to "every day". In addition, seven dietary behavior questions were asked regarding food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

The DII was developed by Cavicchia *et al.* [13] and updated by Shivappa *et al.* and the calculation process was documented elsewhere. [14] High sensitivity CRP measurements were used to examine construct validity of the DII in a longitudinal cohort using 24-hour dietary recall interviews and 7-day dietary recalls, and then the new DII was also validated testifying its effectiveness in four studies among different populations with an extended number of inflammatory biomarkers (e.g., interleukin, IL-6, hs-CRP, and TNF-α).[15, 22–25] In updated version, 1943 peer reviewed articles were reviewed and scored. Forty-five food parameters, including foods, nutrients, and other bioactive compounds, were evaluated based on their inflammatory effect on six specific inflammatory markers, such as CRP, IL-1β, IL-4, IL-6, IL-10 and tumor necrosis factor (TNF)-α. A regionally representative world database provided global daily intake for each of the 45 parameters (i.e. foods, nutrients, and other food components) was used as standard dietary intake to calculate the DII (food consumption from eleven populations globally). 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 percentiles (minimizing effects of outliers/right- skewing), then doubled the value and subtracted 1 to achieve symmetrical distribution with values centred on 0. 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. The inflammatory score for each food parameter derived from a literature review on the basis of 1943 articles representing studies of different design on diet and inflammation. Using the FFQ, we calculated the DII based on energy-adjusted intake of the 33 single food parameters using the energy density approach which calculated per 4184 kJ (1000 kcal) of energy.[26] Overall, 24 of the 45 possible food parameters used for the DII calculation were available in this study, and these food parameters were vitamin $B_{12}$, vitamin $B_6$, β-carotene, carbohydrate, cholesterol, fat, fibre, folic acid, iron, magnesium, monounsaturated fat acids (MUFA), niacin, protein, polyunsaturated fatty acids (PUFA), riboflavin, saturated fat acids(SFA), selenium, thiamin, vitamin A, vitamin C, vitamin E, vitamin D, zinc, niacin, caffeine.

## Outcome

The presence of radiographic symptomatic knee OA was defined as the combination of pain and stiffness (i.e. pain, aching or stiffness in or around the knee on most days during the last year), evaluated using the WOMAC (Western Ontario and McMaster Universities Arthritis Index),[27] and radiographical OA on the baseline fixed flexion radiograph based on the presence of tibiofemoral osteophytes, correspondent to Osteoarthritis Research Society International atlas grades 1–3, clinical center reading.[28] In the OAI, the presence of pain, stiffness, and physical functioning (or disability) due to OA was assessed through the WOMAC (Western Ontario and McMaster Universities Arthritis Index).[27] Briefly, the responses for each subscale (pain, stiffness, disability) are categorized on a five-point Likert scale ranging from none (0 points) to extreme (4 points). The maximum possible score is 68, and the final score was normalized to 100 (range 0–100), with higher scores reflecting greater activity limitations. [27]

We also considered a subgroup analysis according to the presence of radiographic symptomatic knee OA diagnosed only through radiological information defined as grade > 2 of the classification proposed by Kellgren and Lawrence vs. lower grades [29] or the presence of pain at any knee asking the subject if he/she experienced pain most days (i.e. more than half) of a month in past 12 months and categorized as yes vs. no or not more than half days.

## Covariates

Eleven covariates were identified *a priori* as potential confounding factors. These included (other than age and sex): body mass index (BMI); physical activity evaluated using the total score for the Physical Activity Scale for the Elderly scale (PASE)[29]; race; smoking habit (current/previous vs. never), educational attainment level (college or higher vs. others) and yearly income (categorized in <, ≥ $50,000, missing data). Since our previous works reported a significant association between knee OA and depression[30], we included this factor as potential moderator for the analyses using the Center for Epidemiologic Studies Depression Scale (CES-D).[30] Validated general health measures of self-reported comorbidities were assessed through the modified Charlson Comorbidity Index score[31]. Among these, we specifically assessed five common comorbidities: myocardial infarct and failure, stroke, diabetes and cancer. We finally included the use of several medications used for treating symptoms of knee OA such as acetaminophen, non-prescribed (e.g. aspirin) and prescribed (e.g. ibuprofen) NSAIDs, coxibs, narcotics, S-adenosylmethionine, methylsulfonylmethane, or doxycycline.

## Statistical analyses

A Kolmogorov-Smirnov test determined that the continuous variable data were normally distributed. Data were presented as means and standard deviation values (SD) for quantitative measures, and frequency and percentages for all discrete variables. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used. In descriptive analyses (such as those reported in Table 1), p-values were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones. To assess the relationship between DII score and radiographic symptomatic knee OA, a logistic regression analysis was conducted where the presence of radiographic symptomatic knee OA considered the 'outcome' and the DII score as the 'exposure'. DII was also categorized into quartiles and taking in Quartile 1 (=lowest DII) as the reference group. The basic model was not adjusted for any confounders. The fully adjusted model included the following adjustments: age (as continuous); sex; race (whites vs. others); BMI (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Charlson Comorbidity Index; PASE score (as continuous); use of medications for knee OA (yes vs. no); CES-D (as continuous).

Multi-collinearity among covariates was assessed through variance inflation factor (VIF), taking a cut-off of two as reason of exclusion. No covariates were excluded for this reason. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between DII (reported as quartiles) and radiographic

symptomatic knee OA. Similarly, this variable was modelled as continuous (i.e. increase in one standard deviation) and adjusted for the same covariates reported before. A similar analysis was run taking the presence of only radiological knee OA or the presence of pain at one of the two knees as outcomes. Several sensitivity analyses were conducted evaluating the interaction between DII and selected factors (e.g. age below or more than 65 years, overweight/obesity vs. normal weight, yearly income, gender, race, education, smoking habits, yearly income) in the association with radiographic symptomatic knee OA, but no factor was significant ($p>0.05$ for the interaction).

A $p<0.05$ was deemed statistically significant. All analyses were performed using SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois).

## RESULTS

### Sample selection

The OAI dataset includes a total of 4,796 individuals. 438 participants were not included in the analysis. This was due to insufficient data to calculate DII (n=129), hip or knee replacement or did not have a clinical and/or radiological assessment for knee OA (n=247), unreliable caloric intake (<500 or >5000 Kcal/day) (n=62). Accordingly, 4,358 participants were included in these analyses.

### Descriptive characteristics

The cohort consisted of 2,527 females (58.0%). Mean age was 61.2 years (±9.1 years; range: 45–79) and mean DII was −3.17 (±1.67 points; range: −5.65 to 3.57). The prevalence of radiographic symptomatic knee OA (diagnosed per the presence of pain, stiffness and radiographical tibiofemoral osteophytes) was 29.1%.

Table 1 illustrates the baseline characteristics by DII quartiles. Those in the highest quartile (reflecting most pro-inflammatory diet) were significantly younger, more likely to be male, with lower educational level than other participants. Individuals with higher DII levels reported a significant lower prevalence of smokers and whites, used more frequently NSAIDs, were more obese (as shown by higher BMI values) and more depressed compared to other quartiles (Table 1). On the contrary, no significant differences in Charlson Co-morbidity Index and prevalence of some common conditions emerged across DII quartiles, except for heart failure ($p=0.007$) and diabetes ($p=0.05$; Table 1). Finally, people with higher DII scores showed significantly higher consumption of fats, meat and other animal products and lower consumption of cereals, fruits and vegetables ($p<0.0001$ for all comparisons) (Table 1).

### Dietary inflammatory index and osteoarthritis

There was a significantly higher prevalence of radiographic symptomatic knee OA in those with higher DII scores compared to other quartiles (Q4: 35.4% vs. Q1: 24.0%; $p<0.0001$).

Using a logistic regression analysis adjusting for 11 potential confounders, and taking those with the lowest DII as reference (=Q1), participants with the highest DII score (=Q4) had a significantly higher probability of exhibiting radiographic symptomatic knee OA (OR: 1.40;

95% CI: 1.14 to 1.72; p=0.002; Table 2). In the multivariable model, the p for trend was 0.02.

On the contrary, higher DII quartile was not associated with the presence of only radiological knee OA (OR=1.15; 95%CI: 0.95–1.40; p=0.15) or with the presence of pain for knee OA (OR=1.03; 95%CI: 0.86–1.25; p=0.73).

The results did not differ between women and men (p for interaction=0.40), for the presence of overweight/obesity or not (p for interaction=0.76) or for the other covariates.

Modelling DII as a continuous variable, after adjusting for the same 11 confounders listed in the Table 2, each standard deviation of DII (i.e. an increase of 1.67 points) was associated with a higher risk of radiographic symptomatic knee OA by 13% (OR: 1.13; 95% CI: 1.06 to 1.21; p<0.0001).

## DISCUSSION

In this large cross-sectional study, we found that higher DII values were associated with higher prevalence of radiographic symptomatic knee OA. After adjusting for 11 potential confounders, those with the highest DII score (i.e. having a more pro-inflammatory diet) had a significantly higher prevalence of radiographic symptomatic knee OA by approximately 40%. Each increase in one standard deviation (i.e. an increase of 1.67 points) of this score was associated with an increased prevalence of knee OA by 13%, suggesting a linear association between DII and radiographic symptomatic knee OA. However, it should be noted that, when DII was assessed with the presence of knee OA only radiologically or taking pain due to radiographic symptomatic knee OA as outcomes, no association was observed.

Whilst our data is cross-sectional and causality cannot be determined, we can propose several mechanisms that might explain the findings. First, DII is significantly associated with serum inflammation markers.[13] This is supported by findings from Sokolove et al.,[10] where inflammation was present in OA joints before the development of significant radiographic changes (synovitis).[10] These findings were also confirmed by some studies using magnetic resonance imaging (MRI).[32, 33] Chronic low-grade inflammation may therefore be a major driver of ongoing joint degeneration, thus affecting structures typical of knee OA, i.e. cartilages and bones. The role of inflammation in predicting early stages of knee OA was indirectly confirmed by our findings, since higher DII were not associated with knee OA when diagnosed only through radiological information. Further studies including MRI that is more sensitive in detecting cartilage/bone lesions than x-rays are consequently needed Second, it is possible that alterations of extra-cellular matrix (ECM) could play an additional role in the association between DII and knee OA. ECM breakdown is common at sites of inflammation, including the joints affected by OA.[34] Moreover, Homandberg et al. suggested that ECM breakdown products could promote *per se* inflammation and cartilage loss.[35] A pro-inflammatory diet may therefore further drive such a process. Finally, it can be hypothesized that DII inversely correlates with healthy dietary patterns (e.g. Mediterranean diet) that could have a role in protecting people from the

onset of knee OA [40], since people having significantly higher levels of DII consumed more frequently meat, sugars, and fats and less frequently vegetables and fruits.

From a clinical perspective, no randomized controlled trial (RCT) has assessed whether healthy dietary patterns could prevent the onset of this condition. Some small RCTs have reported that specific nutrients with anti-inflammatory properties (e.g. fish oil omega fatty acids[36]) may have a beneficial role in the treatment of knee OA.[37] However data is currently inconclusive with large trials indicating limited effectiveness for vitamin D supplementation (for example) on knee OA symptoms.[38] The appropriate dietary strategy for people affected by knee OA is therefore a research priority, particularly since current therapeutic strategies to address symptoms are largely insufficient, and joint replacement is often not possible or undesirable.[37] Trials are therefore warranted to investigate whether supplementation or replacement with anti-inflammatory diets has an influence on the onset or progression of knee OA.

The findings of our research should be considered within four limitations. The principal limitation is the cross-sectional nature of our research. This precludes any consideration of a potential causal relationship between DII and knee OA. Thus, residual confounding is highly possible. Second, the comorbid medical conditions assessed in this study were self-reported, which would have introduced recall bias. Third, only 24 food parameters were available for DII calculation, while an ideal DII calculation requires 45 food parameters. However, it has been shown that the predictive ability of DII is relatively preserved in calculations using <30 parameters.[22] Finally, the findings deriving from the OAI are not fully generalizable to other populations since this database includes only people having or at high risk of knee OA. However, whilst acknowledging these limitations, among the strengths of this study is the large sample size and that this is the first epidemiological study reporting data on the association between DII and knee OA.

In conclusion, results from our work show that, higher dietary inflammatory index values are associated with a higher prevalence of radiographic symptomatic knee OA, even after considering several important confounders. Our findings suggest an important role of inflammation and unhealthy diet in the pathogenesis of knee OA. However, further longitudinal research, from cohorts derived from other countries and dietary patterns is required to re-examine our findings before trials are justified to examine whether changing dietary habits to lower pro-inflammatory foods reduces the development or progression of knee OA.

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**Table 1**

Characteristics of the participants classified according to their dietary inflammatory index.

| | Q1 (n=1090) DII <−4.43 | Q2 (n=1089) DII −4.43 & −3.64 | Q3 (n=1090) DII −3.63 &−2.42 | Q4 (n=1089) DII ≥−2.42 | P value [a] |
|---|---|---|---|---|---|
| **Age (years)** | 63.1 (8.9) | 62.2 (9.0) | 60.9 (9.1) | 58.6 (9.0) | <0.0001 |
| **PASE (points)** | 161.3 (80.0) | 163.0 (82.6) | 157.5 (82.5) | 164.2 (83.4) | 0.25 |
| **aMED (points)** | 30.7 (4.4) | 28.8 (4.4) | 27.5 (4.7) | 25.3 (5.2) | <0.0001 |
| **Females (n, %)** | 773 (70.9) | 695 (63.8) | 596 (52.2) | 490 (45.0) | <0.0001 |
| **White race (n, %)** | 888 (81.5) | 899 (82.6) | 896 (75.3) | 820 (75.3) | <0.0001 |
| **Smoking (previous/current) (n, %)** | 610 (56.0) | 596 (54.7) | 562 (51.6) | 519 (47.7) | <0.0001 |
| **Graduate degree (n, %)** | 377 (34.6) | 343 (31.5) | 320 (29.4) | 285 (26.2) | <0.0001 |
| **Yearly income (≥ $50,000)** | 637 (58.4) | 654 (60.1) | 672 (61.7) | 619 (56.8) | 0.63 |
| ***Medical conditions*** | | | | | |
| **Use of NSAIDs (n, %)** | 56 (5.1) | 67 (6.2) | 71 (6.5) | 87 (8.0) | 0.007 |
| **BMI (Kg/m$^2$)** | 27.3 (4.5) | 28.3 (4.6) | 29.1 (4.7) | 29.8 (5.0) | <0.0001 |
| **CES-D (points)** | 5.7 (5.8) | 6.1 (6.6) | 6.7 (6.7) | 8.0 (8.2) | <0.0001 |
| **Charlson co-morbidity index (points)** | 0.4 (0.6) | 0.4 (0.8) | 0.4 (0.8) | 0.4 (0.9) | 0.62 |
| **Myocardial infarct (n, %)** | 17 (1.6) | 24 (2.2) | 18 (1.7) | 26 (2.4) | 0.29 |
| **Heart failure (n, %)** | 14 (1.3) | 19 (1.8) | 19 (1.8) | 32 (3.0) | 0.007 |
| **Stroke (n, %)** | 30 (2.8) | 32 (3.0) | 37 (3.4) | 29 (2.7) | 0.92 |
| **Diabetes (n, %)** | 60 (5.6) | 88 (8.2) | 100 (9.4) | 80 (7.6) | 0.05 |
| **Cancer (n, %)** | 46 (4.3) | 41 (3.8) | 43 (4.0) | 32 (3.0) | 0.17 |
| ***Food groups (daily servings)*** | | | | | |
| **Fats, oils, sweets and sodas** | 1.27 (0.81) | 1.74 (0.96) | 2.00 (1.00) | 2.37 (1.20) | <0.0001 |
| **Bread, cereals, rice and pasta** | 3.52 (1.76) | 3.25 (1.68) | 3.14 (1.78) | 3.21 (1.89) | <0.0001 |
| **Fruits** | 1.91 (0.92) | 1.59 (0.87) | 1.27 (0.77) | 1.01 (0.74) | <0.0001 |
| **Vegetables** | 4.44 (2.85) | 3.74 (2.34) | 3.00 (1.81) | 2.33 (1.53) | <0.0001 |
| **Meat, fish, poultry, beans and eggs** | 1.44 (0.81) | 1.76 (0.98) | 1.89 (1.01) | 2.06 (1.24) | <0.0001 |
| **Milk, yogurt and cheese** | 1.34 (0.96) | 1.36 (0.95) | 1.38 (0.97) | 1.31 (1.02) | 0.42 |

**Notes:** The data are presented as means (with standard deviations) for continuous variables and number (with percentage).

[a]P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

**Abbreviations**: aMED: adherence to Mediterranean diet score; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; NSAIDs: non-steroidal anti-inflammatory drugs.



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**Table 2**

Association between dietary inflammatory index and prevalence of osteoarthritis.

| | Cases/total | Prevalence (%) | Unadjusted OR (95%CI) | P value | Fully-adjusted[a] OR (95%CI) | P value |
|---|---|---|---|---|---|---|
| **DII <−4.43** | 262/1090 | 24.0 | 1 [reference] P for trend<0.0001 | | 1 [reference] P for trend=0.02 | |
| **DII −4.43 & −3.64** | 304/1089 | 27.9 | 1.22 (1.00–1.48) | 0.045 | 1.14 (0.93–1.39) | 0.21 |
| **DII −3.63 &−2.42** | 319/1090 | 29.3 | 1.30 (1.07–1.58) | 0.007 | 1.16 (0.94–1.42) | 0.16 |
| **DII ≥−2.42** | 385/1089 | 35.4 | 1.74 (1.44–2.10) | <0.0001 | 1.40 (1.14–1.72) | 0.002 |

**Notes:**

All the data are presented as odds ratios (ORs) with their 95% confidence intervals.

[a]Fully-adjusted model included as covariates: age (as continuous); sex; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; use of medications for knee OA (yes vs. no); CES-D (as continuous).

Abbreviations: CI: confidence intervals; OR: odds ratio.