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TITLE PAGE

Title: The inflammatory potential of diet and pain incidence: a cohort study in older adults

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ABSTRACT

Background: Pain is a highly prevalent and on-the-rise symptom with heavy associated healthcare and social burdens among older adults, yet evidence regarding its prevention is inadequate. The growing knowledge on how diet regulates inflammation may be utilized for pain prevention.

Objective: To examine the association of 3-year changes in the inflammatory potential of diet (2008-2010 to 2012) with pain incidence over the subsequent 3 years (2012 to 2014-2015) among older adults.

Methods: We used data from 820 individuals aged ≥ 60 years and free of pain in 2012, drawn from the Seniors-ENRICA cohort study in Spain. Food consumption was collected with a validated diet history, and the inflammatory potential of diet was estimated via the *a priori* empirical dietary inflammatory index (EDII) and the *a posteriori* dietary inflammatory index (DII). The frequency, severity (impact on daily activities), and number of locations of incident pain were combined into a scale that classified subjects as suffering from no pain, intermediate pain, and highest pain. The associations were summarized with relative risk ratios (RRR) and their 95% confidence interval (CI), estimated with multinomial logistic regression, and adjusted for potential sociodemographic, lifestyle, and morbidity confounders.

Results: Shifting the diet towards a higher inflammatory potential was associated with a subsequent increased risk of intermediate pain [fully adjusted RRR (95% CI) per 1-point increment in the EDII=1.30 (1.03,1.65)] and highest pain [DII=1.14 (1.03,1.26)]. The three components of the pain scale followed similar trends, the most consistent one being with moderate-to-severe pain [EDII=1.26 (1.04,1.54); DII=1.12 (1.01,1.24)]. The association of increasing DII with highest incident pain was only apparent among the least physically active subjects [1.35 (1.17,1.56) vs 0.96 (0.83,1.10); p for interaction <0.001].

Conclusions: An increase in the inflammatory potential of diet was associated with higher pain incidence over the following years. Future studies in older adults should assess the efficacy of pain prevention interventions targeting the inflammatory potential of diet.

Keywords: low back, arthritis, disability, pain treatment, anti-inflammatory, opioids, dietary patterns, Mediterranean diet, longitudinal, elderly.

INTRODUCTION

Background and rationale

Pain is a very common symptom that is estimated to affect 25-35% of adults and up to 60% of people older than 65 years, both in developing and developed countries -close to 1.5 billion people globally (1–4). These figures have increased over the last few decades and are expected to keep on rising, parallel to the world population aging (5). Namely, years lived with disability caused by low back pain rose by 54% between 1990 and 2015 (5), while conditions characterized by the presence of pain accounted for 5 of the top 10 conditions responsible for most of the years lived with disability worldwide (6). Pain, therefore, imposes a heavy, largely elderly-driven, burden on healthcare and social systems –note that low back pain cost alone is reckoned at \$365–560 billion per year in healthcare usage, disability, and lost productivity (1).

Effective response strategies are hence needed to prevent and minimize said burden (5,7). On one hand, evidence on pain prevention is still insufficient, and many widely promoted occupational interventions (e.g., education, back belts, shoe insoles, and ergonomic furniture) do not have a firm evidence base (7). Physical exercise, either alone or combined with education, does seem to be effective for pain prevention, yet the trials conducted so far have mainly been of secondary prevention and involved quite intensive exercise programs, with limited data on cost-effectiveness (7). On the other hand, pain management guidelines advocate for non-pharmacological treatments (e.g. self-management, physical, and psychological therapies) as first-line choices, but this approach is not habitually followed in practice (7). If medication is to be used, opioid analgesic medicines should be limited due to concerns of potential abuse and secondary harm, and non-steroidal anti-inflammatory drugs should be considered instead, yet practitioners are encouraged to prescribe the lowest effective dose for the shortest time (7). Pharmacological management of pain in older adults may be further compromised by polypharmacy and excess toxicity and risks on cognition and organ systems (8,9).

Since there is a large body of evidence indicating that foods, nutrients, and bioactive compounds also play a role in the regulation of chronic inflammation (10,11), there are prospects that interventions targeting the inflammatory potential of diet may be utilized for both adjunctive pain treatment -likely with neither the substantial effects nor the constraints of anti-inflammatory pharmacological therapies- and primary pain prevention -either in the clinic or via cost-effective public health campaigns (7). A few studies have indeed found an association of pro-inflammatory diets with higher pain in patients with osteoarthritis and fibromyalgia, and with a higher incidence of symptomatic knee osteoarthritis (12–14). Additional evidence supports the potential of a vegetarian diet, the Mediterranean diet, and caloric restriction as effective means to reduce pain in patients with rheumatoid arthritis, osteoarthritis, and fibromyalgia syndrome through implied concomitant reductions in chronic inflammation and irrespective of weight loss (15). Nevertheless, a few challenges still lie ahead: 1) More research on how diet can modulate physiology related to pain -and specifically inflammation- is needed to disentangle commonalities among such healthy dietary patterns (16); 2) Despite the inadequate evidence on pain prevention strategies, most published dietary studies focus on pain treatment, where effective pharmacological and non-pharmacological interventions already exist (7); and 3) Since pain may disrupt food hedonics, reverse causation may arise when examining diet and pain relationships -that is, pain may be affecting eating behaviors, instead of the opposite-, so cross-sectional epidemiological designs might not be appropriate (17). Restricting the analyses to the subjects who are free of pain at baseline (18), assessing dietary-related inflammation with evidence-based inflammatory dietary patterns (10,11), focusing on changes in diet instead of single-time measurements (19), and using a longitudinal design without overlapping intervals for dietary exposures and pain outcomes (20) may help overcome these challenges.

Objectives

Our primary objectives were hence to 1) examine the association of changes in the inflammatory potential of diet with subsequent pain incidence among older adults in Spain; and 2) delve into these associations by examining the three main components of pain separately: frequency, severity - defined as its impact on daily activities-, and number of locations (2).

METHODS

Setting, study design, and participants

We used data from the Seniors-ENRICA (ClinicalTrials.gov Identifier: NCT01133093), a cohort of community-dwelling individuals aged 60 years and older in Spain. Study participants were recruited by stratified cluster sampling from March 2008 to September 2010 (wave 0), and followed-up at wave 1 (February to November 2012) and wave 2 (November 2014 to June 2015) (21,22). We studied whether changes in the inflammatory potential of diet from wave 0 to wave 1 were associated with pain incidence from wave 1 to wave 2.

Trained personnel obtained home-based validated electronic diet histories at waves 0 and 1 and conducted comprehensive sets of physical examinations at all waves. Data on pain (at waves 1 and 2) and morbidity, socio-demographic, and lifestyle variables (at all waves) were gathered through computer-assisted telephone interviews (21,22). The Clinical Research Ethics Committee of the “La Paz” University Hospital in Madrid approved the research protocol and all subjects gave written informed consent.

Variables

Inflammatory potential of diet

Food and nutrient consumption was assessed with a face-to-face electronic diet history (21,23), where subjects could report up to 861 foods and recipes habitually consumed during a typical week of the previous year. Portion sizes were estimated with 127 digitized photographs and household

measures. Nutrient and energy intake were estimated with Spanish and other standard food composition tables (23,24). A previous validation study comparing the results of this diet history against seven 24-hour recalls over one year showed a mean correlation coefficient of 0.53 across all 15 food groups considered, 0.76 for energy, and 0.55 across all 41 nutrients studied (23).

To estimate changes in the inflammatory potential of diet while making different assumptions about the effect of dietary patterns on bodily inflammation, we computed the *a priori* dietary inflammatory index (DII) and the *a posteriori* empirical dietary inflammatory index (EDII) (10,11) at waves 0 and 1 and further calculated changes in each index from wave 0 to wave 1, so that positive values indicated a shift to a more pro-inflammatory diet:

DII

The DII is a literature-derived index designed to compare diverse populations on the inflammatory potential of their diets, which was built by Shivappa *et al.* as follows (10). First, a review of 1943 articles identified 45 food components that either increased, decreased, or had no effect on six inflammatory biomarkers (interleukin-1 β , interleukin-4, interleukin-6, interleukin-10, tumor-necrosis-factor- α , and C-reactive protein). Second, every food component was assigned a weighted overall inflammatory effect score, ranging from -0.663 (maximally anti-inflammatory) to 0.373 (maximally pro-inflammatory).

To obtain the DII, we multiplied the overall inflammatory effect scores of the 32 food components available in our study by their corresponding standardized intakes (note that individuals' intakes were normalized using a compilation of eleven food consumption datasets from countries around the world) and then summed them, so that higher values indicate a more pro-inflammatory diet. The inflammatory effect scores and the global vs our study intakes (wave 0 and wave 1) for the components of the DII are shown in Supplemental Table 1.

EDII

The EDII is a hypothesis-driven, empirically derived index that assesses diet quality based on its inflammatory potential. It was developed -and further validated- by Tabung *et al.*(11). The authors entered 39 pre-defined food groups in reduced rank regression models followed by stepwise linear regression analyses to identify a dietary pattern most predictive of 3 plasma inflammatory markers (interleukin-6, tumor-necrosis-factor- α receptor 2, and C-reactive protein). 18 food groups were retained in the final stepwise linear regression model and their regression coefficients -ranging from -1175 (maximally anti-inflammatory) to 252 (maximally pro-inflammatory)- were recorded.

To compute the EDII, we first weighted and then summed the consumption of such 18 food groups by the corresponding regression coefficients. Second, this weighted sum was standardized by subtracting its mean and dividing by its standard deviation. As with the DII, higher values indicate a more pro-inflammatory diet. Said regression coefficients (inflammatory effect scores) and the consumption of the components of the EDII in our study (wave 0 and wave 1) are presented in Supplemental Table 2.

Pain

Self-reported pain in the previous six months was assessed at waves 1 and 2 via a pain scale developed from the Survey on Chronic Pain in Europe (2) and built as the sum of three components: 1) Pain frequency, classified as either sporadic (pain happening <1 time/month, 1-3 times/month, or weekly; which was scored 1 point) or persistent (≥ 2 times/week, every day, or at all times; scored 2 points); 2) Pain severity, classified as light (pain troubling a little or nothing on daily activities; which was scored 1 point) or moderate-to-severe (troubling moderately, a lot, or completely; scored 2 points); and 3) Pain locations out of the six considered (head and neck, back, bones and joints, arms, legs, and other sites -abdomen, chest, or any other site-), further classified as 1-2 pain sites (scored 1 point) or ≥ 3 pain sites (scored 2 points).

Hence, the pain scale ranged from 0 to 6 and was categorized as follows: 1) No pain in the previous six months (0 points in the pain scale); 2) Intermediate pain (3 or 4 points); and 3) Highest pain (5 or 6 points). Finally, we defined incident pain as the presence of intermediate or highest pain at wave 2 among the subjects who had scored 0 points on the pain scale at wave 1.

Potential confounders

We considered several possible confounders of the association of the inflammatory potential of diet with pain incidence. First, sociodemographic characteristics, namely sex, age, and educational level (primary or less, secondary, or university).

Second, lifestyle variables, specifically tobacco smoking (never, former, or current), alcohol consumption [never, former, moderate (≤ 10 g/day in women and ≤ 20 g/day in men), or heavy], and energy intake (kcal/day). Recreational physical activity was assessed with the validated questionnaire developed in the EPIC-cohort study in Spain (25) and expressed as Metabolic Equivalents of task-hours/week (MET-hours/week) (26), while time spent watching television (hours/day) were assessed with the Nurses' Health Study questionnaire validated in Spain (27). Lastly, body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, both measured under standardized conditions (28).

Third, self-reported morbidity. We considered diabetes -either treatment with antidiabetic drugs or the corresponding self-reported medical diagnosis-, cardiovascular disease (coronary heart disease, stroke, or heart failure), respiratory disease, musculoskeletal disease (osteoarthritis, arthritis, or hip fracture), cancer, and depression requiring medical treatment.

Statistical methods

Study size

From the 2519 participants who were followed-up at wave 1 (year 2012), we excluded 1086 (43.1%) prevalent pain cases at wave 1 and 94 (3.7%) participants with no information on pain. From the remaining 1339 individuals free of pain at wave 1, 44 subjects (3.3%) had died and 306 (22.9%) were lost to follow-up at wave 2 (year 2015). From these 989 participants who were followed-up at wave 2, we further excluded 169 (17.1%) with inadequate data (101 subjects had no information on diet at wave 0 or wave 1, 74 on pain at wave 2, and 99 on potential confounders at wave 1; note that one individual may lack data in more than one variable). Hence, the analytical sample comprised 820 individuals (Supplemental Figure 1).

Descriptive data and loss to follow-up

Differences in characteristics of study participants at wave 1 across categories of change in the DII or the EDII from wave 0 to wave 1 were evaluated with Pearson's chi-squared tests for discrete variables and Wilcoxon rank-sum tests for continuous variables. To investigate how loss to follow-up may have affected our findings, we also used such tests to compare the wave 1 characteristics between the participants who were and were not followed at wave 2.

Main statistical methods and control for confounding

Relative risk ratios (RRR) and their 95% confidence interval (CI) for the incidence of intermediate and highest pain -as well as those for the three pain components- were calculated using multinomial logistic regression models. The changes in the inflammatory potential of diet from wave 0 to wave 1 (estimated via DII and EDII) were modeled in the analyses as 1) A continuous variable (per 1-point increment); 2) A dichotomous variable (decrease [reference] vs increase); and 3) A restricted cubic spline (knots located at the 10th, 50th, and 90th percentiles (29)). We used two *a priori* incrementally adjusted models to control for potential confounding at wave 1: the first, adjusted for sociodemographic characteristics, and the second, additionally adjusted for lifestyle variables and morbidity.

Interactions and sensitivity analyses

Since pain prevalence has been found to vary across sexes (2–4), while age, tobacco smoking, recreational physical activity, and BMI are important determinants of pain incidence (1,5,30), we examined if these variables modified the main study associations by using likelihood-ratio tests that compared models with and without interaction terms, defined as the product of said variables by the continuous DII or EDII variables.

We conducted five sensitivity analyses. First, despite its presumed anti-inflammatory properties (10,11), there are both a high prevalence of chronic conditions aggravated by alcohol and frequent use of alcohol-interacting drug treatments among older adults (18), so we calculated the DII without considering alcohol intake (Supplemental Table 1) and the EDII without the beer and wine items (Supplemental Table 2). Second, since some of the EDII foundations may diverge from other healthy dietary patterns (31,32), we calculated alternate versions of the EDII with 1) negative scoring (i.e., pro-inflammatory) for snacks, fruit juice, and pizza (Supplemental Table 2); and 2) positive scoring (i.e., anti-inflammatory) for fish (other than dark-meat fish), other vegetables (i.e. vegetables other than leafy green vegetables and dark yellow vegetables), and tomatoes (Supplemental Table 2). Third, given the close link between musculoskeletal disease and pain (33), we excluded those subjects who suffered from osteoarthritis, arthritis, or hip fracture at wave 1. Fourth, since data on diet and many potential confounders were self-reported, we assessed whether cognitive status might bias our estimates by excluding the study participants with a Mini-Mental State Examination score <24 points at wave 1 (34). Fifth, to check the robustness of the study associations, we switched from our pain scale to a standard Numeric Rating Scale for pain intensity (33), ranging from 1 (no pain) through 10 (a pain I cannot even imagine bearing), which was further categorized as no pain (0 points), light-intensity pain (1-5 points), and moderate-to-high intensity pain (≥ 6 points).

Analyses were performed with Stata® (StataCorp LLC), version 14.

RESULTS

Descriptive and outcome data

Characteristics of study participants are shown in Table 1. Compared with individuals who decreased their DII from wave 0 to wave 1, those who increased it had a lower educational level, energy intake, and BMI at wave 1. Subjects who increased their EDII were less often heavy drinkers and suffered less from depression at wave 1. Compared with participants who were followed at wave 2 (n=989), those who were not (n=350) were older (73.6 vs 71.6 years), less educated (63.4% vs 45.5% had primary studies), and were more likely former drinkers (18.1% vs 13.9%).

During the mean 3.2-year follow-up from wave 0 to wave 1, 393 subjects decreased and 427 increased their DII [mean change (95% CI)=-0.09 (-0.19,0.02)]; corresponding figures for the EDII were 417 and 403 [-0.01 (-0.07,0.05)] (Table 1). Throughout the subsequent mean 2.8 years of follow-up from wave 1 to wave 2, 71 individuals developed intermediate pain and 140 highest pain (Table 2). The incidence of intermediate pain per 1000 person-years (95% CI) for the subjects who decreased vs increased the inflammatory potential of their diet was 33.4 (24.1, 46.3) vs 29.6 (21.2, 41.2) for the DII and 29.4 (21.0, 41.2) vs 33.4 (24.2, 46.1) for the EDII. The corresponding incidence of highest pain for those who decreased vs increased the DII was 52.0 (40.0, 67.6) vs 70.9 (57.3, 87.9), while for EDII it was 58.0 (45.6, 73.7) vs 65.9 (52.4, 82.9).

Main results

The associations of changes in the DII and EDII with pain incidence are shown in Table 2 and Figure 1. Shifting the diet to a higher inflammatory potential was associated with a subsequent increased risk of highest pain [model 2 RRR (95% CI) per 1-point increment in the DII=1.14 (1.03,1.26)] and of intermediate pain [model 2 RRR (95% CI) per 1-point increment in the EDII=1.30 (1.03,1.65)]. The three components of the pain scale followed similar trends: a 1-point

increment in both the DII and the EDII was associated with more severe pain [1.12 (1.01,1.24) and 1.27 (1.05,1.55), respectively], whereas a 1-point increment in the EDII was associated with a higher risk of persistent pain [1.22 (1.02,1.45)] and of pain in 1-2 locations [1.37 (1.12,1.69)].

Interactions and sensitivity analyses

The association of increasing DII with the incidence of highest pain was only apparent among the subjects who were less physically active (≤ 18 MET-hours/week) [model 2 RRR (95% CI) per 1-point increment in the DII=1.35 (1.17,1.56) vs 0.96 (0.83,1.10); p for interaction < 0.001] (Table 3). This differential association was also observed for the three components of the pain scale (Table 3). No interaction between the EDII and physical activity was evident, however (p for interaction regarding intermediate pain incidence=0.88). Neither age [model 2 RRR (95% CI) for highest pain per 1-point increment in the DII=1.18 (1.02,1.37) for ≤ 70 years vs 1.10 (0.96,1.25) for > 70 years; p for interaction=0.47 and for intermediate pain per 1-point increment in the EDII=1.46 (1.04,2.05) for ≤ 70 years vs 1.17 (0.85,1.62) for > 70 years; p for interaction=0.36] nor sex, tobacco smoking, or BMI (data not shown) significantly modified the study associations.

When calculating the DII without considering alcohol intake and the EDII without the beer and wine items, the association of the former with highest pain incidence remained [1.13 (1.02, 1.24)], but that of the latter with increased intermediate pain was all but lost [1.11 (0.88, 1.39)]. When computing alternate versions of the EDII with 1) negative scoring for snacks, fruit juice, and pizza; and 2) positive scoring for fish (other than dark-meat fish), other vegetables (i.e., vegetables other than leafy green vegetables and dark yellow vegetables), and tomatoes, its association with increased intermediate pain incidence vanished [1.05 (0.84, 1.31) and 0.90 (0.72, 1.11), respectively]. The associations of changes in the inflammatory potential of diet with incident pain were rather consistent when: 1) excluding those subjects who suffered from musculoskeletal disease [model 2 RRR (95% CI) for highest pain per 1-point increment in the DII=1.24 (1.04,1.48) and intermediate pain per 1-point increment in the EDII=1.50 (1.06,2.14)]; 2) excluding the participants

with cognitive impairment from the analyses [model 2 RRR (95% CI) for highest pain per 1-point increment in the DII=1.15 (1.04,1.27) and intermediate pain per 1-point increment in the EDII=1.27 (1.00,1.62)]; and 3) assessing pain intensity through a Numeric Rating Scale [model 2 RRR (95% CI) for moderate-to-high intensity pain per 1-point increment in the DII and the EDII (95% CI)=1.09 (0.95,1.24) and 1.24 (1.00,1.54), respectively].

DISCUSSION

Key results

In this cohort study of older adults in Spain, we found that an increase in the inflammatory potential of diet was associated with a subsequent higher incidence of pain. The three components of the pain scale followed similar trends, the most consistent one being with pain severity -that pain troubling moderately, a lot, or completely on daily activities. The association of increasing DII with highest incident pain was only apparent among the subjects who were less physically active.

Interpretation

Relevant findings from other published studies

Our results are mostly in line with the few studies that have directly examined the association between the inflammatory potential of diet and pain-related outcomes. First, a cross-sectional study on 220 patients with knee osteoarthritis from Iran found that a 1-point increase in the DII was associated with higher pain intensity, according to the Visual Analogue Scale (VAS) (Beta coefficient=0.171; p=0.01), and with lower pain-related quality of life, evaluated via the 36-item short-form health survey (-0.161; p=0.02) (12). Second, although in a case-control study on 95 Spanish patients with fibromyalgia syndrome, no association between the DII and the VAS was found in either cases (0.012; p=0.82) or controls (0.048; p=0.42), a consistent association of a higher DII with lower pressure pain thresholds -a measure of pain hypersensitivity- on eight tender

point sites was observed among cases (13). Third, in a US cohort study including 2940 participants, a higher DII at baseline was associated with increased incidence of symptomatic knee osteoarthritis (i.e., a combination of frequent knee pain and radiographic knee osteoarthritis) over 4 years [Odds Ratio (95% CI) per 1-point increment in the DII=1.06 (1.02,1.11)] (14).

Possible mechanisms and explanations

Our findings are also consistent with the evidence indicating that certain foods (such as garlic, onion, and tea), nutrients (e.g., saturated fatty acids, omega-3 fatty acids, and vitamin D), and bioactive compounds (like caffeine and flavonoids) influence chronic, low-grade systemic inflammation (Supplemental Table 1, Supplemental Table 2), as demonstrated by their various associations with interleukin-1 β , interleukin-4, interleukin-6, interleukin-10, tumor-necrosis-factor- α , and C-reactive protein (10,11,35). A thorough description of the possible mechanisms underlying said associations arguably lies outside the scope of this section. To cite a few, saturated fatty acids may lead to increased inflammation due to accumulation of diacylglycerol and ceramide, activation of mitogen-activated protein kinases and subsequent induction of inflammatory genes, decreased oxidation of glucose and fatty acids, and recruitment of immune cells to white adipose tissue and muscle (36). Conversely, omega-3 fatty acids might decrease the production of pro-inflammatory eicosanoids, reactive oxygen and nitrogen species, and cytokines, additionally generating anti-inflammatory mediators (37).

Credible explanations for local and systemic inflammation being potential mechanisms for the development of acute and chronic pain exist as well (1). Specifically, acute noxious stimulation seems to result in the activation of the immune system and the release of inflammatory cytokines (15). Such molecules work to maintain homeostasis and attract cells from both the innate and adaptive immune systems, which are involved in the recognition, repair, and removal of damaged cells (15). It is then plausible that chronic pain may arise through a sustained increase in pro-inflammatory and consequent inhibition of anti-inflammatory cytokines, which, in turn, might

sensitize nociceptors and lower the threshold required to activate them, hence perpetuating the pain experience (15). Not in vain, one commonality to most chronic pain conditions is the presence of elevated levels of pro-inflammatory cytokines (C-reactive protein, interleukin-6, interleukin-8, and tumor-necrosis-factor- α , among others) (14,15).

The distinct association of increasing DII with highest incident pain among more and less physically active subjects (Table 3) is in line with the studies showing that sedentary behavior leads to higher inflammatory and lower anti-inflammatory cytokine concentrations in both local and systemic circulation, contributing to the perpetuation of chronic pain (1). On the other hand, physical activity has well-established anti-inflammatory effects, and exercise has preliminarily shown to reduce systemic inflammation, which in turn might reduce chronic pain (1). Specifically, regular exercise might normalize neuroimmune signaling in the central nervous system, which can prevent and even revert hyperalgesia (1). When taking these findings together, it is then possible that the association of physical activity with inflammation may compensate that of diet, and hence is the reason why the deleterious association of increasing DII with incident pain was only apparent among the subjects who were less physically active (Table 3) -note that, in our study, every 1-MET-hour/week of recreational physical activity at wave 1 was indeed associated with a significantly lower RRR for highest incident pain [0.98 (0.97,1.00)], irrespective of the previous DII change.

Regarding sensitivity analyses, the weaker association of the EDII without the beer and wine items (Supplemental Table 2) with intermediate pain incidence is in line with the mechanistic evidence linking low-to-moderate alcohol intake with reduced inflammation (10,11). Specifically, such a drinking pattern has been associated with attenuated biological markers of inflammation and hemostasis (increased HDL cholesterol and adiponectin, and decreased C-reactive protein, certain interleukins, fibrinogen, C-terminal proendothelin-1, and pentraxin-3 levels) (38,39). We also observed weaker associations with intermediate pain incidence for the alternate EDII versions with 1) negative scoring for snacks, fruit juice, and pizza, and 2) positive scoring for fish (other than

dark-meat fish), other vegetables (i.e., vegetables other than leafy green vegetables and dark yellow vegetables), and tomatoes (Supplemental Table 2). Any explanation for these findings must be conjectural, though possibly reflects food preparation methods (11). On one hand, well-done or browned fried, grilled, or barbecued fish may be more proinflammatory -due to the oxidation of long-chain polyunsaturated fatty acids and the generation of unexpected chemicals such as heterocyclic amines and benzopyrene- (40,41). On the other hand, while the effects of net tomato consumption on concentrations of inflammatory markers are conflictive (42–44), tomato paste contains 2.5- to 4-fold higher bioavailable lycopene than fresh tomatoes (45), which could explain the inverse association of pizza with inflammatory biomarkers, given the anti-inflammatory properties of lycopene (46). These sensitivity analyses suggest that, despite its rather strong dose-response association with lower pain incidence, a maximally anti-inflammatory dietary pattern might not necessarily be optimal from the overall health perspective, so that these dietary indices - especially the EDII- may benefit from slight modifications if they are to be used for primary pain prevention, for 1) The effects of alcohol intake on chronic disease burden, disability, and death are greatly controversial (18,47); and 2) Snacks, fruit juice, and pizza consumption may be associated with increased risk for obesity, diabetes, and cardiovascular disease, contrary to most fish and vegetables (including tomato) (31,48–50).

Limitations

Restricting the analyses to the subjects who were free of pain at wave 1 may have mitigated reverse causation and allowed the study of diet as a potential pain prevention strategy (7,17,18), yet two limitations in this regard should be acknowledged. First, because of the high prevalence of pain at wave 1 (43.1%), we identified relatively few incident pain cases and our analytical sample size was, thus, rather small (Supplemental Figure 1). The consequently reduced precision was more notable for the analyses stratified by physical activity. For instance, the association of the DII (per 1-point-increment) with sporadic pain among the least physically active subjects was not statistically

significant, despite being of a higher magnitude (RRR of 1.24) than other apparent associations tested in the whole sample (Table 2, Table 3). Second, some prevalent pain cases and incident pain events -particularly in their milder forms- were likely missed because most episodes of pain are short-lasting with little or no consequences (7). Nevertheless, the study associations were consistent when excluding those subjects who reported no pain, albeit possibly suffering from some (i.e., diagnosed with musculoskeletal disease), whereas missed cases of chronic and severe pain are unlikely, as we observed a predominance of persistent vs sporadic pain incident cases (159 vs 52) and moderate-to-severe vs light pain (127 vs 84 cases) (Table 2). A further limitation is a somewhat high loss to follow-up rate from wave 1 to wave 2 (roughly 22.9 % of the 1339 pain-free subjects) (Supplemental Figure 1). This led to a selection of younger, more educated subjects with distinctive drinking patterns, which may have biased the study results in any way.

Finally, two remarks on how outcomes, confounders, and exposures were measured are also warranted, as that may leave room for misclassification and residual confounding. First, our pain questionnaire and scale have not been validated, and they do not make distinctions between etiologies and types of pain (e.g., neuropathic, nociceptive), whose biological mechanisms may differ. Nevertheless, the scale items were similar to those used in the Survey on Chronic Pain in Europe (2) and the study associations were relatively consistent when using other widely used instruments for pain assessment, such as the Numeric Rating Scale (33). Second, despite mostly using validated instruments (21,23,25,27), data on many potential confounders and diet were also self-reported. Our estimates remained anyway similar when excluding the participants with cognitive impairment from the analyses, who probably were under increased risk for recall bias. Moreover, our diet history did not collect dietary supplement use (23) and we lacked data on 13 DII food components (ginger, saffron, turmeric, pepper, thyme/oregano, rosemary, isoflavones, anthocyanidins, flavan-3-ol, flavones, flavonols, flavonones, flavan-3-ol, and eugenol [Supplemental Table 1]) (10), both of which may have biased the associations of this dietary inflammatory index with pain incidence in any direction.

Generalizability

It was encouraging that the associations of the EDII with pain incidence were rather consistent with those of the DII (Table 2), even though there was no correlation between the change in one index and that of the other ($r=-0.04$, Table 1). Although we were not able to examine whether the relationship between the inflammatory potential of diet and pain incidence was mediated via inflammatory biomarkers -as we lacked the corresponding data at wave 1-, said consistency suggests that the latent increase in bodily inflammation that underlies both indices may be responsible for the observed higher pain incidence, and highlights the construct validity of both dietary inflammatory indices. Indeed, the EDII has been validated in three independent populations of US men and women (11), and the DII has been standardized to a representative range of dietary intakes based on eleven populations from all around the world and further validated in racially diverse populations of men and women (10,51,52).

Our study population was over 60 years old, and pain etiology in this age subgroup may be different from that in younger adults. Namely, while pain might be more prevalent among workers relative to non-working populations, that pain accompanied by activity limitation seems to increase with age (5). We nevertheless found no evidence that age significantly modified the studied associations and, if anything, their strength seemed to decrease somewhat with increasing age. Finally, the Seniors-ENRICA population was entirely white (99.2 %), which warrants caution when extrapolating our results to multiethnic/multiracial populations.

Conclusions

An increase in the inflammatory potential of diet was associated with a subsequent higher incidence of pain among older adults in Spain, casting some light on its potential role as an adjunctive primary pain prevention strategy. The three main components of pain followed similar trends, the most consistent one being with pain severity -defined as its impact on daily activities. The association of

increasing dietary inflammatory index with highest incident pain was only apparent among the least physically active subjects.

Larger studies with repeated pain measurements are warranted to address whether the link between the inflammatory potential of diet and incident pain is generalizable to younger and ethnically diverse populations. More research assessing the presumed mediation via inflammatory markers of the study associations is also needed. Finally, future studies in older adults should assess the efficacy of pain prevention interventions targeting the inflammatory potential of diet.

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Table 1. Characteristics of 820 older adults free of pain, by categories of change in the Dietary Inflammatory Index (DII) and the Empirical Dietary Inflammatory Index (EDII) over the previous 3.2 years.

	Included in the analyses			
	Change in the DII		Change in the EDII	
	Decrease	Increase	Decrease	Increase
n	393	427	417	403
Change in the DII	-1.70 (1.30)	1.61 (1.22)*	0.06 (2.14)	-0.00 (2.01)
Change in the EDII	-0.02 (1.20)	-0.07 (1.12)	-0.86 (0.89)	0.80 (0.71)*
Sex - Men (%)	212 (53.9)	249 (58.3)	237 (56.8)	224 (55.6)
Age (years)	71.8 (5.76)	71.7 (6.02)	71.9 (6.03)	71.5 (5.75)
Educational level (%)				
Primary or less	162 (41.2)	215 (50.4)*	193 (46.3)	184 (45.7)
Secondary	113 (28.8)	127 (29.7)	112 (26.9)	128 (31.8)
University	118 (30.0)	85 (19.9)	112 (26.9)	91 (22.6)
Tobacco smoking (%)				
Never	222 (56.5)	235 (55.0)	232 (55.6)	225 (55.8)
Former	136 (34.6)	153 (35.8)	147 (35.3)	142 (35.2)
Current	35 (8.91)	39 (9.13)	38 (9.11)	36 (8.93)
Alcohol consumption (%)				
Never	71 (18.1)	63 (14.8)	58 (13.9)	76 (18.9)*
Former	57 (14.5)	59 (13.8)	50 (12.0)	66 (16.4)
Moderate ^c	159 (40.5)	202 (47.3)	176 (42.2)	185 (45.9)
Heavy	106 (27.0)	103 (24.1)	133 (31.9)	76 (18.9)
Recreational physical activity (MET-hours/week)	24.0 (14.4)	22.7 (15.4)	22.4 (14.2)	24.2 (15.6)
Sedentary behaviour (TV hours/day)	2.58 (1.41)	2.61 (1.36)	2.64 (1.43)	2.55 (1.33)
Energy intake (kcal/day)	2102 (501)	1958 (382)*	2005 (461)	2049 (436)
Body mass index (kg/m ²)	28.3 (4.21)	27.4 (3.90)*	27.8 (3.95)	27.9 (4.20)
Diabetes (%) ^d	79 (20.1)	99 (23.2)	87 (20.9)	91 (22.6)
Cardiovascular disease (%)	34 (8.65)	31 (7.26)	29 (6.95)	36 (8.93)
Chronic lung disease (%)	30 (7.63)	39 (9.13)	31 (7.43)	38 (9.43)
Musculoskeletal disease (%)	184 (46.8)	208 (48.7)	198 (47.5)	194 (48.1)
Cancer (%)	12 (3.05)	21 (4.92)	15 (3.60)	18 (4.47)
Depression (%)	32 (8.14)	33 (7.73)	41 (9.83)	24 (5.96)*

Values are numbers (%) or means (standard deviations).

*P-value <0.05 for differences in means (Wilcoxon rank-sum) or proportions (Pearson's chi-squared) across the categories of change in the Dietary Inflammatory Index and the Empirical Dietary Inflammatory Index or between the participants included and excluded from the analyses.

^aDII change categories: Decrease, -6.57 to <0; Increase, >0 to 5.95.

^bEDII change categories: Decrease, -9.52 to <0; Increase, ≥0 to 5.37.

^cModerate drinking: ≤10 g/day in women and ≤20 g/day in men.

^dDiabetes: treated with antidiabetic drugs or diabetes diagnosis.

Table 2. Relative Risk Ratios (95% confidence interval) for the association of 3.2-year changes in the Dietary Inflammatory Index (DII) and the Empirical Dietary Inflammatory Index (EDII) with incidence of pain and its components over the subsequent 2.8 years in 820 older adults.

	Change in the DII ^a			Change in the EDII ^b		
	Decrease	Increase	Per 1-point increment	Decrease	Increase	Per 1-point increment
Pain scale						
Intermediate pain vs no pain						
Cases/n	36/393	35/427	71/820	34/417	37/403	71/820
Model 1 ^b	Ref.	0.99 (0.60,1.63)	0.99 (0.88,1.11)	Ref.	1.17 (0.72,1.93)	1.21 (0.97,1.51)
Model 2 ^c	Ref.	0.91 (0.54,1.53)	0.96 (0.85,1.09)	Ref.	1.32 (0.79,2.22)	1.30 (1.03,1.65)*
Highest pain vs no pain						
Cases/n	56/393	84/427	140/820	67/417	73/403	140/820
Model 1 ^b	Ref.	1.56 (1.07,2.29)*	1.10 (1.00,1.20)*	Ref.	1.19 (0.82,1.73)	1.13 (0.95,1.35)
Model 2 ^c	Ref.	1.84 (1.20,2.80)**	1.14 (1.03,1.26)*	Ref.	1.13 (0.75,1.69)	1.14 (0.95,1.37)
Components of the pain scale						
Pain frequency						
Sporadic pain vs no pain						
Cases/n	23/393	29/427	52/820	29/417	23/403	52/820
Model 1 ^c	Ref.	1.36 (0.76,2.42)	1.03 (0.89,1.18)	Ref.	0.87 (0.49,1.54)	1.11 (0.85,1.44)
Model 2 ^d	Ref.	1.36 (0.74,2.50)	1.02 (0.88,1.19)	Ref.	0.92 (0.51,1.68)	1.17 (0.90,1.52)
Persistent pain vs no pain						
Cases/n	69/393	90/427	159/820	72/417	87/403	159/820
Model 1 ^c	Ref.	1.33 (0.93,1.90)	1.07 (0.98,1.16)	Ref.	1.31 (0.92,1.87)	1.18 (1.00,1.39)*
Model 2 ^d	Ref.	1.43 (0.97,2.11)	1.09 (0.99,1.19)	Ref.	1.31 (0.90,1.91)	1.21 (1.01,1.44)*
Pain severity						
Pain troubled a little vs no pain						
Cases/n	42/393	42/427	84/820	43/417	41/403	84/820
Model 1 ^c	Ref.	1.03 (0.65,1.64)	1.02 (0.91,1.14)	Ref.	1.03 (0.65,1.63)	1.08 (0.88,1.32)
Model 2 ^d	Ref.	0.99 (0.61,1.61)	1.01 (0.89,1.14)	Ref.	1.07 (0.67,1.74)	1.12 (0.90,1.39)
Pain troubled moderately, a lot, or completely vs no pain						
Cases/n	50/393	77/427	127/820	58/417	69/403	127/820
Model 1 ^c	Ref.	1.60 (1.07,2.39)*	1.09 (0.99,1.19)	Ref.	1.30 (0.88,1.92)	1.23 (1.02,1.48)*
Model 2 ^d	Ref.	1.86 (1.20,2.88)**	1.12 (1.01,1.24)*	Ref.	1.30 (0.85,1.98)	1.26 (1.04,1.54)*
Pain locations						
1 or 2 pain sites vs no pain						
Cases/n	43/393	59/427	102/820	45/417	57/403	102/820
Model 1 ^c	Ref.	1.37 (0.89,2.10)	1.05 (0.95,1.16)	Ref.	1.37 (0.89,2.09)	1.32 (1.08,1.60)**
Model 2 ^d	Ref.	1.38 (0.88,2.16)	1.05 (0.94,1.17)	Ref.	1.45 (0.94,2.25)	1.38 (1.12,1.69)**
3 pain sites or more vs no pain						
Cases/n	49/393	60/427	109/820	56/417	53/403	109/820
Model 1 ^c	Ref.	1.29 (0.85,1.97)	1.07 (0.96,1.18)	Ref.	1.03 (0.68,1.56)	1.03 (0.85,1.24)
Model 2 ^d	Ref.	1.46 (0.92,2.32)	1.10 (0.98,1.23)	Ref.	0.97 (0.61,1.53)	1.03 (0.85,1.26)

* $p < 0.05$. ** $p < 0.01$.

^aDII change categories: Decrease, -6.57 to <0 ; Increase, >0 to 5.95 .

^bEDII change categories: Decrease, -9.52 to <0 ; Increase, ≥ 0 to 5.37 .

^cModel 1: Multinomial logistic regression model adjusted for sex, age, and educational level (primary or less, secondary, or university).

^dModel 2: As Model 1 and additionally adjusted for smoking status (never, former, or current), alcohol consumption (never, former, moderate, heavy), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), energy intake (kcal/day), body mass index (kg/m^2), and morbidity (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression) at wave 1.

Table 3. Relative Risk Ratios (95% confidence interval) for the association of 3.2-year changes in the Dietary Inflammatory Index (DII) with incidence of pain and its components over the subsequent 2.8 years in 820 older adults, stratified by recreational physical activity levels.

	Change in the DII ^a					
	Lower physical activity ^b			Higher physical activity ^b		
	Decrease	Increase	Per 1-point increment	Decrease	Increase	Per 1-point increment
Pain scale						
Intermediate pain vs no pain						
Cases/n	15/171	19/215	34/386	21/222	16/212	37/434
Model 1 ^c	Ref.	1.28 (0.62;2.66)	1.03 (0.87;1.23)	Ref.	0.79 (0.39;1.56)	0.94 (0.80;1.12)
Model 2 ^d	Ref.	1.28 (0.60;2.72)	1.01 (0.84;1.22)	Ref.	0.67 (0.32;1.37)	0.93 (0.78;1.10)
Highest pain vs no pain						
Cases/n	22/171	58/215	80/386	34/222	26/212	60/434
Model 1 ^c	Ref.	3.08 (1.76;5.40)***	1.27 (1.11;1.45)***	Ref.	0.73 (0.42;1.29)	0.92 (0.81;1.05)
Model 2 ^d	Ref.	4.01 (2.17;7.40)***	1.35 (1.17;1.56)***	Ref.	0.83 (0.46;1.51)	0.96 (0.83;1.10)
Components of the pain scale						
Pain frequency						
Sporadic pain vs no pain						
Cases/n	6/171	18/215	24/386	17/222	11/212	28/434
Model 1 ^c	Ref.	3.36 (1.28;8.83)*	1.24 (1.00;1.53)*	Ref.	0.68 (0.31;1.50)	0.87 (0.72;1.06)
Model 2 ^d	Ref.	3.58 (1.33;9.65)*	1.23 (0.99;1.54)	Ref.	0.64 (0.28;1.48)	0.88 (0.72;1.08)
Persistent pain vs no pain						
Cases/n	31/171	59/215	90/386	38/222	31/212	69/434
Model 1 ^c	Ref.	2.10 (1.26;3.48)**	1.18 (1.04;1.33)**	Ref.	0.78 (0.46;1.33)	0.95 (0.84;1.08)
Model 2 ^d	Ref.	2.44 (1.43;4.19)**	1.22 (1.07;1.39)**	Ref.	0.82 (0.47;1.42)	0.97 (0.85;1.11)
Pain severity						
Pain troubled a little vs no pain						
Cases/n	17/171	23/215	40/386	25/222	19/212	44/434
Model 1 ^c	Ref.	1.40 (0.71;2.77)	1.05 (0.89;1.23)	Ref.	0.79 (0.42;1.49)	0.99 (0.85;1.16)
Model 2 ^d	Ref.	1.43 (0.71;2.90)	1.04 (0.88;1.24)	Ref.	0.71 (0.36;1.38)	0.99 (0.84;1.17)
Pain troubled moderately, a lot, or completely vs no pain						
Cases/n	20/171	54/215	74/386	30/222	23/212	53/434
Model 1 ^c	Ref.	3.17 (1.77;5.68)***	1.29 (1.12;1.47)***	Ref.	0.73 (0.40;1.32)	0.88 (0.77;1.02)
Model 2 ^d	Ref.	4.05 (2.15;7.63)***	1.35 (1.17;1.57)***	Ref.	0.82 (0.44;1.53)	0.91 (0.79;1.06)
Pain locations						
1 or 2 pain sites vs no pain						
Cases/n	18/171	35/215	53/386	25/222	24/212	49/434
Model 1 ^c	Ref.	2.00 (1.07;3.74)*	1.15 (0.99;1.33)	Ref.	0.94 (0.52;1.72)	0.95 (0.82;1.10)
Model 2 ^d	Ref.	2.11 (1.11;4.02)*	1.16 (0.99;1.34)	Ref.	0.93 (0.50;1.74)	0.96 (0.83;1.12)
3 pain sites or more vs no pain						
Cases/n	19/171	42/215	61/386	30/222	18/212	48/434
Model 1 ^c	Ref.	2.60 (1.42;4.78)**	1.23 (1.06;1.42)**	Ref.	0.59 (0.31;1.10)	0.90 (0.78;1.05)
Model 2 ^d	Ref.	3.35 (1.72;6.52)***	1.31 (1.12;1.54)***	Ref.	0.61 (0.31;1.21)	0.93 (0.79;1.09)

*p<0.05. **p<0.01. ***p<0.001.

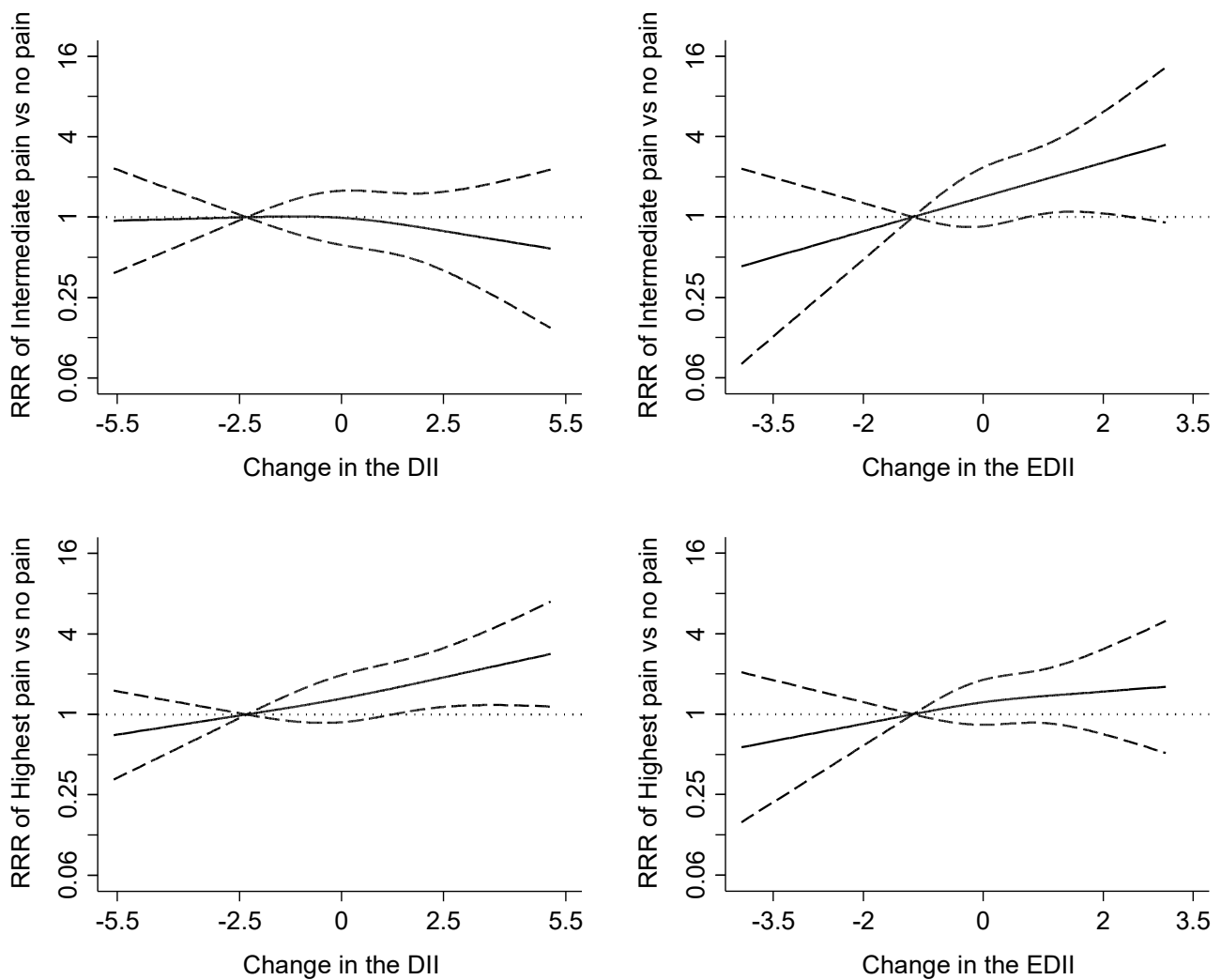
^aDII change categories: Decrease, -6.57 to <0; Increase, >0 to 5.95.

^bRecreational physical activity categories: Lower, 0 to ≤18 MET-hours/week; Higher, >18 to 101 MET-hours/week.

^cModel 1: Multinomial logistic regression model adjusted for sex, age, and educational level (primary or less, secondary, or university).

^dModel 2: As Model 1 and additionally adjusted for smoking status (never, former, or current), alcohol consumption (never, former, moderate, heavy), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), energy intake (kcal/day), body mass index (kg/m²), and morbidity (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression) at wave 1.

Figure 1. Relative Risk Ratios (RRR) for the association of 3.2-year changes in the Dietary Inflammatory Index (DII) and the Empirical Dietary Inflammatory Index (EDII) with incidence of pain over the subsequent 2.8 years in 820 older adults.



Plotted values are Relative Risk Ratios (95% confidence intervals) from a multinomial logistic regression model as Model 2 in Table 2, adjusted for sex, age, educational level (primary or less, secondary, or university), smoking status (never, former, or current), alcohol consumption (never, former, moderate, heavy), leisure-time physical activity (MET-hours/week), sedentary behavior (TV hours/day), energy intake (kcal/day), body mass index (kg/m²), and morbidity (diabetes, cardiovascular disease, chronic lung disease, musculoskeletal disease, cancer, and depression) at wave 1.

Restricted cubic spline knots for the change in the Dietary Inflammatory Index: -2.56, 0.08, 2.59. Reference: -2.33.

Restricted cubic spline knots for the change in the Empirical Dietary Inflammatory Index: -1.28, -0.02, and 1.33. Reference: -1.17.

Supplemental Table 1. Inflammatory effect scores and global and study intakes (wave 0 and wave 1) of the components of the Dietary Inflammatory Index (DII).

	Overall inflammatory effect score	Global daily mean (SD) intake	Study daily mean (SD) intake	
			Wave 0	Wave 1
Anti-inflammatory components				
Alcohol (g)	−0.278	13.98 (3.72)	11.7 (18.3)	10.5 (14.6)
β-Carotene (μg)	−0.584	3718 (1720)	3480 (2583)	3141 (2248)
Caffeine (mg)	−0.110	80.5 (66.7)	74.0 (102)	91.5 (141)
Fiber (g)	−0.663	18.8 (4.9)	24.3 (7.81)	24.6 (7.64)
Folic acid (μg)	−0.190	273 (70.7)	328 (108)	326 (106)
Garlic (g)	−0.412	4.35 (2.9)	0.83 (1.50)	0.80 (1.49)
Magnesium (mg)	−0.484	310.1 (139.4)	326 (93.2)	333 (94.3)
Monounsaturated fat (g)	−0.009	27.0 (6.1)	37.0 (14.2)	36.9 (11.9)
Niacin (mg)	−0.246	25.9 (11.77)	21.4 (7.70)	21.1 (5.86)
ω-3 fatty acids (g)	−0.436	1.06 (1.06)	2.16 (1.30)	1.98 (1.08)
ω-6 fatty acids (g)	−0.159	10.8 (7.5)	12.4 (6.46)	12.2 (5.88)
Onion (g)	−0.301	35.9 (18.4)	12.7 (13.6)	14.8 (19.2)
Polyunsaturated fatty acids (g)	−0.337	13.9 (3.76)	14.7 (7.18)	14.4 (6.53)
Riboflavin (mg)	−0.068	1.70 (0.79)	1.65 (0.52)	1.67 (0.50)
Selenium (μg)	−0.191	67 (25.1)	142 (61.8)	140 (51.1)
Green or black tea (g)	−0.536	1.69 (1.53)	9.55 (43.1)	12.7 (58.7)
Thiamin (mg)	−0.098	1.7 (0.66)	1.38 (0.50)	1.38 (0.42)
Vitamin A (Retinol Equivalents)	−0.401	984 (519)	877 (632)	808 (573)
Vitamin B6 (mg)	−0.365	1.47 (0.74)	1.65 (0.52)	1.67 (0.50)
Vitamin C (mg)	−0.424	118 (43.5)	136 (67.1)	147 (74.6)
Vitamin D (μg)	−0.446	6.26 (2.21)	3.61 (3.44)	3.12 (2.44)
Vitamin E (mg)	−0.419	8.73 (1.49)	10.3 (4.58)	10.6 (5.09)
Zinc (mg)	−0.313	9.84 (2.19)	9.30 (2.64)	9.22 (2.42)
Pro-inflammatory components				
Carbohydrate (g)	0.097	272.2 (40)	215 (61.4)	208 (50.5)
Cholesterol (mg)	0.110	279.4 (51.2)	317 (139)	300 (120)
Energy (kcal)	0.180	2056 (338)	2079 (573)	2027 (449)
Iron (mg)	0.032	13.35 (3.71)	13.4 (3.85)	13.1 (3.39)
Protein (g)	0.021	79.4 (13.9)	93.9 (28.5)	91.9 (21.9)
Saturated fat (g)	0.373	28.6 (8)	25.1 (10.8)	24.5 (9.42)
Total fat (g)	0.298	71.4 (19.4)	84.3 (30.5)	83.3 (24.2)
Trans fat (g)	0.229	3.15 (3.75)	1.75 (1.42)	1.80 (1.31)
Vitamin B12 (μg)	0.106	5.15 (2.7)	6.57 (4.28)	6.15 (3.09)

SD = Standard Deviation.

Supplemental Table 2. Inflammatory effect scores and study consumption (wave 0 and wave 1) of the components of the Empirical Dietary Inflammatory Index (EDII).

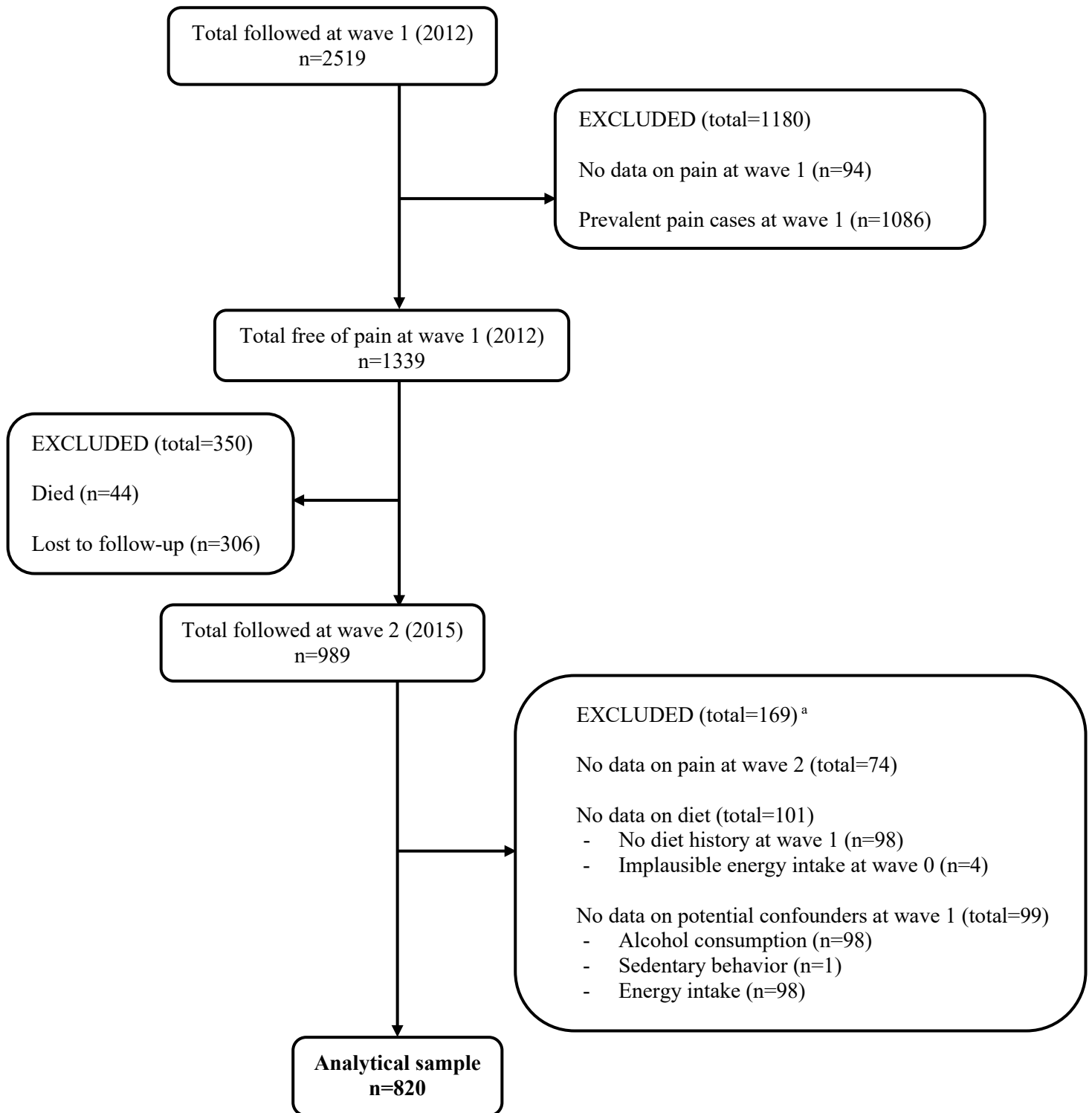
	Overall inflammatory effect score	Study daily mean (SD) servings	
		Wave 0	Wave 1
Anti-inflammatory EDII components ^a			
Beer	−136.99	0.20 (0.62)	0.21 (0.57)
Wine	−249.70	0.88 (1.49)	0.77 (1.17)
Tea	−42.25	0.042 (0.19)	0.056 (0.26)
Coffee	−83.18	1.51 (1.49)	1.53 (1.44)
Dark yellow vegetables	−165.37	0.094 (0.20)	0.088 (0.18)
Leafy green vegetables	−190.29	0.72 (0.77)	0.73 (0.68)
Snacks	−45.08	0.031 (0.15)	0.041 (0.15)
Fruit juice	−58.95	0.16 (0.37)	0.17 (0.35)
Pizza	−1175.21	0.0025 (0.016)	0.0014 (0.011)
Pro-inflammatory EDII components ^b			
Processed meat	165.03	0.90 (1.10)	0.83 (0.70)
Red meat	140.19	0.26 (0.26)	0.25 (0.20)
Organ meat	144.61	0.0051 (0.030)	0.0038 (0.027)
Fish (other than dark-meat fish)	252.45	0.39 (0.69)	0.45 (0.32)
Other vegetables	136.14	0.95 (0.81)	0.87 (0.59)
Refined grains	81.21	2.41 (1.24)	2.25 (1.02)
High-energy beverages	156.85	0.11 (0.33)	0.14 (0.37)
Low-energy beverages	94.77	0.038 (0.23)	0.043 (0.37)
Tomatoes	167.92	0.52 (0.46)	0.59 (0.52)

SD = Standard Deviation.

^a 1 serving of beer = 227 grams (8 ounces). 1 serving of wine = 113 grams (4 ounces) of red or white wine. 1 serving of tea = 227 grams (8 ounces) of tea (not herbal). 1 serving of coffee = 3.5 grams of soluble, 50 grams of espresso, 75 grams of Italian or filtered coffee. 1 serving of dark yellow vegetables = 118 grams (1/2 cup) of carrots, yellow (winter) squash, yams, or sweet potatoes. 1 serving of leafy green vegetables = 118 grams (1/2 cup) of cooked or 59 grams (1/4 cup) of raw spinach, iceberg or head lettuce, or romaine or leaf lettuce. 1 serving of snacks = 28.3 grams (1 ounce) of potato chips, corn chips, popcorn, or crackers. 1 serving of fruit juice = 227 grams (8 ounces) of apple juice or cider, orange juice, grapefruit juice, or other fruit juice. 1 serving of pizza = 160 grams (1 slice).

^b 1 serving of processed meat = 43 grams (1.5 ounces) of processed meats, bacon, or hot dog. 1 serving of red meat = 142 grams (5 ounces) of beef, pork, lamb, or hamburger patty. 1 serving of organ meat = 113 grams (4 ounces) of beef, calf, or pork liver, or 28 grams (1 ounce) of chicken or turkey liver. 1 serving of fish (other than dark-meat fish) = 113 grams (4 ounces) of canned tuna, shrimp, lobster, scallops, fish, or other seafood other than dark-meat fish. 1 serving of other vegetables = 118 grams (1/2 cup) of celery, mushrooms, green pepper, corn, mixed vegetables, eggplant, zucchini, alfalfa sprouts, or cucumber. 1 serving of refined grains = 85 grams (3 ounces) of white bread, English muffin, bagel or roll, muffin or biscuit, pancakes, or waffles; or 250 grams (1 cup) of white rice; or 140 grams (1 cup) of pasta. 1 serving of high-energy beverages = 227 grams (8 ounces) of cola with sugar, other carbonated beverages with sugar, or fruit punch drinks. 1 serving of low-energy beverages = 227 grams (8 ounces) of low-energy cola or other low-energy carbonated beverages. 1 serving of tomatoes = 115 grams (1/2 cup) of fresh tomato, tomato juice, or tomato sauce.

Supplemental Figure 1. Participants' flow chart.



^a Note that one individual may lack data in more than one variable.