SLEEPJ, 2020, 1–9

doi: 10.1093/sleep/zsaa093
Advance Access Publication Date: 14 May 2020
Original Article

ORIGINAL ARTICLE

Changes in dietary inflammatory potential predict changes in sleep quality metrics, but not sleep duration

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Abstract

Study Objectives: Non-pharmacological sleep interventions may improve sleep profiles without the side-effects observed with many pharmacological sleep aids. The objective of this research was to examine the association between sleep and inflammation and to examine how changes in dietary inflammatory potential influence changes in sleep.

Methods: The **I**nflammation **Ma**nagement **I**ntervention Study (IMAGINE), which was a dietary intervention designed to lower inflammation, provided access to 24-h dietary recalls (24HR), objectively measured sleep using Sensewear™ armbands, and a range of self-reported demographics, health histories, lifestyle behaviors, psychosocial metrics, anthropometric measurements, and inflammatory biomarkers. Dietary Inflammatory Index® (DII®) scores were calculated from three unannounced 24HR-derived estimated intakes of whole foods and micro and macronutrients over a 2-week period at baseline and post-intervention (i.e. month 3). Statistical analyses primarily utilized linear regression.

Results: At baseline, for every 1-min increase in sleep onset latency, tumor necrosis factor-α increased by 0.015 pg/mL (±0.008, $p = 0.05$). Every one-percentage increase in sleep efficiency was associated with decreased C-reactive protein (CRP) of –0.088 mg/L (±0.032, $p = 0.01$). Every 1-min increase in wake-after-sleep-onset (WASO) increased both CRP and interleukin-6. Compared to participants with pro-inflammatory DII changes over 3 months, those with anti-inflammatory changes decreased WASO (0 vs. –25 min, respectively, $p < 0.01$) and improved sleep efficiency (–2.1% vs. +2.6%, respectively, $p = 0.04$).

Conclusions: Non-pharmacological treatments, such as anti-inflammatory diets, may improve sleep in some adults. Future research involving dietary treatments to improve sleep should not only focus on the general population, but also in those commonly experiencing co-morbid sleep complaints.

Clinical Trial Information: NCT02382458.

Statement of Significance

Some commonly prescribed pharmacological sleep aids can lead to side-effects that may ultimately impact sleep quality and be habit-forming. Nonpharmacological behavioral approaches to improving sleep have shown promise. One such behavior is diet. Diet is one of the strongest moderators of chronic, systemic inflammation. Inflammation is a biological substrate that has implications in sleep processes. The Dietary Inflammatory Index is a tool that can quantify one's dietary inflammatory potential. This study showed that by lowering dietary inflammatory potential (i.e. making the diet more anti-inflammatory) measures of sleep quality were improved. Although not definitive from a clinical standpoint, this research provides support for pursuing research focusing on improving sleep through dietary changes.

Key words: inflammation; diet; Dietary Inflammatory Index; objective sleep; wake-after-sleep-onset; sleep efficiency

Submitted: 24 January, 2020; **Revised:** 16 March, 2020

Introduction

Sleep, necessary for proper restoration of mental, emotional, and physical health [1], comprises about one-third of the human life. The National Sleep Foundation recommends between 7 and 9 h of sleep per night for adults 18–64 years of age and 7–8 h of sleep for those 65+ years of age [2]. However, data from the National Health Interview Survey suggests that about 30% of the US population receives less than 7 h of sleep per night [3]. Nearly one-third of all adults experience symptoms of transient insomnia with 40% of those individuals developing a more severe chronic form of insomnia [4, 5]. Moderate-to-severe sleep apnea has been reported in 30%–50% of men and 11%–23% of women [5, 6]. These statistics are disconcerting given that poor sleep has been associated with development or progression of a range of chronic conditions such as respiratory illnesses, gastrointestinal disorders, diabetes, cardiovascular disease, depression, and cancer [7–9].

The most common treatments for sleep-related ailments are pharmacological [10, 11]. The most common of these are benzodiazepines and non-benzodiazepine receptor agonists (nBZRAs) [12]. Of particular concern are the benzodiazepines because they are sedative-hypnotic medications that have been shown to be linked with traffic accidents, falls and fractures, dementia, infections, and other adverse effects [10]. Common side effects with a prevalence of 1%–10% include parasomnia, sensory change, gait and coordination, and memory/cognition issues [11]. Common side effects with >10% prevalence include excessive sleepiness, daytime fatigue, and headaches [11]. Additionally, many of these medications can be habit forming [13]. It should be noted that nBZRAs were initially marketed as a safer alternative to benzodiazepines; however, research has shown that similar side-effects can occur with nBZRAs [12, 14].

Common non-pharmacological approaches that have shown improvements in sleep include mindfulness or cognitive behavioral therapy, melatonin supplementation, ear plugs/eye masks (i.e. sensory deprivation), bright light therapy, and exercise [15–18]. Of importance to this work is diet. Normal sleep duration (7–8 h per night) is associated with greater food variety and nutrient intake compared with extreme short (<5 h) or extreme long (>9 h) sleep [19]. High-fat diets are associated with various sleep disorder diagnoses [20, 21]. Conversely, adopting healthy eating patterns (e.g. Mediterranean diet) has been shown to improve symptoms of sleep disorders such as insomnia [20, 22]. Amount and quality of carbohydrates are associated with changes in sleep architecture including rapid-eye-movement (REM) and slow-wave sleep (SWS). Specifically, high-carbohydrate diets, compared with low-carbohydrate diets, tend to decrease SWS, while increasing REM sleep [20, 23, 24].

Foods are eaten in combination with each other and single nutrients do not reflect the overall quality of the diet [25]. There are numerous dietary indices that take into account the whole diet. The Dietary Inflammatory Index® (DII®) measures the overall pro and anti-inflammatory property of one's diet [26]. Besides being validated against inflammatory cytokines in over 20 studies [27, 28], the DII has been associated with other inflammation-related chronic conditions including depressive symptoms [29], cancer (most strongly colorectal cancer) [30], cardiovascular disease [31], and diabetes [32].

Examining associations between the DII and sleep is of particular interest because of the relationship between inflammation and sleep. A review of 72 studies indicated that short (<7 h) and long (>8 h) sleep duration are associated with increased concentration of pro-inflammatory cytokines [33]. Sleep disturbances or poor sleep quality also was associated with elevated c-reactive protein (CRP) and interleukin-6 (IL-6) concentrations, two pro-inflammatory cytokines that are among the most commonly studied pro-inflammatory cytokines [33]. In fact, IL-6 is one among the most important signaling cytokines to activate CRP production and both are strongly associated with inflammation-related conditions such as colorectal cancer and coronary heart disease [34–37]. More recent studies corroborate these findings [38, 39]. Not surprisingly, individuals diagnosed with obstructive sleep apnea (OSA) or insomnia have elevated levels of pro-inflammatory cytokines [40–42]. Given that diet is one of the strongest moderators of chronic systemic inflammation, examining the association between the DII and sleep changes may provide insight into non-pharmacological dietary therapies for sleep-related complaints and disorders.

The two primary aims of this research were to: (1) examine baseline associations between objectively measured sleep and inflammatory markers (i.e. CRP, IL-6, and tumor necrosis factor-α [TNF-α], which also is a pro-inflammatory cytokine) and (2) determine whether anti-inflammatory improvements in DII scores were associated with improvements in sleep duration and quality over a 3-month period. Specifically, it was hypothesized that individuals who consumed a more anti-inflammatory diet after 3 months would increase their total nighttime sleep duration and sleep efficiency and would decrease their wake-after-sleep-onset (WASO) and sleep onset latency (SOL).

Methods

Study population and design

Data were derived from The **I**nflammation **M**anagement **I**ntervention Study (IMAGINE), a self-selection trial which included a 12-week intervention period. Intervention classes occurred weekly for 12 weeks. Topics focused on inflammation reduction through diet, exercise, and stress reduction. Dietary prescriptions were DII-based and focused on consumption of anti-inflammatory plant-based foods. Participants were encouraged to avoid foods devoid of fiber or foods that were pro-inflammatory, such as refined foods (e.g. sugar and flour), meat, and dairy. Participants were provided dietary guidance in group settings (which included hands-on cooking classes) and in one-on-one meetings. An online platform also was created which included three informational blog posts each week. Intervention participants also were encouraged to do moderate-to-vigorous aerobic activities 2–3 days per week for 45–60 min and strength training 2–3 days per week [43]. Stress management techniques following the Diabetes Prevention Program also were practiced [44]. Control participants received information based on readily available cancer prevention educational materials from the American Cancer Society, Centers for Disease Control, American Institute for Cancer, or the National Cancer Institute. The materials did not focus on diet, physical activity, or stress [45, 46].

Participants for the main IMAGINE study, from which data for this analysis were derived, were recruited from the Columbia metropolitan area of South Carolina in the USA between July 2015 and February 2016. To be eligible to participate in that

study, individuals needed to be ≥21 years of age, willing and able to participate fully in the study for a period of one year, and willing to travel to and from the intervention classes. Severe illness, disability, or chronic conditions that prevented participation; taking any medications that might influence inflammation; recent surgery; or current pregnancy or planned pregnancy in the next year were exclusion criteria. The study was approved by the University of South Carolina Institutional Review Board and all participants gave written consent.

Diet ascertainment and the DII

Three unannounced 24-h dietary recalls (24HRs) administered by registered dietitians using the Nutrient Data System for Research software (NDSR, 2015) covering two weekdays and one weekend day were used to obtain estimates of dietary intake. A total of 43 of the 45 DII food parameters were available for use [45]. The complete details on the derivation of DII scores can be found elsewhere [26]. Briefly, each DII food parameter has an "inflammatory effect score" that is based on research from nearly 2,000 peer-reviewed publications. A global database provided global means and standard deviations of the DII food parameters. Subtracting participants' intakes from the global means and dividing by the standard deviations provided z-scores, which were then converted to proportions and centered on 0 by doubling the proportion and subtracting 1. These values were then multiplied by the inflammatory effect scores and were summed across all food parameters to create the DII score. DII scores range from about –8 to +8. More negative scores indicate more anti-inflammatory diets, and more positive scores are indicative of more pro-inflammatory diets [26]. DII scores were calculated per 1,000 calories consumed, which utilized an energy-adjusted global reference database and is referred to as the energy-density DII (E-DII).

Actigraphy-derived sleep metrics

Sleep was measured using the validated Sensewear™ armbands [47, 48]. The device was worn on the upper left arm halfway between the acromion and the olecranon. The sensor activates when it contacts the skin. With the exception of showering or swimming, participants were asked to wear the armbands continuously for 7 days. All armband data were analyzed by computer-based software (SenseWear Professional software version 7.0; BodyMedia Inc.) [45].

Average nighttime sleep measures included sleep/wake times, sleep duration, sleep efficiency, SOL, and WASO. Sleep onset was defined as the first of three consecutive minutes spent asleep, which had to coincide with at least 10 min lying down. SOL was the time between lying down and sleep onset. WASO was the total amount of minutes spent awake of at least 2 min in length after sleep onset until the final wake time. Sleep duration was the sum of all sleep-designated minutes during the nighttime sleep bout. Wake time was the first of 90 consecutive minutes spent awake. Sleep efficiency was the total sleep time divided by the length of the nighttime sleep bout. Previously, the research team observed associations between these sleep definitions and inflammation and body habitus measures in other studies [49, 50]. Table 1 shows categories for the various sleep parameters. Determinations for these categories were twofold. First, a sufficient sample size (i.e. at least 10% of the study sample) was required for each stratum. Second, we sought to use cut-points that were published in previous research to enhance comparability; and, in most cases, the various categories aligned with previous research [49–53].

Inflammatory biomarkers

Twelve-hour, overnight, fasting blood samples were drawn in the morning, typically before 8 am, for inflammatory markers: CRP, TNF-α, and IL-6. Inflammatory biomarkers were assayed using quantitative sandwich ELISA kits provided by R&D Systems, Inc., Minneapolis, MN: IL-6 (Cat. HS600B; sensitivity = 0.11ρg/mL), CRP (Cat. DCRP00; sensitivity 0.022ng/mL), and TNF-α (Cat. HSTA00D; sensitivity = 0.19ρg/mL).

Covariates

Covariates included data on a range of demographic, health history, and lifestyle behaviors collected through self-report questionnaires. Additionally, questionnaires on various psychosocial parameters that could either affect behavior or bias responses or both [54, 55] were completed by the participants. These included: (1) the 33-item Marlowe–Crowne Social Desirability Scale, which ascertains an individual's tendency to display oneself in a favorable social image [56]; (2) depressive symptomology as measured by the Centers for Epidemiologic Studies Depression (CESD) scale [57]; (3) stress as measured by the Perceived Stress Scale (PSS) [58]; and (4) stages of change for physical activity which included stages of precontemplation, contemplation, decision, action, and maintenance. It is possible that the stage of behavior change for physical activity may be representative of stage of change for other behaviors. Hence, this may explain why this measure was selected as a confounder through the model selection process.

Moderate-to-vigorous physical activity also was obtained from the Sensewear armbands. Height was measured using a stadiometer (INVICTA Plastics Limited, England, Model 2007246), weight was measured with a digital scale (Tanita, TBF-300WA), and body fat percent was estimated using dual X-ray absorptiometry (GE Healthcare model 8743, Waukesha, WI). Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured using a sphygmomanometer (Prestige Medical, Northridge, CA).

Statistical analysis

Analyses were conducted using SAS (version 9.4, Cary, NC). Population characteristics including inflammatory biomarkers, sleep metrics, and E-DII scores were described using frequencies and percentages or means and standard deviations, as appropriate.

For specific aim 1 using baseline data only, exposures included bed and wake time, sleep duration, sleep efficiency, SOL, and WASO. Each variable was analyzed continuously and categorically. Outcomes included CRP, IL-6, and TNF-α. For CRP, individuals with a value >10 mg/L were removed from analyses as values above this point are indicative of acute infection. Variable selection began as a series of preliminary analyses (e.g. CRP = sleep metric + covariate). Any covariate

Table 1. Adjusted mean CRP, interleukin-6, and TNF by sleep characteristic

	CRP (mg/L)		Interleukin-6 (pg/mL)		Tumor necrosis factor-Alpha (pg/mL)	
Sleep metric	Mean (95% CI)	*P*	Mean (95% CI)	*P*	Mean (95% CI)	*P*
Bedtime						
<10:30 pm (*n* = 26)	3.26 (2.16–4.37)	REF	1.87 (1.37–2.37)	REF	0.88 (0.63–1.12)	REF
10:30 pm-midnight (*n* = 43)	3.00 (2.12–3.88)	0.67	1.50 (1.14–1.86)	0.18	0.83 (0.64–1.02)	0.71
After midnight (*n* = 25)	3.65 (2.56–4.73)	0.62	1.97 (1.47–2.48)	0.79	0.76 (0.55–0.97)	0.37
Continuous	0.005 ± 0.004	0.21	0.000 ± 0.002	0.95	0.000 ± 0.001	0.96
Waketime						
<6:30 am (*n* = 35)	3.18 (2.18–4.19)	0.65	1.81 (1.40–2.22)	0.24	0.74 (0.54–0.94)	0.72
6:30–7:30 am (*n* = 32)	3.47 (2.47–4.47)	REF	1.48 (1.05–1.90)	REF	0.78 (0.57–1.00)	REF
After 7:30 am (*n* = 25)	3.19 (2.19–4.20)	0.69	1.88 (1.41–2.36)	0.17	0.91 (0.69–1.12)	0.36
Continuous	0.003 ± 0.003	0.38	0.002 ± 0.002	0.27	0.001 ± 0.001	0.25
Total sleep time						
<6 h (*n* = 25)	4.06 (3.00–5.12)	0.07	1.57 (1.10–2.05)	0.40	0.67 (0.46–0.89)	0.26
6–7 h (*n* = 35)	2.82 (1.91–3.74)	REF	1.83 (1.42–2.24)	REF	0.82 (0.62–1.03)	REF
7+ h (*n* = 32)	3.19 (2.27–4.10)	0.18	1.70 (1.25–2.15)	0.64	0.94 (0.73–1.15)	0.34
Continuous	–0.007 ± 0.004	0.09	0.000 ± 0.002	0.94	0.001 ± 0.001	0.290
Sleep latency						
<12 min (*n* = 47)	3.36 (2.56–4.15)	0.75	1.66 (1.31–2.02)	0.65	0.78 (0.61–0.96)	0.52
≥12 min (*n* = 45)	3.19 (2.33–4.05)	REF	1.77 (1.40–2.14)	REF	0.89 (0.66–1.04)	REF
Continuous	0.005 ± 0.039	0.90	0.007 ± 0.017	0.68	0.012 ± 0.007	0.09
Sleep efficiency						
<85% (*n* = 57)	3.62 (2.88–4.36)	0.10	1.81 (1.49–2.13)	0.23	0.79 (0.61–1.96)	0.57
≥85% (*n* = 35)	2.74 (1.84–3.63)	REF	1.52 (1.10–1.94)	REF	0.85 (0.65–1.05)	REF
Continuous	–0.088 ± 0.032	0.01	–0.022 ± 0.015	0.14	0.000 ± 0.007	0.99
Wake after sleep onset						
<40 min (*n* = 32)	2.90 (1.96–3.84)	REF	1.32 (0.89–1.75)	REF	0.74 (0.54–0.94)	REF
40–60 min (*n* = 24)	3.12 (2.07–4.17)	0.73	1.81 (1.36–2.26)	0.10	0.84 (0.62–1.07)	0.39
60+ min (*n* = 36)	3.75 (2.89–4.65)	0.16	1.95 (1.56–2.33)	0.02	0.87 (0.67–1.08)	0.21
Continuous	0.019 ± 0.007	0.01	0.007 ± 0.003	0.04	0.001 ± 0.002	0.70

P-values for all models were derived using adjusted linear regression procedures. All CRP models were adjusted for age, sex, moderate-to-vigorous physical activity hours based on actigraphy, and social desirability. All interleukin-6 models adjusted for age, race, and stages of change for physical activity. All tumor necrosis factor alpha models adjusted for age, race, education, employment status, aspirin use, years of shiftwork experience, depression symptoms scores as measured by the Center for Epidemiologic Studies Depression scale, and perceived stress. A total of 11 participants were removed from CRP analyses given values over 10 mg/L, which indicates an acute infection.
REF, the referent group for comparisons.

with a *p*-value of <0.20 was added to a full model. Next, a backward selection process was used to select the final model which included all covariates that led to a 10% change in the beta coefficient of the sleep metric when removed; or were, themselves, statistically significant. The beta coefficient and 95% CI for the primary exposure were presented. Then, multiple least squares regression was performed to obtain adjusted means of the inflammatory markers by categories of each sleep metric. All models' residuals were assessed for their adherence to assumptions of linear regression for which no violations were observed.

For specific aim 2, changes in the E-DII were examined for their association with changes in each sleep parameter. The change in E-DII score was calculated as post-intervention minus baseline and was analyzed continuously and in tertiles. Higher (i.e. more positive value changes) were indicative of unhealthier changes (i.e. more pro-inflammatory). The opposite was true for more negative change values. The main IMAGINE intervention suffered from noticeable cross-over effects. About 29% of intervention participants, had an E-DII change indicating no change or a pro-inflammatory change. In the control group, about 42% had a E-DII change indicating a transition to a more anti-inflammatory diet [46]. Hence, for specific aim 2, intervention assignment was ignored and participants were grouped according to the changes in their E-DII score; that is, treated as though they were from an observational study. A similar analytic approach, as described for specific aim 1, was conducted to investigate specific aim 2.

Results

The overall study population characteristics have been described in detail elsewhere [46]. In short, a total of 95 participants completed baseline assessments. Of these participants, 81% were females, 62% were White, 74% were at least college graduates, most were married or living with a partner (58%), and 62% were employed full-time. Their average age was 46.9 ± 13.4 years and their average BMI was 31.4 ± 7.1 kg/m^2. The following are average daily values for each sleep metric: bedtime = 11:10 pm ± 72 min; wake time = 6:53 am ± 77 min; sleep duration = 6.5 ± 1.1 h; SOL = 12.6 ± 7.1 min; WASO = 58.3 ± 33.4 min; and sleep efficiency = 81.9 ± 7.8%. The average CRP, IL-6, and TNF-α were 3.4 ± 2.3, 1.7 ± 1.4, and 0.6 ± 0.5 mg/L, respectively. In tying participant sleep durations to recommended values, the minimum and maximum average nightly sleep durations were 3 h 19 min

Table 2. Adjusted mean change in sleep parameters by mean change in the DII

Sleep measures	DII tertile 1	DII tertile 2	DII tertile 3	*P*-value 1 vs. 3	Beta	*P* value Cont.
Total sleep (min)	0.56 (–21.84 to 22.95)	7.65 (–13.75 to 29.04)	5.58 (–16.17 to 27.33)	0.76	3.33 ± 2.34	0.16
WASO (min)	–25.59 (–38.93 to –11.23)	–12.59 (–26.05 to 0.83)	–0.27 (–13.7 to 13.25)	<0.01	3.75 ± 1.33	<0.01
Sleep efficiency (%)	2.57 (0.01 to 5.06)	0.91 (–1.5 to 3.31)	–2.11 (–4.50 to 0.27)	<0.01	–0.56 ± 0.26	0.04
SOL (min)	–3.81 (–7.38 to –0.24)	–1.09 (–4.71 to 2.54)	–1.49 (–4.48)	0.28	0.52 ± 0.31	0.09

P-values for all models were derived using adjusted linear regression procedures. DII tertile 1 represents the most anti-inflammatory changes, DII tertile 3 represents the most pro-inflammatory changes, and DII tertile 2 are more neutral changes. *p* Cont. refers to the *p*-value for the continuous form of the DII. *P* 1 vs. 3 refers to the *p*-value representing the mean difference in outcomes between DII tertile 1 and 3. Adjustments: total nighttime sleep model adjusted for age and moderate-to-vigorous physical activity; WASP model adjusted for years exposed to shiftwork throughout lifetime, perceived health, and age; sleep efficiency model adjusted for age; and SOL model adjusted for employment status, smoking status, and age.
DII, Dietary Inflammatory Index; WASO, wake-after-sleep-onset; SOL, sleep onset latency.

and 8 h 40 min, respectively. The average DII score was 1.36 ± 2.42 (data not tabulated).

Using only baseline data, it was observed that for every 1-min increase in SOL, TNF-α increased (β = 0.015, $p = 0.05$); for every one-percentage increase in sleep efficiency, CRP decreased (β = –0.088, $p = 0.01$); and every 1-min increase in WASO both CRP (β = 0.019, $p = 0.01$) and IL-6 (β = 0.007, $p = 0.04$) increased. Additionally, when examining mean inflammatory values by sleep categories, participants with 60+ min of WASO on average per night had elevated IL-6 compared with those with <40 min of WASO (1.95 vs. 1.32 pg/mL, respectively, $p = 0.02$). No other statistically significant relationship was observed (Table 1).

Table 2 displays mean change in sleep parameters by mean change in the DII from baseline to month 3. To be eligible for this analysis, a participant had to attend both baseline and month 3 clinics. This led to a sample of 79 for specific aim 2. Using continuous DII scores, for every one-unit increase in the change in E-DII score (i.e. moving in the pro-inflammatory direction), WASO increased by 3.75 ± 1.33 min ($p < 0.01$) and sleep efficiency decreased by –0.56 ± 0.26% ($p = 0.04$). Using the change in E-DII score, which was categorized into tertiles with tertile 1 indicating anti-inflammatory changes, tertile 3 indicating pro-inflammatory changes, and tertile 2 representing relatively neutral changes, associations with WASO and sleep efficiency were again observed. Participants in E-DII change tertile 1 decreased their WASO by nearly 26 min ($p < 0.01$) and improved their sleep efficiency by nearly 2.6% ($p < 0.01$) compared to those in E-DII change tertile 3.

Discussion

The first objective of this analysis was to examine the cross-sectional association between sleep duration and quality and inflammation. Only measures of sleep quality were associated with inflammation, specifically CRP and IL-6. For every 1-percentage increment in sleep efficiency, CRP decreased by nearly 0.1 mg/L. For every additional minute of WASO, CRP increased by nearly 0.02 mg/L. Although these numbers do not seem to be biologically meaningful, it is important to note that 1-unit increments in both sleep efficiency and WASO are relatively small.

In a meta-analysis, Irwin and colleagues noted that, overall, subjective and objectively measured continuous sleep duration was not associated with CRP. However, short sleep duration was associated with elevated IL-6. When analyzed categorically, short sleep duration (i.e. <7 h) was not associated with CRP, IL-6, or TNF-α. However, extremely long sleep (a precise definition of extremely long sleep was not provided) was associated with elevated CRP and IL-6 [33]. In the current study, our results trended in the same direction, but did not achieve statistical significance, which may be due either to a small sample size or differences in sleep categorization, or both. It should be noted that Irwin and colleagues combined subjective and objective sleep duration assessment in their meta-analysis as there were too few studies using objectively measured sleep duration [33]; by contrast, we used only objective measures. As for sleep quality, results were fairly congruent with findings presented by Irwin and colleagues. Among papers obtaining sleep-disturbance information through a few questions, a specific questionnaire, or based on diagnostic criteria for insomnia, sleep disturbances were associated with both CRP and IL-6. However, it should be noted that not all studies were in agreement [59, 60]; Irwin and colleagues included only studies using self-reported sleep disturbance; whereas, the current study used objectively measured sleep efficiency, SOL, and WASO. Past studies have demonstrated associations between objectively measured WASO or sleep efficiency and markers of inflammation (e.g. CRP, IL-6, white blood cell counts) [39, 61, 62]; however, not all studies are in congruence with such findings [63]. In the current study, a high mean WASO of nearly 60 min, which is seemingly high, was observed. However, using the same device and same definitions, the authors observed similar or higher WASO values in a population of primarily younger adults (mostly college students) and those living with HIV or AIDS [49, 50]. Additionally, other studies involving overweight or obese populations, similar to the current study, showed similar WASO or sleep efficiency values [52, 64]. Lastly, in a study of long-sleepers compared to age-matched representative values, the representative values had a mean WASO over 60 min on both actigraphy and PSG [65].

The second aim of this analysis examined changes in dietary inflammatory potential, as measured by the E-DII, and changes in sleep duration and quality over 3 months. Compared to those with pro-inflammatory changes, those with anti-inflammatory changes showed clinically and statistically significant reductions in WASO of about 25 min per night and improvements in sleep efficiency of 2.6% per night with no corresponding change in total nighttime sleep duration (i.e. 0.5 min per night). Objectively, it was observed that participants with the most anti-inflammatory changes in diet spent 25 fewer minutes awake at night on average as evidenced by the change in WASO. However, sleep duration did not change. This led to an increase in sleep efficiency of nearly

2.6%. In other words, participants increased their sleep efficiency without having to increase sleep duration to do so. To gain 25 min of sleep at night through reducing WASO without changing sleep duration means that it may be possible to reduce the amount of time-in-bed while providing improved sleep efficiency. However, data are not available to examine sleep structure (e.g. SWS, REM, and non-REM), which may better address this hypothesis. Similarly, subjective data on daytime sleepiness or alertness were not obtained to corroborate findings related to objective sleep-quality changes and subjective perceptions by the participants.

Individual foods or nutrients have been studied with respect to sleep including milk, tart fruits such as kiwi, and fatty fish, among others [20]. However, the findings are inconsistent between studies as to their effects on sleep [66]. The disadvantage of examining foods or nutrients individually is that it does not take into account the complex relationship between foods or nutrients [25]. The DII was developed to specifically measure the overall effect of diet on inflammation [26]. Previously, the DII was found to predict apnea severity and daytime sleepiness depending on age groups, as well as REM latency in obese individuals, among those with OSA. However, the DII was not associated with other sleep characteristics [67]. It should be noted that this previous study was cross-sectional in nature. Also, that study focused on those with mild to severe OSA. It is possible that once OSA develops factors other than diet drive sleep profiles.

There are several biologically plausible explanations linking dietary inflammatory potential to sleep. Sleep initiation and promotion have strong inflammatory underpinnings. Some of these mechanisms are described by Kapsimalis and colleagues [42]. For example, TNF-α and IL-1β have been identified as sleep-promoting cytokines. IL-1β enhances growth hormone-releasing hormone which enhances NREM sleep in humans [68]. IL-6 has been shown to have a circadian rhythm that peaks around the time of sleep onset [42]. Administration of IL-6 can increase fatigue, lead to changes in sleep structure, and decrease ability to concentrate [69]. With respect to this study's findings, it is possible that changes in inflammation mediated the relationship between changes in E-DII and sleep changes. Unfortunately, only small-to-moderate changes in inflammatory markers (primarily CRP, not IL-6 or TNF-α) were associated with changes in the E-DII [46]. However, the effects of inflammation on sleep improvement may not require as large a reduction in inflammatory markers as one would expect to see for reduction in chronic disease risk and may not reflect statistically significant changes.

Previous work has indicated that the correlation between the DII and other dietary indices was only around $|0.55|$, indicating good, but far from perfect, agreement [70]. Presumably, the DII accounts for other sources of variability (e.g. related to inflammation, for which it was designed) compared to other dietary indices. However, there is an overlap between the DII and other diet indices, with about 30% of the variability in the DII being explained by the other indices. Therefore, it is reasonable to suggest that the changes in sleep as a response to changes in the DII may be working through substrates other than inflammation. What follows are just a few examples of mechanisms that are described in detail elsewhere [20, 71, 72]. High-fat diets are associated with decreased sleep efficiency and high carbohydrate diets seem to improve sleep structure [20]. It is possible that those with more pro-inflammatory diets tend to have higher percent calories from fat compared to those with more anti-inflammatory diets. Post hoc analyses revealed that the percent calories from fat was 37% and 33% and the percent calories from carbohydrates was 45% and 49% among those with the most pro-inflammatory and anti-inflammatory diets, respectively. Certain vitamins, such as B12, can contribute to melatonin synthesis, and, therefore, improve sleep quality [72]. Clearly, melatonin and serotonin also are associated with tryptophan and branched amino acid metabolism in general [73, 74]. Carbohydrate consumption can increase tryptophan availability for synthesis of serotonin and then melatonin which could improve sleep [71]. Certain nutrients and minerals (e.g. magnesium which is anti-inflammatory) [26] can lead to γ-aminobutyric acid (GABA) production which is an inhibitory neurotransmitter for the central nervous system which activates GABA(A) receptors which favors sleep [72, 75, 76]. However, not are studies are in agreement with the effect of magnesium on sleep complaints or symptoms [77].

There are a few non-diet related explanations. For one, individuals adopting one healthy practice may adopt others such as exercise or mindfulness. Although exercise factors were examined as potential confounders, information on mindfulness practices, which are associated with sleep [78], was not available. Diet has been linked to stress [79]. Improvement in diet may have led to lower stress levels which improved sleep. Stress was measured subjectively and examined as a potential confounder.

This study had several strengths. For one, this manuscript examined a novel association between dietary inflammatory potential, as estimated by the E-DII, and objectively and validated measures of sleep. In addition to this, changes in the E-DII versus changes in sleep were examined, as opposed to using a single time point. The DII itself is a unique and innovative tool to measure dietary inflammatory potential. Also, it is important to note that the Southeast United States, where this study was conducted, has some of the highest rates of inadequate sleep durations and sleep disorder diagnoses in the USA [80]. Lastly, a range of covariates were examined as potential confounders. Despite its strengths, this study suffered from several limitations. The sample size was relatively small. This limited the ability to stratify analyses by potentially important effect modifiers. Although sleep was objectively measured, diet was assessed via self-report. However, three unannounced 24HRs were obtained over a two-week period at baseline and three months which, based on lowest overall variance compared to other assessment methods, is the gold standard in dietary reporting [81, 82]. The ability to examine mediation is diminished given a lack of a strong association between E-DII scores and inflammatory markers. Also, it is unclear what type of change in circulating inflammation is needed to evince changes in sleep. Although data from pre and post intervention were used, the analysis utilized change metrics. It is possible that changes in sleep parameters led to changes in E-DII scores. However, given this analysis was conducted within the context of a dietary intervention specifically designed to lower DII scores, reverse causation is unlikely. Although sleep was measured using a device validated against polysomnography (PSG) [47, 48], it does not perfectly align with PSG and the direction and amount that any actigraphy device is biased compared to PSG is hard to predict. Also, subjective sleep data (e.g. sleep logs) were not collected, which would have helped to corroborate the high mean WASO value. Lastly,

information on sleep medications was not obtained in the main IMAGINE study.

In conclusion, a change to a more anti-inflammatory diet was associated with improvements in sleep efficiency and WASO with no corresponding change in sleep duration. This may indicate that a more anti-inflammatory diet may improve sleep quality without requiring additional time in bed to do so. More research is needed to apply this hypothesis in populations suffering from chronic conditions associated with comorbid sleep complaints such as in cancer survivors or those with depression. If adoption of anti-inflammatory diets can improve sleep among these individuals, then dependence of pharmacological sleep aids may be reduced in favor of a non-pharmacological treatments. It was outside the scope of this report to focus on meal-timing or chrononutrition. However, timing of food intake also may be associated with sleep [83]. Future studies with larger samples sizes that can fully explore the interaction between diet quality and timing may provide more thorough insights into non-pharmacological means to improve sleep.

Funding

This study was supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest statement. Financial disclosure statement: Dr. James Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company licensing 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. In addition to their University of South Carolina appointments, Drs. Michael Wirth and Nitin Shivappa are employees of CHI. There are no other conflicts to report.

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