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Brief Report

Variable Eating Patterns: A Potential Novel Risk Factor for Systemic Inflammation in Women

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Abstract

Background The timing and regularity of eating patterns could play a role in systemic inflammation, as circadian clocks responsible for daily rhythms of inflammatory signaling are entrained by food intake.

Purpose To evaluate associations of intra-weekly and weekday-weekend differences in eating timing patterns with high-sensitivity C-reactive protein (hsCRP).

Methods A community-based sample of 103 U.S. women from the American Heart Association Go Red for Women Strategically Focused Research Network completed a meal-timing questionnaire and provided a blood sample for measurement of hsCRP. Differences in weekday versus weekend eating start time, eating end time, and nightly fasting duration were calculated as eating jetlag metrics. Intra-weekly variability in eating timing patterns was defined by the standard deviation (*SD*) of these variables. Multivariable linear regression models were used to evaluate cross-sectional associations of eating timing variability metrics with hsCRP.

Results Each additional 30-min difference in weekday–weekend eating end time was related to 13% higher hsCRP (p = .023). Similarly, every 30-min increase in eating end time *SD*, reflecting greater variability in timing of last eating occasion, was associated with 29% higher hsCRP. Per 1-hr weekday–weekend difference in nightly fasting duration, there was a 45% elevation in hsCRP (p = .003). Every 30-min increase in nightly fasting duration SD, representing greater variability in span of the daily fasting/eating periods, was associated with 46% higher hsCRP.

Conclusions Variable eating timing patterns were associated with higher hsCRP. Intervention studies are needed to determine whether stabilizing the timing of eating occasions may represent a novel strategy to reduce chronic inflammation.

Keywords: Eating jetlag · Eating timing variability · Inflammation · Women's health · Chronic disease prevention

Introduction

Chronic systemic inflammation is a risk factor for the leading causes of morbidity and mortality worldwide, including cardiovascular disease, cancer, diabetes, and neurodegenerative disorders [1]. Elevated levels of high-sensitivity C-reactive protein (hsCRP), a biomarker of systemic inflammation, are linked to poor prognoses for these chronic conditions, and more recently to increased severity of COVID-19 [1, 2]. Poor diet quality, characterized by high intakes of ultra-processed foods, trans-fats, and refined sugars, contributes to inflammation [1]. The timing and regularity of eating patterns could also play a role in systemic inflammation, as circadian clocks responsible for daily rhythms of inflammatory signaling are entrained by food intake [3].

Irregular patterns of lifestyle behaviors lead to disruption of circadian rhythms, which has in turn been linked with elevated chronic disease risk [4], including inflammation [3, 5]. For instance, emerging data suggest that social jetlag, the difference between sleep timing on workdays versus non-work days, representing a discrepancy between an individual's endogenous circadian rhythm and timing of daily activities, is related to inflammatory markers [5]. Akin to social jetlag, which affects up to 85% of the non-shift worker adult population [6], is the concept of *eating jetlag*, the extent to which eating timing and span differ between work and non-work days (i.e., weekdays vs. weekends) [7, 8]. This prevalent erratic eating pattern, which typically accompanies irregular sleep patterns, may contribute to

chronic inflammation via similar mechanisms as social jetlag. However, eating timing regularity in relation to systemic inflammation has not been studied in humans. The purpose of this pilot study was to evaluate eating jetlag and day-to-day eating timing variability metrics in relation to hsCRP in a community-based sample of racially and ethnically diverse U.S. women.

Methods

We evaluated the association of eating jetlag with fasting plasma hsCRP levels in a cross-sectional pilot study of 103 women (mean age: 34 ± 12 years, 47% Hispanic ethnicity, mean body mass index (BMI): 26 ± 6 kg/m^2) participating in the American Heart Association Go Red for Women Strategically-Focused Research Network at Columbia University Irving Medical Center (parent study). The purpose of the parent study was to evaluate the associations of psychosocial factors, sleep, and cardiometabolic risk in a 1-year prospective cohort study of 506 women. Details regarding recruitment approaches and procedures in the parent cohort have been previously described [9, 10]. Briefly, participants were women aged 20–79 years without cardiovascular disease recruited from neighboring communities of a large urban medical center in Northern Manhattan.

Our analytic sample represents a subset of female volunteers (n = 103) from the parent cohort who consented to additionally participate in an ancillary study on meal timing. At the 1-year follow-up visit of the parent study (which took place between July 2017 and February 2019), those individuals also completed a novel standardized meal-timing questionnaire and provided a blood sample, from which hsCRP was assessed. Overall, the analytic sample for the present study consisted of women aged 22–65 years, of whom 79% reported being racial/ethnic minorities (compared to ~62% in the parent cohort) and 65% had health insurance (compared to ~76% of the parent cohort), our primary measure of socioeconomic position [9, 10]. This study was approved by the Columbia University Irving Medical Center Institutional Review Board (protocol #AAAQ8196). Study procedures have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

A brief meal-timing questionnaire, specifically developed for this study, queried participants' habitual timing of first and last eating occasion on weekdays and on weekends during a typical 7-day period, asking them: "On average, at what time do you start and stop eating?." Habitual nightly fasting duration, the duration of fasting coinciding with the main sleep period representing the inverse of the daily eating period, was estimated by subtracting the number of hours spanning first-to-last eating occasion from 24 hr. Differences in weekday versus weekend nightly fasting duration, eating start time, and eating end time were calculated as eating jetlag metrics. We used standard deviation (*SD*) of these variables as a marker of overall intra-weekly variability in eating patterns. A fasting blood sample was collected from all participants and used to measure plasma hsCRP using an automated assay on the Roche Integra 400 plus instrument (Roche Diagnostics, Indianapolis, IN) at the Columbia University Irving Medical Center Biomarkers Core Laboratory.

Descriptive statistics were used to characterize the study sample, and histograms were plotted to assess normality of the data. The distribution of hsCRP was skewed to the right with 94% of participants having hsCRP levels <10 mg/L; these data were therefore log-transformed to better approximate a Gaussian distribution. Associations of eating jetlag and day-to-day eating pattern variability metrics with log-transformed hsCRP were evaluated using linear regression models adjusted for age, health insurance status (as a proxy for socioeconomic status), body mass index (BMI), and sleep duration (self-reported on the Pittsburgh Sleep Quality Index [11]). In sensitivity analyses, we excluded individuals with hsCRP concentrations >10 mg/L, given that higher hsCRP levels may be suggestive of acute inflammation rather than chronic low-grade inflammation. SAS version 9.4 was used for all analyses (Cary, NC), and a p-value <.05 was considered statistically significant.

Results

The mean hsCRP level across the full sample was 2.3 ± 4.9 mg/L (**Table 1**); 97 participants (94% of sample) had CRP levels <10 mg/L, and the mean hsCRP level for those individuals was 1.4 ± 1.8 mg/L. Overall, 61% of participants had hsCRP levels <1 mg/L, while 21% and 18% had hsCRP levels of 1–3 mg/L and >3 mg/L, respectively. The average timing of first and last eating occasions was later on weekends compared to weekdays. The average weekday-weekend difference in first eating occasion timing, last eating occasion timing, and nightly fasting duration was 1.4 ± 1.1, 1.2 ± 1.1, and 1.2 ± 1.0 hr, respectively.

In multivariable linear regression models, variability in timing of the first eating occasion was not related to hsCRP. However, each additional 30-min difference in weekday versus weekend eating end time was significantly related to having higher log hsCRP (β[95%CI] = 0.12 [0.02–0.23], p = .023; **Table 2**). In particular, the back-transformed parameter estimates indicated that per 30-min increase in weekday versus weekend eating end time differences, there was a 13% elevation in hsCRP. Similarly, greater variability in the time of last eating occasion across days was associated with higher hsCRP, whereby every 30-min increase in eating end time SD was associated with 29% elevated hsCRP. In sensitivity analyses excluding those with hsCRP>10 mg/L, these associations persisted but were attenuated. Every additional 30-min difference in weekday versus weekend eating end time and eating end time SD across days was related to borderline significant 10% and 22% higher hsCRP, respectively (p = .050).

Every additional 1-hr difference between weekday and weekend nightly fasting duration was significantly associated with higher log hsCRP (β[95%] = 0.37 [0.13–0.61], p = .003). Specifically, the back-transformed parameter estimates indicated that every additional 1-hr difference between weekday and weekend nightly fasting duration was related to 45% elevated hsCRP. Greater nightly fasting duration SD, representing greater intra-weekly variability in the span of the daily fasting/eating periods across days, was also associated with higher hsCRP, such that every 30-min increase in this metric was related to 46% elevated hsCRP. In sensitivity analyses, these associations persisted such that each 1-hr difference in weekday versus weekend nightly fasting duration was associated with 26% higher hsCRP (p = .039); every 30-min increase in nightly fasting duration SD was also associated with 27% higher hsCRP.

Table 1. Descriptive Characteristics of the Study Population (n = 103)

Characteristics	Mean ± *SD*/%
Demographic and Clinical	
Age (years)	34.0 ± 12.2
Racial and/or Ethnic Minority (%)	78.6%
Hispanic Ethnicity (%)	46.6%
Health insurance (%)	65.1%
Body mass index (kg/m^2)	26.0 ± 5.6
C-reactive protein (mg/L)	2.3 ± 4.9
Eating Timing	
First eating occasion	
Time of first eating occasion on weekdays (HH:MM)	8:53 ± 2:13 [range: 4:45–17:00]
Time of first eating occasion on weekends (HH:MM)	10:01 ± 1:45 [range: 6:00–16:00]
Jetlag in time of first eating occasion (hr)	1.4 ± 1.1 [range: 0–5.5]
Time of first eating occasion *SD* (min)	42.1 ± 30.8
Last eating occasion	
Time of last eating occasion on weekdays (HH:MM)	20:37 ± 1:41 [range: 18:00–4:30]
Time of last eating occasion on weekends (HH: MM)	21:43 ± 1:37 [range: 18:00–4:30]
Jetlag in time of last eating occasion (hr)	1.2 ± 1.1 [range: 0–4.0]
Time of last eating occasion *SD* (min)	34.9 ± 32.6
Nightly fasting duration	
Weekday nightly fasting duration (hr)	12.3 ± 2.2 [range: 8.5–21]
Weekend nightly fasting duration (hr)	12.3 ± 1.8 [range: 8–18]
Jetlag in nightly fasting duration (hr)	1.2 ± 1.0 [range: 0–4.5]
Nightly fasting duration *SD* (min)	25.7 ± 29.1

Discussion

We present the first evidence that measures of variability in the timing of eating patterns, including eating jetlag, are associated with higher hsCRP, a robust marker of systemic inflammation, in racially and ethnically diverse U.S. women. Eating timing has previously been linked to hsCRP in women [12]. In a study of ~2,200 women who completed the 2009–2010 National Health and Nutrition Examination Surveys (NHANES) (mean age: 47 years), each 10% increase in the percentage of daily calories consumed in the evening (after 5:00 PM) was associated with a 3% increase in hsCRP [12]. Further, a longer nightly fasting duration was associated with 8% lower CRP only among women who consumed <30% of their daily caloric intake after 5:00 PM. On the other hand, in another analysis using 2005–2016 NHANES, every 1-hr increase in nightly fasting duration and in timing of the first eating occasion was associated with significantly higher CRP [13]. However, in these studies, diet was assessed using a single 24-hr recall, so it was not possible to evaluate the variability of eating timing across days and between weekdays and weekends in relation to hsCRP.

Our results are consistent with data from animal models and human studies of controlled simulations of forced circadian misalignment, which have collectively shown that eating at unconventional circadian times can reset peripheral clocks, result in circadian misalignment, and even increase the expression of pro-inflammatory genes [3, 4, 12, 14]. It is possible that we only observed significant associations for timing of the last eating occasion because greater day-to-day and weekday–weekend variability in timing of the last eating occasion further augments the detrimental effect of eating at unconventional circadian times by consuming a larger evening meal. Indeed, the mean timing of the last eating occasion was after 8 PM in our cohort, which is later than the time beyond which detrimental associations with CRP have been previously reported [12]. In addition, later meal timing, leading to a shorter duration between timing of the last eating occasion relative to the dim light melatonin onset, has been linked to poorer diet quality, greater adiposity, and higher odds of developing metabolic abnormalities, all of which are risk factors for inflammation [15, 16].

Although no previous study has evaluated eating timing variability in relation to inflammation, our findings align with prior evidence from the AHA Go Red for Women cohort that eating jetlag and greater day-to-day variability in timing and span of the eating period are associated with cardiometabolic risk factors such as higher adiposity and blood pressure and worse glycemic control [7]. Eating jetlag has also been linked to greater BMI in young Spanish adults [8]. It is possible that associations of eating timing variability metrics with inflammation are partially mediated by BMI. However, adjustment for BMI in our models did not alter the significance of our findings suggesting that there are additional mechanisms at play. For instance, circadian misalignment may represent an additional underlying mechanism, as it has been shown to increase hsCRP in shift workers [14]. In that population, undertaking two 3-day laboratory protocols that simulated night work comprised of 12-hr inverted behavioral and environmental cycles (circadian misalignment) increased 24-hr hsCRP levels by 11% [14].

Strengths of our study include the novelty of our research approach and findings, the racial and ethnic diversity of our community-based sample, which enhances the generalizability of our results to the broader U.S. population, and the objective assessment of a marker of systemic inflammation that is relevant to the etiology of multiple chronic conditions. The use of timing of the first and last eating occasion and eating span to evaluate eating timing variability is also a strength of our study, given that these metrics may better represent eating patterns than conventional meal categories, which vary across cultures.

However, limitations of our study should also be considered. First, our participants were all female and healthier than the general U.S. population (free of cardiovascular disease and diabetes, hypertension prevalence <5%, and obesity prevalence ~20%), so associations of eating pattern timing variability with inflammation in men and individuals with chronic disease and additional risk factors warrant further investigation. Second, our sample size was modest, so we had limited power for sub-group analyses. Third, we investigated the association of eating timing variability with only

Table 2. Cross-sectional Associations of Eating Timing Variability Measures with C-Reactive Protein (mg/L) in Multivariable Linear Regression Models[a]

Overall Sample (*n* = 103)		
	Log hsCRP[b,d]	**Back-transformed hsCRP[c,d]**
	β (95% CI)	**β (95% CI)**
Eating Jetlag in time of first eating occasion (per 30 min weekday vs. weekend difference)	0.10 (–0.01–0.22)	1.10 (0.99–1.25)
Eating Jetlag in time of last eating occasion (per 30 min weekday vs. weekend difference)	**0.12 (0.02–0.23)**	**1.13 (1.02–1.26)**
Eating Jetlag in nightly fasting duration (per 1 hr weekday vs. weekend difference)	**0.37 (0.13–0.61)**	**1.45 (1.14–1.83)**
Standard deviation of time of first eating occasion (per 30 min increase)	0.21 (–0.03–0.46)	1.24 (0.97–1.58)
Standard deviation of time of last eating occasion (per 30 min increase)	**0.25 (0.03–0.47)**	**1.29 (1.03–1.61)**
Standard deviation of habitual nightly fasting duration (per 30 min increase)	**0.38 (0.14–0.62)**	**1.46 (1.15–1.86)**
Sensitivity Analysis (*n* = 97)		
	Log hsCRP[b,d]	**Back-transformed hsCRP[c,d]**
	β (95% CI)	**β (95% CI)**
Eating Jetlag in time of first eating occasion (per 30 min weekday vs. weekend difference)	0.02 (–0.08–0.13)	1.02 (0.92–1.14)
Eating Jetlag in time of last eating occasion (per 30 min weekday vs. weekend difference)	0.10 (0.00–0.19)	1.10 (1.00–1.21)
Eating Jetlag in nightly fasting duration (per 1 hr weekday vs. weekend difference)	**0.23 (0.01–0.45)**	**1.26 (1.01–1.57)**
Standard deviation of time of first eating occasion (per 30 min increase)	0.05 (–0.17–0.26)	1.05 (0.84–1.30)
Standard deviation of time of last eating occasion (per 30 min increase)	0.20 (0.00–0.39)	1.22 (1.00–1.47)
Standard deviation of habitual nightly fasting duration (per 30 min increase)	**0.24 (0.02–0.46)**	**1.27 (1.02–1.59)**

[a]Linear regression models are adjusted for age, health insurance, BMI, and sleep duration.
[b]Parameter estimates are from linear regression models where the outcome variable hsCRP was log transformed to better approximate a Gaussian distribution.
[c]Parameter estimates have been back transformed to reflect the percent change in the outcome variable hsCRP associated with a 1-unit increase in each exposure variable.
[d]Boldface indicates statistical significance ($p < .05$).

one inflammatory marker, so relations with other markers of systemic inflammation should be evaluated in future studies. Fourth, eating timing was self-reported on a questionnaire, so recall bias is another limitation of the present analysis. Fifth, although we considered several socio-demographic and clinical characteristics as potential confounders, our results are prone to residual confounding by other and unmeasured health factors. Finally, our study design was observational and cross-sectional, which prohibits the establishment of causality and temporality and the assessment of how changes in eating timing variability impact hsCRP levels over time. Future studies are needed to investigate longitudinal associations of eating timing patterns with hsCRP and their interplay with sleep patterns, including social jetlag, in predicting chronic systemic inflammation.

Conclusions

Considering the effect sizes reported herein, our novel findings, if confirmed in larger population-based cohorts and intervention studies, could have important clinical applications, since hsCRP levels of 1–3 mg/L and >3 mg/L correspond to moderate- and high-risk groups for cardiovascular events, respectively [17]. Further, given that inflammation is implicated in at least 8 of the 10 leading causes of death in the USA [1], identification of modifiable behaviors to reduce inflammation is of great public health relevance. Indeed, dose–response associations of similar magnitude have been demonstrated for hsCRP with cardiovascular disease, vascular mortality, and death from certain cancers and lung disease [18]. If our findings are confirmed in intervention studies, stabilizing the timing of eating occasions across days and/or between weekdays and weekends may represent a novel behavioral strategy to reduce chronic inflammation and associated morbidity and mortality. This is particularly important in the current COVID-19 era, in which habitual work, sleep, and eating schedules have been significantly disrupted [19], and hsCRP is noted as an important prognostic factor [2].

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Authors Nour Makarem, Faris M. Zuraikat, Billy Caceres, Dorothy D. Sears, Marie-Pierre St-Onge, Yue Lai, and Brooke Aggarwal declare that they have no conflict of interest.

Author's Contributions Conceptualization (N.M., D.D.S.), data curation (N.M., B.A., D.D.S.), formal analysis (Y.L.), funding acquisition (N.M., B.A., D.D.S.), investigation (N.M., B.A., D.D.S.), methodology (N.M., F.M.Z., B.A.C., D.D.S., B.A.), project administration (N.M., B.A., D.D.S.), resources (N.M., B.A.), software (Y.L.), supervision (N.M., B.A.), validation (N.M., F.M.Z., Y.L., B.A.), visualization (N.M., Y.L., F.M.Z., D.D.S., B.A.C., M.P.S.O.), writing-original draft (N.M.), writing-review and editing (F.M.Z., D.D.S., B.A.C., M.P.S.O., B.A.).

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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