A multifaceted analysis of social stressors and chronic inflammation

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ABSTRACT

Chronic stress has been linked to negative health outcomes, including increased inflammation, which can be measured by high-sensitivity C-reactive protein (CRP). Prior research has focused almost exclusively on relationships between individual social and demographic stressors and CRP. The objective of this study is to assess the role of multiple potential stressors simultaneously to determine which key stressors are related to risk of high CRP, given that sustained stress and resulting inflammation may have long-term health implications. We hypothesized that negative social and environmental factors would be associated with high CRP. Data from two waves of Midlife in the United States were used to predict high CRP with variable selection procedures and logistic regression. Results indicated females, those with greater BMI, those with improvements in family strain, and those with higher A1c had a greater risk of high CRP. There was limited evidence that negative social factors were associated with CRP to the extent seen in prior literature. A key advantage of the study was testing multiple potential determinants of chronic stress and inflammation simultaneously, advancing the existing literature. Results demonstrate the potential usefulness of a multifaceted approach to evaluating the risk of chronic inflammation and high CRP.

1. Introduction

In 2016 and 2017, Americans reported higher stress than 2007 (American Psychological Association, 2017a, 2017b) with symptoms such as anxiety, anger, and fatigue (American Psychological Association, 2017a). Stress profoundly affects humans due to longer periods in psychological stress, compared to other animals. Becks (2004) describes the body’s stress response. Stress is increasing in Americas, it is imperative to investigate health and quality of life outcomes to understand the impact of prolonged stress.

A multitude of factors have been identified as contributing to prolonged stress, including social factors, such as poverty (distinct from low socioeconomic status (SES)), violence exposure, and caregiving (Oliveira et al., 2016). Social stressors turn into prolonged stress when they initiate a stress response in the body (Oliveira et al., 2016). Chronic inflammation results from a prolonged increase in stress hormones (Barr, 2014) and is linked to negative health outcomes (connected to chronic stress (Kubzansky, Seeman, & Glymour, 2014; Riancho & Brennan-Olsen, 2017) and usually associated with advanced age), such as cardiovascular disease (CVD) (Kubzansky et al., 2014). Elevated levels of CRP (≥ 10 mg/L) can indicate the development of CVD (Alley et al., 2006), which may lead to poorer health and quality of life. Fig. 1 illustrates the interplay of social/environmental stressors for inflammation developed from the models of Barr (2014), Kubzansky et al. (2014), and Riancho and Brennan-Olsen (2017). CRP is a convenient biomarker for assessing potential diagnoses of CVD, among other medical conditions, as it can be measured through point-of-care in clinical contexts and through minimal processing of saliva and blood samples in research contexts. Thus, understanding the exact nature of its relationship to environmental and biological factors is important.

Demographic indicators, such as race/ethnicity (Nikulina and Widom, 2014), immigration status (Alley et al., 2006), and gender (Lzucks et al., 2010; Sbarra, 2009) have been demonstrated to predict elevated CRP, albeit with a highly complex pattern. Relatedly, neighborhood SES was implicated for elevated CRP (Uchino et al., 2016), along with neighborhood disorder (Holmes & Marcelli, 2012), and neighborhood quality (deprivation and problems) (Nazmi et al., 2010), although at least in one study obesity and dietary fat intake explained much of the link (Von Känel et al., 2012). The literature shows inconsistencies in the association between SES and CRP, which is in part due to the many ways in which SES was conceptualized and measured, and poverty was associated with very high CRP levels (> 10 mg/L) when compared to those above the poverty level, and when chronic health conditions and obesity were present (Alley et al., 2006). Given such past findings, we too focus on higher levels of CRP (> 3 mg/L and <
10 mg/L) to investigate disparities.

Education, another potential marker of SES, has also been inversely linked to CRP levels (Loucks et al., 2010), consistent with greater trends in health conditions. Later first marriage in men has appeared to be protective in relation to CRP (Sbarra, 2009), but previously married older men displayed higher CRP levels, like married and unmarried women (Sbarra, 2009). Caregiving for a spouse with Alzheimer’s has been associated with increased CRP until the spouse’s death, after which CRP declined (Von Känel et al., 2012), suggesting inflammation increases during prolonged stress.

Social support displayed an inverse relationship to CRP levels in the literature. Research has demonstrated higher CRP levels are associated with social factors in some studies, including low social support or social isolation, with results typically seen in men and sometimes only in narrow age ranges (Heffner et al., 2011; Ford, Loucks, & Berkman, 2006). However, there is limited evidence that high social support can buffer the relationship between chronic stress and CRP (Runsten et al., 2014). Further, spousal support displayed an inverse relationship with age- and sex-adjusted levels of CRP (Yang, Schorpp, & Harris, 2014).

Individuals who have sustained trauma experience prolonged stress (Williamson et al., 2015; Johnson, Delahanty, & Pinna, 2008), but many other circumstances can also affect levels of inflammation in adulthood through epigenetic mechanisms (McDade et al., 2017) (e.g., stressful life events like parental absence). Childhood adverse events are important to examine as they have been associated with greater levels of inflammation in adults, specifically CRP (Danese et al., 2007; Kiecolt-Glaser et al., 2011), and enhance inflammation from adult stressors, such as caregiving (Kiecolt-Glaser et al., 2011). Exposure to violence in childhood was linked to increased CRP continuing into adulthood (Runsten et al., 2014; Danese et al., 2007), as was exposure to poverty (Nikulina & Widom, 2014). Furthermore, childhood adverse events seem to be associated with less social support (Runsten et al., 2014). Therefore, this paper endeavors to examine factors in childhood, their impact on adulthood, and adulthood-specific events, to investigate how they impact markers of inflammation.

The variety of stressors examined in the CRP literature creates a complex picture of stress’s role in elevating CRP. However, the relationship among all of the stressors has not been quantified. Because of the potential for omitted variable bias, it is important to evaluate stressors concurrently (Alley et al., 2006), an approach this paper will take. Drawing from the wide-ranging literature on individual stressors associated with CRP, we developed the following research question: What are the key social stressors affecting Americans that lead to chronic inflammation, as measured by high CRP? This question is of interest because sustained stress and resulting inflammation may compromise long-term health outcomes and quality of life. The main hypothesis is the following: Negative social and environmental factors will be associated with high CRP.

2. Materials and methods

2.1. Materials

Data come from Midlife in the United States: A National Longitudinal Study of Health & Well-Being (MIDUS). We used MIDUS 1, collected in 1995 and 1996, and MIDUS 2, the longitudinal follow-up collected between 2004 and 2006. MIDUS 1 was used to obtain background variables. For MIDUS 2 we used Projects 1 and 4. Project 1 includes a follow-up of MIDUS 1 data, plus additional questions about relevant topics, such as caregiving. Project 4 is the biomarker study, which allowed us to study CRP and potentially related biological factors, such as A1c and cholesterol. There were 1054 individuals who responded to both MIDUS 1 and MIDUS 2, including the biomarker study.

2.2. Sample

We restricted the sample to participants who responded to MIDUS 1, and MIDUS 2 Projects 1 and 4 with full data on the CRP outcome (45 cases dropped); with no exclusionary health conditions (i.e., conditions that may unduly affect the outcome: tuberculosis, burns, autoimmune/Lupus disease) (31 cases dropped); and with full data on our selected predictor variables (201 cases dropped; data missing primarily for BMI at time 1 and menopause status; some additional missing data on biomarkers and predictors such as strain, social support, neighborhood quality, and poverty). Total analytic sample size was 777. Supplementary Table 1 includes descriptive statistics for the analytic sample compared to the full biomarker sample. The full biomarker sample is slightly more female, slightly older on average, and slightly more likely to be caring for an adult at MIDUS 2.

2.3. Variables

The outcome variable was high CRP, measured at MIDUS 2. All
biodmarkerm samples were collected at three General Clinic Research Centers. Participants spent two days at the clinics, staying overnight (Dienberg Love et al., 2010). As there are inconsistencies in how CRP behaves in statistical models (Wu et al., 2015), CRP was modeled using a binary variable with values greater than 3 mg/L indicating increased inflammation (Ishii et al., 2013). Individuals with CRP exceeding 10 were dropped from the analysis as these values indicate a probable underlying medical condition (Pearson et al., 2003). Supplemental models testing the log of continuous CRP as the outcome were also examined (results available on request).

Key predictor variables were identified through the literature review. We included variables from the domains of demographics, trauma-related variables (early life) (Table 1), social relationship variables (Table 1), other potential social stressors (Table 1), and confounders. In the literature demographics are especially important as mediators/modifiers of the effect of other variables (e.g., neighborhood quality). Consistent with this literature we initially included racial/ethnic minority status and perceived neighborhood quality to proxy for neighborhood environmental conditions. We also assessed the role of education because low education is associated with worse outcomes (Locucks et al., 2010).

For a few variables, specifically neighborhood quality, family support and strain, and poverty, we examined changes in these variables over time, along with measures at MIDUS 1 and 2. This helped address the possibility that strain or poverty (for example) at one point in time might have different effects on outcomes compared to persistent strain over time, or improvements or worsening strain. For each of these variables, aside from poverty over time, the comparisons are no change across waves, improvement across waves, and worsening across waves. For poverty, the categories are not in poverty at both waves, in poverty at MIDUS 1 only, in poverty at MIDUS 2 only, and in poverty at both waves.

Although not social stressors per se, we also initially accounted for potentially influential health behaviors and biomarkers. Those with potential negative consequences for outcomes include smoking, alcohol consumption, a count of the health conditions reported, and biomarkers related to inflammation and chronic disease, including A1c, cholesterol measures (i.e., total, HDL, LDL, triglycerides), insulin, and cortisol. Exercise participation could have positive consequences for outcomes because physical activity is thought to reduce stress levels.

Finally, we initially controlled for potential confounders, including whether the respondent was female and menopause status; these variables are correlated with health outcomes. We also initially controlled for body mass index (BMI). Prior research has demonstrated that body size is related to CRP (Park, Park, & Yu, 2005).

### 2.4. Analysis

To identify an appropriate set of variables to include in our models, we employed variable selection methods. We first estimated a model including all predictor and confounding variables and determined which variables were statistically significant (α < 0.05). We then applied the “change-in-estimate” variable selection routine. In this method, a model with only significant predictors from the first step was estimated, and the main predictor coefficient was evaluated for the percentage of change when a non-significant predictor was added back into the model. If the main coefficient changed by 10% or more, the non-significant variable was retained (Maldonado & Greenland, 1993). Our main model of interest, Model 1, used the model-selected predictors to estimate high CRP using logistic regression. The model-selected predictors were female, BMI (wave 2), A1c, HDL cholesterol, and changes in family strain across waves.

### 3. Results

Descriptive statistics for the Model 1 variables are shown in Table 2 (complete descriptive statistics in Supplementary Table 1). Approximately half of the sample was female (49%), and the mean age at MIDUS 2 was 54. On average, the sample was overweight, with a mean BMI of 29.01 at wave 2. The mean A1c level was 5.96%, which is indicative of pre-diabetes. About 24% of the sample had high CRP levels.

The results of Model 1 predicting high CRP are presented as odds ratios with 95% confidence intervals (Table 3). The pseudo R² of 0.1310 indicates the variables weakly predicted high CRP. Women were predicted to have 2.4 times the odds of high CRP compared to men, all else constant (p < 0.001). A higher BMI at wave 2 was associated with 14% higher odds of high CRP (p < 0.001). Improvements in family strain over time were associated with 1.6 times the odds of high CRP (p = 0.048), possibly indicative of reverse causality. A higher A1c was associated with 27% higher odds of high CRP (p = 0.018). Although HDL cholesterol changed the coefficient on female by more than 10%, in Model 1 this variable was not significantly related to risk of high CRP, after accounting for the other predictors.

### 4. Discussion

Returning to our research question, we found the social stressor of family strain and the confounders of being female (consistent with prior research (Doran, Zhu, & Muennig, 2013; Wener, Daum, & McQuillan, 2000)), A1c, and BMI were associated with high CRP. Consistent with our hypothesis, CRP appears to be associated with one social factor (family strain), though not to the extent expected from the prior literature and not in the expected direction. Nevertheless, the results suggest that including multiple social variables as indicators of stress and stress mediators, and using appropriate variable selection procedures, will elucidate a better understanding of the stress-CRP relationship.

Family strain was a significant predictor of CRP, which was unexpected given prior research (Yang et al., 2014). Decreases in strain were significantly associated with increased risk of high CRP, contrary to expectation; decreases in strain should have positive effects on

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1 These are MIDUS-calculated variables based on a set of questions. For example, family strain is calculated from: “Not including your spouse or partner, how often do members of your family make too many demands on you?”; “How often do they criticize you?”; “How often do they let you down when you are counting on them?”; and “How often do they get on your nerves?”

2 Variables not included in the final model, including early life adversities, were not statistically significant predictors of high CRP.
As results of inflammation studies varied so much in the literature it is not surprising that many early life and adulthood experiences were not associated with CRP in this study. Additionally, several factors that could potentially affect CRP were not available in this sample, including exposure to pollution and other environmental contaminants, local government efforts to address social and health disparities, and dietary intake. Overall, the analysis has several limitations related to the data, including a modest sample size and overrepresentation of those with higher SES as noted above. Further, our analytic sample, compared to the full biomarker sample, undercounts females, younger adults, and those caring for an aging adult at MIDUS 2, although the differences between the two samples are relatively small. However, the study has the advantage of testing multiple potential determinants of chronic stress and chronic inflammation in a single model, which advances the existing literature. Furthermore, the results demonstrate the potential usefulness of a multifaceted approach to the risk of chronic inflammation and high CRP. Future studies should extend this approach to examine these relationships in other, more nationally representative, samples (such as the National Health and Nutrition Examination Survey or the Health and Retirement Study), and ideally should incorporate additional contextual variables, such as those related to environmental exposures, policies, and broader socioeconomic environments.

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### Conflicts of interest

None to declare.

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None.

### IRB statement

We (Dr. Margaret Gough and Dr. Kanya Godde) did not collect any data ourselves from human participants in our study “A Multifaceted Analysis of Social Stressors and Chronic Inflammation”; we used secondary public-use data. The data we used were obtained from the Midlife in the United States: A National Longitudinal Study of Health & Wellbeing (MIDUS) and did not contain identifiers. In other words, there is no way to trace a respondent’s answer to a living person. Under the federal regulations for human subjects research (45 CFR 46), secondary data with identifiers do not qualify as human subjects research. Further, our Institutional Review Board (IRB) specifically identifies MIDUS as a dataset that does not require IRB review (https://laverne.edu/irb/wp-content/uploads/sites/28/2018/01/La-Verne-IRB-Secondary-Analysis.pdf). The second author is the Chair and Director of the IRB at University of La Verne and is well versed in the policies and procedures of the IRB and the greater federal regulations, which is why we are confident that these data do not require IRB review and approval.

Table 2

| Mean (SE) | Range |
|----------|-------|
| Female   | 0.49  | 0–1  |
| Body mass index at Wave 2 | 29.01 (5.68) | 14.99–57.40 |
| A1c (%) | 5.96 (0.83) | 3.80–11.91 |
| HDL cholesterol | 53.94 (17.37) | 19–121 |
| Family strain across waves | 0.23 | |
| Unchanged strain across waves | |
| Improved strain from Wave 1 to Wave 2 | 0.44 |
| Worsened strain from Wave 1 to Wave 2 | 0.33 |
| High CRP | 0.24 | 0–1 |
| N       | 777   |

**Statistical significance:**

**p < .01.**

*p < .05.

**p < .001

As health. We posit that some unknown factor was at play because the survey questions do not measure reasons for strain. We tested the possibility the respondent’s health declined, leading to a decrease in family strain but did not find significant evidence that declines in health were associated with declines in family strain. Without knowledge of the causes of family strain, the mechanism underlying this result is unclear and should be tested in another sample.

Many of the factors individually associated with CRP in prior studies were not significantly associated with high CRP in this study. For example, neighborhood quality was not a predictor of elevated CRP, which is not surprising as analyses of adulthood neighborhood quality effects have been inconclusive in the literature. Moreover, it was expected that SES and education would display an inverse relationship with CRP, which was not detected. Overall, this sample represents a higher-SES segment of Americans, and thus low levels of education, extreme poverty, and incredibly poor neighborhood quality were not present; only 4.1% had education of less than high school, and 47.8% were college graduates; average neighborhood quality was 3.5–3.6 out of 4; and median income was $64,500 at MIDUS 2. Furthermore, the sample is not representative of the racial/ethnic diversity of the United States, and the sample size was relatively small, limiting our ability to examine whether minority status was a predictive factor. Similar patterns exist in the data with caregivers (the survey question may be too broad; too few individuals with young minor children) and childhood adverse events (not inclusive of all types of childhood adversity identified in the literature). Our results are in contrast to other studies (Friedman & Herd, 2010; Yang et al., 2016), which is likely due to several issues, including differences in variables selected for models (the initial variables in this paper are more numerous, including measures of strain, among others), treatment of CRP (categorical here vs. continuous in other studies), and variable selection routines (e.g., change-in method here vs. forward or stepwise selection).

Table 3

| Odds Ratio | 95% CI |
|-----------|-------|
| Female    | 2.38*** (1.60, 3.52) |
| Body mass index at Wave 2 | 1.14*** (1.10, 1.18) |
| Strain improved from Wave 1 to Wave 2 | 1.62* (1.01, 2.63) |
| Strain worsened from Wave 1 to Wave 2 | 1.17 (0.70, 1.95) |
| A1c (%) | 1.27* (1.04, 1.55) |
| HDL cholesterol | 0.99 (0.98, 1.01) |
| Constant | 0.001*** (0.0001, 0.001) |
| Pseudo R² | 0.1310 |
| N | 777 |

**Statistical significance:**

**p < .01.**

*p < .05.

**p < .001.
Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ssmph.2018.09.005.

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