Inflammatory biomarkers link perceived stress with metabolic dysregulation

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ABSTRACT

Objective: Perceived stress has been identified as a risk factor for metabolic syndrome. However, the intermediate pathways underlying this relationship are not well understood. Inflammatory responses may be one process by which stress leads to metabolic dysregulation. Prior work has shown that chronic stress is associated with elevated systemic inflammation and that altered inflammatory activity contributes to the pathogenesis of metabolic syndrome. The current analyses tested this hypothesis by examining inflammation as a pathway by which perceived stress affects metabolic health.

Methods: Data from the Midlife in the United States Study (MIDUS) (N = 648; Mean age = 52.3) provided measures of perceived stress, inflammatory biomarkers [C-reactive protein (CRP), interleukin-6 (IL-6), E-selectin, fibrinogen, intracellular adhesion molecule-1 (ICAM-1)] and metabolic health markers. Confirmatory factor analysis (CFA) was used to confirm the fit of a hierarchical model of metabolic syndrome in our sample. Structural equation modeling (SEM) was used to test the assumption that inflammation mediates the association between perceived stress and the latent factor representing metabolic syndrome.

Results: The CFA of metabolic syndrome demonstrated excellent goodness of fit to our sample [CFI = 0.97, TLI = 0.95, RMSEA = 0.06, SMR = 0.05]. Mediation analysis with SEM revealed that the indirect pathway linking stress to metabolic dysregulation through inflammation was significant [B = 0.08, SE = 0.01, z = 3.69, p < .001, 95% confidence interval CI (0.04, 0.13)].

Conclusions: These results suggest that inflammatory biomarkers are a viable explanatory pathway for the relationship between perceived stress and metabolic health consequences. Interventions that target psychosocial stress may serve as cost-effective and accessible treatment options for mitigating inflammatory health risks.

1. Introduction

Psychosocial stressors are ubiquitous in everyday life and engender a cascade of physiological changes to meet environmental demands (Nesse et al., 2016). However, prolonged or severe stress can adversely affect health (Schneiderman et al., 2005; Cohen et al., 2016), including contributing to the development of metabolic syndrome (Ruo et al., 2019). Metabolic syndrome, a clustering of cardiometabolic risk factors characterized by insulin resistance, dyslipidemia, central adiposity, and elevated blood pressure (BP) (Alberti et al., 2005; Grundy, 2006), affects over one third of United States adults (Moore et al., 2017) and is an important predictor for cardiovascular disease (CVD; Mottillo et al., 2010), type II diabetes (Ford et al., 2008), neurodegeneration (Yalcin and Yalcin, 2018), and onset and progression of dementia, including Alzheimer’s disease (AD; Kim et al., 2021).

Perceived stress, or the degree to which individuals appraise experiences in their lives as stressful (Cohen, 1988), is a modifiable determinant of metabolic syndrome (Bergmann et al., 2014). Perceived stress is positively associated with metabolic syndrome severity even after accounting for lifestyle factors (Cardel et al., 2019) and may represent a critical target for intervention for disease prevention and treatment efforts. Given the social and economic burden of conditions associated with metabolic syndrome (Alzheimer’s Association, 2020; American Diabetes Association, 2018; Benjamin et al., 2018; Lozano et al., 2012), understanding the pathophysiological processes by which perceived stress leads to metabolic dysregulation may relieve a significant public health strain.

Although the exact pathways linking stress to metabolic syndrome...
are not fully understood, it is widely believed that inflammatory processes are involved (Black 2003; Brunner et al., 2002). Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and C-reactive protein (CRP), have been observed among individuals exposed to chronic stressors (Kiecolt-Glaser et al., 2003; Johnson et al., 2013; McDade et al., 2006). Moreover, systemic inflammation is characteristic of metabolic syndrome (Rana et al., 2007; Wannamethee et al., 2005) and can predict progression to type II diabetes, incident cardiovascular events, and cognitive impairment among those with the condition (Ridker et al., 2003; Sattar et al., 2003; Yaffe et al., 2004).

While the individual links between stress, inflammation, and metabolic syndrome are well-established, studies investigating the synergistic nature of these relationships are few and results are mixed. In one cross-sectional study of healthy male workers, concurrently high levels of work-related stress and CRP were associated with increased odds of developing metabolic syndrome, but this finding was only present in men with high central obesity. Furthermore, CRP levels significantly attenuated the linear relationship between work-related stress and risk of metabolic syndrome, suggesting that stress, and subsequent elevations in CRP, may synergistically contribute to the development of metabolic syndrome (Almadi et al., 2013). By contrast, another study found no evidence that pro-inflammatory markers mediated the relationship between chronic stress and risk of metabolic syndrome, which was attributed to weak associations between chronic stress and individual inflammatory markers (Ortiz et al., 2015).

The lack of a consistent definition of metabolic syndrome may explain the conflicting findings in the literature. For example, Almadi et al. (2013) used criteria issued by the International Diabetes Federation (IDF, 2005), while Ortiz et al. (2015) used criteria proposed by the National Cholesterol Education Program’s Adult Treatment Panel III (ATP-III; Grundy et al., 2004). Popular definitions differ in their conceptualization of the etiological cause of disease, which is reflected in variable diagnostic criteria and cut-offs (Kassi et al., 2011). The IDF and ATP-II criteria are both widely used in research and practice yet show low diagnostic concordance (Saif-Ali et al., 2020) and vary in their prognostic value (Monami et al., 2007; Deepa et al., 2007). To address this limitation, the current study operationalized metabolic syndrome as a latent variable representing a common pathway between all etiological causes. Prior work has shown that four subfactors (insulin resistance, dyslipidemia, central adiposity, and elevated BP) load onto a general latent factor representing currently accepted definitions of metabolic syndrome (Marsland et al., 2010).

The aim of the current study was to examine systemic inflammation as an intermediate pathway linking perceived stress and metabolic syndrome. Conformatory factor analysis (CFA) was used to examine the fit of the latent structure of metabolic syndrome in a subsample of the Midlife in the United States (MIDUS) Refresher cohort. Structural equation modeling (SEM) was then used to test our proposed model. We hypothesized that perceived stress would be associated with elevated inflammation, which in turn would be associated with greater metabolic syndrome factor scores.

2. Materials and methods

2.1. Participants & procedures

The sample was drawn from the Survey of Midlife in the United States (MIDUS) project. MIDUS is a longitudinal, multi-wave study launched by a multidisciplinary research group in 1995. The purpose of MIDUS is to understand bio-psycho-social factors that influence health and well-being in the context of aging. Additional information can be found at http://midus.wisc.edu/index.php.

A subgroup of participants from the MIDUS Refresher Survey who completed the Biomarkers project provided the data (N = 863). Inclusion criteria for the current study required that participants had completed the Perceived Stress Scale (PSS), a blood draw and a physical examination (N = 843). Exclusion criteria included a self-reported diagnosis of type I or type II diabetes (N = 88) or cardiovascular disease (N = 72). Data collection was approved by the Institutional Review Board at MIDUS testing sites (University of California – Los Angeles, University of Wisconsin – Madison, George Town University) and informed consent was obtained from all participants.

2.2. Measures

2.2.1. Perceived-Stress Scale (PSS-10)

Perceived stress was measured using the 10-item version of the PSS (PSS-10; Cohen, 1988). The PSS-10 is a self-report measure that captures global appraisals of stress in the past month (e.g. “In the past month, how often have you felt that you were unable to control the important things in your life?”). Items are rated on a 5-point Likert scale (1 = “Never” to 5 = “Very Often”). Positively stated items were reverse coded to reflect levels of perceived stress and total scores were obtained by summing all 10 items. The PSS-10 has demonstrated strong psychometric properties, including high test-retest reliability (ICC = 0.72-0.88; Lee, 2012) and internal consistency (α = 0.67-0.91; Liu et al., 2020). Additionally, PSS-10 scores have shown good concurrent validity with self-report measures of anxiety and depression (Lee et al., 2012) and moderate convergent validity with stressful life events (Liu et al., 2020).

2.2.2. Inflammatory biomarkers

Consistent with prior work (Hostinar et al., 2015; Knight et al., 2021), systemic inflammation was indexed by five pro-inflammatory markers collected as part of the MIDUS Biomarkers Study: CRP, IL-6, E-selectin, fibrinogen, and intracellular adhesion molecule-1 (ICAM-1). Participants were provided overnight lodging and completed a fasted blood draw on the morning of the following day. Samples were stored in an ice bath until centrifuged for blood serum and plasma. Following extraction, samples were frozen at −70 °C before being shipped on dry ice for assay.

IL-6 is a pro-inflammatory cytokine produced in response to tissue damage and infection. Quantikine high-sensitivity enzyme-linked immunosorbant assay (ELISA) kits were used to measure serum IL-6 concentrations (R&D Systems, Minneapolis, MN). The average inter-assay and intra-assay CVs for IL-6 were 15.7% and 3.7%.

CRP is an acute-phase protein released in response to rising levels of IL-6. CRP was assayed from citrated plasma using the BNII nephelometer (Dade Behring Inc., Deerfield, IL) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Samples that were undetectable via nephelometric assay were re-assayed using the Meso Scale Diagnostics (MSD) high-sensitivity kit. The average inter-assay and intra-assay CVs for CRP were between 1.4-3.4% and 2.3–4.4%, respectively.

E-selectin is a cell adhesion molecule expressed on endothelial cells that facilitates leukocyte migration during inflammation. This biomarker was assessed with a high-sensitivity ELISA kit (Parameter human E-Selectin Immunoassay; R&D Systems, Minneapolis, MN) with average inter-assay and intra-assay values between 7.1-11.2% and 2.2–4.1%.

Fibrinogen is a soluble blood plasma protein that is essential to blood clotting and was measured via immunochemical reaction using a BNII nephelometer (Dade Behring Inc., Deerfield, IL) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). The average inter-assay and intra-assay values for this biomarker were 4.4–6.6% and 2.7%, respectively.

ICAM-1 is a cell surface glycoprotein that mediates cell-to-cell adhesion and leukocyte recruitment during inflammation. ELISA kits were used to measure ICAM-1 concentrations (R&D Systems, Minneapolis, MN). For this molecule, the average inter-assay values were between 7.5 and 8.2% and intra-assay values were between 3.7 and 5.2%.

Inflammatory biomarker data were log-transformed to correct for non-normality. An inflammation composite score was generated to improve power and reduce multiple comparisons. The composite score
was generated by averaging the log-transformed values of CRP, IL-6, ICAM-1, E-selectin, and fibrinogen.

2.2.3. Metabolic health markers

A physical examination was conducted by a clinician or trained staff member. Three measurements of blood pressure were taken and averaged to reflect mean systolic and diastolic blood pressure. Measurements of height and weight were obtained for computation of body mass index (BMI) and waist circumference was measured in centimeters (cm). Blood serum samples were shipped to Meriter Labs (Madison, WI) for lipid assays and ARUP Laboratories (Salt Lake City, UT) for glucose metabolism assays. The Roche Cobas analyzer (Roche Diagnostics, Indianapolis, IN) was used to determine concentrations of high-density lipoprotein (HDL) cholesterol and triglycerides. Blood glucose was assayed using the Cobas c502 analyzer (Roche Diagnostics) and blood insulin was measured using the ADVIA Centaur (Siemens) immunoassay.

2.2.4. Covariates

Several factors are known to influence the biological pathways investigated here. Immune function declines over the course of life (Larbi et al., 2008) and age is positively associated with peripheral inflammation (Frasca and Blomberg, 2016). Additionally, sex differences have been widely observed in both immune function (Marriott and Huet-Hudson, 2006) and experiences of stress (Bangasser and Wiersielis, 2018). Finally, smoking has been found to alter biological mediators of inflammation which can result in immune suppression (Lee et al., 2012). Therefore, analyses were statistically adjusted for self-reported age, sex (0 = male, 1 = female), and smoking status (0 = non-smoker, 1 = smoker).

2.3. Statistical analyses

Statistical analyses were conducted using R version 4.1.1 (R Core Team, 2022). Prior to structural equation modeling, we inspected our data for multivariate outliers using Cook’s distance. Bivariate regression models were generated between perceived stress and the inflammation composite score. A cut-off score of four times greater than the mean data for multivariate outliers using Cook’s distance. IQRs

3. Results

3.1. Demographics and sample characteristics

Table 1 provides demographic characteristics and descriptive statistics of metabolic and inflammatory markers for our final sample (N = 648). Correlation values between observed variables are reported in Table 2. Participants were mid-to-late life adults (M = 52.3; SD = 13.6; range = 25–75), and there was a relatively equal proportion of males and females (48.0% male, 52.0% female). The majority of the sample had attained an advanced level degree, including associate’s (10.2%), bachelor’s (29.6%), and graduate or professional degrees (26.4%). Most of the sample was legally married (61.3%) and employed (68.8%). Additional sociodemographic and health variables can be found in Supplementary Table 1.

3.2. Metabolic syndrome latent model

The CFA showed excellent goodness of fit in our sample [CFI = 0.97, TFI = 0.95, RMSEA = 0.06, SMSR = 0.05]. Fig. 1 provides standardized factor loadings for the model. All observed measures loaded significantly onto their subfactors, with estimates ranging from 0.52 to 0.87. Similarly, the subfactors loaded strongly on the higher-order factor, with the potential exception of the blood pressure subfactor (λ = 0.29). This finding is consistent with previous work indicating that the blood pressure subfactor tends to load least strongly onto the general latent factor of metabolic syndrome (McCaffery et al., 2007; Marsland et al., 2010).

### Table 1

**Demographics and Sample Characteristics.**

<table>
<thead>
<tr>
<th>Age</th>
<th>N or M or Median</th>
<th>% or SD or IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>52.3</td>
<td>%13.6</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>311</td>
</tr>
<tr>
<td>Female</td>
<td>337</td>
<td>52.0%</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>110</td>
<td>17.0%</td>
</tr>
<tr>
<td>Native American or Alaskan Islander</td>
<td>8</td>
<td>1.2%</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>White</td>
<td>470</td>
<td>72.5%</td>
</tr>
<tr>
<td>Other</td>
<td>48</td>
<td>7.4%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Hispanic/Latinx</td>
<td>27</td>
</tr>
<tr>
<td>Inflammation Variables</td>
<td>CRP (ug/mL)</td>
<td>1.2</td>
</tr>
<tr>
<td>E-Selectin (ng/mL)</td>
<td>36.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Fibrinogen (mg/mL)</td>
<td>331.5</td>
<td>81.5</td>
</tr>
<tr>
<td>ICAM-1 (ng/mL)</td>
<td>241.4</td>
<td>100.8</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Metabolic Variables</td>
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</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>97.6</td>
<td>14.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>96.8</td>
<td>17.3</td>
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<tr>
<td>HDL Cholesterol (mg/dL)</td>
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<td>19.6</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>114.3</td>
<td>65.3</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>126.9</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>77.6</td>
<td>10.1</td>
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<tr>
<td>Stress</td>
<td>Perceived Stress Scale Total Score</td>
<td>22.3</td>
</tr>
</tbody>
</table>

Note. N = number. (N = 648). M = mean. % = percent of total sample. SD = standard deviation. IQR = interquartile range. Median and IQR values are reported for inflammation variables due to non-normality. BMI = Body Mass Index.
3.3. Mediation analysis

The path coefficients for the mediation model are presented in Fig. 2. There was a small but significant direct effect of perceived stress on metabolic syndrome, such that higher appraisals of stress were associated with greater metabolic dysregulation (C path $\beta = .13$, $SE = .02$, $z = 2.63, p = .009$, 95% confidence interval CI [0.04, 0.24]). As hypothesized, the indirect effect was significant ($\beta = 0.08$, $SE = .01$, $z = 3.69, p < .001$, 95% CI [0.04, 0.13]), suggesting that higher stress appraisals were associated with elevated inflammatory biomarkers (A path $\beta = .14$, $SE = .01$, $z = 3.96, p < .001$, 95% CI [0.07, 0.19]), which in turn were associated with increased metabolic dysregulation (B path $\beta = .59$, $SE = .07$, $z = 9.33, p < .001$, 95% CI [0.47, 0.72]). In total, the indirect effect explained 61.5% of the total variance in the relationship between perceived stress and metabolic syndrome.

4. Discussion

This study examined inflammation as an intermediate pathway linking perceived stress to metabolic syndrome in a large sample of mid-to-late life adults. Structural equation modeling revealed that the effect of stress on metabolic dysregulation was mediated by an index of systemic inflammation, accounting for 61.5% of the unique variance in the relationship between perceived stress and metabolic syndrome. Specifically, higher levels of perceived stress were associated with elevated concentrations of inflammatory biomarkers, which in turn were associated with greater metabolic dysregulation.

The findings reported here support the hypothesis that psychological stress increases risk for metabolic syndrome by contributing to a state of low-grade, systemic inflammation (Black, 2003). Previous studies investigating these pathways have yielded inconsistent results. By leveraging latent factor analysis, the present study was able to quantify

Table 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Perceived stress</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Inflammation</td>
<td>.12**</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>3. Insulin</td>
<td>–.02</td>
<td>.28***</td>
<td>–</td>
<td></td>
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<tr>
<td>4. Glucose</td>
<td>.03</td>
<td>.27***</td>
<td>.28***</td>
<td>–</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>5. BMI</td>
<td>.15***</td>
<td>.48***</td>
<td>.33***</td>
<td>.26***</td>
<td>–</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>6. Waist</td>
<td>.08*</td>
<td>.47***</td>
<td>.34***</td>
<td>.38***</td>
<td>.76***</td>
<td>–</td>
<td></td>
<td></td>
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<tr>
<td>7. HDL</td>
<td>.15***</td>
<td>.27***</td>
<td>.30***</td>
<td>.23***</td>
<td>.36***</td>
<td>.45***</td>
<td>–</td>
<td></td>
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<tr>
<td>8. Triglycerides</td>
<td>.08*</td>
<td>.24***</td>
<td>.31***</td>
<td>.32***</td>
<td>.17***</td>
<td>.27***</td>
<td>.45***</td>
<td>–</td>
<td></td>
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<tr>
<td>9. Systolic BP</td>
<td>–.05</td>
<td>.24***</td>
<td>.07</td>
<td>.17***</td>
<td>.16***</td>
<td>.24***</td>
<td>.05</td>
<td>.09*</td>
<td>–</td>
<td></td>
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<tr>
<td>10. Diastolic BP</td>
<td>.02</td>
<td>.17***</td>
<td>.03</td>
<td>.16***</td>
<td>.11**</td>
<td>.25***</td>
<td>.08*</td>
<td>.09*</td>
<td>.67***</td>
<td>–</td>
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</table>


Fig. 1. Confirmatory factor analysis model of metabolic syndrome. $\chi^2 = 117.6$, df = 17, N = 648; CFI = 0.97, TLI = 0.96, RMSEA = 0.06, SMSR = 0.05. Note. BMI = Body Mass Index. Waist = waist circumference (cm). BP = Blood Pressure. CFI = Comparative Fit Index. TLI = Tucker-Lewis Index. RMSEA = root mean squared error of approximation. SMSR = standardized root mean square residual.
synergistic relationships between these variables, revealing an indirect effect of inflammation on the association between stress and metabolic syndrome. These results are consistent with previous work suggesting that stress may lead to metabolic disturbances through inflammatory pathways. Blood plasma levels of pro-inflammatory biomarkers have been found to account for 25% of the unique variance in the relationship between psychosocial stress and obesity (Hamer and Stamatakis, 2008) and lifetime stress exposure has been linked to insulin resistance through elevations in systemic inflammation (Fuller-Rowell et al., 2019).

Although the exact mechanisms underlying these relationships have not been identified, substantial overlap exists between inflammatory pathways and those involved in the stress response and metabolism. The hypothalamus-pituitary-adrenal (HPA)-axis regulates the release of cortisol, a glucocorticoid with important anti-inflammatory and immunosuppressive properties. Cortisol levels typically peak 30 minutes after waking and steadily decline throughout the day (Adam and Kumari, 2014). Catecholamines, such as epinephrine and norepinephrine, are the primary byproduct of SNS activation. These neurotransmitters modulate the immune response via adrenergic receptors present on immune cells. Previous work has found associations between markers of sympathetic tone and concentrations of pro-inflammatory cytokines (Bernstein et al., 2009).

Connections between inflammation and metabolism are also evident in the broader literature. Inflammation is associated with alterations in lipid and lipoprotein metabolism that serve to increase triglyceride and decrease HDL cholesterol production (Khovdunkhkit et al., 2004). Various inflammatory mediators have been shown to block insulin signaling pathways, potentially contributing to the development of insulin resistance (Rehman and Akash, 2016). Inflammatory cytokines also indirectly affect blood pressure regulation (De Miguel et al., 2015; Granger, 2006) and experimental studies have demonstrated that increases in inflammatory markers induce a hypertensive response in mice (Lee et al., 2006; Vongpatanasin et al., 2007).

Clinical trials have consistently shown that anti-inflammatory agents improve metabolic health metrics (Esser et al., 2015; Donath et al., 2019). However, these treatments are currently inaccessible and costly. Stress management techniques may serve as a more cost-effective treatment option for metabolic syndrome. Recent studies have found that stress-management interventions lower inflammatory biomarkers among individuals with overweight or obesity (Jarvela-Reijonen et al., 2020; Villalba et al., 2019). As the effect of perceived stress on metabolic syndrome reported here is relatively small, future work is needed to examine whether the effects of stress reduction on inflammation lead to clinically significant improvements in metabolic health.

Results from the current study should be considered in light of several limitations. Importantly, causality cannot be inferred due to the cross-sectional nature of this study. While evidence is mixed, several previous studies suggest that inflammation can predict later symptoms of distress (Das, 2016; Matthews et al., 2010). Moreover, obesity appears to influence inflammation in a bidirectional manner (Dandona et al., 2004) and individuals with obesity produce larger inflammatory responses to stress (Brydon et al., 2008). Investigating relationships between stress, inflammation and metabolic syndrome longitudinally may further elucidate the complex interactions that exist between these pathways. Furthermore, psychosocial stress is likely to influence disease pathogenesis through several mechanisms. For example, stress can negatively impact health behaviors, such as food and tobacco consumption, that are independently associated with increased inflammation and metabolic disturbances (Khan et al., 2020; Kiecolt-Glaser, 2010). Lastly, these analyses included only pro-inflammatory markers. A more comprehensive index of inflammation, including both pro- and anti-inflammatory markers, may broaden our understanding of the inflammatory consequences of stress and their implications for metabolic health.

5. Conclusions

Results from this study clarify relationships between perceived stress, inflammatory pathways and metabolic syndrome in a large sample of middle-aged adults. Our findings suggest that stress can contribute to a state of chronic, low-grade inflammation that leads to metabolic dysregulation. These results underscore the importance of understanding the inflammatory consequences of stress and implications for metabolic health. Stress-reduction techniques may serve as cost-effective interventions for preventing and treating metabolic disease.
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