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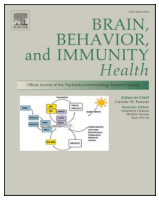

Inflammatory biomarkers link perceived stress with metabolic dysregulation

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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, SMSR = 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 (Kuo 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., 2018) 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

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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 criterion 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. Confirmatory 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 1.1-4.3% 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 (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). 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 Cook's *D* identified 35 cases of multivariate outliers which were removed from these analyses.

CFA was conducted to examine the acceptability of the factor analytic structure of metabolic syndrome in our sample using the Lavaan package (Rosseel, 2012) in R (R Core Team, 2022). This model was derived from prior work demonstrating that measurements of systolic and diastolic blood pressure, BMI, waist circumference, HDL cholesterol, triglycerides, glucose, and insulin load onto four subfactors representing blood pressure, central adiposity, dyslipidemia, and insulin resistance (Marsland et al., 2010). These four subfactors load onto a higher-order factor consistent with clinical definitions of metabolic syndrome. Observed metabolic variables were standardized (mean = 0, SD = 1) over the entire sample to improve model estimation. HDL scores were converted to negative values, for similar interpretation to other measures in the model. The parameters of the CFA were calculated using robust maximum likelihood estimation. Goodness of fit was assessed using the following criteria (Hu and Bentler, 1999): Comparative Fit Index (CFI; > 0.90); Tucker Lewis Index (TLI; > 0.90); Root Mean Square Error of Approximation (RMSEA; < 0.08); Standardized Root Mean Square Residual (SRMR; < 0.06). Chi-squared values were not considered as they can be skewed by large sample sizes.

The latent factor structure representing metabolic syndrome was then included in a structural equation model to test for an indirect effect of inflammation through perceived stress. Inflammation composite scores, total PSS-10 scores and covariates were standardized prior to analysis so that all variables were represented on the same scale. The sem package in R (Fox, 2006) was then used to test for mediation using 5000 bootstrapped samples. The mediation analysis was statistically adjusted for age, sex, and smoking status. Structural equation modeling was used in this context to allow for the inclusion of the metabolic syndrome latent variable.

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 ($\lambda = 0.29$). 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.

	N or M or Median	% or SD or IQR
Age	52.3	13.6
Sex		
Male	311	48.0%
Female	337	52.0%
Race		
Asian	11	1.7%
Black	110	17.0%
Native American or Alaskan Islander	8	1.2%
Native Hawaiian or Pacific Islander	1	0.2%
White	470	72.5%
Other	48	7.4%
Ethnicity		
Hispanic/Latinx	27	4.2%
Inflammation Variables		
CRP (ug/mL)	1.2	2.5
E-Selectin (ng/mL)	36.3	19.2
Fibrinogen (mg/nL)	331.5	81.5
ICAM-1 (ng/mL)	241.4	100.8
IL-6 (pg/mL)	1.9	2.1
Metabolic Variables		
Insulin (uIU/mL)	15.9	16.3
Glucose (mg/dL)	97.6	14.5
BMI (kg/m^2)	29.7	6.9
Waist Circumference (cm)	96.8	17.3
HDL Cholesterol (mg/dL)	59.6	19.6
Triglycerides (mg/dL)	114.3	65.3
Systolic Blood Pressure (mmHg)	126.9	16.9
Diastolic Blood Pressure (mmHg)	77.6	10.1
Stress		
Perceived Stress Scale Total Score	22.3	6.1

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.

Table 2
Correlation Matrix of Observed Variables.

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

Note. N = number (N = 648). Perceived Stress = PSS-10 total score. Inflammation = inflammation composite score (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). BMI = Body Mass Index. Waist = waist circumference (cm). BP = Blood Pressure. *$p < .05$, **$p < .01$, ***$p < .001$.

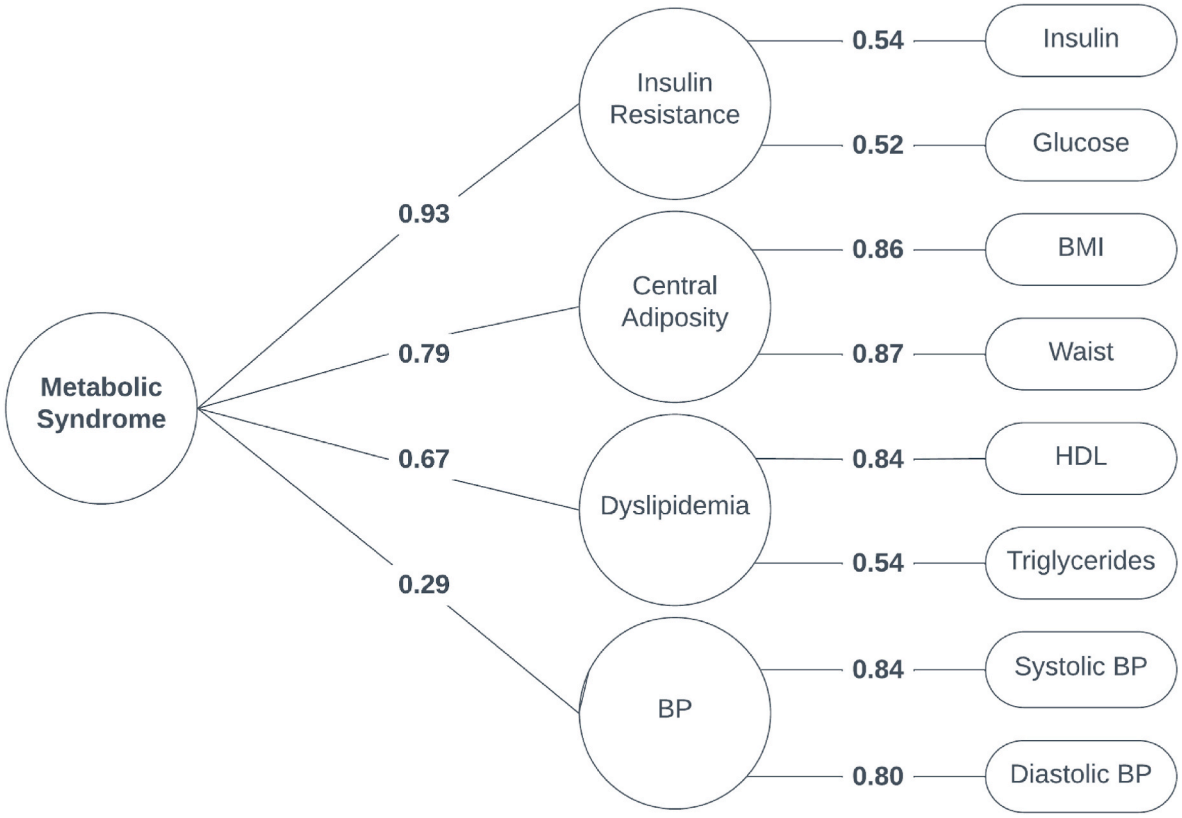

Fig. 1. Confirmatory factor analysis model of metabolic syndrome. $\chi^2 = 117.6$, $df = 17$, N = 648; CFI = 0.97, TLI = 0.96, RMSEA = 0.06, SMSR = 0.05.
Note. BMI = Body Mass Index. Waist = waist circumference (cm). BP = Blood Pressure. CFI = Comparative Fit Index. TLI = Tucker-Lewis Index. RMSEA = root mean squared error of approximation. SMSR = standardized root mean square residual.

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 ß = .13, SE = 0.02, z = 2.63, p = .009, 95% confidence interval CI [0.04, 0.24]). As hypothesized, the indirect effect was significant(ß = 0.08, SE = 0.01, z = 3.69, $p < .001$, 95% CI [0.04, 0.13]), suggesting that higher stress appraisals were associated with elevated inflammatory biomarkers (A path ß = .14, SE = 0.01, z = 3.96, $p < .001$, 95% CI [0.07, 0.19]), which in turn were associated with increased metabolic dysregulation (B path ß = .59, SE = 0.07, 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

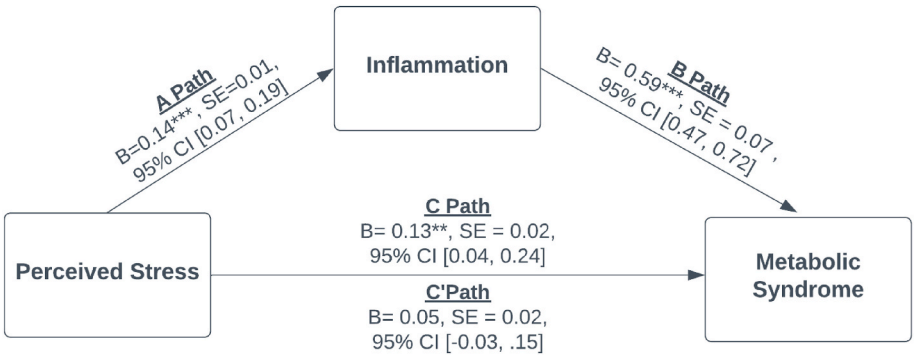

Fig. 2. Pathways of a mediation process of perceived stress, inflammation, and metabolic syndrome with age, sex and smoking status covaried.
Note. Perceived Stress = PSS-10 total score. Inflammation = inflammation composite score (IL-6, CRP, E-selectin, fibrinogen, ICAM-1). Metabolic Syndrome = latent factor scores for metabolic syndrome. $*p < .05$, $**p < .01$, $***p < .001$.

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, 2009). However, prolonged exposure to stress can result in a blunted pattern of cortisol secretion through chronic activation of the HPA-axis (Gallagher-Thompson et al., 2006; Lovell et al., 2011; Young et al., 2019). Stress-related disruptions in cortisol release are thought to reduce glucocorticoid sensitivity on immune cells, subsequently leading to increased pro-inflammatory activity (Liu et al., 2017). Indeed, recent work has demonstrated that HPA-axis dysregulation, as evidenced by blunted diurnal cortisol slopes, is an indirect pathway by which perceived stress leads to heightened systemic inflammation (Knight et al., 2021). It is important to note that Knight et al. (2021) did not report a significant effect of perceived stress on inflammation, despite using a similar approach and dataset to the current study. This discordance may be explained by different focuses of research as well as several methodological differences between studies, including the use of different cohorts from the MIDUS sample, exclusion criteria, and covariates.

The sympathetic nervous system (SNS) represents an additional immunoregulatory system that is sensitive to the stress response (Padro and Sanders, 2014; Bucsek et al., 2018). 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 (Khovidhunkit 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 (Järvelä-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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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is publicly available, link to public data set included in manuscript.

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Data used in conducting this research were provided by the "Midlife in the United States," (MIDUS) study (https://www.midus.wisc.edu/index.php). As such, investigators within the MIDUS study contributed to the design and implementation of MIDUS and/or provided data but did not participate in the analysis or writing of this report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100696.

References

Adam, E.K., Kumari, M., 2009. Assessing salivary cortisol in large-scale, epidemiological research. Psychoneuroendocrinology 34 (10), 1423–1436. https://doi.org/10.1016/j.psyneuen.2009.06.011.

Alberti, K.G., Zimmet, P., Shaw, J., IDF Epidemiology Task Force Consensus Group, 2005. The metabolic syndrome–a new worldwide definition. Lancet (London, England) 366 (9491), 1059–1062. https://doi.org/10.1016/S0140-6736(05)67402-8.

Almadi, T., Cathers, I., Chow, C.M., 2013. Associations among work-related stress, cortisol, inflammation, and metabolic syndrome. Psychophysiology 50 (9), 821–830. https://doi.org/10.1111/psyp.12069.

Alzheimer's-Association, 2020. Alzheimer's disease facts and figures. (2020). Alzheimer's Dementia J. Alzheimer's Assoc. https://doi.org/10.1002/alz.12068, 10.1002/alz.12068. Advance online publication.

American Diabetes Association, 2018. Economic costs of diabetes in the U.S. In 2017. Diabetes Care 41 (5), 917–928. https://doi.org/10.2337/dci18-0007.

Bangasser, D.A., Wiersielis, K.R., 2018. Sex differences in stress responses: a critical role for corticotropin-releasing factor. Hormones (Basel) 17 (1), 5–13. https://doi.org/10.1007/s42000-018-0002-z.

Benjamin, E.J., Virani, S.S., Callaway, C.W., Chamberlain, A.M., Chang, A.R., Cheng, S., Chiuve, S.E., Cushman, M., Delling, F.N., Deo, R., de Ferranti, S.D., Ferguson, J.F., Fornage, M., Gillespie, C., Isasi, C.R., Jiménez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., et al., 2018. Heart disease and stroke statistics-2018 update: a report from the American heart association. Circulation 137 (12), e67–e492. https://doi.org/10.1161/CIR.0000000000000558.

Bergmann, N., Gyntelberg, F., Faber, J., 2014. The appraisal of chronic stress and the development of the metabolic syndrome: a systematic review of prospective cohort studies. Endocrine Connect. 3 (2), R55–R80. https://doi.org/10.1530/EC-14-0031.

Bernstein, I.M., Damron, D., Schonberg, A.L., Sallam, R.M., Shapiro, R., 2009. The relationship of plasma volume, sympathetic tone, and proinflammatory cytokines in young healthy nonpregnant women. Reprod. Sci. 16 (10), 980–985. https://doi.org/10.1177/1933719109338876.

Black, P.H., 2003. The inflammatory response is an integral part of the stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav. Immun. 17 (5), 350–364. https://doi.org/10.1016/s0889-1591(03)00048-5.

Brunner, E.J., Hemingway, H., Walker, B.R., Page, M., Clarke, P., Juneja, M., Shipley, M. J., Kumari, M., Andrew, R., Seckl, J.R., Papadopoulos, A., Checkley, S., Rumley, A., Lowe, G.D., Stansfeld, S.A., Marmot, M.G., 2002. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. Circulation 106 (21), 2659–2665. https://doi.org/10.1161/01.cir.0000038364.26310.bd.

Brydon, L., Wright, C.E., O'Donnell, K., Zachary, I., Wardle, J., Steptoe, A., 2008. Stress-induced cytokine responses and central adiposity in young women. Int. J. Obes. 32 (3), 443–450. https://doi.org/10.1038/sj.ijo.0803767, 2005.

Bucsek, M.J., Giridharan, T., MacDonald, C.R., Hylander, B.L., Repasky, E.A., 2018. An overview of the role of sympathetic regulation of immune responses in infectious disease and autoimmunity. Int. J. Hyperther.: Offic. J. Europ. Soci. Hyperthermic Oncol., North Am. Hyperthermia Group 34 (2), 135–143. https://doi.org/10.1080/02656736.2017.1411621.

Cardel, M.I., Min, Y.I., Sims, M., Musani, S.K., Dulin-Keita, A., DeBoer, M.D., Gurka, M.J., 2018. Association of psychosocial stressors with metabolic syndrome severity among African Americans in the Jackson Heart Study. Psychoneuroendocrinology 90, 141–147. https://doi.org/10.1016/j.psyneuen.2018.02.014.

Cohen, S., 1988. Perceived stress in a probability sample of the United States. In: Spacapan, S., Oskamp, S. (Eds.), The Social Psychology of Health. Sage Publications, Inc, pp. 31–67.

Cohen, S., Gianaros, P.J., Manuck, S.B., 2016. A stage model of stress and disease. Perspect. Psychol. Sci. : J. Assoc. Psychol. Sci. 11 (4), 456–463. https://doi.org/10.1177/1745691616646305.

Dandona, P., Aljada, A., Bandyopadhyay, A., 2004. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 25 (1), 4–7. https://doi.org/10.1016/j.it.2003.10.013.

Das, A., 2016. Psychosocial distress and inflammation: which way does causality flow? Soc. Sci. Med. 170, 1–8. https://doi.org/10.1016/j.socscimed.2016.10.001, 1982.

Deepa, M., Farooq, S., Datta, M., Deepa, R., Mohan, V., 2007. Prevalence of metabolic syndrome using WHO, ATPIII and IDF definitions in asian Indians: the Chennai urban rural epidemiology study (CURES-34). Diabetes Metabol. Res. Rev. 23 (2), 127–134. https://doi.org/10.1002/dmrr.658.

De Miguel, C., Rudemiller, N.P., Abais, J.M., Mattson, D.L., 2015. Inflammation and hypertension: new understandings and potential therapeutic targets. Curr. Hypertens. Rep. 17 (1), 507. https://doi.org/10.1007/s11906-014-0507-z.

Donath, M.Y., Meier, D.T., Böni-Schnetzler, M., 2019. Inflammation in the pathophysiology and therapy of cardiometabolic disease. Endocr. Rev. 40 (4), 1080–1091. https://doi.org/10.1210/er.2019-00002.

Esser, N., Paquot, N., Scheen, A.J., 2015. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expet Opin. Invest. Drugs 24 (3), 283–307. https://doi.org/10.1517/13543784.2015.974804.

Ford, E.S., Li, C., Sattar, N., 2008. Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care 31 (9), 1898–1904. https://doi.org/10.2337/dc08-0423.

Fox, J., 2006. Structural equation modeling with the sem package in R. Struct. Equ. Model. 13 (3), 465–486. https://doi.org/10.1207/s15328007sem1303_7.

Frasca, D., Blomberg, B.B., 2016. Inflammaging decreases adaptive and innate immune responses in mice and humans. Biogerontology 17 (1), 7–19. https://doi.org/10.1007/s10522-015-9578-8.

Fuller-Rowell, T.E., Homandberg, L.K., Curtis, D.S., Tsenkova, V.K., Williams, D.R., Ryff, C.D., 2019. Disparities in insulin resistance between black and white adults in the United States: the role of lifespan stress exposure. Psychoneuroendocrinology 107, 1–8. https://doi.org/10.1016/j.psyneuen.2019.04.020.

Gallagher-Thompson, D., Shurgot, G.R., Rider, K., Gray, H.L., McKibbin, C.L., Kraemer, H.C., Sephton, S.E., Thompson, L.W., 2006. Ethnicity, stress, and cortisol function in Hispanic and non-Hispanic white women: a preliminary study of family dementia caregivers and noncaregivers. Am. J. Geriatr. Psychiatr. : Offic. J. Am. Assoc. Geriatric Psychi. 14 (4), 334–342. https://doi.org/10.1097/01.JGP.0000206485.73618.87.

Granger, J.P., 2006. An emerging role for inflammatory cytokines in hypertension. Am. J. Physiol. Heart Circ. Physiol. 290 (3), H923–H924. https://doi.org/10.1152/ajpheart.01278.2005.

Grundy, S.M., Brewer Jr., H.B., Cleeman, J.I., Smith Jr., S.C., Lenfant, C., American Heart Association, National Heart, Lung, and Blood Institute, 2004. Definition of metabolic syndrome: report of the national heart, lung, and blood Institute/American heart association conference on scientific issues related to definition. Circulation 109 (3), 433–438. https://doi.org/10.1161/01.CIR.0000111245.75752.C6.

Grundy, S.M., 2006. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J. Am. Coll. Cardiol. 47 (6), 1093–1100. https://doi.org/10.1016/j.jacc.2005.11.046.

Hamer, M., Stamatakis, E., 2008. Inflammation as an intermediate pathway in the association between psychosocial stress and obesity. Physiol. Behav. 94 (4), 536–539. https://doi.org/10.1016/j.physbeh.2008.03.010.

Hostinar, C.E., Lachman, M.E., Mroczek, D.K., Seeman, T.E., Miller, G.E., 2015. Additive contributions of childhood adversity and recent stressors to inflammation at midlife: findings from the MIDUS study. Dev. Psychol. 51 (11), 1630–1644. https://doi.org/10.1037/dev0000049.

Hu, L.-t., Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct. Equ. Model. 6 (1), 1–55. https://doi.org/10.1080/10705519909540118.

International Diabetes Federation (IDF), 2005. The International Diabetes Federation consensus worldwide definition of the metabolic syndrome. Retrieved from. http://www.idf.org/metabolic-syndrome.

Järvelä-Reijonen, E., Puttonen, S., Karhunen, L., Sairanen, E., Laitinen, J., Kolehmainen, M., Pihlajamäki, J., Kujala, U.M., Korpela, R., Ermes, M., Lappalainen, R., Kolehmainen, M., 2020. The effects of acceptance and commitment therapy (ACT) intervention on inflammation and stress biomarkers: a randomized controlled trial. Int. J. Behav. Med. 27 (5), 539–555. https://doi.org/10.1007/s12529-020-09891-8.

Johnson, T.V., Abbasi, A., Master, V.A., 2013. Systematic review of the evidence of a relationship between chronic psychosocial stress and C-reactive protein. Mol. Diagn. Ther. 17 (3), 147–164. https://doi.org/10.1007/s40291-013-0026-7.

Kassi, E., Pervanidou, P., Kaltsas, G., Chrousos, G., 2011. Metabolic syndrome: definitions and controversies. BMC Med. 9, 48. https://doi.org/10.1186/1741-7015-9-48.

Khan, N.A., Lawyer, G., McDonough, S., Wang, Q., Kassem, N.O., Kas-Petrus, F., Ye, D., Singh, K.P., Kassem, N.O., Rahman, I., 2020. Systemic biomarkers of inflammation, oxidative stress and tissue injury and repair among waterpipe, cigarette and dual tobacco smokers. Tobac. Control 29 (Suppl. 2), s102–s109. https://doi.org/10.1136/tobaccocontrol-2019-054958.

Khovidhunkit, W., Kim, M.S., Memon, R.A., Shigenaga, J.K., Moser, A.H., Feingold, K.R., Grunfeld, C., 2004. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J. Lipid Res. 45 (7), 1169–1196. https://doi.org/10.1194/jlr.R300019-JLR200.

Kiecolt-Glaser, J.K., 2010. Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. Psychosom. Med. 72 (4), 365–369. https://doi.org/10.1097/PSY.0b013e3181dbf489.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B., Glaser, R., 2003. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc. Natl. Acad. Sci. U.S.A. 100 (15), 9090–9095. https://doi.org/10.1073/pnas.1531903100.

Kim, Y.J., Kim, S.M., Jeong, D.H., Lee, S.K., Ahn, M.E., Ryu, O.H., 2021. Associations between metabolic syndrome and type of dementia: analysis based on the National Health Insurance Service database of Gangwon province in South Korea. Diabetol. Metab. Syndrome 13 (1), 4. https://doi.org/10.1186/s13098-020-00620-5.

Knight, E.L., Jiang, Y., Rodriguez-Stanley, J., Almeida, D.M., Engeland, C.G., Zilioli, S., 2021. Perceived stress is linked to heightened biomarkers of inflammation via diurnal cortisol in a national sample of adults. Brain Behav. Immun. 93, 206–213. https://doi.org/10.1016/j.bbi.2021.01.015.

Kuo, W.C., Bratzke, L.C., Oakley, L.D., Kuo, F., Wang, H., Brown, R.L., 2019. The association between psychological stress and metabolic syndrome: a systematic review and meta-analysis. Obes. Rev. : Offic. J. Int. Assoc. Study of Obesity 20 (11), 1651–1664. https://doi.org/10.1111/obr.12915.

Larbi, A., Franceschi, C., Mazzatti, D., Solana, R., Wikby, A., Pawelec, G., 2008. Aging of the immune system as a prognostic factor for human longevity. Physiology (Bethesda, Md 23, 64–74. https://doi.org/10.1152/physiol.00040.2007.

Lee, D.L., Sturgis, L.C., Labazi, H., Osborne Jr., J.B., Fleming, C., Pollock, J.S., Manhiani, M., Imig, J.D., Brands, M.W., 2006. Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. Am. J. Physiol. Heart Circ. Physiol. 290 (3), H935–H940. https://doi.org/10.1152/ajpheart.00708.2005.

Lee, E.H., 2012. Review of the psychometric evidence of the perceived stress scale. Asian Nurs. Res. 6 (4), 121–127. https://doi.org/10.1016/j.anr.2012.08.004.

Lee, J., Taneja, V., Vassallo, R., 2012. Cigarette smoking and inflammation: cellular and molecular mechanisms. J. Dent. Res. 91 (2), 142–149. https://doi.org/10.1177/0022034511421200.

Liu, X., Zhao, Y., Li, J., Dai, J., Wang, X., Wang, S., 2020. Factor structure of the 10-item perceived stress scale and measurement invariance across genders among Chinese adolescents. Front. Psychol. 11, 537. https://doi.org/10.3389/fpsyg.2020.00537.

Liu, Y.Z., Wang, Y.X., Jiang, C.L., 2017. Inflammation: the common pathway of stress-related diseases. Front. Hum. Neurosci. 11, 316. https://doi.org/10.3389/fnhum.2017.00316.

Lovell, B., Moss, M., Wetherell, M.A., 2011. Perceived stress, common health complaints and diurnal patterns of cortisol secretion in young, otherwise healthy individuals. Horm. Behav. 60 (3), 301–305. https://doi.org/10.1016/j.yhbeh.2011.06.007.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S.Y., Alvarado, M., Anderson, H.R., Anderson, L.M., Andrews, K.G., Atkinson, C., Baddour, L.M., Barker-Collo, S., Bartels, D.H., Bell, M. L., Benjamin, E.J., et al., 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet (London, England) 380 (9859), 2095–2128. https://doi.org/10.1016/S0140-6736(12)61728-0.

Marriott, I., Huet-Hudson, Y.M., 2006. Sexual dimorphism in innate immune responses to infectious organisms. Immunol. Res. 34 (3), 177–192. https://doi.org/10.1385/IR:34:3:177.

Marsland, A.L., McCaffery, J.M., Muldoon, M.F., Manuck, S.B., 2010. Systemic inflammation and the metabolic syndrome among middle-aged community volunteers. Metab., Clin. Exp. 59 (12), 1801–1808. https://doi.org/10.1016/j.metabol.2010.05.015.

Matthews, K.A., Schott, L.L., Bromberger, J.T., Cyranowski, J.M., Everson-Rose, S.A., Sowers, M., 2010. Are there bi-directional associations between depressive symptoms and C-reactive protein in mid-life women? Brain Behav. Immun. 24 (1), 96–101. https://doi.org/10.1016/j.bbi.2009.08.005.

McCaffery, J.M., Shen, B.J., Muldoon, M.F., Manuck, S.B., 2007. Ambulatory blood pressure and the metabolic syndrome in normotensive and untreated hypertensive men. Metab. Syndr. Relat. Disord. 5 (1), 34–44. https://doi.org/10.1089/met.2006.0014.

McDade, T.W., Hawkley, L.C., Cacioppo, J.T., 2006. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago health, aging, and social relations study. Psychosom. Med. 68 (3), 376–381. https://doi.org/10.1097/01.psy.0000221371.43607.64.

Monami, M., Marchionni, N., Masotti, G., Mannucci, E., 2007. IDF and ATP-III definitions of metabolic syndrome in the prediction of all-cause mortality in type 2 diabetic patients. Diabetes Obes. Metabol. 9 (3), 350–353. https://doi.org/10.1111/j.1463-1326.2006.00615.x.

Moore, J.X., Chaudhary, N., Akinyemiju, T., 2017. Metabolic syndrome prevalence by race/ethnicity and sex in the United States, national health and nutrition examination Survey, 1988-2012. Prev. Chronic Dis. 14, E24. https://doi.org/10.5888/pcd14.160287.

Mottillo, S., Filion, K.B., Genest, J., Joseph, L., Pilote, L., Poirier, P., Rinfret, S., Schiffrin, E.L., Eisenberg, M.J., 2010. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J. Am. Coll. Cardiol. 56 (14), 1113–1132. https://doi.org/10.1016/j.jacc.2010.05.034.

Nesse, R.M., Bhatnagar, S., Ellis, B., 2016. Evolutionary origins and functions of the stress response system. Handbook of Stress Series 1, 95–101.

Ortiz, M.S., Myers, H.F., Dunkel Schetter, C., Rodriguez, C.J., Seeman, T.E., 2015. Psychosocial predictors of metabolic syndrome among latino groups in the multi-ethnic study of atherosclerosis (MESA). PLoS One 10 (4), e0124517. https://doi.org/10.1371/journal.pone.0124517.

Padro, C.J., Sanders, V.M., 2014. Neuroendocrine regulation of inflammation. Semin. Immunol. 26 (5), 357–368. https://doi.org/10.1016/j.smim.2014.01.003.

R Core Team, 2022. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL. https://www.R-project.org/.

Rana, J.S., Nieuwdorp, M., Jukema, J.W., Kastelein, J.J., 2007. Cardiovascular metabolic syndrome - an interplay of, obesity, inflammation, diabetes and coronary heart disease. Diabetes Obes. Metabol. 9 (3), 218–232. https://doi.org/10.1111/j.1463-1326.2006.00594.x.

Rehman, K., Akash, M.S., 2016. Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J. Biomed. Sci. 23 (1), 87. https://doi.org/10.1186/s12929-016-0303-y.

Ridker, P.M., Buring, J.E., Cook, N.R., Rifai, N., 2003. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 107 (3), 391–397. https://doi.org/10.1161/01.cir.0000055014.62083.05.

Rosseel, Y., 2012. Lavaan: an R package for structural equation modeling. J. Stat. Software 48 (2), 1–36. URL. https://www.jstatsoft.org/v48/i02/.

Saif-Ali, R., Kamaruddin, N.A., Al-Habori, M., Al-Dubai, S.A., Ngah, W.Z.W., 2020. Relationship of metabolic syndrome defined by IDF or revised NCEP ATP III with glycemic control among Malaysians with Type 2 Diabetes. Diabetol. Metab. Syndrome 12, 67. https://doi.org/10.1186/s13098-020-00575-7.

Sattar, N., Gaw, A., Scherbakova, O., Ford, I., O'Reilly, D.S., Haffner, S.M., Isles, C., Macfarlane, P.W., Packard, C.J., Cobbe, S.M., Shepherd, J., 2003. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 108 (4), 414–419. https://doi.org/10.1161/01.CIR.0000080897.52664.94.

Schneiderman, N., Ironson, G., Siegel, S.D., 2005. Stress and health: psychological, behavioral, and biological determinants. Annu. Rev. Clin. Psychol. 1, 607–628. https://doi.org/10.1146/annurev.clinpsy.1.102803.144141.

Villalba, D.K., Lindsay, E.K., Marsland, A.L., Greco, C.M., Young, S., Brown, K.W., Smyth, J.M., Walsh, C.P., Gray, K., Chin, B., Creswell, J.D., 2019. Mindfulness training and systemic low-grade inflammation in stressed community adults: evidence from two randomized controlled trials. PLoS One 14 (7), e0219120. https://doi.org/10.1371/journal.pone.0219120.

Vongpatanasin, W., Thomas, G.D., Schwartz, R., Cassis, L.A., Osborne-Lawrence, S., Hahner, L., Gibson, L.L., Black, S., Samols, D., Shaul, P.W., 2007. C-reactive protein causes downregulation of vascular angiotensin subtype 2 receptors and systolic hypertension in mice. Circulation 115 (8), 1020–1028. https://doi.org/10.1161/CIRCULATIONAHA.106.664854.

Wannamethee, S.G., Lowe, G.D., Shaper, A.G., Rumley, A., Lennon, L., Whincup, P.H., 2005. The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. Atherosclerosis 181 (1), 101–108. https://doi.org/10.1016/j.atherosclerosis.2004.12.031.

Yaffe, K., Kanaya, A., Lindquist, K., Simonsick, E.M., Harris, T., Shorr, R.I., Tylavsky, F. A., Newman, A.B., 2004. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292 (18), 2237–2242. https://doi.org/10.1001/jama.292.18.2237.

Yalcin, G., Yalcin, A., 2018. Metabolic syndrome and neurodegenerative diseases. J. Geriatric Med. Gerontol. 4 (2), 1–3. https://doi.org/10.23937/2469-5858/1510042.

Young, E.S., Farrell, A.K., Carlson, E.A., Englund, M.M., Miller, G.E., Gunnar, M.R., Roisman, G.I., Simpson, J.A., 2019. The dual impact of early and concurrent life stress on adults' diurnal cortisol patterns: a prospective study. Psychol. Sci. 30 (5), 739–747. https://doi.org/10.1177/2F0956797619833664.