Metabolic Cost of Stress:

Examining the Role of Perceived Health and Sleep Behaviors

By

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ABSTRACT

About 30% of adults have metabolic syndrome worldwide. Uncontrolled metabolic syndrome is a major contributor to cardiovascular diseases and gastrointestinal cancers, the two leading causes of death in the United States. Psychological stress has been linked to metabolic syndrome for decades. However, in previous studies, researchers often examined stress using single-sources instruments (e.g., occupational stress) or the general perceived-stress scale. It remains unanswered whether other sources of stress (e.g., financial stress) yield a similar influence on metabolic outcomes or not. Furthermore, although the stress-metabolism relationship is often explained by allostatic load, the role of perceived health and sleep behaviors in the stress-metabolism relationship is not clearly understood. To fill above gaps in the literature, we conducted a systematic review with meta-analysis and secondary data analyses using the data from the Retirement and Sleep Trajectories (REST) study, an ancillary study of the Wisconsin Sleep Cohort (WSC) Study.

The aim of the meta-analysis is to examine whether the stress-metabolism relationship differs by sources of stress. We found that occupational stress showed the strongest effect (OR=1.692; p=0.004), while perceived general stress showed the weakest effect (OR=1.217; p=0.032). Unfortunately, the effects of financial stress and interpersonal stress on the risk of metabolic syndrome could not be analyzed using meta-analysis, due to the lack of studies.

The aim of the secondary data analyses is to examine the role of perceived health and sleep behaviors in the stress-metabolism relationship. In this cohort, perceived physical health fully mediated the relationship between financial stress and the prevalence of metabolic syndrome, but perceived mental health was not a significant mediator. Sleep curtailment and insomnia both moderated the relationship between financial stress and the prevalence of metabolic syndrome.

This dissertation contributes to nursing science by highlighting the importance of assessing financial stress, perceived physical health, and sleep behaviors in clinical settings to address the risk of metabolic syndrome.

To my Mom and Dad.

Thanks for always being there for me no matter how far I go.

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Chapter 1

Introduction

When working on the community-based and telehealth interventions to promote health behaviors (e.g., physical activity, low-carbohydrate diet, or low-sodium diet) and prevent metabolic abnormalities (e.g., hypertension, diabetes, and metabolic syndrome) in adults, I found that the experience of different sources of stress often prevented participants/patients from attending exercise classes, following the dietary recommendation, or maintaining the established health behaviors. Therefore, this dissertation aims to provide a further understanding in the relationship between psychological stress and metabolic syndrome, as well as the potential pathways that go into this relationship.

Background

Significance of the Problems

The economic burden of metabolic syndrome is substantial: on average, the annual medical costs for adults meeting at least 3 criteria for metabolic syndrome is 60% higher than adults without metabolic syndrome ($5732 versus $3581) (Nichols & Moler, 2011). Currently, the prevention strategy in clinics and worksites focuses on one-one-one CVD risk assessment and lifestyle recommendation. Although psychological stress has been identified as a risk factor for metabolic syndrome for decades, current prevention strategies for metabolic syndrome in the clinics or worksites rarely address psychological stress (Grundy, 2008; Whelton et al., 2018). Meanwhile, stress management is not specified in the clinical guidelines for the prevention of Type 2 Diabetes Mellitus (T2DM), cardiovascular diseases (CVD), and metabolic syndrome, due to the lack of high-quality evidence (American Diabetes Association, 2018; Whelton et al., 2017). Recently, American Heart Association categorized psychological stress into “relatively fixed factor category,” meaning that if stress changed through the use of current intervention techniques, the reduction in stress may still not reduce CVD risk (Whelton et al., 2017). Taken together, although psychological stress might be a risk factor for metabolic syndrome, current practice does not incorporate stress into the preventive strategies for metabolic syndrome.

Metabolic Syndrome

One third of Americans are affected by metabolic syndrome, which is a multifaceted continuum of metabolic dysregulation, including hyperglycemia, hypertension, visceral adiposity, and atherogenic dyslipidemia (Aguilar et al., 2015; Kaur, 2014; Moore, Chaudhary, & Akinyemiju, 2017). Typically, a healthy metabolic state results in controlled metabolic regulation, *i.e.,* normal insulin signaling in adipose tissue, with an anti-lipolytic effect that inhibits free fatty acid efflux out of adipose tissue (Jia, Jia, & Sowers, 2016). However, when circulating levels of free fatty acids and blood glucose chronically remain at a higher level, the metabolic dysregulation occurs due to the excessive oxidative stress and increased intracellular lipid products (*e.g.,* fatty acyl-CoA and ceramide). As the result, the skeletal muscles become insulin resistant. Without proper insulin function, the excessive free fatty acid and dysfunctional adipose tissues secrete cytokines and other pro-inflammatory molecules, which induce abnormal lipogenesis, hepatic steatosis, and the development of metabolic syndrome and cardiovascular diseases (CVD) (Jia, Jia, & Sowers, 2016; Smith & Kahn, 2016; Taskinen, 2003).

Current primary prevention for metabolic syndrome focuses on early screening, including population screening for hyperlipidemia (adults >20 years) and prediabetes (adults >45 years), targeted screening of patients with history of CVD and their relatives, or opportunistic screening when patients actively ask for tests. Cascade screening is another form of targeted screening, which screens patients with familial hyperlipidemia (Bender et al., 2012). The guideline specifies that clinicians could discuss personalized care plan with patients based on the screening results and risk score based on atherosclerotic cardiovascular disease (ASCVD) risk calculator (American Diabetes Association, 2018; American Heart Association, 2018). The personalized care plan includes physical activity, dietary modification, smoking cessation, and adjusting statin or metformin dose accordingly (Bassi et al., 2014; Grundy et al., 2005; Kones, 2011; Koren, Dumin, & Gozal, 2016). Unfortunately, current guideline does not incorporate stress management

into the personalized care plan for preventing or managing metabolic syndrome (Grundy et al., 2018).

Psychological Stress

Stressors could result in physical or psychological stress. *Physical stress* refers to the stressors (e.g., extreme temperature, sharp light, noise, pollution, damage to the skin, or diseases) that work directly to the body and result in disfavored sensation, such as discomfort, fatigue, hunger, or bodily pain (Kogler et al., 2015). On the other hand, *psychological stress* (or perceived stress) refers to the subjective feeling of pressure when an individual perceives threats or challenges from the environmental stimuli (Jones, Bright, & Clow, 2001; Kogler et al., 2015). Physiological stress might result in psychological stress and metabolic syndrome, and thus involve spurious relationship when examining the relationship between psychological stress and metabolic syndrome. Therefore, throughout this dissertation, we adopted two strategies to narrow down the scope of this study and prevent this spurious relationship. First, comorbidity (as the proxy measure of physiological stress) was controlled as a covariate during analysis. Second, for the scope of this dissertation, the exposure variables focus on psychological stress only, *i.e.*, the subjective feeling of pressure based on an individual's cognitive appraisal.

Psychological stress is context-oriented and multi-featured because it comes from different sources embedded in the hierarchy of social contexts (*e.g.,* macro, meso, micro, or individual levels) that people encounter on a daily basis. Stress experience is shaped by contextual factors, including internal/external resources, socioeconomic status, schemas, and coping mechanisms (Avison, Aneshensel, Schieman, & Wheaton, 2009). Stress also involves different features, such as humiliation, entrapment, loss, or danger; researchers have speculated that some features of stressful conditions are associated with greater emotional dysregulation (e.g., negative emotional responses and rumination) and thus induce greater physiological arousal, such as higher catabolic and lower anabolic profiles (Epel, 2009; Epel et al., 2006). Males and females also perceive stressors differently. For instance, according to the recent Stress in

America Survey, females are more likely to report the finance and economy are their primary sources of stress, while males are more likely to report occupation is their major source of stress (American Psychological Association, 2010).

Allostasis, also called *stress arousal,* was first used by Sterling *et al.* to describe the natural physiological process where brains activate neuroendocrine systems, including Sympathetic-Adrenal-Medullary (SAM) and Hypothalamic-Pituitary-Adrenal (HPA) axes to combat against stressful environmental demands (Sterling, 2004). When an individual perceives a level of psychological stress that cannot be managed by regular hemostasis, the brain activates SAM and HPA axes and stimulates adrenal glands to release stress hormones (*e.g*., corticosteroids) and catecholamines (*e.g.,* epinephrine and norepinephrine). Unfortunately, although the regulation of SAM and HPA axes help adults' to combat against stressors, long-term exposure to chronic stress and the accumulation of wear and tear have been linked to poor health outcomes, including metabolic syndrome.

Allostatic load refers to the repeated cycles of activation and deactivation of allostasis over time or failure to disengage or shut off the stress response during and after each stressful life demand can yield the neuroendocrine dysregulations, including HPA and SAM axes (Beckie, 2012; Karatsoreos & McEwen, 2011). These neuroendocrine dysregulations could be phenotyped by glucocorticoids resistance (Miller & Chen, 2006), higher cortisol/DHEA ratio (Lennartsson, Theorell, Kushnir, & Jonsdottir, 2015; Lennartsson, Theorell, Rockwood, Kushnir, & Jonsdottir, 2013; Morgan et al., 2004), or lower level of brain-derived neurotrophic factors (Karatsoreos & McEwen, 2011). These neuroendocrine dysregulations are contributory to chronic inflammation, which increases the risk of multiple chronic diseases, including metabolic syndrome, atherosclerosis, depression, and premature aging. However, although allostatic load explains the direct and indirect physiological pathways in the stress-metabolism relationship, the behavioral and psychological pathways in the stress-metabolism relationship are often overlooked, especially how the stress is developed and where the stress comes from.

Sleep Behaviors in Mid- and Late-life

Normal aging results in shorter periods and fewer cycles of slow-wave sleeps (SWS). SWS, known as deep sleep, is the deepest sleep stage (N3 and N4), during which the arousal thresholds are higher and brains restore brain cells without dreaming (Altevogt & Colten, 2006; Edwards et al., 2010). In normal aging, SWS declines at a rate of 2% about every 10 years, which might contribute to frequent awakenings at night in older adults (Altevogt & Colten, 2006). In addition to normal aging, comorbidities and medication often results frequent awakenings in older adults due to the adverse effects of prescribed medication (*e.g.*, diuretics or beta-blocker) and chronic pain. On average, adults at age of 40 start to lose about 30 minutes of sleep every 10 years (Hood & Amir, 2017).

Gaps in the Literature

Although many observational studies and systematic reviews have reported the influence of stress on metabolic health, to date, stress is still categorized as a "relatively fixed factor" in the prevention and management of metabolic syndrome. Three significant limitations in the literature have challenged scientists' knowledge toward the stress-metabolism relationship and its underlying mechanisms.

First, it is unclear whether different sources of stress influence metabolic outcomes differently. To develop interventions, researchers must understand the attribute of psychological stress and its association with metabolic health. Unfortunately, measuring stress has been a challenge in this area of research. The most common way for researchers to quantify stress is using perceived stress scale, including Cohen's perceived stress scale (10-item or 14-item scale) or global perceived stress scale. Although perceived stress scale allows researchers to compare the score across studies, this scale only represents an individual's general stress without teasing out different sources of stress. Another common way to quantify adults' stress is using the life event scale, including Holmes and Rahe Social Readjustment Scale (n=1) or the life event checklists. Although life event scale could represent a person's life-changing events in the past

year, it does not share any information about the person's chronic stress that might already go on for years. As the result, the psychological stress in prior observational studies often focused on single-source instruments (dominated by occupational stress) or perceived stress scales, without teasing out different sources of stress that middle-aged and older adults often encounter (Babu et al., 2014; Kivimaki, Singh-Manoux, Nyberg, Jokela, & Virtanen, 2015; Tenk et al., 2018). It remains unanswered whether other sources of stress yield similar effect size (Bergmann et al., 2017). The dearth of evidence in this field limits researchers' ability to intervene the potentially modifiable risk for metabolic abnormalities in middle-aged and older adults.

Second, perceived health might be a preclinical factor reflecting a stressed adult's risk of metabolic syndrome, but the role of perceived health in the stress-metabolism relationship is not fully understood. Stress changes adults' perceived health. Specifically, stress decreases an individual's threshold of pain endurance, decreases physical and social functioning, and induces frequent fatigue. Existing evidence suggests that perceived physical health might be a stable physiological trait reflecting chronic inflammation, which mediates the stress-metabolism relationship (Arnberg, Lekander, Morey, & Segerstrom, 2016; Garvin, Nilsson, Ernerudh, & Kristenson, 2016). Prior research also showed that lower perceived physical health is associated with higher risk of obesity and prediabetes 10-years later (Ylitalo et al., 2016). These associations prompt the hypothesis that perceived health might mediate the stress-metabolism relationship. However, in the existing literature, perceived health is often modeled as the consequence of metabolic syndrome, instead of the precursor of metabolic syndrome (Lee et al., 2018; Rani, Kumar, & Krishan, 2018). It is unclear whether perceived health mediates the relationship between stress and metabolic syndrome.

Finally, to date, the roles of health behaviors in the stress-metabolism relationship are not clear. Sleep, in particular, is a fundamental human need on a daily basis (Maslow, 2013). Difficulty falling asleep and sleep curtailment both result in the dysregulation of HPA axis, that are associated with increased risk of metabolic syndrome.(Bonsignore, Borel, Machan, & Grunstein,

2013; Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Liyanarachchi, Ross, & Debono, 2017; Vgontzas & Chrousos, 2002). Financial stress, as a major allostatic load in certain middle-aged and older adults, also results in the dysregulation of HPA (Agbedia et al., 2011; Cohen et al., 2006). However, there is a lack of study examining the interaction effect between sleep behaviors and psychological stress on the risk of metabolic syndrome.

Specific Aims and Methods

The overall purpose of this dissertation is to examine the interrelationships between comprehensive measures of stress and metabolic biomarkers, and potential mediators and moderators. This dissertation contains three specific aims:

The first aim is to examine whether different sources of stress have different levels of influence on metabolic function and whether there is a sex difference in this relationship. Methods: We conducted a systematic review and performed meta-analyses with subgroup analyses to compare the effect sizes across different sources of stress.

The second aim is to examine whether perceived physical/mental health mediates the stress-metabolism relationship. Methods: We conducted a cross-sectional analysis using the data from the REST (Retirement and Sleep Trajectories) Study, an ancillary study of the Wisconsin Sleep Cohort (WSC). We used Structural Equational Modeling (SEM) to test the mediation effect of perceived physical/mental health in the stress-metabolism relationship.

The third aim is to examine the role of sleep behaviors in the relationship between stress and metabolic syndrome. Methods: With the same dataset, we tested whether sleep duration and insomnia symptoms moderate the stress-metabolism relationship using SEM with stacking approach.

Introduction to the Three Papers

The following three papers represent a cohesive program of research aiming to understand the stress-metabolism relationship and its interplay with sleep behaviors and perceived health.

The first paper is located in Chapter 2, titled by "*Does Psychological Stress Increase the Risk of Developing Metabolic Syndrome? Systematic Review and Meta-Analysis.*" This paper provides a summary of literature on stress-metabolism relationship. The results from meta-analysis indicates that adults in the high stress group were about 45% more likely to develop metabolic syndrome than adults in the low stress group. According to the subgroup meta-analysis, occupational stress has the strongest impact on metabolic syndrome, while the impacts of general perceived stress is relatively weaker. This paper also points out a limitation in prior literature, where there is a lack of studies examining the impacts of financial stress or interpersonal stress on the risk of metabolism syndrome.

The second paper is located in Chapter 3, titled by "*Financial Stress Is the Fundamental Stress Leading to Metabolic Syndrome and Abdominal Obesity.*" In this study, we overcame the limitation in prior literature by providing a comprehensive measure of stress, including financial, interpersonal, occupational, and life event stress. We found that financial stress is the fundamental stress associated with the prevalence of abdominal obesity, metabolic syndrome, and dyslipidemia. We further found that perceived physical health mediated the relationship between financial stress and the prevalence of abdominal obesity and metabolic syndrome.

The third paper is located in Chapter 4, titled by "*Sleep Duration and Insomnia Moderate the Influence of Financial Stress on Metabolic Syndrome"* In this paper, we found that the magnitudes of the relationship between financial stress and metabolic syndrome changed according to different sleep durations (Financial stress*Sleep duration: $\beta=0.032$, $p=0.008$) and insomnia symptoms (Financial Stress*Insomnia Symptoms: $\beta= 0.110$, $p=0.032$).

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Chapter 2

Manuscript 1:

The association between psychological stress and metabolic syndrome: A systematic review and meta-analysis

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Abstract

Background: Literature suggests that occupational stress is associated with a higher risk of metabolic syndrome, yet, less is known whether other sources of stress have similar effects. **Objectives:** This review aims to examine whether the relationship between psychological stress and metabolic syndrome differs by sources of stress. **Method:** Three databases (PubMed, Web of Science, and CINAHL) were searched for eligible articles; meta-analyses were conducted using the random effects model. **Results:** After controlling for covariates, adults in the high-stress groups had 45% higher chance of having metabolic syndrome than adults in the low-stress groups (odds ratio [OR]=1.450; 95% CI=1.211-1.735). The subsequent meta-analysis based on cross-sectional studies suggested that occupational stress showed the strongest effect (OR=1.692; 95% CI=1.182-2.424), while perceived general stress showed the weakest effect (OR=1.217; 95% CI=1.017-1.457). Unfortunately, there is a lack of longitudinal studies for subsequent meta-analysis based on sources of stress. **Conclusion:** There is a need for continued research to examine the long-term relationship between different sources of stress and the risk of metabolic syndrome. Traditional recommendations for preventing metabolic syndrome (*e.g.*, low-fat diet and exercise) may not achieve the best outcome if clinicians overlook patients' psychosocial stress.

1. Introduction

About 30% of adults have metabolic syndrome worldwide (Aguilar, Bhuket, Torres, Liu, & Wong, 2015; Misra & Khurana, 2008). The economic burden of metabolic syndrome is substantial. For instance, the annual medical costs for Americans with metabolic syndrome are 60% higher than those without metabolic syndrome (Boudreau et al., 2009; Mahabaleshwarkar, Taylor, Spencer, & Mohanan, 2016; Nichols & Moler, 2011). The development of metabolic syndrome is a multifaceted continuum of metabolic dysregulation, including hyperglycemia, hypertension, visceral adiposity, and atherogenic dyslipidemia (Kaur, 2014).

Psychological stress has been linked to metabolic syndrome for decades, but its underlying mechanism is not yet fully understood. Allostasis refers to a normal physiological process where the brain activates the Sympathetic-Adrenal-Medullary (SAM) and Hypothalamic-Pituitary-Adrenal (HPA) axes, and stimulates adrenal glands to release stress hormones (*e.g.*, corticosteroids) and catecholamine (*e.g.,* epinephrine and norepinephrine) to combat against stressful environmental demands (Sterling, 2004). According to the Allostatic Load Framework (ALF), the repeated cycles of activation and deactivation of allostasis over time, or a failure to disengage the stress response during and after each stressful life demand, could alter adults' diurnal cortisol rhythm and decrease the capacity of glucocorticoids to suppress endotoxin-stimulated cytokine production, resulting in a hormone dysfunction called glucocorticoids resistance (Epel et al., 2006; McEwen, 2015; Tamashiro, Sakai, Shively, Karatsoreos, & Reagan, 2011). Beyond this physiological pathway, psychologists suggested that long-term exposure to psychological stress could alter an individual's perception of need and how they should prioritize needs; this in turn leads to feelings of inadequate personal control. As a result, chronic stress has been linked to unhealthy behaviors which are associated with metabolic syndrome (McEwen & Karatsoreos, 2015; Razzoli, Pearson, Crow, & Bartolomucci, 2017; Stults-Kolehmainen & Sinha, 2014).

Epidemiological evidence has shown that occupational stress is associated with a higher risk of metabolic syndrome (Babu et al., 2014; Cosgrove, Sargeant, Caleyachetty, & Griffin, 2012; Kivimaki et al., 2006; Nyberg et al., 2014; Sui et al., 2016). However, a limitation often found in prior literature reviews is the negligence of covariates reported in each observational studies. For instance, in some observational studies, the authors included sex, age, and education as covariates, but, in other observational studies, the authors also included behavioral factors or inflammatory factors as covariates. As we mentioned earlier, the relationship between psychological stress and metabolic syndrome involves not only physiological, but also behavioral pathways. Therefore, behavioral factors (*e.g.*, physical activity, smoking, and diet) or physiological factors (*e.g.*, cortisol levels or inflammatory markers) might be the mediators in the stress-metabolism relationship, instead of confounding variables. According to Baron and Kenny's mediation hypothesis, controlling for the mediators in an established relationship could diminish (partial mediation) or destruct (complete mediation) the established relationship (Baron & Kenny, 1986). Therefore, when conducting a systematic review summarizing the relationship between stress and metabolic syndrome, a potential strategy is to examine whether each individual observational study treated the potential mediators as covariates and analyze whether the effect size changes after controlling for potential mediators.

Another limitation often found in prior literature reviews is estimating the overall effect size based on the individual effect size derived from the most-adjusted model (*i.e.* the regression model with the highest numbers of covariates) (Babu et al., 2014; Tenk et al., 2018a; Watanabe et al., 2018). Based on this practice, if the most-adjusted model was unavailable, the researchers extracted the effect size derived from the crude model (*i.e.* the regression model without controlling for covariates) and performed meta-analysis accordingly. Given that some covariates might be mediators and some covariates might be the confounding variables, combining the effect sizes derived from both the crude model and the most-adjusted model under the same meta-

analysis might limit our current understanding of the relationship between psychological stress and metabolic syndrome.

Finally, middle-aged and older adults experience a broad array of stress from different sources, including life events, relationships, financial issues, and daily hassles. Researchers have speculated that some features of stressful conditions are associated with greater stress arousal and thus induce physiological arousal, such as higher catabolic and lower anabolic profiles (Epel, 2009; Epel et al., 2006; Kivimaki & Steptoe, 2018). Unfortunately, prior literature reviews which examined the stress-metabolism relationship often limited their analyses to occupational stress or perceived general stress. It is unclear whether other sources of stress have similar effects or not.

To address the above limitations from prior literature reviews, we hypothesized that the effect size of the stress-metabolism relationship might diminish or disappear after controlling for the behavioral pathways (*e.g.*, physical inactivity, diet, and other lifestyle factors) or the physiological pathways (*e.g.*, inflammatory markers). The primary aim of the present systematic review is to examine whether controlling for behavioral factors and inflammatory markers reduces the estimated effect size. The secondary aim is to examine whether the effect sizes differ between cross-sectional studies and longitudinal studies. The final aim is to examine whether different sources of stress have different levels of effect on metabolic syndrome.

2. Method

2.1. Search Strategy and Selection Process

Three databases (Web of Science, Pubmed, and CINAHL) were searched for peer-reviewed journals relating to psychological stress and metabolic syndrome, with a combination of two sets of keywords and exploded controlled vocabulary terms (see Table 2.1.).

All the potential references identified through Web of Science, Pubmed, and CINAHL were imported into Zotero software. The reference screening was based on the following inclusion and exclusion criteria. First, the outcome variables needed to be defined by metabolic syndrome or a

cluster of metabolic abnormalities (*e.g.*, insulin resistance, obesity, hypertension, or dyslipidemia). Studies were excluded if the authors did not analyze the relationship between stress and metabolic syndrome. Second, the study must address psychological stress while including stress, strain, or pressure, as a predictive variable; the psychological stress in question must be defined by each study team. In particular, studies were excluded if they focused on mental disorders that are classified in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), including depression, anxiety, burnout, and psychiatric disorders. This decision was made because the etiology and treatment of mental disorders (*e.g.*, depression or anxiety) are distinct from psychological stress (*e.g.*, occupational stress or financial stress). Third, studies including participants under 18 years of age were excluded, because the stress experience in children is different from adults. Fourth, studies focusing on patients who had already been diagnosed with chronic conditions such as hypertension, T2DM, or cardiovascular diseases (CVD), were excluded, because the physiological changes and medical treatments associated with these conditions can significantly confound the relationship between psychological stress and metabolic outcomes. Finally, studies must be published in peer-reviewed journals and written in English. Reports with only abstracts or unpublished results were excluded from this literature review.

For the articles with an unclear definition of psychological stress, three researchers (LB, LO, and WK) independently reviewed these articles and discussed whether the definition of psychological stress was well-defined in these studies. Reference lists of relevant articles were also scanned for further possible articles to be included.

2.2. Evaluation of Study Quality

The quality for each study was independently rated by two researchers using the quality assessment tool developed by Shona Yates and colleagues (Yates, Morley, Eccleston, & de C Williams, 2005). The Yates' scale quantifies both treatment quality (6 items) and study quality (20 items), thereby allowing researchers to compare the level of evidence for evidence-based practice.

For the scope of this review, all the studies received 0 out of 9 points in the treatment quality, due to the nature of observational studies. The evaluation of study quality includes 8 domains: inclusion/exclusion criteria, guideline for attrition, sample characteristics, risk of bias, quality of outcome, sustainability, vigor of statistics, and quality of comparison group. Each item was rated on a sale of 0 to 2 or 0 to 1, depending on the weights of each study characteristic proposed by the panel experts in Yates' study. The agreement and disagreement between the two researchers were verified through Epidata software. Each identified disagreement was resolved through team discussion and joint review.

2.3. Data Extraction

Two researchers (W.K. & L.B.) decided what components should be extracted into the evidence table based on the clinical importance of each study component. One researcher (W.K.) extracted the data from each study into the evidence table, and the other five researchers (L.B., L.O., F.K., HW, & R.B.) independently examined the evidence table based on each researcher's expertise and clarified any confusion with the main data extractor (W.K.). All disagreements were resolved through discussion and joint review by all team members. For studies with unclear information, we emailed the corresponding authors to request the details (Abraham, Rubino, Sinaii, Ramsey, & Nieman, 2013; Allshouse et al., 2018; Chen et al., 2018; Garbarino & Magnavita, 2015; Hwang & Lee, 2014; Mahanta, Joshi, Mahanta, & Gogoi, 2017); two study teams responded to our request (Chen et al., 2018; Garbarino & Magnavita, 2015).

2.4. Meta-Analysis

We estimated the effect sizes using the subgroup approach. First, all the reported odds ratios were examined and extracted into two groups (*i.e*. the crude models vs. the most-adjusted models) based on the confounding variables reported in the regression analysis. Next, to compare the effect sizes between cross-sectional studies and longitudinal studies, we further conducted subgroup estimates. Because we identified only a few studies reporting hazard ratios using time-

to-event data (analyzed by the Cox proportional hazard model), studies only reporting hazard ratios were excluded from meta-analysis.

During the meta-analysis, additional decisions were made to ensure that each participant was included in a meta-analysis only once. First, if the studies reported psychological stress with more than two definitions, we chose the most common definition. For instance, Magnavita et al. addressed work strain with two definitions: demand/control (D/C) ratio and effort/reward (E/R) imbalance, and we chose the result from D/C ratio, because the D/C ratio is the most common definition in that body of literature (Magnavita & Fileni, 2014). Second, if the authors defined metabolic syndrome based on multiple standards, such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), World Health Organization (WHO), and International Diabetes Foundation (IDF), we chose NCEP ATP III first, with IDF in the second order, and WHO in the last order, based on the frequency of usage in current literature. Third, if the study did not report the crude model, but reported the least adjusted model and most adjusted model, we then pulled the least adjusted results into the crude-model group (Demiral et al., 2006; Frisman & Kristenson, 2009; Garcez et al., 2017; Yamaguchi et al., 2018). Finally, when two articles were published from the same study cohort (*e.g.*, Whitehall II), we chose the article reporting the largest sample size.

2.5. Heterogeneity & Risk of Publication Bias

We used the Q statistic to assess inter- and intra-study differences and used the I^2 index to quantify the proportion of variance across studies that is due to heterogeneity rather than explained by random error (Gami et al., 2007; Higgins, Thompson, Deeks, & Altman, 2003). The Q statistic was calculated as the weighted sum of squared differences between individual study effect sizes (ES_i) and the pooled effect size across studies (ES_{pooled}), with the weights based on standard error (Card, 2011). The I^2 index was obtained from a typical meta-analysis as $I^2 = 100\% \times (Q - \text{degree of freedom})/Q$ (Higgins et al., 2003). We calculated pooled estimates of the odds ratio for participants with high stress versus low stress using the random effects model due to the

heterogeneity indicated by Q statistic and I^2 index. The random effects model assumes that the underlying effect of different sources of stress may vary around the overall central effect and is not absolutely fixed across studies. We further performed meta-regression to examine what factors might explain the total inter-study variance in the pooled effect size across studies. The exploratory variables included sex, geographical region of study, source of stress, and type of study.

Finally, we examined the publication bias via funnel plot, which illustrated the standard error as the function of the log odds ratio. Publication bias occurs when significant findings are more likely to be published than non-significant findings. Thus, the funnel plot asymmetry allows researchers to examine whether studies with a larger sample size tend to report a smaller effect size than studies with a smaller sample size. We also ran Rosenthal's Fail-safe N test and Tweedie's Trim and Fill test to ensure the publication bias could not reverse our estimate of effect sizes. All the meta-analysis, forest plots, and funnel plots were conducted using Comprehensive Meta-Analysis (CMA) (Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R., 2014).

3. Results

3.1. Study Characteristics

The results of the literature search are illustrated in Figure 2.1. We identified 30 studies (32 study records) based on the inclusion and exclusion criteria. The total sample size in the 30 studies was 67,037. The participants' age ranged from 18 years to 78 years. The details of each study are listed in Table 2.2. Among the 30 studies, 11 studies were longitudinal studies, and 19 studies were cross-sectional studies. Among the 11 longitudinal studies, the follow-up year ranged from 2 to 18 years (Mean: 7.2 years).

3.2. Assessment of outcome

As shown in Table 2.2., metabolic syndrome was defined by the National Heart, Lung, and Blood Institute (NHLBI) using NCEP ATP III classification (n=22), IDF classification (n=3), multiple

classification (n=2), or defined by the authors' reference (n=5). All of the study teams collected outcome variables using subjective assessments, along with clinical or laboratory data.

3.3. Assessment of Exposure

The source of stress included occupational stress (n=14), perceived general stress (n=10), stressful life events (n=5), marital stress (n=1), or a combination of financial stress and perceived general stress (n=2). Occupational stress was assessed using the Karasek Job Content Questionnaire (n=8), Siegrist Effort-Reward Imbalance Questionnaire (n=4), or the combination of both instruments (n=2). Perceived general stress was often assessed using the 14-item or 10-item Cohen Perceived Stress Scale (n=7); only a few studies used other perceived stress scales, such as the 4-Item Perceived Stress Scale (n=1), the Global Perceived Stress Scale (n=1), Strodl Perceived Stress Scale (n=1), or single item question (n=1). Life events were assessed according to the Holmes and Rahe Social Readjustment Scale (n=1) or the life event checklists developed by each study team (n=4).

3.4. The Mediation and Moderation Pathways in the Stress-Metabolism Relationship

We identified fifteen studies, which included behavioral factors as covariates and also reported the effect sizes with and without adjusting for covariates. In female samples, 5 studies reported that the odds ratio decreased after controlling for covariates, while 2 studies reported a similar odds ratio after controlling for covariates. However, in male samples this pattern was not found since 4 studies reported an increased odds ratio, while 4 studies reported a decreased odds ratio. This finding suggests that behavioral factors might be the mediators in the stress-metabolism relationship and sex might be a moderator in this mediation relationship. On the other hand, we only identified one study, which included inflammatory markers as covariates and reported the effect size with and without adjusting for covariates. Specifically, Almadi et al. found that the effect size decreased from 4.74 (95% CI=2.13–10.55) to 2.80 (95% CI=1.15–6.78) after controlling for covariates including cortisol expressed in area under curve (AUC). They further found that the interaction between cortisol level and occupational stress was significantly

associated with the prevalence of metabolic syndrome, suggesting that cortisol level might be a moderator in the stress-metabolism relationship (Almadi et al., 2013).

3.5. The Effect Size Estimated from Crude Models (or Least-Adjusted Models)

We identified 14 studies reporting odds ratios using a crude model or least-adjusted model. The pooled odds ratio was 1.377 (95%CI=1.192-1.590). As shown in Figure 2.2., we performed sub-group analysis based on study types; the pooled odds ratio for cross-sectional studies was 1.435 (95% CI=1.176-1.750; p<0.001), while the pooled odds ratio for longitudinal studies was 1.314 (95% CI=1.063-1.625; p<0.012).

To further investigate which source of stress had the strongest impact on the risk of metabolic syndrome, we performed the subsequent meta-analysis stratified by sources of stress and types of study. As shown in Figure 2.3., we found significant association between occupational stress and the prevalence of metabolic syndrome, but this significant effect was not found in perceived general stress or life events. Specifically, for the occupational stress, the pooled odds ratio in cross-sectional studies was 1.695 (95% CI=1.270-2.262; p<0.001), and the pooled odds ratio in longitudinal studies was 1.388 (95% CI=1.027-1.877; p=0.033). For the perceived general stress, the pooled odds ratio in cross-sectional studies was 1.142 (95% CI=0.967-1.350; p=0.118), while there was a lack of longitudinal study reporting the effect of perceived general stress. Finally, for the life events, the pooled odds ratio in longitudinal studies was 1.209 (95% CI=0.801-1.825; p=0.365), while there was a lack of cross-sectional study reporting the effect of life events.

3.6. The Stress-Metabolism Relationship in the Most-Adjusted Model

We identified 13 studies reporting the odds ratios using the most-adjusted model. The pooled odds ratio was 1.450 (95% CI=1.211-1.735). As shown in the Figure 2.4., when we performed the subgroup analysis based on study types, the pooled odds ratio for cross-sectional studies was 1.447 (95% CI=1.176-1.780; p<0.001), while the pooled odds ratio for longitudinal studies was not significant (OR=1.490; 95% CI=0.986-2.252; p=0.058).

Again, we performed the subsequent meta-analysis stratified by sources of stress and types of study to examine which source of stress had the strongest impact on the risk of metabolic syndrome after controlling for covariates. Based on cross-sectional studies, we found that occupational stress, life events, and perceived general stress were significantly associated with the prevalence of metabolic syndrome after controlling for covariates; occupational stress in particular had the strongest effect size, compared to perceived general stress and life events (see Figure 2.5.). Specifically, the pooled odds ratio for occupational stress was 1.692 (95% CI=1.182-2.424; p=0.004), for life events was 1.640 (95% CI=1.180-2.280; p=0.003), and for perceived general stress was 1.217 (95% CI=1.017-1.457; p=0.032). Unfortunately, we did not find significant association in longitudinal studies for any sources of stress.

3.7. Heterogeneity of Study

We assessed the inter-study heterogeneity using I^2 index and Q statistic (see Figure 2.2. and Figure 2.4.). For cross-sectional studies, we found the Q statistics were significant in the crude model (Q=38.4; p<0.001) and most-adjusted model (Q=36.607; p<0.001); the I^2 indexes for both models were close to 75%, indicating a high heterogeneity across these cross-sectional studies (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). For the longitudinal studies, the Q statistics for crude model (Q=9.003; p=0.109) and most-adjusted model (Q=9.427;p=0.093) were not significant, yet, the I^2 indexes for moth models were close to 45%, indicating a moderate heterogeneity across these longitudinal studies (Huedo-Medina et al., 2006). We suspected that the observed variability in effect sizes across the cross-sectional and longitudinal studies is greater than expected due to sampling fluctuation alone. The I^2 indexes provided the justification for using random effects model in meta-analysis.

3.8. Meta-Regression

A set of potential moderators were investigated through meta-regression. Unfortunately, none of the potential moderators were significant (see Table 2.3.).

3.9. Risk of Publication Bias

The funnel plots for study results reported in both the crude model (Figure 2.6.) and the most-adjusted model (Figure 2.7.) were asymmetric, indicating that there was a small publication bias, due either to researchers failing to report non-significant findings or our inability to identify studies with non-significant findings (Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R., 2009). We ran Rosenthal's Fail-safe N test to see how many missing studies were needed to flip our study findings. The Fail-safe N for the studies reporting the crude (or least-adjusted) model was 231, meaning that we would need to have missed over 13 unpublished or undiscovered records for every 1 study we found. On the other hand, the Fail-safe N for studies reporting the most-adjusted model was 188. Again, it is unlikely that we missed 11 unpublished or undiscovered records for every 1 study we found. We further ran the Tweedie's Trim and Fill test, by imputing missing studies and recalculating the effect size. The imputed odds ratio for the crude (or least-adjusted) model was 1.266 (95% CI=1.068-1.501) and for the most-adjusted model was 1.230 (95% CI=1.009-1.498). The imputed effect sizes were slightly smaller than the non-imputed effect sizes.

3.10. Study Quality

For the observational studies with multiple records, we selected the record with the highest score to represent their study quality. During the first grading, the agreement rate between the two graders was 98.21%. The disagreements were resolved through team discussion. We found two major disagreements between graders. First, some studies specified attrition in inclusion/exclusion criteria without listing the attrition reasons in a separate paragraph. The team reached agreement by giving these studies full points if the authors specified either inclusion/exclusion criteria or attrition reasons. Second, the validity and reliability of outcome measures were often graded differently by two graders. Therefore, we achieved consensus that studies with lab data as outcomes received full points for validity and reliability. Studies with medical record/chart reviews as outcomes received full points for validity but partial points for reliability due to the possibility of under-diagnosis. Studies with self-reporting questions as

outcomes received partial points for both validity and reliability. After the team discussion, the mean score of study quality for the 19 cross-sectional studies was 12.53 out of 26 (SD=1.26), and the mean score of study quality for the 11 longitudinal studies was 14.69 out of 26 (SD=2.59). The levels of evidence were moderate due to the nature of observational studies without randomization and control groups. The detail score for each study is listed in Table 2.2.

4. Discussion

Prior literature reviews have shown that psychological stress and occupational stress increase the risk of metabolic syndrome with an estimated effect size of 1.47 (95% CI=1.22-1.78) (Bergmann et al., 2017; Tenk et al., 2018; Watanabe et al., 2018). The present literature review further expand the field's knowledge by comparing the pooled effect sizes among different sources of stress and different types of study (longitudinal study vs. cross-sectional study). This knowledge helps clinicians understand which source of stress is more metabolically detrimental and how time might or might not attenuate this stress-metabolism impact. Furthermore, this literature review overcomes a major limitation in prior reviews by examining the pooled effect sizes separately using the crude (or least adjusted) model and the most-adjusted model. Covariates are crucial factors that can be either the noises affecting the outcome variables (*e.g.*, age and family history of metabolic syndrome) or the potential mediators explaining the underlying mechanisms in the stress-metabolism relationship. Unfortunately, prior systematic reviews rarely pinpointed out how covariates might have influenced the estimated effect sizes.

Overall, the pooled association between psychological stress and metabolic syndrome in the crude (or least-adjusted) model was 1.377 (95%CI=1.192-1.590), while the pooled odds ratio in the most-adjusted model was 1.450 (95% CI=1.211-1.735). In the qualitative synthesis, we found a pattern in female samples wherein the odds ratios decreased after controlling for covariates that contained behavioral factors (*e.g.*, physical activity, diet, sleep, smoking, or alcohol consumption). Conversely, we did not find this pattern in males. We suggest that the sex difference in the stress-metabolism relationship might have involved different physiological and

behavioral pathways; females might be more susceptible to harmful behaviors when experiencing life stressors (*e.g.*, insomnia, physical inactivity, or stressed eating). For instance, many researchers have demonstrated that females were more likely to report stress-eating compared to males (Beydoun, 2014; Thompson, Thompson, & Romeo, 2015). Unfortunately, the subgroup meta-analysis according to biological sex identity was not able to be performed in the present study, due to a low number of studies reporting the results for males and females separately. This challenge has been reported in prior literature reviews aiming to examine the sex difference and its physiological and behavioral pathways in the stress-metabolism relationship (Bergmann, Gyntelberg, & Faber, 2014; Tenk et al., 2018). Future studies are highly needed to clarify these relationships in order to improve intervention design for males and females.

The estimated effect size in cross-sectional studies was strongly significant in both the crude (or least-adjusted) model (OR=1.435; 95% CI=1.176-1.750; p<0.001) and the most-adjusted model (OR=1.447; 95% CI=1.176-1.780; p<0.001). Compared to the cross-sectional studies, the estimated effect size in longitudinal studies was significant in the crude model (OR=1.314; 95% CI=1.063-1.625; p<0.012) and became non-significant in the most-adjusted model 1.490 (95% CI=0.986-2.252; p=0.058). There is a need for continued research to examine the ling-term behavioral and physiological effects in the stress-metabolism relationship. Furthermore, statistical power is higher in the crude model than the most-adjusted model, especially when some studies controlled for more than 10 covariates (Schmidt et al., 2015; Yamaguchi et al., 2018). Therefore, lumping the crude-model and most adjusted model together in the meta-analysis might jeopardize the interpretation of effect size.

Different sources of stress influence metabolic outcomes differently. When comparing the effect sizes among different sources of stress (*e.g.*, perceived general stress, life events, and occupational stress), we found that occupational stress has the strongest impact (OR=1.692; 95% CI=1.182-2.424), while the impacts of perceived general stress on metabolic syndrome was relatively weaker (OR=1.217; 95% CI=1.017-1.457). Our finding is consistent with recent reviews

(Bergmann et al., 2014; Tenk et al., 2018; Watanabe et al., 2018), suggesting that occupational stress has significant influence on metabolic outcomes, but perceived general stress does not. We suspect that because perceived general stress consolidates all sources of stress, these measures may not be as sensitive as more specific measures of individual sources of stress. We also hypothesize that some sources of stress (*e.g.*, financial stress, and occupational stress) might promote the development of metabolic syndrome, while other sources of stress (*e.g.*, daily hassles) may not; thus, the overall stress effect might have been washed out. Unfortunately, psychological stress in the majority of observational studies we found was often measured with single-source instruments (dominated by occupational stress) or perceived stress scales, without teasing out different sources of stress that middle-aged and older adults often encounter. Currently, there is a lack of evidence for researchers to conclude that financial stress and/or other sources of stress (*e.g.*, interpersonal stress) have similar effect sizes or not.

Outliers could be due to extreme samples, measurement error, or experimental error. In order to confirm that the outliers did not distort the pooled effect size away from normal distribution, we performed Grubbs' test to identify the extreme values reported in the observational studies. We identified two studies with Z scores larger than 2 standard deviations (Almadi et al., 2013; Magnavita & Fileni, 2014). After deleting these two outliers, the I^2 dropped from 71% to 0% for the crude-model results, and dropped from 73% to 53% for the most-adjusted results; the estimated odds ratios also dropped accordingly (see Supplement 1). The two outliers were cross-sectional studies and aimed to examine the association between occupational stress and metabolic syndrome. Unfortunately, one study only targeted radiologists (Magnavita & Fileni, 2014), while the other study only targeted male blue-collar workers (Almadi et al., 2013). Both studies cannot represent the occupational characteristics for the general population.

While we completed a comprehensively planned analysis, the findings from this study must be interpreted with respect to the limitations. First, it appears we did not have sufficient power to conduct meta-regression; thus we cannot conclude whether sex, source of stress, and

the types of studies explain the variance in the stress-metabolism relationship or not. However, we did perform the subsequent meta-analysis stratified by sources of stress and study types, which provided a foundation for future studies. Second, based on the aim and scope of this review, we did not include mental disorders (*e.g.,* depression, anxiety, or burnout) in our search terms. Therefore, the study results cannot explain the relationship between mental disorders and the development of metabolic syndrome. Finally, we only included studies published in English, without identifying non-English evidence. This limitation was minimized by comprehensive literature research. As shown in Table 2.2., the study population in this review did cover North America, Europe, Middle East, Asia, and Australia in a global manner.

5. Conclusion

The findings in this review provide the roadmap for future studies to examine the sex difference and the impact of different sources of stress on metabolic syndrome. We conclude that there is a strong need for researchers to examine how other sources of stress that are commonly experienced in middle-aged adults, such as financial stress and interpersonal stress, might impact metabolic outcomes. Meanwhile, our findings provide a robust evidence for clinicians to consider how psychological stress might increase the risk of metabolic syndrome in adults. Therefore, the traditional recommendation for preventing metabolic syndrome (*e.g.,* smoking cessation, low-sodium diet, and physical activity) may not achieve the best outcome if clinicians overlook patients' psychosocial stress. There is a need for agencies to incorporate stress management into current guidelines for preventing metabolic syndrome.

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7. Tables

Table 2.1. *Study eligibility criteria with definition and search terms*

Study eligibility criteria	Definition	Exploded controlled vocabulary terms (search terms)	Study exclusion criteria
Metabolic syndrome	A cluster of metabolic abnormalities, including abdominal obesity, insulin sensitivity, hypertension, and dyslipidemia.	metabolic abnormality, metabolic syndrome, metabolic x syndrome, x syndrome, or metabolic disorder	Studies reported the subcomponents of metabolic abnormality (*e.g.*, obesity or hypertension), instead of metabolic syndrome
Psychological stress	The perception of stress, strain, or pressure that adults experience from different sources, such as life events, occupation, or finance.	• Financial strain or financial stress • Job strain, occupational stress, job stress, or work stress • Interpersonal stress, social stress, family stress, or marital stress • Life event • Perceived stress, psychological stress, psychological distress, or psychosocial stress	Mental disorders: • Depression (ICD-10: F33.0, F33.1, F33.2, F33.3, F33.4, F33.8, F33.9) • Anxiety (ICD-10: F41.9) • Burnout (ICD-10: Z73.0) • Psychiatric disorders (ICD-10: F99)

Note. ICD-10=The 10th revision of the International Statistical Classification of Diseases and Related Health Problems

Table 2.2. *Overview of the selected studies in the meta-analysis.*

Study #	Author Year Reference	Country	Study type (F/U Years)	Sample size	Mean age at baseline *	Sex (%)	Racial identity	Source of Stress	Measure of stress	Definition of MetS	In meta-analysis	Study Quality
1	Abraham 2013[29]	U.S.	CS	429	18-75	M:31% F:69%	White:68%	PGS	Cohen PSS-10-item	ATP III	No	13
3	Allshouse 2018[26]	U.S.	LS (7y)	2371	46	F:100%	Most white	PGS, FS	4-item PSS 1-item FSS	ATP III	Yes	14
4	Almadi 2013[44]	Australia	CS	204	35	M:100%	Jordanian	OS	Siegrist (E/R)	IDF	Yes	13
5	Chandola 2006[38]	U.K.	LS (14y)	7034	35-55	M:70% F:30%	Most white	OS	Karasek (D/C)	ATP III	Yes	14
6	Chandola 2008[39]	U.K.	LS (8y)	6484	35-55	M:67% F:33%	Most white	OS	Karasek (D/C)	ATP III	No	15
7	Chen 2016[45]	Taiwan	CS	345	36	M:70% F:30%	Taiwanese	PGS	Cohen PSS-14-item	ATP III	No	13
8	Chen 2018[32]	Taiwan	LS (7y)	707	44	Unclear	Taiwanese	OS	Karasek (D/C)	ATP III	No	16
9	Cho 2016[46]	Korea	CS	4689	49	M:43% F: 57%	Korean	PGS	1 item	ATP III	Yes	13
10	Demiral 2006[35]	Turkey	CS	450	41	M:100%	Turkish	OS	Karasek (D/C)	ATP III	Yes	11
12	Edwards 2012[47]	U.S.	LS (5y)	2966	28-40	M:47% F:53%	Black:42% White:58%	OS	Karasek (D/C)	ATP III	Yes	15
13	Frisman 2009[36]	Sweden	CS	989	45-69	M:50% F:50%	Swedish	PGS	Strodl PSS	ATP III	Yes	13
14	Garbarino 2015[31]	Italy	LS (5y)	234	35	M:100%	Italian	OS	Karasek (D/C) & Siegrist (E/R)	ATP III	Yes	16
15	Garcez 2017[37]	Brazil	CS	250	37	F:100%	White:90.8%	PGS	Cohen PSS-10-item	ATP III	Yes	14
17	Horri 2010[48]	Iran	CS	351	35-55	F:100%	Iranian	LE	Holmes and Rahe stress scale	ATP III	No	12
18	Hwang 2014[30]	Korea	CS	234	34	M:66% F:34%	Korean	OS	Siegrist (E/R)	ATP III	Yes	12
19	Janczura 2015[49]	Poland	CS	235	41	M:92% F:8%	Polish	PGS	Cohen PSS-10-item	IDF	No	13
20	Kang 2004[50]	Korea	CS	167	47	M:100%	Korean	OS	Karasek (D/C)	Other reference	Yes	11
21	Khan 2015[51]	U.S.	CS	5227	54	M:37% F:63%	African American	PGS	Global PSS	ATP III	No	12

Study #	Author Year Reference	Country	Study type (F/U Years)	Sample size	Mean age at baseline *	Sex (%)	Racial identity	Source of Stress	Measure of stress	Definition of MetS	In meta-analysis	Study Quality
22	Loerbroks 2015[52]	China	LS (2y)	785	39	M:49% F:51%	Chinese	OS	Karasek (D/C)	Other reference	No	7
23	Magnavita 2014[53]	Italy	CS	654	<55 Y/O: 85%	M:69.7% F:30.3%	Italian	OS	Karasek (D/C) & Siegrist (E/R)	Other reference	Yes	11
25	Mahanta 2017[27]	India	CS	3372	47	Unclear	Indian	FS & PGS	Unclear	ATP III	No	11
26	Pedersen 2016[54]	Demark	LS (10y)	3621	M:52 F:49	M:39% F:61%	Danish	LE & work event	Life/work events checklist	ATP III	Yes	17
27	Pyykkonen 2010[55]	Finland	CS	3407	18-78	M:47%; F:53%	Finnish	LE	Life events checklist	ATP III & IDF	Yes	13
28	Raikkonen 2002[56]	U.S.	LS (7.4y)	425	42-50	F:100%	Most white	PGS	Cohen PSS-10-item	ATP III	No	15
29	Raikkonen 2007[56]	U.S.	LS (15y)	432	45-53	F:100%	Most white	PGS	Cohen PSS-10-item	ATP III, WHO, IDF	No	17
30	Rutters 2015[57]	Dutch	LS (6.5y)	1099	50-75	M:47%; F:53%	Dutch	LE	Life events checklist	ATP III	No	16
31	Santos 2018[58]	Brazil	CS	10960	45-54	M:48% F:52%	White:52.4% Brown:30.4% Black:17.1%	OS	Karasek (D/C)	ATP III	Yes	13
32	Schmidt 2015[59]	Germany	CS	4141	41	M:79% F:21%	German	OS	Siegrist (E/R)	Other reference	Yes	13
34	Vogelzangs 2007[60]	U.S.	CS	2917	74	M:48% F:52%	Black:41.1%	LE	Life events checklist	ATP III	No	13
35	Whisman 2012[61]	U.K.	LS (4y)	432	M: 63 F:61	M:50% F:50%	Unclear	Marital stress	Walen's marital stress scale	Other reference	No	16
36	Yamaguchi 2018[34]	Japan	LS (3y)	1040	19-68	M:89% F:11%	Japanese	OS	Karasek (D/C)	IDF	Yes	16
37	Yoo 2009[62]	U.S.	CS	386	39	M:100%	White:100%	PGS	Cohen PSS-14-item	ATP III	No	11

CS=Cross-sectional study; LS=Longitudinal study; F/U=Follow up; M=Males; F=Females; OS=Occupational stress; LE=Life events; PGS=Perceived general stress; D/C=Demand/control imbalance; E/R=Effort/reward imbalance; PSS=Perceived Stress Scale; MetS=Metabolic syndrome; ATPIII=Adult Treatment Panel III (ATP III); IDF=International Diabetes Foundation; WHO=World Health Organization

*Mean age was rounded to the nearest integer

Table 2.3. *Meta-regression*

Exlanatory variables	Unstandardized β (p-value)	
	Crude model	Most-adjusted model
Study type		
Cross-sectional	Reference level (p=0.56)	Reference level (p=0.90)
Longitudinal	-0.16	-0.05
Sources of stress		
GS	Reference level (p=0.81)	Reference level (p=0.87)
LE	0.05	-0.25
OS	2.00	-0.02
Sex		
Both	Reference level (p=0.87)	Reference level (p=0.60)
Male	-0.12	-0.04
Female	-0.19	-0.41
Geogrophic region		
Asia	Reference level (p=0.22)	Reference level (p=0.69)
Australia	1.20	0.85
Europe	0.15	0.40
Middle East	0.04	0.04
South America	-0.30	-0.30

Supplement. 2.1. *The pooled odds ratio of the full record and after deleting two outliers.*

		Pooled OR	95% CI	p-Value	I^2	Q
Crude model	**Cross-sectional study**					
	Full record	1.435	[1.176, 1.750]	<0.001	71%	38.4
	Deleting 2 outliers	1.225	[1.129, 1.328]	<0.001	0%	8.473
	Longitudinal study					
	Full record	1.314	[1.063, 1.625]	0.012	44%	9.003
	Deleting 2 outliers	1.314	[1.063, 1.625]	0.012	44%	9.003
Most-adjusted model	**Cross-sectional study**					
	Full record	1.447	[1.176, 1.780]	<0.001	73%	36.607
	Deleting 2 outliers	1.292	[1.105, 1.511]	0.001	53%	17.119
	Longitudinal study					
	Full record	1.490	[0.986, 2.252]	0.058	47%	9.427
	Deleting 2 outliers	1.490	[0.986, 2.252]	0.058	47%	9.427

OR=Odds ratio; CI=Confidence interval; I^2=I^2 index; Q=Q statistic

8. Figures

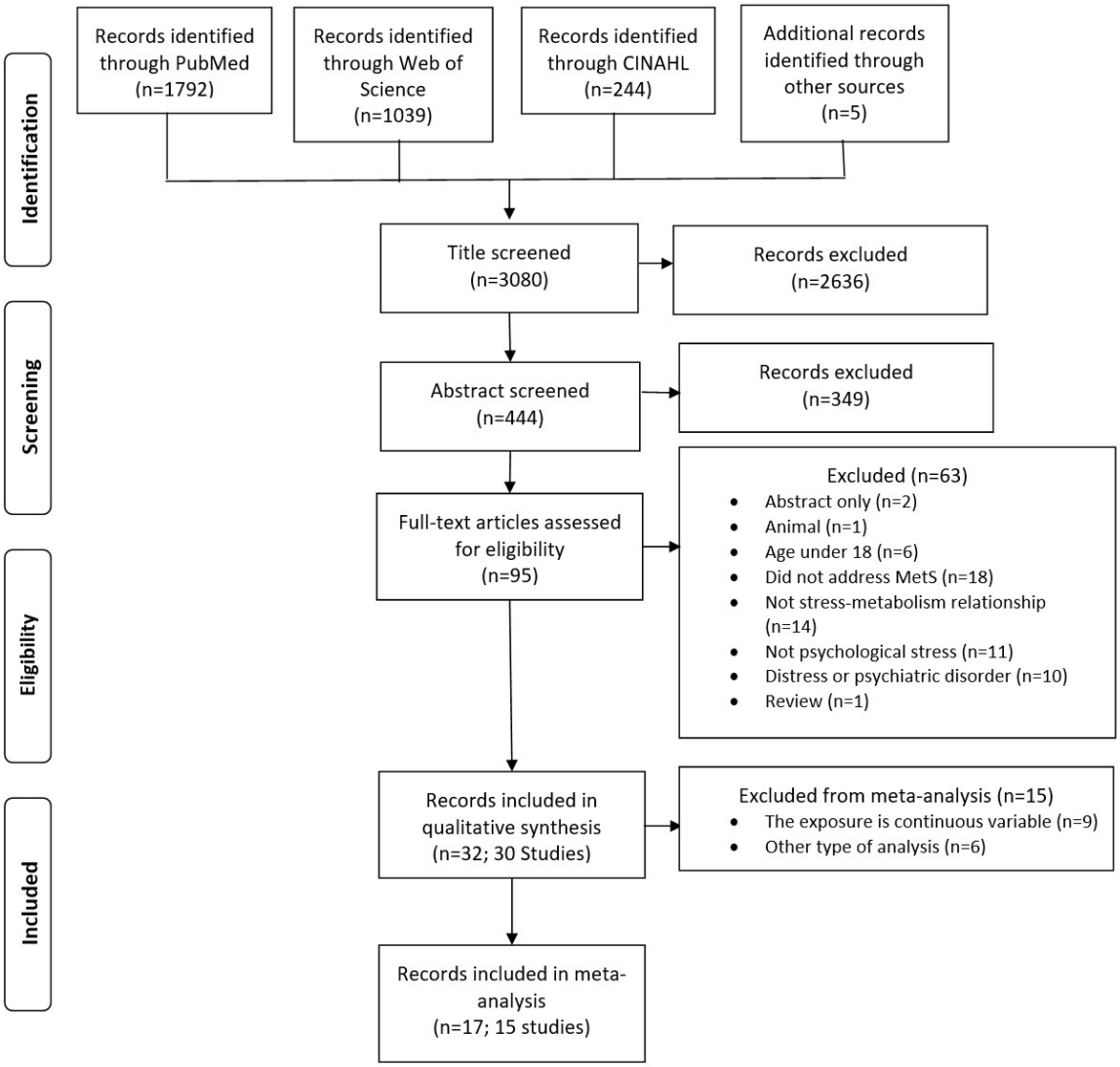

Figure 2.1. The flow chart of the search strategy.

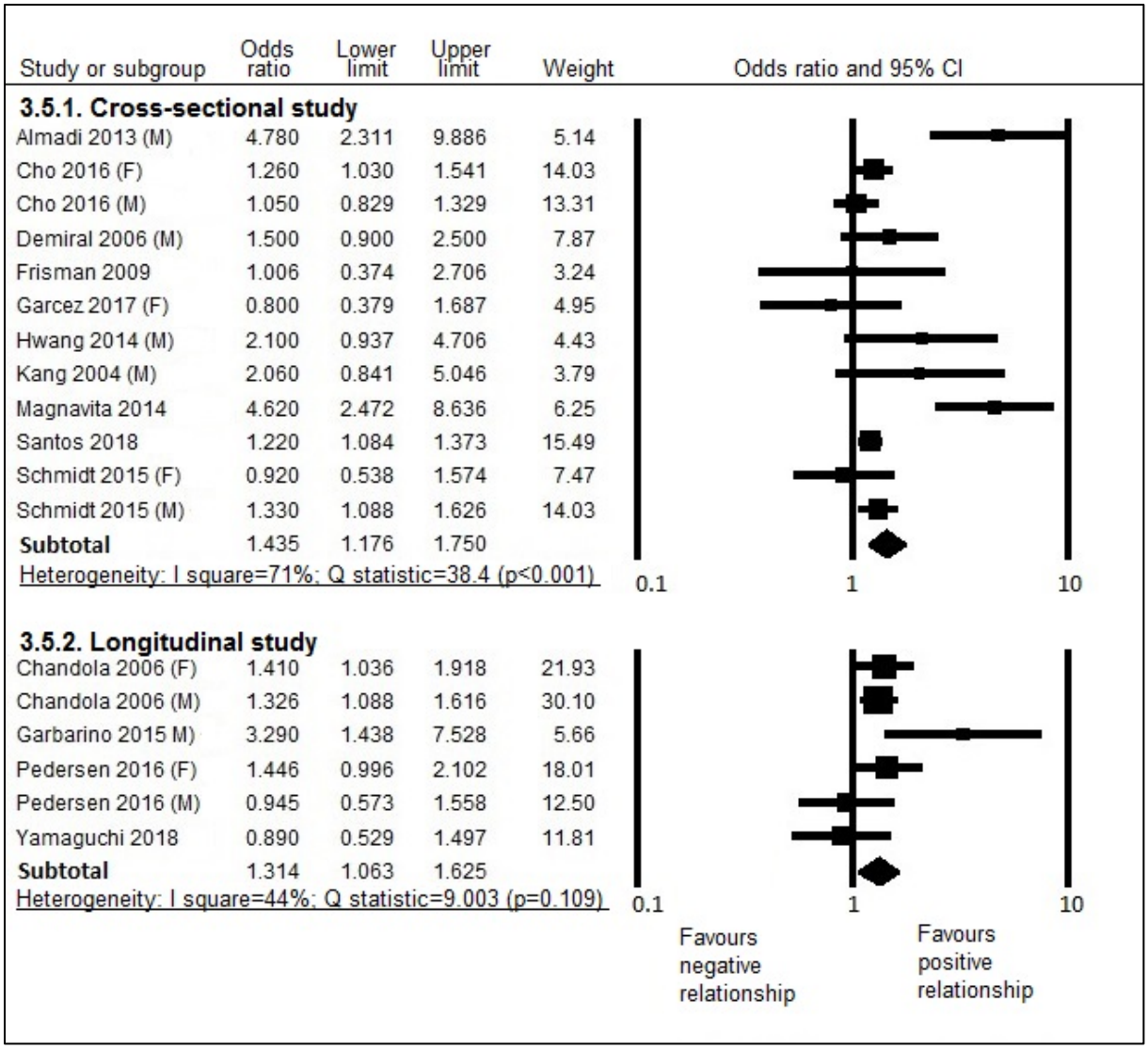

Figure 2.2. Estimates of the stress-metabolism relationship using crude-model or least-adjusted results, stratified by types of study. (F=Female; M=Male; CI=Confidence interval)

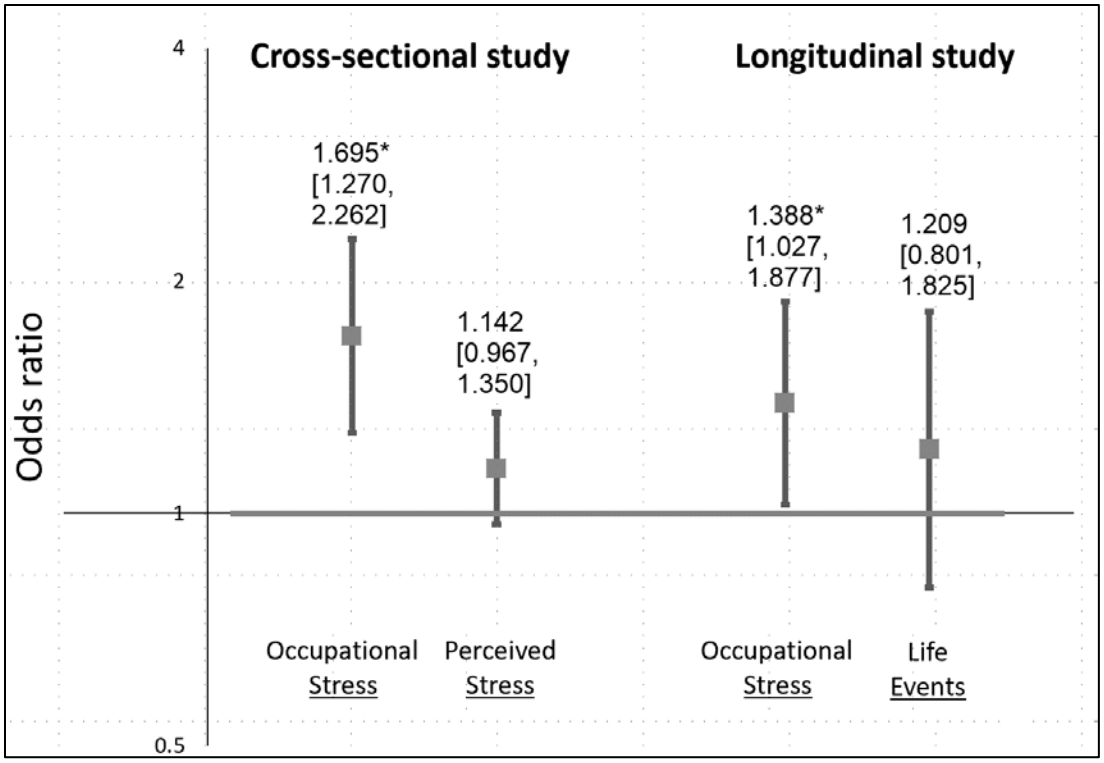

Figure 2.3. Estimates of stress-metabolism relationship stratified by sources of stress and types of study in the crude (or least-adjusted) model. The levels of histogram refer to odds ratio; the whiskers on the top of each histogram refer to 95% Confidence Intervals. The asterisk (*) indicates that the P-value is less than 0.05.

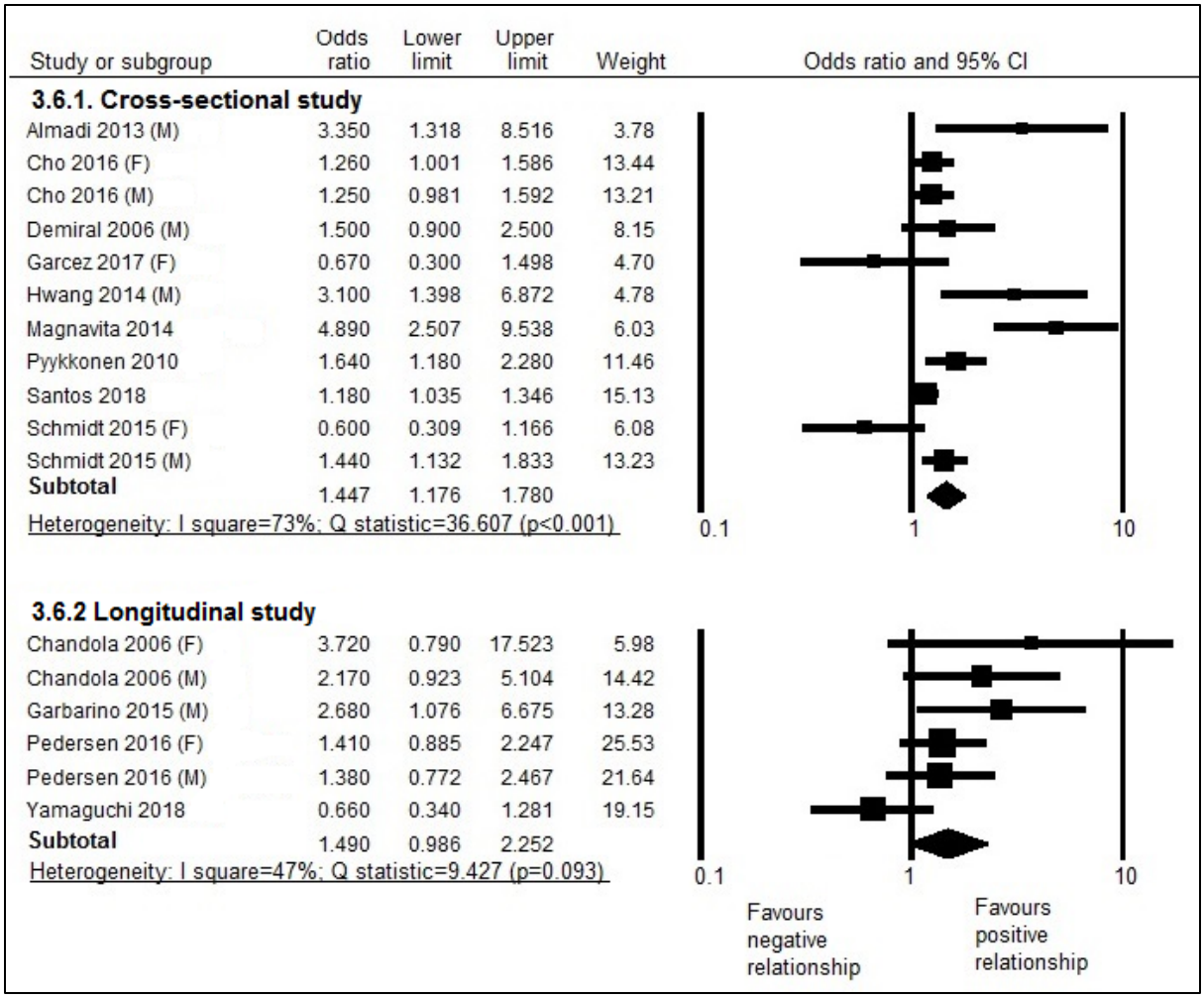

Figure 2.4. Estimates of the stress-metabolism relationship using the most-adjusted model, stratified by types of study. (F=Female; M=Male; CI=Confidence interval)

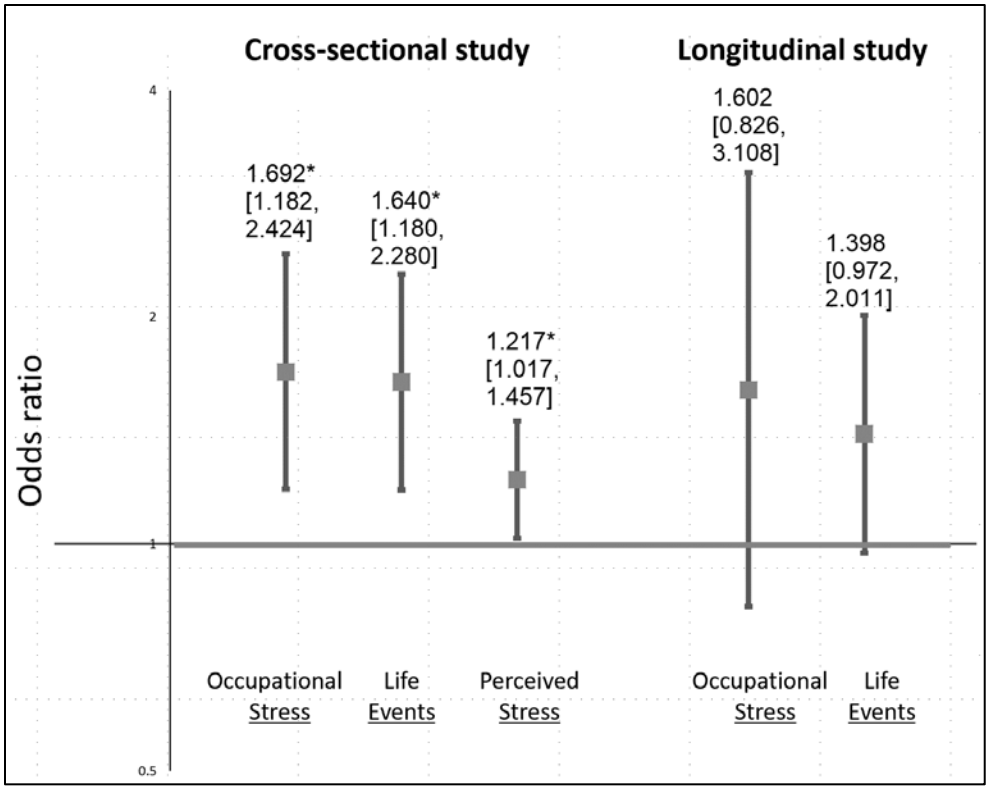

Figure 2.5. Estimates of stress-metabolism relationship stratified by sources of stress and types of study in the most-adjusted model. The levels of histogram refer to odds ratio; the whiskers on the top of each histogram refer to 95% Confidence Intervals. The asterisk (*) indicates that the P-value is less than 0.05.

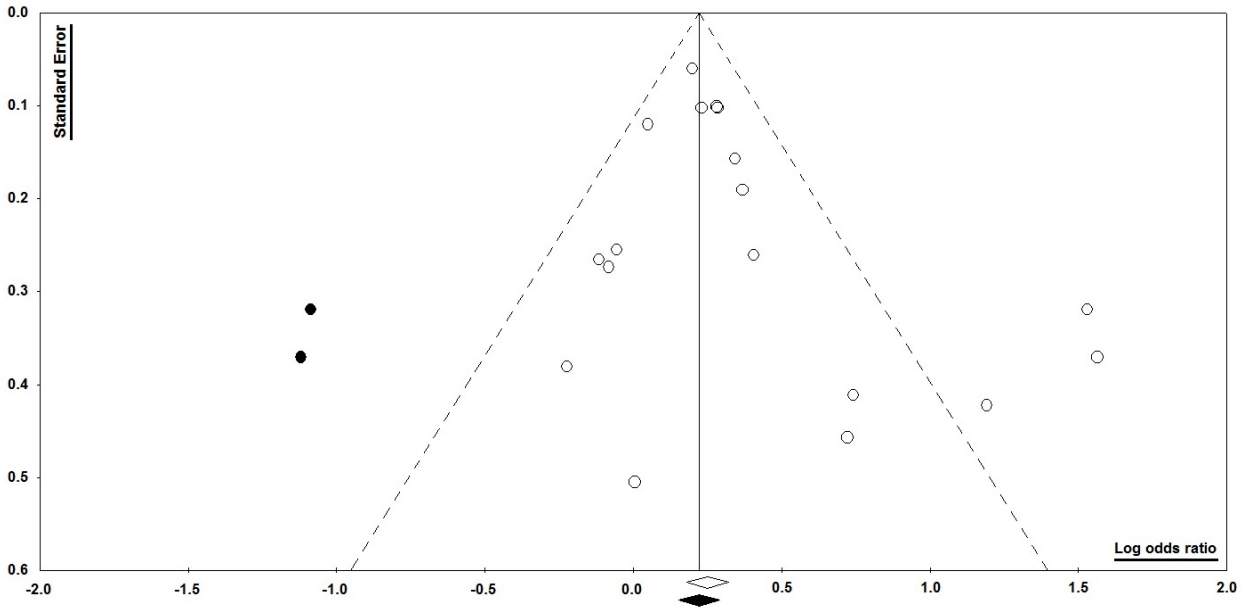

Figure 2.6. Funnel plots of standard error by log odds ratio for the crude (or least-adjusted) model results. (Dashed lines indicated 95% confidence intervals; ● indicates imputed studies; ○ indicates each selected study in meta-analysis)

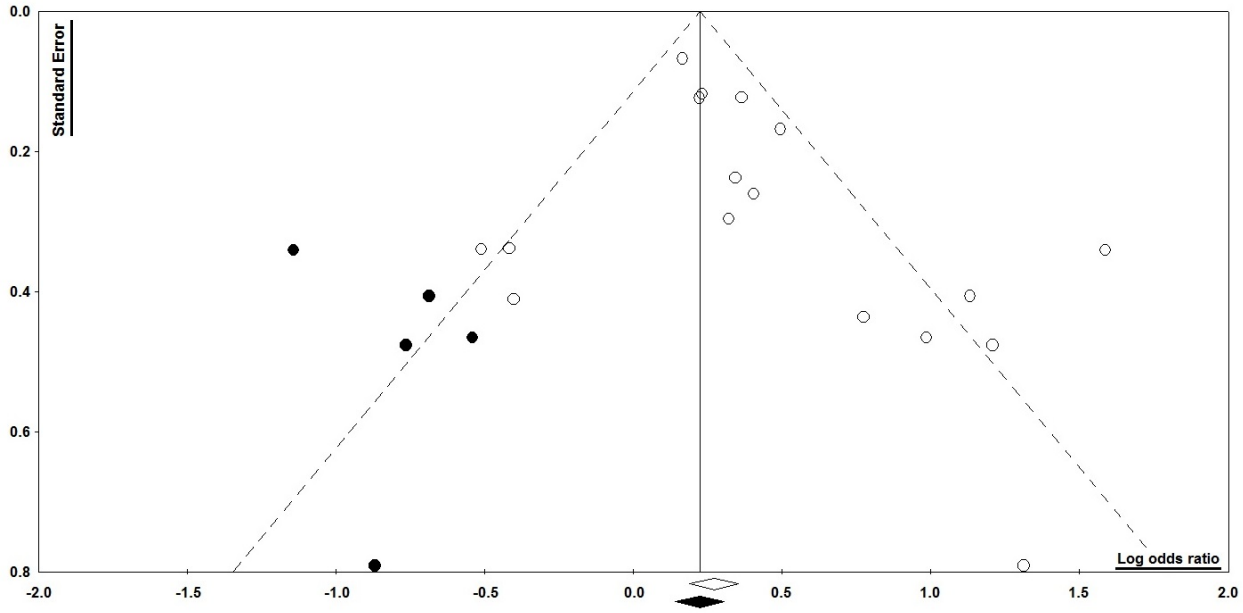

Figure 2.7. Funnel plots of standard error by log odds ratio for the most-adjusted model results. (Dashed lines indicated 95% confidence intervals; ● indicates imputed studies; ○ indicates each selected study in meta-analysis)

Chapter 3

Manuscript 2:

Financial stress is associated with the prevalence of metabolic syndrome: A cross-sectional analysis using Wisconsin Sleep Cohort

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Abstract

Background: Occupational stress and perceived general stress have been shown to be associated with metabolic abnormalities, but the effects of other sources of stress and the role of perceived health in the stress-metabolism relationship remain unclear. **Purpose:** To examine whether different sources of stress influence metabolic outcomes differently, and whether perceived health mediates the relationship between stress and metabolic syndrome. **Method:** A cross-sectional study was conducted using data from the Retirement and Sleep Trajectories (REST) study, an ancillary study of the Wisconsin Sleep Cohort (WSC) Study (N=407 adults, mean [SD] age = 64 [7] years, 45% female). The associations among different sources of stress, perceived physical/mental health, and metabolic outcomes were estimated using structural equation modeling. **Results:** Controlling for age, comorbidity, and lifestyle behaviors, one standard deviation (SD) increase in financial stress was associated with 52% higher odds of abdominal obesity ($p<0.001$), 50% higher odds of metabolic syndrome ($p=0.001$), and 42% higher odds of dyslipidemia ($p=0.009$). Perceived physical health fully mediated the relationship between financial stress and the prevalence of abdominal obesity (indirect effect [$\beta^*=0.536$; $p<0.019$]) and metabolic syndrome (indirect effect [$\beta^*=0.523$; $p<0.028$]). **Conclusion:** Financial stress is associated with a greater prevalence of metabolic syndrome. Perceived physical health might provide a preclinical factor to help clinicians to assess the risk of metabolic syndrome in financially stressed adults.

1. Introduction

In the last 10 years, the overall prevalence of metabolic syndrome in the U.S. increased from 25% to 34% (Aguilar, Bhuket, Torres, Liu, & Wong, 2015; Moore, Chaudhary, & Akinyemiju, 2017). The term, metabolic syndrome, is used to characterize a unique clustering of metabolic abnormalities, which include hypertension, Type 2 Diabetes Mellitus (T2DM), dyslipidemia, and abdominal obesity. This clustering pattern makes untreated metabolic syndrome a major determinant of cardiovascular diseases and gastrointestinal cancers, the two leading causes of death in the U.S. (Heron & Anderson, 2016; Hulten et al., 2017; Juo et al., 2018).

Theoretical models attribute the increasing prevalence and severity of metabolic syndrome to the stress-metabolism pathway, commonly referred to as allostatic load (Beckie, 2012; Karatsoreos & McEwen, 2011). Although this stress-metabolism pathway appears to be consistent, previous studies aimed at determining the specific impact of stress on a specific chronic illness or related alterations in metabolic biomarkers showed that the impact of stress can vary (Cosgrove, Sargeant, Caleyachetty, & Griffin, 2012; M. Kivimaki, Singh-Manoux, Nyberg, Jokela, & Virtanen, 2015; Sui et al., 2016; Tenk et al., 2018). Specifically, the major findings of recent systematic reviews led researchers to draw conclusions that psychological stress is associated with weight gain, abdominal obesity, and metabolic syndrome (M. Kivimaki et al., 2015; Tenk et al., 2018), while there is no significant association between psychological stress and T2DM (Cosgrove et al., 2012; Sui et al., 2016). By showing that the allostatic load of psychological stress in metabolic biomarkers could be illness specific, these findings question a central premise of the stress-metabolism model: is the metabolic impact, or allostatic load, of psychological stress greater on lipid metabolism and adipose tissue than glucose metabolism?

Allostatic load refers to the physiological changes, where psychological stress chronically influences metabolism, that is mediated by chronic inflammation (Beckie, 2012; Karatsoreos & McEwen, 2011). The stress-induced chronic inflammation is often observed through the elevated levels of inflammatory biomarkers, including C-reactive protein (CRP), cytokine interleukin (IL)-6,

cytokine tumor necrosis factor alpha (TNF-α), and pro-inflammatory transcription factor NF-κB (Black & Slavich, 2016; Epel et al., 2016; Miller et al., 2008). Recently, an area of research has been focusing on whether perceived health, as a subjective measure, reflects objective physiological biomarkers, predicts future risk of chronic illness, and summarizes health profile in a way that goes beyond the continuum of biomedical model (Arnberg, Lekander, Morey, & Segerstrom, 2016; Garvin, Nilsson, Ernerudh, & Kristenson, 2016). For instance, researchers found that lower levels of perceived health in middle-aged and older adults could be a stable trait reflecting chronic inflammation, in particular IL-6 and CRP (Arnberg et al., 2016; Garvin et al., 2016). Furthermore, a recent longitudinal study revealed that perceived physical health predicted the incidence of obesity and insulin resistance over 10 years of follow-up (Ylitalo et al., 2016). These findings prompt the hypothesis that perceived health, in physical and mental domains, might be a preclinical sign of metabolic abnormalities in stressed adults. However, when examining the stress-metabolism relationship, researchers have predominantly recognized perceived health as an outcome of metabolic abnormalities, including T2DM (Wu et al., 2018), obesity (Amiri et al., 2018), metabolic syndrome (Rani, Kumar, & Krishan, 2018), and hypertension (Trevisol, Moreira, Kerkhoff, Fuchs, & Fuchs, 2011). To date, it is still unclear whether perceived health mediates the relationship between psychological stress and metabolic abnormalities and precedes the pathological path of metabolic abnormalities.

Middle-aged and older adults encounter different sources of stress (e.g., financial difficulty or occupational stress), that might have varied impacts on metabolic outcomes (Bergmann et al., 2017; Mika Kivimaki & Steptoe, 2018). For instance, studies found that the frequency of financial life events might be more metabolically detrimental than the frequency of family life events (Pyykkonen et al., 2010; Rutters et al., 2014). However, these findings were solely based on life event checklists, without comparing other chronic stressors. Within the existing literature, chronic stress is often measured by perceived stress scales or single-source instruments, such as occupational stress (M. Kivimaki et al., 2015; Tenk et al., 2018). It remains unanswered whether

other sources of stress (e.g., financial stress and interpersonal stress) yield a similar influence on metabolic outcomes or not.

Therefore, the purpose of this study was to investigate the relationships between different sources of stress and metabolic outcomes and the role of perceived health in these relationships. We hypothesized that different sources of stress influence adults' perception of physical and mental health in ways that can alter metabolic outcomes (see Figure 3.1.).

2. Method

2.1. Study Design, Sample, and Setting

This is a cross-sectional study using the data from the Retirement and Sleep Trajectories (REST), an ancillary study of the Wisconsin Sleep Cohort (WSC) study. The WSC study is an ongoing longitudinal study of sleep habits and sleep disorders in adults followed prospectively since 1988. The design of the WSC has been described previously (Peppard et al., 2013; Young et al., 2008). Briefly, participants in the WSC were selected from a random sampling pool of payroll records for State of Wisconsin employees aged between 30 and 60 years old in 1988. Among the 2940 individuals invited to undergo a baseline overnight assessment in the laboratory, 1546 subjects participated. The cohort was then followed up with approximately every 4 years, but the dates of in-laboratory assessment varied depending on the schedule of each participant (Tattersall et al., 2016). The REST study is a longitudinal study consisting of four annual mailed surveys that collected information regarding stress, health behaviors, sleep, health status, and other factors. Participants of the REST study were chosen from the sampling frame of the WSC in 2010. Individuals were eligible for the REST study if they completed either 3 WSC mailed surveys or 1 WSC in-laboratory study protocol and 1 WSC survey (n = 1,164).

The present study included 455 participants who completed the first wave of REST surveys (2010-2011) and completed a WSC in-laboratory assessment after the first wave of REST surveys (See Figure 3.2.). The University of Wisconsin-Madison health sciences institutional review board (IRB) approved this study.

2.2. Measures

2.2.1. Outcomes

The metabolic outcomes of interest included metabolic syndrome, hypertension, T2DM, dyslipidemia, and abdominal obesity. Participants with metabolic abnormalities were identified through in-laboratory assessment of metabolic biomarkers, including waist circumference, resting blood pressure, and blood tests that measured fasting glucose, triglycerides, and high-density lipoprotein cholesterols (HDL). Medication reconciliation was performed through individual interviews and pill-bottle assessments to identify participants who controlled blood pressure, cholesterols, triglycerides, and glucose with prescribed medication. Diagnosis criteria were based on current clinical guidelines provided by the American Heart Association (AHA), the American Diabetes Association (ADA), and the World Health Organization (WHO) (see Table 3.1.).

2.2.2. Exposures

To examine different sources of stress, we assessed the most common sources of stress that middle-aged and older adults often encounter, including financial stress, occupational stress, family stress, networking stress, and life events, through mail surveys from the REST study.

Financial stress was assessed by a financial stress scale used in the "Midlife in the United States" (MIDUS) study (Elliot & Chapman, 2016). This scale contained three questions regarding a respondent's current financial situation, ability to pay monthly bills, and ability to meet life necessities. The respondent's current financial situation was evaluated using an 11-point Likert Scale, ranging from 0 (best) to 10 (worst). The ability to pay monthly bills was assessed using a 4-point Likert Scale, ranging from 1 (not at all difficult) to 4 (very difficult), while the ability to meet life necessities was assessed using a 3-point Likert Scale, ranging from 1 (money more than you need) to 3 (not enough money). The standardized Cronbach's alpha is 0.82 in the present study, indicating a good internal consistency.

Life event stress was assessed using a 20-item Life-Changing Event Scale, adapted from the Louisville Older Persons Event Scale (LOPES), originally developed by Murrell et al. (Murrell

& Norris, 1984; Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003). All items have been shown to be major stressors in older adults. The participants evaluated the occurrence and stressfulness of these life events during the past 12 months (0=not occurred; 1=not at all stressful; 2=a little stressful; 3=somewhat stressful; 4=very stressful; and 5=extremely stressful). The scale was summarized as the frequency of life events that were somewhat stressful, very stressful, or extremely stressful (Pyykkonen et al., 2010). The Cronbach's alpha is 0.70 in the present study, indicating a moderate internal consistency.

Occupational stress was assessed by one item using a 4-point Likert Scale, ranging from 1 (not very stressful) to 4 (very stressful). Participants indicated how stressful has their day-to-day work situation been. The participants in the current sample were either full-time or part-time employees. Similar items, used in previously published studies, indicate good predictive validity for work related stress (Arapovic-Johansson, Wahlin, Kwak, Bjorklund, & Jensen, 2017; Salminen, Kouvonen, Koskinen, Joensuu, & Vaananen, 2014).

Family stress and networking stress were measured using the family strain and networking strain scales from the Relationship Strain Scale, developed by Schuster and colleagues (Schuster, Kessler, & Aseltine, 1990). Participants indicated how often their family members and friends "make too many demands on you," "criticize you," "let you down when you are counting on them," and "get on your nerves." Items were rated on a 4-point Likert scales ranging from 1 (often) to 4 (never). The internal consistency was moderate, with Cronbach's alpha equal to 0.77 in family strain scale and 0.78 in networking strain scale (Brooks et al., 2014).

2.2.3. Mediators

Mediators included perceived physical health and perceived mental health, which were measured by the SF-36 during in-laboratory assessment. Perceived physical health was based on 4 subscales: physical functioning, role-physical, bodily pain, and general health. Perceived mental health was based on 4 subscales: vitality, social functioning, role-emotional, and mental health (Ware, Kosinski, & Keller, 2001). The response options range from 3 (for physical health) to 6 (for

vitality and mental health). The SF-36 was summarized into perceived physical and perceived mental health, by summing factor-weighted scores across all 8 subscales, with factor weights derived from a US-based general population sample. Cronbach's alpha reliabilities for the subscales ranged from 0.73 to 0.93 (mean 0.85) in a primary care setting of adults with similar demographics to those participating in the WSC study (Brazier et al., 1992; Ware et al., 2001).

2.2.4 Covariates

Age, numbers of comorbidities, physical activity (metabolic equivalent [MET-hour/week]), alcohol consumption (number of drinks/week), and cigarette smoking status (current smoker or not) were controlled in the data analysis, because these five factors are contributory to metabolic abnormalities, as noted in the literature. Comorbidities included cancer, myocardial infarction, heart failure, Parkinson's disease, Alzheimer's disease, Glaucoma, restless legs syndrome, emphysema, chronic obstructive disease, and kidney disease (Plante, Finn, Hagen, Mignot, & Peppard, 2017). Lastly, because the exposure variables (different sources of stress) and outcome variables (metabolic biomarkers) were collected at different time points, the duration between the occurrence of exposure variables (REST mailed survey) and the occurrence of outcome variables (WSC in-laboratory assessment) was transformed into days and modeled as the confounding variable. Information regarding dietary intake and family history of each metabolic abnormalities was not available in this dataset.

2.3. Statistical Analyses

The descriptive statistics for the exposures, mediators, and outcomes were calculated. SAS software (Version 9.4, 2013) and Mplus software (Muthén & Muthén, 1998-2017) were used for managing missing data and statistical analyses. All reported p-values were two-tailed with p-values less than 0.05 considered as significant.

Among the 455 eligible participants, 48 participants were excluded due to missing more than 25% of data in stress instruments and SF-36, which left 407 participants for missing-pattern diagnosis and data analyses. The missing patterns were diagnosed using PROC MI in SAS to

confirm that missing values in Y ($Y_{missing}$) were not associated with the measured variables (Y), and rule out the possibility of missing not at random (MNAR). We then performed multiple imputations based on the fully conditional method (FCS), which imputed each missing value based on a separate conditional distribution due to the ordinal variables (Liu & De, 2015).

We used two-phase SEM to examine whether the probability of developing each metabolic abnormality varies among different sources of stress. For the measurement (first) phase, we used Composite Indicator Structural Equation (CISE) alpha modeling because the exposure variables (except occupational stress) and mediators in the present study were composite variables based on self-report instruments. To account for measurement error, we built a measurement error term into each composite variable based on the reliability estimates derived from the following formula: ([1 - Cronbach's alpha of the instruments] x variance of composite variable) (McDonald, Behson, Seifert, & Jaccard, 2005).

In the structural (second) phase, all the outcome variables were binary so we estimated Probit models using weighted least squares mean and variance (WLSMV), and estimated the standardized coefficient and 95% confidence interval (CI) for each exposure variable. WLSMV is a robust estimation for ordinal variables since it does not assume normal distribution (Brown, 2014; Li, 2016). To examine whether perceived physical health and perceived mental health mediated the associations between different sources of stress and metabolic abnormalities, we used two-phase SEM following MacKinnon's mediation process (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). To report mediation effect, we estimated the direct, indirect, and total effects using the probit coefficient, 95% CI, standardized probit coefficient, and odds ratio. For the significant total effects, we transformed probit coefficients to probability values for the binary outcome variables based on the following formula: $P(u=1 \mid x)= F(-threshold + b*x)$. We then plotted the probability curves to indicate the probability of having a specific metabolic abnormality given the specific sources of stress (Muthén & Muthén, 1998-2010). To ensure the estimated model is reasonably consistent with the current sample, we used McKelvey and Zavoina Pseudo

R^2 as the goodness-of-fit index, because the outcome variables were binary (McKelvey & Zavoina, 1975). The McKelvey and Zavoina Pseudo R^2 were assessed via the R^2 for each outcome variable based on the probit model (with WLSMV) in Mplus.

3. Results

3.1. Sample Characteristics and Prevalence of Metabolic Abnormalities

Among the 407 participants, 262 (64%) participants had metabolic syndrome, 310 (76%) had hypertension, 77 (19%) had T2DM, 274 (67%) had dyslipidemia, and 256 (63%) had abdominal obesity. The sample characteristics are presented in Table 3.2.

3.2. Influence of Different Sources of Stress on Metabolic Outcomes

As shown in Table 3.3., financial stress was significantly associated with the prevalence of abdominal obesity (β=0.343; 95% CI= [0.192, 0.494]; p<0.001), metabolic syndrome (β=0.332; 95% CI= [0.172, 0.492]; p=0.001), and dyslipidemia (β=0.281; 95% CI= [0.105, 0.457]; p=0.009), after controlling for age, number of comorbidities, alcohol consumption, current smoking status, and physical activity levels. The standardized results showed that one standard deviation (SD) increase in financial stress increased the odds of abdominal obesity by 52%, metabolic syndrome by 50%, and dyslipidemia by 42%. However, financial stress was not associated with the prevalence of hypertension (p=0.317) and T2DM (p=0.124). In addition to financial stress, family stress (β=0.116; p=0.019) and stressful life events (β=-0.158; p=0.012) were also significantly associated with the prevalence of dyslipidemia, but the effects were relatively small. Occupational stress and networking stress were not associated with any type of metabolic abnormalities. Pseudo R^2 suggested a reasonable model fit, where the model with five sources of stress explained 11% of the variance in hypertension, 18% of the variance in T2DM, 18% of the variance in dyslipidemia, 21% of the variance in abdominal obesity, and 21% of the variance in metabolic syndrome. The covariance and p-value among the five sources of stress are reported in Table 3.4.

3.3. Mediation Effects of Perceived Physical Health in the Stress-Metabolism Relationship

As shown in Table 3.5., perceived physical health fully mediated the relationship between financial stress and the prevalence of abdominal obesity, with a significant indirect effect (β=0.536; 95%CI= [0.161-0.911]; p=0.019). Similarly, perceived physical health fully mediated the relationship between financial stress and the prevalence of metabolic syndrome, with a significant indirect effect (β=0.525; 95%CI= [0.128-0.921]; p=0.029). Perceived mental health did not mediate the relationship between financial stress and the prevalence of metabolic abnormalities. The Pseudo R^2 suggested that this mediational model had better model fit than the model without mediators. Specifically, the mediational model with five sources of stress and perceived physical/mental health explained 32% of the variance in hypertension, 36% of the variance in T2DM, 25% of the variance in dyslipidemia, 56% of the variance in abdominal obesity, and 57% of the variance in metabolic syndrome. Figure 3.3. illustrates the relationships between five sources of stress and metabolic abnormalities, as well as the mediation effect estimated by CISE-alpha modeling. Figure 3.4. shows the probabilities of having abdominal obesity (p<0.001), metabolic syndrome (p=0.001), and dyslipidemia (p=0.008), given the composite score of financial stress based on the significant total effects estimated from the mediation model.

4. Discussion

In this cohort of middle-aged and older adults, we observed a high prevalence of metabolic abnormalities, including hypertension, metabolic syndrome, T2DM, dyslipidemia, and abdominal obesity. Prior evidence suggested that psychological stress increases the risk of developing metabolic abnormalities (Bergmann et al., 2017; Tenk et al., 2018). The present study adds to the body of literature by further examining this association across different sources of stress with different types of metabolic abnormalities. In this cross-sectional analysis, we found that financial stress was significantly associated with the prevalence of abdominal obesity, dyslipidemia, and metabolic syndrome, but we found no relationship between stress, from any source, and T2DM

or hypertension. This result is consistent with previous literature reviews, suggesting that psychological stress might have more direct impacts on lipid metabolism, but less direct impacts on glucose metabolism (Bergmann et al., 2017; Cosgrove et al., 2012; Sui et al., 2016; Tenk et al., 2018).

In the present study, financial stress was strongly associated with the prevalence of metabolic syndrome, abdominal obesity, and dyslipidemia, while other sources of stress were not. This finding is in line with previous studies suggesting that the frequency of financial life events is associated with the odds of metabolic syndrome, while the frequency of family life events and health issues are not significant (Pyykkonen et al., 2010; Rutters et al., 2014). Older adults coping with financial difficulty are more likely to use Medicare. Unfortunately, Medicare currently only reimburses the cost of lipid test very five years (American College of Obstetricians and Gynecologists, 2018). Our findings highlight the urgency and importance for agency to conduct longitudinal risk analysis and reconsider whether older adults under Medicare need to have more frequent screenings for hyperlipidemia.

We found significantly positive covariance among the five sources of stress (Table 3.4.). It is possible that one source of stress might proliferate into secondary and tertiary sources. Stress proliferation refers to a phenomenon where one stressor could lead to other stressors and entrap an individual in a vulnerable condition with higher risk of comorbidity and mortality, known as the stress process (Pearlin, 2010; Wheaton, Young, Montazer, & Stuart-Lahman, 2013). According to Stress Process Model, although coping mechanisms and social support could potentially modify one's stress process, disadvantaged socioeconomic status has been shown to limit one's access to these moderators and exacerbate the stress proliferation process (Avison, Aneshensel, Schieman, & Wheaton, 2009; Kahn & Pearlin, 2006). In this cohort, occupational stress was not directly associated with metabolic outcomes. We speculated that several exogenous factors (e.g., coping resources or dietary choices) might attenuate the effects of occupational stress on metabolic outcomes, and financial stress could have limited adults' access to these exogenous

factors (Glazer & Liu, 2017). Stress proliferation likely is one of the several poorly understood factors and mechanisms underpinning the relationship between financial stress and metabolic syndrome. Large-scale prospective studies are needed to unveil the phenomenon of stress proliferation in financially stressed adults and its long-term effects on metabolic outcomes.

The underlying mechanisms in the relationship between financial stress and metabolic syndrome are complex. In this sample, our cross-sectional analysis indicates that this relationship could be mediated by lower levels of perceived physical health. Future longitudinal study is highly needed to establish this mediation relationship with causal inference. In adults with financial stress, lower levels of perceived physical health might be a preclinical sign highlighting the potential of metabolic syndrome. When older adults who are having difficulty coping with financial stress reported lower perceived physical health, this self-report might signal the onset of increased risk of metabolic syndrome. Although our findings strengthen the assumption that perceived physical health might be a stable psychological correlate of chronic metabolic inflammation (Arnberg et al., 2016; Garvin et al., 2016), our findings alone are not sufficient evidence to draw such a conclusion. It is also possible that stress reshapes adults' "perception" toward their physical health, rather than their actual physical health. For instance, prior studies found that adults experiencing psychological stress are more likely to perceive frequent fatigue or higher levels of pain responses under similar pain stimuli (Maghout-Juratli, Janisse, Schwartz, & Arnetz, 2010; McEwen & Kalia, 2010). Shafir, Mullainathan, and Shan also proposed the Scarcity Mindset Hypothesis, explaining that the long-term exposure to financial stress alters adults' perception about what they need most and what they should prioritize (Shah, Mullainathan, & Shafir, 2012). It is possible that adults with financial stress tend to perceive lower levels of physical health, but they often put financial needs, instead of physical health, as their priority (Shah, Shafir, & Mullainathan, 2015). Consequently, financially stressed adults could be more vulnerable to food deserts, in the situation where people living in economically depressed areas often lack access to sources of healthy nutrition. Meanwhile, this population might be more physically inactive or have lower sleep quality due to

the decline in perceived physical health. Prospective studies with better measures of perception and inflammatory biomarkers are highly needed to examine this paradox in human perception under stress and interpret the physiological pathways in the stress-metabolism relationship.

The strengths of the present study include a relatively large sample size, incorporating five metabolic indicators, and assessing multiple sources of psychological stress that middle-aged and older adults often encounter. However, the present study also has limitations. First, due to the cross-sectional and observational nature of the study, causal inference and recursive relationships between the exposure and outcome variables cannot be concluded. However, there is still a sequential order between our predictors and outcomes. Specifically, based on the study design, the exposure variables were assessed during the REST surveys, while outcome variables were assessed during the WSC in-laboratory visits, which occurred after the REST surveys to ensure a logical sequential order. Second, the present study used a single item to assess occupational stress, instead of more comprehensive occupational stress questionnaire. Nevertheless, prior studies have shown good validity by using this single item to assess occupational stress (Arapovic-Johansson et al., 2017; Salminen et al., 2014). Third, in order to include all participants with different marital statuses (e.g., single, divorced, separated, or married), the family stress in the present study did not take any spousal/partner relationship into consideration. Thus, the family stress in the present study only referred to the direct and indirect family members, such as siblings, children, parents, or extended family members. Finally, the current sample is based on WSC, which featured less racial diversity (97% of participants were white) (Young et al., 2008). While the current sample represents the diverse socioeconomic status in a white population, caution should be taken when generalizing the results to other racial/ethnic backgrounds.

5. Conclusion

In middle-aged and older adults, financial stress is associated with abdominal obesity, metabolic syndrome, and hyperlipidemia. Perceived physical health might provide a preclinical

factor to help clinicians to assess the risk of metabolic syndrome in financially stressed adults. Large prospective studies are highly needed to examine what are the underlying mechanisms explaining financially stressed adults' perception of physical health, decision making on health behaviors, and risk of metabolic syndrome.

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7. Tables

Table 3.1. *Current guideline for metabolic outcomes in present study*

Metabolic outcomes	Criteria	Guidelines
MetS	At least three of the criteria below: • BP ≥ 130/85 mmHg or medicated • FPG ≥ 100 mg/dL or medicated • TG ≥ 150 mg/dL or medicated • HDL < 40 (males), <50 (females) • WC > 40 (males), >35 (females)	NCEP-ATP III, NHLBI, AHA
Hypertension	BP ≥ 130/80 mmHg or medicated	JNC 7, AHA
T2DM	FPG ≥ 126 mg/dL or medicated	ADA
Dyslipidemia	Any one of the criteria below: • TG ≥ 150 mg/dL or medicated • HDL < 40 (males), <50 (females)	NCEP-ATP III, NHLBI, AHA
Abdominal obesity	WC > 40 (males), >35 (females)	WHO

Note. MetS=Metabolic Syndrome. T2DM=Type 2 diabetes Mellitus. BP=Blood pressure. FPG=Fasting plasma glucose. TG=Triglycerides. HDL=High-density lipoprotein. WC=Waist circumference. NCEP-ATP III=National Cholesterol Education Program, Adult Treatment Panel III. AHA=American Heart Association. JNC 7=The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. ADA=American Diabetes Association. WHO=World Health Organization.

Table 3.2. *The demographic, psychological, and metabolic characteristics of the study sample*

Characteristics	N=407
Age, mean (SD)	63.9 (6.77)
Sex (% male)	55%
Race (% white)	97%
Education (%)	
High school or less	19%
Some college	32%
College or more	49%
Health insurance (%)	98%
BMI, mean (SD)	31.27 (6.94)
Number of comorbidities (%)	
None	66%
One	27%
Two or more	7%
Alcohol per week (drinks), mean (SD)	3.95 (5.58)
Current smoker (%)	7%
Physical activity (MET-hour/week), mean (SD)	23.8 (31.4)
HTN (%)	76%
T2DM (%)	19%
Abdominal obesity (%)	63%
Dyslipidemia (%)	67%
Metabolic syndrome (%)	64%
Occupational stress, mean (SD)	2.48 (0.96)
Networking stress, mean (SD)	7.37 (1.90)
Family stress, mean (SD)	8.33 (2.37)
Financial stress, mean (SD)	
Paying bills	1.72 (0.77)
Paying life necessities	1.77 (0.59)
Current financial strain	3.24 (1.73)
Stressful life events, mean (SD)	1.29 (1.71)
Perceived physical health, mean (SD)	48.16 (9.47)
Perceived mental health, mean (SD)	54.63 (8.11)

Table 3.3. *The relationship between the five sources of stress and metabolic abnormalities*

Direct Effect Path	Unstandardized			Standardized		
	Probit*	95% CI	OR	Probit*	OR	P-value
Financial stress (FS)						
FS → HTN	0.102	[-0.066, 0.269]	1.19	0.074	1.13	0.317
FS → T2DM	0.185	[-0.013, 0.382]	1.37	0.132	1.25	0.124
FS → AO	0.343	[0.192, 0.494]	1.79	0.246	1.52	<0.001
FS → MetS	0.332	[0.172, 0.492]	1.76	0.240	1.50	0.001
FS → Dyslipidemia	0.281	[0.105, 0.457]	1.61	0.208	1.42	0.009
Occupational stress (OS)						
OS → HTN	-0.043	[-0.170, 0.085]	0.93	-0.037	0.94	0.581
OS → T2DM	-0.106	[-0.237, 0.025]	0.84	-0.089	0.86	0.182
OS → AO	-0.083	[-0.200, 0.035]	0.87	-0.070	0.89	0.246
OS → MetS	-0.103	[-0.224, 0.017]	0.84	-0.088	0.86	0.158
OS → Dyslipidemia	-0.094	[-0.217, 0.029]	0.85	-0.082	0.87	0.208
Family stress (FAS)						
FAS → HTN	0	[-0.095, 0.095]	1.00	0.000	1.00	0.998
FAS → T2DM	-0.018	[-0.100, 0.065]	0.97	-0.032	0.95	0.725
FAS → AO	-0.071	[-0.153, 0.012]	0.89	-0.131	0.80	0.158
FAS → MetS	0.061	[-0.019, 0.141]	1.11	0.113	1.21	0.212
FAS → Dyslipidemia	0.116	[0.035, 0.197]	1.22	0.222	1.46	0.019
Networking stress (NES)						
NES → HTN	0.021	[-0.068, 0.111]	1.04	0.033	1.06	0.694
NES → T2DM	0.069	[-0.024, 0.162]	1.12	0.106	1.20	0.221
NES → AO	0.095	[0.011, 0.180]	1.18	0.147	1.28	0.064
NES → MetS	0.084	[-0.003, 0.171]	1.15	0.130	1.25	0.112
NES → Dyslipidemia	0.064	[-0.025, 0.153]	1.11	0.102	1.19	0.236
Stressful life events (SLE)						
SLE → HTN	-0.015	[-0.144, 0.114]	0.97	-0.019	0.97	0.849
SLE → T2DM	-0.08	[-0.172, 0.012]	0.87	-0.101	0.84	0.154
SLE → AO	0.017	[-0.097, 0.131]	1.03	0.022	1.04	0.808
SLE → MetS	-0.117	[-0.225, -0.008]	0.82	-0.150	0.77	0.076
SLE → Dyslipidemia	-0.158	[-0.262, -0.055]	0.76	-0.208	0.70	0.012

Note. HTN=Hypertension. T2DM=Type 2 Diabetes Mellitus. AO=Abdominal obesity. MetS=Metabolic syndrome. PPH=Perceived physical health. PMH=Perceived mental health. 95% CI=95% confidence interval. OR=Odds ratio. *Age, number of comorbidities, alcohol consumption, current smoking status, and physical activity levels were controlled as covariates in this model.

Table 3.4. *The covariance among the five sources of stress*

	Covariance	P-value
FS-OS	0.104	0.003
FS-SLE	0.370	<0.001
FS-NES	0.037	0.529
FS-FAS	0.207	0.016
OS-SLE	0.271	0.001
OS-NES	0.157	0.05
OS-FAS	0.196	0.06
SLE-NES	0.500	<0.001
SLE-FAS	1.166	<0.001
NES-FAS	1.480	<0.001

Note. FS=Financial stress; OS=Occupational stress; SLE=Stressful life events; NES=Networking stress; FAS=Family stress.

Table 3.5. *The mediation effects of perceived physical/mental health in the relationship between financial stress and metabolic outcomes with direct effect, indirect effect, total indirect effect, and total effect paths.*

	Probit estimates*	95% CI	P-value	Standardized Probit estimate*	Standardized OR
Direct effect paths					
FS→HTN	-0.299	[-0.725, 0.127]	0.249	-0.218	0.690
FS→T2DM	-0.202	[-0.610, 0.207]	0.417	-0.144	0.783
FS→AO	-0.191	[-0.592, 0.210]	0.433	-0.137	0.792
FS→MetS	-0.188	[-0.606, 0.231]	0.461	-0.136	0.794
FS→Dyslipidemia	0.112	[-0.278, 0.502]	0.637	0.083	1.152
Indirect effect paths					
FS→PPH→HTN	0.402	[0.026, 0.777]	0.079	0.293	1.646
FS→PPH→T2DM	0.39	[0.048, 0.731]	0.061	0.279	1.607
FS→PPH→AO	**0.536**	**[0.161, 0.911]**	**0.019**	**0.385**	**1.924**
FS→PPH→MetS	**0.525**	**[0.128, 0.921]**	**0.029**	**0.379**	**1.905**
FS→PPH→Dyslipidemia	0.174	[-0.146, 0.495]	0.37	0.129	1.245
FS→PMH→HTN	0	[-0.010, 0.010]	0.967	0	1.000
FS→PMH→T2DM	0	[-0.006, 0.006]	0.971	0	1.000
FS→PMH→AO	0	[-0.006, 0.006]	0.968	0	1.000
FS→PMH→MetS	-0.001	[-0.044, 0.042]	0.965	-0.001	0.998
FS→PMH→Dyslipidemia	-0.001	[-0.053, 0.051]	0.965	-0.001	0.998
Total indirect effect paths					
FS→HTN	0.401	[0.026, 0.777]	0.078	0.293	1.646
FS→T2DM	0.389	[0.048, 0.731]	0.061	0.279	1.607
FS→AO	**0.536**	**[0.160, 0.912]**	**0.019**	**0.386**	**1.927**
FS→MetS	**0.523**	**[0.131, 0.916]**	**0.028**	**0.378**	**1.901**
FS→Dyslipidemia	0.173	[-0.149, 0.495]	0.376	0.128	1.243
Total effect paths					
FS→HTN	0.103	[-0.067, 0.272]	0.319	0.075	1.136
FS→T2DM	0.188	**[-0.011, 0.387]**	0.12	0.135	1.258
FS→AO	**0.345**	**[0.192, 0.499]**	**<0.001**	**0.248**	**1.524**
FS→MetS	**0.336**	**[0.173, 0.498]**	**0.001**	**0.243**	**1.511**
FS→Dyslipidemia	**0.285**	**[0.107, 0.463]**	**0.008**	**0.211**	**1.431**

Note. FS=Financial stress. HTN=Hypertension. T2DM=Type 2 Diabetes Mellitus. AO=Abdominal obesity. MetS=Metabolic syndrome. PPH=Perceived physical health. PMH=Perceived mental health. 95% CI=95% confidence interval. OR=Odds ratio. *****Age, number of comorbidities, alcohol consumption, current smoking status, and physical activity levels were controlled as covariates in this model.

8. Figures

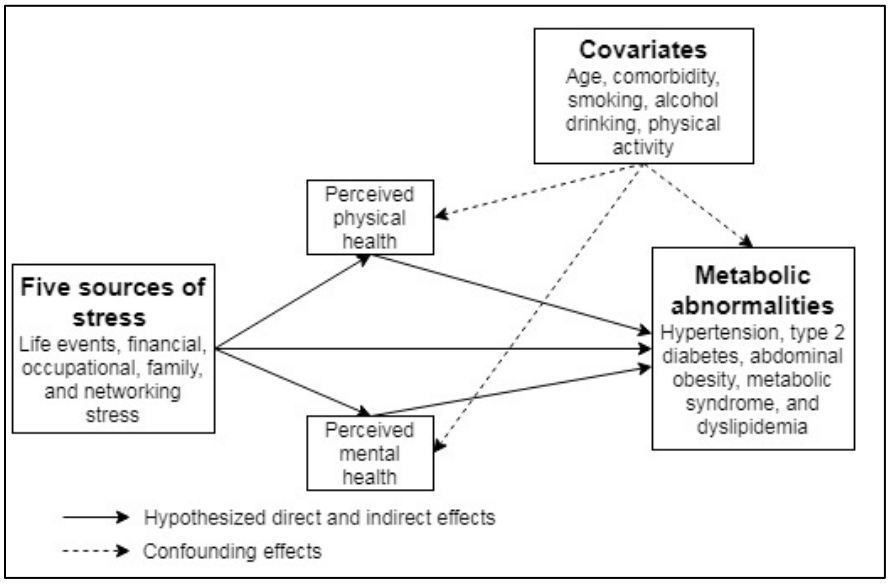

Figure 3.1. The hypothesized direct and indirect effects of perceived physical health and perceived mental health on the relationship between different sources of stress and metabolic outcomes.

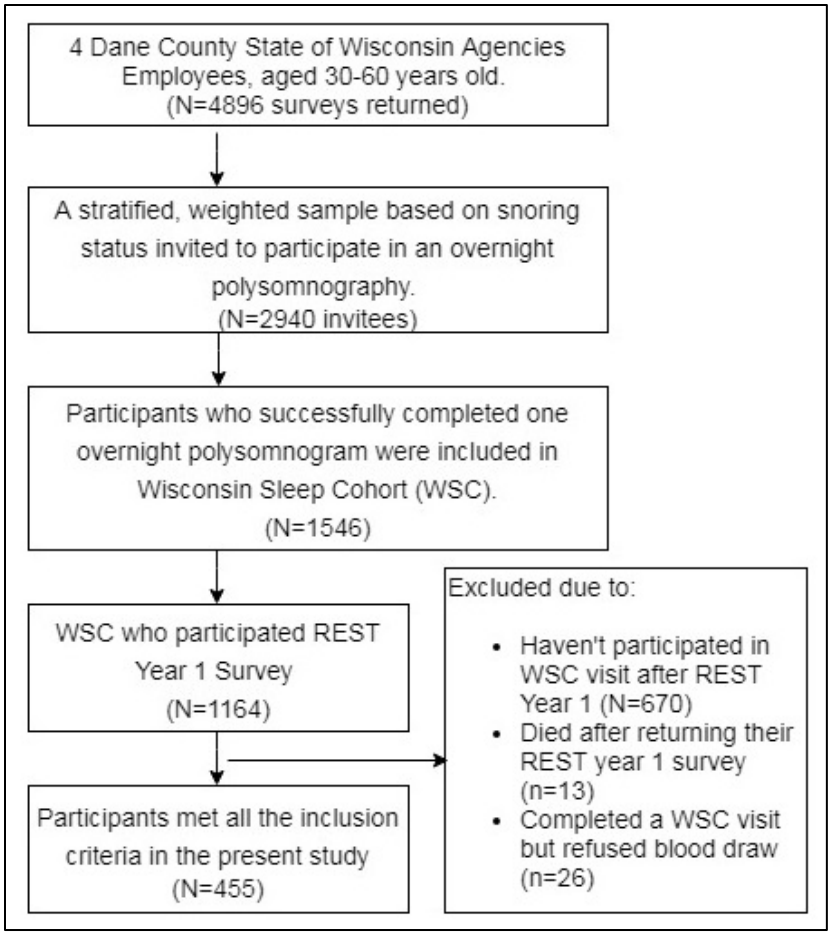

Figure 3.2. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement: Flow chart of the sample size in present study.

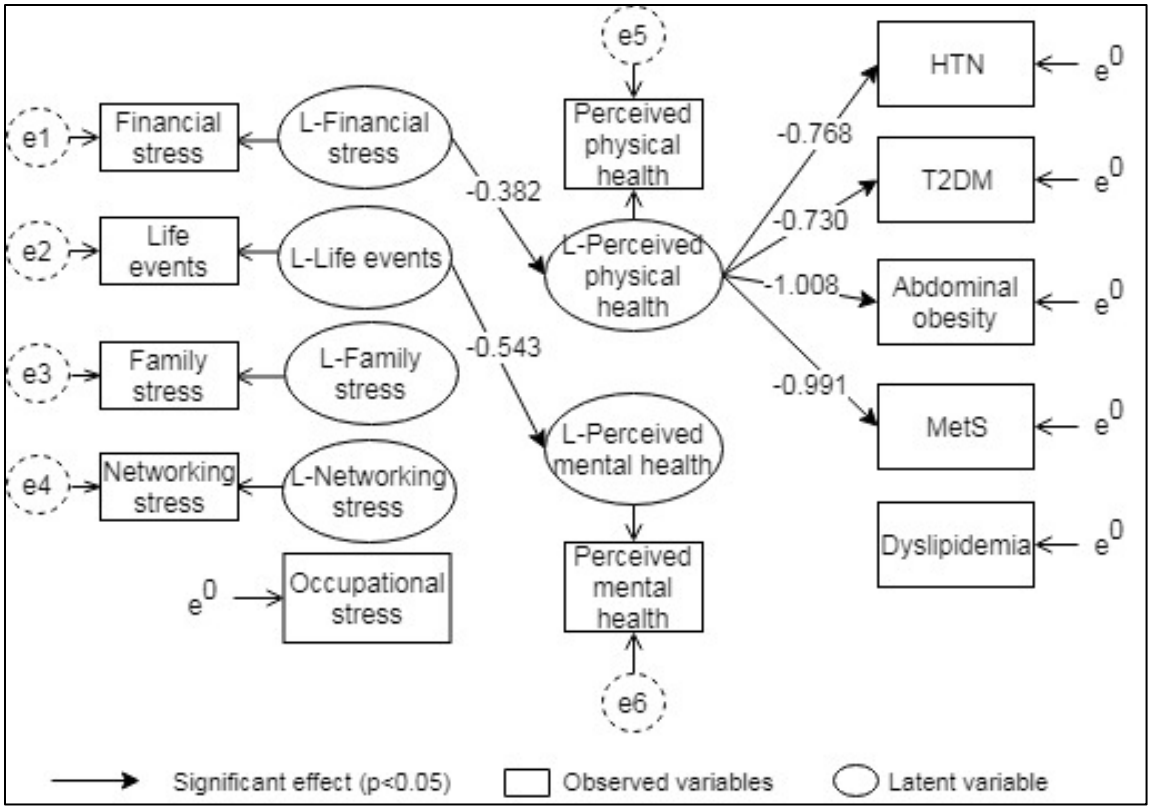

Figure 3.3. The relationships among exposures, mediators, and outcomes estimated by CISE-Alpha Modeling with significant standardized probit coefficients.

Note. The variance of **e1**, **e2**, **e3**, **e4**, **e5**, and **e6** were fixed to equal to ([1 - Cronbach's alpha] x variance of composite variable). The measurement error represented by $\mathbf{e^0}$ was assumed to be zero. Age, number of comorbidities, alcohol consumption, current smoking status, and physical activity levels were controlled as covariates in this model.

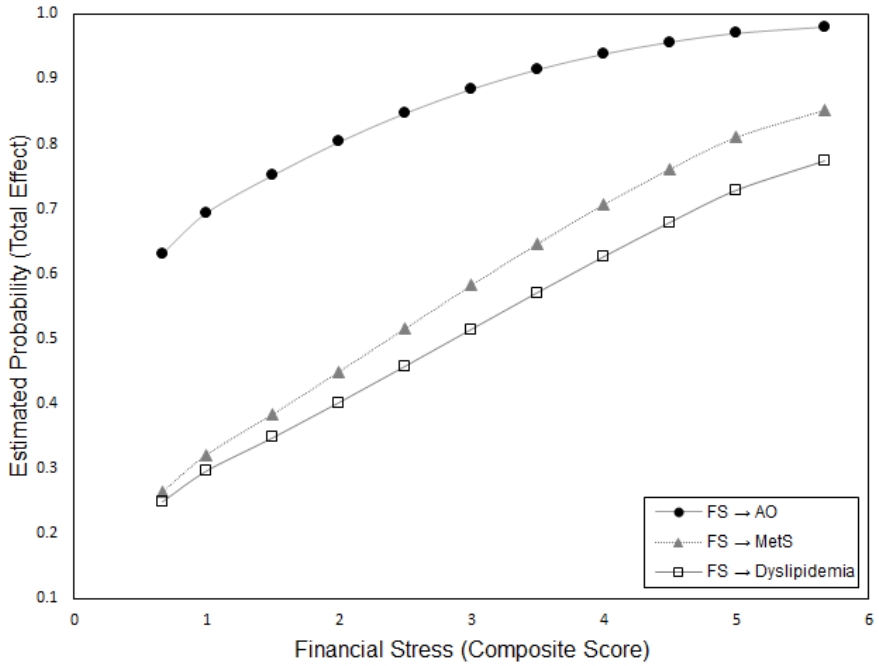

Figure 3.4. For the significant total effects estimated from the mediation model, we plotted the probability curves to present the probabilities of having abdominal obesity (p<0.001), metabolic syndrome (p=0.001), and dyslipidemia (p=0.008), given the composite score of financial stress. *Note.* AO=Abdominal obesity.

Chapter 4

Manuscript 3:

Sleep Duration and Insomnia Moderate the Relationship between Financial Stress and Metabolic Syndrome

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Financial stress; insomnia; sleep duration; metabolic syndrome

Running title:
Financial stress and sleep health

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Abstract

Background: Financial stress has been identified as a potential risk factor for metabolic syndrome. Recent evidence also suggests that sleep curtailment and insomnia are associated with the dysregulation of HPA axis and the development of metabolic syndrome. The purpose of this study was to examine whether sleep duration and insomnia moderate the relationship between financial stress and the prevalence of metabolic syndrome. **Method**: A cross-sectional study was conducted using data from the Retirement and Sleep Trajectories (REST) study, an ancillary study of the Wisconsin Sleep Cohort (WSC) Study (N=455 adults, mean [SD] age = 64 [7] years, 56% males). The moderation effects were tested using Composite Indicator Structural Equation Modeling (Alpha) with stacking approach. **Results**: There was a significant interaction between financial stress and sleep duration (Financial Stress*Sleep Duration: β=0.029, p=0.004). We found an asymmetrical U-shape relationship where the sleep curtailment group (<7 hours per night) showed the strongest relationship and longer sleep group (>8 hours per night) showed the second strongest relationship, while the relationship in the adequate sleep group (7-8 hours per night) was not significant. There was also a significant interaction between financial stress and the number of insomnia symptoms (Financial Stress*Insomnia Symptoms: β= 0.110, p=0.032). The relationship between financial stress and metabolic syndrome was stronger among adults who were having difficulty falling asleep (β=1.932, p=0.021), who reported waking up too early (β=2.040, p=0.027), and that they experienced nonrestorative sleep (β=1.843, p=0.029). **Conclusion**: Sleep curtailment may worsen the relationship between financial stress and the prevalence of metabolic syndrome. Prospective longitudinal studies are needed to confirm the causal relationships.

1. Introduction

The overall prevalence of metabolic syndrome in the U.S. increased from 25% to 34% over the past 10 years (Aguilar, Bhuket, Torres, Liu, & Wong, 2015; Moore, Chaudhary, & Akinyemiju, 2017). The term, metabolic syndrome, is used to characterize a unique clustering of metabolic abnormalities, which include hypertension, Type 2 Diabetes Mellitus (T2DM), dyslipidemia, and abdominal obesity. This clustering pattern makes untreated metabolic syndrome a major determinant of cardiovascular diseases and gastrointestinal cancers, the two leading causes of death in the U.S. (Heron & Anderson, 2016; Hulten et al., 2017; Juo et al., 2018). Current preventive strategies for Metabolic syndrome have been focusing on routine screening, dietary modification, and active lifestyle; several randomized controlled trials utilizing these strategies have demonstrated promising effects on promoting health behaviors. Unfortunately, these RCTs also identified a challenge in long-term behavioral maintenance, where body weight and behaviors tend to rebound to baseline after participants graduated from the programs (Howlett, Trivedi, Troop, & Chater, 2019; Knowler et al., 2002; Ramachandran et al., 2006).

Scientists have found that health behavior, whether under conscious control or occurring in a habitual pattern, is easily maintained under a supportive environmental and social context (Kwasnicka, Dombrowski, White, & Sniehotta, 2016). Unfortunately, disadvantaged financial status has been shown to limit adults' access to the supportive environment for health behaviors and link to higher prevalence of metabolic syndrome (Avison, Aneshensel, Schieman, & Wheaton, 2009; Blanquet et al., 2016; Kahn & Pearlin, 2006; Keita et al., 2014; Pearlin, 2010). Researchers also found that adults who reported difficulty coping with financial stress tended to show a slower decline in the diurnal cortisol level over the day or higher evening levels of cortisol, indicating a chronic dysregulation of hypothamic-pituitary-adrenal (HPA) axis (Agbedia et al., 2011; Cohen et al., 2006).

Currently researchers hypothesized that insomnia may also play a role in the dysregulation of HPA axis (Huang et al., 2017). Insomnia is characterized by chronic dissatisfaction with sleep quantity or quality with varied symptoms, including difficulty falling asleep, difficulty maintaining sleep, awakening too early, difficulty returning to sleep after awakenings, and nonrestorative sleep (Levenson, Kay, & Buysse, 2015). According to prior epidemiologic studies, difficulty falling asleep, is associated with increased risk of metabolic syndrome, yet, it is unclear whether other insomnia symptoms are associated with the risk of metabolic syndrome, due to conflicting results reported in the literature (Lin et al., 2016; Troxel et al., 2010). Most adults who have difficulty falling asleep reported longer sleep latency (i.e., the amount of time it takes to fall asleep after the lights have been turned off), which is associated with a decline in cortisol awakening rise (30-37% of difference in slope [$p = 0.02$]) (Castro-Diehl et al., 2015; Huang et al., 2017).

Sleep curtailment describes a pattern where people chronically sleep less than the average sleep duration. Several studies have suggested that habitual sleep curtailment is associated with slower rate of cortisol decline later in the day or higher evening levels of cortisol (Abell, Shipley, Ferrie, Kivimaki, & Kumari, 2016; Castro-Diehl et al., 2015; Huang et al., 2017). In a recent meta-analysis, Iftikhar et al. concluded that sleep curtailment (<7 hours per night) is associated with higher odds of metabolic syndrome (Odds ratio=1.23, $p<0.001$), but their finding did not support the association between long sleep duration (>8 hours per night) and metabolic syndrome (Iftikhar et al., 2015).

Although insomnia, sleep curtailment, and financial stress might share similar pathways toward the dysregulation of the HPA axis and the development of metabolic syndrome, the existing evidence is insufficient for scientists to conclude the interaction effect between sleep factors and financial stress on the prevalence of metabolic syndrome. We hypothesized that insomnia and sleep curtailment could interact with financial stress, and this interaction effect may increase the prevalence of metabolic syndrome in middle-aged and older adults (See Figure 4.1.).

Therefore, the primary aim of the current study is to examine whether insomnia symptoms and sleep duration moderate the relationship between financial stress and metabolic syndrome. The secondary aim is examine whether the odds ratio of having metabolic syndrome change according to different sleep duration and insomnia symptoms.

2. Method

2.1. Study Design, Sample, and Setting

This is a cross-sectional study using the data from the Retirement and Sleep Trajectories (REST), an ancillary study of the Wisconsin Sleep Cohort (WSC) study. The WSC study is an ongoing longitudinal study of sleep habits and sleep disorders in adults followed prospectively since 1988. The design of the WSC has been described previously (Peppard et al., 2013; Young et al., 2008). Briefly, participants in the WSC were selected from a random sampling pool of payroll records for State of Wisconsin employees aged between 30 and 60 years old in 1988. Among the 2940 individuals invited to undergo a baseline overnight assessment in the laboratory, 1546 subjects participated. The cohort was then followed up with approximately every 4 years, but the dates of in-laboratory assessment varied depending on the schedule of each participant (Tattersall et al., 2016). The REST study is a longitudinal study consisting of four annual mailed surveys that collected information regarding stress, health behaviors, sleep, health status, and other factors. Participants of the REST study were chosen from the sampling frame of the WSC in 2010. Individuals were eligible for the REST study if they completed either 3 WSC mailed surveys or 1 WSC in-laboratory study protocol and 1 WSC survey (n = 1,164).

The current study included 455 participants who completed the first wave of REST surveys (2010-2011) and completed a WSC in-laboratory assessment after the first wave of REST surveys (See Figure 4.2.). The University of Wisconsin-Madison health sciences institutional review board (IRB) approved this study.

2.2. Measures

2.2.1. Outcomes

Metabolic syndrome was identified through medication reconciliation and in-laboratory assessment of metabolic biomarkers, including waist circumference, resting blood pressure, and blood tests that measured fasting glucose, triglycerides, and high-density lipoprotein cholesterols (HDL). Medication reconciliation was performed through individual interview and pill-bottle assessments to identify participants who took prescribed medication to controlled blood pressure (e.g., Beta-blocker, diuretics, ACE inhibitors, etc.), dyslipidemia (e.g., statin, fibrates, niacin, etc.), and glucose (e.g., metformin, sulfonylureas, DPP-4 inhibitors, etc.). Diagnosis criteria were based on current clinical guidelines provided by the American Heart Association (see Table 4.1.).

2.2.2. Exposures

Financial stress was assessed by a financial stress scale used in the Midlife in the United States (MIDUS) study (Elliot & Chapman, 2016). This scale contained three questions regarding a respondent's current financial situation, ability to pay monthly bills, and ability to meet life necessities. The respondent's current financial situation was evaluated using an 11-point Likert Scale, ranging from 0 (best) to 10 (worst). The ability to pay monthly bills was assessed using a 4-point Likert Scale, ranging from 1 (not at all difficult) to 4 (very difficult), while the ability to meet life necessities was assessed using a 3-point Likert Scale, ranging from 1 (money more than you need) to 3 (not enough money). The standardized Cronbach's alpha is 0.82 in current study, indicating a good internal consistency.

2.2.3 *Moderators*

Insomnia Symptoms. Insomnia symptoms were assessed with five items regarding difficulty falling asleep, frequent awakenings, awakening too early, difficulty returning to sleep after awakenings, and nonrestorative sleep (Buysse, 2013). This questionnaire has been validated and used in the National Health and Nutrition Examination Survey and the Wisconsin

Sleep Cohort Study (Young, 2009). Each item was rated on a 5-point Likert scale with the following response anchors: 0 (Never), 1 (Rarely; once a month), 2 (Sometimes; 2-4 times a month), 3 (Often; 5-15 times a month), and 4 (Almost/Always; >15 times a month). For each individual insomnia symptom, we created a dichotomous variable (active symptom versus non-active symptom) by indicating Never/Rarely/Sometimes as non-active symptom, and Often/Almost Always as active symptom. Second, we created a continuous variable to summarize how many active insomnia symptoms each participant experienced.

Sleep duration. Average sleep duration was estimated by asking the participants how many hours and minutes they sleep on a typical workday and on a typical non-work day. The average daily sleep duration was computed as ([5 × workday sleep] + [2 × weekend sleep])/7 (Givens et al., 2015; Hagen, Mirer, Palta, & Peppard, 2013). Based on prior literature reviews, we categorized the sleep duration per night into 3 subgroups (<7 hours, 7-8 hours, and >8 hours) and 4 subgroups (<6 hours, 6-6.9 hours, 7-7.9 hours, $\geq$8 hours) for separated data analysis. We were not able to performe five-group analysis due to the very small portion of participants (n=22) who slept more than 9 hours per night in this cohort.

2.2.4 Covariates

Age, number of comorbidities, physical activity (metabolic equivalent [MET-hour/week]), alcohol consumption (number of drinks/week), cigarette smoking status (current smoker or not), and depression were controlled in the data analysis, because these five factors are associated with insomnia, sleep duration, and metabolic syndrome, as noted in the literature (Szklo-Coxe, Young, Peppard, Finn, & Benca, 2010). Comorbidities included cancer, myocardial infarction, heart failure, Parkinson's disease, Alzheimer's disease, Glaucoma, restless leg syndrome, emphysema, chronic obstructive disease, and kidney disease (Plante, Finn, Hagen, Mignot, & Peppard, 2017). Depression was assessed by using the Center for Epidemiologic Studies Depression Scale (CES-D) with high validity and reliability (Cosco, Prina, Stubbs, & Wu, 2017; Himmelfarb & Murrell, 1983). Physical activity was assessed using the Paffenbarger Physical

Activity Questionnaire (PPAQ), which has been validated in middle-aged and older adults (Paffenbarger, Wing, & Hyde, 1995). Because the exposure variables (different sources of stress) and outcome variables (metabolic biomarkers) were collected at different time points, the duration between the occurrence of exposure variables (REST mailed survey) and the occurrence of outcome variables (WSC in-laboratory assessment) was transformed into days and modeled as the confounding variable. Information regarding dietary intake and family history of each metabolic abnormalities was not available in this dataset.

2.3. Statistical Analyses

The descriptive statistics for the financial stress, sleep disorders, and metabolic syndrome were calculated. SAS software (SAS, 2019) and Mplus software (Muthén & Muthén, 1998) were used for managing missing data and statistical analyses. All reported p-values were two-tailed with p-values less than 0.05 considered as significant. The missing patterns were diagnosed using PROC MI in SAS to confirm that missing values in Y ($Y_{missing}$) were not associated with the measured variables (Y), and rule out the possibility of missing not at random (MNAR). We then performed multiple imputations based on the fully conditional method (FCS), which imputed each missing value based on a separate conditional distribution due to the ordinal variables (Liu & De, 2015; Van Buuren, Brand, Groothuis-Oudshoorn, & Rubin, 2006).

We used two-phase SEM to examine the relationship between financial stress and the prevalence of metabolic syndrome. For the measurement (first) phase, we used Composite Indicator Structural Equation (CISE) alpha modeling because the exposure variable is a composite variable based on self-report instruments (Baumgartner & Homburg, 1996; R. A. McDonald, Behson, Seifert, & Jaccard, 2005). To account for measurement error, we built a measurement error term into the composite variable based on the reliability estimates derived from the following formula: ([1 - Cronbach's alpha of Financial Stress Scale] x variance of financial stress score) (McDonald, Behson, Seifert, & Jaccard, 2005).

In the structural (second) phase, we followed Baron and Kenny's moderation analysis to examine whether insomnia and sleep duration moderate the association between financial stress and the prevalence of metabolic syndrome (Baron & Kenny, 1986). Specifically, we estimated Probit models using weighted least squares mean and variance (WLSMV), and estimated the standardized coefficient and 95% confidence interval (95% CI) for the relationship between exposure and outcome and the relationship between moderator and outcome. We used WLSMV because it is a robust estimation for binary outcome variables since it does not assume normal distribution (Brown, 2014; Li, 2016).

To examine the interaction effects, we used two approaches. For the first approach, we treated the numbers of insomnia symptoms and sleep duration as continuous variables and built the interaction terms (i.e., FS*Insomnia and FS*sleep duration), as suggested by Baron and Kenny (Baron & Kenny, 1986). For the second approach, we treated the sleep duration and each insomnia symptom (e.g., difficulty falling asleep, difficulty maintaining sleep, awakening too early, difficulty returning to sleep after awakenings, or nonrestorative sleep) as categorical variables and categorized the participants into different subgroups. We then used stacking approach to simultaneously estimate the the relationship between financial stress and metabolic syndrome under different subgroups. Stacking technique allows researchers to meaningfully categorize the participants into subgroups according to the cutoff points for each moderator, and observe how the relationship between the exposure and outcome differs by each subgroup. Furthermore, stacking technique also permits the estimation of models containing multiple interactions (Byrne, 1998). To ensure the estimated probit model is reasonably consistent with the current sample, we used McKelvey and Zavoina Pseudo R^2 as the goodness-of-fit index, because the outcome variables were binary (McKelvey & Zavoina, 1975; Veall & Zimmermann, 1992). The McKelvey and Zavoina Pseudo R^2 were assessed via the R^2 for each outcome variable based on the probit model with WLSMV (Muthén & Muthén, 1998). Finally, we first transformed the probit coefficients

and 95% confidence intervals (95% CI) into odds ratios as the effect sizes, and illustrated forest plots to show the effect sizes for each subgroup.

3. Results

The participants were between 46 to 81 years old, with an average age of 64. Among the 455 participants, 56% were males and 65% had metabolic syndrome. Demographic characteristics for the sample are shown in Table 4.2.

3.1. The Interaction Effect between Sleep Duration and Financial Stress

As shown in Table 4.3., when sleep duration was treated as continuous variable, we found a significant interaction term between financial stress and sleep duration (Financial Stress*Sleep Duration: β=0.029, p=0.004). In the 3-group analysis, we found a marginally significant change in slope between sleep<7 hours (Group 1) and sleep 7-8 hours (Group 2). While the estimated slope for sleep>8 hours (Group 3) did not significantly differ with other groups. In the 4-group analysis, we found two marginally significant changes in slope. First, the slope in Group 1 (sleep<6 hours) was different from the slope in Group 3 (7-7.9 hours). Second, the slope in Group 2 (6-6.9 hours) was different from Group 3 (7-7.9 hours). Again, the slope in Group 4 was not significantly different from other groups. The probit estimates and p-value for interaction terms are presented in Table 4.3.

During the subgroup analysis, we found an asymmetrical U-shape relationship where the sleep curtailment group had the strongest odds ratio and longer sleep group had the second strongest odds ratio, while the odds ratio in adequate sleep group (7-8 hours per night) was not significant (See Figure 4.3.). The detailed probit estimates, OR, 95% CI, standard error (SE), and p-values are presented in Table 4.4.

3.2 The Interaction Effect between Insomnia and Financial Stress

The results of probit models examining whether insomnia symptoms moderated the relationship between financial stress and metabolic syndrome are displayed in Table 4.5. First, when insomnia was treated as the continuous variable, we found a significant interaction term

between financial stress and insomnia symptoms (Financial Stress*Insomnia Symptoms: β= 0.110, p=0.032).

When each individual insomnia symptom (active symptom V.S. non-active symptom) was examined, we found that the relationship between financial stress and metabolic syndrome is stronger among adults who were having difficulty falling asleep (β=1.932, p=0.021), compared to adults who did not have difficulty falling asleep (β=1.565, p=0.005). Similarly, the relationship between financial stress and metabolic syndrome was stronger among adults who reported waking up too early (β=2.040, p=0.027), compared to adults who did not have this problem (β=1.562, p=0.005). The relationship between financial stress and metabolic syndrome was stronger among adults who reported experiencing nonrestorative sleep (β=1.843, p=0.029), compared to adults who did not have this problem (β=1.565, p=0.009).

4. Discussion

Prior evidence suggested that financial stress, sleep curtailment, and insomnia are associated with higher prevalence of metabolic syndrome (Blanquet et al., 2016; Iftikhar et al., 2015; Keita et al., 2014). Based on gaps identified in the current literature, this study further examines whether insomnia symptoms and sleep duration moderate the relationship between financial stress and metabolic syndrome.

In this cohort of middle-aged and older adults, sleep duration significantly moderates the relationship between financial stress and the prevalence of metabolic syndrome. Specifically, there is an asymmetrical U-shape relationship indicating that the magnitudes of the relationship between financial stress and metabolic syndrome increases in adults who sleep less than 7 hours per night or sleep more than 8 hours per night (See Figure 4.3.). Furthermore, the relationship between financial stress and metabolic syndrome is strongest among those with sleep curtailment, especially for those who sleep less than 6 hours per night. Our finding is supported by Iftikhar and colleagues who reported in a recent meta-analysis that shorter sleep duration (<7 hours) is associated with higher odds of metabolic syndrome (OR=1.23, p<0.001) (Iftikhar et al., 2015).

Beyond their finding, we further found that when financial stress interacts with shorter sleep duration, the synergic effect further exacerbates the risk of metabolic syndrome; demonstrated by an even higher odds ratio (OR=2.384, p=0.001). A potential explanation for this moderation effect is that the sleep curtailment and the allostatic load (from financial stress) both trigger the dysregulation of HPA axis, and that disruption accelerates chronic inflammation and the development of metabolic syndrome (Kim et al., 2018). It is also possible that chronic sleep curtailment compromises human's attention and self-control, which in turn influence adults' choices of detrimental health behaviors that are associated with higher risk of metabolic syndrome. Further, Scarcity Mindset Hypothesis posits that the long-term exposure to financial stress alters adults' perception about what they need most and what they should prioritize. This re-prioritization could also negatively influence their choice of behaviors (Shah, Mullainathan, & Shafir, 2012; Shah, Shafir, & Mullainathan, 2015). In other words, sleep curtailment and financial stress might synergistically influence the decision-making process related to health behaviors. Prospective longitudinal studies are needed to examine the underlying physiological and behavioral pathways and causal relationships. If the causal relationships are confirmed by longitudinal studies, future multi-approach interventions, designed to combat both financial stress and sleep problems, may show higher efficacy at decreasing risk of metabolic syndrome than single approach interventions.

Insomnia in older adults is a complex phenomenon. Normal aging results in changes to circadian rhythm, which moves older adults' biological clock earlier, and results in going to bed earlier and waking up earlier. Normal aging is also associated with decreased slow wave sleep and decreased total sleep time with a nearly 10-minute reduction per decade of age (Floyd, Janisse, Jenuwine, & Ager, 2007; Moraes et al., 2014). In addition to the normal circadian changes that are related to aging, insomnia could also result from emotional disturbance, comorbidity, chronic pain, or the adverse effects from medication, such as diuretics and beta-blocker (Gooneratne & Vitiello, 2014). In the current study, we found a significant interaction effect between insomnia and financial stress. Although we did not find significant differences in the

slopes during subgroup analysis based on each insomnia symptom, we did find that the odds ratios were stronger among adults who had difficulty falling asleep, reported waking up too early, and having nonrestorative sleep. Our findings highlight the importance for clinicians to assess middle-aged and older adults' financial stress and insomnia symptoms. Given the fact that different insomnia symptoms could have different pathophysiological pathways toward the dysregulation of HPA axis and the risk of metabolic syndrome (Huang et al., 2017), the assessment of insomnia symptoms should be more specific with a comprehensive assessment of sleep history to help patients manage their symptoms. For instance, difficulty falling asleep might be triggered by pre-sleep condition, that could potentially be managed by stimulus control therapy or cognitive therapy; frequent nocturnal awakenings might be due to the adverse effect of diuretics or beta-blockers, that providers might consider revising dosing times or replacing with other medications.

In the current sample, the composite financial stress score ranged from 1 to 5.7, with a medium of 2.3. In other words, about 40% of participants were considered financially stressed when using composite financial stress score=2.7 as cut-off point. This is less than the nearly 48% of older adults in the U.S. who are considered "economically vulnerable," which is defined as having an income that is less than two times the supplemental poverty threshold (Gould & Cooper, 2013). Middle-aged adults with financial difficulty tend not to receive recommended care for sleep hygiene and are more likely to delay treatments, especially for those who are uninsured (Walker et al., 2010). The treatment of insomnia requires long-term adherence and regular clinical evaluation, but adults with financial stress tend to have more challenges to receive the long-term treatment. According to a recent survey, more than half of older adults (59%) had used a potentially inappropriate over-the-counter medication containing diphenhydramine or doxylamine to improve sleep without consulting the health care providers or pharmacists (Abraham, Schleiden, & Albert, 2017; Abraham, Schleiden, Brothers, & Albert, 2017; Stone et al., 2017). There is a priority for agencies and government to improve the awareness of the safety risks of over-the-

counter medications and providing low-cost health access for adults to seek professional treatment for insomnia and sleep apnea. In particular, according to the current guideline, behavioral treatments should be considered whenever possible, and medications should be limited to the lowest necessary dose and shortest necessary duration (Buysse, 2013; Levenson et al., 2015; Sateia, Buysse, Krystal, Neubauer, & Heald, 2017). Our findings would suggest that clinicians need to provide more comprehensive insomnia evaluations, along with screening for financial related stress.

The strengths of the current study include a relatively large sample size, an extensive exploration of sleep duration, the adjustment of measurement error for the exposure variable, and a comprehensive adjustment of important factors to reduce the confounding effects. Furthermore, adults with lower income do not necessarily have debts, while adults with higher income may suffer from debts. The assessment of financial stress in the current study overcomes this phenomenon by incorporating three domains of financial stress, including financial status and ability to pay monthly bills and life necessity. In other words, the assessment of financial stress may reflect more information regarding debt-to-income ratios. However, this study also has limitations. First, the current sample features less racial diversity (97% of participants were white) (Young, 2009). Caution should be taken when generalizing the results to other racial/ethnic backgrounds. For example, it is unclear whether the moderation is stronger or weaker in other racial/ethnic backgrounds or low-income neighborhoods. Second, due to the cross-sectional and observational nature of the study, causal inference and recursive relationships between the exposure and outcome variables cannot be concluded. However, there is still a sequential order between our predictors and outcomes. Specifically, based on the study design, the exposure variables were assessed during the REST survey, while outcome variables were assessed during a WSC in-laboratory visit, which occurred after the REST survey to ensure a logical sequential order.

5. Conclusion

In this cohort of middle-aged and older adults, sleep duration and insomnia symptoms significantly moderate the relationship between financial stress and metabolic syndrome. In particular, the impact of financial stress on metabolic syndrome was strongest among adults with sleep curtailment. Further research is needed to examine the underlying physiological and behavioral pathways, where sleep curtailment may interact. Financial status and sleep characteristics should be routinely assessed in geriatric clinics to address patients' risk of metabolic syndrome.

6. References

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7. Tables

Table 4.1. *Current guideline for metabolic outcomes in current study*

Outcome	Criteria	Guidelines
Metabolic syndrome	At least three of the criteria below: • BP ≥ 130/85 mmHg or medicated • FPG ≥ 100 mg/dL or medicated • TG ≥ 150 mg/dL or medicated • HDL < 40 (males), <50 (females) • WC > 40 (males), >35 (females)	NCEP-ATP III, NHLBI, AHA

Note. T2DM=Type 2 diabetes Mellitus. BP=Blood pressure. FPG=Fasting plasma glucose. TG=Triglycerides. HDL=High-density lipoprotein. WC=Waist circumference. NCEP-ATP III=National Cholesterol Education Program, Adult Treatment Panel III. AHA=American Heart Association.

Table 4.2. *The demographic, psychological, and metabolic characteristics of the study sample*

Characteristics	N=455
Age, mean (SD)	63.9 (6.99)
Sex (% male)	253 (56%)
Race (% white)	441 (97%)
Education (%)	
High school or less	85 (19%)
Some college	152 (33%)
College or more	218 (48%)
Health insurance (%)	8 (98%)
BMI, mean (SD)	31.14 (6.83)
Number of comorbidities (%)	
None	290 (66%)
One	132 (29%)
Two or more	33 (5%)
Alcohol per week (drinks), mean (SD)	4.08 (5.68)
Current smoker (%)	35 (8%)
Physical activity (MET-hour/week), mean (SD)	22.42 (22.42)
Metabolic syndrome (%)	297 (65%)
Financial stress, mean (SD)	
Paying bills	1.74 (0.78)
Paying life necessities	1.77 (0.60)
Current financial strain	3.24 (1.81)
Sleep duration	7.24
Difficulty falling asleep	79 (17%)
Difficulty maintaining sleep	212 (47%)
Awakening too early	75 (16%)
Difficulty returning to sleep after awakenings	94 (21%)
Nonrestorative sleep	113 (25%)

Table 4.3. *The β coefficient and p-value for interaction terms between financial stress and sleep duration*

Interaction Terms (Slope Difference)	Probit (Δβ)	p-value
Financial stress* Sleep durations	0.028**	0.006**
3 groups		
G1-G2	0.266	0.166
G1-G3	0.169	0.439
G2-G3	0.097	0.685
4 groups		
G1-G2	0.429	0.355
G1-G3	0.784*	0.083
G1-G4	0.516	0.257
G2-G3	0.354*	0.076
G2-G4	0.086	0.676
G3-G4	-0.268	0.132

Table 4.4. *The estimated CISE alpha modeling results for the relationship between financial stress and metabolic syndrome under different levels of sleep duration.*

Total 455	Probit (β)	Probit 95% CI	OR	OR (95% CI)	SE	P-value
3-group sleep duration						
G1: <7 hours (139)	0.479	[0.245, 0.713]	2.384	[1.560, 3.645]	0.142	0.001
G2: 7-8 hours (252)	0.155	[-0.023, 0.334]	1.325	[0.959, 1.833]	0.108	0.151
G3: >8 hours (64)	0.466	[0.171, 0.762]	2.329	[1.364, 3.983]	0.180	0.009
5-group sleep duration						
G1: <6 hours (40)	0.886	[0.169, 1.603]	4.988	[1.359, 18.311]	0.436	0.042
G2: 6-6.9 hours (99)	0.456	[0.195, 0.718]	2.287	[1.424, 3.678]	0.159	0.004
G3: 7-7.9 hours (186)	0.102	[-0.096, 0.301]	1.203	[0.840, 1.726]	0.121	0.396
G4: ≥8 hours (130)	0.370	[0.155, 0.586]	1.956	[1.325, 2.895]	0.131	0.005

Note. The probit estimate (β) indicates the slope of probit relationship

Table 4.5. *The estimated CISE alpha modeling results for the relationship between financial stress and metabolic syndrome under different symptoms of insomnia.*

Total 455	Probit (β)	Probit 95% CI	OR	OR (95% CI)	SE	P-value
Numbers of active insomnia symptoms						
0 active symptom (190)	**0.330**	**[0.13, 0.531]**	**1.819**	**[1.266, 2.620]**	**0.122**	**0.007**
1 active symptom (147)	**0.356**	**[0.119, 0.592]**	**1.907**	**[1.241, 2.926]**	**0.144**	**0.013**
2-5 active symptoms (118)	0.208	[0, 0.417]	1.458	[1.000, 2.130]	0.127	0.100
Difficulty falling asleep						
Yes (79)	**0.363**	**[0.105, 0.622]**	**1.932**	**[1.210, 3.090]**	**0.157**	**0.021**
No (376)	**0.247**	**[0.101, 0.392]**	**1.565**	**[1.201, 2.036]**	**0.088**	**0.005**
Difficulty returning to sleep after awakenings						
Yes (94)	0.290	[0.044, 0.536]	1.692	[1.083, 2.644]	0.150	0.052
No (361)	**0.287**	**[0.142, 0.433]**	**1.683**	**[1.294, 2.193]**	**0.088**	**0.001**
Frequent awakenings						
Yes (212)	0.212	[0.021, 0.404]	1.469	[1.039, 2.081]	0.116	0.068
No (243)	**0.354**	**[0.183, 0.525]**	**1.900**	**[1.394, 2.592]**	**0.104**	**0.001**
Awakening too early						
Yes (75)	**0.393**	**[0.1, 0.686]**	**2.040**	**[1.199, 3.470]**	**0.178**	**0.027**
No (380)	**0.246**	**[0.102, 0.391]**	**1.562**	**[1.203, 2.032]**	**0.088**	**0.005**
Nonrestorative sleep						
Yes (113)	**0.337**	**[0.082, 0.591]**	**1.843**	**[1.160, 2.921]**	**0.155**	**0.029**
No (342)	**0.247**	**[0.092, 0.402]**	**1.565**	**[1.182, 2.073]**	**0.094**	**0.009**

8. Figures

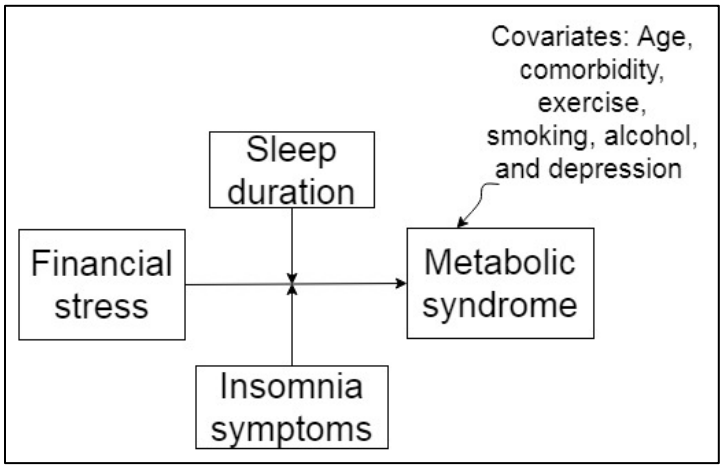

Figure 4.1. The central hypothesis of the current study: Insomnia symptoms and sleep duration moderate the relationship between financial stress and the prevalence of metabolic syndrome

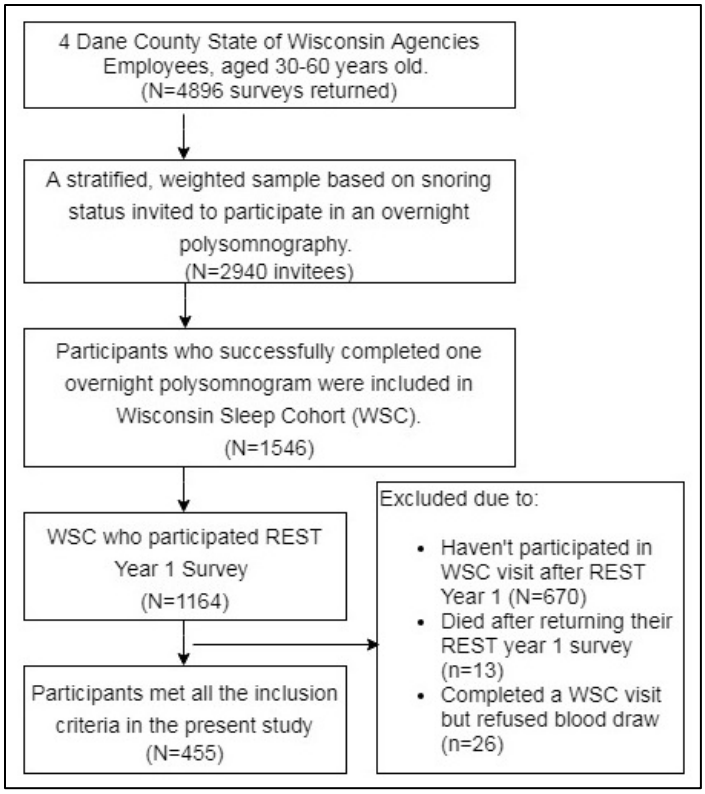

Figure 4.2. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement: Flow chart of the sample size in current study.

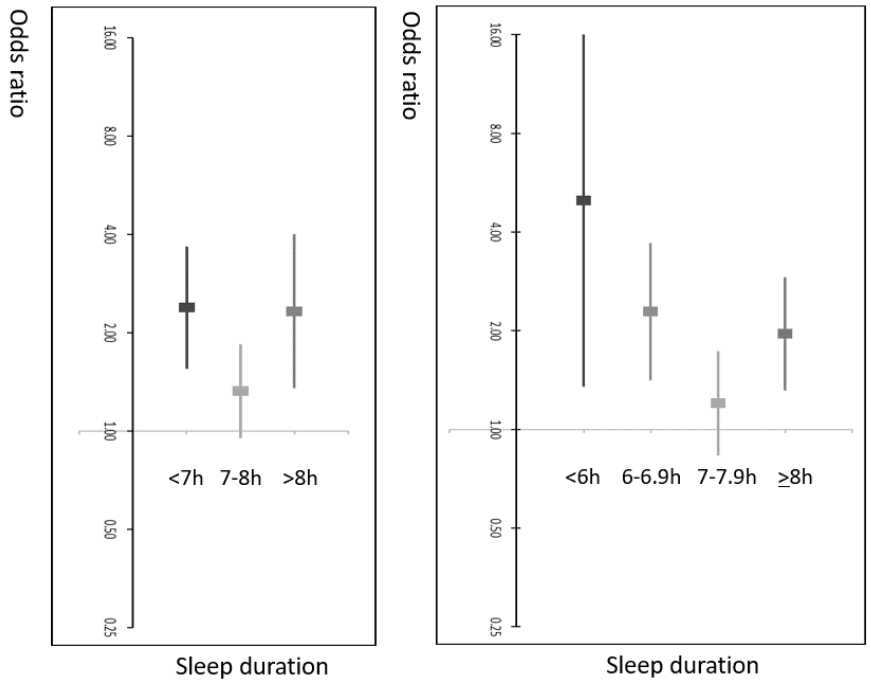

Figure 4.3. The relationship between financial stress and the prevalence of metabolic syndrome under different levels of sleep duration.

Chapter 5

Discussion

This dissertation contributes to nursing science by revealing the intertwined relationships between different sources of stress and different types of metabolic outcomes, as well as their interplay with sleep behaviors in middle-aged and older adults. This chapter will summarize the key findings from this dissertation and discuss the implications for future research, practice, and policy.

Key Findings

Existing literature indicates that psychological stress is associated with an increased risk of metabolic syndrome, but does the effect size vary by study design? We conducted a systematic review with meta-analysis to further expand the field's knowledge by comparing the effect sizes among different sources of stress and different study designs. We found that the estimated effect size in cross-sectional studies was strongly significant in both the crude (or least-adjusted) model (OR=1.435; p<0.001) and the most-adjusted model (OR=1.447; p<0.001). Compared to the cross-sectional studies, the estimated effect size in longitudinal studies was smaller in the crude model (OR=1.314; p<0.012) and became non-significant in the most-adjusted model (OR=1.490; p=0.058).

Adults experience different sources of stress, but which sources of stress is more metabolically detrimental? We conducted a cross-sectional study using data from the Retirement and Sleep Trajectories (REST) study, an ancillary study of the Wisconsin Sleep Cohort (WSC) Study (N=407 adults, mean [SD] age = 64 [7] years, 45% female). We found that one standard deviation (SD) increase in financial stress was associated with 52% higher odds of abdominal obesity (OR*=1.52; p<0.001), 50% higher odds of metabolic syndrome (OR*=1.50; p=0.001), and 42% higher odds of dyslipidemia (OR*=1.42; p=0.009), after controlling for age, comorbidity, and lifestyle behaviors. Unexpectedly, family stress (p=0.019) and stressful life events (p=0.012) were negatively associated with the prevalence of dyslipidemia, although the effects were relatively small.

Could perceived health be a preclinical factor mediating the relationship between stress and metabolic syndrome? We found that the relationship between financial stress and metabolic syndrome was mediated by lower levels of perceived physical health. Specifically, perceived physical health fully mediated the relationship between financial stress and the prevalence of abdominal obesity (indirect effect [$\beta^*=0.536$; $p<0.019$]) and metabolic syndrome (indirect effect [$\beta^*=0.523$; $p<0.028$]). However, perceived mental health did not mediate the relationship between financial stress and metabolic syndrome ($p=0.998$).

Do sleep related factors moderate the relationship between financial stress and metabolic syndrome? We found that both insomnia symptoms and sleep duration moderated the relationship between financial stress and metabolic syndrome, with significant interaction effects. Specifically, we found an asymmetrical U-shape relationship where the sleep curtailment group (<7 hours per night) showed the strongest relationship, and longer sleep group (>8 hours per night) showed the second strongest relationship, while the relationship in the adequate sleep group (7-8 hours per night) was not significant. Further, the relationship between financial stress and metabolic syndrome was stronger among adults who were having difficulty falling asleep ($\beta=1.932$, $p=0.021$), who complained waking up too early ($\beta=2.040$, $p=0.027$), and who complained nonrestorative sleep ($\beta=1.843$, $p=0.029$).

Implication for Future Research

Stress has been identified as a risk factor for multiple chronic illnesses, including the illnesses that comprise metabolic syndrome, e.g., obesity, hypertension, and diabetes. However, the underlying mechanisms that explain the relationship between stress and metabolic syndrome have not been comprehensively studied. In this dissertation, we comprehensively assessed the relationship between different sources of stress and metabolic syndrome, and examined the role of perceived health and sleep behaviors in the stress-metabolism relationship. Importantly, our findings serve to inform future research. Specifically, our findings provoke two further important questions:

- *Do financial stress and sleep disturbances synergistically influence adults' perception, attention, and self-control, which may in turn increase the risk of unhealthy behaviors?*
- *Do inflammatory profiles and sleep patterns change when adults experience chronic stress?*

To answer these two questions, researchers should incorporate real-time assessments (e.g., Actigraphy or ecological momentary assessment), stress biomarkers (e.g., diurnal cortisol, dehydroepiandrosterone [DHEA], telomeres, and NF-κB), and more precise measures for perception, attention, and self-control in order to examine the interaction effects between sleep and stress on adults' behaviors and metabolism (McEwen, 2015; Peppard & Hagen, 2018).

Furthermore, carefully designed longitudinal studies are needed to understand the phenomenon of stress proliferation and its relation to metabolic health. Although longitudinal studies have been conducted to examine the association between psychological stress (exposure) and metabolic syndrome (outcome), we found a weakness in these studies where researchers modeled the exposure at baseline (e.g., Study Wave 1) and examined the outcome after years later (Study Wave 2). This approach ignores the changes in stress proliferation, coping mechanisms, and behavioral adaptation over time (Pearlin, 2010; Zapf, Dormann, & Frese, 1996). Continuous research is needed to better understand the trajectory of stress proliferation in adults living in financial deprived conditions and its impacts on metabolism using growth mixture modeling.

Finally, although perceived physical health mediates the relationship between financial stress and metabolic syndrome in this population, it is unclear which components of perceived physical health (e.g., pain or physical functioning) are particularly critical in this pathway. Future studies should incorporate real-time assessments and objective biomarkers to examine how and to what extend bodily pain and physical functioning interact with sleep disturbance and further influence metabolism in adults with financial stress and how this population cope with pain and the decline in physical functioning.

To untangle the interrelationships among financial stress, perceived health, health behaviors, sleep, and metabolism syndrome, several well-established cohort studies, such as Wisconsin Sleep Cohort (WSC), National Survey of Midlife Development in the United States (MIDUS), and Social Environmental and Biomarkers of Aging Study (SEBASE) could be leveraged. These cohort studies have incorporated validated psychosocial measurements and objective biomarkers that could provide valuable preliminary investigations. Meanwhile, the National Institutes of Health (NIH) has several funding priorities for the research aimed to answer the following unanswered questions:

- Does the trajectory of stress proliferation differ by socioeconomic status and racial/ethnic backgrounds? How do these differences in the trajectory of stress proliferation affect health disparities and current preventive strategies and treatment for metabolic syndrome and other CVDs? (NIH, 2019a, PA-19-226)
- Do financial stress and sleep disturbances synergistically influence adults' pain perception, attention, and self-control that increase the risk of unhealthy behaviors? Do inflammatory profiles and sleep patterns change when adults experience chronic stress? (NIH, 2019b, PA-19-200)
- Do interventions addressing stress and sleep show higher effects on the maintenance of health behavior over time? (NIH, 2019c).
- Do biobehavioral interventions (e.g., horticulture therapy and medcomics) influence older adults' perceived stress, telomere length and chronic inflammation? (NIH, 2019d, PA-19-073)

Implication for Practice, Public Health, and Policy

In adults with financial stress, lower levels of perceived physical health might be a preclinical sign highlighting the potential risk of metabolic syndrome. When older adults are experiencing financial stress, they may self-report lower perceived health, which may signify an

increased risk of metabolic syndrome. Clinicians should assesse patients' financial stress, perceived health, and sleep habits in middle aged and older adults to help them prevent (or manage) metabolic syndrome. Furthermore, when assessing insomnia, it is important for clinicians to help patients pinpoint which insomnia symptoms they are experiencing and provide tailored interventions according to individual symptoms.

Evidences indicates that adults with financial difficulty are less likely to seek medical services regarding metabolic syndrome and insomnia due to the uncertainty toward the percentage of copayment (Howard, 2019; Stone et al., 2017). Instead, they tend to take over-the-counter medication or supplements to manage their insomnia and hypercholesterolemia (Abraham, Schleiden, & Albert, 2017; Ambizas, 2017). Therefore, there is a priority for agencies and the government to improve awareness surrounding the safety of over-the-counter medications and provide low-cost health access to professional treatment for insomnia and metabolic syndrome. Meanwhile, clinicians should actively discuss the available low-cost options with patients and provide related health education. For instance, based on current guidelines, behavioral treatments should be considered whenever possible, and medications should be limited to the lowest necessary dose with shortest necessary duration (Buysse, 2013; Levenson, Kay, & Buysse, 2015; Sateia, Buysse, Krystal, Neubauer, & Heald, 2017).

Finally, middle-aged and older adults coping with financial difficulty are more likely to use Medicare or Medicaid. Unfortunately, Medicare/Medicaid currently only reimburses the cost of lipid test very five years (American College of Obstetricians and Gynecologists, 2018). Our findings highlight the urgency and importance for agencies to conduct longitudinal risk analysis and reconsider whether middle-aged and older adults under Medicare/Medicaid require more frequent screenings for hyperlipidemia.

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