

Symptom Clusters of Midlife Menopausal Women with Metabolic Syndrome

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
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ABSTRACT

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Abstract

Background: Midlife menopausal women with metabolic syndrome experience co-occurring symptoms that adversely affect their health outcomes. The purposes of this dissertation were to describe the symptom experience and presence of symptom clusters in midlife menopausal women with metabolic syndrome; to identify the number and types of symptom clusters and key symptoms based on symptom occurrence and severity dimension; and to identify the subgroups of midlife menopausal women with metabolic syndrome at high-risk for greater symptom cluster burden over time and their associated characteristics.

Methods: A scoping review and two quantitative studies with cross-sectional and longitudinal approach using secondary data analysis were used in this dissertation. The Joanna Briggs Institute (JBI) Scoping Review methodology served as a guide for the scoping review. A total of eight articles were included and systematically evaluated. Network analysis was used to identify symptom clusters and key symptoms. Multi-trajectory analysis using latent class growth analysis was conducted to identify the high-risk subgroup of midlife menopausal women with metabolic syndrome for greater symptom cluster burden over time. Descriptive statistics was used to explain the demographic characteristics of each symptom cluster burden subgroup and bivariate analysis (analysis of variance, chi-square test) was conducted to examine the association between each symptom cluster burden subgroup and demographic characteristics.

Results: Midlife menopausal women with metabolic syndrome experienced urogenital symptoms, vasomotor symptoms, psychological symptoms, sleep symptoms, and somatic symptoms. Urogenital symptoms were the most frequently assessed while sleep and somatic symptoms were the least frequently assessed. However, there were no current studies that examined the presence of symptom clusters in this population. The cross-sectional study using network analysis found that midlife menopausal women with metabolic syndrome experienced the psychological/somatic/genital cluster (key symptom: frequent mood change), the sleep/urinary cluster (sleep disturbance), and the vasomotor cluster (cold sweat) in the symptom occurrence dimension. In addition, they experienced the psychological/somatic/sexual cluster (anxiety), the sleep/urinary cluster (sleep disturbance), and the vasomotor/genital cluster (night sweat) in the symptom severity dimension. A total of four classes were identified with Class 1 (low symptom cluster burden), Class 2 and Class 3 (moderate symptom cluster burden), and Class 4 (high symptom cluster burden). Social support was a significant predictor of high symptom cluster burden subgroup.

Conclusions and Implications: This dissertation is the first to identify the symptom clusters and key symptoms in midlife menopausal women with metabolic syndrome. In addition, this dissertation identified four subgroups of midlife menopausal women with metabolic syndrome based on their symptom cluster trajectory over time. This has allowed for an understanding of a high-risk subgroup for greater symptom cluster

burden. Clinicians need to routinely assess symptom clusters and offer targeted symptom cluster interventions in clinical settings.

Dedication

To God who has been the strong pillar and source of my strength during my ups and downs in my life and during this program.

To my parents who have always loved me and sacrificed for me unconditionally. I have been in the United States since I was 14 years old to study in a bigger world with enriching opportunities and their endless support in my decision has made this memorable moment possible. I would not have been here without your continuous support and encouragement.

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1. Introduction

1.1 Target Population

Metabolic syndrome is a cluster of metabolic abnormalities that places an individual at higher risk for developing type 2 diabetes, cardiovascular disease, stroke, myocardial infarction, and cancer (Rochlani et al., 2017; Zimmet et al., 2005). These metabolic abnormalities include central obesity, hypertension, insulin resistance, and atherogenic dyslipidemia (reduced high-density lipoprotein cholesterol or raised triglycerides). At least three conditions need to co-occur for a clinical diagnosis of metabolic syndrome (Rochlani et al., 2017). It initially affected the Western world due to rapid changes in human environment such as development of technology and transportation that led to increased consumption and easy accessibility of high caloric food and decreased physical activity (Hutcheson & Rocic, 2012; Saklayen, 2018; Zimmet et al., 2005). With the influence of Western lifestyle across the globe, metabolic syndrome has now become a global public health problem, impacting one fourth of the world's adult population (Saklayen, 2018a).

While all genders are affected by metabolic syndrome, women have a higher prevalence of metabolic syndrome than men (Beigh & Jain, 2012; Carr, 2003; Jouyandeh et al., 2013). Several unique factors place women at higher risk for metabolic syndrome than men which include genetics such as a silent polymorphism in the gene encoding low density lipoprotein receptor-related protein-associated protein-1 (LRPAP1),

pregnancy-related weight gain, gestational diabetes, and menopause (Bentley-Lewis et al., 2007; Marc, 2007). Among women across all life stages, midlife (age 40-65 years) is the most vulnerable time for women to develop metabolic syndrome. During this period of time, they experience intra-abdominal adipose tissue accumulation regardless of their body weight and fluctuating hormonal levels, such as a decrease in estrogen and progesterone, associated with aging and menopause (Harlow & Derby, 2015). As a result, midlife menopausal women develop metabolic abnormalities that characterize metabolic syndrome (Jouyandeh et al., 2013).

Clinical characteristics of metabolic syndrome such as central obesity, hypertension, insulin resistance, and atherogenic dyslipidemia facilitate aging in midlife women which results in a unique set of symptoms (Shoelson et al., 2007). For example, people with central obesity show a higher level of inflammatory markers than their counterparts (Shoelson et al., 2007). Inflammation is a part of the aging process common in midlife women and midlife women with metabolic syndrome are at higher risk for inflammation (Chedraui, 2019). Such inflammation seems to play an important role in generating multiple symptoms in midlife women with metabolic syndrome (Chedraui, 2019). In addition, having metabolic syndrome may put an additional psychological burden that can negatively influence a healthy lifestyle and develop symptoms related to lifestyle such as feeling of loneliness and cognitive decline (Furihata et al., 2018;

Miley-Akerstedt et al., 2018). As a result, midlife women with metabolic syndrome experience a complex array of symptoms associated with metabolic syndrome.

Midlife women in peri-menopause and post-menopause experience more prevalent and severe symptoms than those in pre-menopause (Elsabagh & Allah, 2012; Mulhall et al., 2018). There are three stages of menopause that include pre-menopause, peri-menopause, and post-menopause (Bromberger et al., 2013; Butler & Santoro, 2011; Delamater & Santoro, 2018; El Khoudary et al., 2019). Pre-menopause refers to a period of regular menstrual cycles with no change in cycle regularity or length (Butler & Santoro, 2011). Peri-menopause refers to a period of time when a woman experiences irregularity in the menstrual cycles of at least 7 days from fluctuating hormonal levels or skips a menstrual cycle (Butler & Santoro, 2011; El Khoudary et al., 2019). This period includes early peri-menopause when a woman experiences variability in one menstrual cycle length of more than 7 days from normal and late peri-menopause when a woman skips at least two menstrual cycles and has amenorrhea for at least 60 days (Bromberger et al., 2013; Butler & Santoro, 2011; El Khoudary et al., 2019). When a woman does not have menses for more than 12 consecutive months, they enter into post-menopause (Butler & Santoro, 2011). Post-menopause is the period of time after when a woman has not had a menstrual period for more than 12 consecutive months (Delamater & Santoro, 2018). When comparing the three stages of menopause, the fluctuating hormonal levels during peri-menopause and post-menopause further contribute to development of

menopausal symptoms (Harlow & Derby, 2015). When these menopausal symptoms are not assessed or managed in clinical settings, midlife menopausal women experience significant symptom burden that adversely affects their health-related quality of life (Whiteley et al., 2013).

Midlife menopausal women with metabolic syndrome are prone to experiencing a complex array of symptoms because they experience symptoms associated with menopause and metabolic syndrome concurrently. To date, research has focused on understanding individual symptoms associated with menopause or metabolic syndrome or symptom clusters in menopausal women only. However, an individual suffering from chronic conditions experience co-occurrence of multiple symptoms or a symptom cluster (Miaskowski et al., 2004). When these symptoms are left undiagnosed or undertreated, they can result in significant symptom burden and adversely impact patient health outcomes such as impaired health-related quality of life and functional ability (Miaskowski et al., 2004). In addition, some of these symptoms may be indicative of other serious health conditions such as hemorrhage (Miaskowski et al., 2004). As a result, there is a critical need to understand the co-occurrence of multiple symptoms in midlife menopausal women with metabolic syndrome which can inform the future development of targeted symptom management interventions, thereby reducing their symptom burden and improving patient health outcomes.

1.1.1 Symptoms Associated with Menopause

Commonly reported menopausal symptoms are often categorized into somatic symptoms, psychological symptoms, and urogenital symptoms (Chedraui et al., 2007). Somatic symptoms include hot flashes, heart discomfort, sleeping problems, and muscle and joint problems (Chedraui et al., 2007). Psychological symptoms include depression, anxiety, irritability, and physical and mental exhaustion (Chedraui et al., 2007). Urogenital symptoms include sexual disturbance, bladder problems, and vaginal dryness (Chedraui et al., 2007). When comparing the three main stages of menopause, midlife women in peri-menopause and post-menopause experience more severe symptoms than those in pre-menopause (Nisar & Sohoo, 2010; Yim et al., 2015). For example, the mean scores for somatic, psychological, and urogenital symptoms increased significantly from pre-menopause to post-menopause (Yim et al., 2015). Psychological symptoms (i.e. depression and anxiety) and urogenital symptoms (i.e. difficulty urinating, increased frequency of urination) were more severe in peri-menopause and post-menopause women than pre-menopause women (Nisar & Sohoo, 2010). This may be due to fluctuating hormonal levels and changes in menstrual cycles that begin with peri-menopause and continue through post-menopause (El Khoudary et al., 2019). These menopausal symptoms often result in significant symptom burden and lower health-related quality of life for midlife menopausal women (Kaunitz & Manson, 2015; Whiteley et al., 2013).

1.1.2 Symptoms Associated with Metabolic Syndrome

Prevalent symptoms of metabolic syndrome include fatigue, pain, sexual dysfunction, cognitive dysfunction, and altered mood (Kazlauskaite et al., 2020; Kim et al., 2018; Maloney et al., 2010; Mäntyselkä et al., 2010; Repousi et al., 2018; Wolk & Somers, 2007). As a result, midlife women with metabolic syndrome experience more complex symptoms than those without metabolic syndrome (Kazlauskaite et al., 2020; Tziallas et al., 2012). For example, a recent study of midlife women revealed that the presence of metabolic syndrome significantly accelerated the loss of perceptual speed in their cognitive function (Kazlauskaite et al., 2020). Similarly, having metabolic syndrome may lead to increased psychological burden which can negatively influence a healthy lifestyle and can developed symptoms related to lifestyle such as depression and feeling of loneliness (Furihata et al., 2018; Miley-Akerstedt et al., 2018). In addition, metabolic syndrome was associated with decreased sexual activity, desire, and satisfaction among post-menopausal women (Trompeter et al., 2016). As such, midlife women with metabolic syndrome experience a wide array of symptoms and are likely to suffer from impaired health-related quality of life than those without metabolic syndrome (Tziallas et al., 2012).

1.1.3 Symptom Clusters

Midlife women, who are concurrently experiencing peri-menopause and/or post-menopause along with metabolic syndrome, are at potentially higher risk for

experiencing multiple co-occurring symptoms. Multiple co-occurring symptoms are also referred to as “symptom cluster” which is defined as two or more symptoms that are related to each other and occur together (Kim et al., 2005; Matzka et al., 2018). A symptom cluster consists of stable group of symptoms that hold a strong relationship with each other and are relatively independent of other symptom clusters (Kim et al., 2005; Matzka et al., 2018). However, little is known about symptom clusters in midlife menopausal women with metabolic syndrome. Identification of symptom clusters will allow for the targeting of symptom-management strategies that could reduce symptom burden and improve their capacity to maintain a good quality of life over time (Miaskowski et al., 2017).

1.1.4 Multidimensional Characteristics of Symptoms

Contemporary theoretical models conceptualize symptoms as a multidimensional interactive phenomenon (Jablonski, 2007). Symptoms are often characterized based on occurrence, severity, frequency, and distress (Jablonski, 2007). Current symptom cluster research often focuses on one symptom dimension and does not examine whether the number and types of symptom clusters differ based on each symptom dimension (Baggott et al., 2012; Miaskowski et al., 2017). Only a few studies in oncology and advanced chronic kidney diseases have identified and compared symptom clusters using multiple symptom dimensions (Almutary et al., 2016; Baggott et al., 2012; Burrell et al., 2018). A multidimensional approach is needed to understand

what types of symptoms constitute a symptom cluster and to examine if the number and types of symptom clusters are different for each symptom dimension in midlife menopausal women with metabolic syndrome.

1.1.5 Analytic Approaches to Symptom Cluster Research

Miaskowski (2007) discusses two analytic approaches to symptom cluster research using secondary data analysis that include identification of symptom clusters and identification of subgroups of patients who share similar symptom experience using prespecified symptom clusters (Miaskowski et al., 2007). Identification of symptom clusters is a variable-centered approach where highly correlated symptoms are grouped within a symptom cluster and the number and type of symptom clusters are determined (Miaskowski et al., 2007). When using cross-sectional data, one of the commonly used variable-centered statistical methods includes factor analysis such as exploratory factor analysis and confirmatory factor analysis (Miaskowski et al., 2007). Recently, machine-learning based network analysis has been used as another variable-centered method to identify symptom clusters through the use of Walktrap algorithm, a type of data-driven clustering algorithm that uses a series of random walk on a graph trend to find clusters in the network (Papachristou et al., 2019). When using longitudinal data, researchers conduct factor analysis at each time point or multigroup factor analysis to understand the stability in the number and types of symptom clusters over time (Steinmetz et al., 2009).

Another conceptual approach is the person-centered approach where prespecified symptom clusters are used to group patients into meaningful subgroups (Miaskowski et al., 2007). Researchers use latent class/profile analysis for cross-sectional data and latent class growth analysis, growth mixture modeling, and latent transition analysis for longitudinal data (Berlin et al., 2014; Muthén & Muthén, 2000). The cross-sectional person-centered approach identifies latent, homogeneous subgroups within a heterogeneous population based on a set of symptom variables at one point in time (Miaskowski et al., 2007). Similarly, the longitudinal person-centered approach aims to identify latent subgroups of people who follow similar growth curve shapes for the outcome variable over time using the prespecified symptom clusters (Berlin et al., 2014; Muthén & Muthén, 2000).

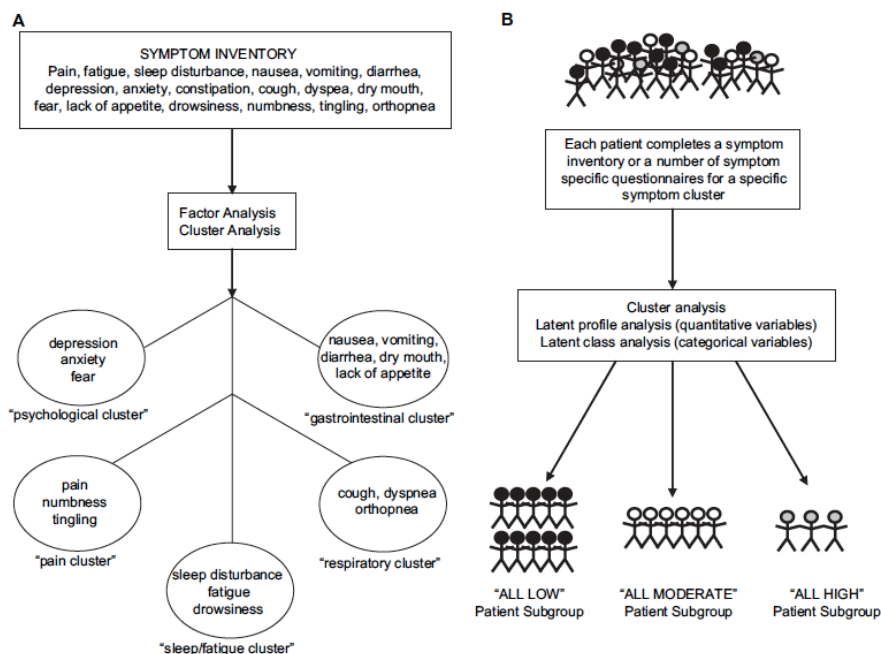


Figure 1: Analytic Approaches to Symptom Cluster Research

(Reprinted from Miaskowski, C., Aouizerat, B. E., Dodd, M., & Cooper, B. (2007). Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. *J Natl Cancer Inst Monogr*, (37), 39-46. By permission of Oxford University Press.)

This dissertation used both the variable-centered approach and the person-centered approach. The variable-centered approach was conducted to identify symptom clusters de novo in midlife menopausal women with metabolic syndrome. In addition, the person-centered approach was conducted to identify latent subgroups of midlife menopausal women with metabolic syndrome at higher risk for greater symptom burden over time.

1.2 Middle Range Nursing Theories

A middle range nursing theory is defined as “a set of related ideas that are focused on a limited dimension of the reality of nursing” (Smith & Liehr, 2018). It

depicts the key concepts and the relationship among concepts which are often used to guide nursing practice and scholarly research (Smith & Liehr, 2018). Two middle range nursing theories, The Theory of Symptom Management and the Theory of Unpleasant Symptoms, have been selected to inform the dissertation study with their relevance to symptom research (Bender et al., 2018; Humphreys et al., 2014; Smith & Liehr, 2018).

1.2.1 The Theory of Symptom Management

The Theory of Symptom Management (TSM) is a middle range theory that is often used as a guide in symptom cluster and symptom management research. The purpose of TSM is to understand the interrelated relationship among the three key concepts, including symptom experience, symptom management strategies, and symptom outcomes. Symptom experience includes perception of symptoms, response to symptoms, and evaluation of symptoms that simultaneously interact with each other. Symptom management strategies include specifications of who, what, when, where, to whom, how much, how, and why the strategy is delivered. Symptom outcomes are measurable outcomes that consist of symptom status as primary outcome and functional status, emotional status, mortality, morbidity and co-morbidity, quality of life, costs, and self-care as distal outcomes. These three key concepts are nested within the domains of nursing science which are person, health/illness, and environment (Bender et al., 2018; Humphreys et al., 2014; Smith & Liehr, 2018).

1.2.2 The Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms (TOUS) is another middle range theory that is often used as a guide in symptom cluster research. TOUS aims to improve understanding of multiple symptoms that occur simultaneously and to provide information for future symptom management interventions, all of which will assist in managing unpleasant symptoms and their negative symptom outcomes. TOUS has three key concepts of influencing factors, symptom, and performance outcome. Influencing factors affect the multidimensional symptom experience in its time, intensity, quality, and distress dimension and consist of physiological, psychological, and situational factors that interact with each other. Symptom is defined as the perceived changes in normal functioning experienced by the patient. It has multiple measurable symptom dimensions and can occur in isolation or multiple symptoms can co-occur. Performance is an outcome that refers to an individual's ability to perform physical, cognitive, and social roles. TOUS highlights the multidimensionality of symptoms and co-occurrence of multiple symptoms (Bender et al., 2018; Lenz et al., 1997; Smith & Liehr, 2018).

1.3 The Conceptual Model for Dissertation

The Symptom Cluster Model (SCM) is adapted from the Theory of Symptom Management and the Theory of Unpleasant Symptoms. SCM will be used to guide the study of symptom clusters in midlife menopausal women with metabolic syndrome. SCM has three key concepts: symptom predictors, symptom cluster experience, and

symptom outcome. Symptom predictors are categorized into physiologic, psychological, and situational factors—all of which influence the symptom cluster experience.

Symptom cluster experience consist of multiple symptom clusters and each symptom cluster has two or more symptoms that are related to each other and occur together. The number and types of symptom clusters may vary according to each symptom dimension (occurrence, severity, frequency, distress). The current dissertation will focus on the most commonly reported symptom dimensions (occurrence, severity). In addition, symptom clusters are likely to change over time and impact symptom outcome such as symptom burden. As a result, different symptom cluster typologies may impact the severity of symptom burden among midlife menopausal women with metabolic syndrome. Therefore, the current dissertation will identify the different symptom cluster typologies of midlife menopausal women with metabolic syndrome at the highest risk for greater symptom burden over time.

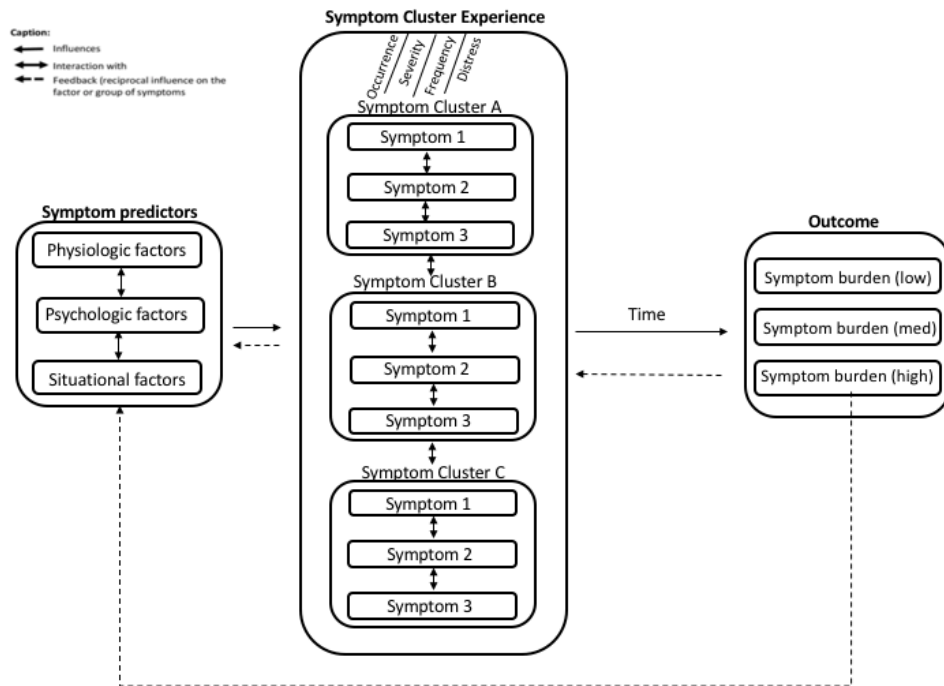


Figure 2: The Symptom Cluster Model

1.4 Purpose Statement and Research Aims

The purpose of this dissertation is to understand the symptom cluster experienced by midlife menopausal women with metabolic syndrome. The following study aims will be fulfilled through five chapters:

Chapter 1 (Aim 1): To provide a rationale for the target population and the importance of symptom cluster research in midlife menopausal women with metabolic syndrome within the theoretical framework used to guide this dissertation

Chapter 2 (Aim 2): To systematically review the current literature in understanding symptoms experienced by midlife menopausal women with metabolic syndrome

Chapter 3 (Aim 3): To identify symptom clusters and key symptoms in midlife menopausal women with metabolic syndrome in a cross-sectional study

Chapter 4 (Aim 4): To identify symptom cluster typologies of midlife menopausal women with metabolic syndrome at high risk for greater symptom burden over time in an exploratory longitudinal study

Chapter 5 (Aim 5): To synthesize the study findings from each study in this dissertation, to discuss study limitations, and to provide recommendations for future nursing research and clinical practice

2. Are There Differences in Symptoms Experienced by Midlife Climacteric Women With and Without Metabolic Syndrome? A Scoping Review

2.1 Introduction

Impacting an estimated quarter of the world's population, metabolic syndrome has become a global public health problem due to its association with type 2 diabetes, cardiovascular disease, and cancer (Saklayen, 2018; Zimmet et al., 2005) Metabolic syndrome is a cluster of metabolic abnormalities and requires at least three metabolic abnormalities to co-occur for its clinical diagnosis (Rochlani et al., 2017). These metabolic abnormalities include elevated waist circumference, elevated triglyceride levels, reduced high-density lipoprotein(HDL), elevated blood pressure, and elevated blood glucose (Zimmet et al., 2005). Women have a higher prevalence than men due to hormonal changes associated with menopause that lead to metabolic disturbances (Beigh & Jain, 2012; Jouyandeh et al., 2013).

To date, symptoms associated with metabolic syndrome have been examined. Clinical diagnostic criteria of metabolic syndrome such as central obesity, hypertension, insulin resistance, and atherogenic dyslipidemia facilitate aging and inflammation in midlife women and result in a unique set of symptoms (Shoelson et al., 2007). These symptoms include pain, sleep disturbance, sexual dysfunction, and altered mood (Kim et al., 2018b; Mäntyselkä et al., 2010; Repousi et al., 2018; Shoelson et al., 2007; Wolk & Somers, 2007). In addition, having metabolic syndrome may lead to a psychological

burden, which can negatively influence a healthy lifestyle and develop symptoms related to lifestyle such as feeling of loneliness (Furihata et al., 2018; Miley-Akerstedt et al., 2018). A cross-sectional cohort study found that people with metabolic syndrome are more likely to suffer from neck pain compared to healthy people (Mäntyselkä et al., 2010). In addition, the diagnosis of metabolic syndrome has been significantly associated with a higher prevalence of sexual dysfunction (Francesco et al., 2018). As such, midlife women with metabolic syndrome experience a complex array of symptoms that leads to significant symptom burden and impaired health-related quality of life (Repousi et al., 2018; Saboya et al., 2016; Shoelson et al., 2007; Wolk & Somers, 2007).

There are three main stages of menopause that include pre-menopause, peri-menopause, and post-menopause (Butler & Santoro, 2011). Peri-menopause refers to a period of time when a woman experiences irregularity in the menstrual cycles of at least 7 days from fluctuating hormonal levels or skips a menstrual cycle (Butler & Santoro, 2011; El Khoudary et al., 2019). When a woman does not have menses for more than 12 consecutive months, they enter into post-menopause. Peri-menopause and post-menopause are also referred to as the climacteric which is a period of time from the decline to end in ovarian activity and function (Taechakraichana et al., 2002). Hormonal changes, such as a decrease in estrogen, and changes in menstrual cycles start during peri-menopause and continue through post-menopause (El Khoudary et al., 2019). A climacteric woman has shown to experience significantly more menopausal symptoms

such as hot flashes, night sweats, sleep disturbances, and altered mood than a woman in pre-menopause (Freeman, 2010; Gao et al., 2013). These troublesome symptoms often last more than a decade which results in impaired health-related quality of life (Bruce & Rymer, 2009; Kaunitz & Manson, 2015; Nelson et al., 2005; Whiteley et al., 2013).

Midlife refers to a period of life between age 40 to 65 years in which a complex interaction of biological, psychological, and social factors exists and affects the overall well-being of women (A. J. Thomas et al., 2018; Wong et al., 2012). This is when women begin to experience biochemical changes with aging and psychological distress with social role changes (Wong et al., 2012). Compared to other life stages, midlife is a vulnerable period of time when women begin to experience adverse changes in lipid and endocrine profiles that accelerate with peri-menopause (Harlow & Derby, 2015).

When the two conditions of metabolic syndrome and climacteric co-occur, midlife climacteric women with metabolic syndrome are placed at a higher risk for significant symptom burden (Bruce & Rymer, 2009; Nelson et al., 2005). This may be due to the combined effects of symptoms associated with metabolic syndrome and climacteric respectively. To date, there are studies that systematically reviewed only certain types of symptoms (i.e. vasomotor symptoms) experienced by midlife climacteric women with metabolic syndrome (Kravitz et al., 2014). Yet, none of the studies have provided a broad review of their symptoms and how their symptoms may differ from midlife climacteric women without metabolic syndrome (Bruce & Rymer, 2009; Nelson

et al., 2005). A comprehensive understanding of symptoms experienced by midlife climacteric women with metabolic syndrome is critical because when these symptoms are underdiagnosed or undertreated, they may have a negative impact on patient outcomes such as quality of life, functional ability, and health outcomes (Miaskowski et al., 2004, 2017). Furthermore, findings from this scoping review will serve as a knowledge basis to inform future development of targeted symptom management interventions (Miaskowski et al., 2004, 2017).

An initial search of PROSPERO, Open Science Framework (OSF), Cochrane Database of Systematic Reviews, and the Joanna Briggs Institute Database of Systematic Reviews and Implementation Reports indicated that there are neither systematic reviews nor scoping reviews, published or in progress, on this topic. A scoping review synthesizes research evidence and aims to map the existing literature pertaining to a research question (Pham et al., 2014). A scoping review was selected for this study because there is a critical need for examining the extent of research on the symptom experience in midlife climacteric women with metabolic syndrome and to identify gaps for future research (Munn et al., 2018; Pham et al., 2014). Therefore, the objective of this scoping review is to systematically review the current literature and to answer the following research questions.

- 1) What are the types and prevalence of symptoms experienced by midlife climacteric women with metabolic syndrome?

- 2) Do differences exist in the types and/or prevalence of symptoms between midlife climacteric women with and without metabolic syndrome?
- 3) Do the symptoms occur in clusters in midlife climacteric women with metabolic syndrome?

2.2 Methods

The Joanna Briggs Institute (JBI) Scoping Review methodology served as a guide for this scoping review (Peters et al., 2020; Peters et al., 2015). An a priori scoping review protocol was utilized which provides a detailed plan for the scoping review and decreases the risk of reporting bias (Peters et al., 2020; Peters et al., 2015). In addition, we adhered to the Preferred Reporting Items for and Meta-Analysis extension for Scoping Review for the development of this manuscript (PRISMA-ScR) (Tricco et al., 2018). The project was registered with Open Science Framework (Registration DOI: 10.17605/OSF.IO/8NV67).

Eligibility criteria

Eligibility criteria were selected in alignment with the review questions. The criteria categories included participants, concept and context as well as types of evidence (Aromataris & Munn, 2020). Details of the criteria are presented below.

Participants

Participants included midlife women with metabolic syndrome. Metabolic syndrome is defined as having three or more of the following conditions: elevated waist

circumference, elevated triglyceride, reduced HDL, elevated blood pressure, and elevated blood glucose (Zimmet et al., 2005). Midlife women aged 40-65 years were included (A. J. Thomas et al., 2018). Studies of mixed population of age were included as long as there was a sub-analysis with midlife women. For the second aim, studies that provided a comparison of the types and/or symptoms between midlife women with and without metabolic syndrome were included.

Concepts

The concepts included symptom(s) and symptom cluster(s). Symptom is defined as the subjective expression of physical or mental disturbances experienced by the patient (Cox et al., n.d.; Miaskowski et al., 2017). Symptom cluster is defined as a group of two or more co-occurring symptoms that are associated with each other (Cox et al., n.d.; Miaskowski et al., 2017). Therefore, studies that explored the types (category of symptoms) and/or prevalence of symptoms experienced by midlife women with metabolic syndrome in peri-menopause and post-menopause were identified. In addition, studies that identified symptom clusters in this population were also included.

Context

This scoping review considered studies that included the context of climacteric that includes peri-menopause (early and late peri-menopause) and/or post-menopause (Taechakraichana et al., 2002).

Types of evidence

Study designs considered included quantitative, qualitative, and mixed methods study designs. Additionally, case studies, systematic reviews, conference and abstract papers, and dissertations were included in this scoping review. Exclusion criteria consisted of editorials, letters to the editor, commentaries, and literature reviews without systematic approach due to their potential for bias and animal-only studies due to lack of data relevance during the searching.

The Search

Information sources

The databases searched included PubMed (MEDLINE), Embase (Elsevier), Web of Science (Clarivate), CINAHL (EBSCO), PsycInfo (APA). Sources of unpublished studies and grey literature included Proquest Dissertation & Theses, and Open Grey.

Search strategy

The search strategy aimed to find both published and unpublished primary studies including grey literature. A three-step search strategy was conducted. First, there was an initial exploratory search of PubMed (MEDLINE) and CINAHL (EBSCO) to identify relevant articles on the topic. With the help of a medical research librarian (LL), an analysis of keywords included in the title and abstracts of relevant articles as well as index terms was conducted to finalize a search strategy within PubMed (MEDLINE). Table 1 details the search strategy used for PubMed (MEDLINE). Second, the finalized PubMed (MEDLINE) search strategy was translated into each included database using

the appropriate syntax and index terms for that database to search for relevant articles. The search was not limited by language or date. Search hedges or database filters were used to remove publication types such as editorials, letters, case reports, and comment as was appropriate for each database. The search was conducted on February 2, 2021 and found a total of 6,462 citations. Complete reproducible search strategies, including date ranges and search filters, for all databases is detailed in Appendix I. Third, the reference lists of the final included articles were reviewed and citation tracking in Web of Science and Scopus was used to identify relevant studies for full text review but none were added.

Table 1: Search Strategy for PubMed (MEDLINE)

Included dates: 1966 and selected coverage of literature prior to that period to February 2, 2021

1	"Metabolic Syndrome"[Mesh] OR "Abdominal obesity metabolic syndrome" [Supplementary Concept] OR "Metabolic syndrome"[tw] OR "Metabolic Syndromes"[tw] OR "Insulin Resistance Syndrome X"[tw] OR "Metabolic X Syndrome"[tw] OR "Dysmetabolic Syndrome X"[tw] OR "Reaven Syndrome"[tw] OR "Metabolic Cardiovascular Syndrome"[tw] OR "Metabolic Cardiovascular Syndrome"[tw] OR "Syndrome X"[tw]	61,460
2	"Menopause"[Mesh] OR "Postmenopause"[Mesh] OR "Perimenopause"[Mesh] OR Menopause[tw] OR perimenopause[tw] OR "peri menopause"[tw] OR "post menopause"[tw] OR "postmenopause"[tw] OR Postmenopausal[tw] OR "Post menopausal"[tw] OR menopausal[tw] OR perimenopausal[tw] OR "peri menopausal"[tw] OR Menopauses[tw] OR "Climacteric"[Mesh] OR Climacterics[tw] OR climacterium[tw]	114,305
3	#1 AND #2	1527
4	NOT (Editorial[pt] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh])	1429

Selection of Evidence Sources

After the search, all identified studies were uploaded into Covidence (Veritas Health Innovation, Melbourne, Australia), a software system for managing systematic reviews and duplicates were removed by the software. A final set of 3,813 citations was left to be screened in the title/abstract phase. A pilot screening was conducted for a random sample of 30 articles in order to test the pre-determined inclusion and exclusion and to train the screeners. Two independent reviewers then screened the titles and abstracts against the finalized inclusion/exclusion criteria. For the full-text screening stage, papers were also reviewed in detail by two independent reviewers and were excluded if they did not meet the inclusion criteria. Any conflicts between the two independent reviewers were resolved through discussion at each stage of the selection process. For papers not published in English that met the inclusion criteria during the title/abstract screening, the abstracts were reviewed for usable data. However, we chose not to have these papers translated due to restrictions in funding and they were excluded at the full text screening phase. The results of the search are presented PRISMA-ScR flow diagram (Tricco et al., 2018).

Data charting

We used a modified JBI data extraction tool (JBI SUMARI, Adelaide, Australia) for data charting. Two independent reviewers charted and reviewed the data. The data included study characteristics such as name of author(s), year of publication, study location, study design, and symptom rating instrument. In addition, we charted

population characteristics (demographic and clinical characteristics), concept (types and/or prevalence of symptoms defined as the reported frequency/percentage of population experiencing symptoms, comparison of symptoms between metabolic syndrome and without metabolic syndrome group; presence of symptom clusters), context (climacteric stage), and key study findings related to the scoping review questions (Reilly et al., 2013; Spronk et al., 2019). Any conflicts between the two independent reviewers were resolved through discussion during charting.

Data synthesis

Data was analyzed using the charted data according to each review question and the results were discussed with two independent reviewers. Data was presented in a tabular format aligning with the questions. A narrative summary accompanies the tables and aligns the results with the review questions.

2.3 Results

Study inclusion

Database searches yielded 6,462 articles with 2,649 duplicates articles removed, thereby leaving 3,813 articles for title and abstract screening. After title and abstract screening, the full texts of the 48 articles were assessed in accordance to inclusion criteria with 39 articles were excluded. As a result, a total of 9 articles initially met inclusion for this scoping review. See Figure 3 for the PRISMA-ScR flow diagram of search results.

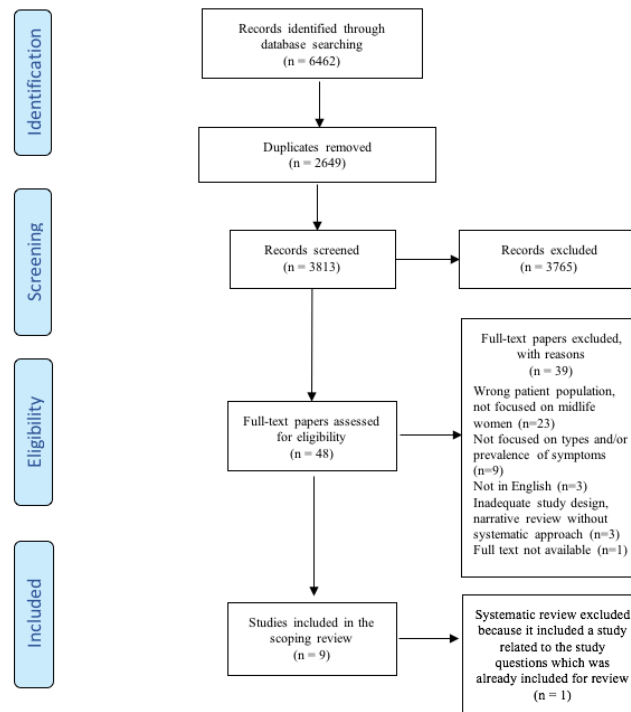


Figure 3: PRISMA-ScR Flow Diagram of Search Results

Characteristics of included studies

Study characteristics of all included studies in this review is presented in Table 2 (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llaneza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018; van Dijk et al., 2015). Among a total of nine articles, seven were cross-sectional design with one prospective cohort study, and one systematic review. The systematic review conducted in Netherlands by van Dijk et al 2015 has been excluded from data analysis because it included only one study related to our questions (Lee et al., 2012), which was already included for review, thereby leaving eight articles. All included studies were published between 2009 and 2020 and were conducted outside the United States. A variety of

symptom rating instruments were used to measure the symptoms with Female Sexual Function Index as the most commonly used instrument (Dutra da Silva et al., 2020; Kim et al., 2011; Martelli et al., 2012; Otunctemur et al., 2015). Midlife women in all of the studies were in post-menopause and only one study included women in both peri-menopause and post-menopause.

Table 2: Study Characteristics

Author (Year)	Location	Study design	Symptom Rating Tool	Population	Population characteristics	Climacteric stage
da Silva et.al., (2020)	Brazil	Cross-sectional design	Female Sexual Function Index	<ul style="list-style-type: none"> • N=291 post-menopausal women in total • N=153 with metabolic syndrome (52.6%) • N=138 without metabolic syndrome (47.4%) 	<ul style="list-style-type: none"> • Aged between 40 and 65 years; • Mean age: 54.4 ± 6 years, Race: White (58.2%), Brown (26.1%), Black (15.7%) • Mean age: 53.4 ± 4.8 years; p=0.118, Race: White (58.0%), Brown (24.6%), Black (17.4%); p=0.908 	Post-menopause
Kim et.al., (2011)	South Korea	Cross-sectional design	Female Sexual Function Index	<ul style="list-style-type: none"> • N=773 menopausal women • N=94 (12.2%) with metabolic syndrome; 	<ul style="list-style-type: none"> • Aged 40-65 years (median: 48 years); • Median age: 50 (47-55) years, comorbidity of 	Pre-menopause*, perimenopause, post-menopause

				<ul style="list-style-type: none"> • N=679 (87.8%) without metabolic syndrome 	<p>hypertension and hypercholesterolemia (32.98%, 24.47%);</p> <ul style="list-style-type: none"> • Median age: 48 (45-51) years; p<0.001**, comorbidity of hypertension and hypercholesterolemia (4.27%, 3.39%); p<0.001** 	
Lee et.al., (2012)	South Korea	Cross-sectional design	Menopause Rating Scale	<ul style="list-style-type: none"> • N=183 post-menopausal women; • N=64 (35.0%) with metabolic syndrome; • N=119 (65.0%) without metabolic syndrome 	<ul style="list-style-type: none"> • NS • Mean age: 56.1 ± 6.8 years, Years since menopause: 6.8 ± 4.2 years • Mean age: 54.2 ± 4.9 years; p=0.020**, Years since menopause: 5.3 ± 4.2 years; p=0.026** 	Post-menopause
Llaneza et.al., (2009)	Spain	Prospective cohort study	Cervantes Scale	<ul style="list-style-type: none"> • N=110 insulin resistant post-menopausal women; • N=56 (50.9%) with 	<ul style="list-style-type: none"> • Aged between 50 and 65 years • NS • NS 	Post-menopause

				metabolic syndrome <ul style="list-style-type: none"> • N=54 (49.1%) without metabolic syndrome 		
Martelli et.al., (2011)	Italy	Cross-sectional design	Female Sexual Function Index, Female Sexual Distress Scale	<ul style="list-style-type: none"> • N=208 post-menopausal women with metabolic syndrome • N=103 (49.5%) with metabolic syndrome; • N=105 (50.5%) without metabolic syndrome 	<ul style="list-style-type: none"> • Aged between 50 and 65 years • Mean age: 57.7 ± 4.9 years; Years of menopause: 8.2 ± 5.9 years • Mean age: 56.5 ± 5 years; p=0.08, Years of menopause: 7.2 ± 5.5 years; p=0.22 	Post-menopause
Otuncemur et.al., (2014)	Turkey	Prospective cross-sectional design	Female Sexual Function Index	<ul style="list-style-type: none"> • N=400 women with metabolic syndrome • N= 200 pre-menopause and post-menopause with metabolic syndrome • N=200 pre-menopause and post- 	<ul style="list-style-type: none"> • NS • Mean age: 48.52 ± 8.16 years, Diagnosis of hypertension: 62% • Mean age: 48.81 ± 8.31 years); p=0.52, Diagnosis of hypertension: 42.5%; p<0.001** 	Pre-menopause*, Post-menopause

				menopause without metabolic syndrome		
Ryu et.al., (2015)	South Korea	Cross-sectional design	Menopause Rating Scale	<ul style="list-style-type: none"> • N=1,906 Korean postmenopausal women • N=370 (19.4%) with metabolic syndrome 	<ul style="list-style-type: none"> • Aged between 45-65 years • NS 	Post-menopause
Sayan et.al., (2018)	Turkey	Cross-sectional design	Study-Designed Questionnaire	<ul style="list-style-type: none"> • N=200 postmenopausal women; • N=48 (24.0%) with metabolic syndrome; • N=152 (76.0%) without metabolic syndrome 	<ul style="list-style-type: none"> • Mean age: 51.9 ± 5.65 years, Menopause age: 46.8 ± 5.2 years • NS • NS 	Post-menopause
Van Dijk et.al., (2014)	Netherlands	Systematic review	Menopause Rating Scale	<ul style="list-style-type: none"> • N=1 study by Lee et.al., (2012) focused on the association between vasomotor symptoms and metabolic syndrome 	<ul style="list-style-type: none"> • NA 	Post-menopause

NS: not specified; NA: not applicable; NR: not reported

*Not included in this analysis

** Statistically Significant $p < 0.05$

The type and prevalence of symptoms

Urogenital symptoms, vasomotor symptoms, psychological symptoms, sleep symptoms, and somatic symptoms were consistently observed in midlife climacteric women with metabolic syndrome (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llanaez et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). Urogenital symptoms were the most frequently assessed while sleep and somatic symptoms were the least frequently assessed. Some of the studies reported aggregated symptoms based on a specific body system whereas other studies focused on specific individual symptoms. To account for such difference, symptoms were categorized into either grouped symptoms or individual symptoms to allow for a better comparison across the studies. Refer to Table 3 for further details.

Urogenital symptoms: grouped symptoms

More than half of the articles (75%) discussed urogenital symptoms experienced by midlife climacteric women with metabolic syndrome (Dutra da Silva et al., 2020; Lee et al., 2012; Llanaez et al., 2009; Otunctemur et al., 2015). These urogenital symptoms were categorized into grouped urinary symptoms which is a constellation of difficulty in urinating, increased need to urinate, bladder incontinence, and sexual symptoms which is a constellation of change in sexual desire, arousal, lubrication, satisfaction, orgasm, and pain during sexual intercourse. Among all the grouped symptoms, urogenital symptoms had the highest prevalence. The prevalence of grouped urinary symptoms

was 67.2% which was reported in only one study (Lee et al., 2012) while the prevalence of grouped sexual symptoms ranged from 46.0% to 81.3% (Dutra da Silva et al., 2020; Lee et al., 2012; Llanaez et al., 2009; Otunctemur et al., 2015).

Urogenital symptoms: individual symptoms

Among the six studies on grouped urogenital symptoms, three studies also focused on reporting individual sexual symptoms (Kim et al., 2011; Lee et al., 2012; Martelli et al., 2012) One study discussed the prevalence of individual sexual symptoms in midlife climacteric women with metabolic syndrome while two studies included those only in post-menopause (Kim et al., 2011; Lee et al., 2012; Martelli et al., 2012). Some of the most frequently reported individual sexual symptoms were vaginal dryness (62.5%), change in sexual desire (44.7%), and decreased sexual lubrication (13.8%-44.7%) (Kim et al., 2011; Lee et al., 2012; Martelli et al., 2012). None of these studies included individual urinary symptoms experienced in this population.

Vasomotor symptoms: grouped symptoms

Vasomotor symptoms and their prevalence were identified for midlife women with metabolic syndrome in post-menopause in three studies (Lee et al., 2012; Ryu et al., 2015; Sayan et al., 2018). These grouped vasomotor symptoms included hot flash, sweating, and night sweats. The overall reported prevalence of grouped vasomotor symptoms ranged from 65.4% to 75.0% (Lee et al., 2012; Ryu et al., 2015; Sayan et al., 2018). In addition, the number of clinical diagnostic components of metabolic syndrome

had a significant linear association with the prevalence of vasomotor symptoms (Ryu et al., 2015). For example, there was a 65.4% prevalence with three diagnostic components satisfied and it increased to 68.3% when four diagnostic components were satisfied (Ryu et al., 2015).

Vasomotor symptoms: individual symptoms

There were no studies that focused on individual vasomotor symptoms and their prevalence.

Psychological symptoms: grouped symptoms

One study reported the prevalence of their grouped psychological symptoms which is a combination of depression, anxiety, and irritability (Llaneza et al., 2009). This study reported that 71.4% of midlife women with metabolic syndrome in post-menopause suffer from low-medium level psychological symptoms and 10.7% from a high level of psychological symptoms. Low-medium level symptoms refer to psychological symptom scores between -1 SD and +1 SD over the reference score and high level between +1 SD and +2 SD over the reference score on the Cervantes Scale (Llaneza et al., 2009). Among them, 8.9% were experiencing a severe degree of psychological symptoms who had psychological symptoms scores +2 SD or over than the reference score (Llaneza et al., 2009).

Psychological symptoms: individual symptoms

The prevalence of individual symptoms of psychological symptoms were discussed in one study which included mental exhaustion, irritability, depressive mood, and anxiety (Lee et al., 2012). Among them, mental exhaustion (84.4%) was the most commonly reported while other individual psychological symptoms such as irritability, depressive mood, and anxiety had a reported prevalence rate between 50.0% and 51.6% (Lee et al., 2012).

Sleep symptoms: grouped symptoms

One study discussed the grouped sleep symptoms experienced by midlife women with metabolic syndrome in post-menopause (Lee et al., 2012). These grouped sleep symptoms were a combination of difficulty falling asleep, difficulty staying asleep, and early morning awakenings (Lee et al., 2012). More than half (57.8%) of midlife women with metabolic syndrome in post-menopause reported these sleep symptoms (Lee et al., 2012).

Sleep symptoms: individual symptoms

There were no studies that focused on individual sleep symptoms and their prevalence.

Somatic symptoms: grouped symptoms

None of the studies have discussed the prevalence of grouped somatic symptoms experienced by midlife climacteric women with metabolic syndrome.

Somatic symptoms: individual symptoms

One study reported that midlife women with metabolic syndrome in post-menopause experienced a wide array of individual somatic symptoms such as muscle and joint discomfort, and heart discomfort (Lee et al., 2012). The most commonly reported individual somatic symptom was the muscle and joint discomfort (76.6%) (Lee et al., 2012).

Table 3: Prevalence of Symptoms

Author (Year)	Reported Symptoms	Prevalence of Symptoms	Prevalence of Severe Symptoms
Urogenital Symptoms			
da Silva et.al., (2020)	Hypoactive sexual dysfunction disorder (HSDD): sexual desire, arousal, lubrication, orgasm, satisfaction, pain	Grouped Symptom: <ul style="list-style-type: none"> • HSDD (61.4 %) Individual Symptom: NA	NA
Kim et.al., (2011)	Impaired sexual function (sexual desire, arousal, lubrication, orgasm, satisfaction, pain)	Grouped Symptom: NA Individual Symptom: <ul style="list-style-type: none"> • Impaired sexual desire (44.7%) • Impaired arousal (29.8%) • Impaired lubrication (13.8%) • Impaired orgasm (20.2%) • Impaired satisfaction (19.1%) • Pain during intercourse (11.7%) 	NA

Lee et.al., (2012)	Sexual problem (change in sexual desire, in sexual activity, and satisfaction), bladder problem (difficulty in urinating, increased need to urinate, bladder incontinence), vaginal dryness	Grouped Symptom: <ul style="list-style-type: none"> Sexual problem (81.3%) Bladder problem (67.2%) Individual Symptom: <ul style="list-style-type: none"> Vaginal dryness (62.5%) 	NA
Llaneza et.al., (2009)	Sexual problem (sexual desire, arousal, orgasm, satisfaction, lubrication, pain)	Grouped Symptom: <ul style="list-style-type: none"> Low-medium level of sexual problem (46.4%) High level of sexual problems (46.4%) Individual Symptom: NA	Grouped Symptom: <ul style="list-style-type: none"> Severe sexual problem (1.8%) Individual Symptom: NA
Martelli et.al., (2011)	Sexual dysfunction (sexual desire, arousal, lubrication, orgasm, satisfaction, pain during intercourse)	Grouped Symptom: NA Individual Symptom: <ul style="list-style-type: none"> Decreased sexual desire (44.7%) Decreased arousal (37%) Decreased lubrication (44.7%) Decreased orgasm (39.8%) Decreased satisfaction (36.9%) Pain during intercourse (40.8%) 	NA
Otunctemur et. al., (2014)	Female Sexual Dysfunction (sexual desire, arousal, lubrication, orgasm, satisfaction, pain)	Grouped Symptom: <ul style="list-style-type: none"> Female sexual dysfunction (46%) Individual Symptom: NA	NA
Vasomotor Symptoms			
Lee et.al., (2012)	Hot flushes, sweating	Grouped Symptom: <ul style="list-style-type: none"> Hot flushes and sweating (75.0%) Individual Symptom: NA	NA

Ryu et.al., (2015)	Hot flushes, sweating, night sweats	<p>Grouped Symptom:</p> <ul style="list-style-type: none"> Number of diagnostic components of metabolic syndrome and presence of vasomotor symptoms, p=0.001** <p>0: 53.6%* 1: 56.8%* 2: 57.1%* 3: 65.4% 4: 68.3% 5: 65.4%</p> <p>Individual Symptom: NA</p>	<p>Grouped Symptom:</p> <ul style="list-style-type: none"> Number of diagnostic components of metabolic syndrome and severity of vasomotor symptoms, p=0.093 <p>0: 23.0%* 1: 24.9%* 2: 21.5%* 3: 28.8% 4: 27.7% 5: 38.5%</p> <p>Individual Symptom: NA</p>
Sayan et.al., (2018)	Hot flushes, sweating, night sweats	<p>Grouped Symptom:</p> <ul style="list-style-type: none"> Hot flushes, sweating, night sweats (70.9%) <p>Individual Symptom: NA</p>	<p>Grouped Symptom:</p> <ul style="list-style-type: none"> No severity of hot flushes, sweating, night sweats (29.2%) Moderate severity of hot flushes, sweating, night sweats (2.1%) Severe severity of hot flushes, sweating, night sweats (68.8%) <p>Individual Symptom: NA</p>

Psychological Symptoms			
Lee et.al., (2012)	Mental exhaustion, irritability, depressive mood, anxiety	Grouped Symptom: NA Individual Symptom: <ul style="list-style-type: none"> • Mental exhaustion (84.4%) • Irritability (51.6%) • Depressive mood (50.0%) • Anxiety (50.0%) 	NA
Llaneza et.al., (2019)	Psychological domain (depression, anxiety, irritability)	Grouped Symptom: <ul style="list-style-type: none"> • Low-medium level of psychological symptoms (71.4%) • High level of psychological symptoms (10.7%) Individual Symptom: NA	Grouped Symptom: <ul style="list-style-type: none"> • Severe psychological symptoms (8.9%) Individual Symptom: NA
Sleep Symptoms			
Lee et.al., (2012)	Sleeping problem (difficulty falling asleep, difficulty staying asleep, early morning awakenings)	Grouped Symptom: <ul style="list-style-type: none"> • Sleeping problem (57.8%) Individual Symptom: NA	NA
Somatic Symptoms			
Lee et.al., (2012)	Muscle and joint discomfort, heart discomfort	Grouped Symptom: NA Individual Symptom: <ul style="list-style-type: none"> • Heart discomfort (59.4%) • Muscle and joint discomfort (76.6%) 	NA

HSDD: hypoactive sexual dysfunction disorder; NA: Not applicable

**Not included in this analysis*

*** Statistically Significant $p < 0.05$*

Metabolic syndrome vs. Without metabolic syndrome group

Comparison in types and/or prevalence of symptoms between midlife climacteric women with and without metabolic syndrome is shown in Table 4. These symptoms

included grouped and/or individual urogenital symptoms, vasomotor symptoms, psychological symptoms, sleep symptoms, and somatic symptoms.

Urogenital symptoms: grouped symptoms

Among the six studies, five studies compared the grouped urogenital symptoms between midlife women with metabolic syndrome group and without metabolic syndrome group in post-menopause (Dutra da Silva et al., 2020; Lee et al., 2012; Llanaza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015). For the grouped urogenital symptoms, all of the studies found a higher prevalence of grouped urogenital symptoms in the metabolic syndrome group compared to the without metabolic syndrome group, but statistical significance was only reached in four studies (Dutra da Silva et al., 2020; Llanaza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015). In contrast, one study yielded a contradictory finding that a low-medium level of grouped sexual problems was more prevalent in the without metabolic syndrome group (57.4% vs. 46.4%, $p>0.05$) even though a high level of grouped sexual problems was more prevalent in the metabolic syndrome group (46.4% vs. 27.8%, $p=0.044$) (Llanaza et al., 2009).

Urogenital symptoms: individual symptoms

Three studies focused on comparing the individual urogenital symptoms between the two groups (Kim et al., 2011; Lee et al., 2012; Martelli et al., 2012). While the three studies reported majority of urogenital symptoms to be more prevalent in the

metabolic syndrome group, statistical significance was reached in only study (Martelli et al., 2012).

Vasomotor symptoms: grouped symptoms

Two studies have compared the prevalence of grouped vasomotor symptoms between midlife women with and without metabolic syndrome in post-menopause (Lee et al., 2012; Sayan et al., 2018). These grouped vasomotor symptoms included hot flashes, night sweats, and cold sweats. Among them, one study found that the grouped vasomotor symptoms of hot flashes and sweating (75%) were more prevalent in the metabolic syndrome group than the without metabolic syndrome group (60.1%) which was statistically significant, $p=0.034$ (Lee et al., 2012). In contrast, a study by Sayan et al (2018) reported mixed findings based on the severity of grouped vasomotor symptoms between the two groups (Sayan et al., 2018).

Vasomotor symptoms: individual symptoms

There were no studies that compared the individual vasomotor symptoms and their prevalence between midlife climacteric women with and without metabolic syndrome.

Psychological symptoms: grouped symptoms

One study compared the prevalence of grouped psychological symptoms that included depression, anxiety, and irritability in midlife women with and without metabolic syndrome in post-menopause (Llaneza et al., 2009). The without metabolic

syndrome group experienced more low-medium level of grouped psychological problems while the metabolic syndrome group experienced more high level of grouped psychological problems, but the difference was not statistically significant (Llaneza et al., 2009).

Psychological symptoms: individual symptoms

One study compared the prevalence of individual psychological symptoms between midlife women with and without metabolic syndrome in post-menopause (Lee et al., 2012). The without metabolic syndrome group experienced higher prevalence in depressive mood (50% vs. 63.9%; $p = 0.049$), irritability (51.6% vs. 54.6%; $p=0.405$), and mental exhaustion (84.4% vs. 86.6%; $p=0.422$) (Lee et al., 2012). In contrast, the metabolic syndrome group reported a higher prevalence in only anxiety (50.0% vs. 42.9%, $p=0.221$) (Lee et al., 2012).

Sleep symptoms: grouped symptoms

While it did not reach significance, one study reported that the without metabolic syndrome group frequently experienced grouped sleep symptoms that is a constellation of difficulty falling asleep, staying asleep, and early morning awakenings (Lee et al., 2012).

Sleep symptoms: individual symptoms

There were no studies that compared the individual sleep symptoms and their prevalence between midlife climacteric women with and without metabolic syndrome.

Somatic symptoms: grouped symptoms

None of the included studies compared the grouped somatic symptoms and their prevalence between midlife climacteric women with and without metabolic syndrome.

Somatic symptoms: individual symptoms

One study by Lee et al (2012) found that the prevalence of individual somatic symptoms that included muscle and joint discomfort and heart discomfort (Lee et al., 2012). All of the individual somatic symptoms were higher in the metabolic syndrome group than without metabolic syndrome group, but was not statistically significant (Lee et al., 2012).

Table 4: Metabolic Syndrome vs. Without Metabolic Syndrome Group

Author (Year)	Symptom	Metabolic Syndrome Group	Non-Metabolic Syndrome Group	P value
Urogenital Symptoms				
da Silva et.al., (2020)	Grouped symptom <ul style="list-style-type: none">Hypoactive sexual disorder	61.4%	42.8%	0.001**
Kim et.al., (2011)	Individual symptom <ul style="list-style-type: none">Impaired sexual desire	44.7%	39.3%	0.369
	<ul style="list-style-type: none">Impaired sexual arousal	29.8%	33.7%	0.485
	<ul style="list-style-type: none">Impaired sexual lubrication	13.8%	11.0%	0.391
	<ul style="list-style-type: none">Impaired sexual orgasm	20.2%	19.6%	0.890
	<ul style="list-style-type: none">Impaired sexual satisfaction	19.1%	13.3%	0.151
	<ul style="list-style-type: none">Pain during intercourse	11.7%	7.1%	0.143
Lee et.al., (2012)	Grouped symptom <ul style="list-style-type: none">Sexual problem	81.3%	73.1%	0.147

	<ul style="list-style-type: none"> • Bladder problem 	67.2%	58.0%	0.145
	Individual symptom			
	<ul style="list-style-type: none"> • Vaginal dryness 	62.5%	58.8%	0.373
Llaneza et.al., (2009)	Grouped symptom			
	<ul style="list-style-type: none"> • Low-medium level of sexual problems 	46.4%	57.4%	>0.05
	<ul style="list-style-type: none"> • High level of sexual problems 	46.4%	27.8%	0.044**
Martelli et.al., (2011)	Grouped symptom			
	<ul style="list-style-type: none"> • Sexual dysfunction 	37.9%	19.0%	0.003**
	Individual symptom			
	<ul style="list-style-type: none"> • Impaired sexual desire 			
	<ul style="list-style-type: none"> • Impaired sexual arousal 	44.7%	34.1%	0.002**
	<ul style="list-style-type: none"> • Impaired sexual lubrication 	37.0%	17.1%	0.004**
	<ul style="list-style-type: none"> • Impaired sexual orgasm 	44.7%	17.1%	<0.0005**
	<ul style="list-style-type: none"> • Impaired sexual satisfaction 	39.8%	19.0%	0.002**
	<ul style="list-style-type: none"> • Pain during intercourse 	36.9%	15.2%	<0.0005**
		40.8%	16.2%	<0.0005**
Otunctemur et.al., (2014)	Grouped symptom			
	<ul style="list-style-type: none"> • Female sexual dysfunction 	46.0%	34.0%	<0.05**
Vasomotor Symptoms				
Lee et.al., (2012)	Grouped symptom			
	<ul style="list-style-type: none"> • Hot flushes, sweating 	75.0%	60.1%	0.034**
Sayan et.al., (2018)	Grouped symptom			
	<ul style="list-style-type: none"> • No severity of hot flushes, sweating, night sweat 	29.2%	15.8%	0.037**
	<ul style="list-style-type: none"> • Moderate severity of hot flushes, sweating, night sweat 	2.1%	10.5%	0.026**
	<ul style="list-style-type: none"> • Severe severity of hot flushes, sweating, night sweat 	68.8%	73.7%	0.164

Psychological Symptoms				
Lee et.al., (2012)	Individual symptom			
	• Depressive mood	50.0%	63.9%	0.049**
	• Irritability	51.6%	54.6%	0.405
	• Anxiety	50.0%	42.9%	0.221
Llaneza et.al., (2009)	Grouped symptom			
	• Low-medium level of psychological problems	71.4%	74.1%	>0.05
	• High level of psychological problems	10.7%	9.3%	>0.05
Sleep Symptoms				
Lee et.al., (2012)	Grouped symptom			
	• Sleeping problem	57.8%	61.3%	0.378
Somatic Symptoms				
Lee et.al., (2012)	Individual symptom			
	• Heart discomfort	59.4%	58.0%	0.491
	• Muscle and joint problem	76.6%	72.2%	0.328

** Statistically Significant $p < 0.05$

Presence of Symptom Clusters

There were no studies that reported the presence of symptom clusters in midlife women with metabolic syndrome in peri-menopause and post-menopause.

Synthesis of Results

This scoping review included a total of eight studies in the analysis on the topic of symptoms experienced by midlife climacteric women with metabolic syndrome (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llaneza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018).

Symptoms

The included studies reported that these midlife climacteric women with metabolic syndrome experience urogenital, vasomotor, psychological, sleep, and somatic symptoms with a wide range of prevalence. Their overall symptom experience yielded different and mixed findings when comparing midlife climacteric women with and without metabolic syndrome. However, none of the studies have focused on symptom clusters in this population (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llanaeza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018).

Symptom Rating Instrument

Many symptom rating instruments with established validity and reliability were used to measure the prevalence and severity of symptoms in midlife climacteric women with metabolic syndrome. These symptom rating instruments included Female Sexual Function Index, Menopause Rating Scale, Cervantes Scale, Female Sexual Distress Scale, and study-designed questionnaire (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llanaeza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). The most commonly used symptom rating instrument was the Female Sexual Function Index, followed by the Menopause Rating Scale.

2.4 Discussion

To the best of our knowledge, this is the first study to review the current literature to understand the types and prevalence of symptoms and symptom clusters

experienced by midlife climacteric women with metabolic syndrome and to compare them to midlife climacteric women without metabolic syndrome.

The grouped urogenital symptoms had the highest prevalence among all other grouped symptoms in midlife climacteric women with metabolic syndrome (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llanaza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). In regards to individual symptoms, the most commonly occurring symptom was mental exhaustion (84.4%) (Lee et al., 2012). It is interesting to note that mental exhaustion had the highest prevalence among all the individual symptoms while psychological symptoms did not have the highest prevalence among other grouped symptoms. As such, the authors of the included studies used different symptom classifications to examine their prevalence with some using grouped symptoms that included multiple individual symptoms while others focused on an individual symptom (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llanaza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). This may be due to different symptoms rating tools used in the studies. For example, Menopausal Rating Scale tool examines broad symptom experience in menopausal women (Lee et al., 2012; Ryu et al., 2015) whereas Female Sexual Function Index tool asks specific sexual problems that include change in sexual desire and lubrication (Dutra da Silva et al., 2020; Kim et al., 2011; Martelli et al., 2012; Otunctemur et al., 2015). While both symptom rating tools may measure the same

concept of symptoms, one of them measures sexual symptoms as a grouped symptom category and the other measures specific and individual types of sexual symptoms. Without consistent classification of symptoms, this may impact the overall study findings and make it difficult to compare symptom prevalence across the studies.

A wide range of prevalence was reported for both grouped symptoms and individual symptoms which may be due to culture or ethnic differences of midlife women. Symptoms might have been overreported or underreported from six different study locations and the influence of each culture on reporting of their symptoms (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llaneza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). For example, Asian population tends to hold negative attitude towards climacteric and believes that climacteric symptoms should not be treated (Gang et al., 2017; Jin et al., 2015). Therefore, Asian population are less likely to report vasomotor symptoms than the North American and European populations (Melby et al., 2005). In addition, a strong societal stigma exists in the Hispanic community that hinders Hispanics from reporting their symptoms, leading to further problems such as underutilization of mental health services (Eghaneyan & Murphy, 2019). With the potential influence of culture on symptom reporting, future studies should be conducted with midlife climacteric women with metabolic syndrome located in similar geographical location or in similar culture/ethnicity.

In addition, the symptom experience yielded different and mixed findings between midlife women with and without metabolic syndrome in post-menopause (Dutra da Silva et al., 2020; Kim et al., 2011; Lee et al., 2012; Llaneza et al., 2009; Martelli et al., 2012; Otunctemur et al., 2015; Ryu et al., 2015; Sayan et al., 2018). The metabolic syndrome group reported higher prevalence of majority symptoms while the without metabolic syndrome group reported a higher prevalence of certain symptoms such as depressive mood, irritability, mental exhaustion, and low-medium level of vasomotor symptoms (Lee et al., 2012; Llaneza et al., 2009). This may be a result of differences in demographic and clinical characteristics (Mulhall et al., 2018) in the included studies. Midlife climacteric women with metabolic syndrome may vary in their time to menopause which may have affected their overall symptom experience. Time to menopause has been associated with accelerated epigenetic aging which in turn leads to development of severe vasomotor symptoms (Thurston et al., 2020). While our study aimed to identify characteristics of both groups, they were not reported consistently across the studies. For example, only three studies included information on time to menopause (Lee et al., 2012; Martelli et al., 2012; Ryu et al., 2015). Such understanding will help us conceptualize their symptom profile and determine which group is at the highest risk for worse symptom profile. This will allow the clinicians to engage in a more targeted symptom assessment, diagnosis, and management.

While the studies discussed various types of symptoms, none of the studies reported presence of symptom clusters. People with chronic conditions generally present with more than one symptom (Miaskowski et al., 2017). For example, a study of chronic kidney disease patients found five symptom clusters that include fluid volume, neuromuscular, gastrointestinal, sexual, and psychological symptom clusters (Almutary et al., 2016). When symptom clusters are left underdiagnosed or undertreated, they may have a negative impact on patient outcomes (Miaskowski et al., 2017). Therefore, it is critical that we understand what types of symptoms constitute a symptom cluster in midlife climacteric women with metabolic syndrome and the nature of clinically significant symptom clusters. Identification of symptom clusters will allow for reduction in symptom burden that may improve their capacity to maintain a good quality of life over time (Miaskowski et al., 2017).

2.5 Limitations and Implications

This is the first study to review current literature on symptoms experienced by midlife climacteric women with metabolic syndrome. Our review has several limitations. First, most of the studies were cross-sectional studies. Therefore, we were not able to understand their trajectory of symptom experience over time. Future research should use a longitudinal approach that will allow us to capture how symptoms may change. Second, different time points (i.e. years since menopause) were used to measure symptoms or these time points were not reported across the studies. It is important to

use similar time points to avoid any possible errors such as time-specific differences in their symptom experience. Third, different symptom definitions and measurement tools were used to measure symptoms. A consistent definition and symptom rating tools should be used for a more accurate comparison of symptoms in this population. Fourth, majority of the studies included primarily women in post-menopause. As midlife women's symptom experience may vary based on their menopausal status, it is critical for future research to include women in other menopausal status and to examine if their symptom experience is different. Last, a methodological decision was made not to conduct a quality appraisal, which may impact interpretation of results. However, this is consistent with scoping review methodology (Peters et al., 2015). Future research could consider the addition of quality assessment to increase the reliability and validity of study findings.

2.6 Conclusion

The current literature was reviewed to understand the symptoms experienced by midlife climacteric women with metabolic syndrome. Midlife climacteric women with metabolic syndrome experienced grouped and individual urogenital symptoms, vasomotor symptoms, psychological symptoms, sleep symptoms, and somatic symptoms with a wide range of prevalence reported across the eight studies. In addition, their symptom profile was different when compared to the symptom profile of midlife climacteric women without metabolic syndrome, with majority of symptoms to

be more prevalent in midlife climacteric women with metabolic syndrome and some mixed findings on the prevalence and severity of certain individual and grouped symptoms. Our findings will serve as a knowledge basis for clinicians to better understand the complex symptom experience in midlife climacteric women with metabolic syndrome and to assist in developing future targeted symptom interventions.

*Note: Chapter 2 has been published in the *Women's Health Journal*. Reprinted by permission of the SAGE Publishing Permission Team.

Min, S. H., Yang, Q., Min, S. W., Ledbetter, L., Docherty, S. L., Im, E. O., & Rushton, S. (2022). Are there differences in symptoms experienced by midlife climacteric women with and without metabolic syndrome? A scoping review. *Women's Health, 18*, 17455057221083817.

3. Symptom Clusters and Key Symptoms Among Midlife Peri-Menopausal and Post-Menopausal Women With and Without Metabolic Syndrome

3.1 Introduction

Metabolic syndrome is a constellation of metabolic abnormalities that occur together which are characterized by abdominal obesity, high blood pressure, high blood sugar level, and atherogenic dyslipidemia (Rochlani et al., 2017). With the rapid spread of Western lifestyle around the world, the prevalence of metabolic syndrome has continued to increase in the past few decades (Saklayen, 2018). The increasing prevalence of metabolic syndrome has critical health implications due to its association with development of diabetes, cardiovascular disease, and cancer (Rochlani et al., 2017; Saklayen, 2018). Unique factors place women at higher risk for metabolic syndrome than men such as pregnancy-related weight gain, gestational diabetes, and menopause (Bentley-Lewis et al., 2007).

Midlife is the most vulnerable life stage for women to develop metabolic syndrome. This is a period of time when they experience changes in their body fat distribution and fluctuating hormonal level, such as elevated follicle-stimulating hormone (FSH) which is an endocrinological hallmark of peri-menopause and decrease in estrogen and progesterone—all of which are associated with aging and menopause (Harlow & Derby, 2015; Santoro & Randolph, 2011). As a result, midlife women develop metabolic abnormalities that characterize metabolic syndrome. Midlife women with

metabolic syndrome are more likely to experience a complex array of symptoms than those without metabolic syndrome. For example, a cross-sectional study found that midlife women with metabolic syndrome had a significantly higher degree of depression and anxiety than midlife women without non-metabolic syndrome (Roohafza et.al., 2012). Other studies reported that midlife women with metabolic syndrome experience sleep disturbance and accelerated decline in perceptual speed (Hall et al., 2012; Kazlauskaite et al., 2020). Clinical characteristics of metabolic syndrome such as abdominal obesity, high blood pressure, and atherogenic dyslipidemia facilitate aging in midlife women and result in a unique set of symptoms (Shoelson et al., 2007). As such, midlife women with metabolic syndrome experience a complex array of symptoms that often results in significant symptom burden and impaired health-related quality of life

Midlife women experience symptoms regardless of their menopausal stage. Yet, previous research has shown that midlife women in peri-menopause and post-menopause experience more severe symptoms than those in pre-menopause. There was a significant positive linear trend in the mean scores for vasomotor, psychosocial, physical, and sexual symptoms from pre-menopause to post-menopause (Yim et al., 2015). In addition, peri-menopause was associated with a higher risk of depression and post-menopause with a higher risk of anxiety than pre-menopause (Mulhall et al., 2018). Therefore, midlife women in peri-menopause and post-menopause experience more

prevalent and severe symptoms than those in pre-menopause and their symptom experience warrants further investigation (Mulhall et al., 2018; Yim et al., 2015).

When midlife women experience menopause and metabolic syndrome concurrently, they are likely to experience co-occurrence of multiple symptoms or symptom clusters that often result in significant symptom burden (Bruce & Rymer, 2009). Symptom clusters have been identified and evaluated using advanced statistical methods such as factor analysis, cluster analysis, latent class/profile analysis, and latent transition analysis (Miaskowski, 2016). One study has examined and compared the types of symptom clusters between midlife peri-menopausal and post-menopausal women with and without metabolic syndrome using exploratory and confirmatory factor analysis (Min et al., 2021). Another study has used latent transition analysis to examine symptom clustering and to model symptomatology across women in pre-menopause, peri-menopause, and post-menopause (Harlow et al., 2017). However, these statistical methods do not evaluate the relationship between symptoms and symptom clusters which hinders us from identifying key symptoms that may derive the overall symptom experience (Papachristou et al., 2019).

Recent use of machine-learning based network analysis have filled in such gap through a better understanding of symptom clusters in oncology patients (Papachristou et al., 2019). Network analysis provides a graph visualization of the complex network structure among various symptoms and symptom clusters and identifies key symptoms

through providing centrality measures (Papachristou et al., 2019). The use of Walktrap algorithm, a type of data-driven clustering algorithm, uses a series of random walk on a graph trend to find symptom clusters in the network (Papachristou et al., 2019). Through the use of network analysis and the Walktrap algorithm, it is important to understand the relationship among symptoms and to identify symptom clusters as well as key symptoms that may serve as potential target for future symptom management interventions in midlife peri-menopausal and post-menopausal women with metabolic syndrome. Such understanding will assist in reducing their overall symptom burden and improving health-related quality of life.

The purpose of this current study is to (1) examine the relationship among symptoms through visualization of the network structure and (2) identify and compare symptom clusters and key symptoms across symptom occurrence and symptom severity dimension in midlife peri-menopausal and post-menopausal women with and without metabolic syndrome.

3.2 Methods

Design and Data Collection

The current study used cross-sectional visit 5 data from the Study of Women's Health Across the Nation (SWAN). SWAN participants were assessed at baseline and followed up annually (1996-2016). Visit 5 was selected to capture a greater number of midlife women in peri-menopause and post-menopause with metabolic syndrome

because previous visits had more midlife women in pre-menopause and less midlife women in peri-menopause and post-menopause.

Description of the Data Set

SWAN is a multi-site and multi-ethnic community-based study that examines the health of midlife women. A total of 3,302 participants from five ethnic groups were enrolled at baseline. More details can be found elsewhere (Torréns et al., 2009).

Participants

A total of 519 participants met the inclusion criteria for midlife peri-menopausal and post-menopausal women with metabolic syndrome and 1584 participants met the inclusion criteria for midlife peri-menopausal and post-menopausal women without metabolic syndrome. The inclusion criteria for midlife menopausal with metabolic syndrome was as follows: (1) midlife women aged 40-65 years, (2) in peri-menopause or post-menopause, and (3) meeting diagnostic criteria for metabolic syndrome based on National Cholesterol Education Program Adult Treatment Panel III guidelines. At least three of the following conditions is required to be clinically diagnosed with metabolic syndrome: a) waist circumference ≥ 88 cm for Caucasian, African American, and Hispanic participants and ≥ 80 cm for Chinese and Japanese participants; (b) blood pressure ≥ 130 mm Hg systolic, ≥ 85 mm Hg diastolic, or use of antihypertensive medication; (c) fasting serum glucose ≥ 100 mg/dL or use of insulin; (d) serum triglycerides ≥ 150 mg/dL or medication for hypertriglyceridemia; and (e) HDL

cholesterol \leq 50 mg/dL or use of medication for low HDL cholesterol (Marchi et al., 2017). The inclusion criteria for midlife peri-menopausal and post-menopausal women without metabolic syndrome remained the same except that it excluded the diagnostic criteria for metabolic syndrome.

Measures

Demographic and Clinical Characteristics

Demographic and clinical characteristics were obtained from self-report using SWAN-designed questionnaire. These demographic and clinical characteristics included age, race/ethnicity, level of education, marital status, annual household income, health perception, menopausal stage, and body mass index (BMI).

Menopausal Stage

Menopausal stage was based on self-reported menstrual bleeding patterns in the past 12 months. Peri-menopause refers to having menstrual period in the past 3 months which change in cycle regularity in the past 12 months or no menstrual period in the past 3 months with intermittent menstrual bleeding within the past 12 months. Post-menopause refers to having no menstrual period in the past 12 months (Bromberger et al., 2011).

Metabolic Syndrome Characteristics

Height, weight, waist circumference, blood pressure, fasting blood works needed for clinical diagnosis of metabolic syndrome were collected using standardized study protocols (Hall et al., 2012).

Symptoms

Twelve symptoms were selected based on broad selection of symptom studied in the SWAN study as well as symptoms commonly reported in the current literature and Menopausal Rating Scale (Hall et al., 2012; Lee et al., 2012; Martelli et al., 2012).

Menopause Rating Scale is one of the most commonly used symptom rating tool in midlife peri-menopausal and post-menopausal women and has shown good internal consistency with Cronbach's alpha between .60 and .90 (Heinemann et al., 2004). The included symptoms were depression, anxiety, frequent mood change, sexual disturbance, stiffness or soreness in joints, neck, or shoulder, sleep disturbance, night sweat, cold sweat, hot flash, getting up to urinate, vaginal dryness, and forgetfulness.

Among these symptoms, sexual disturbance is a constellation of sexual symptoms that include decreased sexual desire, satisfaction, and arousal and sleep disturbance is a constellation of sleep-related symptoms that include early morning awakenings, difficulty falling asleep, and difficulty staying asleep.

Depression was measured with the Center for Epidemiological Studies of Depression (CES-D) scale. CES-D scale has shown to be a reliable and valid measure of depressive symptoms in midlife U.S adults with Cronbach's alpha of .90 (Cosco et al.,

2017). Anxiety was measured using a composite score of four anxiety symptoms that include irritability, nervousness, feeling fearful, and heart pounding. This approach has been used in previous literature and the composite score has shown a good convergent validity with the Generalized Anxiety Disorder (GAD-7) scale with Spearman's rho of .71 (Bromberger et al., 2013). Other symptoms were measured based on self-report from SWAN-designed questionnaire that asked about the frequency of each symptom in the past two weeks and symptom composite score was derived for each symptom dimension. For the symptom occurrence dimension, each symptom variable was dichotomized based on the presence and absence of symptoms (0=absent, 1=present). For the symptom severity dimension, the symptom composite score ranged from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe).

Network Analysis

Symptoms are referred to as nodes and relationships between the symptoms are referred to as edges in the constructed networks (Papachristou et al., 2019). A Pairwise Markov Random Field (PMRF), an undirected graphical model, was used to formulate network structure to examine the relationship between nodes and for the subsequent network analysis (Dalege et al., 2017; Papachristou et al., 2019). When a relationship exists between two nodes independent of other nodes, these two nodes are connected by an edge (Papachristou et al., 2019). To estimate edges in the symptom occurrence network, the Ising model (IsingFit in R-package) was used with gamma value of 0. A

parameter in the objective function used to fit the model, called gamma, controls the tradeoff between the fitness of the model and the sparsity of the model (number of connected nodes) and this parameter is determined by the researcher (Hevey, 2018). Its value ranges between 0 and 1, with higher gamma value representing a more simple and sparse model (Hevey, 2018). In an exploratory research, gamma value is usually set as 0 to estimate more edges (Hevey, 2018). The Ising model has shown to be computationally efficient in estimating connections in networks with binary data (Dalege et al., 2017; van Borkulo et al., 2015). To estimate edges in the symptom severity network, the polychoric correlation method (qgraph in R-package) with the graphical “least absolute shrinkage and selection operator” (glasso) algorithm was used with gamma value of .25. This method was used to minimize number of spurious edges without incurring false results from multiple testing significance of individual pairwise conditional dependency between two nodes (Epskamp et al., 2018). R statistical software was used to conduct network analysis.

Network Assessment

In the network, circles represent nodes (symptoms) and lines represent edges (the relationship between symptoms) (Christian et al., 2020; Papachristou et al., 2019). An edge represents a full conditional relationship between the two nodes in the network (Christian et al., 2020; Papachristou et al., 2019). A green/blue edge indicates positive relationship between the two nodes and a red edge indicates negative relationship

(Christian et al., 2020; Papachristou et al., 2019). A thick line indicates a strong relationship between the two nodes and a thin line indicates a weak relationship (Christian et al., 2020; Papachristou et al., 2019). The layout of network was based on the Fruchterman-Reingold algorithm which provides optimal layout and places nodes with stronger connection close to each other (Papachristou et al., 2019).

Three centrality indices (i.e. betweenness, closeness, and strength) were estimated to understand the importance of each node within the network. Betweenness measures the frequency of a node that lies on the shortest path between two other nodes (Papachristou et al., 2019; Watts & Strogatz, 1998). This index indicates which nodes play as key role as a bridge between other nodes in the network (Papachristou et al., 2019; Watts & Strogatz, 1998). Closeness measures the average distance of a node to all other nodes in the network (Papachristou et al., 2019). A node with high closeness indicates it may have a significant influence on all other nodes and affect the overall network (Papachristou et al., 2019). Strength indicates a node that is strongly connected to other nodes. It identifies which node is the most connected within a network (Papachristou et al., 2019). Nodes with high centrality indices are considered to be key nodes (symptoms) in the network (Papachristou et al., 2019).

Network Accuracy and Stability

After the network has been identified, we used bootstrapping method to test for statistical significance between edge weights with $\alpha = .05$ based on 1000 bootstrap

iterations. We dropped cases from the dataset, estimated correlations between parameters using bootstrap method, and measured the correlation stability coefficient (Cs-coefficient), an index of stability of each centrality index. There is no cut-off value for Cs-coefficient but a minimum value of .25 is recommended (Epskamp et al., 2018).

The Walktrap Algorithm

The Walktrap algorithm was used to understand what nodes were highly correlated and grouped the highly correlated nodes into a cluster. Walktrap algorithm is a type of data-driven clustering algorithm that uses a series of random walk on a graph trend to find clusters in the network (Papachristou et al., 2019). It is under an assumption that random walk occurs mostly within the same community where the edges are strong (Papachristou et al., 2019). Each symptom cluster was assigned a clinically meaningful name based on the characteristics of included symptoms.

Ethical considerations

The de-identified datasets, codebooks, and survey questionnaires from the SWAN study were downloaded and stored in an encrypted server at Duke University. This study was approved by Duke university human subjects ethical review board [Pro00106232].

3.3 Results

Sample Characteristics

Midlife Peri-Menopausal and Post-Menopausal Women with Metabolic Syndrome

The mean age of participants was 51.50 years (2.74). Most participants were White (48.69%) and African American (30.30%) followed by Hispanic (10.91%), Japanese (5.86%), and Chinese (5.86%). Half of the participants were in peri-menopause (51.84%) and the other half (48.16%) were in post-menopause. The mean BMI was 34.76 kg/m² (7.01). See Table 5.

Midlife Peri-Menopausal and Post-Menopausal Women without Metabolic Syndrome

The mean age of participants was 50.98 years (2.68). The highest proportion was White (47.96%), followed by African American (30.13%), Hispanic (11.38%), Japanese (6.05%), and Chinese (4.47%). More than half (60.67%) were in peri-menopause and the remaining were in post-menopause (39.33%). The mean BMI was 26.88 kg/m² (6.33). See Table 5.

Table 5: Demographic Characteristics

	Metabolic syndrome group, N=519	Without metabolic syndrome group, N=1584	P-value
Age, mean (SD)	51.50 (2.74)	50.98 (2.68)	.0001*
Race/ethnicity, n (%)			.9959
White	241 (48.69)	729 (47.96)	
African American	150 (30.30)	458 (30.13)	
Chinese	29 (5.86)	68 (4.47)	
Japanese	29 (5.86)	92 (6.05)	
Hispanic	54 (10.91)	173 (11.38)	
Education, n (%)			.9651
Less than high school	46 (8.91)	147 (9.31)	
High school graduate	142 (27.52)	440 (27.87)	
Some college	158 (30.62)	499 (31.60)	
College graduate	84 (16.28)	241 (15.26)	
Post graduate	86 (16.67)	252 (15.96)	
Marital status, n (%)			.9604

Single, never married	60 (11.63)	190 (12.07)	
Married	333 (64.53)	1024 (65.06)	
Separated	106 (20.54)	307 (19.50)	
Widowed	17 (3.29)	53 (3.37)	
Annual household income, n (%)			<.0001*
Less than \$19,999	104 (21.01)	112 (7.45)	
\$20,000 to \$49,999	131 (26.46)	379 (25.22)	
\$50,000 to \$99,999	155 (31.31)	556 (36.99)	
\$100,000 or more	81 (16.36)	376 (25.02)	
Health perception, n (%)			.6553
Poor	17 (3.29)	276 (17.51)	
Fair	83 (16.05)	523 (33.19)	
Good	174 (33.66)	481 (30.52)	
Very good	161 (31.14)	523 (33.19)	
Excellent	82 (15.86)	276 (17.51)	
Menopausal stage, n (%)			.0022*
Early perimenopause	203 (39.12)	759 (47.92)	
Late perimenopause	66 (12.72)	202 (12.75)	
Post-menopause	250 (48.16)	623 (39.33)	
BMI in kg/m², mean (SD)	34.76 (7.01)	26.88 (6.33)	<.0001*

* Statistically significant at $p < .01$

Network Accuracy and Stability

Strength was the most reliable centrality index with Cs-coefficient higher than .50 across both symptom dimensions for midlife peri-menopausal and post-menopausal women with metabolic syndrome (symptom occurrence=strength .516, betweenness .127, closeness 0; symptom severity=strength .672, betweenness 0, closeness 0) and without metabolic syndrome (symptom occurrence=strength .672, betweenness .128, closeness 0; symptom severity=strength .750, betweenness .205, closeness .283).

Symptom Clusters and Key Symptoms (Symptom Occurrence)

A total of three symptom clusters with a single isolated symptom were identified for midlife peri-menopausal and post-menopausal women with and without metabolic syndrome (Figure 4).

Midlife Peri-Menopausal and Post-Menopausal Women with Metabolic Syndrome

Three symptom clusters were identified which consisted of psychological/somatic/genital cluster, sleep/urinary cluster, and vasomotor cluster. Psychological/somatic/genital cluster (red) included anxiety, depression, frequent mood change, forgetfulness, stiffness, or soreness in joints, neck, or shoulder, and vaginal dryness. Sleep/urinary cluster (blue) had sleep disturbance and getting up from sleep to urinate. Vasomotor cluster (green) included hot flash, night sweat, and cold sweat. In addition, there was a single isolated symptom of sexual disturbance that did not belong to any cluster. When examining the central indices, frequent mood change had the overall highest centrality values with betweenness (18), closeness (.048), and strength value (3.975) in the psychological/somatic/genital cluster, sleep disturbance with betweenness (5), closeness (.035), and strength value (1.671) in the sleep/urinary cluster, and cold sweat with betweenness (10), closeness (.041), and strength value (4.681) in the vasomotor cluster (Table 6). Therefore, the key symptom was frequent mood change for psychological/somatic/genital cluster, sleep disturbance for sleep/urinary cluster, and cold sweat for vasomotor cluster in midlife peri-menopausal and post-menopausal women with metabolic syndrome.

Midlife Peri-Menopausal and Post-Menopausal Women without Metabolic Syndrome

There were three symptom clusters that included psychological cluster, sleep/somatic/genitourinary cluster, and vasomotor cluster with an isolated symptom of sexual disturbance. Psychological cluster (red) had both mood-related and cognitive symptoms such as anxiety, depression, frequent mood changes, and forgetfulness. Sleep/somatic/genitourinary cluster (green) consisted of sleep disturbance, stiffness, or soreness, in joints, neck, shoulder, vaginal dryness, and getting up from sleep to urinate. Vasomotor cluster (blue) included night sweat, hot flash, and cold sweat. However, sexual disturbance was a single isolated symptom that did not belong to any cluster. Several key symptoms were identified after examining three centrality indices. In the psychological cluster, anxiety had the highest betweenness (19), closeness (.040), and strength (5.225). In the sleep/somatic/genitourinary cluster, sleep disturbance had the highest betweenness (9), closeness (.029), and strength (2.991). In the vasomotor cluster, night sweat had the highest betweenness (10), closeness (.030), and strength (5.143) (Table 7). As a result, anxiety was the key symptom in the psychological cluster, sleep disturbance in the sleep/somatic/genitourinary cluster, and night sweat in the vasomotor cluster for midlife peri-menopausal and post-menopausal women without metabolic syndrome.

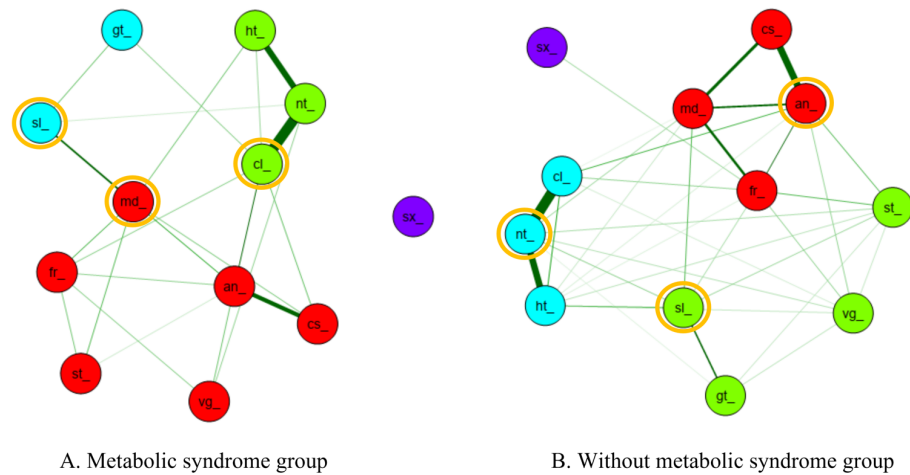


Figure 4: Symptom Cluster and Key Symptom (Symptom Occurrence)

Symptom Clusters and Key Symptoms (Symptom Severity)

Three symptom clusters were identified for midlife peri-menopausal and post-menopausal women with metabolic syndrome and four symptom clusters were identified for midlife menopausal peri-menopausal and post-menopausal without metabolic syndrome (Figure 5).

Midlife Peri-Menopausal and Post-Menopausal Women with Metabolic Syndrome

The identified three symptom clusters were psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster. Psychological/somatic/sexual cluster (green) included anxiety, depression, frequent mood change, forgetfulness, stiffness, or soreness in joints, neck, or shoulder, and sexual disturbance. Sleep/urinary cluster (orange) had sleep disturbance and getting up from sleep to urinate.

Vasomotor/genital cluster (yellow) consisted of cold sweat, night sweat, hot flash, and vaginal dryness. Anxiety had the highest betweenness (2.164), closeness (.835), and strength value (1.129) in the psychological/somatic/sexual cluster. Sleep disturbance had the highest betweenness (.194), closeness (-.054), and strength value (-.113) in the sleep/urinary cluster. Night sweat had the highest betweenness (.552), closeness (.354), and strength value (.542) in the vasomotor/genital cluster. Therefore, the key symptom for psychological/somatic/sexual cluster was anxiety, sleep disturbance for sleep/urinary cluster, and night sweat for vasomotor/genital cluster (Table 6).

Midlife Peri-Menopausal and Post-Menopausal Women without Metabolic Syndrome

Midlife peri-menopausal and post-menopausal women without metabolic syndrome experienced an additional symptom cluster, resulting in four symptom clusters. These four symptom clusters were psychological/somatic cluster, sleep/urinary cluster, vasomotor cluster, and sexual/genital cluster. Psychological/somatic cluster (green) consisted of mostly psychological symptoms such as anxiety, depression, frequent mood change, forgetfulness with one somatic symptom of stiffness, or soreness in joints, neck, or shoulder. Sleep/urinary cluster (orange) consisted of sleep disturbance and getting up from sleep to urinate. Vasomotor cluster (yellow) included hot flash, night sweat, and cold sweat. The last symptom cluster was the sexual/genital cluster (blue) which had sexual disturbance and vaginal dryness. Anxiety was the key symptom for the psychological/somatic cluster with the third highest betweenness (-.156) and

highest closeness (.750) and strength value (1.270), sleep disturbance for sleep/urinary cluster with highest betweenness (1.508), closeness (.715), and strength value (.496), night sweat for the vasomotor cluster with highest betweenness (1.300) and strength (1.169) and second highest closeness value (.139), and vaginal dryness for the sexual/genital cluster with highest betweenness (.884), closeness (-.641), and strength value (-1.086) (Table 7).

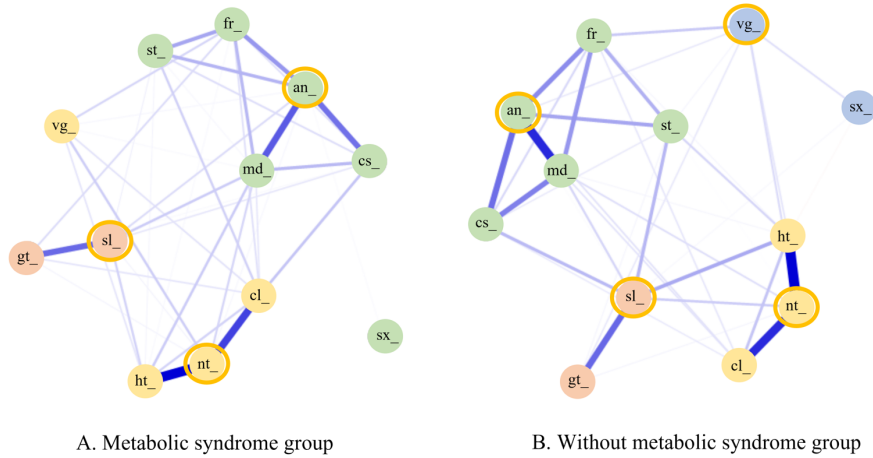


Figure 5: Symptom Cluster and Key Symptom (Symptom Occurrence)

Table 6: Summary of Centrality Measures for Symptom Clusters (Midlife Menopausal Women with Metabolic Syndrome)

Symptom	Betweenness	Rank	Closeness	Rank	Strength	Rank
Symptom Occurrence						
Psychological/somatic/genital cluster						
Mood change	18	1	.048	1	3.975	3
Anxiety	14	2	.046	2	3.937	4
Forgetfulness	1	7	.036	6	2.359	6
Depression	0	8	.034	8	2.256	7

Vaginal dryness	0	8	.028	10	1.283	9
Stiffness	0	8	.027	11	1.154	10
Sleep/urinary cluster						
Sleep disturbance	5	5	.035	7	1.671	8
Getting up from sleep to urinate	0	8	.029	9	1.054	11
Vasomotor cluster						
Cold sweat	10	3	.041	3	4.681	1
Night sweat	7	4	.040	4	4.211	2
Hot flash	3	5	.038	5	2.387	5
Symptom Severity						
Psychological/somatic/sexual cluster						
Anxiety	2.164	1	.835	1	1.129	2
Mood change	1.089	2	.735	2	.796	3
Forgetfulness	.194	5	.405	5	.309	6
Depression	-.343	8	.441	3	.056	7
Stiffness	-1.059	9	.249	8	-.454	10
Sexual disturbance	-1.059	9	-2.93	12	-2.216	12
Sleep/urinary cluster						
Sleep disturbance	.194	5	-.054	9	-.113	8
Getting up from sleep to urinate	-1.059	9	-.351	10	-.760	10
Vasomotor/genital cluster						
Night sweat	.552	3	.354	7	.542	1
Hot flash	.373	4	.421	4	.497	5
Cold sweat	.015	7	.348	6	.542	4
Vaginal dryness	-1.059	9	-.455	11	-1.189	11

Table 7: Summary of Centrality Measures for Symptom Clusters (Midlife Menopausal Women without Metabolic Syndrome)

Symptom	Betweenness	Rank	Closeness	Rank	Strength	Rank
Symptom Occurrence						
Psychological cluster						
Anxiety	19	1	.040	1	5.225	1

Forgetfulness	13	2	.033	4	3.940	5
Frequent mood change	9	4	.037	2	4.326	3
Depression	0	6	.035	3	2.817	8
Sleep/somatic/genitourinary cluster						
Sleep disturbance	9	4	.029	7	2.991	7
Stiffness	0	6	.027	8	2.402	9
Getting up from sleep to urinate	0	6	.023	10	1.486	11
Vaginal dryness	0	6	.021	11	1.732	10
Vasomotor cluster						
Night sweat	10	3	.030	5	5.143	2
Cold sweat	10	3	.029	6	4.059	4
Hot flash	4	5	.026	9	3.788	6
Symptom Severity						
Psychological/somatic cluster						
Anxiety	-.156	6	.750	1	1.270	1
Forgetfulness	.468	4	.284	6	.175	6
Depression	.052	5	.670	4	.149	7
Stiffness	-.572	7	.720	2	-.389	9
Frequent mood change	-.780	8	.574	5	.912	3
Sleep/urinary cluster						
Sleep disturbance	1.508	1	.715	3	.496	5
Getting up from sleep to urinate	-1.196	9	-.259	9	-1.133	11
Vasomotor cluster						
Night sweat	1.300	2	.139	8	1.169	2
Hot flash	.884	3	.280	7	.560	4
Cold sweat	-1.196	9	-.445	10	-.137	8
Sexual/genital cluster						
Vaginal dryness	.884	3	-.641	11	-1.086	10
Sexual disturbance	-1.196	9	-2.788	12	-1.986	12

3.4 Discussion

Our study found that the relationship among symptoms is different for midlife peri-menopausal and post-menopausal women with and without metabolic syndrome through the visualization of network structure. In addition, the number and type of symptom clusters were different for the two groups which is consistent with previous research (Min et al., 2021). For both groups, sexual disturbance was an isolated symptom that did not belong to any symptom cluster in the symptom occurrence dimension. Sexual disturbance is one of the most commonly reported symptoms in both midlife peri-menopausal and post-menopausal women with and without metabolic syndrome (Martelli et al., 2012). Previous research has reported that psychological symptoms such as depression and anxiety can lead to decreased sexual desire (Althof & Needle, 2013). Another study of postmenopausal women has found that sleep disturbance is associated with decreased sexual function (Kling et al., 2017). As a result, our study findings are contradictory to current evidence as sexual disturbance did not belong to any symptom cluster in the symptom occurrence dimension for both groups. To date, limited research focuses on exploring symptoms in midlife menopausal women with metabolic syndrome and assumes that their symptom experience is similar to midlife menopausal women without metabolic syndrome. However, our study found that these two groups have different symptom cluster experience which may be due to different demographic and clinical characteristics or the presence of metabolic syndrome which may generate

or worsen symptoms. For example, differences in age and stages of reproductive aging have led to differences in symptom clusters among midlife women (Harlow et al., 2017). In addition, metabolic syndrome has been associated with abnormal brain lipid metabolism, oxidative stress, and neuroinflammation, all of which may exacerbate an individual's cognitive function in multiple domains such as memory and executive functioning (Guicciardi et al., 2019). As a result, clinicians should first understand the different symptom cluster experience between midlife peri-menopausal and post-menopausal women with and without metabolic syndrome and the additional influence of metabolic syndrome on their symptom cluster experience. With this new knowledge, clinicians need to take a more targeted approach in symptom assessment and management for midlife peri-menopausal and post-menopausal women with metabolic syndrome because they are more likely to experience significant burden.

Midlife peri-menopausal and post-menopausal women with and without metabolic syndrome experienced different number and types of symptom clusters. Three symptom clusters were identified for midlife peri-menopausal and post-menopausal women with metabolic syndrome and four symptom clusters for midlife peri-menopausal and post-menopausal women without metabolic syndrome in the symptom severity dimension. In contrast, previous study has found six different latent classes that ranged from highly symptomatic to relatively asymptomatic (Harlow et al., 2017). Such different findings may be due to different inclusion criteria of the

participants as well as the type of analytic method used. For example, Harlow et al 2017 included pre-, peri-, and post-menopausal women and did not consider the clinical diagnosis of metabolic syndrome (Harlow et al., 2017). In addition, latent transition analysis was conducted which is a person-centered approach using longitudinal data that identifies latent classes of people with similar profiles of symptoms and examines changes in class membership over time (Harlow et al., 2017). In contrast, network analysis is a variable-centered approach using cross-sectional data that provides a graphic visualization of the complex network structure among symptoms and uses a series of random walk to find clusters in the network (Papachristou et al., 2019). As such, different analytic method may lead to different symptom clustering findings.

To date, symptom cluster research has identified distinct symptom clusters such as psychological symptom cluster, and somatic symptom cluster (Almutary et al., 2016). However, our study has identified mixed types of symptom clusters such as the psychological/somatic/sexual cluster and sleep/urinary cluster. This supports the high correlation and complex relationship among the symptoms in midlife peri-menopausal and post-menopausal women with and without metabolic syndrome (Miaskowski et al., 2004; Min et al., 2021). When comparing two groups, midlife peri-menopausal and post-menopausal women with metabolic syndrome are more likely to suffer from a more complex array of symptom clusters because they experience symptoms associated with menopause and metabolic syndrome concurrently. Therefore, it is important to identify

the subgroup of midlife peri-menopausal and post-menopausal women with metabolic syndrome who are at high risk for greater symptom burden using the identified symptom clusters and their associated characteristics. Such understanding will allow clinicians to take a timely and personalized symptom management approach.

Through the ranking of centrality indices, key symptoms were identified for each symptom cluster. The key symptoms for midlife peri-menopausal and post-menopausal women without metabolic syndrome were similar across both symptom dimensions. However, there was only one common key symptom which was the sleep disturbance across both symptom dimensions for midlife peri-menopausal and post-menopausal women with metabolic syndrome. Previous research has focused on the prevalence and severity of individual symptoms experienced by midlife peri-menopausal and post-menopausal women with metabolic syndrome (Lee et al., 2012). As a result, there have been significant challenges in managing these individual symptoms simultaneously. It is imperative to understand the presence of different key symptoms that derives the overall symptom experience. These key symptoms may serve as potential targets for future targeted symptom management interventions that allows for better reduction in their symptom burden and enhanced health-related quality of life (Miaskowski, 2016; Papachristou et al., 2019).

Our study has several limitations to consider. First, this is an exploratory study using network analysis and Walktrap algorithm to understand the relationship

among symptoms and to identify symptom clusters and key symptoms in midlife peri-menopausal and post-menopausal women with and without metabolic syndrome.

Future studies should replicate the use of network analysis and the Walktrap algorithm in a different sample and compare the study findings. Second, the number and types of symptom clusters may vary according to age and stages of reproductive aging in midlife women with and without metabolic syndrome. It is important for future work to address the differences in age and stages of reproductive aging and to examine how the symptom cluster experience may vary based on each stage. Third, only two symptom dimensions were used for the current study and thus other symptom dimensions (i.e. frequency) should be considered. Fourth, we used cross-sectional data to conduct the data analysis. The relationship among symptoms, symptom clusters, and key symptoms are likely to change over time as midlife women age or transition into other reproductive staging. Future studies should be conducted using longitudinal data to study symptom clusters and to understand their temporal patterns over time.

3.5 Conclusion

Midlife peri-menopausal and post-menopausal women with and without metabolic syndrome experienced different number and types of symptom clusters across symptom occurrence and symptom severity dimension. Future studies should identify the high-risk subgroup at greater symptom burden or impaired health-related quality using the identified symptom clusters.

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Min, S. H., Yang, Q., Docherty, S. L., Im, E. O., & Hu, X. (2022). Symptom Clusters and Key Symptoms Among Midlife Perimenopausal and Postmenopausal Women With and Without Metabolic Syndrome. *Nursing Research*, 71(4), E28-E38.

4. Identification of High-Risk Symptom Cluster Burden Group Among Midlife Menopausal Women with Metabolic Syndrome Using Latent Class Growth Analysis.

4.1 Introduction

Metabolic syndrome is a constellation of metabolic risk factors that increases an individual's likelihood of developing chronic disease conditions such as diabetes, cancer, and cardiovascular disease (Rochlani et al., 2017). These metabolic risk factors include central obesity, hypertension, insulin resistance, and dyslipidemia, among which at least three of the metabolic risk factors need to co-occur for a clinical diagnosis of metabolic syndrome to be made (Han & Lean, 2015). In the United States, an estimated 40 to 50 million adults are clinically diagnosed with metabolic syndrome and significantly affected by its health consequences (Han & Lean, 2015; Oladejo, 2011). The overall prevalence of metabolic syndrome is higher in women than all other genders (Aguilar et al., 2015). Several factors unique to women contribute to the high prevalence that include pregnancy-related weight gain, hormonal contraceptive use, polycystic ovary syndrome, and menopause (Bentley-Lewis et al., 2007; Marc, 2007). When stratified by age group, midlife women are the highest risk population to develop metabolic syndrome (Harlow & Derby, 2015). Aging and menopause during midlife leads to adverse changes in their hormonal and lipid profiles, such as decreased level of estrogen and increased level of progesterone (Burger et al., 2002; Mešalić et al., 2008; Min

et al., 2022). Such adverse changes cause accumulation of fat in the intraabdominal and gluteo-femoral area and reduce lean body mass muscle, which characterize the metabolic risk factors (i.e. central obesity, dyslipidemia) for metabolic syndrome (Carr, 2003). These midlife menopausal women with metabolic syndrome experience multiple co-occurring symptoms or symptom clusters that often result in significant symptom burden because they experience symptoms associated with both menopause and metabolic syndrome concurrently (Min et al., 2022).

Midlife menopausal women experience distinct symptom trajectories over time (Kravitz et al., 2017; Tepper et al., 2016; Woods & Mitchell, 2005). For example, previous study identified four heterogeneous patterns of vasomotor symptom trajectories among midlife women that include onset early with decline after menopause, onset near the final menstrual period with later decline, onset early with persistently high frequency, and persistently low frequency (Tepper et al., 2016). Another longitudinal study found four distinct trajectories for sleep-related symptoms based on their prevalence in midlife women such as low prevalence, moderate prevalence, increasing prevalence, and high prevalence trajectory group (Kravitz et al., 2017). While there is an established body of literature that supports the different symptom trajectory experience among midlife menopausal women, no studies have focused on identifying symptom trajectories in midlife menopausal women with metabolic syndrome despite being a high-risk symptom burden group. Understanding their symptom trajectories over time will allow

for future development of targeted interventions that will change the developmental trajectory of their symptom experience into poor patient outcomes. In addition, we need to further examine if there are any subgroups who share similar symptom trajectories among midlife menopausal women since the diagnosis of metabolic syndrome and their associated characteristics. This new knowledge will allow the clinicians to understand the different level of risk for symptom burden among subgroups of midlife menopausal women with metabolic syndrome, and prioritize the need for patient care in clinical settings.

Given that women do not experience these symptoms in isolation but in clusters of symptoms, one way of studying the co-occurring symptoms of midlife menopausal women with metabolic syndrome would be to study the symptom trajectory for each symptom. Min et al. found that midlife menopausal women with metabolic syndrome experienced three symptom clusters that include the psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster based on symptom severity dimension (Min et al., 2022). In this study, Min et al. examined the number and types of symptom clusters in midlife women in peri-menopause and post-menopause together due to the issue of sample size (Min et al., 2022). While there are conflicting results on how their symptom experience may differ by menopausal stage, Min et al. conducted another study that examined and compared the symptom network structure between midlife women in peri-menopause and post-menopause, which found the symptom

networks to be similar in terms of global strength, network structure, and specific centrality measures (Min et al., 2022). Thus, the types of symptom clusters identified by Min et al. can be used to study symptom trajectories in midlife menopausal women with metabolic syndrome. Studying symptom trajectories within the dimension of symptom cluster provides an opportunity for us to examine symptom burden for each cluster using a symptom cluster composite score instead of examining each individual symptom. The identification of the high-risk subgroup for greater symptom cluster burden over time can provide opportunity for clinicians to deliver targeted, timely and personalized symptom management interventions in clinical settings (Miaskowski, 2016; Miaskowski et al., 2017). It may also help researchers to identify underlying mechanism for different symptom cluster experience in midlife menopausal women with metabolic syndrome and distinct characteristics associated with each subgroup.

Multi-trajectory analysis using latent class growth analysis (LCGA) has been used to analyze relationships among the developmental trajectories of multiple outcomes of interest that evolve simultaneously (Jones & Nagin, 2007), identifies distinct joint trajectory patterns, and further examines the common correlates of these outcomes—all of which could provide an important basis for future development of universal interventions (Jones & Nagin, 2007; Zhou et al., 2022). Given the high correlation among symptoms, the three symptom clusters identified by Min et al. are assumed to be distinct but related to each other, and experienced simultaneously by

midlife menopausal women with metabolic syndrome (Min et al., 2022). Yet, there are no studies that have identified joint trajectories of three symptom clusters together. The use of multi-trajectory analysis can join the different developmental trajectories of three symptom clusters to identify meaningful subgroups and high-risk subgroup for greater symptom cluster burden over time (Fanti, 2014).

The aims of this current study are to identify meaningful subgroups of midlife menopausal women with metabolic syndrome based on their distinct symptom cluster burden trajectories, and to describe the demographic, social, and clinical characteristics of different symptom cluster burden subgroups.

4.2 Methods

Design and data collection

This is a secondary data analysis using longitudinal data from baseline to visit 10 from the Study of Women's Health Across the Nation.

Description of the data set

The Study of Women's Health Across the Nation (SWAN) is an ongoing prospective cohort study that aims to examine the health and wellness of midlife women in the community across multiple domains (physical, biological, psychological, and social). The study includes midlife women from multi-ethnic groups across the United States (MI, MA, IL, CA, NJ, and PA). These women were initially assessed at baseline in 1996 and followed up annually until 2015-16. Midlife women were eligible to participate

at baseline study if they were: (1) 42-52 years of age, (2) had an intact uterus and at least one ovary, (3) had at least one menstrual cycle in the past three months, (3) did not use reproductive hormones in the past three months, and (4) self-identified as one of the following: White, African American, Hispanic, Japanese, and Chinese. A total of 3,302 participants met the eligibility criteria and were enrolled at baseline. More details on the SWAN study can be find elsewhere (Torréns et al., 2009).

Participants

The eligibility criteria for the current study was: (1) midlife women aged 40-65 years, (2) in peri-menopause or post-menopause, (3) met diagnostic criteria for metabolic syndrome at any point from baseline, visit 1, visit 3, visit 5, visit 7, and visit 9, based on the National Cholesterol Education Program Adult Treatment III guidelines. The variables required for the clinical diagnosis of metabolic syndrome were collected only during these visits. A total of 557 participants met the eligibility criteria for midlife menopausal women with metabolic syndrome.

Measures

Demographic Characteristics

Demographic characteristics, including age, race/ethnicity, level of education, marital status, current employment status, annual household income, degree of difficulty paying for basics, level of social support, health perception, number of comorbidities, menopausal status, and body mass index (BMI) were measured at each

time point and we used the demographic information at the time of initial diagnosis of metabolic syndrome.

Metabolic Syndrome Characteristics

The SWAN study used standardized study protocols to measure height, weight, waist circumference, blood pressure, and fasting blood work—all of which are needed for clinical diagnosis of metabolic syndrome. Height and weight were measured without shoes using the stadiometer. Waist circumference was measured at the umbilicus. Blood pressure was measured twice with a two-minute interval using standard mercury sphygmomanometers and these two blood pressure values were averaged. Fasting blood work was conducted in the morning after fasting for at least eight hours to obtain values for blood glucose, triglyceride, high-density lipoprotein (HDL) cholesterol (Hall et al., 2012).

Symptom Clusters and Cluster Composite Score

The types of symptom clusters were selected based on our earlier work which reported that midlife menopausal women with metabolic syndrome experienced the psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster based on symptom severity dimension. Psychological/somatic/sexual cluster included anxiety, depression, frequent mood change, forgetfulness, stiffness, or soreness in joints, neck, or shoulder, and sexual disturbance. Sleep/urinary cluster included sleep disturbance and getting up from sleep to urinate. Vasomotor/genital cluster included

cold sweat, night sweat, hot flash, and vaginal dryness (Min et al., 2022). Some symptoms such as sexual disturbance and getting up from sleep to urinate were not measured at all visits. A composite symptom cluster score was derived for each symptom cluster that represents the symptom burden, with scores ranging from 0 to 3 (0=none, 1=mild, 2=moderate, 3=severe). Missing data was considered to be missing at random (MAR) and multiple imputation was conducted to create values for sexual disturbance and getting up from sleep using the complete values from other related symptoms in the same symptom cluster (Jakobsen et al., 2017).

Ethical Considerations

The SWAN study database, codebook, and survey questionnaires are currently available for public access from the Inter-university Consortium for Political and Social Research (ICPSR) website. All the materials were downloaded to a secure, encrypted server at Duke University. Only the de-identified information was archived and analyzed. All datasets, corresponding codebooks, and statistical programs were stored on a secure, encrypted server at Duke University. The current study received Duke university institutional review board declaration of exemption [Pro00106232].

Data Analysis

Data analysis was conducted using SAS 9.4 (SAS Ins. Cary, NC, USA). The SWAN data was panel survey data that were collected from baseline to visit 10. In order to study each participant's symptom trajectory after their initial diagnosis of metabolic

syndrome, we first realigned all participant data for the starting time to be their years since initial diagnosis. After the realignment, some participants had fewer or more time points than others in the analysis data depending on when they were initially diagnosed with metabolic syndrome. Then, a multi-trajectory modeling using LCGA was used to explore distinct patterns of symptom cluster burden trajectory in midlife menopausal women with metabolic syndrome. This approach assigns class membership in trajectory classes across all three symptom clusters while considering the longitudinal change over time (Fanti, 2014). In addition, the multi-trajectory modeling is designed to measure the linkages between the trajectories of three distinct but related outcomes and to obtain the joint estimation of trajectory models (Jones & Nagin, 2007). The model was built in two stages. The first stage was an exploratory step to learn the overall trend (linear, quadratic) of the trajectory of each symptom cluster composite score which helped build the final multi-trajectory model in the second stage. Using the information from the first stage, the multi-trajectory modeling was conducted to jointly model the trajectories for three symptom clusters composite scores together. This allowed us to examine three symptom clusters together, instead of each symptom cluster separately.

Stage 1: Exploring symptom cluster composite score trajectories

Each symptom cluster composite score was continuous with approximately normal distributions and was modeled individually using the censored norm (CNORM) model in SAS Proc Traj. First, we examined the empirical summary plot to illustrate the

trajectories of three symptom clusters: the psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster. Linear and quadratic trend models were tested and parameter estimates were obtained for each symptom cluster. Statistical fit indices such as Akaike information criterion (AIC) and Bayesian information criterion (BIC) were considered to determine the number of symptom cluster trajectory subgroups. The statistical fit of the model was tested for 2-, 3-, 4-, 5- class models. The final model was chosen based on the statistical fit indices, clinical interpretability of each symptom cluster trajectory subgroup, and clinical judgement of the authors. Then, the conditional probabilities linking latent class membership across the symptom cluster trajectory subgroups were calculated. Based on the conditional probabilities, there was a high correlation between the vasomotor/genital cluster and psychological/somatic/sexual cluster which led us to conduct Stage 2 and to model multi-trajectories based on the three symptom clusters together.

Stage 2: Modeling multi-trajectories of three symptom clusters

From Stage 1, we decided that a quadratic trend model is suitable for each symptom cluster. Thus, parameter estimates for quadratic trend model (i.e. intercept, slope, quadratic) were obtained for each symptom cluster and used as starting values for the multi-trajectory model. The multi-trajectory model of three symptom clusters were tested for 2-, 3-, 4-, and 5- class models. All equal conditional group percentages were assumed based on the high correlation among the symptom clusters and thus each

group of conditional group percentages added up to 100. Then, each multi-trajectory model was fitted with linear and quadratic trend. Statistical fit indices such as Akaike information criterion (AIC), Bayesian information criterion (BIC), clinical interpretability of each symptom cluster trajectory subgroup, and clinical judgement of the authors were used to select the optimal number of classes.

After the two-stage group-based trajectory modeling, descriptive statistics was used to explain the participant demographic characteristics of each symptom cluster trajectory subgroup at the time of initial diagnosis of metabolic syndrome. Then, bivariate analysis (analysis of variance, chi-square test) was conducted to examine the association between each symptom cluster trajectory subgroup and demographic characteristics.

4.3 Results

Characteristics of Study Sample

Our total study sample included 557 participants with a mean age of 45.76 years. The highest percentage of race/ethnicity was White (49.25%), followed by African American (29.89%), Hispanic (10.90%), Japanese (5.83%), and Chinese (4.14%). More than a quarter of the participants received high school education (28.16%) and some college education (30.32%). The majority were currently working, with annual household income \$20,000 to \$49,999 (27.65%) and \$50,000 to \$99,999 (37.70%) and no difficulty paying for basics (56.62%). The mean time since initial diagnosis of metabolic

syndrome was 3.30 years and the mean body mass index (BMI) was 28.06 kg/m² in the overweight range. Table 8 further details the participant characteristics.

Table 8: Characteristics of Study Sample

	Total (n=557)
Age, mean (SD)	45.79 (2.66)
Race/ethnicity	
White	262 (49.25)
African American	159 (29.89)
Chinese	22 (4.14)
Japanese	31 (5.83)
Hispanic	58 (10.90)
Education	
Less than high school	48 (8.66)
High school graduate	156 (28.16)
Some college	168 (30.32)
College graduate	89 (16.06)
Post graduate	93 (16.79)
Marital status	
Single, never married	63 (11.39)
Married	358 (64.74)
Separated	113 (20.43)
Widowed	19 (3.44)
Currently working	434 (78.34)
Annual household income	
Less than \$19,999	87 (15.62)
\$20,000 to \$49,999	154 (27.65)
\$50,000 to \$99,999	210 (37.70)
\$100,000 or more	87 (15.62)
Refused	19 (3.41)
Difficulty paying for basics	
Not hard at all	312 (56.62)
Somewhat hard	170 (30.85)
Very hard	69 (12.52)
Social support	
None of the time	12 (2.15)
A little of the time	25 (4.49)
Some of the time	61 (10.95)
Most of the time	190 (34.11)

All of the time	269 (48.29)
Health perception	
Poor	17 (3.06)
Fair	91 (16.40)
Good	185 (33.33)
Very good	174 (31.35)
Excellent	88 (15.86)
Comorbidity	
0	181 (32.50)
1-2	311 (55.83)
>2	65 (11.67)
Menopausal status	
Peri-menopause	242 (44.08)
Post-menopause	307 (55.92)
Time since initial diagnosis of metabolic syndrome, mean (SD)	3.30 (3.83)
BMI in kg/m², mean (SD)	28.06 (6.82)

The empirical summary plot presents the overall trend of trajectory for each symptom cluster across all the participants (Figure 6). Based on the empirical summary plot, the severity for psychological/somatic/sexual cluster drops temporarily until year 1, increases until year 7, and then remains constant over time. In contrast, the severity for both sleep/urinary cluster and vasomotor/genital cluster fluctuates over time.

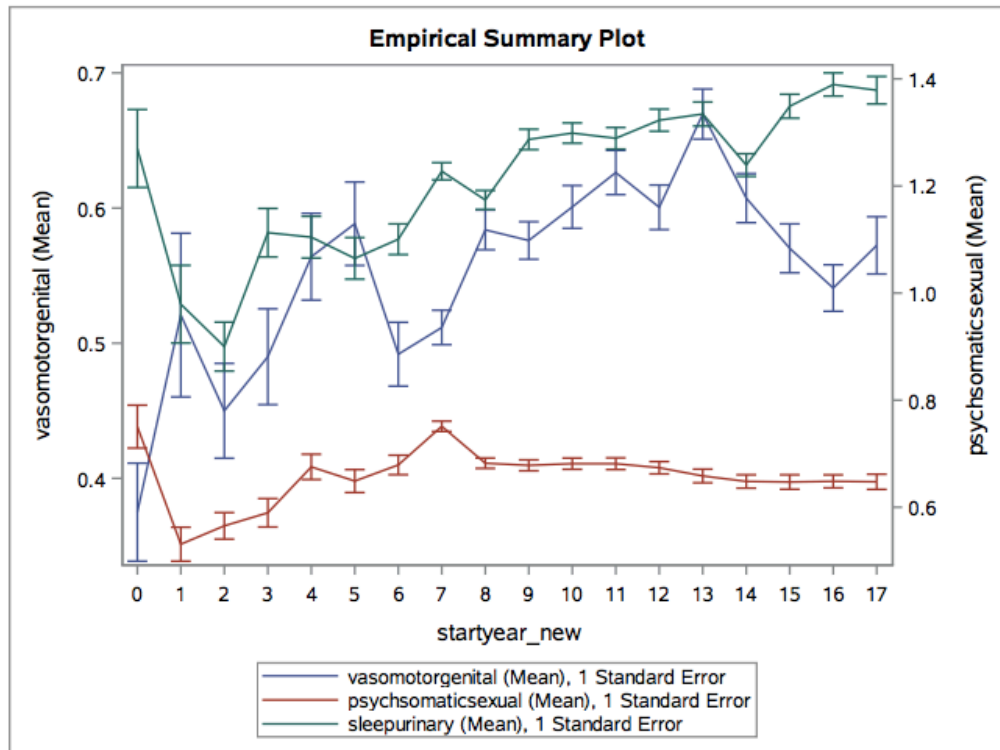


Figure 6: Empirical Summary Plot for Symptom Clusters

Multi-trajectory Model Results

A 4-class model with quadratic trend for multi-trajectory model of three symptom clusters was selected based on the statistical fit indices (AIC=-10897.16, BIC=-11055.25), clinical interpretability, and clinical judgement of the authors (Table 9). While the 5-class model had the lowest AIC and BIC, the identified trajectory subgroups were not clinically interpretable or distinct from each other. The VLMR and LMR-LRT was non-significant for all models but was close to reaching statistical significance for the 4-class model which shows that 4-class model is highly likely to be better than the 3-class model, and thus we choose the 4-class as the final model.

Table 9: Multi-trajectory Model Fit by Number of Classes

Number of Classes	AIC	BIC	Log Bayes Factor	Log-likelihood	BLRT	VLMR	LMR-LRT	entropy	% per class
2	-11717.21	-11800.22	N/A	-11695.21	NA	NA	NA	0.890	66.0%, 34.0%
3	-11164.90	-11285.35	1029.74	-11132.90	<.001	0.2209	0.2233	0.834	38.1%, 44.9%, 17.0%
4	-10897.16	-11055.25	460.2	-10855.16	<.001	0.0661	0.0668	0.857	32.5%, 25.5%, 25.6%, 16.4%
5	-10690.64	-10886.38	337.74	-10638.64	<.001	0.7070	0.7079	0.862	32.7%, 21.6%, 16.4%, 14.4%, 14.8%

NA: Not applicable

For the psychological/somatic/sexual cluster (Figure 7), Class 1 was the consistently low symptom burden subgroup (32.5%) with an initial decrease in symptom severity and no significant changes over time. Class 2 was the moderately high symptom burden subgroup (25.5%) and Class 3 in the moderately low symptom burden subgroup (25.6%). When comparing Class 2 and Class 3, they showed a similar pattern but Class 2 remained consistently higher. Class 4 was the consistently severe symptom burden subgroup which was significantly higher than all other classes for most of the time. For the sleep/urinary cluster (Figure 8), Class 1 was the consistently low symptom burden subgroup (32.5%) given its overall trend. In contrast to the psychological/somatic/sexual cluster, Class 2 was the moderately low symptom burden subgroup with increasing trend and Class 3 was the moderately high symptom burden

subgroup with consistent trend. Class 4 was the severe symptom burden subgroup with fluctuating trend over time. For the vasomotor/genital cluster (Figure 9), Class 1 and Class 2 were the low symptom burden subgroup that were interactive with each other. Class 3 was the moderate symptom burden subgroup with an increasing trend and Class 4 was the severe symptom burden subgroup with an initial sudden drop in its severity and a significant quadratic trend ($\beta=-0.004$, $p=0.017$, Table 10). Similarly, Class 3 and Class 4 had an interactive relationship with each other.

Table 10: Latent Class Growth Analysis Multi-trajectory Model Results

Types of symptom cluster	Trajectory Subgroup	Parameter	β	SE	t-value	p-value
Group Membership	Class 1		35.257	2.523	12.892	<0.001*
	Class 2		25.499	2.515	10.140	<0.001*
	Class 3		25.623	2.452	10.449	<0.001*
	Class 4		16.351	1.727	9.469	<0.001*
Psychological/somatic/sexual cluster, Sleep/urinary cluster, Vasomotor/genital cluster	Class 1	Intercept	0.647	0.108	5.981	<0.001*
		Linear	-0.008	0.022	-0.379	0.704
		Quadratic	0.001	0.001	1.254	0.210
	Class 2	Intercept	0.706	0.163	4.334	<0.001*
		Linear	0.087	0.032	2.755	0.006*
		Quadratic	-0.002	0.001	-1.570	0.116
	Class 3	Intercept	1.295	0.102	12.690	<0.001*
		Linear	0.044	0.022	1.998	0.046*
		Quadratic	-0.002	0.001	-1.731	0.084
	Class 4	Intercept	1.244	0.182	6.835	<0.001*
		Linear	0.106	0.036	2.960	0.003*
		Quadratic	-0.004	0.002	-3.249	0.017*

** Statistically Significant $p<0.05$

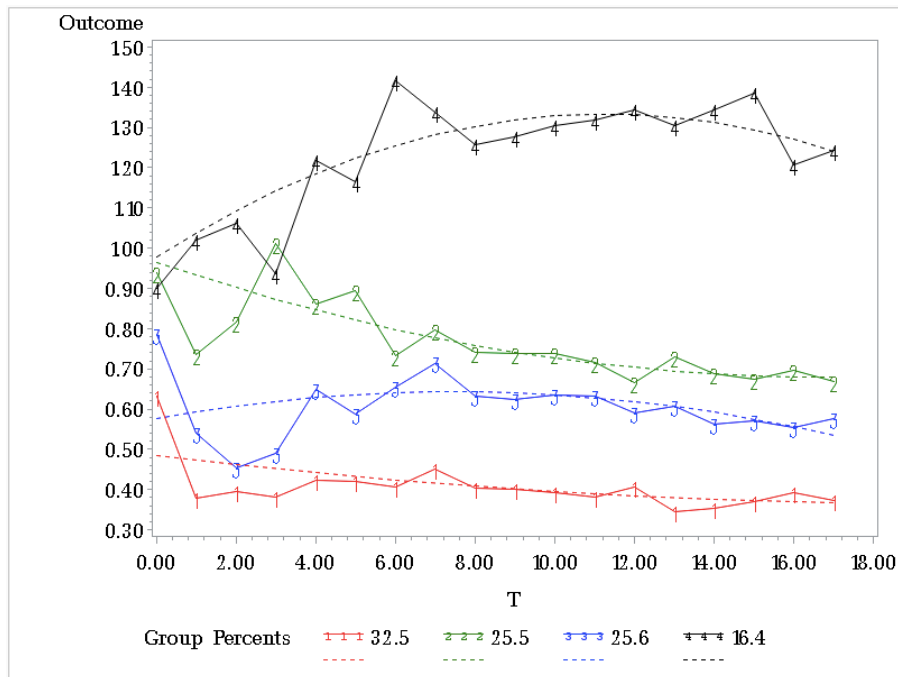


Figure 7: Multi-trajectory Model for Psychological/Somatic/Sexual cluster

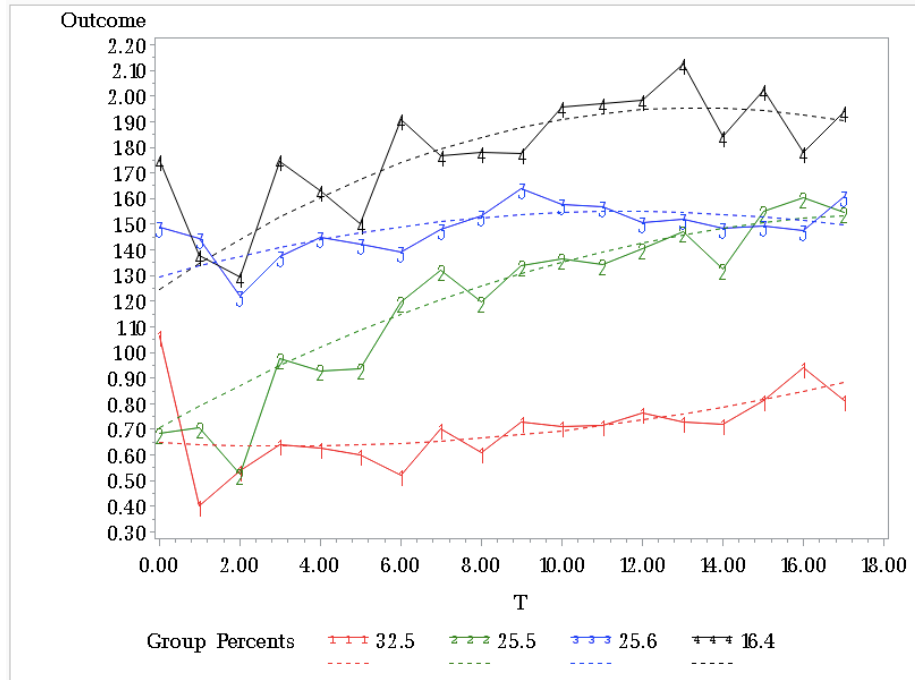


Figure 8: Multi-trajectory Model for Sleep/Urinary cluster

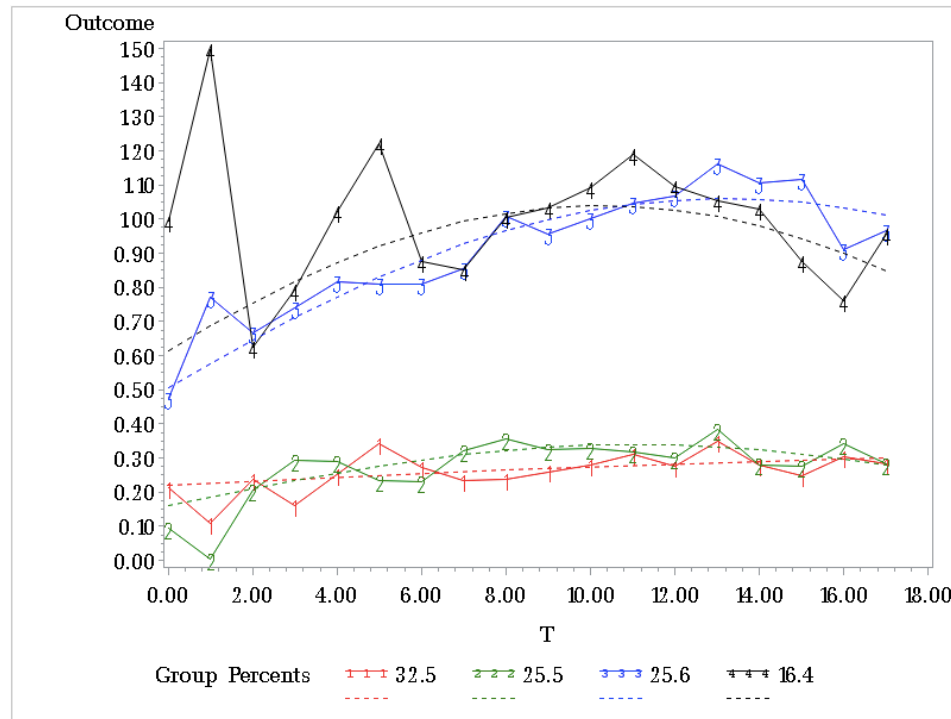


Figure 9: Multi-trajectory Model for Vasomotor/Genital cluster

Individual Characteristics of Multi-trajectory Subgroups

When comparing the four classes, Class 4 had the highest mean age of 46.09 years and Class 2 had the lowest mean age of 45.73 years. There was the highest percentage of African American (34.11%) and Japanese (6.98%) in Class 2, Chinese (5.93%) and Hispanic (12.59%) in Class 3, and White (52.69%) in Class 4. In relation to the level of education, Class 1 had the highest percentage of participants with high school graduate degree or less (42.31%) and Class 4 with college graduate degree or beyond (39.14%). Majority of the participants (>70%) were currently working across all classes with no difficulty or somewhat difficulty paying for basics. In addition, Class 1 had the highest percentage of participants in peri-menopause (51.96%) and Class 3

(61.54%) and Class 4 (61.29%) in post-menopause. However, all of these differences in their demographic characteristics were not statistically significant. A statistically significant difference was examined in the level of social support ($p=0.02$) in which Class 4 had the highest percentage of receiving social support none of the time (6.45%) to a little of the time (7.53%). In contrast, Class 1 had the highest combined percentage of receiving social support most of the time (33.15%) to all of the time (51.09%). Table 11 further details the participant characteristics for the four classes.

Table 11: Characteristics for Each Multi-trajectory Group

	Comparisons among latent classes, N (%)				Statistics (F or t, p-value)
	Class 1 (n=184)	Class 2 (n=135)	Class 3 (n=145)	Class 4 (n=93)	
Age, mean (SD)	45.82 (2.64)	45.73 (2.75)	45.61 (2.53)	46.09 (2.76)	0.65, 0.58
Race/ethnicity					6.36(12), 0.89
White	89 (50.86)	60 (46.51)	64 (47.41)	49 (52.69)	
African American	48 (27.73)	44 (34.11)	38 (28.15)	29 (31.18)	
Chinese	8 (4.57)	4 (3.10)	8 (5.93)	2 (2.15)	
Japanese	11 (6.29)	9 (6.98)	8 (5.93)	3 (3.23)	
Hispanic	19 (10.86)	12 (9.30)	17 (12.59)	10 (10.75)	
Education					18.54(12), 0.10
Less than high school	14 (7.69)	13 (9.63)	14 (9.66)	7 (7.61)	
High school graduate	63 (34.62)	28 (20.74)	43 (29.66)	22 (23.91)	
Some college	44 (24.18)	49 (36.30)	48 (33.10)	27 (29.35)	
College graduate	36 (19.78)	21 (15.56)	14 (9.66)	18 (19.57)	
Post graduate	25 (13.74)	24 (17.78)	26 (17.93)	18 (19.57)	
Marital status					3.87(9), 0.92
Single, never married	16 (8.74)	18 (13.33)	19 (13.19)	10 (10.99)	
Married	123 (67.21)	81 (60.00)	93 (64.58)	61 (67.03)	
Separated	37 (20.22)	31 (22.96)	27 (18.75)	18 (19.78)	

Widowed	7 (3.83)	5 (3.70)	5 (3.47)	2 (2.20)	
Currently working	144 (79.12)	105 (77.78)	115 (79.31)	70 (76.09)	0.45(3), 0.93
Annual household income					18.42(18), 0.43
Less than \$19,999	31 (16.85)	18 (13.33)	22 (15.17)	16 (17.20)	
\$20,000 to \$49,999	49 (26.63)	38 (28.15)	44 (30.34)	23 (24.73)	
\$50,000 to \$99,999	71 (38.59)	54 (40.00)	52 (35.86)	33 (35.48)	
\$100,000 or more	26 (14.13)	21 (15.56)	23 (15.86)	17 (18.28)	
Refused	7 (3.80)	4 (2.96)	4 (2.76)	4 (4.30)	
Difficulty paying for basics					5.77(6), 0.45
Not hard at all	107 (58.79)	68 (51.13)	77 (53.85)	60 (64.52)	
Somewhat hard	53 (29.12)	45 (33.83)	46 (32.17)	26 (27.96)	
Very hard	22 (12.09)	20 (15.04)	20 (13.99)	7 (7.53)	
Social support					24.56(12), 0.02*
None of the time	2 (1.09)	3 (2.22)	1 (0.69)	6 (6.45)	
A little of the time	9 (4.89)	5 (3.70)	4 (2.76)	7 (7.53)	
Some of the time	18 (9.78)	17 (12.59)	20 (13.79)	6 (6.45)	
Most of the time	61 (33.15)	48 (35.56)	59 (40.69)	22 (23.66)	
All of the time	94 (51.09)	62 (45.93)	61 (42.07)	52 (55.91)	
Health perception					12.95(12), 0.37
Poor	7 (3.83)	3 (2.22)	7 (4.86)	0 (0.00)	
Fair	31 (16.94)	22 (16.30)	27 (18.75)	11 (11.83)	
Good	57 (31.15)	48 (35.56)	52 (36.11)	28 (30.11)	
Very good	61 (33.33)	38 (28.15)	40 (27.78)	35 (37.63)	
Excellent	27 (14.75)	24 (17.78)	18 (12.50)	19 (20.43)	
Comorbidity					2.81(6), 0.83
0	65 (35.33)	42 (31.11)	44 (30.34)	30 (32.26)	
1-2	101 (54.89)	73 (54.07)	85 (58.62)	52 (55.91)	
>2	18 (9.78)	20 (14.81)	16 (11.03)	11 (11.83)	
Menopausal status					10.12(6), 0.12
Peri-menopause	93 (51.96)	58 (43.28)	55 (38.46)	36 (38.71)	

Post-menopause	86 (48.04)	76 (56.72)	88 (61.54)	57 (61.29)	
BMI in kg/m ² , mean (SD)	28.48 (6.54)	27.57 (7.49)	27.90 (6.59)	28.20 (6.76)	0.48, 0.69

** Statistically Significant $p < 0.05$

High Symptom Cluster Burden Group

Class 4 remained high across all three symptom clusters. The mean age was 46.09 years with majority participants being White (52.69%) or African American (31.18%). There was a similar percentage of participants with high school degree (23.91%), some college degree (29.35%), college graduate degree (19.57%), and post-graduate degree (19.57%). More than half were married (67.03%) with the other half separated (19.78%), single/never married (10.99%), or widowed (2.20%). A majority was currently working (76.09%) with annual household income \$50,000 to \$99,999 (35.48%). While half of the participants (55.91%) reported having social support all of the time, there was the highest percentage of participants receiving social support none of the time (6.45%) to a little of the time (7.53%). These participants had good (30.11%) to excellent (20.43%) perception of their health with 1-2 health comorbidities (55.91%). There were more participants in post-menopause (61.29%) than peri-menopause (61.29%). The mean time since initial diagnosis of metabolic syndrome was the longest (3.72 years) and the mean body mass index was 28.20 kg/m² in the overweight range.

4.4 Discussion

Previous studies have found different trajectory subgroups based on an outcome of interest (ex. health behaviors) in various populations and the associated characteristics of each trajectory subgroup (Lee et al., 2021). Similar to their approach, our study used LCGA but with multi-trajectory modeling approach to identify homogeneous subpopulations based on symptom cluster trajectories within the heterogeneous population of midlife menopausal women with metabolic syndrome, which is critical in understanding the similarities and differences in their individual characteristics of homogeneous subpopulations based on their similar symptom trajectories over time. A total of four classes were identified (Class 1-Class 4) which showed distinct and interactive symptom cluster trajectories over time. Our study findings provide a critical knowledge basis for clinicians to identify high-risk symptom cluster burden group and to effectively manage their symptom clusters through targeted symptom assessment and management in clinical settings.

Overall, there was a temporary sharp decrease or increase in symptom cluster severity after initial diagnosis of metabolic syndrome for the identified classes across three symptom clusters. The diagnosis of metabolic syndrome may be an additional psychological burden for some people and can negatively influence a healthy lifestyle and development of negative symptoms related to lifestyle such as feeling of loneliness and cognitive decline (Furhata et al., 2018; Miley-Akerstedt et al., 2018). This may

further explain the sharp increase in symptom cluster severity shortly after the initial diagnosis of metabolic syndrome among midlife menopausal women. In contrast, there is an established literature that lifestyle modifications are effective in resolving or reducing the severity of metabolic syndrome (Bo et al., 2007; Kwaśniewska et al., 2009; Yamaoka & Tango, 2012). Such lifestyle modifications have been used in various patient population, which has shown to improve symptoms and quality of life among patients with irritable bowel syndrome (Kang et al., 2011). It may be possible that some midlife women adapted lifestyle modifications after their initial diagnosis of metabolic syndrome that led to sharp decrease in symptom cluster severity.

Our study identified four classes based on the psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster. The severity trend for Class 1 (low symptom burden) and Class 4 (high symptom burden) remained relatively stable across all three symptom clusters. However, the severity trend for Class 2 and Class 3 (both moderate symptom burden) changed for the psychological/somatic/sexual cluster and sleep/urinary cluster. More specifically, Class 2 was the moderate-high symptom burden group and Class 3 was the moderate-low symptom burden group in the psychological/somatic/sexual cluster. In contrast, in the sleep/urinary cluster, Class 2 becomes the moderate-low symptom burden group and Class 3 becomes the moderate-highs symptom burden group. To date, studies have identified the same severity trend across all symptoms and symptom clusters and do not consider the dynamic, changing

nature of symptom clusters and their severity over time (Cao et al., 2021; Guérin et al., 2017). For example, two different symptom subgroups of a consistently lessening symptom group and moderately worsening symptom group were found to be identical across all different symptoms among formerly abused women (Cao et al., 2021). However, symptoms are not always associated with other symptoms which means that, in other words, a severely depressed patient may not have severe urinary incontinence problem but rather none to mild urinary incontinence problem (van der Vaart et al., 2007). This is further supported by our study findings in which severity trend for moderate-low and moderate-high symptom burden groups changed based on the psychological/somatic/sexual cluster and sleep/urinary cluster. With this new knowledge, clinicians should understand the dynamic nature of symptom clusters and their severity trend and carefully assess for any changes in symptom cluster severity over time. In addition, future research needs to focus on developing targeted interventions tailored to each class of midlife menopausal women with metabolic syndrome, which will help prevent the developmental trajectory changing into greater symptom burden.

In addition, an interactive relationship among the different symptom cluster subgroups was identified in the vasomotor/genital cluster. For example, Class 1 and Class 2 shared a similar trend as well as Class 3 and Class 4. Our study finding adds to the current body of literature because previous studies have only identified symptom

cluster subgroups that are distinctly different with each other (Hockenberry et al., 2017). There is a strong evidence that the symptoms within a symptom cluster may share interactive mechanisms (Parker et al., 2005). For example, a study of older women with vasomotor symptoms reported to experience vaginal dryness, both symptoms that consist the vasomotor/genital cluster (Zelege et al., 2016). However, none of the studies have reported the potential interactive relationship among the symptom cluster subgroups within a symptom cluster. This highlights the need for future research to understand the potential interactions among symptom cluster subgroups and their underlying mechanisms, which can propose common pathways that may underlie this relationship. Furthermore, the use of symptom management interventions that target both the interactive clusters should be considered such as cognitive behavioral therapy which has shown to be effective in improving symptom clusters among cancer patients undergoing chemotherapy (Zhang et al., 2019)

The demographic, social, and clinical characteristics for each class were identified and tested for within-class differences. Among them, social support was significantly different among the four classes. Class 4 (high symptom burden) had the highest percentage of participants who had social support none of the time to a little of the time. This aligns with previous study findings in which lower social support was associated with greater symptom burden (Atkins et al., 2010; Santos Salas et al., 2019). Furthermore, social support predicted patient outcomes such as health-related quality of life and well-

being which emphasizes the importance of social support (Alshraifeen et al., 2020). As midlife women experience challenges in their social, psychological, and biological domains including menopause, they often suffer from significant symptom burden and stress (Thomas et al., 2018). Therefore, it is important to understand the role of social support in reducing their symptom burden and improving health outcomes, to offer social resources, or to involve friends or family members, if necessary, to clinical care (Thomas et al., 2017).

While not statistically significant, the potential impact of menopausal status at the initial diagnosis of metabolic syndrome should be considered. Class 1 (low symptom burden) had the highest percentage of midlife women in peri-menopause and Class 4 (high symptom burden) had the highest percentage in post-menopause. Our study findings support the current body of literature where post-menopausal women experienced more prevalent and severe symptoms than those in peri-menopause (Ruan et al., 2017). In consequence, among all menopausal stages, the health-related quality of life is most affected during the post-menopause stage (Ceylan & Özerdoğan, 2014). This may be due to different hormonal profile (estrogen, follicle-stimulating hormone) and rate of adipose tissue metabolism between peri-menopause and post-menopause among midlife menopausal women with metabolic syndrome (Ferrara et al., 2002; Randolph et al., 2004). With this in mind, future research should be conducted with a larger sample size where statistical significance may be reached in regards to their menopausal stage.

Our study has several limitations to consider. First, our sample consists of midlife menopausal women with metabolic syndrome of five racial/ethnic groups. When LCGA is applied to a larger sample for replication, the results may be different even with acceptable model fit indices because LCGA is specific to the study population which is one of the limitations of LCGA (Lee et al., 2021). Second, there was a small sample size of 557 who met the study eligibility criteria. With the 4-class model, there was an average of 139 participants in each class, thereby limiting its generalizability. Third, data was collected retrospectively via self-report which is prone to recall bias. Therefore, the results should be carefully interpreted with caution.

4.5 Conclusion

The current study identified four symptom cluster trajectory subgroups in midlife menopausal women with metabolic syndrome. In addition, we found a dynamic and interactive nature of symptom cluster trajectory subgroups. Social support was a significant predictor of symptom cluster trajectory subgroup which needs to be provided routinely. Clinicians should understand the different symptom cluster trajectory subgroups and their dynamic nature, and offer targeted and routine symptom cluster assessment and management in clinical settings.

5. Conclusion

5.1 Summary

The purpose of this dissertation was to describe and identify symptom clusters in midlife menopausal women with metabolic syndrome. This purpose was fulfilled through (1) a scoping review of the literature (Chapter 2) to describe the symptom experience and presence of symptom clusters in midlife menopausal women with metabolic syndrome; (2) a quantitative study of secondary data analysis using machine-learning based network analysis (Chapter 3) to identify the number and types of symptom clusters and key symptoms based on symptom occurrence and severity dimension; (3) a quantitative study of secondary data analysis using longitudinal, person-centered approach (Chapter 4) to identify the subgroups of midlife menopausal women with metabolic syndrome at high-risk for greater symptom cluster burden over time and their associated characteristics.

Our findings from Chapter 2 (scoping review) identified important gaps in literature and served as a basis for later chapters. This scoping review found that midlife menopausal women with metabolic syndrome experienced grouped and individual urogenital symptoms, vasomotor symptoms, psychological symptoms, sleep symptoms, and somatic symptoms with a wide range of prevalence. In addition, their symptom profile was different when compared to the symptom profile of midlife menopausal women without metabolic syndrome. While the majority of symptoms were more

prevalent in midlife menopausal women with metabolic syndrome, there were some mixed findings on the prevalence and severity of certain individual and grouped symptoms between the two groups. In addition, there were no studies that focused on understanding symptom clusters in this population. Our study findings provide insights into the unique symptom experience of midlife menopausal women with metabolic syndrome. Given the potential influence of menopause and metabolic syndrome on their symptoms, our findings highlighted the need to fulfill the gap in literature through investigating symptom clusters in midlife menopausal women with metabolic syndrome which led to Chapter 3.

Chapter 3 focused on identifying and comparing the number and types of symptom clusters and key symptoms in midlife menopausal women with and without metabolic syndrome based on symptom occurrence and severity dimension. This cross-sectional study found that the number and types of symptom clusters differed between the two groups. Midlife menopausal women with metabolic syndrome experienced the psychological/somatic/genital cluster (key symptom: frequent mood change), the sleep/urinary cluster (sleep disturbance), and the vasomotor cluster (cold sweat) in the symptom occurrence dimension and the psychological/somatic/sexual cluster (anxiety), the sleep/urinary cluster (sleep disturbance), and the vasomotor/genital cluster (night sweat) in the symptom severity dimension. In contrast, midlife menopausal women without metabolic syndrome experienced the psychological cluster (anxiety), the

sleep/somatic/genitourinary cluster (sleep disturbance), and the vasomotor cluster (night sweat) in the symptom occurrence dimension and the psychological/somatic cluster (anxiety), the sleep/urinary cluster (sleep disturbance), and the vasomotor cluster (night sweat), and the sexual/genital cluster (vaginal dryness) in the symptom severity dimension. When comparing the two groups, our study reported that midlife menopausal women with metabolic syndrome are more likely to suffer from a more complex array of symptom clusters because they experience symptoms associated with menopause and metabolic syndrome concurrently. Therefore, it is important to take a person-centered approach to further identify the subgroup of midlife menopausal women with metabolic syndrome who are at high risk for greater symptom burden using the identified symptom clusters and their associated characteristics which led to Chapter 4. Such understanding will allow clinicians to take a timely and personalized symptom management approach in clinical settings and help reduce symptom cluster burden in this population.

Chapter 4 identified meaningful subgroups of midlife menopausal women with metabolic syndrome based on their distinct symptom cluster burden trajectories of psychological/somatic/sexual cluster, sleep/urinary cluster, and vasomotor/genital cluster, and described the demographic, social, and clinical characteristics of different symptom cluster burden subgroups. This longitudinal study found that there were four classes based on their symptom cluster burden trajectories: Class 1 (low symptom

cluster burden), Class 2 and Class 3 (moderate symptom cluster burden), and Class 4 (high symptom cluster burden). Social support was a significant predictor of Class 4 (high symptom cluster burden) and highlights the need to provide social support to reduce symptom cluster burden in this population. In addition, an interactive relationship among the different symptom cluster subgroups was noted in the vasomotor/genital cluster which indicates the potential interactive relationship among the symptom cluster subgroups within a symptom cluster. Therefore, clinicians should understand the different symptom cluster burden trajectory subgroups and their associated characteristics, as well as the dynamic nature of different subgroups.

In summary, this dissertation is the first to identify symptom clusters and key symptoms as well as subgroups of midlife menopausal women with metabolic syndrome based on their symptom cluster burden trajectories and their associated characteristics. Based on our dissertation findings, clinicians need to understand the symptom cluster and key symptoms in midlife menopausal women with metabolic syndrome, and initiate targeted symptom cluster assessment and management in clinical settings. Additional research is needed to understand the potential different symptom cluster experience between midlife peri-menopausal and post-menopausal women with metabolic syndrome, respectively.

5.2 Limitations

There are several limitations of this dissertation. First, our sample consists of midlife menopausal women with metabolic syndrome of five racial/ethnic groups: White, African American, Hispanic, Japanese, and Chinese. The number and types of symptom clusters and key symptoms might be different for other racial/ethnic groups which need to be considered. Second, all the symptoms were collected retrospectively via self-report which is prone to recall bias. Therefore, our study findings should be carefully interpreted with caution. Third, we examined midlife women in perimenopause and post-menopause together due to the small sample size given the large number of included symptoms. It is important to understand their potential differences in the symptom experience by menopausal stage among midlife women.

5.3 Implications

This dissertation provided an important basis of knowledge about symptom clusters and key symptoms in midlife menopausal women with metabolic syndrome and subgroups who share similar symptom cluster burden trajectories over time. However, the symptom research in this population is still in its infancy. Findings from this dissertation have several implications for future research, clinical practice, and policy.

5.3.1 Implications for Research

To date, symptom science research has used advanced statistical methodologies (i.e. latent class/profile analysis, factor analysis) to identify symptom clusters and subgroups based on the symptom or symptom cluster experience over time. However, there are still several areas for future research to further advance symptoms science. Future research should understand the multidimensional characteristics of symptoms and identify symptom clusters using different dimensions of symptoms—for example, symptom occurrence, severity, frequency, and distress—in midlife menopausal women with metabolic syndrome. Second, future research should identify symptom clusters and key symptoms in a larger, and more diverse population as well as the socioeconomically disadvantaged. Third, the relationship among symptoms, symptom clusters, and key symptoms are likely to change over time as midlife women age or transition into other reproductive staging. Therefore, additional research is warranted using longitudinal data to understand the temporal patterns of symptoms, symptom cluster, and key symptoms over time. Fourth, the number and types of symptom clusters may also vary based on biological age and stages of reproductive aging in midlife women with metabolic syndrome. Future research needs to address the differences in biological age and stages of reproductive aging and to examine how the symptom clusters may vary. Fifth, the association between subgroups of midlife menopausal women with metabolic syndrome and other important patient outcomes such as health-related quality of life

and functional ability should be studied. Sixth, future research should focus on developing symptom management interventions that targets key symptoms in midlife menopausal women with metabolic syndrome. Key symptoms are assumed to derive the overall symptom cluster experience and may serve as important targets for future symptom management interventions. Furthermore, it is imperative to identify the underlying biomarkers and omics mechanisms (i.e. genetics, epigenetics) for different subgroups of midlife menopausal women with metabolic syndrome based on different patient outcomes. Precision medicine has been a priority for advancing nursing science because it considers individual variability in personal and environmental characteristics such as biomarkers, genetic, epigenetic, and other omics factors (Fu et al., 2019). This new knowledge will identify new biological targets for future symptom management interventions and will lead to a development of more precise and effective symptom management interventions in midlife menopausal women with metabolic syndrome.

5.3.2 Implications for Practice

This dissertation informed the clinicians of the different symptom cluster experience between midlife menopausal women with and without metabolic syndrome and the additional influence of metabolic syndrome on their overall symptom cluster experience. As a result, midlife menopausal women with metabolic syndrome are more likely to experience significant symptom cluster burden and requires thorough symptom cluster management in clinical settings. In addition, this dissertation provided

a critical knowledge basis for the different symptom cluster burden subgroups and their associated demographic, social, and clinical characteristics. The identification of the high-risk subgroup for greater symptom cluster burden over time can provide opportunity for clinicians to deliver timely and more intense symptom management interventions and to provide appropriate referrals to other providers. Furthermore, clinicians need to understand the importance of social support in symptom cluster burden and encourage family members to engage in care. For other symptom cluster burden subgroups, clinicians need to monitor them carefully for any signs of worsening symptom cluster experience and provide targeted and personalized care.

Furthermore, there has been a continuous effort in adopting precision-based practice in nursing science that involves identification of subgroups of individuals at risk for certain disease conditions or symptom burden and an understanding of their individual characteristics including genomic variation and biomarkers—all of which can assist in future development of targeted and individualized nursing interventions (Miaskowski, 2016; Miaskowski et al., 2017). Such precision-medicine based approach should be incorporated in future nursing interventions in clinical practice to target metabolic syndrome and other outcomes in midlife menopausal women. This will allow the clinicians to enhance precise diagnosis and assessment based on the midlife menopausal women's unique combination of genetic/genomic and personal/environmental characteristics and deliver personalized intervention to those at-

risk for metabolic syndrome or other symptom outcomes (i.e. greater symptom burden) (Fu et al., 2019). With the precision medicine-based approach, midlife menopausal women will significantly reduce their risk for developing metabolic syndrome and other symptom outcomes. In addition, they will experience improved health and health-related quality of life, health care utilization cost reduction, and increased treatment adherence (Chow et al., 2018; Hickey et al., 2019).

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Biography

Se Hee Min joined the PhD program at Duke University School of Nursing in the Fall of 2019. Se Hee received her bachelor of science in nursing from University of Pennsylvania in 2016 and master of science in nursing from Yale University in 2019. She is a licensed advanced practice registered nurse in psychiatric mental health nursing. During her three years at DUSON, she has published 8 peer-reviewed manuscripts and has 9 manuscripts currently under review. She also made 18 presentations for her research work and received several awards at regional and international conferences and was selected as the Rising Star at the Sigma Theta Tau International Nursing Research Congress. She was a recipient of the Ruth L. Kirschstein National Research Service Awards (NSRA) Pre-doctoral Individual Fellowship, Ann S. Jhin Scholarship from the Global Korean Nursing Foundation-USA, AAPINA Scholarship from the Asian American/Pacific Islander Nurses Association, Student Scholarship from the North Carolina Korean Nurses Association, Student Pilot Funding and Summer Research Fellowship from the Duke University School of Nursing. In her next journey of her academic career, she strives to continue her passion in aging, symptom science, women's health, and advanced methodologies.