Study of Women Veterans In Menopause

by

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Dedication

In memory of Joseph Edward Rouen (1926 – 1968) and

in honor of Doreen Sharkey Rouen

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Table of Contents

List of Tables

List of Figures

Abstract

In healthy women, menopause symptoms have been associated with decreased quality of life, limitations in physical functioning and perceived declines in health status. Most menopause research is limited to the study of healthy women and little is known as to how menopause symptoms manifest themselves in women with type 2 diabetes. This study employed a comparative group design to examine the menopause symptom experience of three groups of women veterans receiving care in the Veteran Affairs Healthcare system: women without diabetes (n = 90), women with controlled diabetes (hemoglobin A1c [HbA1c] $\leq$ 7%; n = 135) and women with poorly controlled diabetes (HbA1c > 7%; n = 102). Participants were recruited from an ethnically diverse postmenopausal sample (n = 536) who responded to a national mailed survey (n = 900) and consented to clinical data access. As a group, the women were obese, of low income with more than one chronic illness. On average, menopause symptom prevalence rates were higher compared to those observed in previous community-based investigations of ethnically diverse non-veteran cohorts. However, despite higher BMI and increased disease-related co-morbidities, diabetic participants experienced menopause at the same age and reported similar menopause symptoms as the non-diabetic cohort.

Among respondents with diabetes, glucose control was an important clinical correlate of menopause symptom severity, independent of obesity, surgical menopause, and non-European ethnicity. With the exception of vasomotor symptoms, women

veterans with poor glucose control demonstrated higher menopause symptom severity scores (total score, psychological and somatic factor scores) than their controlled peers of comparable body size, years postmenopause and psychological status. Further, both menopause symptom severity and glucose control were significant correlates of perceived physical health in the diabetic cohort. These findings substantiate the importance of addressing menopause health issues in the clinical management of women veterans with diabetes using services in the VA healthcare system. For this group already in poor health, interventions targeting glucose control may also improve their menopause symptom experience. Future studies are warranted to better understand the relationship between military service and the menopause experience of women veterans, and confirm these findings in non-veteran diabetic populations.

Chapter 1

Introduction

The menopause is considered a natural biologic event that affects every woman. For most women, the menopause transition coincides with the midlife years and is characterized as a time of multiple physiological, psychological and social changes that can impact a women's health (North American Menopause Society [NAMS], 2000). Physiologically, the estrogen decline with menopause is believed to magnify the risk for diseases such as diabetes, cardiovascular disease (CVD) and osteoporosis in the postmenopause (Wenger, Paoletti, Lenfant, Pinn, & Barrett-Connor, 2002; Bishop & Simpkins, 1992; D'Eon & Braun, 2002; Collins, Wenger, Rossouw & Paoletti, 2002; Sowers & Tisch, 2000). For women, psychosocial changes during midlife such as caring for aging parents or coping with sole responsibility of a household can leave women vulnerable to low incomes and increased stressors that can diminish both their physical and psychological health (Sabolski, Solomon, & Manson, 2001; Kumari, Stafford & Marmot, 2005).

A wide variety (over 100) of symptoms (Ditkoff, Crary, Cristo & Lobo, 1991; Perz, 1997) are reported in midlife women during the menopause transition including hot flashes, night sweats, vaginal dryness, urinary incontinence, alterations in mood, sleep disturbances, changes in sexuality, cognitive difficulties such as forgetfulness and somatic complaints (NIH State of the Science Panel, 2005; NAMS, 2007; Wenger et al., 2002). While not every menopausal woman reports symptoms, approximately 85% of midlife women report at least one symptom and 10% visit a health care provider regarding these concerns (Woods & Mitchell, 2005, Sherman, Miller, Nerurkar & Schiff, 2005; McKinlay, Brambilla & Posner, 1992).

Menopause symptoms affect women's health status and have been associated with decreased quality of life (Daly, et al., 1993; Jacobs, Hyland & Ley, 2000; Avis, Assmann,

Kravitz, Ganz & Ory, 2004; Laferrere, et al., 2002; Li, Holm, Gulanick, & Lanuza, 2000; Ledesert, Ringa & Breart, 1994), impaired work performance (Burton, Pransky, Conti, Chen & Edington, 2004), limitations in physical functioning (Sowers, Pope, Welch, Sternfeld & Albrecht, 2001) and perceived declines in health status (Kumari, Stafford & Marmot, 2005). In the United States (US), the issue of menopause symptoms and their management has reached center stage such that the National Institute of Health (2005) and Agency for Healthcare Research and Quality (AHRQ) conducted a conference to discuss these issues and review the current scientific evidence regarding menopause symptoms (NIH State of the Science Panel, 2005; Nelson et al., 2005).

Until the 1990's the majority of menopause research was limited to the study of healthy Euro-American Caucasian women. In the past decade cross-sectional studies have provided data on the menopause experience of women from diverse ethnic backgrounds (Lock, 1994; Im & Meleis, 2002; Carolan, 2000; Berger & Forster, 2001; Adekunle, Fawole & Okunlola, 2000; Obermeyer, Reher & Saliba, 2007) and the only longitudinal multiethnic investigation, the Study of Women Across the Nation (SWAN) is now providing insight into variations of the menopause experience in African-American, Caucasian, Chinese, Japanese and Hispanic women in the US (Sowers et al., 2000). These data demonstrate the unique presentations of symptoms in subgroups of women as well as the great diversity in menopause symptomatology. Symptom patterns vary in combination, intensity, and duration both between and across women of different cultures or ethnicity status (Avis et al., 2001; NIH State of the Science Panel, 2005; Obermeyer, 2000; Melby et al., 2005; Avis, Brockwell & Colvin, 2005). Yet, while menopause research has expanded to include women of diverse ethnic backgrounds, there are still subgroups of women not routinely included for study.

In particular, women with special needs or pre-existing illnesses such as CVD, cancer or diabetes have been excluded from study and relatively nothing is known about these women and the interactions of their health conditions with the biological and psychosocial changes of menopause. The scarce available literature suggests these women may have a different menopause trajectory or suffer increased health risks during this time. Increased seizure risk during menopause has been documented in women with epilepsy (Abbasi, Krumholz, Kittner & Langenberg, 1999), increased menopause

symptoms were observed in HIV infected women compared to non-infected women (Miller et al., 2005; Ferriera, Pinto-Neto, Conde, Costa-Paiva, Morais & Magalheas, 2007), and post polio women were found to experience greater severity of both post polio and menopause symptoms at midlife than their non-disabled peers (Kalpijian, Touissant, Quint & Reame, 2005). These data highlight the important effects of menopause in women with pre-existing health conditions and suggests it is imperative that research be expanded to include these groups of women.

Women with diabetes mellitus (DM) are a unique subset of the female population that may face a different menopause experience and have been excluded from most menopause studies. The dynamics of pre-existing DM may affect a woman's response to the midlife experience and further, the physiological interplay between these two endocrine processes, one metabolic and one reproductive, may influence symptom presentation or timing of the menopause transition. Prior research of this unique interplay as it relates to pregnancy and menstrual cycle patterns demonstrates diabetes does impact reproductive function. Though limited exclusively to the study of type 1 diabetic women, this literature indicates women with type 1 DM experience delayed menarche (Danielson, Palta, Allen & D'Alessio, 2005; Griffin et al., 1994; Kjaer, Hagen, Sando & Eshoj, 1992; Yeshaya, Orvieto, Dicker, Karp &Ben-Rafael, 1995), greater menstrual cycle abnormalities (Kjaer et al., 1992; Griffin et al., 1994; Yeshaya et al. 1995; Strotmeyer, Steenkiste, Foley, Berga & Dorman, 2003), higher rates of failure to conceive, fewer pregnancies, a greater number of stillbirths (Strotmeyer et al., 2003; Durando et al., 2003; Rosenn & Miodivnik, 2005) and an earlier menopause (Dorman et al., 2001) compared to women without DM. Glycemic control was an important variable affecting these outcomes as those with good glucose control experienced a near normal age of menarche (Thrailkill, 2005; Schriock, Winter, & Traisman, 1984) and less menstrual cycle disturbances (Schroeder, Herweek, Sanfilippo & Foster, 2000).

There is very little understanding of the impact of type 2 DM, the major form of the disease, on reproductive functions as until recently few women of reproductive age had type 2 DM. The interaction between type 2 DM and menopause has been primarily examined to quantify the health risks associated with estrogen decline, and usually investigated in the context of hormone therapy (HT) use. From this body of literature,

the menopausal estrogen decline is associated with adverse changes in central adiposity (Toth, Tchernof, Sites & Poehlman, 2000) and glucose and insulin metabolism (Wenger et al., 2002; Sowers & Tisch, 2000; Carr, 2003) that may be deleterious to diabetic women. In clinical trial data, HT use reduced new onset DM risk in healthy women (Kanaya et al., 2003; Margolis et al., 2004) and improved glycemic control in those with type 2 DM (Andersson & Mattsson, 1999; Araujo, Farias & Andreade, 2002; Crespo, Smit, Snelling Sempos & Anderson, 2002; Friday, Dong & Fontenot, 2001; Ferrara, Karter, Ackerson, Liu & Selby, 2001).

How diabetes affects menopause and its related symptoms remains an enigma. In two cross-sectional studies of healthy and type 2 diabetic Mexican women, one group of researchers (Malacara, Huerta, Rivera, Esparza & Fajardo, 1997) documented an earlier age at menopause for women with diabetes, while others observed no differences in menopause age (Lopez-Lopez, Huerta & Malacara, 1999). Few investigations have examined the symptom experience of women with diabetes. Lopez-Lopez and colleagues (1999) observed no differences in vasomotor symptom prevalence between age and BMI-matched Mexican women (n = 400) with and without diabetes, but hot flashes were the only symptom investigated. In another community sample of age and BMI-matched diabetic and non-diabetic Mexican women (n = 100), women with diabetes demonstrated higher scores for depressive symptoms and the 'empty nest syndrome', but similar levels of anxiety and sleep disturbances compared to healthy controls (Malacara et al., 1997). Six separate measurement instruments were used in this study but only one was psychometrically sound and none evaluated vasomotor symptoms, the most commonly reported menopause complaint. Chedraui and associates (2007) evaluated menopause symptoms in postmenopausal Ecuadorian women with the metabolic syndrome. Higher physical and psychological symptom scores but similar scores for sexual and vasomotor symptoms were detected in the women with the metabolic syndrome compared to their non-affected peers. Only a small portion of the women with metabolic syndrome (16%) demonstrated hyperglycemia, making it difficult to clearly assess the relationship between elevated glucose and the symptoms.

Diabetes may affect adversely affect menopause symptoms. Symptoms of vaginal inflammation, urinary incontinence and poor sleep, already associated with DM,

may accelerate during the menopausal estrogen decline. Further, clinical features of DM such as glycemic control may intensify or ameliorate menopause symptoms. One investigation (Charkoudian, 2005) suggested women with DM-related microvascular complications might be unable to cutaneously dissipate the heat generated from a hot flash and experience more severe symptoms. In an experimental study of healthy women (Dormire & Reame, 2003), hot flash symptom frequency varied with blood glucose concentrations in the fasting state and may have implications for women with DM.

The overlay of diabetes may affect the process and progress of the menopause transition in women, but little is known as to how menopause symptoms manifest themselves in these women, much less what are appropriate treatment strategies. As there is virtually no scientific evidence to guide clinical decision-making, these concerns are often not addressed by health care providers (Larme & Pugh, 1998; Esposito, 2005) and potential mistreatment could lead to decreased quality of life and/or increased risk for DM related micro- or macrovascular complications. Systematic study is needed to obtain accurate clinical information regarding the menopause symptom experience of women with type 2 DM to inform the direct healthcare management of these women.

Another group of women not previously included in menopause investigations include women veterans receiving care in the Veterans Affairs (VA) Healthcare system. Historically, men have been the predominant users of VA care, but with the increased proportions of women entering military service, women veterans are the fasting growing segment of the VA healthcare population (Meehan, 2006). Women veterans currently represent 5.5% of all VA users, but those numbers are expected to reach 10% by the year 2010 and 15% by 2020 (Hayes, 2008; Goldzweig, Balekian, Rolon, Yano & Shekelle, 2006). Robust evidence and decades of clinical experience has documented the needs of male veterans receiving care in the VA system, but little is known about the gender specific health needs of women users (Frayne et al, 2006). Mental health services for women have been the primary focus in the past (Goldzweig et al., 2006), but a new initiative, congruent with the current mean (49.5 years) and median (47 years) ages of the VA female population (Hayes, 2008; Office of Policy and Planning, 2007) has identified menopausal issues as a high priority (Frayne et al., 2007).

Menopause Research

In the past decade, research has begun to establish an understanding of the menopause and women's health but much work remains as significantly larger numbers of women enter this sentinel time period in their lives. Worldwide, the median age of menopause is estimated at 45-55 years of age, while in white women from industrialized nations, the median age is 50-52 years (Birkhauser, Dennerstein, Sherman & Santoro, 2002). As the mean life expectancy for women worldwide has risen from 50 to 81.7 years of age, women now spend at least one third of their lives postmenopause (NAMS, 2000). The proportion of women over age 50 (and likely menopausal) has tripled in the past century and is projected to reach 467 million by the year 1990 and 1,200 million by the year 2030 (United States Department of Commerce, Economics and Statistics Administration, 1996). In the US, the numbers of middle aged women are expected to increase from 27 million in the mid 1990's to 41 million by the year 2010 (Beckles, French, Hill & McNair, 2001), with approximately 35 to 40 million women having reached menopause by the year 2000 (United States Census Bureau, 2000).

While considered a universal experience, the menopause is at the same time unique, as significant individual and racial/ethnic variations in the timing, presentation and manifestation of the menopause transition are beginning to be discerned and need to be further explored (Birkhauser et al., 2002). Achieving a thorough scientific understanding of menopause though, is a daunting task. In the past decade research has been conducted from multiple philosophic and theoretical perspectives that while expanding the state of the science, these approaches are at the same time so varied that attempts at comparison or systematic review are difficult.

Theoretical Issues of Menopause Research

The positivistic scientific paradigm embraces testing hypotheses with objective, quantitative methods to determine a universal truth (Curd & Cover, 1998; Whall & Hicks, 2002). Historically, this view of science has dominated and informed the understanding of menopause via numerous experimental and observational, cross sectional and longitudinal studies. In the mid 1900's, some of this evidence resulted in the conceptualization of menopause as a disease state related to 'estrogen deficiency' and

management of the transition focused on the subsequent 'cure' with estrogen replacement therapy (Andrist & MacPherson, 2001; Taylor & Woods, 2001; Klima, 2001). However further randomized controlled clinical trials, such as the Women's Health Initiative (WHI) have clarified the risks and benefits of hormone therapy (HT) and delimited HT use (Writing Group for the WHI, 2002). Multiple quantitative studies have addressed the endocrinology of the menopause and its related issues such as bone health, sexuality, symptom management and quality of life. This growing body of evidence has been used to develop clinical guidelines, in particular, primers produced by the National Institute of Health (National Heart Lung and Blood Institute et al., 2002) and the North American Menopause Society (2007).

Knowledge derived from the positivist paradigm is often physiologic or biomedical in nature. Whereas this knowledge is both critical and essential, it does not completely describe the menopause from a holistic perspective and may miss the contextual factors that influence this experience for individual women. The postmodernism perspective embraces a broader interpretation of science and describes scientific truth as the product of culture and context, embracing the study of individuals and their real world experience (Reed, 1995; Whall & Hicks, 2002). In the late 20th century, use of postmodern and more qualitative perspectives brought forth other critical dimensions of the menopause, reclaiming it as a natural developmental stage for women and centering the focus of research on women's experiences during this transition (Klima, 2001; Andrist & MacPherson, 2001). Yet while the postmodernism perspective brought new understanding to menopause, it also brought fragmentation and over-analysis as no truth was considered universal (Whall & Colling, 2001; Letourneau & Allen, 1999) creating as Rolfe (1999) noted a "bottomless swamp" (p.668) of inadequate knowledge!

A neomodern paradigm provides a valuable approach for the integration of knowledge. Neomodernism accepts the best aspects of positivism and postmodernism, and moves beyond those perspectives to understand the wholeness of phenomenon. Neomodernism accepts diversity of viewpoints and methods in the development of knowledge with the goal of better understanding phenomenon (Reed, 1995;Whall & Hicks, 2002). It challenges experts of different scientific disciplines and philosophic backgrounds to come together to move the science forward. The neomodernist paradigm

is not yet fully explicated, but descriptions suggest it is inclusive of a variety of ways of knowing regarding major phenomena (Whall & Hicks**,** 2003).

In the past decade, the beginning of a neomodern approach to menopause research is evident. Interdisciplinary organizations, such as the North American Menopause Society, have emerged and as part of their mission bring together experts from a variety of disciplines to discuss, debate, and share data. The Society for Menstrual Cycle Research, founded in the late 1970's by a group of nurse-researchers, anthropologists and social scientists in response to the medicalization of premenstrual symptoms, now includes menopause as a research priority. In 2005 in the US, the National Institute of Health along with the National Institute on Aging and the Office of Medical Applications of Research came together to sponsor an interdisciplinary 'state of the science' conference specifically to address the issues related to menopause symptoms. Further, research designs have become multidimensional, including both quantitative and qualitative data collection and interdisciplinary, including researchers from various disciplines. The Study of Women's Health Across the Nation (SWAN), a community based multi-site, multiethnic longitudinal investigation of women's health across the menopause transition is one such example of this multiplicative approach.

Nursing Science and Menopause Research

Nursing is in a unique position to develop and contribute to a neomodern understanding of menopause as it embraces both positivistic and postmodern perspectives. Nursing science is empirical, holistic, value-laden and interdisciplinary. Rooted in positivism since the time of Nightingale, a "traditional empiricist" (Reed, 1995, p. 73), nurse researchers are concerned with value-laden phenomena (such as cultural sensitivity, spirituality, feminism) that affect health. Nursing theoretical frameworks embrace the multidimensional (biological, psychosocial, cultural) nature of individuals, groups and communities and set the stage for research that informs these dimensions.

In menopause research, evidence of such nursing contributions is evident. Nurse scientists have conducted both descriptive and interventional research with menopausal women from several theoretical approaches (physiological, historical, behavioral,

feminist, phenomenological) (Taylor & Woods, 2001) on a variety of phenomena (Table 1.1): neuroendocrinology (Reame, Wyman, Phillips, de Kretser, & Padmanabhan, 1998; Reame, Lukacs, Ansbacher, Carlson, & Padmanabhan, 2002; Reame, Lukacs, Olton, Ansbacher & Padmanabhan, 2007), bone health and nutrition status (Lukacs & Reame, 2000; Lukacs, Booth, Kleerekoper, Ansbacher, Rock, & Reame, 2006), menstrual cycle patterns (DiJulio, Mitchell & Woods, 2005; Mansfield & Voda, 1997), urinary incontinence (Sampselle, Harlow, Skurnick, Brubaker, & Bondarenko, 2002; Waejten, Feng, Ye, Johnson, Greendale, Sampselle et al., 2008), sleep (Clark, Flowers, Boots & Shettar, 1995;Lukacs et al., 2004; Shaver, Giblin, & Paulsen 1991), depressed mood (Woods & Mitchell, 1996; Woods, DiJulio, Percival, Tao, Mariella & Mitchell, 2008) midlife development (Kagawa-Singer et al., 2002; Sampselle, Harris, Harlow & Sowers, 2002; Villarruel, Harlow, Lopez & Sowers, 2002; Woods & Mitchell, 1997), obesity (McCrone, Dennis, Tomoyasu & Carroll, 2000), quality of life (Li, Holm, Gulanick, & Lanuza, 2000), patterns of dietary intake (Bunyard, Dennis & Nicklas, 2002), memory (Mitchell & Woods, 2001), exercise (Li & Holm, 2003; Nicklas, et al., 2003; Wilbur, Vassalo, Chandler, McDevitt & Miller, 2005), perceptions of menopause (Berger & Forster, 2001; Bertero, 2003; Carolan, 2000; Chen, Voda & Mansfield, 1998; George, 1996; George, 2003), hot flash triggers (Dormire & Reame, 2003) and hormone therapy (Andrist, 1998; Akkuzu & Eroglu, 2005; Becker, Stuifbergen & Gordon, 2002). Further, the Seattle Midlife Women's Health Study initiated in 1990 by nurse researchers (Woods & Mitchell, 1997) is one of the major longitudinal population-based cohort studies of women across the menopause transition.

While the majority of this research included primarily Caucasian Euro-American women, nurse scientists have also examined the perceived issues of menopause across cultures (Table 1.1) including women of African American (Sampselle et al., 2002; Woods & Mitchell, 1997), Australian (Berger & Forster, 2001), Chinese (Chen, Voda & Mansfield, 1998), Filipono (Berg & Taylor, 1999), Japanese (Kagawa-Singer et al, 2002), Korean (Im & Meleis, 2002), Israeli (Rotem, Kushnir, Levine & Ehrenfeld, 2003), Latino (Villarruel, Harlow, Lopez & Sowers, 2002), Irish (Carolan, 2000), Swedish (Bertero, 2003), and Turkish (Akkuzu & Eroglu, 2005) descent. As most nursing studies have considered the menopause experience of healthy women and very few have examined

women with health conditions such as disabilities (Becker et al., 2002) or chronic illness, further research to expand the evidence base for nursing practice is needed.

The growing number of midlife and soon to be menopausal women, coupled with the exploding numbers of persons with diabetes (CDC, 2008) are compelling health concerns for nurse clinicians and scientists. The overlay of diabetes may affect the process and progress of the menopause transition in women with diabetes, but little is known as to how menopause symptoms manifest themselves in these women, much less what are appropriate nursing management strategies.

Purpose

The purpose of this dissertation is to describe the menopause symptom experience of women veterans with and without type 2 diabetes, determine the influence of diabetes on menopause symptom severity and explore the relationship between menopause, diabetes and perceived health status in midlife women.

Specific Aims

Aim I. Describe the menopause symptom experience of women veterans with and without type 2 diabetes.

Research Question 1. What is the perceived prevalence and severity of menopause symptoms in midlife women with type 2 diabetes?

Research Question 2. What are the associated factors and correlates of perceived menopause symptoms in type 2 diabetic women?

Aim II. Determine the influence of type 2 diabetes on the menopause symptom experience.

Research Question 3. Do perceived menopause symptom patterns differ between women with and without type 2 diabetes?

Research Question 4. What is the relationship between clinical features of type 2 diabetes (glycemic control, diabetes duration, diabetes symptoms) and perceived menopause symptom severity?

Aim III. Determine the influence of menopause symptoms on perceived health status in postmenopausal women veterans with and without type 2 diabetes.

Research Question 5. Does the concomitant presence of type 2 diabetes affect perceived health status in postmenopausal women?

The review of the literature in chapter 2 presents the complex and multifactorial nature of the intersection between menopause and diabetes and concludes with a theoretical framework to guide the proposed investigation. The methods and research plan are described in chapter 3. Chapter 4 presents the study results and chapter 5 discusses the study findings and offers implications for clinical practice and future investigation.

Table 1.1 Menopause Research and Nursing Science

Menopause Phenomenon	**Nurse Scientists**	**Design/Sample**
Bone Health & Nutrition State	Lukacs, J. L. & Reame, N. E. (2000). Concentrations of follicle stimulating hormone correlate with alkaline phosphatase and a marker for vitamin K status in the perimenopause. *Journal of Women's Health and Gender Based Medicine 9*, 731-739. Lukacs, J. L., Booth, S., Kleerekoper, M., Ansbacher, R., Rock, C., & Reame, N. E. (2006). Differential associations for menopause and age in measures of vitamin K, osteocalcin and bone density: A cross-sectional exploratory study in healthy volunteers. *Menopause 13,* 799-808.	Physiologic, Descriptive, N=37 Caucasian Comparative Group Design, N=59 Caucasian
Obesity	McCrone, S. Dennis, K., Tomoyasu, N., & Carroll, J. (2000). A profile of early versus late onset obesity in postmenopausal women. *Journal of Women's Health and Gender Based Medicine 9*, 1007-1013.	Descriptive, N=135 Caucasian African American
Exercise Physical Activity	Wilbur, J., Vassalo, A., Chandler, P., McDevitt, J., & Miller, A. M. (2005). Midlife women's adherence to home-based walking during maintenance. *Nursing Research 54*(1), 33-40. Nicklas, B. J., Dennis, K. E., Berman, D., Sorkin, J., Ryan, A. & Goldberg, A. (2003). Lifestyle intervention of hypocaloric dieting and walking reduces obesity and improves coronary heart disease risk factors in obese, postmenopausal African American and Caucasian women. *Journals of Gerontology 58A*(2), 181-189. Li, S., & Holm, K. (2003). Physical activity alone and in combination with hormone replacement therapy on vasomotor symptoms in postmenopausal women. *Western Journal of Nursing Research 25*(3), 274-288.	Intervention, N=90 African American Caucasian Intervention, N=76 African American Caucasian Correlational, N=239 Caucasian African American

Menopause Phenomenon	Nurse Scientists	Design/Sample
Diet	Bunyard, L., Dennis, K. E., Nicklas, B. J. (2002). Dietary intake and changes in lipoprotein lipids in obese, postmenopausal women placed on an American Heart Association Step 1 diet. *Journal of the American Dietetic Association 102*(1) 52-57	Intervention N=55
Hormone Therapy	Becker, H., Stuifbergen, A. & Gordon, D. (2002). The decision to take hormone replacement therapy among women with disabilities. *Western Journal of Nursing Research 24*(3), 264-281. Andrist, L. C. (1998). The impact of media attention, family history, politics, and maturation on women's decisions regarding hormone replacement therapy. *Health Care for Women International 19,* 243-260. Akkuzu, G., & Eroglu, K. (2005). The effect of education and counseling services on compliance to therapy of women taking hormone therapy for the first time. *Menopause 12*(6), 763-773.	Descriptive, N=166 Caucasian, African American, Hispanic Exploratory, N=21 European American Intervention, N=119 Turkish
Hot Flashes	Dormire, S. L. & Reame, N. K. (2003). Menopausal hot flash frequency changes in response to experimental manipulation of blood glucose. Nursing Research 52(5), 338-343.	Physiologic Experimental, N=10
Midlife Development	Kagawa-Singer, M., Wu, K., Kim, S., Kawanishi, Y., Greendale, G., Adler, S. et al. (2002). Comparison of the menopause transition between Japanese American and European American women. *Medical Anthropology Quarterly 16*(1), 64-91. Sampselle, C. Harris, V., Harlow, S. & Sowers, M. F. (2002). Midlife development and menopause in African American and Caucasian women. *Health Care for Women International 23,* 351-363. Villarruel, A. M., Harlow, S. D., Lopez, M., & Sowers, M. (2002). El cambio de vida: Conceptualizations of menopause and midlife among urban Latina women. *Research & Theory for Nursing Practice 16*(2), 91-102.	Qualitative, N=52 Japanese European American Qualitative, N=30 Caucasian, African American Qualitative, N=16-20 Hispanic

Menopause Phenomenon	Nurse Scientists	Design/Sample
	Woods, N. F., & Mitchell, E. S. (1997). Women's images of midlife: Observations from the Seattle midlife women's health study. *Health Care for Women International 18*, 437-453.	Qualitative, N=131 Caucasian, African American, Asian
Quality of Life	Li, S., Holm. K., Gulanick, M., & Lanuza, D. (2000). Perimenopause and the quality of life. *Clinical Nursing Research 9*(1), 6-26.	Descriptive, N=214 Caucasian
Menopause Symptoms	Berg, J., & Taylor, D. (1999). Symptom experience of Filipino American midlife women. *Menopause 6*, 115-121. Mitchell, E. S., & Woods, N. F. (1996). Symptom experiences of midlife women: Observations from the Seattle midlife women's health study. *Maturitas 25*, 1-10. Rotem, M., Kushnir, T., Levine, R., & Ehrenfeld, M. (2005). A psycho-educational program for improving women's attitudes and coping with menopause symptoms. *JOGNN 34*, 233-240.	Descriptive, N=165 Filipino Descriptive, N=301 Caucasian, African American, Asian Quasi-Experimental, N=82, Israeli
Mood Symptoms	Woods, N. F., & Mitchell, E. S. (1996). Patterns of depressed mood in midlife women: Observations from the Seattle midlife women's health study. *Research in Nursing & Health 19*, 111-123. Woods, N. F., Smith-DuJulio, K., Percival, D., Tao, E., Mariella, A. & Mitchell, E. (2008). Depressed mood during the menopausal transition and early postmenopause: Observations from the Seattle midlife women's health study. *Menopause 15*, 223-232.	Descriptive, N=301 Caucasian, African American, Asian Longitudinal Descriptive, N=508 Caucasian, African American, Asian
Sleep	Shaver, J. L. F., Giblin, E., & Paulsen, V. (1991). Sleep quality subtypes in midlife women. *Sleep 14*, 18-	Exploratory, N=76 Caucasian

Menopause Phenomenon	Nurse Scientists	Design/Sample
	Clark, A. J., Flowers, J., Boots, L., & Shettar, S. (1995). Sleep disturbances in midlife women. *Journal of Advanced Nursing 22,* 562-	Correlational, N=23 Caucasian
	Lukacs, J. et al. (2004). Midlife women's responses to a hospital sleep challenge: Aging and menopause effects on sleep architecture. *Journal of Women's Health 13*(3), 333-340.	Experimental, N=51 Caucasian
Memory Changes	Mitchell, E. & Woods, N. F. (2001). Midlife women's attributions about perceived memory changes: Observations from the Seattle midlife women's health study. *Journal of Women's Health & Gender Based Medicine 10* (4), 351-362.	Descriptive, N=230 Caucasian, African American, Asian
Perceptions of Menopause	Berger, G., & Forster, E. (2001). An Australian study on the sociocultural context of menopause: Directions for contemporary nursing practice. *Contemporary Nurse 11*(2-3), 271-282.	Qualitative-Narrative, N=70, Australian
	Bertero, C. (2003). What do women think about menopause? A qualitative study of women's expectations, apprehensions and knowledge about the climacteric period. *International Nursing Review 50*, 109-118.	Descriptive, N=39 Swedish
	Chen, Y., Voda, A. M., Mansfield, P. K. (1998). Chinese midlife women's perceptions and attitudes about menopause. *Menopause 5,* 28-34.	Descriptive, N=208 Chinese
	George, T. (1996). Women in a South Indian fishing village: Role identity, continuity, and the experience of menopause. Health Care for Women International 17, 271-279.	Descriptive, N=190 Indian
	George, S. A. (2003). The menopause experience: A women's perspective. Journal of Obstetrical, *Gynecological and Neonatal Nursing 31*(1), 77-85.	Qualitative, N=15 Caucasian

Menopause Phenomenon	Nurse Scientists	Design/Sample
	Im, E. O., & Meleis, A. I. (2002). Meanings of menopause to Korean immigrant women. *Western Journal of Nursing Research 22*, (1) 84-102. Kaufert, P., Boggs, P., Ettinger, B., Woods, N. F., & Utian, W. (1998). Women and menopause: Beliefs, attitudes and behaviors: The North American Menopause Society 1997 Survey. *Menopause 5*(4), 197-202. Carolan, M. (2000). Menopause: Irish women's voices. *JOGNN 29*(4), 397-404	Qualitative, N=21 Korean Descriptive, N=750 Multi-ethnic Phenomenological, N=6, Irish
Instrumentation	Laffrey, S. C., & Asawachaisuwikrom, W. (2001). Development of an exercise self- efficacy questionnaire for older Mexican American women. *Journal of Nursing Measurement 9*(3), 259-73.	Psychometric Testing N=75 Mexican American
Neuroendocrinology of the Menopause	Reame, N. E., Wyman, T. L., Phillips, D. J., de Kretser, D. M., Padmanabhan, V. (1998). Net increase in stimulatory input resulting from a decrease in inhibin B and an increase in activin A may contribute in part to the rise in follicular phase follicle stimulating hormone of aging cycling women. *Journal of Clinical Endocrinology & Metabolism 83*, 3302-3307. Reame, N. E., Lukacs, J. L., Ansbacher, R., Carlson, N., Padmanabhan, V. (2002). Circadian patterns in gonadotropin secretion at menopause: Evidence that loss of estrogen, not aging is responsible for the dampened rhythms in both LH & FSH. *Menopause 9,* 515- Reame, N. E., Lukacs, J. L., Olton, P., Ansbacher, R., & Padmanabhan, V. (2007). Differential effects of aging on activin A and its binding protein, follistatin, across the menopause transition. *Fertility & Sterility 88*, 1003-1005	Experimental, N=17 Caucasian Physiologic, N=37 Caucasian Observational, N=79 Caucasian

Menopause Phenomenon	Nurse Scientists	Design/Sample
Menstrual Cycle Patterns	Smith-DiJulio, K., Mitchell, E. S., & Woods, N. F. (2005). Concordance of retrospective and prospective reporting of menstrual irregularity by women in the menopausal transition. *Climacteric 8*, 390-397. Mansfield, P. K., & Voda, A. M. (1997). Woman-centered information on menopause for health care providers: Findings from the Midlife Women's Health Survey. *Health Care for Women International 18*(1), 55-72.	Instrumentation testing N=161 Multi-ethnic Descriptive, N=400 Multiethnic
Urinary Incontinence	Sampselle, C. M., Harlow, S. D., Skurnick, J., Brubaker, L., & Bondarenko, I. (2002). Urinary incontinence predictors and life impact in ethnically diverse perimenopausal women. *Obstetrics & Gynecology 100*, 1230-1238. Waetjen, LE, Feng, W., Ye, J., Johnson, W. O., Greendale, G. & Sampselle, C. M. (2008). Factors associated with worsening and improving urinary incontinence across the menopausal transition. *Obstetrics & Gynecology 111*, 667-677.	Descriptive, N=3,258 African American Caucasian, Chinese, Hispanic, Japanese Descriptive, N= 2,415 African American Caucasian, Chinese, Hispanic, Japanese

Chapter 2

Review of the Literature

The literature review is organized to address the major domains of menopause and diabetes and establishes a conceptual framework to guide the research investigation. The menopause literature presented includes the primary physiological features and sociocultural challenges of the transition, followed by a detailed review of the symptoms associated with menopause. The diabetes literature is reviewed with a particular focus on women and their reproductive health. The intersection of diabetes and menopause in midlife women as it relates to the symptom experience is also considered. Lastly, the conceptual framework that guides this study is presented.

Physiological Features of Menopause

One of the most intensely studied areas of investigation is the underlying physiology and endocrinology of the menopause. Physiologically, the menopause transition features the progressive loss of ovarian function and is characterized by significant changes in hormonal levels, especially estrogen and the gonadotropins (NAMS, 2007). These changes result in loss of the tight feedback loop responsible for menstrual cycle regularity and changes in the menstrual bleeding pattern become evident (Reame, 2000). Ultimately, there is cessation of menses and estrogen production. Natural menopause has occurred when there has been 12 months of amenorrhea following a final menstrual period (FMP)(NAMS, 2007).

Perimenopause is the time preceding the menopause and continues through the 12 months after the FMP. It is during this time that changes in circulating level of gonadotropins starts to occur and subsequently, changes in menstrual cyclicity. Both central nervous system and ovarian mechanisms are thought to be involved in the

disruption of usual patterns. Longitudinal and cross-sectional studies of reproductive aging have documented that as the number of ovarian follicles decline and levels of inhibin B fall, preservation of normal estrogen production and regular ovulation is maintained, but there is a gradual loss of the physiologic restraint on follicular stimulating hormone (FSH). The progressive rise in FSH, but not luteinizing hormone (LH) is termed the monotropic rise and serves as the hallmark sign of reproductive aging (Sherman & Korenman, 1975) to support follicular development and ovulation (Burger et al., 1999; Klein, et al, 1996; Reame, 2000; Robertson & Burger, 2002; Randolph et al., 2004). Other FSH regulatory peptides have also been discovered and are believed to play a role in this phenomenon (Reame, Wyman, Phillips, de Kretser, & Padmanabhan, 1998). Because inhibins and other growth factors are produced in minute quantities and are difficult to assay with current technologies, they have not been clinically useful as predictive markers of the menopause transition. Later in the transition, as the numbers of ovarian follicles continue to decline, there is a limited response of the follicles to FSH and luteinizing hormone (LH), resulting in anovulation and a missed menstrual cycle.

These patterns earmark the perimenopause and its early and late stages. Early perimenopause is marked by a change in menstrual cycle length of >7 days difference from normal. Late perimenopause is characterized by ≥2 skipped cycles and an interval of amenorrhea of ≥60days (NAMS, 2007). During this time, the follicular phase is prolonged and the overall cycle becomes longer. In both early and late perimenopause, rising FSH (>10 mIU/l) levels during the early follicular phase of the cycle (days 2-5) are documented; at menopause FSH levels are consistently > 30mIU/ml (NAMS, 2007).

The rise in FSH occurs earlier and is disproportionate to the rise in LH that occurs during perimenopause. In early perimenopause, LH levels are relatively unchanged. Secretion remains stable and is relatively resistant to the declining ovarian reserve until just prior to menopause (Reame, 2000). This divergence in the secretion of both LH and FSH during perimenopause has been puzzling as gonadotropin releasing hormone (GnRH) stimulates both hormones. Hypotheses suggest either the decline in ovarian feedback or the alteration of the hypothalamic GnRH pulse generator with aging is responsible for these changes. In regular cycling women, there is a normal pulsatile pattern in GnRH secretion that increases in amplitude and frequency during the follicular

phase of the menstrual cycle until the time of the LH surge. After the LH surge and usually subsequent ovulation, the pulsatile pattern slows down. Studies measuring LH pulsatility in aging women have demonstrated variable findings. In a tightly controlled study with LH sampling every ten minutes at three different points in the menstrual cycle, Reame and colleagues (1998) documented increased luteal phase LH pulse frequency and amplitude in women in their forties. In contrast, studies by Wilshire and associates (1995) and Klein et al (1996) with less frequent sampling (every 12 hours and every 20 minutes respectively) at only one time point in the cycle, observed no change in LH pulses between older and younger women.

Estrogen production demonstrates variability throughout the perimenopause with relatively normal (Burger et al, 1999) and at times elevated levels of estradiol (E_2) possibly from the excessive FSH secretion noted in early perimenopause (Santoro et al, 1996). In the six months immediately before and after the FMP, there is a marked and steep decline in estrogen production (Andrews, 2000; Burger, 1997; Burger et al., 1999; Lobo, 1998; Reame, 1997). A more gradual decline in estrogen occurs in the subsequent postmenopause (PM) years (NAMS, 2007). Hypoestrogenism marks the postmenopause state, as the ovary was the major source of estradiol (E_2) production. In the postmenopausal women some production of the weaker estrogen, estrone (E_1) occurs from the peripheral conversion of androstenedione.

The production of progesterone (PG) during the menopause transition is dependent on the integrity of the menstrual cycle and successful ovulation. In the early perimenopause, PG levels often remain normal as long as the cycles are ovulatory. In later perimenopause, with a greater number of anovulatory cycles and missed menses, PG levels subsequently wane (Reame, 2000; NAMS, 2007).

While there is a marked decline in estrogen production with menopause, only a minimal decline in the androgens occurs (Birkhauser, Dennerstein, Sherman, & Santaro, 2002). In women, the major androgens include dehydroepiandrosterone sulfate (DHEAS), dehydro-epiandrosterone (DHEA), androstenedione (A), testosterone (T) and dihydrotestosterone (DHT) (Burger, 2002). DHEAS, DHEA and A are pro-androgens and are usually converted to T, the most potent androgen in women. Produced by both the ovary and the adrenal gland, T levels do not change significantly with menopause, but

rather fall slowly with age (Burger et al., 2000). The progressive decline in T production starts prior to menopause usually between the ages of 21-40 (Labrie et al., 2003) with one investigation reporting a 50% decrease in T, DHEA, and DHEAS concentrations in premenopausal women during this time (Zumoff, Strain, Miller, & Rosner, 1995). Preliminary data from the multiethnic prospective SWAN study, show that DHEAS levels did not decline at a steady state during the menopause transition and even transiently increased in women during the late perimenopause period (Lasley et al., 2002). While not significantly different across ethnicity, the increases in DHEAS were larger for Chinese, Japanese and Hispanic women than for African Americans or Caucasians (Lasley et al., 2002). Burger (2002) points out that the menopause may actually also be a time of 'relative' hyperandrogenicity for women due to either the greater decline in estrogen than the slower age-related decline in androgens or decreased levels of sex hormone binding globulin (SHBG) resulting in relatively higher concentrations of unbound testosterone.

Physiologic Differences: Race/Ethnicity

The major longitudinal studies (Burger et al, 1999; Rannevik, Jeppsson, Johnell, Borulf, & Svanberg, 1995; Metcalf, Donald & Livesey, 1981; Avis & McKinlay, 1995) of the menopause included subjects that were primarily healthy Caucasian European, Australian and American women. Only recently have the SWAN data demonstrated that the endocrine and cycle changes of the menopause transition might differ across race/ethnicity status. In a cross-sectional study of a multiethnic (African American, Caucasian, Chinese, Japanese, Hispanic) cohort of pre and perimenopausal women (n = 848) of the larger SWAN project, Santoro and associates (2004) measured daily urinary hormone levels of LH, FSH, and metabolites of E_2 and PG for an entire menstrual cycle or up to 50 days. Menstrual cycle patterns and hormone measures were compared against a group of young reproductive age controls to determine evidence of luteal activity (ELA). As expected, the controls had more ELA cycles compared to early perimenopausal women. No differences in the numbers of ELA cycles were observed by ethnic status, but total cycle length, follicular and luteal phase lengths were significantly associated with ethnicity. Hispanic women had longer luteal phases, a greater number of longer menstrual cycles (> 33 days), and fewer shorter cycles (< 22 days) than the other

ethnicities (Santoro et al., 2004). Ethnic differences were detected in the urinary hormone measures with lower rates of E_2 excretion demonstrated in the Chinese and Japanese women than other ethnic groups (Santoro et al., 2004).

Randolph and colleagues (2003) measured baseline serum concentrations of E_2, FSH, T, DHEAS and SHBG in 2,930 SWAN premenopausal and early perimenopausal participants. No differences in FSH levels were noted among the ethnic groups, but unadjusted values of serum E_2 and T did differ by ethnicity. Asian (Chinese and Japanese) women had lower unadjusted E_2 levels than African American, Caucasian and Hispanic women; Hispanic women had lower unadjusted serum T concentrations compared to the other ethnic groups. When the hormone concentrations were adjusted to account for confounding factors such as BMI or smoking behavior, most of these differences were eliminated. However, adjusted serum E_2 concentrations were 13% lower in Asian women compared to Caucasians. Adjusted FSH values were higher and T concentrations were lower in Hispanic women than Asian and Caucasian women (Randolph et al., 2003). Adjusted serum T levels were also lower and FSH concentrations higher in African American women compared to Asian and Caucasian women (Randolph et al., 2003). Mean FSH concentrations did increase over the stages from premenopause to perimenopause in all ethnic groups with little change in E_2, T and SHBG noted in early perimenopause (Randolph et al., 2003). These SWAN data confirm the pattern of change in reproductive hormones across the menopause previously described in other longitudinal and cross sectional studies.

In subsequent work with 3 years of annual serum hormone measures in 3,257 SWAN subjects across the stages of reproductive aging Randolph and associates (2004) documented the inverse relationship of concentrations of E_2 and FSH across the menopause transition in all ethnic groups (African American, Caucasian, Chinese, Japanese, Hispanic). A similar pattern in these hormones was seen in all ethnic groups: E_2 concentrations decreased and FSH values increased significantly with age, with the steeper decline of E_2 and the rise of FSH noted at higher ages. While the pattern of hormone production was similar, the actual levels of these hormones differed by ethnic group (Randolph et al., 2004). Independent of reproductive aging stage, Chinese and Japanese women had lower E_2 concentrations but similar FSH levels compared to

Caucasians. Higher FSH levels but comparable E_2 levels were detected in African American women compared to Caucasians.

Metabolic Consequences of Menopause

Osteoporosis, Diabetes, Cardiovascular Disease

Physiologically, the estrogen decline with menopause is associated with increased risk for major health alterations including diabetes, cardiovascular disease (CVD) and osteoporosis (Wenger et al., 2002; Lindsay, et al., 2002: Collins et al., 2002; Sowers & Tisch, 2000). *Osteoporosis* (OP), the most common metabolic bone disease (NAMS, 2002b), is a skeletal disorder characterized by reduced bone strength and deterioration in the bony skeleton that increases the risk for fracture (Fitzgerald, 1999). Osteoporosis affects an estimated 20% of the female population over age 50 (Cooper, 2003), but prevalence rates increase with age to approximately 52% in women over age 80 (Looker et al., 1995). Ethnic differences are noted with higher prevalence rates in Asians and lower rates in African Americans (Finkelstein et al., 2002; NAMS, 2002b).

Peak bone mass is reached near the end of the second decade of life. Near midlife, bone loss begins to occur at a slow rate (0.5% per year) but accelerates during the menopause transition resulting in approximately a 10% loss of bone in the spine and 5-7% in the hip during this time (NAMS, 2002b; Recker, Lappe, Davies, & Heaney, 2000). After menopause, the rate of bone loss slows but varies from 1-5% per year (Mazess, 1982; Department of Health and Human Services [DHHS], 2004). Fracture risk parallels the increases in bone loss. The prevalence of vertebral fractures increased from 5% in women aged 50 to 15% at age 65 and 20% by age 70 (Cooper, 2003). In white women over age 50, the lifetime risk of any fracture from OP is approximately 40% (Cooper, 2003). Further, OP is the primary cause of approximately 90% of all hip and spine fractures in Caucasian women aged 65-84 years of age (Melton et al., 1997).

Several hormones play a role in bone health, regulating the processes of bone resorption and formation, including the sex steroids: testosterone and estrogen (DHHS, 2004). In females, estrogen produced in early puberty is associated with increased rates of bone growth and subsequently, estrogen deficiency associated with disease states such

as Turner's syndrome, athletic amenorrhea or anorexia nervosa during this time, is linked to low bone mass (Fitzgerald, 1999). The estrogen decline at menopause is associated with increased rates of bone turnover and rapid acceleration of bone loss. Reduced activity in the estrogen receptors in the bone is considered a primary factor in this large increase in bone resorption with reduced bone formation at menopause (DHHS, 2004). The end result is thinning of the outer cortical shell of bone and damage to the trabecular bone structure. Correction of menopausal estrogen deficiency with hormone therapy (HT) in women who are on average a decade past the menopause (mean age of 63 years) preserves bone integrity, prevents bone loss and reduces fracture risk (DHHS, 2004; Cauley et al., 2003). Stimulation of the estrogenic bone receptors with selective estrogen receptor modulators (SERM) also demonstrate similar effects on bone without the deleterious adverse effects associated with HT (Lindsay et al., 2002).

The slower continuous phase of bone loss in older women may be affected by decreased dietary intake of vitamin D and calcium, and decreased physical activity, all of which are factors that maintain bone health (DHHS, 2004). Estrogen loss can affect the absorption of vitamin D and calcium and interfere with bone formation. Calcium, a critical elemental building block for bone is absorbed from the intestine in the presence of activated vitamin D formed in the kidney (Fitzgerald, 1999). Estrogen receptors in the intestinal wall have been shown to facilitate the absorption of calcium in the presence of estrogen (Arjmandi, Salih, Herbert, Sims & Kalu, 1993) and subsequent estrogen loss may impair calcium absorption. The amount of available activated vitamin D is also affected by estrogen loss as estrogen stimulates both vitamin D synthesis and the renal enzyme required to form the active vitamin metabolite (DHHS, 2004).

Cardiovascular Disease (CVD) and Diabetes Mellitus (DM). The risks for CVD and DM increase after the menopause and may be related to the loss of the protective metabolic effects of estrogen in women (Carr, 2003). Estrogen decline at menopause has been associated with unfavorable changes in body topology, lipoprotein levels, and glucose and insulin metabolism that potentiate the development of both diabetes and cardiovascular disease.

Estrogen and glucose homeostasis

Estrogen decline at menopause is associated with changes in glucose and insulin metabolism that increase the risk for diabetes (DM) (Godsland, 1996; Collins, Wenger, Rossouw, & Paoletti, 2002; Sowers & Tisch, 2000: Louet, LeMay, & Mauvais, 2004). Estrogen exerts anti-diabetic actions via several mechanisms that affect glucose homeostasis. Directly, estrogen improves glucose control as it stimulates peripheral tissue uptake of glucose (Louet et al., 2004; Bishop & Simpkins, 1992; D'Eon, & Braun, 2002). In animal models, this has been well demonstrated and estrogens have been shown to increase glucose metabolism in peripheral tissues, primarily uterine, hepatic and skeletal muscle tissue (Garris, Coleman & Morgan, 1985; Matute & Kalkhoff, 1973; Puah & Bailey, 1985). In human subjects, reduction in peripheral insulin sensitivity, increased hepatic clearance of glucose and reduced pancreatic secretion of insulin has been described in post menopausal women suggesting the loss of estrogen may impact these changes (Godsland, 1996; Lindheim, 1994; Toth 2000; Walton, Godsland, Proudler, Wynn, & Stevenson, 1993).

Clinical trials of several estrogen (ET) and estrogen with progestin therapies (EPT) provide evidence for the favorable effect of estrogen on glucose in postmenopausal women. While most are small experimental studies of non-diabetic and primarily Caucasian women (Cagnacci et al., 1992; Crook, Godsland, Hull, & Stevenson, 1997; Kimmerle, Heinemann, Heise, 1999; Lindheim et al., 1993. Lobo, Bush, Carr, Pickar, 2001; O' Sullivan, & Ho, 1995; Spencer et al., 2000) findings from the prospective, larger randomized controlled clinical trials (Postmenopausal Estrogen Progestin Intervention trial [PEPI], Heart and Estrogen/progesterone Replacement Study [HERS]) and the Women's Health Initiative (WHI), demonstrated this same benefit (Espeland et al., 1998; Kanaya et al., 2003, Margolis et al., 2004). Most compelling is the significant reduction in DM incidence in the EPT group compared to placebo demonstrated in both the HERS and WHI (Kanaya et al., 2003; Margolis et al., 2004). In the WHI (Margolis et al., 2004), these effects remained significant even after adjusting for body mass index and waist circumference. These findings support a role for EPT in the prevention of DM in postmenopausal women. Yet despite this benefit, postmenopausal EPT use has also been associated with increased rates of adverse CVD events (heart attack, stroke) and breast

cancer and is no longer considered a health promotion strategy for women (Writing Group for the WHI, 2002).

In women with type 2 DM, use of postmenopausal ET/EPT is also associated with lower fasting glucose and HgbA1c levels in both experimental and observational studies. Analysis of the NHANES III data demonstrated that diabetic women on EPT had better glycemic control than never or previous users of EPT (Crespo, Smit, Snelling, Sempos, & Andersen, 2002). Several small experimental studies (Andersson et al., 1997; Andersson et al., 1999; Brussard et al., 1997; Friday et al., 2001; Samaras et al., 1999) conducted over short durations (8 weeks to 6 months), noted improvement in the measures of glucose control with only one study (Araujo, Farias, & Andrade, 2002) reporting no change in glucose measures. The HERS study (Kanaya et al., 2003), a large prospective randomized placebo controlled four year study of EPT, included a subset of women with DM (N=734) equally randomized to placebo or EPT treatment. While data on the diabetic subjects were not analyzed separately in their report, women in the placebo group with and without diabetes at baseline had significant worsening of fasting glucose values compared to women with and without diabetes receiving EPT (Kanaya et al., 2003).

Estrogen and Intra-Abdominal Fat (IAF)

The increased distribution of intra-abdominal visceral fat has been associated with estrogen loss in the menopause (Poehlman, 2002; Poehlman, Toth, & Gardner, 1995; Ferrara, Lynch, Nicklas, Ryan, & Berman, 2002). In women, estrogen promotes the deposition of fat in the gluteo-femoral region and results in the female gynoid or "pear" shape (Krotkiewski, Bjorntorp, & Sjostrom, 1983; Carr, 2003). Several studies, both cross-sectional (Toth, Tchernof, Sites, & Poehlman, 2000; Gower, Nagy, Goran, Toth, & Poehlman, 1998; Zamboni, et al., 1992; Svendsen, Hassager, & Christiansen, 1995) and longitudinal (Poehlman et al., 1995; Bjorkeland, Lissner, Andersson, Lapidus, & Bengtsson, 1996) that measured fat distribution by high quality techniques (CT scan, DEXA scan) have demonstrated the menopause transition is associated with a preferential distribution of adipose tissue centrally, resulting in a more android or "apple" shape. This change in fat distribution has been noted to be independent of aging, weight gain, and total body adiposity (Poehlman et al., 1995; Toth et al., 2000; Gower et al., 1998; Zamboni, et al., 1992; Bjorkeland et al., 1996).

The use of EPT may attenuate this change in body topology. Hormone use in short-term prospective experimental studies appears to prevent (Gambacciani et al., 1997; Reubinoff, et al., 1995; Haarbo, Marslew, Gotfredsen, & Christiansen, 1991) and favorably reverse (Cefalu, 2001; Samaras et al., 1999) the pattern of central fat deposition adding support to the estrogen deficiency hypothesis. In larger, longer placebo controlled studies of EPT, similar findings were noted as hormone users had significantly smaller waist circumferences compared to placebo (Kanaya et al., 2003; Margolis et al., 2004; Espeland et al., 1997). However, the varied methods used to estimate central adiposity varied significantly in these studies. CT scan provides greater precision and reproducibility in the measurement of subcutaneous and visceral adipose compared to anthropometric measures such as waist circumference or waist/hip ratio (WHR)(Poehlman, 2002). While DEXA scanning is as accurate as CT scanning in the measurement of total abdominal fat, it is unable to differentiate visceral fat from subcutaneous fat (Jensen, Kanaley, Reed & Sheedy, 1995). None of the EPT studies used CT scan to measure the abdominal fat compartment, while two studies (Samaras et al., 1999; Gambacciani et al., 1997) used DEXA scan for evaluation. Other investigations (Kanaya et al., 2003; Margolis et al., 2004; Haarbo et al., 1991) used waist circumference, with only one study (Espeland et al., 1997) utilized WHR, a less accurate measure.

IAF, Insulin Resistance and Menopause

The increase in IAF associated with menopause is disconcerting**.** Central adiposity is more strongly associated with DM and CVD than overall obesity (Wei, Gaskill, Haffner, & Stern, 1997) and this association is stronger among women than men (Kanaya, Harris, Goodpaster, Tylavshy, & Cummings, 2004). More importantly, IAF in both lean and obese persons is the major predictor of changes in insulin resistance (IR)(Cnop et al., 2002). Insulin resistance (IR) is the reduced sensitivity in target body tissues to the action of insulin, especially the ability to mediate glucose uptake in muscle (Carey, Jenkins, Campbell, Freund, & Chisholm, 1996; Despres, 1993; Pascot et al., 2001). In response, pancreatic β cells secrete increased amounts of insulin. With the resulting hyperinsulinemia, adipocyte lipolysis occurs, releasing free fatty acids (FFA) into the circulation (Goldstein, 2002; Lamendola, 2004). Increased levels of FFA

enhance glucose output from the liver and reduce glucose disposal in skeletal muscle, challenging glucose homeostasis (Goldstein, 2002; Carr, 2003; Lamendola, 2004). IR is considered the major underlying abnormality in type 2 DM (Goldstein, 2002; Reusch, 2002) with its presence noted years before the DM is confirmed (Karam, 1999; Ferrannini, 1998). IR is a major risk factor for CVD (Reusch, 2002; Lamendola, 2004) and linked to adverse health outcomes such as hypertension (Mason, 2004), breast (Stoll, 2002) and endometrial (Petridou, 2003) cancer in women.

The emergence of IR is noted with the menopause**,** but it is not clear whether increased IR is a function of estrogen deficiency, normal aging or the increase in IAF (Poehlman, 2002; Carr, 2003). A few studies have examined this relationship but have not measured IR in the same way. Fasting insulin levels, glucose tolerance tests, HOMA (homeostasis model assessment) modeling or hyperinsulinemic-euglycemic clamp technique, have all been used as indicators for IR, thus prohibiting a conclusive answer (Carr, 2003). Insulin levels alone are an imprecise measure of insulin secretion. The glucose tolerance test or glycemic clamp protocol is more sensitive, distinguishing the sensitivity of insulin secretion in response to glucose from the sensitivity of glucose to the disappearance of insulin (Godsland, 1996). Studies comparing insulin and glucose levels, demonstrated higher fasting insulin levels in postmenopausal women compared to premenopausal women (Walton, et al., 1993; Poehlman et al., 1995; Lindheim et al., 1994) when matching for BMI (Lindheim et al., 1994). However, Toth and colleagues (2000) evaluated pre- and postmenopausal women via the hyperinsulinemic-euglycemic clamp technique, a more accurate assessment of IR, and found no changes in insulin sensitivity between groups, suggesting menopause does not affect IR.

Observational studies have considered the relationship between endogenous estrogen levels to indexes of IR in groups of pre, peri or postmenopausal women. The large multiethnic SWAN study observed no relationship between estrogen and IR in pre and peri menopausal women studied at a single time point (Sowers, Derby, Jannausch, Torrens, & Pasternak, 2003), but differences were noted by race/ethnicity status, with higher IR values observed in African American and Hispanic women compared to Asians and Caucasians.

In contrast, in the baseline data of the 845 postmenopausal PEPI subjects, higher levels of total and bioavailable estrogen were associated with higher IR values (Kalish, Barrett-Connor, Laughlin, & Gulanski, 2003). These findings remained significant after adjusting for WHR (measure of central adiposity), but when adjusted by BMI (measure of total adiposity) and BMI with WHR, the association was nonsignificant in subjects with lower total and bioavailable estrogen measures (Kalish et al., 2003). A number of subjects (26%) in this study were noted to have elevated glucose values indicating diabetes at baseline, but were still included in the analysis and may likely have confounded the IR values.

The Metabolic Syndrome and Menopause

The increased distribution of IAF with menopause and the suspected increase in IR during this time, has taken on new meaning as both conditions have been repeatedly identified as the central underlying features of the metabolic syndrome and the associated dysfunctions of glucose intolerance, dyslipidemia, hypertension, and hypercoaguability (Goldstein, 2002; Carey et al., 1996). Although the metabolic syndrome has recently been refuted as a disease state and identified as a constellation of signs and symptoms (Grundy, 2006), the presence of these features in postmenopausal women warrants attention. Recent secondary analysis of NHANES III data (Park et al., 2003) demonstrated a 60% increased risk for the metabolic syndrome associated with postmenopausal status. This is of concern as the presence of the metabolic syndrome dramatically increases the risk for type 2 DM and CVD (Alexander, 2003; Expert Panel, 2001). More disconcerting for women, the metabolic syndrome is suspected to be the underlying mechanism in almost half of cardiac events in women (Wilson, Kannel, Silbershatz, & D'Agostino, 1999).

Menopause and other CVD risk factors

Longitudinal and cross sectional data demonstrated that as women age, changes in serum levels of lipoproteins, fibrinolytic and inflammatory markers occur that increase CVD risk but it is not clear to what extent the menopausal hormone decline contributes to these changes (Collins et al., 2002). These alterations may be independently related to menopause or may be the result of other adverse changes noted with menopause such as increased central adiposity and changes in glucose and insulin metabolism (Carr, 2003).

Increases in low density lipoproteins (LDL), total cholesterol (TC) and triglyceride (TG) levels and decreases in high density lipoproteins (HDL) values have been observed in both longitudinal and cross sectional research comparing pre and postmenopausal women (Lindquist, 1982; Jensen et al., 1990; Collins et al., 2002; Carr et al, 2000) with one longitudinal study observing no change in HDL across the transition (Do et al., 2000). Clinical trials of several estrogen (ERT) and hormone replacement therapies (HRT) provide evidence for the favorable effect of estrogen on lipid profiles in postmenopausal women with lower levels of TC and LDL, and increases in HDL documented in women using estrogen and progestin therapy (Crespo, Smit, Snelling, Sempos & Anderson, 2002; Writing Group for the WHI, 2002; Brussard, et al., 1997, Andersson & Mattsson, 1999; Hulley et al., 1998; Writing Group for the PEPI Trial, 1995). In the larger trials (WHI, PEPI, HERS), however, an unfavorable increase in TG levels was observed. Yet despite this improvement in lipid profiles, postmenopausal EPT use was paradoxically associated with increased rates of adverse CVD events (heart attack, stroke) (Writing Group for the WHI, 2002) suggesting another mechanism mediates this effect. Herrington (2002) observed a genetic variant in the estrogen receptor gene that resulted in a doubling of the HDL cholesterol levels in women using ET replacement therapy, suggesting responses to ET may be a function of genetic encoding.

Beyond genetics, scientists have also reconsidered the discordant findings of CVD risks and HT use noted between prospective observational investigations where HT use was cardioprotective and clinical trials in which significant adverse CVD events occurred (Alison & Manson, 2006). It has been suggested that observational studies did not completely capture early CVD events resulting in underestimates of CVD risks or that differences in hormone therapy, estrogen alone or estrogen plus progestin may account for these findings (Manson, Bussuk, Harman, Brinton, Cedars, Lobo et al., 2006). More notably the major difference between observational studies and clinical trials has been the timing of initiation of HT and the baseline ages of the study participants, suggesting early HT initiation when atherosclerotic changes includes only fatty plaques may provide favorable effects, while HT initiation at later ages and greater years postmenopause when atherosclerotic plaques are likely to have progressed may result in adverse outcomes (Manson et al., 2006). This new hypothesis is currently being tested in

two clinical trials. The Kronos Early Estrogen Prevention Study (KEEPS) is a 5 year randomized clinical trial evaluating the effects of low dose oral and transdermal estrogen on atherosclerotic change in younger (aged 42 -58 years) women in the early postmenopausal (within 3 years) stage (Manson et al., 2006). Another clinical trial, the Early versus Late Intervention Trial with Estradiol (ELITE) is measuring change in intima-media thickness of the distal common carotid artery in response to estradiol with or without vaginal progesterone in women either less than 6 years postmenopause or more than 10 years postmenopause (http://clinicaltrials.gov/show/NCT00114517).

Some fibrinolytic and inflammatory markers (C-reactive protein [CRP], plasminogen activator inhibitor [PAI-1], interleukin-6 [IL-6]) are predictive of CVD risk but relatively little is known about the effect of menopause on these markers. Levels of both CRP and PAI-1 are positively associated with central adiposity (Carr, 2003), suggesting increases in the central fat depot with menopause may influence circulating levels of these factors, but few studies have addressed this hypothesis. Higher levels of PAI-1 and IL-6 (Lindoff, Petersson, Lecander, Martinsson & Astedt, 1993; Pfeilschifter, Koditz, Pfohl, & Schatz, 2002) have been noted in postmenopausal women compared to those of reproductive age but no differences have been observed in CRP levels between pre and postmenopausal subjects (Sites et al., 2002), precluding a clear understanding of whether estrogen deficiency at menopause affects regulation of these factors.

Relative Androgenicity in Menopause

The loss of estrogen has been considered 'responsible' for the increased health risks of DM and CVD in postmenopausal women, but the possible role of the androgens warrants consideration. While estrogen decline is the primary feature of menopause, it has been suggested that menopause is a time of relative hyperandrogenicity as there is greater decline in estrogen than the slower age-related decline in androgens (Burger et al., 1999). Androgen excess is associated with deterioration in glucose homeostasis, total and central adiposity, and IR - all clinical features that characterize the postmenopause period and are linked to CVD and DM risk (Golden et al., 2004).

No conclusive findings have been documented in the literature. In a small study of 34 nondiabetic older postmenopausal women (mean age 72), androgenicity was associated with insulin sensitivity independent of obesity status, suggesting the higher

androgen levels were responsible for the change in insulin sensitivity in these postmenopausal women (Lee, Kasa-Vubu & Supiano, 2004). In one longitudinal study, decreased levels of sex hormone binding globulin (SHBG) resulting in relatively higher concentrations of unbound T were observed in postmenopausal women (Burger et al, 1999), while other studies have documented modest changes in SHBG but no significant changes in levels of free androgens with menopause (Santoro, 2002). Maturna and Spritzer (2002) observed no differences in features of androgen excess between pre and postmenopausal women with similar levels of hyperinsulinemia, suggesting reproductive status does not influence androgenic state. Yet, several cross sectional studies have shown estrogen replacement therapy significantly reduces androgen bioavailability (Simon, 2002). Recently, investigators from the SWAN study documented as androgenicity progresses across the menopause transition, the prevalence of the metabolic syndrome increases (Janssen, Powell, Crawford, Lasley & Sutton-Tyrell, 2008). This effect was independent of aging, ethnicity and BMI and suggests the hormone changes with menopause are related to increased risk for the metabolic syndrome.

Factors Affecting Age at Menopause

A variety of clinical host characteristics and lifestyle factors may also affect the endocrine milieu and the eventual timing of the menopause transition. This is of interest as hormone levels and cycle patterns may influence the intensity of menopause symptoms and even more importantly may affect the age at which menopause occurs. An earlier age at menopause is associated with increased rates of both morbidity and mortality and increases a women's risk for cardiovascular disease and osteoporosis (Birkhauser et al., 2002). In prospective cohort studies of large numbers of American (Mondul, Rodriguez & Calle, 2005) and Norwegian (Jacobsen, Huech, & Kvale, 2003) women, age at natural menopause was inversely related to all cause mortality. Hu and colleagues (1999) had previously demonstrated an increased risk of coronary heart disease (CHD) for women with a younger age at menopause, while Mondul and associates (2005) observed not only

increased mortality rates from CHD for these women but additional risks of higher mortality from respiratory or genitourinary disease as well.

Host Characteristics: BMI

Increased BMI has been hypothesized to elevate estrogen levels, from the increased aromatase activity converting androstenedione to estrogen (Zumoff, 1982), and as such may contribute to longer reproductive functioning and a later age at menopause. To date, the relationship of BMI to age at menopause has been inconclusive (Gold, 2000). Increased BMI has been associated with both a later age at natural menopause (Greendale et al, 1995; Daniel, 1978; Willet et al., 1983), and an earlier age of menopause (Santoro & Chervenak, 2004) with some studies detecting no relationship between BMI and menopause age (Gold et al., 2001; Bromberger et al., 1997; Stanford, Hartge, Brinton, Hoover, & Brockmeyer, 1997).

In contrast, elevated BMI at the level of obesity (> 30kg/m^2) is also associated with compromised ovarian function that may induce an earlier age at menopause (Garner, 1990). Santoro and colleagues (2004) observed the influence of BMI on cycle patterns in subjects in the multiethnic SWAN study. Women with BMI $\geq$ 25 kg/m^2 had longer menstrual cycles than those with lower BMI of normal weight status (BMI <25 kg/m^2). Normal weight women had a greater proportion of cycles with evidence of luteal activity compared to those of either overweight or obesity status. BMI was the strongest predictor of follicular and luteal phase lengths; longer follicular and shorter luteal phases were noted in larger women. While women of greater BMI were more likely to have longer and more anovulatory cycles than normal weight women, no effect of BMI on age at natural menopause has been detected in the SWAN subjects (Gold et al., 2001).

Santoro et al (2004) and Randolph et al (2003) documented the impact of BMI on reproductive hormones in the multiethnic SWAN subjects. In each ethnic group as BMI increased, serum concentrations of E_2, FSH, DHEAS, and SHBG decreased while T levels increased (Randolph et al., 2003). In a more recent study including subjects in late perimenopause and the postmenopause (PM) (Randolph et al., 2004), increased BMI was significantly associated with decreased serum concentrations of E_2 in pre- and early perimenopausal women while increased levels were observed in late perimenopause and PM subjects (Randolph et al., 2004). Decreased levels of FSH were found in women

with increased BMI and women with diabetes across the transition (Randolph et al., 2004). In the urinary measures of reproductive hormones, Santoro et al (2004), described similar findings with women of increased BMI (≥ 25 kg/m^2) had lower urinary LH, FSH, and progesterone levels but similar levels of estradiol metabolites compared to normal weight women (Santoro et al., 2004).

Cross sectional studies (Klinga, Von Holst, & Runnebaum, 1981; Pasquali et al., 1987; Malacara, Fajardo, & Nava, 2001; Zumoff, 1982) and one longitudinal study (Burger et al., 1999), not as large or as tightly controlled as the SWAN project, have also examined the effect of BMI on reproductive hormones. These studies have yielded conflicting results most likely due to differences in design, populations sampled and lack of control for other confounding variables (diet, exercise habits, etc). Burger and colleagues (1999) observed no significant effects of BMI on E_2 levels in a longitudinal study of Australian women. In cross sectional studies comparing obese and normal weight women, no differences in E_2 levels were noted between obese and normal weight women (Klinga, Von Holst, & Runnebaum, 1981; Pasquali et al., 1987; Malacara, Fajardo, & Nava, 2001; Zumoff, 1982) but E_1 levels were significantly higher in the obese group in the Malacara et al. (2001) and Zumoff (1982) studies. In a review of hormone risks for endometrial cancer, Hale and associates (2002) found as well that studies of obese and normal weight postmenopausal women with and without endometrial cancer, report increased, decreased or no difference in the levels of E_1 and E_2 between obese and normal weight women.

Host Characteristics: Genetics

Genetic conditions that affect the age of menopause are beginning to be defined (Santoro & Chervenak, 2004). Known chromosomal abnormalities, such as Fragile X syndrome, or X chromosome deletions predispose women to an earlier age of menopause (Santoro, 2002). As the science of genomics explodes, the once mysterious human gene code is now providing insights into mechanisms that affect health status. Genetic variants in the steroid hormone receptor genes have been established and investigations are now evaluating the estrogen receptor (ER) genes (Herrington, 2002). Gene sequence variations, known as single nucleotide polymorphisms (SNPs), have been described for the ERα and ER β gene and the genes responsible for estrogen biosynthesis and

metabolism (Deroo & Korach, 2006; Hefler et al., 2005). These genetic variants may affect peripheral and tissue bound estrogen concentrations and modulate aspects of reproduction such as menstruation, fertility, or ovarian aging (Hefler et al., 2005).

Genetic markers associated with an earlier age of menopause have been identified primarily in Caucasian women including an FSH receptor polymorphism in Finnish women (Aittomaki et al, 1995), and an estrogen metabolizing gene polymorphism (CYP1B1) in Austrian women (Hefler et al, 2005). In another study, ER β polymorphisms were associated with ovarian dysfunction and lower serum levels of FSH, LH and progesterone in a study of Asian women but no relationship with age at menopause was detected (Sundarrajan, Liao, Roy & Ng, 2001). In a more recent study, Mitchell and colleagues (2008) recently documented polymorphisms in the estrogen synthesis pathway (CYP19, HSDB1, CYP1P1*2) and the ESR1 gene were associated with age at menarche and menopause in a small sample of women (n =152) from the Seattle Midlife Women's Study.

Weel and colleagues (1999) noted an association of an ER-α polymorphism, P*vu*II with both an early age at natural menopause and an increased risk for hysterectomy in women from the Netherlands. In contrast, Gorai and colleagues (2003) documented no relationship between polymorphisms of the ER α gene (the P*vu*II and X*ba*I genotypes) with age at natural menopause in Japanese postmenopausal women. Similarly, Kok and colleageues (2005) reported no relationship between the P*vu*II and X*ba*I variants of the ER-α gene with age at natural menopause in Dutch women. These conflicting reports suggest other environmental factors or host characteristics may likely influence the actual expression of the genetic code.

Other Host Characteristics

Previous treatment for childhood cancers (Chiarelli et al., 1999), low weight (Willet et al., 1983) and reproductive factors such as nulliparity or having fewer children (Bromberger et al., 1997; Stanford, Hartge, Brinton, Hoove, & Brookmeyer, 1987), earlier age of menarche, or shorter menstrual cycles (Bromberger et al., 1997) have also been associated with early menopause (Gold et al., 2001). Oral contraceptive use, increased parity, later age at menarche and high cognitive scores in childhood has been associated with a later age at menopause (Birkhauser et al., 2002; NAMS, 2007).

Of all lifestyle behaviors, smoking has been consistently empirically identified as a cause of an earlier menopause by one to two years (McKinlay, Bifano & McKinlay, 1985; Midgette & Baron, 1990; Bromberger et al., 1997; Wise, Krieger, Zierler, & Harlow, 2002; Blanck, et al., 2004; Reynolds & Obermeyer, 2005). Demographic characteristics associated with early menopause include lower socioeconomic status (Lawlor, Ebrahim, & Smith, 2003; Hardy & Kuh, 2005;Wise et al., 2002), lower educational levels (Wise et al., 2002), lifetime history of major depression (Harlow, Wise, Otto, Soares & Cohen, 2003) and lifetime exposure to abuse (Allsworth, Zierler, Krieger & Harlow, 2001).

Race/Ethnicity status has been thought to play a role in determining age at menopause as cross-sectional data suggest menopause occurs at a later age in Japanese women (Tamada & Iwasaki, 1995 as cited in Gold et al., 2001), and a younger age in African American (Bromberger et al., 1997) and Latino women (Beyene, 1986). In the SWAN investigation, the most controlled and diverse study to date (Gold et al., 2001), factors associated with age at natural menopause were evaluated. Among the multiethnic sample (African American, Caucasian, Chinese, Japanese, Hispanic), ethnicity was not predictive of an earlier age at menopause but Japanese ethnicity was independently associated with a later age at menopause (Gold et al., 2001).

The SWAN study data support previous findings that among multiethnic women, smoking and lower educational attainment is associated with an earlier age of menopause and parity, previous oral contraceptive use is associated with a later age of menopause. Gold et al (2001) detected not being married, a history of non-employment and heart disease were associated with early menopause. Findings from small cross sectional studies suggested a relationship between age of menopause and BMI, physical activity and dietary habits (Gold, 2000), but these relationships were not observed in this multiethnic sample. The relationship between diet and menopause age has not been well studied, although vegetarian diet has been associated with earlier age of menopause (Gold, 2000). In this study where Japanese women had a later age at menopause, dietary intake was not evaluated (Gold et al, 2001). Of interest though, in another SWAN study, isoflavone intake was reported to be 2 times greater in Japanese than Chinese women,

suggesting diet may have some relationship to reproductive endocrine function and further study is needed (Randolph et al., 2004).

Summary

The menopause transition features progressive loss of ovarian function and is characterized by changes in hormonal levels (NAMS, 2007). Longitudinal and cross-sectional studies consistently document a progressive decline in the number of ovarian follicles and level of inhibin B that result in the monotropic rise of FSH to support follicle development and ovulation (Sherman & Korenman, 1975; Klein, et al, 1996; Reame et al., 1998; Burger et al., 1999; Robertson & Burger, 2002; Randolph et al., 2004; NAMS, 2007). With continued ovarian decline, anovulation occurs. Initially this disrupts menstrual cycle regularity, but ultimately menstruation ceases. Both central nervous system and ovarian mechanisms are thought to be involved in this process.

These patterns of estrogen and gonadotropin change with the menopause are similar across ethnic groups although actual hormone levels vary by ethnic status (Randolph et al., 2004). The timing of menopause may be affected by several clinical and host characteristics. Smoking behavior has been consistently associated with an earlier age at menopause, while the evidence is mixed regarding the influence of other characteristics such as reproductive characteristics or socioeconomic status. A growing body of scientific literature is beginning to document the effects of genetic variants and BMI on the endocrinology of the menopause.

Estrogen loss at menopause is associated with increased risk for major health alterations including diabetes and cardiovascular disease (CVD), the first and seventh leading causes of death of women in the US (Collins et al., 2002; CDC, 2007). The literature suggests that the increased risk for these diseases, particularly diabetes, at menopause is under the influence of the relationships among estrogen, glucose homeostasis, central adiposity, and insulin resistance. Most menopause research has been limited to the study of healthy Caucasian women. While in the past decade there is a growing body of evidence describing ethnic variations in menopause, there are still subgroups of women not routinely included in research. In particular, women with chronic illnesses such as CVD or diabetes have been excluded and given the increased risks for these diseases associated with menopause, further exploration is warranted.

Sociocultural and Developmental Challenges of the Menopause

For most women, the midlife years encompass the menopause transition and as such the study of midlife women has most frequently centered around this biologic event. Beyond menopause, midlife women experience other psychosocial transitions at midlife that can impact their health and wellness during this time. Major shifts in psychosocial roles occur for women in the middle years and can include a shift from childbearing to childrearing, a return to the work force, caring for aging parents or coping with sole responsibility of a household (Sabolski, Solomon, & Manson, 2001; Woods & Mitchell, 1997). Such circumstances leave middle-aged women vulnerable to lower incomes, inadequate health care coverage, increased family responsibilities, and stress levels that can diminish their physical and psychological health (Sabolski et al, 2001). Yet, until recently relatively little was known about women's perceptions of this period in their lives (NAMS, 2007; Sabolski et al, 2001; Sampselle, Harris, Harlow & Sowers, 2002).

Several challenges exist in the study of midlife women. Woods and Mitchell (1997) note that even defining 'midlife' is difficult. Researchers have commonly used specific age ranges such as 35 to 65 years or 40 to 60 years to delineate the midlife period, while others used reproductive characteristics, such as menopause (Collins, 2002; Woods & Mitchell, 1997). Lippert (1997) notes that roles of women have also been used to define and distinguish midlife, such as the postparental period, or the return to the workplace, but ideally the individual woman should define when and what is midlife. While an admirable approach, such a definition could be complex and makes it difficult to clarify the extent to which the midlife experience is universal, if at all.

Another important factor to consider in the study of midlife women is the context of their past and current sociopolitical and cultural environments. Women born in different eras will have different lived experiences and may perceive midlife development differently (Woods & Mitchell, 1997). For example, midlife women of the 1950's where women devoted themselves to marriage and family may describe different concerns than women of the new millennium who have had opportunities to control reproduction and achieve personal objectives such as advanced education or independent

careers (McQuaide, 1998). As well, women from various ethnic backgrounds are likely to perceive the midlife differently for religious or cultural reasons.

Midlife Development

Psychological theorists have provided models to understand human development from infancy to older adulthood. These models, varied in their approach, address different aspects of human development, such as cognitive operations, moral reasoning or psychological growth. The most familiar early models such as Erikson (1950) and Levinson (1978) were grounded in observational research primarily of male subjects and as Gilligan (1982) describes, "in all of these accounts, the women are silent" (p. 155) suggesting the possibility of "a different truth" (p. 170) for women.

In recent years, researchers and theorists have studied women and elucidated themes in midlife women's development. These themes include 1) introspective reflection and evaluation of one's life experiences, 2) developing a truer sense of self, 3) reappraisal of roles and relationships due to changes in family or work status, and 4) an awareness of one's mortality and health (Brown, 1992; Josselson, 1996; Woods & Mitchell, 1997; Liebert, 2000; Orr, 2000; Sampselle et al., 2002; Morrow, 2004; Pavalko & Gong, 2005). Despite these common themes, individuals or groups of women from various cultures or social groups may identify different midlife issues from the influence of sociocultural norms (Gilligan, 1982; Collins, 2002; Kaufert, 1998). Belenky and colleagues (1986) caution the meaning of midlife events for women is so contextual that one cannot ignore "the complexities and uniqueness of an individual women's thought and life" (p.15).

Midlife Women's Perceptions of Menopause

As the menopause transition occurs at midlife and has been the subject of a significant amount of research, it is a good place to start when examining the perceptions of women at midlife. Since the 1990's, feminists and nursing scholars brought forth critical dimensions of the female menopause and several studies with multiple methodologies have informed our understanding of women's lived experience of this midlife transition (George, 2002; Bertero, 2003; Berg & Taylor, 1999; Berger & Forster, 2001; Im, Meleis & Park, 1999; Kaufert, 1998; Sampselle et al., 2002; Woods & Mitchell, 1997). While once again, these studies are so varied in their methodologic approach that attempts at comparison are difficult, several themes do emerge.

Attitudes toward menopause. In the US and many western countries the menopause has been perceived largely in negative terms, described as an 'estrogen deficiency' state that impairs health or a time of social upheaval due to the 'empty nest', fertility loss, or the 'abandonment' of women (Morrow, 2004; Birkhauser et al., 2002). This negative characterization of menopause may be due an over-sampling of women who presented to clinics for menopause symptom management in the earliest research studies (Lock & Kaufert, 2001). Pharmaceutical marketing campaigns advocating EPT to preserve youthfulness and prevent disease coupled with the relative absence of women over age 40 in most forms of mass media imagery (movies, television, magazines) have contributed to this negative perception of menopause and midlife (Hust & Andsager, 2003; Cousins & Edwards, 2002; Gannon & Stevens, 1998).

More recent research demonstrates attitudes and beliefs about menopause may vary considerably, but most women view menopause as a normal developmental stage (Andrist & MacPherson, 2001; Taylor & Woods, 2001). Longitudinal and cross sectional studies in the US and Europe of primarily Caucasian women documented most women identify menopause as a positive-optimistic (36-67%) or neutral (42-57%) experience with few women reporting a negative-pessimistic perception (22-31%)(Busch, Barth-Olofsson, Rosenhagen & Collins, 2003; Avis & McKinlay, 1995; Kaufert, Boggs, Ettinger, Woods, & Utian, 1998). Menopause stage and type of menopause (natural vs. surgical) affect attitudes. Postmenopausal women were more likely to appraise menopause positively than perimenopausal women (Busch et al., 2003; Kaufert et al., 1998) while women with a surgically induced menopause were more negative in their appraisal than women experiencing a natural menopause (Avis & McKinlay, 1995).

Differences by Race/Ethnicity. Across cultures, several similarities and differences are noted. In the ethnically diverse SWAN study of African-American, Caucasian, Chinese, Japanese, and Hispanic women in the US, mean attitude scores for all ethnic groups were on the positive side of neutral. Across ethnic groups, African American women had the most positive attitude toward menopause while Chinese and Japanese women had the least positive attitudes (Sommer et al., 1999). An effect of acculturation was noted in the Japanese and Chinese women; the women considered less acculturated (primary education occurred outside the US) had the lowest attitude scores.

In the entire sample, women in a later stage of menopause had more positive attitudes than those of pre or early perimenopausal status, but interestingly women who experienced a surgical menopause had the most positive attitudes (Sommer et al., 1999). Across ethnic groups, menopause stage was a significant predictor of attitude with the exception of the Chinese women (Sommer et al., 1999).

Early studies of the menopause in women from different countries were modeled after the traditional disease oriented North American and European designs and failed to discern important social and cultural differences. Data were also 'lost in translation' with the use of instruments previously tested in primarily upper to middle class Caucasian populations that were not appropriate for women of other cultures. Since the 1990's, social scientists and anthropologists have embraced culturally sensitive research designs and provided more accurate data on the perceptions of menopause in women from several ethnic backgrounds.

In Lock's (1998) work with women from urban, rural and suburban Japan, she noted that in contrast to western cultures, the Japanese have no word for 'hot flash' or a specific word for the menopause. The Japanese word for the midlife phase, *konenki* describes a broad social rather than a narrow biological transition during the mid forties to mid fifties (Lock, 1998). Konenki is viewed as distinct from the cessation of menses, known as the *heikei* and is regarded as the release from one's primary role identity as a menstruating woman, to a time of greater fulfillment as a human being (Lock & Kaufert, 2001; Kagawa-Singer et al., 2002). Among Thai women, the term *modlyad*, translated to mean out of menstrual blood, is used to describe the midlife but again is interpreted to signal the entry to a more spiritual phase of life (Lock & Kaufert, 2001). Korean women (Im, Meleis & Park, 1999) specifically differentiate between menopause and aging using two separate terms to describe symptoms at midlife: *gangnyunki jeungsang* (symptoms related to aging) and *pekyungki jeungsang* (symptoms related to menopause).

Similar to the Japanese women, rural Mayan women in Mexico also had no concept or perception of the hot flash but did recognize menopause as the end of menstruation and childbearing (Beyene, 1986). In general, Mayan women look forward to menopause, perceiving it as a time of freedom and release from taboos and restrictions. Similar perceptions of a positive attitude towards menopause and the view of this life

phase as freeing were also noted in rural Greek (Beyene, 1986), Southern Indian (George, 1996), Northern Indian (Singh & Arora, 2005), and Nigerian (Adekunle & Okunlola, 2000) women. In contrast to the western view of menopause and the public attention it receives in the media, Korean (Im, Meleis & Park, 1999) and Thai (Punyahotra & Street, 1998) women consider menopause a private experience, give it less attention but similar to other cultures perceive it as a normal experience.

Researchers have suggested that religious belief systems or socioeconomic factors (education, wealth) may influence the cultural expectations and perceptions of menopause in women (Punyahotra & Street, 1998; Collins, 2002; Andrist & MacPherson, 2001; Kaufert, 1998). For example, Punyahotra and Street (1998) describes the Buddhist tenets, such as 'creating harmony' may have influenced the normalization of menopause in the Thai women. In contrast to industrialized nations where the menopause is more negatively characterized, menstruating Indian women required to abide by restrictive religious rules of behavior find the menopause to be a relief and a time of great freedom (Singh & Arora, 2005).

Kaufert (1998) contends that "women's bodies at menopause are not all the same" (p. 173) and perceptions of the menopause are affected by the multitude of factors such as diet, access to health care, and work. For example, the daily physical challenges of work in rural or impoverished women may preclude the time to even consider the menopause as a time of ill health. Khademi and Cooke (2003) examined this in their investigation of Iranian women, observing differences in attitudes toward menopause between urban and rural women in the same country. Rural women placed a higher priority on fertility and had negative attitudes toward menopause compared to women living in urban areas. Despite similar religious beliefs, Blumberg and associates (1996) also noted differences in Israeli women living in different countries. Israeli women born in North America and other Middle Eastern countries had more negative attitudes toward menopause compared to native Israeli women.

Nursing Research

Using qualitative approaches, nurse researchers have further examined the experiences of midlife women of various ethnic backgrounds: Australian, African American, Asian American, Caucasian, Irish, Latina and Swedish (Berger & Forster,

2001; Bertero, 2003; Carolan, 2000; George, 2002; Sampselle et al., 2002; Woods & Mitchell, 1997; Villarruel, Harlow, Lopez & Sowers, 2002). Sampselle and colleagues (2002), and Woods and Mitchell (1997), conducted focus groups with women regarding midlife development, while Bertero (2003), Carolan (2000), George (2002), Berger and Forster (2001) and Villarruel and colleagues (2002) specifically addressed the menopause. Several common themes emerged from the data. Similar to previous quantitative studies, women perceived midlife as a normal developmental stage (Carolan, 2000; Bertero, 2003; Sampselle et al., 2002; Woods & Mitchell, 1997; Villarruel et al., 2002). In all studies, most subjects anticipated and expected changes to occur (Villarruel et al., 2002) and for the most part this change was welcomed and seen as freeing. The feelings of freedom were viewed as either opportunities for personal growth and greater self-esteem (Berger & Forster, 2001; George, 2002; Sampselle et al, 2002; Woods & Mitchell, 1997; Villarruel et al., 2002) or the freedom to have sexual relations without fears of pregnancy (Bertoro, 2003; Berger & Forster, 2001; George, 2002), although the Irish women expressed sadness over the loss of fertility (Carolan, 2000).

Fears regarding the physical changes associated during midlife surfaced in all studies, but in the studies that were multiethnic (Sampselle et al., Woods & Mitchell, 1997), the Caucasian American women expressed more worry regarding age related changes, such as their physical appearance and weight gain. In contrast, the Australian women noted they seemed to be less concerned about this than expected unlike what they "had read about in books, women's magazines and newspapers" (Berger & Forster, 2001, p.274). Symptoms of menopause were another source of concern, with symptoms such as hot flashes and mood changes most commonly mentioned (Carolan, 2000; Berger & Forster, 2001; Bertero, 2003; George, 2002). In the more recent papers, women reported confusion regarding options for treatment of menopause symptoms given the problems identified with HT and the inability of health care providers to adequately answer questions (Bertero, 2003; George, 2002).

Summary

The midlife is a time of multiple physiologic, psychologic and developmental changes for women. While the cessation of menstruation is a universal biologic event for midlife women, the sociocultural milieu can have a powerful and complex impact on

women's perception of these life changes. Attitudes and beliefs about menopause vary considerably both within and across cultures. Most women perceive the midlife transition as a normal developmental phase, often viewing this life stage as a time of freedom and opportunity for greater personal growth. To date, research investigations have assumed homogeneity in the health status of the women from the different ethnic backgrounds studied. Given the variety of perceptions amongst these essentially healthy women, it is likely that women experiencing chronic illnesses or alternations in health will have a unique and different response to the menopause that warrants further investigation.

Symptoms of the Menopause

A wide variety of symptoms (over 100) are reported in midlife women during the menopause transition (Ditkoff, Crary, Cristo & Lobo, 1991). The most common symptoms identified include hot flashes, night sweats, vaginal dryness, urinary incontinence, alterations in mood, sleep disturbances, changes in sexuality, cognitive difficulties such as forgetfulness and somatic complaints (NIH State of the Science Panel, 2005; NAMS, 2007; Wenger et al., 2002). While not every menopausal woman reports symptoms and controversy exists over which symptoms are related to ovarian decline or aging in general, approximately 85% of midlife women report at least one symptom and 10% visit a health care provider regarding these concerns (Woods & Mitchell, 2005, Sherman, Miller, Nerurkar & Schiff, 2005; McKinlay, Brambilla & Posner, 1992). There is great diversity in menopause symptomatology; symptom patterns vary in combination, intensity, and duration both between and across women of different cultures or race/ethnicity status (Avis et al., 2001; NIH State of the Science Panel, 2005; Obermeyer, 2000; Melby et al., 2005). With the now known deleterious health risks from hormone therapy (HT) (Writing Group for the WHI, 2002), the issue of menopause symptom management has reached center stage in the US such that the National Institute of Health (2005) and Agency for Healthcare Research and Quality (AHRQ) recently conducted a conference to review the current scientific evidence regarding menopause symptoms, delineate safe menopause therapies and identify future research opportunities (NIH State of the Science Panel, 2005; Nelson et al., 2005).

Vasomotor Symptoms

The most common identifiable sign of the menopause transition is a change in bleeding pattern (NAMS, 2000) but vasomotor symptoms (hot flashes, night sweats) are the most commonly reported symptom (Freedman, 2005a; Love, 2003). In their review of the major US and international menopause research investigations, Avis and colleagues (2005) conclude that despite the great number and variety of symptoms reported in every study, vasomotor symptoms consistently cluster as a unique symptom of menopause.

Hot flashes are recurrent transient periods of flushing, perspiration and a sensation of heat that may be accompanied by palpitations or a feeling of anxiety (Kronenberg, 1990). Hot flashes that occur with perspiration during sleep are labeled night sweats (NAMS, 2004). While the precise cause of hot flashes remain unknown neuroendocrine hypothalamic mechanisms are hypothesized to be responsible. Changes in the central opioidergic and adrenergic systems, the thermoneutral zone, or cerebral glucose levels have all been hypothesized to be responsible for hot flashes (NAMS, 2004; Freedman, 2005b; Dormire & Reame, 2003).

Presentation with Menopause. Evidence from longitudinal and cross-sectional studies document the temporal association between vasomotor symptoms and menopause (Nelson et al., 2005). Hot flashes rarely occur before perimenopause and are reported with increased frequency during late perimenopause and the early postmenopausal period (Avis et al., 2005; Woods & Mitchell, 2005; NIH State of the Science Panel, 2005; Gold et al., 2006). In their review of the major longitudinal studies (US, Europe, Australia) and using the STRAW criteria to distinguish the menopause stage, Woods and Mitchell (2005) documented prevalence rates of hot flashes range from 6-13% in premenopausal women to 26-79% in late perimenopause and early postmenopausal women.

In the Melbourne Women's Midlife Health Project (MWMHP), prevalence rates of hot flashes increased from 10% in premenopause women to 15% in early perimenopausal women and to 42% in both late peri- and postmenopausal women (Dennerstein, Dudley, Hopper, Guthrie, & Burger, 2000). Higher prevalence rates but similar patterns were noted in the SWAN (Gold et al., 2000) and the Penn Ovarian Aging (Freeman et al., 2005) studies (Table 2.1). In the SWAN subjects, 19.4% of premenopausal women complained of hot flashes and night sweats compared to 36.9% of

early perimenopausal women, 56.8% of late perimenopausal women and 48.8% of postmenopausal women (Gold et al., 2000). Among the women of the Penn Ovarian Aging study, higher rates were reported with 37% of premenopausal women noting hot flashes, compared to 48% of those in early perimenopause, 63% of those in late perimenopause and 79% of those postmenopause (Freeman et al., 2005). Malacara and colleagues (2002) compared vasomotor symptoms between pre and postmenopausal women in Mexico also observing a wide range in symptom prevalence in women from three different geographic areas. The prevalence of vasomotor symptoms ranged from 4-48% in the women of reproductive age and 32-73% in postmenopausal women.

Estrogen loss plays a role in the manifestation of hot flashes as these symptoms occur in women at the time of either natural or surgical menopause, and women on medications that reduce ovarian hormone production (Freedman, 2005a). Further, a substantial body of evidence demonstrates that exogenous estrogen administration relieves these symptoms (Dennerstein, Guthrie, Birkhauser & Sherman, 2002a). Yet, despite this observed relationship between estrogen decline and hot flashes, Freedman (2005a) notes there are "no correlations between hot flash occurrence and plasma, urinary, or vaginal levels of estrogens" (p.139). Interestingly, in longitudinal analysis of SWAN data, Randolph and colleagues (2005) recently demonstrated elevated FSH concentrations were positively associated with both the prevalence and frequency of vasomotor symptoms.

Hot flashes may last 30 seconds up to 10 minutes and range from 5 per year to 50 per day (Freedman, 2005b) but the frequency, duration and severity varies among individuals (NIH State of the Science Panel, 2005; NAMS, 2004). In most women, hot flashes persist for 6 months to 2 years (Kronenberg, 2000) but can last as long as 5 years (Feldman, Voda & Groseth, 1985) although most studies have not followed subjects long enough to discern when hot flashes stop completely (Woods & Mitchell, 2005).

Race/Ethnicity. Prevalence rates of vasomotor symptoms (including hot flashes and night sweats) vary considerably in the world literature (Freeman & Sherif, 2007; Obermeyer, Reher & Saliba, 2008). In samples of primarily North American and European Caucasian women prevalence rates of hot flashes range from 26-79% (Woods & Mitchell, 2005) compared to Asian women (10-12%) and no reports of hot flashes in

Mayan women (Beyene, 1986; Obermeyer, 2000; Lock, Kaufert & Gilbert, 1988). In Obermeyer's review (2000) of vasomotor symptoms in developing countries (Nigeria, Ghana, Tanzania) though, hot flash prevalence rates ranged from 30-80% similar to North American and European countries.

In the SWAN data, vasomotor symptom reporting differed by race/ethnicity status with higher rates reported by African American (46.5%) and Hispanic (43.5%) women compared to Caucasian women (36.6%)(Gold et al., 2004). Similar to previous literature that Asian American women report lower rates of hot flashes, fewer Japanese (34.3%) and Chinese (28.9%) women reported vasomotor symptoms compared to the Caucasian women (Table 2.2)(Gold et al., 2004).

The variance in vasomotor symptom prevalence rates across and within cultures may be due to several reasons. Methodologic differences such as variation in the time frames for symptom reporting from past 2 weeks to up to the past year makes it difficult to compare results. Obermeyer (2000) suggests differences in vasomotor symptom reporting are likely due to cultural norms. For example, in rural Greece hot flashes are believed to be the mechanism by which the body clears itself of harmful substances. Viewed as beneficial, women may be more likely to report them (Beyenne, 1986). In Thailand, women consider menopause an intimate private experience that leads to greater spirituality and in compliance with social norms may not voice symptoms (Punyahotra & Street, 1998). Melby and colleagues (2005) further suggest cross-cultural differences in vasomotor symptom reporting may be due to other undetermined biological and lifestyle factors, requiring continued exploration.

Factors Affecting Symptoms: Climate. Peripheral heat and warm ambient temperatures can provoke hot flashes (Freedman, 2005b) and cooler air temperatures are associated with reduced incidence of vasomotor symptoms (NAMS, 2004). Working from the hypothesis that women in different geographic locations develop climate specific thermoneutral zones that may explain population specific hot flash frequencies, Sievert and Flanagan (2005) reviewed menopause symptom studies from 54 different locations of women. Average temperature of the coldest month, mean annual temperature, difference in temperature between the hottest and coldest month and latitude

were significant predictors of hot flash frequency in regression equations (Sievert & Flanagan, 2005, p. 440).

The study findings suggest that acclimatization and adaptation to temperature may be the mechanism explaining hot flash frequencies, as the more variation in the temperature (either seasonal or monthly), the greater the hot flash frequency (Sievert & Flanagan, 2005). Several issues limit the study findings. The sample populations used for comparison ranged in age from 35 to 89 years and included premenopausal, perimenopausal and postmenopausal (PM) women. There was variety in the time frames used to measure of hot flash frequency from the previous 2 weeks to past year, and the investigators collapsed hot flash symptoms into 2 categories, past 2 weeks or 'ever'. Geographic latitudes were not compared on the specific location of the sample subjects (city or state) but were determined by country, even in large countries that covered several latitudes. Lastly, confounding variables, such as BMI were not controlled for.

Lifestyle and Demographic Factors. In major review papers of cross-sectional and longitudinal studies, high BMI, increased adiposity and smoking behavior are consistently associated with increased vasomotor symptoms (Thurston et al., 2008; Greendale & Gold, 2005; Freedman, 2005b, NIH State of the Science, 2005, NAMS, 2004). Data describing the relationship of alcohol consumption with hot flashes is mixed (Greendale & Gold, 2005) largely due to differences in measurement of alcohol intake (measured as 'yes or no' versus the amount ingested in a week or a month). In the SWAN data (Gold et al., 2004) and the Melbourne Women's Midlife Health Project (Guthrie et al., 1996), no relationship between vasomotor symptoms and alcohol consumption were detected. In contrast, Freeman and colleagues (2001) documented greater hot flash frequency in African American and Caucasian women who consumed alcohol. In a large cross sectional study of Swedish women (N = 6,917), Li and associates (2003) observed no difference in vasomotor symptom frequency but rather more severe vasomotor symptoms in women who consumed alcohol.

The relationship between physical activity (PA) level and vasomotor symptoms is not clear and may be affected by variation in the conceptualization and measurement of PA. While Freedman and Krell (1999) noted hot flashes were triggered by exercise, studies that controlled for relevant covariates have not demonstrated an effect of PA on

vasomotor symptoms (Greendale & Gold, 2005; Freedman, 2005b). In the multiethnic SWAN study, lower levels of PA were associated with increased reporting of vasomotor symptoms in baseline survey data (N = 16,065) (Gold et al., 2000), but in multivariate modeling of the cohort data (N = 2,823), no relationship between PA and vasomotor symptoms was found. Li and colleagues (2003) obtained data on work activity and leisure time activity in their prospective study of Swedish women. Increased hot flash frequency was observed in women who participated in heavy activities at work, but when adjusted by covariates a significant relationship was not detected. However in this same study, a lower risk for hot flashes was associated with participation in vigorous physical leisure time exercise for more than 3 hours per week.

In other observational studies, decreased hot flash incidence was noted in women (age 45-55) who regularly engage in PA (Ivarsson, Spetz & Hammar, 1998; Hammar, Berg & Lindgren, 1990) and similar findings were also noted with older subjects (mean age 63 years) in the prospective WHI data (Barnabei et al., 2003). In an intervention study, Aiello and colleagues (2004) tested the effect of a yearlong moderate intensity exercise program on menopause symptoms in postmenopausal women. Compared to controls, hot flash severity increased during the intervention. These findings may have been confounded by the older age (mean age 61 years) of the subjects, likely past the peak incidence of hot flashes, and the obese (mean BMI 31 kg/m^2) and sedentary status of the participants who may have been sweating secondary to exercise intolerance and not necessarily a hot flash.

A relationship between perceived stress and vasomotor symptoms is not well supported when studied systematically (NAMS, 2004). In the SWAN data, measures of perceived stress were negatively related to vasomotor symptoms in early perimenopausal women (Gold et al., 2004), yet, levels of interpersonal stress were not related to vasomotor symptoms in the Melbourne Women's Midlife Health Project (Dennerstein et al., 2000). In a comparative study of menopause symptoms among clinic patients and non-patients, while higher levels of stress were reported in the women attending the menopause clinic, the prevalence rates of hot flashes were similar between the two groups (Ballinger, 1985). Interestingly, Freeman and colleagues (2005) recently observed anxiety was strongly associated with hot flashes in African American and Caucasian

women in the Penn Ovarian Aging study. Women with moderate anxiety scores were three times more likely and women with high anxiety scores were five times more likely to report hot flashes compared to women with normal anxiety scores. This association of anxiety with hot flashes was independent of race, smoking behavior, BMI, age, estradiol levels and the presence of depressive symptoms (Freeman et al., 2005).

The effect of socioeconomic variables on vasomotor symptoms is not clear. In the SWAN data, less frequent vasomotor symptoms were reported in women who never married, were widowed or divorced compared to currently married women (Gold et al., 2000). Vasomotor symptoms were more prevalent in women with lower educational levels and difficulty paying for basic needs (Gold et al., 2004; Gold et al., 2000). Similar findings were noted in rural Mexican women (Malacara et al., 2002), while Sievert and associates (2002) documented higher rates of vasomotor symptoms in more educated Mexican women. In Swedish women, Li and colleagues (2003) observed less frequent hot flashes in women with higher education levels.

The ethnically diverse SWAN study also examined the relationship of dietary nutrients with vasomotor symptoms. High dietary intake of isoflavones (phytoestrogens) has been hypothesized to reduce hot flash frequency, as their chemical structure is similar to estrogen. Clinical trials though have demonstrated conflicting data that may be due to differences in sample populations and the relative short length of these investigations (Albertazzi et al., 1998; Washburn, Burke, Morgan, & Anthony, 1999; St Germain, Peterson, Robinson, Alekel & Lee, 2001). In the SWAN data, dietary intake of isoflavones was not associated with vasomotor symptoms even though both Chinese and Japanese women had higher dietary intake of isoflavones and reported significantly less vasomotor symptoms compared to Caucasian women (Gold et al., 2004). In multivariate analysis, no dietary nutrients were associated with vasomotor symptoms, although in unadjusted analysis both high dietary fat and total calorie intake were associated with increased vasomotor symptom reporting (Gold et al., 2004)

Genetics. The influence of genetic mediators on vasomotor symptoms is a very recent line of investigation. Investigations are now evaluating variations in the estrogen receptor (ER) genes (ER-α, ER-β) and genes responsible for estrogen biosynthesis or metabolism (Deroo & Korach, 2006; Sharp, Cardy, Cotton, & Little, 2004). Variations in

the gene sequence, single nucleotide polymorphisms (SNPs) have been identified for the ER-α gene (ESR1), but only a few are well characterized, notably the P*vu*II and the X*ba*I (Deroo & Korach, 2006; Herrington, 2002).

Recent work has suggested polymorphisms of the ER-α and ER-β genes and the cytochrome P450 (CYP 17) gene affect circulating estradiol levels and may play a role in menopause symptomatology (Schuit et al., 2005; Sharp et al., 2004). Malacara and colleagues (2004) evaluated the association of hot flashes with polymorphisms (P*vu*II and X*ba*I) of the ER-α gene in 177 postmenopausal Mexican women. No differences in E_2, estrone or LH levels were noted among all the genotypes, but FSH levels were higher in women with the xx genotype of the X*ba*I polymorphism compared to the Xx genotype (Malacara, Lugue, Garza, & Marin, 2004). A relationship between the genotypes of the X*ba*I polymorphism and vasomotor symptoms was not detected, but genotypes of the P*vu*II polymorphism were associated with hot flash scores. Women with Pp genotypes appear to have lower hot flashes scores compared to those with the pp genotype although the paper includes conflicting reports of the data (Malacara et al., 2004).

In a study of 51 Japanese women, Takeo and colleagues (2005) investigated the relationship of polymorphisms in the ER-β gene with vasomotor symptoms. Four genotypes (EL, SS, SL, LL) of the cytosine-adenine polymorphism of ER β were identified in the subjects, and women with the EL or the SS genotypes were found to be at increased risk for vasomotor symptoms (Takeo et al., 2005). Visvanathan and colleagues (2005) evaluated whether polymorphisms of the cytochrome P450 gene, known to be involved in the enzymatic biosynthesis of estrogen, were associated with hot flashes in perimenopausal Caucasian and African American women. Independent of E_2 and estrone levels, women homozygous or heterozygous for the CYP1B1 polymorphism were 30% more likely to report moderate to severe hot flashes that persisted for more than a year compared to women without the polymorphism (Visvanathan et al., 2005). Consistent with other reports, Woods and colleagues (2006) also observed more severe and frequent hot flashes in women with the CYP19 polymorphism. In more recent work from the SWAN study, race/ethnicity specific associations have been identified between vasomotor symptoms prevalence and polymorphisms in the sex steroid metabolizing enzymes (Crandal, Crawford & Gold, 2007).

Vaginal Dryness

Physical changes in the genital tract at menopause are associated with several symptoms reported by women including vaginal dryness, irritation, itching, infection, and dyspareunia (NAMS, 2007). The menopausal estrogen decline results in anatomic changes in the genital tract. The cervix, ovaries and uterus decrease in size (Rousseau, 1998). The vagina shortens and narrows; capillary bed loss results in tissue pallor (NAMS, 2000). Estrogen loss inhibits the maturation of vaginal epithelial cells and thinning of vaginal epithelium, reduction in mucus production, loss of tissue elasticity occurs (NAMS, 2000; Rousseau, 1998). Hypoestrogenism also results in a change in vaginal pH from the normal acidic environment to a more alkaline state that can alter the normal microbial flora and precipitate infection (Nachtigall, Nachtigall, Goern & Lowestein, 2005). These changes correlate strongly with the estrogen decline during menopause (NIH State of the Science Panel, 2005). Further, substantial clinical trial data demonstrated exogenous estrogen use relieves these symptoms (Nachtigall et al., 2005)

Presentation with Menopause. The most common complaint associated with genital atrophy, vaginal dryness, is reported with increased prevalence across the menopause transition (Woods & Mitchell, 2005). In the Melbourne Women's Midlife Health Project, approximately 4% of women in the early perimenopause complained of vaginal dryness and this increased to 21% in late perimenopause and 47% in the PM (Dennerstein et al., 2000)(Table 2.1). In the SWAN data, 7% of premenopausal women complained of vaginal dryness but this rose to approximately 13% in early perimenopausal women and to 18% in late perimenopausal women and 21% in PM women (Gold et al., 2000). Malacara and colleagues (2002) compared vaginal dryness complaints in pre and PM Mexican women from three different areas of the country observing prevalence rates ranging from 2-18.4% in premenopausal women and rising to 23.6-41.4% in PM women.

Factor Affecting Symptoms: Lifestyle and Demographic Factors. Very few studies identified variables that influence vaginal dryness in the menopause. In the multiethnic SWAN data, complaints of vaginal dryness differed by lifestyle and demographic factors. Women who were less physically active, had less than a 12th grade education and had trouble paying for the basics (the indicator for socioeconomic status) reported more

complaints of vaginal dryness (Gold et al., 2000). Less complaints of vaginal dryness were reported from never married, widowed or divorced women compared to those who were married. BMI, smoking behavior and employment status were not related to complaints of vaginal dryness (Gold et al., 2000). In a study of postmenopausal women from the WHI, women who were obese and had diabetes reported more vaginal symptoms (Pastore, Carter, Hulka & Wells, 2004).

In an observational study of 6917 Swedish women, similar findings were noted as women who vigorously exercised and had higher education levels reported less vaginal symptoms and women who were married had more complaints of vaginal dryness at menopause (Li et al., 2003). In contrast to the SWAN data, the prevalence of genital atrophic complaints were higher in women who smoked, who suffered from chronic disease such as diabetes or cancer, and were of higher BMI (Li et al., 2003). Malacara et al (2002) observed increased reporting of atrophic vaginal symptoms women who lived in rural areas compared to those in more urban environments and similar to both Gold et al (2000) and Li et al (2003), women with lower levels of education offered increased complaints of vaginal dryness (Malacara et al., 2002)(Table 2.3).

Race/Ethnicity. Ethnic differences were observed in the SWAN investigation. Twenty percent of Hispanic and approximately 15% of African American women reported vaginal dryness compared to only 11% of Caucasian, 10% of Chinese and 7% of Japanese women (Table 2.2)(Gold et al., 2000). In contrast, more complaints of vaginal dryness were observed in Caucasian women compared to African American women by Wilbur and associates (1998). Malacara and colleagues (2002) reported high prevalence rates of vaginal dryness symptoms (35-63%) in Mexican women. Higher rates of vaginal complaints were also noted in the WHI findings. Postmenopausal women of Hispanic descent reported twice as many vaginal symptoms (dryness, itching, irritation) compared to Caucasians or African Americans (Pastore et al., 2004).

Genetics. To date, one investigation has considered a genetic influence on vaginal dryness symptoms. Malacara and colleagues (2004) documented that polymorphisms of ER α gene, X*ba*I and P*vu*II, were associated with vaginal dryness symptoms in postmenopausal Mexican women. Both the X*ba*I and P*vu*II polymorphisms were associated with vaginal dryness. Women with the xx genotype of the X*ba*I

polymorphism had lower vaginal dryness scores (less complaints) compared to women with the XX genotype. Carriers of the pp genotype of the P*vu*II polymorphisms also had significantly lower vaginal dryness scores (less complaints) compared to women with the PP and Pp genotypes (Malacara et al., 2004).

Depressed Mood

While a number of menopause studies have demonstrated the temporal relationship between menopause with vasomotor and vaginal symptoms, evidence of such a relationship between symptoms of depressed mood and menopause is controversial (Hardy & Kuh, 2003). Early cross-sectional studies of midlife women described complaints of psychological symptoms (irritability, anxiety, depressed mood) that were assumed to be related to the hormone flux with menopause and led to the hypothesis that women in menopause were more at risk for depression (Dennerstein, Randolph, Taffe, Dudley, & Burger, 2002b; Miller & Daniels-Brady, 2005). However, complaints of psychological symptoms do not impose a diagnosis of major depression but many menopause studies have not been able to discern this difference methodologically.

Most menopause research has been cross-sectional capturing symptoms at only one point during the menopause transition. Standardized instruments with sound psychometric properties are not readily available and researchers have often created their own symptom lists (Green & Holte, 1998). While established measures for psychiatric symptoms are available and could clarify the difference between transient symptoms and more serious mental health concerns, many menopause studies did not employ these instruments (Miller & Daniels-Brady, 2005; Schmidt, 2005). Lastly, research designs did not tightly control for confounding variables (sociocultural and lifestyle factors) that may affect psychological symptomatology (Miller & Daniels-Brady, 2005).

Women have higher rates of major depression than men at all ages, but an increase in the rates of major depression are not seen during the menopause transition and in fact, actually decline in the postmenopause (Schmidt, 2005; Kessler, McGonagle, Swartz, Blazer & Nelson, 1993; Bebbington et al., 1998). Early longitudinal population based studies of primarily Caucasian women did not provide evidence that the transition to menopause increases a women's risk for depression (Avis, Brambilla, McKinlay, & Vass, 1994; Kaufert, Gilbert, & Tate, 1992, Hardy & Kuh, 2003; Harlow et al., 2003;

Dennerstein, Guthrie, Clark, Lehert, & Henderson, 2004; Woods, Marietta & Mitchell; 2002). The more carefully designed studies distinguish depression from mood changes and suggest that women with histories of previous mood disorders and stressful life circumstances are those more likely to develop depression during midlife (Hardy & Kuh, 2002; Kuh et al., 2003; Schmidt, 2005; Woods et al., 2008).

Physiologically estrogen acts centrally via receptors in the limbic system and hypothalamus and is thought to have modulating effects on several neurotransmitters, such as serotonin and norepinephrine (Sohrabji, Miranda, & Toran-Allerand, 1994). Estrogen loss has therefore been hypothesized to modulate mood, suggesting low levels of estradiol are associated with depression and estrogen therapy may be an effective treatment for midlife depressive symptoms (Schmidt, 2005; Miller & Daniels-Brady, 2005). A consistent relationship between ovarian hormone production and depression is not evident. Schmidt and colleagues (2002) did not detect differences in reproductive hormone levels in women who developed depression during perimenopause, while Freeman et al (2004) noted that women with increasing E_2 levels reported more depressive symptoms and women with rapidly increasing FSH levels had fewer depressive symptoms. In the longitudinal Harvard Study of Moods and Cycles, lower E_2 levels and higher FSH levels were observed in women with a history of major depression compared to those without depression (Harlow et al., 2003).

Very few (3) clinical trials have assessed the effect of estrogen in treating major depression in menopause. All three trials utilized estrogen solely. In the placebo-controlled trials of perimenopausal women who met criteria for minor and major depression, clinical improvement in depression scores were noted with therapy (Schmidt et al., 2000; Soares et al., 2001). In a third study (Morrison et al, 2004), women 5-10 years postmenopause were treated for depression with estrogen but no significant improvements noted.

Depressed Mood Patterns: Presentation with Menopause. Although the menopause is not associated with the onset of major depression, many women report symptoms of psychological distress and depressed mood during this time (Woods et al., 2002; Kuh et al., 2002; Bromberger et al., 2003; Schmidt, 2005). Avis and colleagues (2001) detected that besides vasomotor symptoms, psychological symptoms consistently

emerge as another cluster in menopause research. In their summative review of longitudinal studies that clearly delineated reproductive aging stages, Woods and Mitchell (2005) noted the prevalence of depressed mood symptoms ranges from 19 to 29% (p. 15S). Prevalence rates are similar across the stages of the menopause transition, ranging from 24.5 to 29% in the late reproductive (premenopause) stage, 19-29% during perimenopause and 23-34% postmenopause (Woods & Mitchell, 2005). The prevalence rate data are difficult to reconcile and generalize, as there was great variation in measurement methodology.

In the Massachusetts Women's Health Study (MWHS), subjects were evaluated for the complaint of 'feeling blue' in the past two weeks while SWAN study subjects, were asked if they felt tense or more irritable in previous week (Avis, Brambilla, McKinlay & Vass, 1994; Bromberger, Meyer, & Kravitz et al., 2001). Twenty nine percent of premenopausal women reported mood symptoms compared to 28% of perimenopausal women and 33.8% of postmenopausal women in the MWHS (Avis et al., 2001b). In earlier SWAN data, similar findings of no progression in symptoms across the menopause transition are noted. Prevalence rates of irritable symptoms were noted in approximately 21% of premenopausal women, 29% of perimenopausal women and 22% of postmenopausal women (Bromberger et al., 2001)(Table 2.1).

In studies that employed a standardized scale (Center for Epidemiologic Studies Depression Scale [CES-D]) to measure depression, the prevalence of depressed mood ranged from 11.6-15% in women of reproductive age, 1-19% for women in early perimenopause, 13-15% in late perimenopausal women and 1-17% in those postmenopause (Woods & Mitchell, 2005). Freeman and colleagues (2004) interviewed subjects at baseline and four years later using the CES-D inventory with scores $\geq$16 indicating depressed mood. Prevalence rates of depressed mood were similar across the menopause transition although early perimenopause rates were lower (Table 2.1) 12-15% premenopause, 1.4-7.8% early perimenopause, 13-18.3% late perimenopause and 1-13.8% postmenopause (PM).

Bosworth and colleagues (2001) also used the CES-D but defined depressed mood as a CES-D score above 10 and as such documented higher prevalence rates of depressed mood across the menopausal transition compared to Freeman et al (2004).

Seven percent of premenopause subjects reported depressed mood symptoms and this increased to 30.5% and 37.7% in early and late perimenopause respectively but declined to 24.6% in PM women (Bosworth et al., 2001). In the SWAN cohort at enrollment, pre and perimenopausal women were evaluated for dysphoric mood symptoms that were present for more than 6 days/week (Bromberger et al., 2003). Rates of persistent mood symptoms were higher among early perimenopausal women (14.3-18.4%) compared to premenopause women (8.8-12%)(Bromberger et al., 2003) but more similar to those noted by Freeman and colleagues (2004)(Table 2.1).

In longitudinal and cross-sectional studies, the perimenopause appears to be the peak phase of the menopause transition when psychological symptoms may be reported (Schmidt, 2005). Avis and colleagues (2005) consolidated data on psychological symptoms from the longitudinal multiethnic SWAN study, observing symptoms tend to increase in early perimenopause and slowly decrease in late perimenopause to postmenopause. Several investigations have observed an increase in depressive symptoms in perimenopausal women compared to those postmenopause (Freeman et al., 2004; Bromberger et al., 2003; Woods et al., 2002; Hardy & Kuh, 2002) while still others have noted no differences in psychological symptoms across the menopause transition (Avis et al., 1994; Kaufert et al., 1992, Dennerstein, et al., 2004). However, the most recent data emerging from the major ethnically diverse longitudinal studies provides strong evidence of an association between depressed mood symptoms with the menopause transition, with one investigation corroborating the increase in these symptoms with changes in reproductive hormone measures (Bromberger et al, 2007; Freeman et al., 2007; Bromberger et al., 2007; Woods et al., 2008).

Factors Affecting Symptoms. Longitudinal studies of women experiencing depressed mood during menopause have identified several factors associated with these symptoms. Consistently studies have demonstrated previous history of mood disturbance, lower educational levels, inadequate financial income, poorly perceived health status, low social support, family dysfunction and high stress levels are associated with increased psychological symptom reporting during the menopause, either natural or surgical (Bromberger et al., 2003; Bosworth et al., 2001; Kuh et al., 2002; Woods et al., 2002; Hardy & Kuh, 2002; Malacara et al., 2002). Woods and associates (2002) and Kuh and

colleagues (2002) found that a more stressful life trajectory was the most critical variable likely to predict perimenopausal mood symptoms at midlife.

Other variables (Table 2.3) less frequently associated with increased depressed mood symptoms during the menopause transition include physical inactivity (Bosworth et al., 2001), increased BMI (Malacara et al., 2002), the presence of hot flashes (Avis et al., 1994), poor sleep (Bromberger et al., 2003), smoking (Bosworth et al., 2001; Malacara et al., 2002; Ford et al., 2005) rural residence (Malacara et al., 2002) and negative attitudes toward the menopause (Dennerstein et al., 2004; Woods et al., 2002). Hardy and Kuh (2002) and Ford and colleagues (2005) observed an increase in depressive symptoms in women using HT, but Bosworth and colleagues (2001) detected no differences in symptoms between women using or not using HT. One study demonstrated no relationship between estrogen genotype variants and emotional symptoms (Malacara et al., 2004), but SWAN investigators have identified several estrogen related polymorphisms across races and ethnicities that increased the odds for depressive symptoms across the menopause transition (Kravitz, Janssen, Lotrich, Kado & Bromberger, 2006).

Race/Ethnicity. The majority of women included in menopause studies are Caucasian American or Europeans. Few studies have examined the influence of race/ethnicity status on mood symptoms with the menopause transition. In a small cross-sectional study (N = 153), Caucasian women reported significantly more psychological symptoms compared to African American women (Wilbur, Miller, Montgomery & Chandler, 1998). In a larger cross-sectional study of Japanese (N = 848) and Australian (N = 886) women, Anderson and colleagues (2004) observed similar increases in depressive symptoms during perimenopause between both groups of women. However, in the postmenopause period reports of depressive symptoms remained high in postmenopausal Japanese women while complaints of these symptoms decreased in the Australian subjects.

In the multiethnic longitudinal SWAN study, baseline prevalence rates of persistent depressed mood symptoms (> 6 days in the previous 2 weeks) were higher in perimenopausal women compared to premenopausal women and differed among the ethnic groups (Bromberger et al., 2003). More Hispanic women (15.8%) reported mood

symptoms and fewer Chinese (5.8%) and Japanese (4.7%) women reported symptoms compared to Caucasian (13.2%) women (Bromberger et al., 2003)(Table 2.2).

In further SWAN work, using the Center for Epidemiologic Studies Depression scale [CES-D]), prevalence rates for depressed mood again were highest in Hispanic (43%) women and lowest among Chinese (14.3%) and Japanese (14.1%) women (Bromberger et al., 2004). Depressive symptoms were associated with health related and psychological factors including low socioeconomic status (SES), poor health status, low social support, and high stress levels in univariate regression in all ethnic groups (Bromberger et al., 2004). With multivariate regression, controlling for these variables, particularly SES significantly reduced the effect of ethnicity in both African American and Hispanic women. These confounding factors also had differential effects among ethnic groups in regression modeling, suggesting the predictors of depressed mood also varies among ethnic groups (Bromberger et al., 2004).

Sleep Disturbances

Reports of sleep disturbances increase with aging in both sexes, but prevalence rates of disordered sleep are consistently higher in women (Baldwin et al., 2001; Shaver & Zenk, 2000). Hormone fluctuations associated with menstruation, pregnancy and menopause have been hypothesized to play a role in the increased prevalence of sleep disturbances in women (Shaver, 2002; Kravitz et al., 2003). While sleep disturbances are common in midlife women, it is not clear if this is an effect of menopause versus aging (NIH State of the Science Panel, 2005; Nelson et al., 2005). With most studies using self-report of sleep pattern and quality, and few studies employing physiologic hormone measures or polysomnography to document alterations, it is difficult to reach consensus of the relationship of sleep with the menopause (Shaver & Zenk, 2000).

Hot flashes and night sweats, a frequent complaint with menopause have been identified in one longitudinal study as a strong predictor of disturbed sleep (Pien, Sammel, Freeman, Lin & DeBlassis, 2008), but high quality laboratory studies of sleep have challenged this hypothesis. Freedman and Roehrs (2004) evaluated symptomatic and asymptomatic pre- and postmenopausal women in a controlled laboratory setting, documenting that hot flashes followed rather than preceded the arousal from sleep. In another epidemiologic study (N = 589) that included laboratory polysomnography, no

differences in sleep quality were observed between symptomatic and asymptomatic peri- and postmenopausal women (Young, Rabago, Zgierska, Austin, & Finn, 2003).

Presentation with Menopause. From longitudinal data, sleep disturbances appear to increase across the menopause transition (Woods & Mitchell, 2005; NIH State of the Science Panel, 2005). While an early report from the Penn Ovarian Aging study (Hollander et al., 2001), noted no changes in prevalence rates for altered sleep in the first 2 years when most women were still cycling regularly, the most recent data demonstrated an increase in sleep complaints over the transition (Freeman et al., 2007). Other longitudinal studies demonstrate progressive increases in sleep disturbances across the menopause transition. In the Australian Melbourne Women's Midlife Health Project, prevalence rates of altered sleep increased from 31% in the late reproductive stage, to 32% in early perimenopause, to 38% in late perimenopause and ranged from 38-43% in the postmenopause (PM) period (Table 2.1)(Dennerstein et al., 2000). In the multiethnic SWAN study, a similar progression is noted except in the postmenopause period. Prevalence rates of disordered sleep increased from 31.4% in premenopausal women, to 39.4% of those in early perimenopause, to 45.4% in late perimenopause (Kravitz et al., 2003). Recent publications from the SWAN study (Kravitz et al., 2008; Sowers et al., 2008) demonstrated increased sleep complaints across the menopause transition and strong associations between these symptoms and reproductive hormone level changes. In another prospective investigation, Freeman et al (2007) noted only a minimal increase in sleep complaints compared to the magnitude of change in reproductive hormones.

In other less detailed reports of longitudinal investigations, altered sleep was a distinct symptom cluster related to menopause in a study of British women (Kuh et al., 1997) but in a smaller study of bone health across the menopause transition in 121 Michigan women, sleep problems were predicted by BMI and not menopause stage (Ford et al., 2005). Cross sectional data also demonstrate conflicting data. In a tightly controlled study of young cycling (YC; age 20-30 yrs), older cycling (OC; age 40-50 yrs), ovariectomized women on HT (OVX; age 40-50 yrs), and naturally postmenopausal women (PM; age 40-50 yrs) with serum hormone measures and polysomnography, despite similar estrogen concentrations the OC women had reduced sleep efficiency compared to the YC women (Lukacs, Chilimigras, Cannon, Dormire & Reame, 2004).

Sleep efficiency was reduced and wake times longer in the three older groups compared to the young controls suggesting that middle aged women, regardless of ovarian function, experience greater sleep disturbances than younger women as a function of aging and not menopause status (Lukacs et al., 2004). In another cross-sectional study, the prevalence and severity of sleep apnea was greater in PM women compared to premenopausal subjects even after controlling for age, BMI and neck circumference suggesting menopause status may account for the differences (Dancey, Hanly, Soong, Lee, & Hoffman, 2001). Clinical trials of HT have demonstrated modest improvement in sleep quality and sleep apnea with hormone use and the subsequent resurgence of symptoms with HT discontinuance (Keefe, Watson, & Naftolin, 1999; Ockene et al., 2005; Schiff, Regestein, Tulchinsky, & Ryan, 1979; Shaver & Zenk, 2000).

Factors Affecting Symptoms. Several factors are associated with sleep disturbances. BMI is a known risk factor for sleep disturbances and directly correlated to sleep apnea, number of nighttime awakenings, and self-reports of trouble sleeping in both cross-sectional and longitudinal studies (Dancey et al., 2001; Ford et al., 2005; Shaver & Zenk, 2000). Poor sleep was associated with low levels of estradiol (Hollander et al., 2001) and better sleep related to high levels of estradiol (Ford et al., 2005), but in seminal studies such as the WHI, hormone use was associated with only a minimal (2%) improvement in sleep disturbance scores and but no overall improvement in perceived quality of life (Brunner et al., 2005).

The presence of vasomotor symptoms and psychological symptoms such as depressed mood and anxiety were associated with greater reporting of sleep disturbances in both the SWAN study and the Penn Ovarian Aging study (Kravitz et al., 2003; Hollander et al., 2001). Other variables associated with altered sleep during the menopause transition include smoking, physical inactivity, perceptions of poor health, oophorectomy without HT, increased stress, arthritis and caffeine consumption (Hollander et al., 2001; Kravitz et al., 2003). Both high (Kravitz et al., 2003) and low (Hollander et al., 2001) educational levels were noted to affect sleep quality. No studies have evaluated the influence of genetic background on sleep (Table 2.3).

Race/Ethnicity. Few studies have evaluated sleep behavior in women of different ethnic groups. Ethnic differences were noted in the Penn Ovarian Aging study with

African American women were more likely to report poor sleep compared to Caucasians (Hollander et al., 2001). In the SWAN data, Caucasian (40.3%) and Hispanic (38.0%) women had the highest rates of disturbed sleep, followed by lower rates in African American (35.5%), Chinese (31.6%) and Japanese (28.2%) women (Table 2.2) (Kravitz et al., 2003). Kravitz and colleagues (2003) also evaluated sleep difficulty by menopausal status and ethnicity, finding the highest rates of altered sleep were reported by late perimenopausal Caucasian, African American and Japanese women, early perimenopausal Chinese women and naturally postmenopausal Hispanic women.

Urinary Incontinence

Urinary continence is a complex process requiring coordination between the bladder, urethra, pelvic muscles, surrounding tissues and neurologic system (Norton & Brubaker, 2006). Urinary incontinence (UI), the involuntary leakage of urine (Abrams et al., 2002) is the result of a disturbance in either the storage or emptying functions of the lower urinary tract, structural problems in the surrounding pelvic organs or neurologic dysfunction. UI is two times more common in women than men and its prevalence increases as women age (Brown et al., 1996; Van Vorrhis, 2005). Estrogen receptors are present in the vagina, urethra, bladder and surrounding pelvic floor musculature and affect smooth muscle and alpha adrenergic tone (Iosif et al, 1981) suggesting estrogen loss at menopause has the potential to affect urinary function (Grady et al., 2001; Robinson & Cardazo, 2003)

Presentation with Menopause. UI is a common complaint during the menopause transition, but data from cross-sectional and longitudinal menopause studies do not definitively establish a temporal or an independent relationship of UI with the menopause (Van Voorhis, 2005). The difficulty in discerning the true incidence of UI during the menopause transition is complicated by variation in the instrumentation used to collect symptom information. In most studies, type of incontinence (stress or urge) was not routinely determined (Van Voorhis, 2005). The presence of symptoms alone (measured as yes or no) was often used to determine incontinence rates, while others collected more specific data on volume, frequency and severity of the incontinence. Time frames for symptoms ranged from past 2 weeks to past 12 months and measures of severity vary from visual analogue scales to adjective descriptors such as "mild, moderate or severe" or

"any or significant" (Avis et al., 2005; Gold et al., 2000; Hannestad, Rortveit, Sandvik, & Hunskaar, 2000; Li et al., 2003; Pastore et al., 2004; Wilbur et al., 1998). Few studies used reliable and valid indicators of severity of UI such as the Sandvik et al method (1993) in which the scaled scores of frequency of UI and the leakage volume are multiplied to achieve a score for severity. Most often only one question was asked and in longitudinal studies, data were collected once a year (Gold et al., 2000; Li et al., 2003; Pastore et al., 2004; Sherburn, Guthrie, Dudley, O'Connell, & Dennerstein, 2001).

In the Melbourne Women's Midlife Health Project, increases in the prevalence of urinary symptoms were not observed across the menopause transition. Seventeen percent of premenopausal women reported urinary symptoms, while only 12% of early perimenopausal, 14% of late perimenopausal and 14% of postmenopausal women noted these symptoms (Dennerstein et al., 2000)(Table 2.1). In SWAN data collected during enrollment screening (N = 12,425), the prevalence of urine leakage was greatest in the perimenopausal women and women who had a surgical menopause. Twelve percent of premenopausal women reported urine leakage in the past year, compared to 20.6% of early perimenopausal women and 19.6% of late perimenopausal women. Only 17.7 % of postmenopausal women reported these symptoms, while 22.1% of women who had a surgical menopause complained of urine leakage (Gold et al., 2000). In the summative review of the literature by the NIH State of the Science Panel (2005) and AHRQ (Nelson et al., 2005), the prevalence of urinary symptoms in menopause were noted to vary little from "10-36% in the premenopause, from 17-39% in perimenopause and 15-36% in the postmenopause (natural or surgical menopause)"(p.1006), leading the reviewers to conclude there is not a temporal relationship between urinary complaints and the menopause transition. Updated analyses from the SWAN study corroborate this conclusion. Waetjen and colleagues (2008) found worsening UI symptoms were not related to menopause transition, but rather other clinical factors such as weight gain.

Clinical trials of HT do not provide support for improvement in UI (Jackson, Shepherd, Brookes & Abrams, 1999; Moehrer, Hextall & Jackson, 2005; Norton & Brubaker, 2006; Robinson & Cardozo, 2003). In both the prospective HERS trial and WHI, daily estrogen and estrogen plus progestin therapy was associated with worsening UI symptoms especially for stress incontinence (Grady et al., 2001; Hendrix et al., 2005),

although the Cochrane database review suggests estrogen may improve urge incontinence (Moehrer et al., 2005). In another report, the use of selective estrogen receptor modulators was also associated with an increase in urogenital prolapse (Robinson & Cardozo, 2003).

Factors Affecting Symptoms. Several risk factors for UI are unique to women and include parity, events associated with childbirth (i.e., infant birth weight, epidural analgesia, etc), hysterectomy, and menopause (Persson, Wolner-Hanssen, & Rydhstroem, 2000; Rortveit, Daltveit, Hannestad, & Hunskaar, 2003; Sampselle et al., 2002). In menopause studies, several factors were noted to affect the prevalence of UI. Age, BMI and parity were most commonly associated with UI (Gold et al., 2000; Sherburn et al., 2001, VanVoorhis, 2005). Physical inactivity, low socioeconomic status, smoking, and surgical menopause have also been associated with UI risk (Gold et al., 2000; Sherburn et al., 2001; Sampselle et al., 2002; Pastore et al., 2004). Urine leakage was reported less frequently among never married, widowed or divorced women compared to those who were married in the multiethnic SWAN study and in another study of Thai women (Gold et al., 2000; Manonai et al., 2004). Seminal studies of the peri and postmenopausal experience (SWAN, WHI, NHANES, Nurses Health Study) have provided compelling evidence that diabetes (Sampselle et al., 2002; Pastore et al., 2004; Danforth, Townsend, Lifford, Curhan, Resnick & Grodstein, 2006; Waetjen et al., 2007) and impaired fasting glucose (Brown, Vittinghoff, Lin, Nyberg, Kuser & Kanaya, 2006) are important risk factors for urinary incontinence. No studies to date have documented a genetic risk for increased UI risk at menopause (Table 2.3).

Race/Ethnicity. Differences in UI symptoms were noted by race/ethnicity status. In the WHI data, Hispanic ethnicity demonstrated an independent association for urinary symptoms with menopause. In SWAN baseline data (n = 12,425), Hispanic women reported more UI symptoms and African American, Chinese and Japanese reported fewer symptoms compared to Caucasian women (Table 2.2)(Gold et al, 2000). In a cross-sectional study comparing only African American and Caucasian women, Caucasian women noted more urine leaking compared to the African American women (Wilbur et al., 1998).

In the SWAN cohort (N = 3302), Sampselle and colleagues (2002) more precisely evaluated UI among multiethnic women collecting information on the frequency and duration of incontinence and the volume of leakage. The data were used to calculate the severity of incontinence and women categorized into groups based on degree of UI symptoms: any, mild, moderate or severe (Sampselle et al., 2002). Sixty six percent of Caucasian women reported 'any' UI symptoms, compared to only 42% of Hispanic women while similar prevalence rates of approximately 50% were observed in African American, Chinese and Japanese women (Table 2.2). Severe UI was more frequently reported by Caucasian women (12.1%) but least frequently noted in Chinese women (4.4%)(Sampselle et al., 2002).

Ethnic differences were evident but more difficult to discriminate, as within individual ethnic groups, other risk factors affected the association with UI. For example, when BMI was entered into the regression models, the effects for ethnicity were lost (Sampselle et al., 2002). Overall, compared to Caucasian women, African American, Hispanic, Chinese and Japanese were less likely to report 'any' UI. However, African American women with a history of leiomyomata had almost a two-fold increase in the odds of having UI compared to Caucasian women with leiomyomata. Chinese women with greater than a college education had more than a two fold increase in the odds (odds ratio 2.53) of having leakage compared to Caucasian women of similar status (Sampselle et al., 2002). Ethnicity was not associated with moderate to severe UI (Sampselle et al., 2002). In the most recent update of SWAN findings using Caucasian women as the reference group, Hispanic ethnicity was associated with increased odds for worsening stress and urge incontinence, while African Americans had higher odds for worsening of any and stress incontinence (Waejten et al., 2008).

In the same SWAN cohort of subjects, Sampselle and colleagues (2002) also evaluated how bothersome UI symptoms were to the subjects. Fifty percent of women reported they were moderately to extremely bothered by UI. Chinese women were least likely to report the symptoms as moderately or severely bothersome while Hispanic women were most likely to do so (Sampselle et al., 2002). These findings are particularly compelling as it differs from previous studies that only examined prevalence rates by

ethnic status and provides more insight into the other factors (i.e. severity) that may influence the reporting of UI symptoms in ethnically diverse women.

Changes in Cognition

Complaints of forgetfulness, trouble concentrating and difficulty thinking have been reported by midlife women and hypothesized as related to the menopausal estrogen decline (Love, 2003). As estrogen receptors have been mapped in the relevant brain areas such as the hypothalamus, cerebral cortex, midbrain, brainstem (Henderson, Klein, & Resnick, 2002) and both animal and in vivo studies document estrogen modulates a variety of cognitive processes (Sherwin, 2003; McEwen, 2002), this hypothesis has been considered physiologically plausible. Gender differences in cognitive functioning also support a role for the sex steroids: despite overlapping ranges that fall well within the norm, women outperform men on tasks of memory, fine motor and verbal skills, while men outperform women at visual-spatial and mathematical tasks (Sherwin, 2003). Further, menstrual cycle studies have demonstrated evidence of variation in cognitive processes between the early follicular (low estrogen) and mid-luteal (high estrogen) phases. In these studies, women's verbal skills, fluency and fine motor skills were enhanced during the high estrogen phase, while in the low estrogen phase their performance on the more male oriented visual-spatial tasks improved (Hampson, 1990; Kimura & Hampson, 1994). While these menstrual cycle differences were statistically significant, they are not clinically relevant as scores were still within normal ranges.

Presentation with Menopause. Both the NIH State of the Science Panel (2005) and the AHRQ (Nelson et al., 2005) summative reviews of menopause symptom research conclude there is insufficient data to establish a relationship between symptoms of cognitive disturbance (forgetfulness, trouble concentrating) with the menopause transition. Many cross-sectional studies have not distinguished cognitive complaints from somatic or psychological symptoms, thus precluding the ability to identify a clear menopause effect (Avis et al., 2005). Moreover, investigations of cognitive function are typically limited to studies of a single dimension, most often verbal memory. Data collection methods were also quite varied from open-ended more qualitative approaches (Mitchell & Woods, 2001) to close ended measurement (yes or no) (Gold et al., 2000) or standardized sound psychometric instruments (Digit Span Backward, Symbol Digit

Modality test) (Meyer et al., 2003) and limit ability to compare results or draw conclusions.

In baseline survey data from the SWAN study (N = 12,425), premenopausal women reported less symptoms of forgetfulness than perimenopausal and PM women. The prevalence of symptoms increased from premenopause (31.2%) to early perimenopause (44 %), but little difference in prevalence rates were noted in late perimenopause (44.8%) or women who experienced either natural (42%) or surgical (43.8%) menopause (Table 2.1) (Gold et al., 2000).

In a subset (N = 805) of the longitudinal cohort of SWAN, Meyer and associates (2003) evaluated two dimensions of cognitive function (working memory, perceptual speed) over a 2 year period in African American and Caucasian women. Most women were in the premenopause or early perimenopause stage during the duration of the study; few had progressed to late perimenopause or the postmenopause (Meyer et al., 2003). Working memory was assessed with the Digit Span Backward test (DSB) and perceptual speed was measured with the Symbol Digit Modality test (SDMT) (Meyer et al., 2003). Expecting to find a decline in cognitive functioning, the researchers instead observed an improvement over time in working memory in pre and early perimenopausal women, with little difference in the rate of change in test scores in late perimenopause and more importantly, no decline in the PM (Meyer et al., 2003). Perceptual speed scores (SDMT) improved over the menopause transition until the postmenopause when a decrease in the scores were observed but this change was noted to be congruent with expected age-related declines in SDMT scores by one item per year (Meyer et al., 2003).

Episodic memory was evaluated with variables of estrogen exposure, menopause transition stage, estradiol level, use of HT, and time from the FMP) during the year 8 annual visit in a cross sectional substudy of the Melbourne Women's Midlife Health Project (Henderson, Guthrie, Dudley, Burger & Dennerstein, 2003). Episodic memory was evaluated with a word list recall task. Ten words were read aloud and subjects asked for immediate recall (IR) and delayed recall (DR) 5 minutes later. Episodic memory scores did not vary by menopause stage, years from the FMP, use of HT or serum concentrations of estradiol, again suggesting no effect of estrogen on this cognitive function (Henderson et al., 2003).

Barlow (2006) suggests that relationships between cognitive performance at or during the menopause transition can be confounded by variations in cognitive performance over the lifespan. Kok and colleagues (2006) examined cognitive function in a cohort of British women followed since birth through age 53. Cognitive testing data were available as far back as age 8 and age 43 for some participants and permitted the evaluation of cognitive changes with menopause in the context of previous cognitive abilities (Kok et al., 2006).

No changes in verbal memory were detected across the menopause transition in all groups, natural or surgically menopausal, HT users and non-HT users. PM women had significantly lower reading ability scores compared to pre and perimenopausal women, but only a trend for decline in search speed and concentration abilities was observed in postmenopausal women (Kok et al., 2006). In multivariate analyses controlling for childhood cognitive abilities, lifetime social circumstances, and education levels, no differences among the groups were evident suggesting menopause did not have an effect on these measures of cognitive function.

In further follow-up at age 57, menopause could be confirmed for 624 women who had completed cognitive performance tests at all three time points. Women with the oldest age of menopause (age 55-56) had the highest performance on all cognitive tests. But again in multivariate regression, these effects were attenuated by childhood cognitive abilities, socioeconomic and educational factors suggesting these variables are more likely to affect cognitive function and not the estrogen decline (Kok et al., 2006).

Taken together, these data from previous longitudinal studies do not support a relationship between cognitive symptoms and the menopause transition. The most recent updates from both the SWAN study (Luetter et al., 2007) and the Penn Ovarian aging study (Freeman et al., 2008) corroborate these findings and provide additional evidence that these changes were not associated with changes in reproductive hormones.

Using a qualitative approach, Mitchell and Woods (2001) interviewed women regarding perceived memory changes at midlife. Women were asked to describe any memory changes they had noted and further, what they thought was responsible for these changes. Five categories of memory change were noted but were attributed by the participants to their perceived stress burdens, physical health status and aging and not

associated with the menopause stage (Mitchell & Woods, 2001). These findings reinforce previous quantitative data suggesting midlife cognitive changes are not related to the menopause and more likely a function of life stressors.

Estrogen therapy has been considered an option to preserve cognitive function or treat dementia in postmenopausal (PM) women, but reviews of hormone therapy do not establish the benefits of treatment. In her review, Sherwin (2003) reports controlled trials and observational longitudinal studies have demonstrated beneficial effects of HT on cognitive function. Small clinical trials in women post-ovariectomy have documented improved verbal memory and learning skills after HT use; other observational studies suggest HT preserves cognition and reduces dementia risk in healthy women (Sherwin, 2003). However, intervention trials of HT in women with Alzheimer's dementia have not demonstrated improvements in existing deficits or prevented further deterioration (Sherwin, 2003). Rather, the largest randomized controlled trial of HT use for cognitive preservation, the WHI memory study, was stopped prematurely because of adverse effects that included a two fold increased incidence of dementia in PM women aged 65 or older receiving estrogen and progestin therapy (Shumaker et al., 2002).

The Cochrane database review (2006) concludes there is "little evidence of the effect of HT or ET on overall cognitive function in healthy postmenopausal women" (Hogervorst, Yaffe, Richards & Huppert, 2006, p. 2), although analysis of the data were complicated by the myriad of different dimensions of cognition measured (verbal memory, abstract reasoning, speed of information processing, etc) and the variety of instruments used to measure these functions. In most studies there was no evidence of an effect of ET or HT on verbal or visuospatial memory, mental rotations, speed or accuracy measures. Yet, young surgically menopausal women receiving monthly estradiol injections demonstrated improvements in abstract reasoning, speed and accuracy and verbal memory (Hogervorst et al., 2006).

Re-appraisals of hormone therapy use have considered the age and timing of initiation as a critical factor in reconciling the disparate results between observational studies and clinical trials (Maki, 2006; Matthew & Manson, 2006). A pilot study of 428 Australian women demonstrated early initiators (started HT before age 56 in natural menopause or within 5 years of a surgical menopause) performed better on the measures

of global cognition, attention and concentration than late initiators (started HT after age 56 or after 5 years of a surgical menopause) (MacLennan et al., 2006). Late initiators performed worse than never users on measures of global cognition and verbal fluency and all users of either HT or ET performed better on measures of attention and concentration compared to never-users. These data suggest early initiation of HT at menopause may be beneficial, while delaying HT use until late menopause may actually be detrimental (MacLennan et al., 2006, p. 28). A new 5-year randomized clinical trial (Kronos Early Estrogen Prevention Study [KEEP]) to evaluate a low dose oral and transdermal estrogen on atherosclerotic progression in perimenopausal women a decade younger than those in the WHI will include an ancillary study of cognitive effects (Manson et al., 2006).

Factors Affecting Symptoms. In menopause studies, lower levels of educational attainment and socioeconomic status (employment, finances) are consistently associated with subjective symptom perceptions and objective measures of cognitive decline (Gold et al., 2000; Henderson et al., 2003; Kok et al., 2006). In the SWAN data (Gold et al., 2000) increased parity was associated with increased reporting of forgetfulness symptoms, while in the Melbourne Women's Midlife Health Project (MWMHP), increased parity correlated positively with measures of memory function (Henderson et al., 2003). In both the SWAN and MWMHP data, no relationship with BMI was observed with cognitive symptoms. Other factors associated with increased cognitive difficulties at menopause included past smoking, low physical activity levels (Gold et al., 2000), negative mood (Henderson et al., 2003) and childhood cognitive abilities (Kok et al., 2006). Alcohol use (1 or more drinks per week) was positively associated with verbal memory scores in the MWMHP (Henderson et al., 2003). In the SWAN data, several different sex steroid hormone gene polymorphisms were associated with performance differences on cognitive tests (primarily episodic memory) and varied among the different ethnic groups (Kravitz, Meyer, Seeman, Greendale & Sowers, 2006).

Race/Ethnicity. Few investigations included race/ethnicity as a variable for study. In those studies that are multiethnic, cognitive symptoms are not consistently included and preclude any interpretation of a race/ethnicity effect on cognitive symptoms at menopause. Ethnic differences were observed in the SWAN investigation. Forty six

percent of Hispanic women, 43% of African American and 41% of Chinese women reported symptoms of forgetfulness compared to 33% of Japanese and 35% of Caucasian women (Table 2.2)(Gold et al., 2000). However when adjusted by covariates, all ethnic groups (Chinese, Japanese, Hispanic, African Americans) had higher odds ratios for symptoms of forgetfulness than Caucasian women. In an ancillary SWAN study that measured working memory and perceptual speed, small improvements in cognitive performance were noted in early perimenopause among African American and Caucasian women but an effect of race/ethnicity was not observed (Meyer et al., 2003).

Somatic symptoms

A myriad of somatic complaints have been reported with midlife: fatigue, stiffness, palpitations, headache, joint pain, backache, numbness/tingling, shortness of breath (Obermeyer, 2000; Gold et al., 2000; Dennerstein et al., 2000; Mitchell & Woods, 2000) but as both women and men experience these symptoms throughout their lifetime, it is difficult to relate them to the menopause transition (Woods & Mitchell, 2005). Most menopause symptom instruments assess somatic complaints but there is considerable variation as to which symptoms are included and whether they are categorized into a somatic or psychological domain (Greene, 1998; Avis et al., 2005). These methodological variances preclude systematic attempts to compare these symptoms either across the menopause transition or between different populations.

Presentation with Menopause. Both the NIH State of the Science Panel (2005) and the AHRQ (Nelson et al., 2005) in their summative reviews of the menopause symptom literature report no association of somatic symptoms with menopause. Prevalence rates of experiencing "stiffness/soreness over the past 2 weeks" were documented in the baseline survey data from the SWAN study (Gold et al., 2000). The prevalence of these symptoms (Table 2.1) increased from 45.8% in the premenopause (late reproductive phase) to 57.9% in early perimenopause and 58.4% in late perimenopause. The prevalence of symptoms of stiffness and soreness fell slightly in the naturally postmenopausal women (54.8%) but were increased in women experiencing a surgical menopause 59.4%(Gold et al., 2000).

The MWMHP (Dennerstein et al., 2000) compiled a list of > 20 somatic symptoms. Women were asked if they had experienced each symptom in the previous 2

weeks and to rate the severity of each symptom on a 5 point scale (0 = not present to 4 = debilitating). Aches or stiff joints were the most common somatic complaint reported. Prevalence rates for these symptoms increased across the menopause transition (Table 2.1) from 41% in the premenopause to 47% in early perimenopause, 53% in late perimenopause and 57% in women 2 years PM (Dennerstein et al., 2000). Backaches and headaches (HA) were the next most frequently reported somatic symptoms. The prevalence of backache symptoms increased across the menopause transition from 30% in the premenopause to 34% in both early and late perimenopause and 37% in women 2 years postmenopause. Prevalence rates of HA varied little over the stages of reproductive aging. The complaint of HA was reported in 38% of premenopausal women, 37% of early perimenopause women, and 36% in both late perimenopausal and PM women (Dennerstein et al., 2000). Mean symptom severity scores in the pre and early perimenopause period were compared to mean severity scores in the late peri- and postmenopause by paired t tests. Severity scores for aches and stiff joints, backaches and headaches did not demonstrate significant changes with the menopause transition (Dennerstein et al., 2000).

In their longitudinal study of British women, Kuh and colleagues (1997) reported no relationship of somatic symptoms with the menopause transition. In a study comparing Australian and Japanese women, somatic symptoms were observed to decrease after menopause in Australian women but continued to be prevalent in the postmenopause period for Japanese women (Anderson et al., 2004).

Recent data suggest an association between the musculoskeletal complaints of aching joints and muscles with the menopause. Dugan and colleagues (2006) documented higher prevalence rates for joint pain and muscle stiffness in the postmenopausal women of the SWAN study compared to those premenopausal. Freeman and colleagues (2007) provided strong evidence of an association between musculoskeletal complaints documenting the association of these symptoms with both the menopause stage and changes in reproductive hormones. In the Penn Ovarian Aging study, headache symptoms were also strongly associated with menopause stage, but found to decrease over the menopause rather than increase (Freeman et al., 2008).

Factors Affecting Symptoms. As there was no evidence that the somatic complaints of stiff joints, backaches or headaches were related to menopause, assessment of factors affecting those symptoms was not reported in the MWMHP. In the SWAN data, variables associated with increased risk for complaints of stiffness or soreness were: high BMI $\geq$ 27 kg/m^2, smoking behavior, difficulty paying for basics and low levels of physical activity (Gold et al., 2000). To date no studies have documented a genetic risk factor for somatic symptoms at menopause (Table 2.3).

Race/Ethnicity. Somatic complaints of joint stiffness or muscle soreness were similar amongst the ethnic groups in the SWAN study. Prevalence rates (Table 2.2) for African American women (55.7%) were slightly higher and prevalence rates for Hispanic (47.1%), Japanese (50.3%) and Chinese (48.2%) women were slightly lower than Caucasian women (54.8%)(Gold et al., 2000). Adjusted for covariates, all ethnic groups had lower odds ratios for somatic symptoms than Caucasian women (Gold et al., 2000). In another study comparing Australian and Japanese women, mean scores for somatic symptoms were similar between Japanese and Australian women (Anderson et al., 2004).

In contrast to the western world, somatic complaints are often the principal menopause symptoms among other ethnicities. Taiwanese women most often complained of backache and fatigue at menopause. In Lebanonese women the principal menopause complaints are fatigue and irritability (Obermeyer, 2000). In her work with midlife Japanese women (N = 1141, aged 45 to 55) from urban and rural areas of Japan, Lock (1994) used a 51-item checklist to survey menopausal complaints in the past 2 weeks. The most frequently described symptoms were shoulder stiffness and headache (reported by 52% and 28% of the women respectively)(Lock, 1994). More compelling, of the 5 most frequently reported midlife symptoms in Japanese women, four were somatic (shoulder stiffness, headache, lumbago, constipation) and the more commonly reported menopause symptoms of western women, hot flashes and night sweats were only reported by 9.5% and 3.2% of Japanese women (Lock, 1994). These paradoxical findings suggest that while current US evidence does not support a relationship with somatic symptoms, in less westernized cultures, this may not be the case.

Sexuality

A decline in sexual function occurs with aging but several changes in sexuality have been reported in midlife women and hypothesized as related to the menopause transition (Dennerstein, Lehert, Burger, & Guthrie, 2005). Consequences of the menopausal estrogen decline include urogenital atrophy, vaginal dryness and decreased tissue elasticity all of which can result in dyspareunia and affect sexual behavior in women. These symptoms are distinctly related to menopause and improve with HT (Nelson et al., 2005; Alexander et al., 2004). Several other changes in sexual function are reported at midlife including impaired body image, decreased libido, decreased arousal, or decreased orgasm, but the impact of the menopause transition on these dimensions of sexual behavior is not clear and the subject of great debate (Avis et al., 2005b; Bachmann & Leiblum, 2004). As a complete discussion of this topic is well beyond the scope of this paper, the sentinel issues will be briefly presented.

Conceptual and methodological issues preclude the ability to establish a definitive relationship between sexual dysfunction and menopause (Hendrix, Dennerstein, & Pinn, 2002). For the past 40 years, the traditional model (Masters & Johnson, 1966; Kaplan, 1979) of the human sexual response: Desire → Arousal → Orgasm → Resolution has guided the understanding of sexual behavior and served as the framework to define, diagnosis and manage sexual dysfunction as well as direct programs of scientific research. This framework is linear and unidirectional and fails to account for the subjective, contextual nature of female sexual behavior (Basson, 2000).

Basson (2000) identified dimensions of the female sexual response that cannot be conceptualized in the traditional model. Essentially, womens' sexual desires are facilitated by subjective feelings of arousal and are under the influence of psychological (fear, body image, past relationships) and biological factors (fatigue, medical conditions) rather than the physical feedback from genital congestion (Basson, 2000). Desire and arousal coexist and reinforce each other throughout the sexual experience for women, in contrast to the linear fashion described in the Masters and Johnson model (Basson, 2000). This conceptualization of the female sexual response suggests the current understanding of female sexual dysfunction is likely flawed. New definitions of female sexual

dysfunction have been recommended (Basson, 2004; Dennerstein et al., 2005) and there is a need to redesign scientific inquiry to reflect these changes.

The sociopolitical and cultural environment has also changed. Until the past decade most studies of female sexual behavior centered on western white middle-class women from the pre Baby Boomer era, thus reflecting an outdated and narrow experiential norm (Manderson, 2005; Avis et al., 2005b). Modern middle-aged women who have had opportunities for education and careers, control of reproduction and exposure to mass media sexual messages may have very different sexual behaviors and beliefs. As well, little is known about the sexual health of midlife women from different ethnic backgrounds.

Many menopause studies do not inquire about sexual functioning but in those that do, methodologic issues exist that preclude the ability to clarify the association of sexual dysfunction with the menopause. Few longitudinal studies exist to help disentangle the effects of aging on sexual behavior from those related to menopause. Cross-sectional studies are extremely varied and attempts at systematic comparison are complicated by the myriad of different dimensions of sexual function measured (libido, desire, arousal, frequency of activity, satisfaction, orgasm, pain, types of sexual practices) (Dennerstein et al., 2005; Avis et al., 2005b; Dennerstein, Alexander & Kotz, 2002). Few studies include all aspects of sexual function, but rather collect data on one or two dimensions.

Instrumentation is another concern. Several studies have not used instruments with sound psychometric properties (Dennerstein et al., 2005). Most measures are subjective self-reports and include questionnaires, diaries and events logs, or structured interviews. Questionnaires range in length from a single item to a 245-item inventory (Rosen, 2002). Few studies have included objective measures such as serum hormone measures or photoplethysmography to measure the physiologic responses of the vagina (Dennerstein et al., 2005; Rosen, 2002).

Sample bias is an issue in studies of sexual function. The intimate nature of the topic and pressing sociocultural norms may influence subject's responses and/or sample recruitment (Hendrix et al., 2002). Lastly, sexuality is a multidimensional concept substantially influenced by psychosocial and cultural factors. Thus to study it in the

context of menopause, a time of developmental and physiologic change, makes control of confounding variables an intense challenge.

Presentation with Menopause. While cross-sectional studies report mixed findings regarding sexual functioning across the menopause, evidence of a decline in sexual functioning in naturally menopausal women was noted in the longest observational study to date (Dennerstein, Alexander, & Kotz, 2003). The MWMHP evaluated sexual functioning in 226 Australian women for 8 years across the stages of menopause (Dennerstein, Randolph, Taffe, Dudley & Burger, 2002b; Dennerstein & Lehert, 2004). The Short Personal Experiences Questionnaire (SPEQ) evaluated domains of sexual function: sexual responsivity (orgasm), frequency of sexual activities, and libido. SPEQ scores of menstruating women in the early menopause transition in year 1 were compared to SPEQ scores of those same women who were postmenopausal in year 8. At year one, 42% of early perimenopausal women reported sexual dysfunction; this increased to 88% of the sample in year 8 (Dennerstein et al., 2002b). Increases in reports of dyspareunia and decreases in SPEQ scores for sexual responsivity, frequency of sexual activity, and libido occurred as the women reached the postmenopause (PM) phase (Dennerstein & Lehert, 2004).

In the Massachusetts Women's Health Study (Avis, Stellato, Crawford, Johannes & Longcope, 2000), dimensions of sexual function (satisfaction, desire, frequency of intercourse, arousal compared to younger age, difficulty reaching orgasm, pain) and serum estradiol concentrations were obtained in pre-, peri- and postmenopausal women. Lower levels of sexual desire and arousal were observed in PM women compared to pre- and perimenopausal women; however, no differences in frequency of sexual intercourse, difficulty reaching orgasm, satisfaction or pain with intercourse were noted by menopause stage (Avis et al., 2000).

In the SWAN data, measures of sexual functioning were compared cross-sectionally in pre and perimenopausal women at baseline (Avis, Zhao, Johannes, Ory, Brockwell & Greendale, 2005b). No differences in frequency of sexual intercourse, desire, arousal, orgasm or emotional satisfaction were noted between the two groups of women, but greater pain with intercourse was noted in the early perimenopausal group (Avis et al., 2005b).

Decreased libido was evaluated in two cross-sectional studies, with both documented menopause status was a risk factor for the decline in sexual desire (Valadares et al., 2008; Gracia et al., 2007). However, Freeman and colleagues (2008) measured the complaint of decreased libido over time in Caucasian and African American women and observed no changes this symptom over the menopause transition, despite the documented changes in reproductive hormones

In a cross-sectional study of Australian and Japanese women in various stages of the menopause transition, one dimension of sexual function was measured: loss of interest in sex. In both Japanese and Australian women, postmenopausal women reported greater loss of interest in sex compared to premenopausal women (Anderson et al., 2004). Similar findings were noted in a cross sectional study of Mexican women (N = 7632), with postmenopausal women reporting a greater decrease in libido compared to premenopausal women (Malacara et al., 2002). PM women also reported more symptoms of vaginal dryness but not dyspareunia compared to the premenopausal women. In a cross-sectional survey of women (N = 601) from 12 European countries in different stages of the menopause transition, menopause status influenced only one dimension of sexual functioning, that of sexual responsivity. No difference in sexual intercourse frequency was noted by menopause stage (Dennerstein & Lehert, 2004).

A marked decline in estrogen occurs with menopause, but androgen concentrations, particularly testosterone, decline progressively with age starting in the mid 20's (Birkhauser et al., 2003; Labrie et al., 2003). While both estradiol and androgens have been hypothesized to affect sexual function with menopause, hormone concentrations of estradiol or the androgens are not consistently related to sexual functioning. In the MWMHP, measures of E_2 were significantly related to symptoms of dyspareunia, sexual responsivity (enjoyment, arousal, orgasm), frequency of sexual activity, and libido (Dennerstein & Lehert, 2004), while in the Massachusetts Women's Study, E_2 levels were related only to dyspareunia, but not sexual satisfaction, desire, frequency of intercourse (Avis et al., 2000). No relationship between E_2 and libido was observed in the Penn Ovarian Aging Study (Gracia et al., 2004).

In two investigations, mean androgen levels were not related to any dimensions of sexual functioning (Dennerstein & Lehert, 2004; Gracia et al., 2004). However, in the

Penn Ovarian aging study, Gracia and colleagues (2004) found the degree of variability in testosterone levels was associated with decreased libido. Women reporting decreased libido were noted to have more variability in their total testosterone levels over time suggesting that fluctuation in serum hormone levels may be more important than mean levels in evaluating sexual function across the reproductive stage (Gracia et al., 2004).

Review papers have addressed the effect of HT on sexual functioning in postmenopausal women. The majority of studies of oral estrogen, testosterone and estrogen plus testosterone therapy in naturally and surgically menopausal patients demonstrate improvement in various dimensions of sexual function including increased frequency of sexual activity, arousal, desire, satisfaction, vaginal lubrication and decreased dyspareunia and vaginal dryness (Sherwin, 2002; Alexander et al., 2004). The degrees of improvement (mild, moderate, etc) in sexual function though were more difficult to determine due to variation in instrument measurement, route of administration, and hormone dose (Sherwin, 2002; Alexander et al., 2004). Recently the testosterone transdermal patch has shown promise in ovariectomized women received estrogen in improving a variety of sexual responsiveness measures (Simon, et al., 2005).

Factors Affecting Symptoms. Several factors have been evaluated for effect on sexual function during the menopause transition (Table 2.3). Increased BMI has been associated with decreased libido (Malacara et al., 2002; Gracia et al., 2004), but not associated with sexual responsitivity (enjoyment, arousal, orgasm) (Dennerstein & Lehert, 2004). Other factors associated with decreased sexual functioning in midlife women include stress (Dennerstein & Lehert, 2004; Hartmann, Philippsohn, Heiser & Ruffer-Heise, 2004), parity (Malacara et al., 2002; Dennerstein & Lehert, 2004; Gracia et al., 2004), depressed mood (Gracia et al., 2004; Avis et al., 2000; Hartmann et al., 2004) and smoking (Avis et al., 2000). Perceived health status affected sexual function in both the Massachusetts Women's Health Study and the SWAN study, with women reporting better health also reporting better sexual function (Avis et al., 2000; Avis et al., 2005b). Education levels were not found to have a relationship with sexual function (Dennerstein & Lehert, 2004; Malacara et al., 2002).

Relationships with partners were an important factor affecting sexual function in midlife women. The presence of a sexual partner or a change in partner was associated

with increases in sexual responsitivity and frequency of sexual intercourse (Cain et al., 2003; Dennerstein & Lehert, 2004; Avis et al., 2000; Gracia et al., 2007). Positively perceived partner relationships were associated with increased physical and emotional sexual satisfaction (Cain et al., 2003).

Race/Ethnicity. Few studies have considered the effect of ethnicity on sexual function during the menopause transition. No differences in sexual dysfunction prevalence rates were noted between pre- and postmenopausal Australian and Japanese women in the menopause transition by Anderson and colleagues (2004). No differences in reporting decreased libido between African American and Caucasian women were observed in the Penn Ovarian Aging Study (Gracia et al., 2004). In a study of middle-aged women's sexual functioning in 12 European countries, only one domain of sexual functioning (frequency of intercourse) differed among the countries included. Women of Latin and Southern European countries (France, Portugal, Italy, Spain) had higher rates of intercourse than from the Netherlands, United Kingdom, Denmark, Croatia, Switzerland, German and Austria (Dennerstein & Lehert, 2004).

In the baseline SWAN data of the pre and perimenopausal subjects, ethnic differences in sexual functioning were noted for arousal, desire, pain and frequency of sexual intercourse (Table 2.2) (Avis et al., 2005b). Compared to Caucasian women, African American reported higher frequency of sexual intercourse and Hispanic women reported more pain and lower levels of physical arousal and pleasure with sexual activity. Both Japanese and Chinese women reported less arousal with sexual functioning compared to Caucasian women, while Chinese women also noted more complaints of pain and less desire for sexual activity (Avis et al., 2005b). Values and beliefs regarding sexual activity also differed by ethnic status. Compared to Caucasian women, African American were more likely to rate sexual activity as important in their lives, while Japanese and Chinese women were less likely to rate sex as important (Cain, Johannes, Avis, Mohr, Schocken, Skurnick & Ory, 2003). Similar values regarding the important of sex were noted between Hispanic and Caucasian women (Cain et al., 2003).

Obermeyer (2000) in her review of menopause across cultures noted that prevalence rates of dyspareunia vary globally with higher rates reported in the US and Europe compared to Asian countries. The prevalence of other dimensions of sexual

function with menopause varies across ethnicities and may be a function of social or religious factors. For example, Muslim women fulfill pilgrimages to Mecca during midlife and are more devoted to these religious pursuits and attach less importance to sexual needs of their partners or themselves (Obermeyer, 2000). But as few investigations have compared sexual function with menopause in women cross-culturally, further study is needed.

Menopause Symptoms in Women with Chronic Conditions

While menopause research has expanded to include women of diverse ethnic backgrounds, most subjects are still healthy women. Subgroups of women with pre-existing health conditions (CVD, diabetes, cancer) have not been included for study and virtually nothing is known about how menopause symptoms manifest themselves in the context of chronic illness. Do women with chronic conditions have a different menopause symptom experience?

A unique problem for assessing menopause symptoms in women with chronic conditions is the difficulty distinguishing menopause related symptoms from those of the disease. In a study of post-polio women that included control groups of non-disabled women and post-polio men, Kalpakjian and colleagues (2005) detected that post polio women experience greater severity of post polio and menopause symptoms than their non-disabled peers. Miller and colleagues (2005) examined menopause symptoms in HIV infected and uninfected women observing HIV infected women reported more complaints of arthralgia and vasomotor, psychological and genitourinary symptoms compared to non-infected women. Interestingly though, in HIV infected women not receiving antiretroviral therapy as CD4 counts declined, menopause symptoms decreased suggesting immune status may play a role in symptom patterns but further study is needed (Miller et al., 2005).

A few studies have examined the experiences of women with cancer and menopause. Higher rates of vasomotor symptoms and worse hot flash severity have been observed in women receiving adjuvant treatment for breast cancer (Crandall, Petersen, Ganz & Greendale, 2004; Hunter et al., 2004). In a cross sectional study, Hunter and colleagues (2004) observed 80% of breast cancer patients on tamoxifen experienced on average 30 episodes of hot flashes and night sweats per week. The high rates of

vasomotor symptoms were associated with reports of anxiety, sleep disturbances and poorer emotional functioning (Hunter et al., 2004).

Crandall and colleagues (2004) examined menopause symptoms in breast cancer survivors (n = 476) who were diagnosed at a younger age (before age 50). On average the subjects were 6 years post diagnosis. Few were premenopausal (n = 64) or perimenopausal (n = 76); most were postmenopausal status (n = 336). Higher rates of vasomotor symptoms (51% of perimenopause women; 71% of PM women) and vaginal dryness (26% of perimenopause women; 62% of PM women) (Crandall, Peterson, Ganz & Greendale, 2004) were noted in comparison to prevalence rates of vasomotor symptoms (15-42 % in perimenopause; 42-49% in the PM) and vaginal dryness (4-18 % perimenopause; 21-25% PM) previously observed in population based studies such as the SWAN study and the MMWHP (Dennerstein et al, 2000, Gold et al., 2000). These differences are compelling and suggest prior history of breast cancer increases the potential for more prevalent vasomotor and genital symptoms in the menopause transition and merits further study.

Li and colleagues (2003) included women with chronic illness (CVD, DM, hypertension) in their menopause symptoms study but did not separate out the specific illnesses in the analysis. In general, women with chronic illness reported more vasomotor and vaginal dryness symptoms, but a relationship of these symptoms to a specific health condition was not assessed. In other cross-sectional studies of menopause, women with DM were noted to have increased symptoms of vaginal dryness and UI (Sampselle et al., 2002; Pastore et al., 2004) and women with pre-existing arthritis experienced more sleep disturbances (Hollander et al., 2001).

The current understanding of the menopause symptom experience is primarily derived from the experiences of healthy women and despite an increasing number of ethnically diverse studies, virtually nothing is known about the menopause experience of women with chronic health conditions. As the Baby Boomer generation ages, life expectancy increases and rates of chronic illness, particularly diabetes, accelerate (CDC, 2005a; Fischman, 2001) larger numbers of women with chronic illness will enter menopause in the next decade and it is important that research be expanded to inform our understanding of the menopause experience for these women.

Summary

While many symptoms have been attributed to menopause, symptom patterns differ and are influenced by race/ethnicity status, genetic, sociodemographic and psychological factors suggesting there is not a universal menopause syndrome. The literature is confounded by differences in research design (cross-sectional vs. longitudinal vs. anthropological), and instrumentation and measurement issues. Populations have been limited to primarily Caucasian European and American women and while an increasing number of ethnically diverse studies are being conducted, most subjects are still healthy women. Subgroups of women with pre-existing health conditions at menopause are not included and thus are in particular need of further study.

Certain patterns are evident in the menopause symptom literature. Vasomotor symptoms are the most frequently reported symptoms and with vaginal dryness are the symptoms most distinctly associated with the menopause. Factors shown to affect vasomotor symptom reporting include race/ethnicity status, estrogen receptor polymorphisms, BMI, smoking behavior and low socioeconomic status (Greendale & Gold, 2005; Freedman, 2005b, NIH State of the Science, 2005, NAMS, 2004; Gold et al., 2000; Lock, Kaufert & Gilbert, 1988; Melby, Locke & Kaufert, 2005). Increased symptoms of vaginal dryness have been observed in Hispanic women and women with diabetes or estrogen receptor polymorphism (Malacara et al., 2002; Malacara et al., 2004; Gold et al., 2000)

While psychological symptoms are the second most frequent complaints at midlife, evidence of a relationship between symptoms of depressed mood and menopause remains controversial although new data suggest menopause is associated with increased risk for depressive symptoms (Hardy & Kuh, 2003; Schmidt, 2005; Bromberger et al., 2007; Freeman et al., 2006; Freeman et al., 2007). Consistently studies have demonstrated that other factors such as a stressful life trajectory, previous history of mood disturbance, lower educational levels, inadequate financial income, poorly perceived health status, low social support, family dysfunction and high stress levels are important contributors to psychological symptoms with menopause (Woods, Mitchell & Mariella, 2002; Bromberger et al., 2003; Bosworth et al., 2001; Kuh et al., 2002; Woods et al., 2002; Hardy & Kuh, 2002; Malacara et al., 2002).

A growing body of evidence suggests sleep disturbances are associated with the menopause transition (Kuh et al., 1997; Dennerstein et al., 2000; Kravitz et al., 2003; Dancey et al., 2001; Shaver & Zenk, 2000; Schiff et al., 1979; Keefe et al., 1999; Ockene et al., 2005). UI is a common complaint during the menopause transition, but data from cross-sectional and longitudinal studies do not support a temporal or an independent relationship of UI with the menopause (Van Voorhis, 2005; Dennerstein et al., 2000) and further, HT use does not demonstrate improvement in these symptoms (Norton & Brubaker, 2006; Robinson & Cardozo, 2003; Moehrer, Hextall & Jackson, 2005).

While somatic complaints do not appear to be related to the menopause transition (Woods & Mitchell, 2005; Kuh et al., 1997) emerging evidence from prospective cohort studies demonstrate musculoskelatal complaints are likely menopause related (Dugan et al., 2006; Freeman et al., 2007; Freeman et al., 2008). Race/ethnicity status may play an important role in somatic symptom reporting as studies of Japanese, Lebanonese and Taiwanese women indicate these complaints are the principal menopause symptoms reported in these non-western cultures (Obermeyer, 2000; Lock, 1994; Melby, Lock & Kaufert, 2005).

As estrogen modulates a variety of cognitive processes (Henderson, Klein, & Resnick, 2002; Sherwin, 2003), cognitive decline with the menopause has been considered physiologically plausible. Longitudinal cohort studies have not demonstrated an effect of menopause on cognitive function (Kok et al., 2006; Henderson et al., 2003) but several observational studies and controlled clinical trials have demonstrated beneficial effects of HT on cognitive performance most notably for verbal memory skills (Sherwin, 2003). Studies evaluating cognitive function are confounded by the myriad of different dimensions of cognitive performance measured by a variety of instruments, precluding a clear relationship between any aspect of cognition and menopause. Factors other than menopause, such as childhood cognitive abilities, lifelong stress burden, overall health status, socioeconomic and educational factors may be more likely to affect cognitive function than menopause (Kok et al., 2006; Mitchell & Woods, 2001).

A clear relationship between sexual dysfunction and menopause is not identified. While some consequences of menopause such as vaginal dryness are likely related to dyspareunia and affect sexual function, other sexual symptoms such as decreased arousal,

desire and orgasm are not clearly related to the menopause transition. Cross-sectional studies report mixed findings regarding sexual functioning across the menopause transition (NIH State of the Science Panel, 2005), although evidence of a decline in sexual functioning with menopause was noted in the longest observational study to date (Dennerstein, Alexander, & Kotz, 2003). A new conceptualization of the female sexual response (Basson, 2000) suggests the previous data derived from the Masters and Johnson (1966) male-centric model of sexual function is likely flawed and further work is needed to clarify the effect of menopause on dimensions of sexuality.

Lastly, several differences in menopause symptoms have been noted by race/ethnicity status. African American women report more vasomotor symptoms while Chinese and Japanese women report fewer vasomotor symptoms compared to Caucasian women (Gold et al., 2000). Hispanic women report more complaints of vaginal dryness and UI (Gold et al., 2000; Sampselle et al., 2002; Pastore et al., 2004; Malacara et al., 2002). Mood symptoms were more commonly reported by Hispanic women and less frequently reported by Chinese and Japanese women compared to Caucasian women (Bromberger et al., 2003). In the SWAN data, Caucasian and Hispanic women had the highest rates of disturbed sleep, with lower rates noted in African American, Chinese and Japanese women (Kravitz et al., 2003).

While somatic symptoms were reported at similar rates among the SWAN ethnic groups, previous work by social scientists (Lock, 1994) suggests somatic symptoms are the primary menopause symptom in other cultures. Cross-cultural differences in sexual symptom reporting are also notable. African Americans reported higher frequency of sexual intercourse and were more likely to rate sexual activity as important, while Japanese and Chinese women noted lower levels of physical arousal and pleasure and are less likely to rate sexual activity as important (Avis et al., 2005b; Cain et al., 2003).

The evidence demonstrates the variation in menopause symptom patterns and suggests there is not a universal menopause syndrome (Avis et al., 2005). There is a continued need to distinguish menopause related symptoms from those associated with health conditions, biological factors or sociocultural issues. Future research should address the symptom patterns unique to subgroups of women in the hopes of providing

women with specific insights and strategies to guide their individual menopause transitions.

Diabetes

Overview

Diabetes is a major health concern in the United States (US) and now affects nearly twenty-four million Americans, reflecting an increase of more than three million in the past two years (Center for Disease Control [CDC], 2008). The demographics of an aging US population, and the rising incidence of obesity, a risk factor for diabetes, suggest this trend will continue and could cause the number of those affected to double by 2050 (CDC, 2008). Similar trends have also been observed globally and the number of persons with diabetes is estimated to increase from 135 million in 1995 to 300 million by the year 2025 (King, Aubert, & Herman, 1998).

The annual costs (direct and indirect) of diabetes in the US are approximately $174 billion dollars (CDC, 2007). These costs are related to diabetes care, primarily the management of the serious health complications of this disease. Diabetes is the seventh leading cause of death in the US, but it is the leading cause of blindness, limb amputation and renal failure (CDC, 2007; DHHS, 2003). Further, diabetes is an independent risk factor for the development of cardiovascular diseases (CVD), particularly heart disease and stroke, the first and third leading causes of death in the US (CDC, 2008).

Diabetes Mellitus (DM) represents a group of metabolic diseases characterized by disordered carbohydrate metabolism and hyperglycemia due to either an absolute deficiency of insulin secretion, a reduction in insulin action or both (ADA, 2008a; Karam, 1999). The diagnosis of DM is confirmed by either a fasting serum glucose concentration $\geq$126 mg/dl or a two hour post prandial level of $\geq$ 200 mg/dl on two separate occasions. In individuals with symptoms, a random non-fasting glucose level $\geq$ 200 mg/dl is also diagnostic for the disease (ADA, 2008a). There are four clinical classes of DM: three forms specifically identified (type 1, type 2, gestational) and a fourth category of variant forms of DM usually due to genetic defects, medications or chemical

exposures (ADA, 2008a). Type 1 and type 2 are the most common forms of DM and are differentiated by the primary core defect in glucose metabolism (ADA, 2008a).

Type 1 diabetes accounts for approximately 5-10% of all diabetes cases and is characterized by destruction of the pancreatic beta islet cells resulting in an absolute deficiency of insulin (ADA, 2008a). Most often an autoimmune response has been responsible for the beta cell destruction, but a genetic predisposition is also usually present (ADA, 2008a). Genes within the human leukocyte antigen (HLA) region of chromosome 6 particularly loci DR3 and DR4 are associated with increased risk for type 1 DM (Reece & Homko, 2005). Other genes are suspected to also confer susceptibility for type 1 DM, as many patients with type 1 diabetes do not have HLA antigens (Reece & Homko, 2005). This form of DM develops abruptly and often presents in childhood or adolescence but can occur at any age.

Type 2 diabetes is the most common form of the disease accounting for 90-95% of all cases (ADA, 2008a). Type 2 diabetes is heterogeneous and characterized by various patterns of dual defects in glucose metabolism: impaired insulin action and impaired beta cell secretion of insulin (Karam, 1999; ADA, 2008a). Impaired insulin action, known as insulin resistance (IR) is present in most persons with type 2 DM and occurs when target tissues fail to respond to normal circulating levels of insulin. Pancreatic beta cells respond by producing increased amounts of insulin to maintain normoglycemia, but over time, the beta cells fail to maintain these high rates of insulin secretion and impaired glucose tolerance develops (Goldstein, 2002; Weissman, 2002). The onset of this form of diabetes is slow and insidious as the IR and the overproduction of insulin are present years before symptoms develop and the diagnosis is confirmed (ADA, 2008a).

The etiology of type 2 DM is multifactorial: genetic factors, autoimmune processes and host characteristics, such as age and obesity, all contribute to the development of this disease (ADA, 2008a; Metzger, Cho & Brickman, 2005). Type 2 DM is considered polygenic as a specific genetic trait for the disease has not been identified. Rather several genetic traits or clusters of traits likely influence the disease development in the context of environmental factors (Metzger et al., 2005).

Risk factors. Several risk factors for type 2 diabetes (Table 2.4) have been identified and include age over 45 years, overweight status (BMI $\geq$ 25kg/m^2), habitual physical inactivity, hypertension (BP $\geq$ 140/90 mmHg), HDL cholesterol level $\leq$ 35mg/dl and/or a triglyceride level $\geq$ 250 mg/dl, a first degree relative with DM, history of polycystic ovarian syndrome, vascular disease or clinical conditions associated with IR such as acanthosis nigricans (ADA, 2008b). Ethnicity is a risk factor for DM: African Americans, Latinos, Native Americans, Asian Americans and Pacific Islanders are at high risk for type 2 DM. Additional risk factors include previous gestational diabetes or delivery of a baby weighing > 9 lbs, any previous history of impaired fasting glucose (IFG; fasting serum glucose level of 100-125 mg/dL) or impaired glucose tolerance (IGT; 2 hour postprandial glucose level of 140-199 mg/dL) (ADA, 2008b).

Overweight status is an important risk factor for type 2 DM. Most persons with type 2 diabetes are overweight or obese (BMI $\geq$ 30kg/m^2) and obesity has been repeatedly associated with IR, the underlying abnormality in type 2 DM (Carey, Jenkins, Campbell, Freund, & Chisholm, 1996; Goldstein, 2002; Reusch, 2002). While most persons with type 2 DM are over age 40, with the rising incidence of obesity in all ages of the population, type 2 DM is now occurring in younger adults, and children at alarming rates (CDC, 2002a; Fagot-Campagna et al., 2000). Regardless of weight status, the pattern of body composition and fat distribution is also important. An increased percentage of body fat, particularly a greater distribution in the central abdomen directly correlates with IR and may predicate hyperglycemia and eventual DM (Carey et al., 1996; Despres, 1993).

Symptoms of Diabetes

Symptoms related to hyperglycemia signal diabetes development. The common presenting symptoms include fatigue, polyuria, polydipsia, polyphagia, weight loss, and blurred vision (Karam, 1999). Recurring or unresolving infections are another characteristic symptom associated with hyperglyemia. In children, impaired growth may be a noticeable finding (ADA, 2008a). With severe elevations in glucose levels, life-threatening symptoms of ketoacidosis or nonketotic hyperosmolar syndrome may indicate DM (ADA, 2008a).

Once the diagnosis is established and management initiated, persons with diabetes may experience symptoms of either hyperglycemia or hypoglycemia. Chronic hyperglycemia may result in additional symptoms from target organ damage, such as progressive changes in vision from retinopathy or parasthesias from peripheral neuropathy (ADA, 2008a). Autonomic neuropathy, a complication of DM is associated with multiple symptoms such as tachycardia, hypotension, gastroparesis, impaired thermoregulation, urinary incontinence and erectile dysfunction (Vinik, Maser, Mitchell, & Freeman, 2003).

Low levels of serum (<70mg/dL) and cerebral glucose concentrations precipitate hypoglycemia (Gonder-Frederick, 1998). Hypoglycemia is distinguished by symptoms related to the release of autonomic regulatory hormones (glucagons, epinephrine) to raise glucose concentrations and symptoms that indicate severely low levels of central nervous system glucose concentrations (neuroglycopenia)(Zammit & Frier, 2005). Headache, hunger, nausea, weakness, lightheadedness, sweating, tachycardia, trembling, extremity tingling, difficulty concentrating and completing tasks characterize mild hypoglycemia (Gonder-Frederick, 1998). More severe symptoms such as lethargy, mental confusion, convulsions, unconsciousness and coma can occur with severe hypoglycemia (Zammit & Frier, 2005; Gonder-Frederick, 1998).

Diabetes Management

Diabetes prevention and treatment strategies are predominantly behavioral. The cornerstones of care include therapeutic lifestyle modifications (diet, physical activity), self-management skills, and the appropriate use of medications (ADA, 2008b). The major goal of DM management is control of blood glucose levels as large clinical trials have demonstrated good glycemic control significantly reduces complications (Diabetes Control & Complications Trial [DCCT], 1993; United Kingdom Prospective Study Group [UKPSD], 1998). *Glycemic control* represents optimal plasma concentrations of glucose and several measures reflect glycemic control: hemoglobin A1c (HgbA1c), preprandial and peak postprandial glucose levels (ADA, 2008b). As it measures stability of glucose levels over the preceding 3 months, HgbA1c is the preferred test of glycemic control (ADA, 2008b; Sacks et al., 2002). A normal range for HgbA1c is 4.0-6.0%; levels below 7.0% are recommended for persons with DM (ADA, 2008b).

Diabetes in Women

Diabetes is an important health concern for women, who are disproportionately affected by this disease. Approximately 10.2% of all women age 20 years or older currently have diabetes (CDC, 2008), up from 8.8 % only 2 years ago. Women have higher lifetime risks of developing diabetes than men at all ages (Narayan, Boyle, Thompson, Sorenson, & Williams, 2003) as the risk factors for DM (obesity and physical inactivity) are more common in women (Rewers & Hamman, 1995; DHHS, 2003). More disconcerting, the incidence and severity of diabetic complications, particularly those related to CVD, are increased in women (Barrett-Connor, Cohn, Windgard & Edelstein, 1991; Barrett-Connor, 2003; Beckles & Thompson-Reid, 2001).

Ethnicity. Non-white women are even more disproportionately affected by diabetes. The prevalence rate for DM is two to four times higher among African American, Hispanic, American Indian and Asian Pacific Islander women than Caucasian women (DHHS, 2003). In middle-aged women, the prevalence rate for type 2 DM is 23% in African Americans, 24% in Hispanic Americans and increases to 41% in Navajo Indians (DHHS, 2003). New projections place the lifetime risk for diabetes at 40% for African Americans and 50% in Hispanic females (CDC, 2008).

Risk factors for DM are more prevalent among these women than white women at all levels of socioeconomic status (Beckles & Thompson-Reid, 2001). Higher rates of mortality, disability and complications of DM are noted among African American and Hispanic women than Caucasian women (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 1999, NIDDK, 1998). The seventh leading cause of death nationally, diabetes is the fourth leading cause of death in middle-aged (45-64 years) African American women and the third leading cause of death in middle-aged Hispanic women (DHHS, 2003).

The current minority (non-white) portion of the US population is expected to increase from 28% to 47% by the year 2050 (US Census Bureau, 2001). It is expected that the numbers of Hispanic women will double and the numbers of African American women will increase by two thirds between the years 1995-2010 (Beckles & Thompson-Reid, 2001). Given the increased risk of DM in both women and minority groups, these trends will have significant impact on the national prevalence of diabetes.

Socioeconomic Disparities. Diabetes is more prevalent among persons of lower socioeconomic and educational levels (Rimmer, Silverman, Braunschweig, Quinn & Liu, 2002). Women, again, are profoundly more affected by this reality. "Women with diabetes are more likely than women without diabetes to be over age 45; nonwhite; divorced, separated or widowed; living alone; retired; or unable to work"(Morbidity and Mortality Weekly Report [MMWR], 2002, p. 147). Regardless of race/ethnicity status, women with DM are also more likely to have a lower level of formal education and twice more likely to have incomes under $25,000 than women without DM (MMWR, 2002; DHHS, 2003).

For women, these socioeconomic inequalities can contribute to the risk of diabetes and it's progression by limiting options for diabetes prevention and management. Persons of lower education and income levels, are often less able to afford good nutrition, have less access to exercise facilities and less available time to engage in such activities due to the demands and stressors of daily life (Wing et al., 2001; Black, 2002). Diabetic women of lower socioeconomic status are also more likely to be uninsured and have less access to quality health care, making management of their DM an incredible challenge (Burnet, Plaut, Courtney & Chin, 2002; Wing et al., 2001; US Census Bureau, 2001).

The Intersection of Diabetes and Gender: The Social Position of Women

The social position of women has been implicated in the increased risk and complicated course of diabetes in women. Until the 1990's, women were not included in most research studies, precluding evidence of gender effects (Beckles & Thompson-Reid, 2001; White, Russo & Travis, 2001). While federal regulations mandate inclusion of women, the biomedical model has continued to dominate in scientific investigations. This model has made tremendous contributions to the scientific knowledge of diabetes risk, etiology and management, but its narrow view of health conceptualizing gender as a dichotomous variable limits understanding of how disease experience or health status are engendered (Taylor & Woods, 2001; LaVeist, 1994; Kreiger & Gruskin, 2001).

Feminist writers make the case that a broader conceptualization of gender within the social and cultural environment is needed (Kneipp & Drevdahl, 2003; Riger, 1998). Gender roles are constructed and shaped within the context of historical, political, social and cultural environments. Once embedded in a women's identity, these constructions

influence women's behaviors and health status (Amaro & Raj, 2000; Kreiger & Gruskin, 2001; Williams, 2002). Kreiger and Gruskin (2001) proposed an eco-social framework asserting that persons biologically incorporate dimensions of the surrounding environment in which they live. Societal assignments by power and privilege, living conditions (property, resources, daily life experiences) and biologic exposures interact over time to contribute to the expression of health or the manifestation of disease (Kreiger & Gruskin, 2001).

This broader conceptualization has been suggested in the diabetes literature. Black (2002) argues that women appear to have only a slightly elevated risk for DM based purely on sex, and rather it is the social position of women that substantially elevates the risk and influences the manifestation of the disease. In the jointly authored public health perspective on diabetes and women's health by the CDC and DHHS (Beckles & Thompson Reid, 2001), this has been acknowledged and the "rigorous examination of the economic, social and environmental factors that affect the health of women" (p. 3) recommended. Anderson and Robins (1998) as well advocated for qualitative inquiry of the contextual factors that influence diabetic clients self-management behaviors.

Studies in DM care have been able to predict adherence to self-management skills, but concentrated on individual demographic variables (Fisher et al., 2002). Limited attention has been given to influences on behavior beyond the individual, such as the social networks of family or community (Fisher et al, 2002; Wing et al, 2001). Recent research has explored the social contextual factors that influence DM management in diverse groups of women and these are briefly summarized.

Many women report that work and family demands preclude the ability to engage in health promoting behaviors (Cagle, Appel, Skelly & Carter-Edwards, 2002). In studies of diabetic women, the burdens of family responsibilities, as the head of the household with the dual need to care for others and provide financial support is consistently noted as a deterrent to DM self-management by Caucasians, African Americans and Latinos (Eyler et al., 2002; Nies, Vollman & Cook, 1999; Banks-Wallace, 2000; Cagle et al., 2002; Carter-Edwards, Skelly, Cagle & Appel, 2004). In a study of African American women with DM, women describe on average at least six daily caregiving roles (mother,

partner, worker, family chauffeur, cook and church member)(Cagle et al., 2002, p. 559). Acknowledging the need to care for one's health as important, these women still prioritize their activities putting family first, work second and the self, often last (Banks-Wallace, 2000; Cagle et al., 2004)

Across ethnic groups (Caucasian, African American, Hispanic), women described increased stress and family discord when implementing diabetic dietary requirements that conflicted with cultural or family food preferences (Hepworth, 1999; Samuel-Hodge, Ammerman, Skelly & Headen, 1997; Samuel-Hodge et al., 2000; Anderson et al., 1998). In diabetic African American women (Cagle et al., 2002), the role of cook was described as complicated. Women identified the burden of preparing traditional foods for family and other foods for one's self. But more distressing to the women were feelings of isolation when eating separate foods at meals, usually considered a pleasant communal experience (Cagle et al., 2002).

Diabetic women also identified several barriers to participation in physical activity including environmental factors, social support issues and family responsibilities with the exception of the unique deterrent in African American women of avoiding exercise for fear of "sweating and messing up one's hair" (Eyler et al., 2002, p.248). In studies of women in rural and urban settings, environmental issues, such as lack of access to public parks or safety concerns related to local crime rates, were identified as deterrents to physical activity (Eyler et al., 2002; Nies, Vollman & Cook, 1999; Wing et al., 2001; King et al., 2000).

Perceived social support from family and friends is the one variable positively associated with greater adjustment to diabetes and improved DM management (Gallant, 2003; Willoughby, Kee & Demi, 2000; Plotnikoff, Brez & Hotz, 2000), although Gallant (2003) asserts most studies "largely ignored gender issues"(p.189) and notes social support predicts better care among men but not women. Recent qualitative data indicate diabetic women suffer from a lack of social support and instead are the primary providers of support to members in their social network (Banks-Wallace, 2000; Eyler et al., 2002; Keyserling et al., 2002; Samuel-Hodge et al., 2000; Edwards, Skelly, Cagle & Appel, 2004). Family and friends are identified as 'caring' but lack understanding of the

women's needs and do not provide support to enact health promoting diabetes behaviors (Carter-Edwards et al, 2004).

In qualitative studies, women with DM expressed feelings of stress that were related to not only their work responsibilities and care giving roles, but also to the diabetes diagnosis (Samuel-Hodge et al., 2000; Patterson, Thorne & Dewis, 1998; Carter-Edwards et al., 2004). Women described the burden of DM in their daily lives as it related to activities of daily living, but also reported fear and worry about potential diabetic complications as they recognized their non-adherence to DM management behaviors (Samuel-Hodge et al., 2000; Carter-Edwards et al., 2004). This is particularly disconcerting as the physiologic stress response adversely affects glucose control (Aikens & Mayes, 1997). Cumulatively, the data suggest the social positions midlife women occupy in families and social networks may critically affect diabetes progression, and such concepts are important to consider in developing appropriate management strategies for women.

The Intersection of Diabetes and Gender: Diabetes and Menstrual Function

Gender differences in diabetes prevalence and progression suggest an etiologic role for the sex steroids. While there is likely interplay between reproductive and diabetic endocrinology, the specific mechanisms that characterize this relationship remain enigmatic (Case & Reid, 1998; Rasouli & Elbein, 2005; Arrais & Dib, 2006). Most research has addressed this 'interplay' as it relates to issues of menstrual function or glucose control.

Glucose Homeostasis with Menstruation. Menstrual cycle variations in glucose control have been reported primarily in insulin dependent type 1 diabetic women but only a few studies of Caucasian European and American women have examined this concern. Moreover, no studies to date have examined this issue in women with type 2 DM. In studies relying on self-report questionnaire data, both increased glucose levels and increased insulin needs during the luteal phase of the menstrual cycle were reported (Cawood, Bancroft & Steel, 1993; Lunt & Brown, 1996; Walsh & Malin, 1977), but changes in long term glucose control were not detected (Lunt & Brown, 1996). Only two studies (Widom, Diamond & Simonson, 1992; Trout et al., 2007) obtained precise measures of glucose and insulin values via euglycemic clamp technique during both the

follicular and luteal phases of the menstrual cycle. Widom and associates (1992) observed hyperglycemia and reduced insulin sensitivity in the luteal phase of the menstrual cycle compared to the follicular phase in almost half, but not all subjects, while Trout and colleagues (2007) also observed luteal phase elevations in glucose, insulin sensitivity was not affected.

While these limited data might suggest higher luteal phase estradiol levels are associated with reduced insulin sensitivity in some women with type 1 DM, it is interesting to note that in healthy women a similar decline in glucose and insulin metabolism is observed with waning estrogen levels at menopause (Godsland, 1996). Further, subsequent estrogen therapy in these women improves glucose and insulin homeostasis and even reduces diabetes incidence (Espeland et al., 1998; Kanaya et al., 2003; Margolis et al., 2004).

In diabetic (mostly type 2) postmenopausal women using HT, similar improvements in glucose homeostasis have been observed in experimental and observational studies. From retrospective analysis of HMO registry data, Ferrara and colleagues (2001) noted lower HgbA1c values in type 2 diabetic HT users compared to non-HT users. As well, lower fasting glucose and HgbA1c levels were observed in diabetic women using HT than never or previous users of HT in the NHANES III data (Crespo et al., 2002). Several small short-term clinical trials of HT in primarily type 2 diabetic women (Samara et al., 1999; Andersson et al., 1997; Andersson et al., 1999; Brussard et al., 1997; Friday et al., 2001) also documented lower fasting glucose, fasting insulin and HbgA1c values in women using HT.

Diabetes Effects on Menarche, Menstrual Cycle & Menopause. Several investigators have evaluated the relationship between DM and menstrual disturbances. Most studies have addressed menstrual dysfunction in women with type 1 DM, as until recently few women of reproductive age had type 2 diabetes. Study participants are primarily Caucasians; few studies are ethnically diverse. A variety of hypotheses have been entertained suggesting ovarian function is impaired in diabetic females secondary to autoimmune antibodies, neuroendocrine dysfunction in the HPO axis or toxic exposure from insulin resistance and glycosylated proteins, but a specific ovarian mechanism has not been elucidated (Arrais & Dib, 2006; Bairey-Merz et al., 2003).

Women with Type 1 Diabetics. A delay in menarche of approximately 1 year has been noted in type 1 diabetics particularly if the diabetes developed in the pre-pubertal years (Danielson, Palta, Allen & D'Alessio, 2005; Griffin et al., 1994; Kjaer, Hagen, Sando & Eshoj, 1992; Yeshaya, Orvieto, Dicker, Karp &Ben-Rafael, 1995), although in adolescents with good glucose control, the age of menarche is near normal (Thrailkill, 2005; Schriock, Winter, & Traisman, 1984). More than one third of type 1 diabetic women report menstrual cycle abnormalities such as irregular cycling, amenorrhea, polymenorrhea, or menorrhagia in observational studies (Kjaer et al., 1992; Griffin et al., 1994; Yeshaya et al. 1995; Strotmeyer, Steenkiste, Foley, Berga & Dorman, 2003). Similar to menarche, glycemic control appears to be an important factor, as women with type 1 diabetes and regular menses had significantly lower HbgA1c values compared to those reporting menstrual disturbances (Schroeder, Herweek, Sanfilippo & Foster, 2000).

Women with type 1 diabetes also experience higher failure to conceive rates, fewer pregnancies, and a greater number of stillbirths than women without diabetes (Strotmeyer et al., 2003; Durando et al., 2003; Rosenn & Miodivnik, 2005). Only one study examined age at menopause in women with type 1 diabetes. Dorman and colleagues (2001) compared 143 women with type 1 diabetes with their nondiabetic sisters and an unrelated control group, noting an earlier age at menopause for the women with DM (41.6 years) compared to their sisters (49.9 year) and the controls (48 years).

Altered sex steroid levels have been noted in women with type 1 DM. In regularly cycling adolescent girls, increased levels of free and total testosterone (T) and decreased levels of sex hormone binding globulin (SHBG) have been documented (Adcock et al., 1994; Meyer et al., 2000; Rudberg & Persson, 1995), while low levels of total and free T, SHBG and E_2 were detected in amenorrheic diabetic girls (Djursing et al., 1985). In adult women with type 1 DM, a high prevalence of hyperandrogenic disorders, namely hirsutism and polycystic ovarian syndrome (PCOS) have been observed (Escobar-Morreale et al., 2000). Studies of sex steroid levels in postmenopausal insulin dependent diabetics demonstrated conflicting findings. Nyholm and colleagues (1989) noted higher levels of serum E_2 and estrone but similar concentrations of total and free T in diabetic postmenopausal women compared to non-diabetic women of similar body size, but Luan

and associates (1996) demonstrated lower E_2 values in the diabetic subjects compared to healthy menopausal women.

Women with Type 2 Diabetics. There is no data on the effects of diabetes on menarche in females with type 2 DM. The increase in growth hormone during puberty accentuates insulin resistance and reduces insulin mediated glucose disposal. This effect is noted to be more pronounced in girls and has been associated with the development of type 2 DM in at-risk adolescents during this developmental stage (Thrailkill, 2005). Three times as many girls than boys develop type 2 DM with adolescence (Fagot-Campagna et al., 2000). Oligomenorrhea, amenorrhea, and elevated testosterone levels have been observed in adolescent girls with type 2 DM, obesity, acanthosis nigricans or PCOS (Thrailkill, 2005).

While cycle patterns in type 2 DM women have not been examined, long or highly irregular menstrual cycles from early adulthood were predictive of risk for type 2 DM in both obese and non-obese women in the observational Nurse's Health Study (N=101,073) (Solomon et al., 2001). Yet, in a smaller prospective study of 668 Caucasian college educated women, there was no association between age at menarche, cycle length, cycle variability or frequency of long cycles to diabetes risk (Cooper, Ephross, & Sandler, 2000).

Two cross-sectional studies of Hispanic women examined age at menopause in women with type 2 DM. Malacara and colleagues (1997) studied 51 diabetic and 49 nondiabetic women of similar BMI, documenting an earlier age of menopause in the diabetic women (45.7 years) compared to their non-diabetic counterparts (48 years). An earlier age at diagnosis of DM was positively correlated with an earlier age at menopause. The diabetic subjects in this study were not well controlled at the time of the study (mean HgbA1c values of 11.3%), but it is difficult to evaluate if the diabetes had been poorly controlled for years and may have contributed to the early menopause findings. In a larger study of BMI-matched healthy (n = 409) and type 2 diabetic (n = 404) women with regular menstrual cycles prior to menopause, no differences in the age of menarche or menopause were observed between the groups (Lopez-Lopez, Huerta, & Malacara, 1999).

Few studies examined the relationship between the sex steroids and type 2 DM in women. Phillips and colleagues (2000) examined serum hormone concentrations in 20 women with type 2 diabetes and 29 healthy Hispanic postmenopausal women of similar BMI and not using HT or insulin. Significantly higher serum levels of E_2, free T and DHEAS and marginally higher serum estrone concentrations were observed in women with diabetes compared to the healthy controls (Phillips et al., 2000). In another study of 20 women with type 2 diabetes and 20 healthy age- and BMI-matched postmenopausal women, higher urinary levels of E_2 and estrone and lower levels of FSH and LH were detected in the women with DM but androgen measures were not obtained (Quinn, Ruffe, Brown, & Ennis, 1981). In both studies, measures of glycemic control were not provided to permit comparison of the sex steroid levels with the degree of glucose dysfunction.

The findings from both studies suggest elevated levels of estrogen may be associated with type 2 DM. This is an intriguing finding in lieu of the clinical trial data that demonstrated HT use in women with type 2 DM improved glucose control, but it is difficult to evaluate its significance as measures of glycemic control were not obtained in both studies. The association of hyperandrogenemia with type 2 DM by Phillips and colleagues (2000) was also observed in the prospective Rancho Bernardo study in which increased levels of testosterone in women were associated with the development of type 2 DM (Oh, Barrett-Connor, Wedick, & Windgard, 2002). As well, androgen excess is a central feature of polycystic ovarian syndrome (PCOS) another condition strongly associated with type 2 DM in women (Cibula et al., 2000; Eisenberg, 2005; Maturna & Spritzer, 2002).

A few other studies have reported on sex steroid measures in women with diabetes but have not clearly identified if the subjects had type 1 or type 2 DM. In the multiethnic SWAN data, a trend for lower serum E_2 levels was observed in pre- and perimenopausal women with DM (Sowers, Derby, Jannausch, Torrens, & Pasternak, 2003) while decreased levels of FSH were observed in diabetic women across the stages of the menopause transition (Randolph et al., 2004). Malacara and colleagues (1997) also observed decreased levels of FSH in diabetic Hispanic women compared to healthy controls.

In the Women's Ischemia Syndrome Evaluation (WISE) study examining gender issues of coronary artery disease (CAD), significantly lower levels of E_2 and estrone were observed in premenopausal women with CAD (Bairey-Merz et al., 2003). Of these women, 46% had a history of DM, yet none had a history of PCOS. These findings are compelling as they suggest hypoestrogenemia is a potent risk factor for CAD, but further, disruption of sex steroid production may occur in women with DM and could explain the link between increased rates of CAD in diabetic women (Bairey-Merz et al., 2003).

Diabetes affects several dimensions of reproduction function in women (Table 2.5). While relatively little data are available, degree of glycemic control appears to be an important mediator of menstrual disturbances. Differences in the age of menarche and menopause or patterns of menstrual dysfunction between type 1 and type 2 diabetes are not clear as until recently few women of reproductive age developed type 2 diabetes. There is no clear consensus in the existing literature as to the effect of diabetes on sex steroid production. With the exception of the SWAN data and a few studies of Hispanic women, most data are derived from the study of Caucasian women. Certainly with the increased prevalence of type 2 DM in women and especially among African Americans and Hispanics, additional investigation is warranted.

Diabetes and Disease Risk in Women

The incidence and severity of diabetic complications (nephropathy, retinopathy, neuropathy) are increased in women (Beckles & Thompson-Reid, 2001) and even more so in African American and Hispanic women (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] 1999, NIDDK, 1998). Most notably women with DM are more at risk for CVD (Abbot et al., 1988; Barrett-Connor, Cohn, Windgard & Edelstein, 1991; Barrett-Connor, 2003) and experience significantly higher cardiovascular mortality rates compared to diabetic men (Shaw et al., 2006). Among women, the age adjusted prevalence rates of CVD are almost two times higher in women with diabetes compared to those without diabetes with the highest rates noted for African American women (CDC, 2004). Besides diabetes, other risk factors for CVD such as insulin resistance (IR) and the metabolic syndrome are more common in women than men and may account for these gender differences (Carr, 2003; Park et al, 2003; Wilson, Kannel, Silbershatz, & D'Agostino, 1999). Increased central adiposity associated with

the menopausal estrogen decline also contributes to CVD risk. More recently hypoestrogenemia in diabetic women has been documented as a risk for CVD in premenopausal women (Bairey-Merz et al., 2003; Shaw et al., 2006).

Women with DM are also more vulnerable to other medical problems. Postmenopausal (PM) women with type 1 DM have lower bone mineral density (BMD) than healthy PM women while women with type 2 DM often have higher BMD compared to other PM women (Akin, Gol, Akturk, & Erkaya, 2003; Brown & Sharpless, 2004; Eisenberg, 2005; Rachon, Mysliwska, & Suchecka-Rachon, 2003). Women with type 1 diabetes are more likely to experience osteoporosis and increased fracture risk; hip fracture risk has been reported to be 12.25 time higher in type 1 diabetic postmenopausal women than non-diabetics (Nicodemus & Folsom, 2001). In a large prospective cohort study, Schwartz and colleagues (2001) documented that despite increased BMD, women with type 2 DM still experienced higher fracture risk compared to non-diabetics. Complications from diabetes including poor vision and peripheral neuropathy (possibly increasing risk for falls) were documented in these women and perhaps influenced the fracture risk (Schwartz et al., 2001).

Increased cancer susceptibility is noted in women with DM. Epidemiologic data suggests an association with DM and breast cancer (Lawlor, Smith & Ebraihim, 2004). More specifically, IR a central feature of type 2 DM has been linked to breast cancer (Stoll, 2002). Endometrial cancer has also been associated with IR (Petridou et al., 2003). In a population based study of Swedish women, risk for endometrial cancer was 1.5 fold higher in women type 2 DM and 13.3 fold higher in those with type 1 DM (Weiderpass et al., 2000). Prospective studies have documented the association of colorectal cancer with type 2 DM (Hu et al., 1999; Nilson & Vatten, 2001).

Diabetes may be associated with enhanced cognitive decline in women. Studies report anywhere from a 50% to 200% increased risk for dementia in persons with DM (Gregg & Brown, 2003). In a recent review, Coker and Shumaker (2003) assert most studies have not evaluated cognitive functioning with rigorous neuropsychological testing and further, few have included women, precluding an accurate assessment of the dementia risk for women with diabetes. In a prospective study of older women (over age 65) and osteoporosis, Gregg and colleagues (2000) observed lower levels of cognitive

function in women with DM than non-diabetics at baseline and further, diabetic women experienced greater cognitive decline during the duration of the study (6 years) compared to non-diabetic women.

Higher rates of depression are associated with DM and again women are disproportionately affected. Early epidemiologic studies noted a prevalence of depression in persons with DM ranging from 8.5 to 27.3% (Gavard, Lustman & Clouse, 1993) but a more recent meta-analysis of 39 studies of depression and DM, demonstrated the diagnosis of DM doubles the risk for depression (Anderson, Freedland, Clouse, & Lustman, 2001). Depression prevalence was significantly higher in diabetic women (28%) than in men (18%) with diabetes. No difference in the prevalence rates for depression were observed between type 1 and type 2 diabetics by Anderson and colleagues (2001), but depression has been associated with poor glycemic control (Lustman, Anderson, Freedland, deGroot, & Carney, 2000) and increased risk of diabetic complications (deGroot, Anderson, Freedland, Clouse & Lustman, 2000). Treatment with anti-depressive medications is associated with improvement in mood symptoms and glycemic control (Lustman & Clouse, 2005; Lustman et al., 1997), but it is not clear if the improved glycemic control is from relief of the depression or the metabolic activities of the pharmacotherapeutic agent (Rosenow & Autio, 2002). Few studies though, have specifically examined the unique needs of middle-aged women with diabetes (Zauszniewski, McDonald, Krafcik, & Chung, 2002).

Summary: The Plight of Women with Diabetes

Diabetes is a national health problem that disproportionately affects women, especially African Americans and Hispanics (CDC, 2005a). Women with diabetes are more likely to experience disabling complications from this chronic illness and are also more at risk for other deleterious health problems such as CVD, osteoporosis, cancer and depression (Beckles & Thompson-Reid, 2001; Khoo & Perera, 2005; Shaw et al., 2006).

The plight of women with DM has been recognized as a serious public health issue (Beckles & Thompson-Reid, 2001). The US DHHS in conjunction with the CDC (2002) issued policy recommendations to increase DM prevention in women, and expand ethnic and gender relevant health management strategies (CDC, 2002). Improved diabetes care, particularly to reduce disparities related to gender and ethnicity was also

identified in Healthy People (HP) 2010. Of the 28 areas of focus, DM was ranked as the 5th priority (DHHS, 2000). Annually, the ADA (2008a) reviews scientific evidence and updates the standards of care for DM management. Several clinical recommendations are part of this document including DM care in specific populations (i.e., children) and settings (day care centers, correctional institutions) but with the exception of preconception counseling, no recommendations address the distinctive needs of women.

Middle-aged (45-55 years) women represent a unique subset of the female diabetic population as both the physiological and psychosocial changes associated with midlife challenge DM management and health status. The social position of midlife women may affect the risk and complicates the course of DM in women (Black, 2002). Sociocultural norms have charged midlife women with multiple role responsibilities that constrain their abilities to fully engage in DM health behaviors. Significant socioeconomic inequalities, environmental barriers and limited access to health care services also contribute to the engendered features of this disease (MMWR, 2002; Beckles & Thompson-Reid, 2001). Studies of midlife diabetic women indicate they are overwhelmed with multiple responsibilities and continue to put the needs of others ahead of their own, at the potential expense of their health.

For most women, the menopausal transition coincides with the midlife years. The estrogen decline at menopause is believed to be associated with increased central adiposity and deteriorations in glucose and insulin metabolism that magnify women's risks for diabetes (Collins, Wenger, Rossouw & Paoletti, 2002; NAMS, 2002; Sowers & Tisch, 2000). These changes are significant for women with pre-existing DM, as menopause may affect already disrupted glycemic function, imposing an even greater risk for complications of the disease (Sowers & Tisch, 2000). Yet relatively little is known about these physiologic changes in midlife diabetic women as most research excluded women with pre-existing co-morbidities. Observational studies have provided insights about the increased health risks for diabetic women at menopause, notably the metabolic syndrome and CVD. Small controlled studies of primarily white women have demonstrated improved HgbA1c values and fasting glucose levels with HT use. Yet, there is not a clear understanding of the endocrinological interplay of reproductive aging with diabetes.

The menopause is a developmental stage marked by symptoms. In western cultures, over 100 symptoms have been attributed to the menopause with approximately 85% of midlife women reporting at least one of them and 10% of women seeking assistance for these concerns (Woods & Mitchell, 2005, Sherman et al, 2005; McKinlay, et al 1992). What is becoming increasing clear in the menopause literature is that there is not a universal menopause syndrome; rather certain patterns in symptoms are evident and vary by race/ethnicity status, genetic, sociodemographic and psychological factors.

Our understanding of the menopause symptom experience is primarily derived from the experiences of healthy women and despite an increasing number of ethnically diverse studies, virtually nothing is known about the menopause experience of women with diabetes. As the Baby Boomer generation ages, the numbers of middle aged women in the US are rising, and expected to increase from 27 million to 41 million by the year 2010 (Beckles, French, Hill & McNair, 2001). Coupled with rising prevalence rates of obesity and diabetes (Fischman, 2001; CDC 2005b), larger numbers of women with diabetes will enter menopause in the next decade and it is increasingly important that the relevant health needs of these women at menopause be clearly discerned and elucidated.

The Intersection of Diabetes and Menopause

Overview

Scientific and medical advances in diabetes management have improved the health of diabetic women, but such care is rarely gender specific. Women are a distinctive subset of the diabetic population, disproportionately affected by this disease and its complications. Yet, with the exception of pregnancy, relatively little is known about the unique interplay of diabetes with female reproductive function. Previous research has primarily addressed issues of menstrual cycle function and glucose control and exclusively addressed these issues in type 1 diabetic women.

The interaction between diabetes and menopause has been examined primarily to quantify the health risks associated with estrogen decline, and usually investigated in the context of hormone therapy use. From this literature, estrogen loss has been associated with adverse changes in central adiposity and glucose and insulin metabolism that increase diabetes risk and have the potential to worsen glycemic function in women with

diabetes. Subsequent HT use appears to prevent diabetes incidence in healthy women and significantly improve glycemic control in those with diabetes. To date, few investigations have considered the interaction of diabetes and menopause age or symptoms. With the exception of one study, all have been conducted in Mexican or Central American women.

A retrospective study examined age at menopause in type 1 diabetic women, noting an earlier age at menopause by 6 years for women with DM compared to their sisters and healthy controls (Dorman et al., 2001). Two cross-sectional studies of age- and BMI-matched type 2 diabetic and healthy Mexican women evaluated age at menopause. One investigation documented an earlier age of menopause for those with diabetes (Malacara et al., 1997), while the other observed no differences in age of menopause among the women (Lopez-Lopez et al., 1999). Two studies examined the menopause experience of women with type 2 DM but evaluated few symptoms. In a community sample of age and BMI-matched Mexican women, Malacara and colleagues (1997) noted increased reporting of depressive symptoms and the 'empty nest syndrome' but similar levels of anxiety and sleep alterations in women with diabetes compared to healthy controls. The study used several separate measurement tools, only one of which was psychometrically sound, but primarily queried the women regarding psychological symptoms. Of note, the most frequently reported symptoms associated with menopause, hot flashes, were not assessed. In their study of age of menopause in women with diabetes, Lopez-Lopez and colleagues (1999) measured hot flashes symptom prevalence only, noting no differences between the healthy and diabetic women of similar BMI. A recent study examined menopause symptoms in Ecuadorian women with the metabolic syndrome (Chedraui et al., 2007), observing increased psychological and physical symptoms but similar sexual and vasomotor symptoms in the women with metabolic syndrome compared to healthy peers. Most of the women with the metabolic syndrome (84%) did not demonstrate hyperglycemia, making it difficult to determine if these findings were related to the other features of the metabolic syndrome (hypertension, dyslipidemia, central adiposity).

The overlay of diabetes may affect the process and progress of the menopause transition in women with diabetes, but virtually nothing is known as to how menopause

symptoms manifest themselves in women with diabetes. With menopause, midlife diabetic women are likely to experience symptoms but it is difficult to distinguish if these symptoms are menopause-related or diabetes-related, precluding specific management strategies. Treatment of symptoms may be misdirected at either the diabetes or the menopause and may not be successful or potentially unsafe.

There is a pressing need to examine the unique needs of diabetic women in the menopause transition and define appropriate health management strategies. Since the release of the WHI data documenting the adverse effects of HT, women and health care professionals have been stymied as to how to effectively manage menopause symptoms. In national survey data, women ranked relief of menopause symptoms as their top concern, and providers were most disturbed with the confusing scientific and media messages regarding menopause treatment options (Singh et al., 2005). These concerns spurred the recent NIH sponsored conference to discuss the management of menopause related symptoms (Voelker, 2005).

In women with diabetes, menopause issues are often not even considered. Health care professionals have rated diabetes significantly harder to treat than other diseases such as hypertension, angina, arthritis and hyperlipidemia (Larme & Pugh, 1998) and this may influence providers to avoid menopause issues. In a recent study of health care professionals and Hispanic women with chronic illnesses (diabetes, CVD), providers believed the menopause was overshadowed by the medical problems and viewed it as an unimportant health issue (Esposito, 2005). But beyond getting health care providers to acknowledge the concerns of diabetic women, there is literally no scientific understanding of what may be most problematic for these women during this time.

From personal clinical practice, diabetic women have reported difficulty controlling their glucose levels during the menopause transition despite continued rigorous attention to their diabetes self-management behaviors. In glucose logs, hot flashes have been linked to spurious rises in glucose levels. Other women have perceived hot flashes as hypoglycemia and over-treated resulting in hyperglycemia. Many have voiced increased somatic, sleep and emotional complaints during this time. From a provider perspective, there is little scientific evidence to guide clinical decision-making and clarify which symptoms are menopausal or diabetic in origin, which clinical or

situational factors influence these symptoms in diabetic women and further, which symptoms need to be treated and which can be tolerated.

The Intersection of Diabetes with Menopause Specific Symptoms

How might diabetes affect the menopause symptom experience of midlife women? This next section reviews the clinical features and symptoms of diabetes for their distinctive or overlapping characteristics with menopause. Scientific evidence demonstrates vasomotor symptoms, vaginal dryness and dyspareunia are distinctly related to estrogen loss, while other symptoms such as disturbed sleep, urinary incontinence, cognitive changes, mood alterations and somatic complaints cannot be directly attributed to the menopausal estrogen decline (NIH State of Science Panel, 2005). Primary symptoms of diabetes include hypoglycemia, hyperglycemia or symptoms from diabetic complications.

Vasomotor Symptoms. There is little evidence of the relationship of vasomotor symptom with menopause in women with diabetes. In one study of age and BMI-matched healthy and diabetic postmenopausal women, no differences in hot flash prevalence rates were observed (Lopez-Lopez et al., 1999). A large observational study of Swedish women (n = 6,917), documented higher vasomotor symptoms prevalence rates among women with chronic conditions (diabetes, CAD, hypertension)(64%) compared to healthy controls (55%) but further analysis by type of chronic illness was not conducted (Li et al., 2003).

Hot flashes may be easily misidentified as hypoglycemia by women with diabetes as the presentation of both symptoms is similar. Hot flashes are described as the sudden sensation of heat in the chest, face, arms or head and are usually accompanied by skin flushing and perspiration. Palpitations and feelings of anxiety, nausea, or chest pressure are often noted (Freedman, 2000). Hypoglycemia is characterized by symptoms related to the release of autonomic hormones to raise glucose concentrations (Zammit & Frier, 2005) and includes similar symptoms such as tachycardia, feelings of warmth, sweating, nausea, or lightheadedness (Hepburn et al., 1991). Hypoglycemia may be able to be distinguished from the menopausal hot flash as neuroglycopenic symptoms, such as difficulty concentrating, fatigue or weakness often precede the autonomic response to hypoglycemia (Gonder-Frederick, 1998; Hepburn et al., 1991).

Hot flashes typically dissipate spontaneously within 5 minutes (NAMS, 2004) whereas hypoglycemic symptoms will progress if untreated. Mild hypoglycemia symptoms are usually alleviated quickly by drinking or eating glucose or carbohydrate containing foods but more severe symptoms may require glucagon injection. If symptoms remain untreated, serious consequences can occur such as loss of consciousness, coma and even death (ADA Workgroup on Hypoglycemia, 2005) that would clearly indicate a hot flash had not occurred.

Women with diabetes may have opportunity to assess a capillary blood glucose level to differentiate the hot flash from hypoglycemia, but depending on the severity of the symptoms and the women's previous idiosyncratic history with hypoglycemia, treatment may be initiated for the purposes of safety. The glycemic thresholds for symptoms of hypoglycemia also vary by age, gender and diabetes type making it more difficult for women to distinguish these symptoms accurately. Counter regulatory responses are spontaneously initiated at higher blood glucose levels in type 2 diabetics than those with type 1 DM, but commence at lower glucose levels in women than men (Zammit & Frier, 2005, p. 2952). With aging, the neuroglycopenic and autonomic responses often occur simultaneously (Zammit & Frier, 2005), precluding the ability to distinguish these symptoms from the hot flash.

Hot flashes may have adverse effects in women with diabetes. One of the key responses to a hot flash is a change in the thermoregulatory control of blood flow to the skin. During the menopausal hot flash, sympathetic responses activate peripheral vasodilation in cutaneous vessels to dissipate heat (Freedman, 2000). Charkoudian (2003) observed women with type 2 DM had less cutaneous vasodilation in response to non-painful local warming compared to age-matched healthy controls, suggesting women with DM may not be able to sufficiently dissipate the heat generated with a hot flash, increasing the risk for heat stress. Charkoudian (2003) hypothesized this reduced vasodilatory response is most likely related to cutaneous microvascular changes from the diabetes but further study is needed.

While the precise cause of hot flashes remains unknown, several neuroendocrine hypothalamic mechanisms are hypothesized to be responsible. Freedman (2000) has proposed a narrowing in the thermoneutral zone triggers a central autonomic reaction that

results in the hot flash and includes the release of cortisol, norepinephrine (NE) and other mineralocorticoids (Kronenberg, 1990). This response has potential to be detrimental for women with DM, as both NE and cortisol stimulate other physiologic mechanisms to increase glucose availability. This could suggest frequent hot flashes potentially affect glycemic control, but to date this hypothesis has not been tested.

Another model proposes hot flashes may result from transient declines in central nervous system glucose transport (Dormire & Reame, 2003). In ovarectomized rats, hypoestrogenemia was associated with decreased stimulation of glucose transporter 1 and diminished glucose availability in neuroendothelial cells (Shi & Simpkins, 1997). In animal studies, hot flashes were induced with reductions in blood glucose levels and conversely hot flashes were prevented with elevations in glucose levels (Bishop & Simpkins, 1992; Simpkins, Katovich & Millard, 1990).

In a tightly controlled experimental study, Dormire and Reame (2003) evaluated 10 healthy postmenopausal women taking HT. The participants stopped HT for 7-10 days and when hot flashes recurred, they were admitted for a 30 hour protocol that involved skin conductance monitoring, frequent blood sampling and two experimental periods when blood glucose levels were manipulated to compare hot flash frequency during the fasting and postprandial state (Dormire & Reame, 2003).

Hot flash frequency varied with blood glucose concentrations. The incidence of hot flashes was significantly higher in the fasting state (FPG < 110 mg/dl) compared to the experimentally induced postprandial state (glucose 130-140 mg/dl) suggesting glucose concentrations in the fasting state may induce hot flashes in healthy women (Dormire & Reame, 2003). This data may have implications for women with diabetes, as rigorous compliance with recommended fasting and preprandial glucose levels (<90-130 mg/dl) may affect hot flash incidence with the menopause.

Women with DM might have increased rates of vasomotor symptoms, as several of the clinical and sociodemographic factors associates with hot flash prevalence rates are common to women with diabetes: high BMI, low socioeconomic and educational levels, African American or Hispanic ethnicity (CDC, 2008a; Rimmer et al., 2002). Anxiety is another factor strongly associated with hot flashes (Freeman et al., 2005) and also common in women with diabetes (Grigsby et al., 2002).

While hot flashes are generally associated with the menopausal estrogen decline, estrogen concentrations do not correlate with hot flash occurrence (Freedman, 2005a), but elevated FSH levels have demonstrated such a relationship (Randolph et al., 2004). Few studies have measured reproductive hormone levels in diabetic women with menopause and both noted serum and urinary FSH concentrations were significantly lower in the women with diabetes (Quinn et al., 1981; Randolph et al., 2004). This might suggest women with diabetes are less likely to experience hot flashes with the menopause. However, increased BMI, a characteristic of women with DM, has also been associated with *both* decreased FSH concentrations and increased reporting of vasomotor symptoms (Gold et al., 2004) precluding any clear conclusion regarding these relationships in women with diabetes.

Vaginal Symptoms. Atrophic changes in the genital tract occur with menopause and are associated with several symptoms including vaginal dryness, irritation, itching, infection, and dyspareunia (NAMS, 2000). Diabetic women may be more likely to report these symptoms due to diabetes-related impaired leukocyte activity (Rosenn & Miodovnik, 2005) coupled with the increased urinary and vaginal glucose levels that also predicate vaginal irritation and infection (Star, 1995; Williams, Knight, King & Harris, 1975). Microvascular changes with poorly controlled diabetes may also affect vaginal tissue health but to date, no studies have investigated this diabetic complication (Poirer-Solomon, 2002a). Again, characteristics of women with diabetes are also covariates associated with increased prevalence of vaginal symptoms in healthy women and include African American or Hispanic ethnicity (CDC, 2008), and lower socioeconomic and educational levels (Rimmer et al., 2002) and high BMI (Pastore et al., 2004)

Two menopause investigations have documented symptoms of vaginal dryness or irritation in women with diabetes at menopause. In a large cross-sectional study of postmenopausal Swedish women, Li and colleagues (2003) observed non-significantly higher prevalence rates of vaginal dryness in women with chronic disease (diabetes, CAD, hypertension) (36%) compared to healthy women (31%) but this data included women using HT. Controlling for obesity, postmenopausal women with diabetes in the WHI study were 3.2 times more likely to report symptoms of severe vaginal irritation or itching compared to healthy women (Pastore et al., 2004).

Depressed Mood. How might diabetes affect mood symptoms in women experiencing the menopause? Depression is a common co-morbid condition with diabetes with women more often affected (Anderson et al., 2001; Lustman et al., 2000), but to date, no studies have specifically examined the unique needs of middle-aged women with diabetes during menopause (Zauszniewski, McDonald, Krafcik, & Chung, 2002). In most studies of depression in persons with DM, the mean age of participants is over 55 unless the sample was specifically younger aged adults with type 1 diabetes (<30 years), and no investigations have evaluated menopause as a covariate (Anderson et al., 2001; Nichols & Brown, 2003; Pouwer, et al., 2003; Katon, et al., 2004). The lone depression study that specifically examined postmenopausal type 2 diabetic women was a clinical trial testing the effects of paroxetine on pre-existing depressive symptoms (Paile-Hyvarinen, Wahlbeck, & Eriksson, 2003).

Studies of healthy women demonstrate the menopause does not increase a women's risk for depression but rather suggest that women with histories of previous mood disorders and stressful life circumstances are more likely to develop depression during midlife (Avis et al., 1994; Hardy & Kuh, 2002; Harlow et al., 2003; Dennerstein et al., 2004; Woods et al., 2002; Kuh et al., 2003). It is possible that the significant socioeconomic inequalities (MMWR, 2002), and overwhelming responsibilities midlife women face in managing the demands of their families as well as their diabetes (Keyserling et al., 2002; Samuel-Hodge et al., 2000; Edwards, Skelly, Cagle & Appel, 2004), are stressors that may increase the risk for mood symptoms during the menopause in diabetic women. Characteristics associated with increased depressed mood symptoms during the menopause transition in healthy women such as increased BMI (Malacara et al., 2002) and African American and Hispanic ethnicity (Bromberger et al., 2003) are similar characteristics of diabetic women and may confound the ability to clearly distinguish the effect of diabetes on such symptoms.

In the only study that evaluated menopause symptoms between BMI- and age-matched diabetic and non-diabetic Hispanic women (Malacara et al., 1997), women with diabetes had higher depression (Hamilton Rating Scale) and empty nest syndrome scores (an itemized scale created by the researchers) compared to healthy women. While similar levels of anxiety were observed between the women, the instrument was likely not stable

as the researchers created their own tool by adding scores for symptoms of breathlessness, palpitations, tremors, agitation and fear of madness to determine this parameter.

Disturbed sleep. From longitudinal data of healthy women, sleep disturbances appear to increase across the menopause transition (Kravitz et al., 2003; Kuh et al., 1997; Dennerstein et al., 2000) while cross-sectional studies demonstrate mixed findings (Lukacs et al., 2004; Dancey et al., 2001). There is, however, little evidence of the prevalence or pattern of sleep disturbances in diabetic women during the menopause transition. In a sleep study of diabetic Indian men (n = 151) and women (n = 33), menstrual status was not associated with the presence of sleep disturbances in the women subjects (Sridhar & Madhu, 1994). However, the researchers did not provide specific details as to the age ranges of the diabetic women subjects, how reproductive status was determined, or how many women were pre-, peri- or postmenopause (Sridhar & Madhu, 1994). In the only study to compare age and BMI-matched postmenopausal women with and without diabetes, Malacara and colleagues (1997) observed no differences in self-reported sleep scores among the women.

Diabetes may have an effect on symptoms of altered sleep in women during menopause. Sleep disorders are described in persons with diabetes, particularly difficulty initiating and maintaining sleep and demonstrated a relationship to disease severity (Lamond, Tiggeman & Dawson, 2000). Although midlife women were not specifically studied, cross-sectional investigations demonstrate diabetic complications such as neuropathies and restless leg syndrome negatively affect the sleep quality in women and men (Lopes et al., 2005; Lamond et al, 2000; Sridhar & Madhu, 1994).

Again, characteristics of women with diabetes, such as high BMI, a known risk factor for sleep disturbances (Dancey et al., 2001; Ford et al., 2005; Shaver & Zenk, 2000) could accelerate or intensify sleep symptoms when associated with menopause. Lastly, a better understanding of sleep disturbances during the menopause transition in diabetic women is important as cross-sectional studies have demonstrated sleep disordered breathing, sleep deprivation and obstructive sleep apnea impair glucose regulation and increase insulin resistance (Boethel, 2003; Gottlieb et al., 2005; Ip et al.,

2002). This suggests sleep disturbances at menopause have the potential to adversely affect glucose control for women with DM and may require clinical management.

Urinary Incontinence. Many midlife women report urinary incontinence (UI), but longitudinal and cross-sectional studies do not establish a causal relationship of the menopause with UI. Diabetes is a well-documented risk factor for urinary incontinence (Sampselle et al., 2002; Brown et al., 2006; Danforth et al., 2005; Waejten et al., 2007; Pastore et al., 2004) and women with diabetes at menopause may be more likely to report urinary symptoms.

Features of women with DM may affect the prevalence rates of urinary symptoms with the menopause. High BMI, a common characteristic of women with type 2 DM is a known risk factor for UI (Sampselle et al., 2002; Jackson et al., 2005). Glycemic control may also affect UI symptom prevalence as higher rates of urinary incontinence were observed in diabetic women with HgbA1c values > 7.5% than those women with good glycemic control (HgbA1c $\leq$ 7.5%)(Jackson et al., 2005). Further, data from the Diabetes Prevention Project (DPP) demonstrated that lifestyle management strategies (diet, exercise) to improve glycemic control were accompanied by decreased prevalence rates of urinary incontinence (Brown et al., 2006). Lastly, microvascular destruction from chronic hyperglycemia can damage innervation of the bladder and urethral sphincter and the detrusor muscle contributing to urinary retention, overflow incontinence, and bacterial colonization that can predicate increased both UI symptoms and infection risk in diabetic women (Brown et al., 2005).

Changes in Cognition. Complaints of forgetfulness, trouble concentrating and difficulty thinking have been reported by midlife women and hypothesized as related to the menopausal estrogen decline (Love, 2003), but a clear relationship between symptoms of cognitive disturbance with the menopause transition has not been established (Nelson et al., 2005). To date, no studies have evaluated the effect of diabetes on cognitive symptoms with the menopause transition.

In general, relatively little is known about the effects of diabetes on cognition in women. In a review of the effects of type 2 DM on cognition in middle aged and older adults, Coker and Shumaker (2003) identified a total of 32 studies, of which only two investigations focused entirely on women. Those two studies included only older

postmenopausal women (mean ages of 72 or 74 years) and one investigation primarily evaluated osteoporosis outcomes (Gregg et al., 2000). Both studies reported diabetic women had lower levels of cognitive function compared to non-diabetics (Gregg et al., 2000; Grundstein, Chen, Wilson & Manson, 2001), but each tested different dimensions of cognition precluding the ability to link any one aspect of cognitive impairment with diabetes in women.

Review papers indicate middle-aged adults with diabetes are less likely to suffer from impaired cognition. Coker and Shumaker (2003) observed that most (67%) studies of older adults reported a positive association between diabetes and cognitive impairment, while the few small case control studies of middle-aged adults reported no consistent associations of diabetes with cognitive performance. In their review of learning and memory functioning in middle-aged and older adults with type 1 and type 2 DM, Ryan and Geckle (2000) observed a similar pattern; impaired performance was limited to the older (over age 60) diabetic participants. However, few of the reviewed studies had sufficient female participants to report findings by gender, prohibiting a clear understanding of the effect of diabetes on cognition in midlife women.

While virtually nothing is known about the prevalence of cognitive symptoms in diabetic women during the menopause transition, features of diabetes (hypoglycemia, hyperglycemia) have been associated with cognitive impairment and may affect the risk for such symptoms in women with menopause. Good glycemic control has been positively associated with cognitive performance (Kumari & Marmot, 2005), but tight control increases the risk of hypoglycemia and ultimately may affect cognitive function. Frequent or repeated episodes of hypoglycemia can cause damage to the cortical neurons and cumulatively result in permanent cognitive impairments (Zammitt & Frier, 2005).

Chronically elevated glucose levels also have adverse effects on neurological functions. Hyperglycemia can trigger oxidative and inflammatory processes that damage cerebral vascular and endothelial tissues and ultimately impair cognitive processes (Ryan & Geckle, 2000; Gregg & Brown, 2003). While specific mechanisms are yet to be elucidated, hyperinsulinemia has been associated with cognitive impairment and increased dementia risk in persons with and without diabetes (Ryan & Geckle, 2000; Gregg & Brown, 2003; Lushinger, Tang, Shea & Mayeux, 2004). A recent clinical trial

has provided evidence that treatment with oral insulin sensitizing medication in type 2 diabetes, not only improves glycemic control but working memory as well (Ryan et al., 2006) suggesting tight metabolic control of glucose and insulin benefits cognitive functioning. But in this study as with the others, less than half of the subjects were women and the mean age of participants was age 60, and very little continues to be known about middle-aged women with diabetes.

Somatic symptoms. How might diabetes affect somatic symptoms in women experiencing the menopause? There are no studies that systematically assess somatic symptoms in midlife women with diabetes. High BMI and low socioeconomic status, common characteristics of women with diabetes, were factors associated with increased reporting of somatic complaints among the pre- and early perimenopausal women in the SWAN study (Gold et al., 2000) and suggests diabetic women may report more of these symptoms with the menopause transition. It is also possible that women with poorly controlled DM or those with diabetic complications such as neuropathy may report increased somatic symptoms during this time as the manifestations of hyperglycemia and neuropathy mimic many somatic complaints such as fatigue, palpitations, headache, backache, numbness or tingling (Vinik et al., 2005).

One unusual symptom associated with both menopause and DM is burning mouth syndrome (BMS). This syndrome is described as a burning or painful sensation in the oral cavity accompanied by normal mucosa (Rouseau & Gottlieb, 2004). BMS has been reported by 5-19% of women attending menopause clinics (Forman & Settle, 1990) and 90% of all patients with BMS are postmenopausal (Rousseau & Gottlieb, 2004). This syndrome has been linked to ACE inhibitor use, vitamin B and zinc deficiencies but also type 2 DM. In studies of burning mouth syndrome, 10-39% of the postmenopausal women with this complaint have diabetes or abnormal glucose tolerance tests (Forman & Settle, 1990). While BMS may also be a manifestation of diabetic neuropathy, most women experiencing this symptom are postmenopausal suggesting a relationship of this symptom to estrogen decline, but no studies have specifically evaluated this phenomenon.

Sexual Dysfunction. Dyspareunia associated with vaginal atrophy is distinctly related to the menopausal estrogen decline but other changes in sexuality such as

decreased libido, impaired body image, or decreased sexual response have not been consistently associated with the menopause transition (Dennerstein et al., 2005; Alexander et al., 2004; Nelson et al., 2005). How might concomitant diabetes affect symptoms of sexual dysfunction at menopause? In the only study of age- and BMI-matched postmenopausal diabetic and non-diabetic women, no differences were noted in attitudes toward sexuality among the women but there was no detailed assessment of other parameters of sexual function (Malacara et al., 1997).

In the diabetes literature, hyperglycemia-related fatigue, vascular insufficiency, depressed mood and both peripheral and autonomic neuropathy have been hypothesized to adversely affect sexual function in adults with diabetes but most studies have tested these hypotheses in men (Basson, Rucker, Laird & Conroy, 2001; Doruk et al., 2005). The limited studies of diabetic women have primarily addressed sexual dysfunction in younger type 1 diabetic women. Only two investigations enrolled female subjects with both type 1 and type 2 DM (Basson et al., 2001; Doruk et al., 2005), but none have exclusively examined sexuality at menopause in women with diabetes.

In a study of age-matched women with type 1 diabetes and healthy controls (mean age 35 years), measuring four dimensions of sexual function ((libido, vaginal lubrication, orgasm, dyspareunia), despite increased reports of sexual dysfunction from the diabetic women a significant difference was only noted for decreased lubrication (Enzlin et al., 2002). Characteristics of the women (age, BMI) or features of diabetes (HgbA1c values, duration of diabetes, diabetic complications) were not associated with reports of sexual dysfunction, although women with more than one diabetic complication reported more sexual dysfunction. Symptoms of depressed mood were similar among the healthy and diabetic women and predictive of sexual dysfunction in both groups (Enzlin et al., 2002).

Salonia et al (2006) examined age- and BMI-matched women with type 1 DM and healthy controls in both phases of the menstrual cycle, using the female sexual function index (FSFI) and serum hormone measures. No differences in hormone concentrations or sexual function measures were observed between the groups during the follicular phase. In the luteal phase, women with DM had higher testosterone and lower E_2 and progesterone concentrations than their healthy peers. The diabetic cohort also reported diminished responses for arousal, lubrication, and orgasm with increased

dyspareunia during this part of the cycle suggesting the hormonal milieu may affect sexual function. Depression was measured in both the follicular and luteal phase as a covariate but scores were similar among the women and did not account for the findings. HgbA1c was measured but not associated with sexual dysfunction (Salonia et al., 2006).

In the two studies that included type 1 and type 2 diabetic women, conflicting findings are reported. Doruk and colleagues (2005) evaluated overall sexual function using the composite score of the FSFI in three groups of women: type 1 and type 2 diabetics and healthy women aged 22 to 60 years. Prevalence rates for sexual dysfunction were higher in type 1 diabetic women (71%) compared to type 2 diabetics (42%) and healthy women (37%). Diabetic complications and HgbA1c values were not obtained precluding the ability to evaluate the effect of diabetes on sexual function. The researchers reported menopause status predicted sexual dysfunction in the healthy women but not the diabetic subjects, although how menopause was determined or if the women were using HT was not documented.

Basson and colleagues (2001) surveyed type 1 and type 2 diabetic and healthy women (aged 20-87 years) using items from previous validated questionnaires to assess sexual satisfaction, desire, vaginal lubrication, dyspareunia, arousal and orgasm. Additional questions evaluated diabetic complications but data on glucose control was not obtained. Sexual desire, orgasm, arousal and sexual satisfaction were similar among all three groups. Prevalence rates for 'difficulty with vaginal lubrication' were higher in type 2 DM women (47%) compared to type 1 diabetics (40%) and healthy controls (34%). Dyspareunia was also more prevalent among women with type 2 DM (42%) than type 1 diabetics (31%) and healthy women (26%)(Basson et al., 2001). Similar levels of depressed mood were noted among all subject groups, but less women with type 2 DM were using HT compared to the other subjects and this may have affected the findings.

No relationship between sexual function and diabetes complications was observed. Of note, the type 1 diabetic women reported concerns about the risk of hypoglycemia with sexual activity (Basson et al., 2001). An effect of menopause on sexual function in either the diabetic or healthy women was not reported.

These studies suggest aspects of sexual dysfunction, particularly lubrication and dyspareunia may be more prevalent in women with type 1 or type 2 DM but an effect of

menopause was either not assessed or well controlled for. Features of diabetes (glycemic control, incidence of complications) were not associated with sexual function, but not measured in all investigations. Studies either addressed sexual function in younger age type diabetics or included subjects from a wide age range; none specifically addressed sexual function in midlife women, precluding the ability to confirm an effect of diabetes on sexual function in women during the menopause transition.

Summary

While in the past decade, menopause has been the subject of much investigation, most of this knowledge is derived from the experience of Caucasian Euro-American healthy women and relatively little is known about the menopause symptom experience of women with diabetes. The major prospective clinical trials and observational studies of menopause the past decade suffered from the 'healthy women' bias, having excluded women with chronic illness. In the few menopause studies that included small numbers of women with chronic illness such as diabetes, the women were grouped together precluding clear identification of the impact of the specific illness on the menopause symptoms (Li et al., 2003; Mannoai et al., 2004). Further, clinical characteristics of the diabetes that have potential to affect menopause symptoms such as glycemic control, or presence of diabetic complications were seldom measured or considered

Diabetes may adversely affect menopause symptoms. Symptoms of vaginal dryness, inflammation, infection and urinary incontinence already associated with diabetes may accelerate during the menopausal estrogen decline. Diabetes may magnify the sleep disturbances reported at menopause especially those experiencing diabetic complications such as neuropathies (Lamond et al., 2000; Lopes et al., 2005). Other symptoms related to diabetes mimic symptoms related to menopause. Treatment may be misdirected at either the diabetes or the menopause and not be successful or potentially unsafe. Vasomotor symptoms, in particular, mimic hypoglycemic symptoms and can be easily misinterpreted, subsequently mistreated and result in hyperglycemia, complicating diabetes care. Cognitive changes may be mistaken for menopause symptoms when they are actually diabetes-related and subsequently inappropriately treated.

Clinical characteristics of diabetes (glycemic control, presence of diabetic complications) may affect menopause symptomatology but have yet to be

comprehensively investigated. Other unique features of diabetic women such the significant socioeconomic inequalities (MMWR, 2002) and overwhelming responsibilities these midlife women face in managing their families and diabetes (Keyserling et al., 2002; Samuel-Hodge et al., 2000; Edwards et al., 2004), are factors not well addressed in the literature in the context of both menopause and diabetes. To date, there is virtually no scientific evidence to guide clinical decision-making and clarify which symptoms are menopausal or diabetic in origin, which diabetic women are most likely to experience symptoms and further, which symptoms need to be treated and which can be tolerated. Systematic study is needed to obtain accurate information regarding the menopause symptom experience of women with type 2 diabetes to guide safe and effective health management strategies for these women.

Theoretical Framework

Overview

The Theory of Unpleasant Symptoms (Lenz, Pugh, Milligan, Gift & Suppe, 1997) provides a useful framework to conceptualize the interplay of menopause symptoms in women with diabetes (Figure 2.1). A middle range theory, the Theory of Unpleasant Symptoms (TOUS) was developed in 1995 by nurse researchers to improve the "understanding of the symptom experience in various contexts" (Lenz & Pugh, 2003, p.69) and further refined in 1997 to more accurately represent the complex interactive nature of the symptom experience (Lenz et al., 1997, p. 14). The TOUS provides an organizing schema for the interplay of the many aspects of the symptom experience and has been used in nursing research to measure, describe and explicate symptom patterns in a variety of health conditions such as COPD (Reishtein, 2005; Jablonski, Gift & Cook, 2008), mitral valve prolapse (Scordo, 2005), pregnancy (O'Brien, Evans & White-McDonald, 2002), renal failure (McCann & Boore, 2000), Alzheimer's dementia (Hutchinson & Wilson, 1998) and cancer (Barsevick, Dudley & Beck, 2006). In clinical practice, nursing interventions for symptom management have also been derived and tested using the TOUS.

The theory uniquely allows for the presence of multiple symptoms, rather than one symptom in isolation and contends that symptoms may interact with one another in a

multiplicative manner (Lenz et al., 1997). The theory has three major concepts: the symptoms, the influencing factors that affect symptoms, and the consequences of the symptom experience. Symptoms are the central concept in the theory (Lenz & Pugh, 2003) and are defined as "perceived indicators of change in normal functioning as experienced by patients" (Rhodes & Watson, 1987, p. 242). This definition assumes the individual is aware of the change and this perception is subjectively based. As such, symptoms are measured subjectively, and whether objective symptom measures can be explained by the theory has not yet been tested (Lenz & Pugh, 2003).

In the TOUS (Lenz et al., 1997), symptoms can be conceptualized alone or in combination with other symptoms (Figure 2.1). Symptoms have four dimensions: intensity, timing, distress and quality. *Intensity* describes the strength or the severity of the symptoms; *timing* reflects the duration of the symptom or the frequency at which it occurs. *Distress* is the degree of discomfort or bothersome nature of the symptom and *quality* refers to descriptors the individual uses to characterize the symptom (Lenz et al., 1997). Intensity and frequency have been the dimensions of symptoms most often evaluated. Distress has also been consistently measured as it is thought to represent individual's interpretation of the symptom experience and is often the reason for seeking health care services for symptom relief (Lenz et al., 1997).

Antecedent factors are categorized as physiological, psychological or situational variables that influence the occurrence, intensity, timing, distress and quality of symptoms (Lenz et al., 1997). These three categories interact with symptoms and with one another and further, aspects within each category may be interrelated to one another (Lenz et al., 1997). In the TOUS, moderating or mediating interaction effects are possible between symptoms and more than one antecedent variable (Figure 1.1).

Physiologic factors include but are not limited to disease states, fluctuations in hormone or energy levels, genetic predispositions, or age. *Psychological factors* are conceptualized to include affective and cognitive components, including mental state, level of depression or anxiety, or affective reaction to the illness as well as the person's knowledge of the symptoms. *Situational variables* refer to the relevant social and physical environmental factors that may affect the person's symptom experience. Social factors can include ethnicity, socioeconomic status, marital status, social support, and

lifestyle behaviors such as diet or exercise. Physical environmental factors include temperature, humidity, noise levels or air pollution as they relate to the phenomenon of study (Lenz et al., 1997).

The last component of the TOUS is performance, representing the consequences of the symptom experience. Performance is considered an outcome and has been broadly conceptualized to include functional (physical activity levels, social or role performance) and cognitive (ability to concentrate, problem solving) skills. In the updated TOUS model (Lenz et al., 1997), performance has a potential reciprocal relationship to the symptom experience. For example, the symptom of pain may decrease physical activity, which in turn may increase pain.

The TOUS has provided a guiding framework to organize findings or design interventions in several nursing investigations and has demonstrated clinical usefulness to inform nursing science. The multivariate assessment of symptoms and their relevant influencing factors within the context of biopsychosocial paradigm in the TOUS is consistent with the tenets of nursing science and is the theory's major strength. Described by the authors as a 'work in progress' (Lenz et al., 1997, p. 14), opportunities for additional conceptual improvements have been identified. The symptoms and the antecedent influencing factors have been the most rigorously studied, but most research has focused on the severity and distress components of symptoms, whereas, the time dimension has been less empirically evaluated (Gift, Stommel, Jablonski & Given, 2003). Hutchinson and Wilson (1998) utilized the TOUS to investigate objective signs with subjective symptoms for the first time and this is an area for further testing of the theory's applicability. Lastly, Lenz and Pugh (2003) advise the performance component of the model is more complex than currently conceptualized and the original emphasis on functional and cognitive outcomes while pragmatic may not be broad enough. Critics suggested a more inclusive measure such as quality of life may be useful, but this needs to "be explored conceptually and empirically" (Lenz & Pugh, 2003, p.89).

Menopause Symptoms in Women with Diabetes

How might the TOUS guide the study of the menopause symptom experience of women with diabetes? As the phenomenon of interest is the interplay between diabetes (a physiologic disease state) with menopause (a natural physiologic experience) and the

resulting pattern of symptoms, the TOUS provides a schema to integrate the core concepts in a logically congruent fashion. The central component of the TOUS, symptoms, is the primary focus of this proposed research. The TOUS uniquely allows for the presence of multiple symptoms, and accounts for the possible interaction of these symptoms with one another in a multiplicative manner (Lenz et al., 1997). This has been demonstrated in the review of the menopause literature; multiple symptoms are reported during the menopause transition in healthy women and some of these symptoms have been documented to affect other menopause symptoms in longitudinal study. For example, in prospective studies complaints of sleep disturbances at menopause have been related to vasomotor and mood symptoms (Kravitz et al., 2003; Hollander et al., 2001) and symptoms of sexual dysfunction with the menopause transition have been related to symptoms of depressed mood (Gracia et al., 2004; Avis et al., 2000).

The TOUS accounts for antecedent factors that affect symptoms presentation, including physiological, psychological and situational variables. Numerous factors have been demonstrated to affect the primary menopause symptoms in healthy women including BMI, smoking behavior, physical activity, marital status, socioeconomic status, education levels, and race/ethnicity which can be operationalized within the TOUS. More importantly, the TOUS enables the conceptualization of diabetes and its clinical features as important antecedent factors that may affect the menopause symptom experience. While not the focus of this investigation, the theory also provides opportunity to examine the reciprocal influence of symptoms on an individual's physiological, psychological or situational status (Lenz et al., 1997).

The TOUS permits the examination of the complex interactions that may occur between physiological, psychological and situational factors which together influence menopause symptoms in women with diabetes. The theoretical framework is broad enough to be inclusive, but detailed enough to permit specificity. Previous nursing investigations demonstrate its adaptability to pursue a variety of research questions using either specific components of the framework or the entire model. The TOUS provides a suitable framework to begin to describe the menopause symptom experience in diabetic women and determine the relevant antecedent factors that affect these symptoms. Drawing from the literature of healthy women and the sparse data of women with

diabetes, Figure 2.2 demonstrates delimited use of the framework to operationalize the research questions in this study.

Conclusions

Diabetes is a major health concern that disproportionately affects women. In the midlife years, the menopause is a sentinel transition characterized by physiological, psychological and social changes that can affect health status. As individual phenomenon, both diabetes and menopause has been the subject of many investigations from multiple theoretical perspectives but little inquiry has examined the symptom experience of women with diabetes during the menopause transition. This paper has presented an overview of the menopause transition in healthy women including the physiological dynamics, sociocultural responses and health risks associated with this period in women's lives. Symptoms associated with menopause were thoroughly reviewed for prevalence patterns across the stages of reproductive aging, the factors likely to affect these symptoms and evidence of an empirical relationship to menopause.

The unique features of women with diabetes were detailed including the relevant physiological and sociocultural characteristics of these women as they may affect overall health status. As only one study has examined menopause symptoms in women with diabetes and virtually nothing is known about how menopause symptoms manifest themselves in the context of diabetes, the last section of this paper addressed the potential interplay of diabetes on symptoms of menopause as a premise for further investigation. Lastly, a model for understanding the intersectionality of diabetes and menopause in the context of the symptom experience was proposed using the theory of unpleasant symptoms (Lenz et al., 1997).

Figure 2.1 Theory of Unpleasant Symptoms

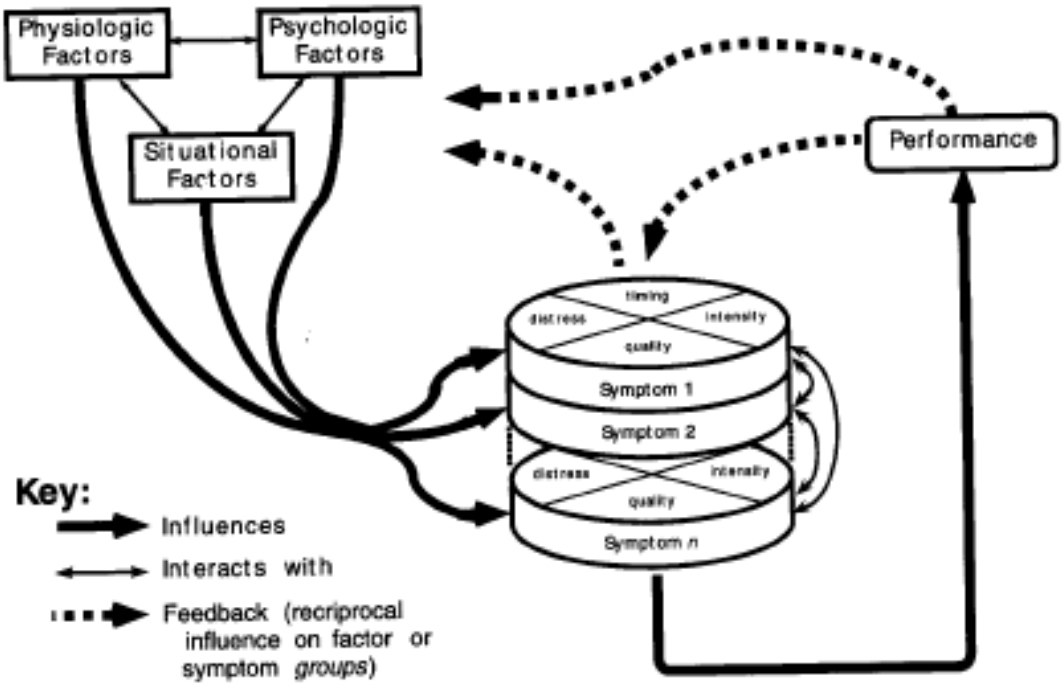
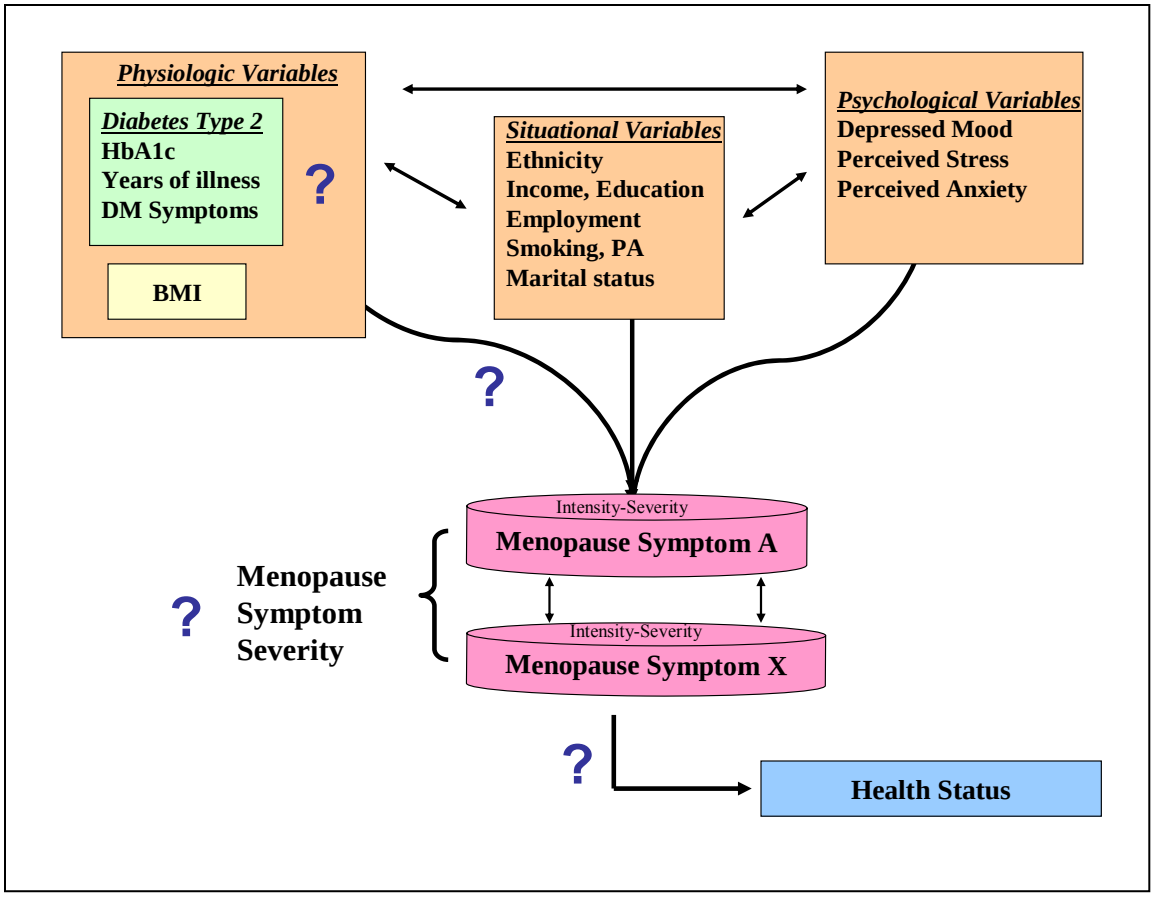


Fig 2. Updated version of the middle-range theory of unpleasant symptoms.

Lenz, E. R., Pugh, L. C., Milligan, R. A., Gift, A. G. & Suppe, F.. (1997). The middle- ranges theory of unpleasant symptoms: An update. *Advances in Nursing Science 19*(3), 14-27.

Figure 2.2 Theory of Unpleasant Symptoms for SWIM study



BMI, Body Mass Index; DM, Diabetes Mellitus, HbA1c, Hemoglobin A1c levels; PA, Physical Activity; SWIM, Study of Women veterans in Menopause.

Table 2.1 Prevalence Patterns of Menopause Symptoms

Symptom Category	Author	Late Reproductive: Premenopause	Early Perimenopause	Late Perimenopause	Postmenopause
Vasomotor: Hot Flashes, Night Sweats	SWAN (Gold et al 2000)	19.4%	36.9%	56.8%	48.8%
	MWMHP Dennerstein et al (2000)	10%	15%	42%	42%
	Malacara et al (2002)	4.0-48.4%	NA	NA	32.1-72.8%
	Penn Ovarian Aging Freeman et al (2005)	37%	48%	63%	79%
Vaginal Dryness	MWMHP Dennerstein et al (2000)	NA	4%	21%	47%
	Malacara et al (2002)	1.7-18.4%	NA	NA	23.6-41.4%
	SWAN (Gold et al 2000)	7.1%	12.9%	18.2%	21.2%
Disturbed Sleep	SWAN Kravitz et al (2003)	31.4%	39.6%	45.4%	43.2%
	MWMHP Dennerstein et al (2000)	31%	32%	38%	38-43%

Symptom Category	Author	Late Reproductive: Premenopause	Early Perimenopause	Late Perimenopause	Postmenopause
Cognitive Changes	SWAN: forgetfulness (Gold et al 2000)	31.2%	44.0%	44.8%	42.0%
Mood Disturbance	*General Symptoms* Massachusetts Women's Health Study (Avis et al., 1994)	29.1%	NA	28.1%	33.8%
	SWAN: irritability, blue Bromberger et al (2001)	20.9%	NA	28.9%	22%
	Persistent Mood Symptoms SWAN: mood change >6 days/week Bromberger et al (2003)	8.8-12%	14.3-18.4%	NA	NA
	Bosworth et al (2001) CES-D scores >10	7.2%	30.5%	37.7%	24.6%
	Freeman et al (2004) Penn Ovarian Aging CES-D scores >16	12-15%	1.4-7.8%	13.1-18.3%	1-13.8%
Urinary Incontinence	MWMHP Dennerstein et al (2000)	17%	12%	14%	14%
	SWAN (Gold et al 2000)	12.3%	20.6%	19.6%	17.7%

Symptom Category	Author	Late Reproductive: Premenopause	Early Perimenopause	Late Perimenopause	Postmenopause
Somatic Complaints	SWAN: stiff/sore (Gold et al 2000)	45.8%	57.9%	58.4%	54.8%
	MWMHP: Dennerstein et al (2000)				
	Stiff/sore	41%	47%	53%	57%
	Headache	38%	37%	36%	36%
	Backache	30%	34%	34%	37%
Sexual Function	MWMHP: Dennerstein et al (2000)		42%		88%

Table 2.2. Prevalence Patterns of Menopause Symptoms by Race/Ethnicity

Symptom Category	African American	Caucasian	Chinese	Hispanic	Japanese
Vasomotor Symptoms SWAN (N = 12,357) Gold et al (2000)	46.5%	36.6%	28.9%	43.5%	34.3%
Vaginal Dryness SWAN (N = 12,357) Gold et al (2000) WHI (N = 98,705) Pastore et al (2004) *=Asian	15% 30.8%	11% 26.3%	10% 27%*	20% 33.5%	7% 27%*
Disturbed Sleep SWAN (N = 12, 603) Kravitz et al (2003)	35.5%	40.3%	31.6%	38%	28.2%
Cognition: Forgetfulness SWAN (N = 12,357) Gold et al (2000)	43%	35%	41%	46%	33%

Symptom Category	African American	Caucasian	Chinese	Hispanic	Japanese
Somatic symptoms: stiff/sore SWAN (N = 12,357) Gold et al (2000)	55.7%	54.8%	48.2%	47.1%	50.3%
Urinary Incontinence SWAN (N = 12,357) *Past 2 weeks* Gold et al (2000)	16.7%	18.2%	11%	20.4%	12.6%
SWAN cohort (N = 3258) *Any UI in past year* Sampselle et al (2002)	49.5%	66%	50.2%	41.5%	52.9%
Sexual Function SWAN cohort (N =3302)* Avis et al (2005b)					
Desire (daily or 1x/week)	62.5%	63.5%	38.7%	62.9%	32.2%
Intercourse frequency (daily)	38.8%	29.8%	20.6%	36.2%	17.3%
Arousal (always)	70.2%	77.8%	57%	43.9%	63.1%
Emotional satisfaction (very)	54.8%	58.5%	58%	38.3%	44.9%
Physical Satisfaction (very)	65.2%	64.1%	46.3%	39.4%	41.2%
Pain (sometimes/always)	23.8%	17.2%	27.3%	28%	21.9%

Symptom Category	African American	Caucasian	Chinese	Hispanic	Japanese
Mood disturbance					
SWAN (N = 3015) Bromberger et al (2004) *Depression CES-D ≥ 16*	27.4%	22.3%	14.3%	43%	14.1%
SWAN (N = 3161)* Bromberger et al (2003) *Feeling blue ≥ 6 days*	13.5%	13.2%	5.8%	15.8%	4.7%

*pre/perimenopause only

Table 2.3. Factors Associated with Menopause Symptoms

Factor	Vasomotor Symptoms	Vaginal Dryness	Disturbed Sleep	Urinary Incontinence	Somatic Symptoms	Cognitive Decline	Mood Symptoms	Sexual Dysfunction
↑BMI	↑	+/–	↑	↑	↑	NA	↑	+/–
Smoking	↑	+/–	↑	↑	↑	↑	↑	↑
Physical Activity	+/–	↑: Physical inactivity	↑: Physical inactivity	↑: Physical inactivity	↑: Physical inactivity	↑: Physical inactivity	↑: Physical inactivity	NA
Education	↑: Lower education levels	↑: Lower education levels	+/–	+/–	NA	↑: Lower education levels	↑: Lower education levels	No relationship
Socioeconomic Status	↑: Lower incomes	↑: Lower incomes	↑: Lower incomes	↑: Lower incomes	↑: Lower incomes	↑: Lower incomes	↑: Lower incomes	NA
Diet	No relationship	NA	↑caffeine	NA	NA	NA	NA	NA
Marital status	↓ Never married, widowed or divorced	↓ Never married, widowed or divorced	No relationship	↓ Never married, widowed or divorced	No Relationship	NA	NA	Availability of partner
Stress	No relationship	NA	↑	NA	NA	NA	↑	↑
Rural Residence	↑	↑	NA	NA	NA	NA	↑	NA
ETOH	+/–	NA	NA	NA	NA	1 drink/wk improved function	NA	NA

Factor	Vasomotor Symptoms	Vaginal Dryness	Disturbed Sleep	Urinary Incontinence	Somatic Symptoms	Cognitive Decline	Mood Symptoms	Sexual Dysfunction
Health Status	NA	NA	↑ With perceived poor health	NA	NA	NA	↑ With perceived poor health	↑ With perceived poor health
Parity	NA	NA	NA	↑	NA	+/–	↑	↑
Race/Ethnicity	↑ African Americans ↑ Hispanics ↓ Asians	↑ Hispanic ↑ African Americans ↓ Asians	↑ African Americans ↑ Hispanic ↑ Caucasian	↑ Hispanic ↑ African Americans with leiomyomata	↑ African Americans **primary symptom in Japanese women	↑ Hispanic	↑ Hispanic ↓ Asians	African Americans: ↑frequency Hispanics: ↓ arousal, pleasure Chinese: ↑ pain
Other Factors that ↑ Symptoms	**Climate**: greater seasonal variation	**Diabetes**	**Vasomotor & Mood Symptoms** **Arthritis**	**Diabetes** **Childbirth factors** **Hysterectomy**		**Childhood Cognitive Abilities**	**Prior Mood Disturbance** **↓ Social Support** **Family Stress**	**Depressed Mood** **Relationship with Partner**

NA = not available

Table 2.4. Risk Factors for Type 2 Diabetes*

Age $\geq$ 45
First degree relative with diabetes
Member of a high-risk ethnic group (African American, Latino, Native American, Asian American and Pacific Islander)
Overweight status (BMI $\geq$ 25kg/m^2)
Habitual physical inactivity
Hypertension (BP $\geq$ 140/90 mmHg)
HDL cholesterol < 35 mg/dl and/or Triglyceride level $\geq$ 250mg/dl
History of gestational diabetes or having delivered a baby weighing >9 lbs
History of IFG or IGT
History of vascular disease
Clinical conditions associated with Insulin Resistance: Polycystic ovarian syndrome or acanthosis nigricans

*American Diabetes Association, 2008.

Table 2.5. Diabetes Effects: Reproductive Function

	Type 1 Diabetes	**Type 2 Diabetes**
Menarche	Delayed by 1 year if DM developed pre-puberty (Danielson et al., 2005; Griffin et al., 1994; Kjaer et al., 1992; Yeshaya et al., 1995) If glucose is controlled, menarche age is near normal (Thrailkill, 2005; Schriock et al., 1984)	No data
Menstruation Cycle Dysfunction	1/3 have cycle abnormalities: Irregular cycle patterns amenorrhea, polymenorrhea, menorrhagia (Kjaer et al., 1992; Griffin et al., 1994; Yeshaya et al., 1995; Strotmeyer et al., 2003) If glucose controlled, stable menstrual cycle pattern (Schroeder, Herweek, Sanfilippo & Foster, 2000)	No data Long, irregular cycles predicts type 2 DM (Solomon et al., 2001) No association between cycle length, variability or frequency with type 2 DM risk (Cooper, Ephross, & Sandler, 2000)
Glucose Control during the Menstrual Cycle	Reduced insulin sensitivity during the luteal phase (Widom, Diamond & Simonson, 1992) Luteal phase glucose elevation without change in insulin sensitivity. (Trout, Rickels, Schutta, Petrova, Freeman & Tkacs et al.,2007)	No data
Pregnancy	High failure to conceive rates, fewer pregnancies, increased stillbirths (Strotmeyer et al., 2003; Durando et al., 2003; Rosenn & Miodivnik, 2005)	No specific studies IR is associated with anovulation & infertility (Maturna & Spritzer, 2002; Eisenberg, 2005; Cibula et al., 2000)
Age at Menopause	Earlier age: 6 years (Dorman et al., 2001)	Earlier age: 2 years (Malacara et al., 1997) No difference in age (Lopez-Lopez et al., 1999)
Sex Steroid Levels	Mixed data: both ↑↓ levels of E_2 & T, & free T (Adcock et al., 1994; Meyer et al., 2000; Rudberg & Persson, 1995; Escobar-Morreale et al., 2000; Nyholm et al., 1989; Luan et al., 1996)	↑estrone, E_2 & T in type 2 DM (Phillips et al., 2000; Quinn et al., 1981) ↓ FSH and ↓ E_2: in adult women but DM type not specified (Randolph et al., 2004; Sowers et al., 2003; Bairey-Merz et al., 2003)

Chapter 3

Methods

This exploratory study employed a comparative group design to examine the menopause symptom experience of three groups of women veterans receiving care in the national Veteran's Affairs (VA) Healthcare system: women without type 2 diabetes (DM), women with controlled type 2 DM (Hemoglobin A1c [HbA1c] $\leq$ 7.0%), and women with poorly controlled DM (HbA1c > 7.0%). The study entailed a mailed self-administered participant survey and with consent, the extraction of relevant clinical data.

Sample

After approval of the Ann Arbor Veteran's Affairs Medical Center and the University of Michigan - Health Institutional Review Boards, a national sample of women with and without type 2 diabetes were recruited from patients receiving care in the national Veteran's Affairs (VA) Healthcare system. Veterans using the VA healthcare system met eligibility criteria for military service at the time of enlistment, which included the ability to speak English and excluded anyone with type 1 diabetes. A pool of potentially eligible participants was identified using Current Procedural Terminology (CPT), International Classification of Diseases-9 (ICD-9) and drug class codes from national VA data sets (laboratory, pharmaceutical, service utilization) from fiscal years 2006 and 2007. Participant eligibility criteria included: 1) age 45-60 years, 2) an intact uterus and at least one ovary and 3) experienced spontaneous cessation of menses for at least 12 months, 4) no current or recent (past 2 year) history of substance abuse, 5) no current or past history of severe psychiatric illness, renal failure, breast, uterine, ovarian or cervical cancer, or hysterectomy, 6) no current or recent (past six months) use of the

following prescribed or over the counter hormone products: oral contraceptives, hormone replacement therapy (estrogen, progesterone, testosterone, anti-estrogen or gonadatropin hormone receptor agonists, 7) no current or recent (past six months) use of corticosteroid or anabolic steroids, 8) no current or recent (past six months) use of antipsychotic medications on a daily basis and 9) no current or recent (past six months) use of more than two classes of psychoactive medications on a daily basis.

Eligibility criteria for women with diabetes included: 1) type 2 diabetes for at least 12 months duration, 2) two or more outpatient visits with a diabetes related diagnosis codes per year in the past 24 months or one inpatient hospitalization with a diabetes related diagnosis code and 3) at least two documented HbA1c values in the past 12 months. Women with diabetes were categorized as controlled or poorly controlled based on their last HbA1c value.

Reproductive status could not be adequately evaluated within the available databases and was screened at the level of the survey. Screening for eligible participants occurred in a 3-step process (Table 3.1) and resulted in a pool of potential subjects consisting of 62,645 non-diabetic women, 787 women with controlled diabetes and 900 women with poorly controlled diabetes.

From the groups of potentially eligible participants, a random sample of 900 (300 per study group) women was drawn. A sample size of 100 subjects per group provided 80% power to detect a moderate effect size with an alpha significance level of 0.05 (two sided) for all planned analyses. The projected sample size was multiplied by three to accommodate expected attrition and the anticipated loss of women who were pre- or perimenopausal or had undergone hysterectomy with oopherectomy, criteria that were screened at the level of the survey.

Recruitment Procedures

Each potential participant was mailed a cover letter explaining the study, an informational brochure, the self-administered written survey, two copies of the consent form, a stamped return envelope and a small token of appreciation ($10 gift card to a national retailer). The consent form requested permission to examine their medical record data for two years prior to the study and one year after completing the survey to assess clinical information, such as laboratory results. Participants were asked to return

the survey and one signed copy of the consent form. A reminder letter was sent two weeks after the first mailing and a second survey and consent form sent two weeks after the reminder letter. Survey data collection closed 4 weeks after the third mailing.

Final Sample Determination

A total of 538 surveys were returned (59.8%) with most (n = 508; 94%) granting consent for medical repository data access. Two respondent surveys did not indicate reproductive status and could not be used; another only completed pages 1-2. Eighty-six (16%) responders were premenopausal women (mean age 48.7 $\pm$ 0.3 years) and another 27 women (5%; mean age 52.5 $\pm$ 0.3 years) had stopped cycling but had not been amenorrheic for at least 12 months, and were not eligible for study. The majority (n = 423; 79%) of women reported they were in menopause (mean age 55.0 $\pm$ 0.2 years) and were potential study participants.

Among those who consented, with additional review of survey and clinical (pharmacy, laboratory) data, a total of ninety-five subjects (n = 9 with more than one excluding characteristic) were eliminated from analysis. Four women experienced a premature menopause, several respondents (n = 27) had or were being treated for cancer, and another 29 were taking either an anti-psychotic medication or more than two classes of psychoactive medications on a daily basis in the past six months. An additional 44 women were currently using or had been using daily corticosteroid (n = 3), hormone replacement (n = 40) or anti-estrogen (n = 1) therapy for the past six months.

Pharmacy and laboratory data (past 24 months) coupled with survey responses revealed that some women had developed diabetes, or experienced either worsening or improved glucose control in the interval period from time of sample selection and study group assignment to survey launch (a 6 month delay). Participants were reclassified after examining patterns of HbA_{1c} values prior to and concurrent with the survey completion. This resulted in a final sample of 327 subjects: women without diabetes (n = 90), women with controlled diabetes (n = 135) and women with poorly controlled diabetes (n = 102).

The majority (55.2%) of women veterans in this sample had not experienced a natural menopause, but rather an induced menopause for primarily surgical (53.1%) or other (2.1%) reasons. This prevalence pattern was similar across all study groups. Eliminating those subjects with a non-natural menopause would significantly restrict the

sample and as this is the first US study to explore menopause symptom prevalence and severity in women with diabetes, the entire sample was used for analysis controlling for type of menopause in analyses.

Measurement

The study survey (Appendix A) collected primary data about the menopause symptom experience and health status of all women and for women with diabetes, additional information on diabetes management. Standard instruments with established psychometric properties were embedded in the survey to measure the primary variables (perceived menopause symptoms, health status, diabetes symptoms) and known covariates. The 131-item survey was reviewed by menopause, diabetes and literacy experts to ensure readability. With consent, clinical data two years prior to the study and up to one year post-study were extracted to support the study aims. These data were used to characterize glycemic control and examine its relationship with reported menopause symptom severity.

Dependent variables

Menopause symptoms were defined as the perceived indicators of change in normal functioning (Rhodes & Watson, 1987, p. 242) experienced by women during a natural menopause. Menopause symptom prevalence and severity were measured with the Menopausal Symptom List (MSL) (Freeman, Sammel, Liu & Martin, 2003). On the scale, participants are asked to indicate the prevalence, frequency and severity of 12 symptoms in the past month. The symptoms include hot flashes/night sweats, vaginal dryness, memory trouble, irritability, mood swings, feeling sad or blue, trouble sleeping, feeling anxious or nervous, muscle aches or joint pains, headaches, leaking urine and decreased libido. Symptom severity was rated on a 4-point scale from 0 (none) to 3 (severe) over the past month. The symptom list has been tested in populations of Caucasian and African American women. Convergent validity was established with standard measures of mood, stress, health and quality of life. Factor analysis identified three factors (psychological, somatic, vasomotor) of symptoms that were consistent over

time in longitudinal data. The coefficient for internal consistency was reported at 0.77; in this investigation, it was 0.85. Permission for use was received from Dr. Freeman.

To address National Institutes of Health (2004) recommendations, additional data on vasomotor symptoms were collected to calculate a *Hot Flash score*. This measure was created from the work of several researchers (Sloan et al., 2001; Carpenter, 2001; Newton, 2007) and the Food and Drug Association (FDA, 2003). Respondents were asked to record the total number of hot flashes and night sweats for the past two days and indicate number of hot flashes/night sweats that were mild, moderate or severe. The hot flash score was calculated by multiplying symptom frequency and severity with the following formula: [number of mild hot flashes] + [2 x number of moderate hot flashes] + [3 x number of severe hot flashes]. A score of zero was recorded for respondents who indicated no symptoms during the two-day period. The Cronbach alpha coefficient for the hot flash score was 0.91 in this investigation.

Perceived health status was defined as the perception of wellness based on one's abilities to complete physical activities of daily living with adequate energy, and without interference from pain or emotional concerns (Ware, Kosinski & Keller, 1996). Participant's self-reports of perceived general health and mental state were measured by the composite score of the Short Form 12 (SF-12), a shorter, valid alternative derived from the Medical Outcomes Study Short Form-36 (Ware, Kosinski, & Keller, 1996). The survey consists of 12 items with response scales that range from 4 to 6 levels and measures eight concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The 12 items are combined using an algorithm to produce standardized physical and mental component scores; scores range from 0-100 with higher scores indicating better health status. The composite physical health and mental heath scores represented health status in this study.

The standard (4 week recall) version of the instrument was used. The validity and reliability of the SF-12 have been documented in a variety of patient populations (Ware et al., 1995; Ware et al., 1996; Bennet et al., 2003; Muller-Nordhorn, Roll & Willich, 2004). In this study, the reliability coefficient was 0.91. A license for use was purchased from Quality Metric Incorporated (www.sf36.org).

Independent variables

Menopause status was determined by self-report. The Stages of Reproductive Aging Workshop (STRAW) criteria (Soules et al., 2001) were used to categorize the reproductive status of the participants As shown in Figure 3.1, postmenopause is defined as ≥12 months of amenorrhea. Early postmenopause is amenorrhea of ≥ 12 months but less than 60 months from FMP; late postmenopause is ≥ than 5 years (NAMS, 2002). As additional staging criteria for late menopause have not been determined, for the purposes of this study, late menopause was further categorized into sub-stages to reflect the sample characteristics as A: late postmenopause (6-10 years), B: late postmenopause (11-20 years) and C: late postmenopause (> 20 years).

Age of menopause was defined as the age at which cessation of menses occurred and determined by self- report. This definition was used for all subjects, including those with hysterectomy with or without one ovary removed, as it was not possible to accurately determine the actual onset of menopause in those participants. Most (61%; n = 51/84) respondents with hysterectomy either indicated they could not identify the onset of menopause, or reported an age that was concurrent with the procedure or 1-2 years after surgery. Prospective (Farquhar, Sadler, Harvey & Stewart, 2005) and retrospective (Ahn, Bai, Song, Kim, Jeong & Kim et al., 2002) data support this decision, documenting compromised ovarian function post uterus removal and subsequently an earlier age of menopause, within 5 years of the procedure and even earlier if one ovary was removed.

Type 2 Diabetes (DM) was determined by self-report. *Glycemic control* was defined as optimal levels of serum glucose (ADA, 2007a) and measured by the serum glycated hemoglobin (HbA_{1c}) level. HbA_{1c} values were obtained from the clinical database; levels less than or equal to 7% indicated controlled diabetes and values greater than 7% indicated poorly controlled diabetes. *Diabetes Duration* was defined as the number of years of type 2 diabetes and determined using self-reported data of age at diabetes diagnosis subtracted from current age in years.

Diabetes Symptoms were defined as the perceived indicators of change in normal functioning (Rhodes & Watson, 1987, p. 242) attributed to type 2 diabetes. In this study, diabetes symptoms were measured by the standardized global and sub-dimension scores from the Diabetes Symptom Checklist-Revised (DSC-R) (Grootenhuis, Snoek, Heine, &

Bouter, 1994). The DCS-R is a self-report questionnaire that measures the prevalence and perceived burden of 34 diabetes related symptoms over the past 4 weeks. Perceived burden is rated on a from 0-5. A score of '0' indicates the symptom is not present; if present, symptom burden was evaluated on a 1-4 scale from 1 (no burden) to 4 (extremely burdensome). A total, global and 8 sub-dimension or domain scores can be calculated. The total score ranges from 0-170 and accounts for each item separately. Sub-dimension scores are the summed score of each item in the dimension divided by the number of items. The sub-dimensions include hyperglycemia, hypoglycemia, neuropathic-sensation, neuropathic-pain, psychological-fatigue, psychological-cognition, cardiovascular, and ophthalmologic symptoms. The DSC-R global is a summed measure of the sub-dimension scales and equally reflective of these scale domains.

The DSC-R has been used in several populations of diabetic men and women of different race and ethnicity (McGill et al., 2007; Wagner & Tennen, 2007; Weijman et al., 2003). Validity was established with factor analysis and convergent validity (Grootenhuis et al., 1994). Test-retest reliability coefficients range from 0.79-0.94; Cronbach alpha coefficients range from 0.76 to 0.95. In this study, the alpha coefficient was 0.91. Permission for DSC-R use was granted from the MAPI research trust.

Covariates

Depressive symptoms were measured using the short form of the Center for Epidemiologic Studies Depression Scale 10 (CES-D), designed for use in community populations (Radloff, 1977). The shortened 10-item scale measures current symptoms of affective depression but has internal consistency and a factor structure similar to the original 20-item CES-D. Respondents indicate how often specific symptoms occurred during the last week and score them on a 4-point ordinal scale from 0 (rarely or none of the time; less than one day) to 3 (most or all of the time; 5-7 days). Scores range from 0 to 30 with higher scores reflective of greater levels of depressive symptoms. A score of 10 or higher indicates probable depression. Test-rest reliability correlations range from 0.71-0.84; Cronbach alpha values are reported to range from 0.78 to 0.81 (Carpenter et al., 1998; Andresen et al., 1994; Turvey, Wallace & Herzog, 1999). In this study, the alpha reliability coefficient was 0.85. The instrument was publicly available for use in non-funded academic research.

Perceived Anxiety was measured by the Generalized Anxiety Disorder (GAD-7) scale (Spitzer, Kroenke, Williams & Lowe, 2006). Developed from Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria, the GAD-7 measures symptoms of generalized anxiety in community populations. On the 7-item scale, respondents indicate how often they experienced specific symptoms in the last 2 weeks on a 0 (not at all) to 3 (nearly every day) scale. An additional non-scored question asks respondents if they checked off any concerns, how difficult these problems made it to do their daily work. The points for each item are summed for a total score; the maximum score is 21. A score of 10 or greater is indicative of generalized anxiety. Scores are categorized as follows: minimal anxiety (0-4), mild (5-9), moderate (10-14) and severe (15-21). Tested in 15 primary care clinics, the GAD-7 strongly correlated with other established measures of anxiety (Beck Inventory; Symptom Checklist 90). Criterion, construct, factorial and procedural validity have been reported (Spitzer, Kroenke, Williams & Lowe, 2006). Cronbach alpha for internal consistency was 0.92 and the test-test reliability coefficient was 0.83; for this study, it was 0.92. Permission for use was granted by Dr. Kroenke.

Perceived Stress was measured with the Perceived Stress Scale (PSS), a 10-item scale derived from the original 14-item tool evaluating the degree to which situations in one's life are appraised as stressful (Cohen, Kamarck, & Mermelstein, 1983). Subjects rate the items on a 5-point scale from 0 (never) to 4 (very often). Total scores are obtained by reverse scoring the four positive items and then summing across all 10 items. The PSS was designed for use with community samples; it is written in simple language. Reliability and validity have been established. Cronbach alpha was reported at 0.85 and for this study it was 0.89. The PSS has been correlated with depression and anxiety, but shown to measure a different and independent predictive construct of appraised stress (Cohen et al., 1983). The instrument is publicly available for use.

Information regarding s*ociodemographic, lifestyle and clinical factors,* that previously demonstrated relationships with menopause symptom prevalence and severity, were collected as part of the study survey. This included items such as race/ethnicity, relationship status, level of education, self report of height and weight to calculate body

mass index (BMI: kg/m^2), health habits such as smoking and medical history data including co-morbid illnesses, current prescribed and over the counter medication use.

Protection of Human Subjects

Permission to conduct this study was obtained from both the Veterans Affairs Healthcare System - Ann Arbor and the University of Michigan - Health Institutional Review Boards. The risks and benefits of participation were provided to all potential participants. Respondents agreeing to extraction of their clinical data for analysis signed a HIPAA-compliant consent form approved by the both Institutional Review Boards. All subjects were informed their participation was voluntary and they could withdraw at any time. Participants had direct access to both phone numbers and email addresses of the study investigators, and phone access to the research office.

During the study every effort was made to minimize risks to the participants and ensure confidentiality. A temporary database with participant contact information was maintained during the survey phase of the study on a secure network drive with access restricted to study staff only. All physical data collection forms only used study ID numbers and were stored separately in a locked file cabinet with access limited to project staff members. Consent forms were stored separately from surveys in a locked cabinet.

Data Management and Analysis

The data were de-identified, double entered and compared to ensure accuracy. Data were coded and analyzed using STATA version 10.0 (Stata Corporation, College Station, TX). Frequency distributions were evaluated for normality and transformed as needed. Scatterplots were generated to assess linearity between variables. Descriptive statistics were used to characterize the entire sample and the study groups. Chi square with the Fisher exact test was used to compare differences in menopause symptom prevalence and other categorical variables between the study groups; *t* tests and analysis of variance with post-hoc analyses were used to examine group differences in continuous variables, particularly menopause symptom severity, diabetes symptom scores, general

health status, and both the physical and mental health composite scores of the SF-12. Relationships between sociodemographic, lifestyle, clinical factors and covariates with the dependent variables were assessed by Pearson r correlations.

Multivariate regression techniques were used to examine the association between independent variables and dependent variables, with variables having either evidence of a statistical relationship or theoretical support included in the analysis. Multiple regression models of menopause symptom severity (total score, factor scores) and health status were constructed for the full sample and women with diabetes. The level of significance for all statistical tests was set at $p \leq 0.05$.

The independent variable of interest, diabetes, was measured using two categorical variables to indicate glucose control status (controlled DM or poorly controlled DM) with women without diabetes as the reference group. In models of women with diabetes, a dichotomous variable (poor control) was used to indicate glucose control status with controlled diabetes as the reference group. Ethnicity was measured using three categorical variables: black, Hispanic and other, with white women as the reference group. Years postmenopause and age of menopause were highly correlated (Pearson r = -0.9) and measuring the same concept, so only age of menopause was used in the regression analysis. Type of menopause (natural, surgical) was measured as a dichotomous variable with natural menopause as the reference group.

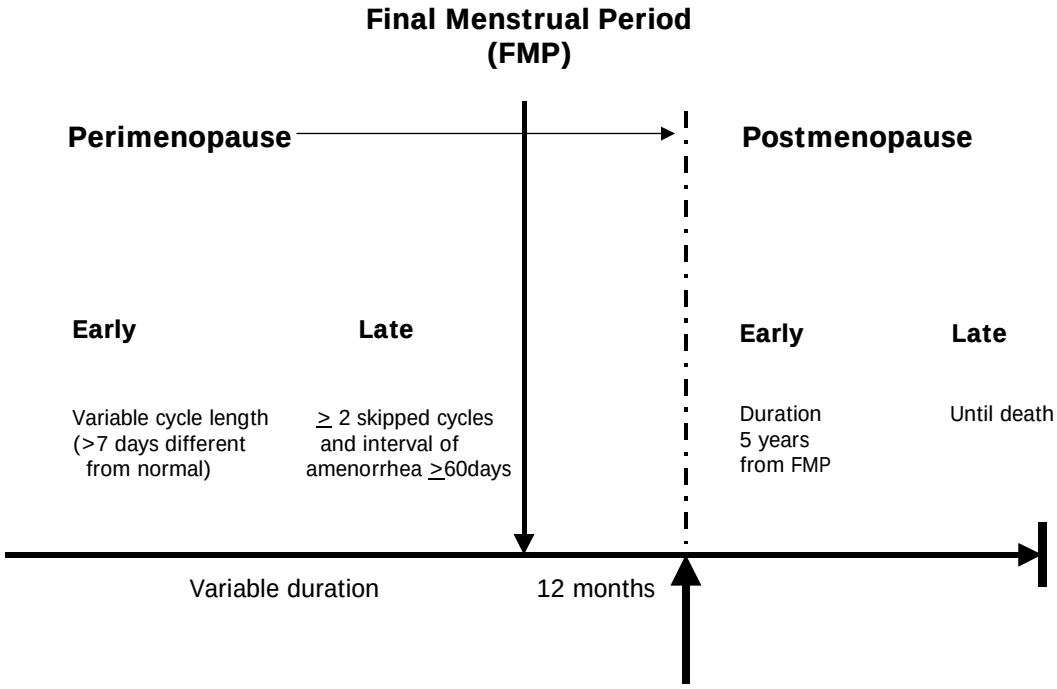
The measures for depressive symptoms (CESD-10 score), and anxiety (GAD-7 score), were highly correlated with the MSL scores (Pearson r = 0.7 for both scales) as these instruments share similar items (sadness, mood swings, anxiety, irritability, etc). Entering these scores into the regression model for the MSL severity score was problematic as similar measures of anxiety or depressive symptoms were used in defining both the dependent and independent variable, resulting in artificially high R^2 values up to 0.50 because of the commonality in measurement.

Yet, altered mood is an important variable to consider when evaluating the severity of the menopause symptom experience. As longitudinal assessment was not possible in this study and given the common measurement among the instruments noted, the survey health history item for a current diagnosis of altered mood (depression, anxiety

or stress disorder) was used as the indicator of this concept in regression models for the total MSL severity score, the MSL factor 1 (psychological) score and health status.

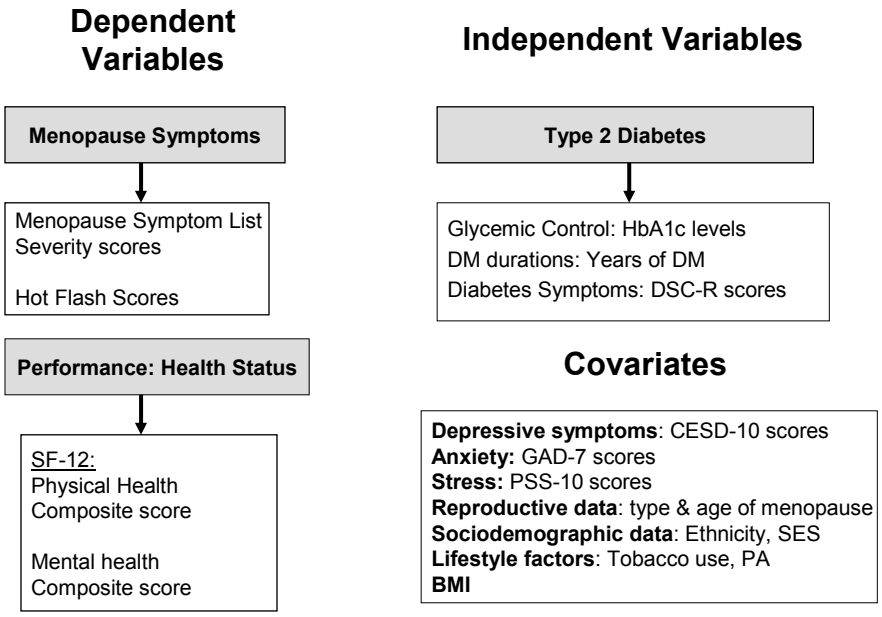
Among the major variables and covariates, the amount of missing data was less than 8% (average was 6%). A systematic pattern was not observed in the missing data. Missing data was not replaced and listwise deletion was used in all analyses.

Figure 3.1. Stages of Reproductive Aging Workshop (STRAW)* Criteria



*Adapted from Soules, M. R., Sherman, S., Parrott, E., Rebar, R., Santoro, N. Utian, W. et al. (2001). Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertility & Sterility 76,* 874-878

Figure 3.2 Measurement of Major Variables



BMI, Body Mass Index; DM, Diabetes Mellitus; DSC-R, Diabetes Symptoms Checklist-Revised; CESD-10, Center for Epidemiologic Studies Short Depression scale; GAD-7, Generalized Anxiety Disorder-7 scale; HbA1c, Hemoglobin A1c; PA, Physical Activity; PSS-10, Perceived Stress Scale-10; SES, Socioeconomic status data; SF-12, Short Form Survey-12.

Table 3.1. Study of Women veterans In Menopause (SWIM): Sample Selection Process

Step 1	**Step 2**	**Step 3**
Screen using the following general eligibility criteria: 1) females age 45-60 (FY 07) 2) 2 or more visits in the past 2 years 3) No current or recent (past 2 year) history of substance abuse diagnosis (ICD-9 codes: 303.x, 304.x, 305.x) 4) No current or recent (past 2 year) history of: a. severe psychiatric illness (ICD-9 codes: 290.x, 295.x, 296.8, 298.x, 307.1, 307.51, 309.81, 331.0) b. renal failure (ICD-9 codes: 585.6, 586, CPTcodes: 39.95) c. breast cancer (ICD-9 codes: 174.x, 184.9, 199.0) d. uterine cancer (ICD-9 codes: 180, 184.9) e. ovarian cancer (ICD-9 codes: 180, 183) f. cervical cancer (ICD-9 codes: 180, 233.1) g. hysterectomy: (CPT codes: 68.39-68.9)	From the step 1 pool, query pharmaceutical data from the past 12 months for the following criteria: 1) no current or recent (past 6 months) use of the following hormone products: a. oral contraceptive: HS 200 b. hormone replacement therapy: HS 300, HS 800, HS 100 c. anti-estrogens: AN 500, AN 900 d. gonadotropin hormone receptor agonists: none on formulary 2) no current or recent (past 6 months) use of corticosteroid or anabolic steroids on a daily basis: HS 051, HS 100 3) no current or recent (past 6 months) use of antipsychotic medications on a daily basis: CN 709, CN 701 4) no current or recent (past 6 months) use of more than two classes of psychoactive medications on a daily basis: CN 609, CN 601, CN 602, CN 302, CN 309, CN 400	From the resulting cohort, identify women with diabetes using the additional criteria of: 1) 2 or more outpatient visits per year in the past two years (24 months) with a type 2 diabetes diagnosis codes (250.x) **or** 1 inpatient visit with a diabetes related code (250.x) **or** a prescription for a diabetes medication (HS 501-insulin, HS 502-oral hypoglycemic agent) 2) documentation of at least 2 HbA1c values in the past 12 months 3) From this data, further sort into 2 groups by last HbA1c values: a) controlled diabetes: HbA1c $\leq$ 7% b) poorly controlled diabetes: Hb A1c > 7%

Chapter 4

Results

This chapter presents the results from analyses. The findings are organized around the research questions.

Study Participants

Clinical Characteristics

Table 4.1 presents the clinical characteristics of the study groups. Respondents were a mean 55.0 $\pm$ 0.2 years of age and 11.30 $\pm$ 0.2 years postmenopause. The women veterans were obese (mean body mass index [BMI] 33.9 $\pm$ 0.4 kg/m^2) and had on average 4.7 $\pm$ 0.1 chronic medical conditions. Women without diabetes mellitus were younger, of smaller BMI, and had fewer chronic medical problems than those with diabetes.

Higher concentrations of cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) were demonstrated in women without diabetes compared to those with the chronic illness but these differences are likely due to the higher percentage of the women with diabetes using lipid lowering agents. By design, hemoglobin A_{1c} (HbA_{1c}) levels were higher in those women with poorly controlled DM compared to those with controlled diabetes. While none of the respondents were using hormone therapy, approximately one-third of the women with diabetes were on psychoactive medications that have been used to manage vasomotor symptoms (selective serotonin reuptake inhibitors (SSRI), selective serotonin-norepinephrine reuptake inhibitors (SNRI), gabapentin).

As expected, women with diabetes demonstrated increased prevalence of most co-morbid conditions (Table 4.2), although more than 50% of the women without diabetes reported a history of hypertension. The prevalence of mood disorders (depression, anxiety, post traumatic stress disorder), thyroid disease and lung conditions were similar

across all groups. Levels of anxiety, perceived stress, and depressive symptoms were also found to be similar among the participant groups (Table 4.1).

Demographic Characteristics

Fifty eight percent of the respondents were white, 28 percent were black, and another seven percent were of Hispanic ethnicity (Table 4.3). The remaining seven percent were Native American Indian (n = 4), Asian (n =2), Hawaiian Pacific Islander (n =1) or identified with more than one race (n = 14). Of those reporting more than one race, 10 of the 14 (71%) indicated they were of Native American Indian descent. Race/ethnicity was collapsed into four groups (white, black, Hispanic, other) for analysis and was similar across all study groups. Relationship status was also similar among the groups. Almost half (n =156; 48%) of the sample reported a defined relationship (married, partner) and the remainder (n = 166; 52%) of respondents were divorced, separated, widowed or never married.

The majority of the sample (n = 186; 58%) had secondary education: some college courses, technical training or an associate's degree (Table 4.3). There were group differences in education level, with a higher percentage of respondents with a high school education or less observed in the women with poorly controlled diabetes group. While most of the women were working full or part time (n = 178; 56%), more than half of the total household income levels were below the United States (US) median income with one-third (n = 94; 30%) below the poverty level (US Census Bureau, 2006 data). Employment did not differ by study group, but income did vary. A higher percentage of those with incomes above $50,000 were noted among women without diabetes and almost 70% of those with poorly controlled diabetes had incomes below the US median.

Lifestyle Behaviors

The majority of respondents did not smoke (86%) or drink alcohol (68%) (Table 4.4). Group differences were noted; women with controlled diabetes reported lower prevalence rates of tobacco use and women without diabetes reported more alcohol use (Table 4.4). Among women reporting alcohol use (n = 104), most (60%) consumed alcohol 0-1 days per week and had only one drink (60%) at that time (data not shown). Study respondents were physically inactive. Two thirds of the sample (66%) reported

walking for exercise less than 60 minutes total in the past week and 75% reported no aerobic exercise at all. There were no group differences in exercise behaviors.

Women with Diabetes Mellitus

Women with DM (Table 4.5) were 55.5 ± 0.5 years of age, obese (BMI 35.9 ± 0.7 kg/m^2) and had diabetes for 7.6 ± 0.4 years. One-third of women were diagnosed during their reproductive years while the majority (n = 155; 67%) developed diabetes after menopause. The average age of DM diagnosis was 47.9 ± 0.5 years, but as expected, age of diagnosis was significantly younger (42.7 ± 0.9 yrs) among those diagnosed in their reproductive years compared to those developing DM postmenopause (50.4 ± 0.4 yrs; $t = -7.6$, $p < 0.0001$).

Age of DM diagnosis also differed by degree of glucose control (Table 4.5). Those with poorly controlled DM were diagnosed at an earlier age (45.4 ± 0.8 vs. 49.8 ± 0.5 yrs; $t = 4.7$, $p < 0.0001$) and had the condition longer (10.1 ± 0.7 vs. 5.7 ± 0.5 yrs; $t = -5.0$, $p < 0.0001$) than those with controlled DM. Most (n = 100; 65%) women with controlled DM were diagnosed postmenopause, while the majority (n = 43; 58%) of those with poorly controlled DM were found to have diabetes during their reproductive years.

Oral medications, self glucose monitoring and diet were the most common treatment interventions reported by women with DM (Table 4.6). Insulin was used by one third of the subjects, most often in a twice daily dose. There were differences in the percent using diet, exercise and insulin treatment options among the study groups, with greater use of insulin in the poorly controlled group and greater use of diet and exercise by women with controlled diabetes. Both groups of women reported similar levels of perceived adherence with recommended diabetes self care management behaviors over the past 6 months.

Menopause Characteristics

Type of menopause

The majority (55.1%) of women experienced an induced menopause for surgical or other reasons rather than a natural menopause. This pattern was consistent across all three study groups (Table 4.7). The most common form of induced menopause was

surgical, either a total abdominal hysterectomy with bilateral salpingoopherectomy (TAH-BSO) or uterus with or without one ovary removed (hysterectomy). A few women (n = 7) experienced menopause related to drug/chemical exposure, trauma or a non-gynecological procedure. While it appears that there is a lower prevalence rate of TAH-BSO and a higher rate of hysterectomy in women with poorly controlled diabetes, statistically significant group differences were not detected ($p = 0.09$).

Women with Diabetes Diagnosis Pre- or Postmenopause. Group differences (Table 4.8) were noted in the type of menopause experienced by women with diabetes during their reproductive years compared to those who developed the condition in the postmenopause. Most women with a premenopausal diabetes diagnosis ($n = 48$; 67%) experienced natural menopause; the remaining one third ($n = 24$) had a surgical menopause, most often a TAH-BSO ($n = 15$; 62.5%). In contrast, only thirty five percent of women with diabetes diagnosed postmenopause (n = 52) had experienced a spontaneous menopause. The majority had a surgical menopause (n = 98; 65%), most often a hysterectomy.

Age of menopause

The average age of menopause (inclusive of all causes) was 43.3 $\pm$ 0.4 years and similar across all study groups (Table 4.9). Among women with natural cessation of menses, the average age of menopause was 49.2 ± 0.3 years and did not differ by diabetes status, but is earlier than the mean of 51 years common to Western women. In women with an induced or surgical event, the average age of menopause was 39 years and did not differ by study group. Menopause age was similar among women who had a TAH-BSO, but in women post-hysterectomy, a younger age of menopause was noted in women with poorly controlled DM (n = 34) compared to women without DM (n =22) with a trend for significance compared to those with controlled DM (n = 28; $p = 0.06$).

Women with Diabetes: Diagnosis Pre- or Postmenopause. In women with a diabetes diagnosis in their reproductive years who experienced natural menopause, cessation of menses occurred at an average age of 51.0 ± 0.6 years, comparable to the norm for western women. In contrast, a younger age of natural menopause (47.3 ± 0.7 years; $t = 4.8$; $p < 0.001$) was observed in women with a postmenopausal diagnosis of DM. Menopause due to surgical causes occurred at a younger age for women who

developed DM in the postmenopause (37.8 ± 0.8 years) while women with DM during their reproductive years experienced a surgical menopause at an older age (43.5 ± 1.6 years; t = 3.2, p = 0.003).

Years Postmenopause

Number of years postmenopause (PM) was similar between the diabetes study groups, while women without DM were fewer years postmenopause compared to those with poorly controlled DM. Collapsed into one group, women with DM had been in menopause longer than those without diabetes (DM: 12.2 ± 0.6 yrs vs. No DM: 8.9 ± 0.8 yrs, t = -3.01; p = 0.000). Approximately one-third (n = 97; 31%) of the respondents were in the early postmenopausal period (0-5 years) as defined by the Stages of Reproductive Aging Workshop (STRAW) criteria (Table 4.10), while the remainder were in late postmenopause. Women in late postmenopause were divided into substages to reflect the population characteristics. While there were no significant group differences in the distribution of subjects by PM stage, almost 25% of women with poorly controlled diabetes had been in menopause for more than 20 years compared to only 10% of the women without diabetes.

The majority (n = 72; 75%) of women in the early PM (0-5 years) period experienced a natural menopause at an average age of 50.2 ± 0.4 years. Most (70%) of the women who were 11-20 years PM and all of the women more than 20 years PM had experienced a surgical menopause, at an early age (mean 35.4 ± 0.6 years; data not shown).

Perceived Difficulty of Menopause

Women rated the difficulty of their menopause experience on a 0 (not difficult/no problems) to 10 (very difficult/many problems) scale. The sample mean was 4.7 $\pm$ 0.2, just below the 50th percentile (a score of 5). Perceived difficulty with menopause did not differ by study group (Table 4.11), but women with a surgical menopause reported greater difficulty compared to those with natural cessation of menses.

Main Findings: Menopause Symptom Prevalence and Severity

This section addresses research questions one and three: what is the perceived prevalence and severity of menopause symptoms in women with and without type 2 DM and do perceived menopause symptoms differ between women with and without DM? Analyses comparing women without DM and the entire group of women with DM demonstrated few differences in perceived menopause symptom prevalence or severity, but when stratifying the sample by both DM and glucose control status, interesting findings were evident. The data are presented in that order and to avoid redundancy where possible, the tables have been compressed.

Menopause Symptoms: Perceived Prevalence

Most (n = 313; 95%) of the sample reported at least one menopause symptom. Muscle and joint aches, hot flashes and trouble sleeping were the most commonly reported symptoms in all groups, while vaginal dryness was the least prevalent symptom. Perceived menopause symptom prevalence was similar between women veterans with and without DM (Table 4.12). When examined using the three study groups accounting for glucose control differences in diabetic women, greater prevalence of headaches and anxiety were observed in women with poorly controlled DM (Table 4.13).

Symptom prevalence was similar between women without DM and those with controlled DM (Table 4.13). Comparisons between women veterans with controlled diabetes and poorly controlled DM demonstrated additional differences. Besides headaches and anxiety, women with poor glucose control reported greater prevalence of memory loss, trouble sleeping, and decreased libido than those with controlled DM.

Menopause Symptoms: Perceived Severity

<u>Women with and without Diabetes</u>

Total menopause symptom list (MSL) severity scores, MSL factor scores (psychological, somatic, vasomotor) and mean 2 day recall hot flash scores were similar

between women veterans with and without diabetes (Table 4.14). Item specific menopause symptom severity scores were also similar except for mood swings, with greater severity of that symptom reported by women with diabetes. In all respondents, muscle and joint aches, trouble sleeping, hot flashes and decreased libido were the symptoms with the highest severity scores; vaginal dryness, headaches and anxiety received the lowest severity scores.

Women with and without Diabetes by Glucose Control Status

By ANOVA, women with poorly controlled diabetes demonstrated higher total (Figure 4.1) and psychological MSL factor scores compared to women veterans without DM and those with controlled DM (Table 4.15). Women with poor glucose control also reported greater severity of anxiety and sleep symptoms than their controlled diabetic peers, greater severity of mood swings compared to women without DM but not those with controlled DM, and greater severity of headaches compared to both groups. Somatic and vasomotor factor MSL scores and 2 day recall hot flash scores were similar among the three groups, as were the individual symptom severity scores for vaginal dryness, memory changes, irritability, feelings of sadness, muscle and joint aches, urinary leakage, and decreased libido.

Women with Controlled Diabetes and Women without Diabetes

Women with controlled diabetes and women without diabetes had similar symptom severity scores for all item specific menopause symptom scores, the total MSL score, MSL factor scores and 2 day recall hot flash scores (Table 4.15).

Women with Controlled and Poorly Controlled Diabetes

Comparing women with controlled DM to their poorly controlled peers, several differences emerged. Total MSL severity scores and both psychological and somatic factor scores were higher in women with poor glucose control, yet MSL vasomotor factor scores did not differ (Figure 4.2). Women with poor glucose control reported greater severity of anxiety, headaches, trouble sleeping and diminished libido (Table 4.15). Perceived severity of vaginal dryness, hot flashes, memory loss, irritability, sadness, muscle/joint aches and urinary incontinence symptoms was similar between the women.

Main Findings: Factors Associated with Menopause Symptoms

This section addresses research questions two and four: what are the associated factors and correlates of perceived menopause symptoms in women with and without type 2 diabetes and what is the relationship between clinical features of type 2 diabetes mellitus and perceived menopause symptom severity?

Correlates of Menopause Symptom Severity

Entire Sample

Correlational analyses suggested menopause symptom severity (total MSL score) was positively associated with glucose control group status (r = 0.16; $p = 0.009$). Years postmenopause, non-white, non-black, non-Hispanic ethnicity and cigarette use were also positively associated with the MSL score (Table 4.16), while BMI only demonstrated a trend for a positive association ($p = 0.07$). Age of menopause, aerobic exercise, and employment status were inversely associated with the MSL score. There was no association between menopause symptom severity and age, walking exercise, alcohol use, type of menopause (natural, surgical), relationship status, income, and education. The CESD-10, PSS-10, GAD-7 and Diabetes Symptom Checklist-Revised (DSC-R) scale scores were highly correlated with the MSL score (r = 0.53-0.70), and reflect the common measurement items on the MSL that are duplicated on these instruments.

In women with diabetes, the direction and significance of the relationships between the above variables were similar (Table 4.16). The only variables associated with menopause symptom severity in women without diabetes were altered mood diagnosis and the CESD-10, GAD-7, PSS-10 and diabetes symptoms scores.

Women with Diabetes

Among women with diabetes, level of glycemic control as measured by HbA_{1c} was positively associated with menopause symptom severity (r = 0.17; $p = 0.02$). Use of insulin, and the diabetes symptoms (DSC-R) global and subscale scores were positively associated with menopause symptom severity (Table 4.17) while the respondent's perceived adherence to diabetes self-care behaviors (diet, exercise, weight control) were

inversely associated. No relationship between the menopause symptom severity score and age of diabetes diagnosis, diabetes duration, number of diabetes medications, or diabetes diagnosis before/after menopause was observed.

In both groups of women with diabetes, all DSC-R scores were positively associated with the perceived menopause symptom severity. The only glucose related variable associated with the MSL severity score in women with controlled diabetes was perceived adherence to dietary management ($r = -0.20$; $p = 0.03$). In women with poorly controlled diabetes, a diabetes diagnosis before menopause was positively associated with the MSL severity score ($r = 0.25$; $p = 0.02$).

Menopause Symptom Severity: Multivariate Analysis

Table 4.18 presents the final multivariate models for menopause symptom severity. Adjusting for ethnicity, tobacco use, a diagnosis of altered mood, BMI, age of menopause and type of menopause, glucose control status did not demonstrate a statistically significant association ($\beta = 0.12$; $p = 0.09$ uncontrolled DM; $\beta = -0.02$; $p = 0.68$ controlled DM) with menopause symptom severity (MSL total score) in the full sample of women veterans. Cigarette smoking and a diagnosis of altered mood were significantly and positively associated with menopause symptom severity after controlling for diabetes/glucose control status and sociodemographic characteristics.

Among women with diabetes, poorly controlled diabetes had a statistically significant positive association ($\beta = 0.15$; $p = 0.03$) with perceived menopause symptom severity after adjusting for ethnicity, age of menopause, tobacco use, BMI, type of menopause and altered mood. Both cigarette smoking and a diagnosis of altered mood continued to demonstrate a positive association with menopause symptom severity.

Correlates of Menopause Symptom Severity: Factor Scores

<u>MSL Factor 1: Psychological Symptoms</u>

Symptoms of irritability, anxiety, sadness, mood swings, memory loss, trouble sleeping and headaches are included in the MSL Factor 1 score. Factor 1 severity scores

were positively associated with tobacco use, years postmenopause, HbA1c levels, aerobic exercise, and income (Table 4.19). This factor score was positively related to an altered mood diagnosis and highly correlated with the perceived stress, anxiety and depressive symptoms scores. Age of menopause and employment (working or not) were negatively associated with the psychological factor score while age, diabetes, BMI, type of menopause, alcohol consumption, walking exercise or relationship status demonstrated no association.

MSL Factor 2: Somatic Symptoms

The somatic factor severity score represents urinary incontinence, vaginal dryness and decreased libido symptoms. BMI, years postmenopause, cigarette smoking, relationship status (partner, no partner), and measures of anxiety, perceived stress and depressive symptoms were positively related to the factor 2 score, while exercise measures and black ethnicity were inversely associated (Table 4.19). There was no association between somatic symptom severity and glucose control, diabetes diagnosis, age, type of menopause, alcohol use, income, or education.

MSL Factor 3 Vasomotor Symptoms

This factor included hot flashes and muscle aches. Very few variables demonstrated an association with the factor 3 severity scores (Table 4.19). Measures of perceived stress, anxiety and depressive symptoms along with a diagnosis of mood disorder were positively associated with factor 3 scores. Age of menopause was inversely related to the vasomotor symptom severity score but demonstrated only a trend for significance ($p = 0.06$).

Menopause Symptom Severity Factor Scores: Multivariate Analysis

Factor 1: Psychological symptom severity

There was not a statistically significant association between controlled or poorly controlled diabetes status and the factor 1 severity score after adjusting for ethnicity, cigarette smoking, type of menopause, altered mood diagnosis, BMI, and age of menopause (Table 4.20). Variables that were independently associated with psychological symptom severity included altered mood ($\beta = 0.33$; $p = 0.000$), tobacco use

(β = 0.13; p = 0.02), and non-white, non-black, non-Hispanic ethnicity (β = 0.13; p = 0.02). Although the association between diabetes status and the factor 1 severity score was not statistically significant after adjustment for all variables in the model, the magnitude of the effect for those with poorly controlled diabetes (β = 0.13; p = 0.07) was similar in magnitude to that associated with altered mood and non-white, non-black, non-Hispanic ethnicity. In women with diabetes, poorly controlled diabetes and altered mood were both positively and statistically significantly associated with the MSL factor 1 severity score after adjustment for cigarette smoking, altered mood, ethnicity, age of menopause, type of menopause and BMI.

Factor 2: Somatic symptom severity

Adjusting for ethnicity, tobacco use, measures of depressive symptoms and anxiety, type of menopause, age of menopause, relationship status (no partner as reference group) and BMI, diabetes status did not demonstrate a relationship to somatic symptom severity scores (Table 4.21). On the other hand, a statistically significant and positive association with the MSL factor 2 severity scores was noted for BMI, cigarette smoking, Hispanic ethnicity, perceived anxiety and having a partner. In women with diabetes, glucose control was not associated with the severity of somatic symptoms while cigarette smoking, Hispanic ethnicity, anxiety levels and having a partner remained positively associated (Table 4.21) after adjustment for the other variables in the model.

Factor 3: Vasomotor symptoms severity

Very few variables demonstrated a relationship to the vasomotor symptoms factor score. Glucose control or diabetes status was not statistically significant in any models tested. Variables with previous theoretical support (BMI, ethnicity, tobacco use, depressive symptoms, anxiety, and type of menopause) were tested with only depressive symptoms demonstrating an independent and positive association to vasomotor symptom severity both in the full sample and among women with diabetes (Table 4.22).

Other Covariates

BMI demonstrated only a trend for a positive association (r = 0.11; p = 0.07) with the total menopause symptom severity score. BMI was not related to the MSL 1 factor,

MSL 3 factor, or the two day recall hot flash score but was positively associated (r = 0.14; $p = 0.02$) with the somatic severity score and the item specific severity score for urinary incontinence (r = 0.27, $p = 0.000$). BMI did not demonstrate an association with any other item specific menopause symptom severity score, type of menopause (natural, surgical) or age of menopause.

BMI was positively associated with the DSC-R total (r = 0.13; $p = 0.02$), global scores (r = 0.14; $p = 0.02$), and subscales scores for hyperglycemia (r = 0.13; $p = 0.02$), psychological-fatigue (r = 0.15; $p = 0.006$) and psychological-cognitive (r = 0.13; $p = 0.02$) symptoms. As expected, cholesterol (r = -0.18, p = 0.001), LDL (r = -0.21, p = 0.005) and HDL (r = -0.21, p < 0.0001) concentrations were inversely associated with BMI while triglyceride levels were positively related (r = 0.17; $p = 0.004$). BMI was negatively related to cigarette smoking (r = -0.16; $p < 0.0001$) but did not demonstrate an association with HbA_{1c} levels, education, employment, income, or measures of anxiety, perceived stress and depressive symptoms.

Glucose control (HbA_{1c} values). Among women with diabetes, HbA_{1c} values were positively associated with cholesterol (r = 0.21; p =0.001) and LDL (r = 0.14; p =0.05) but had no relationship with triglyceride or HDL values. HbA_{1c} values were inversely associated with alcohol use (r = -0.19; $p = 0.003$) and employment status (r = -0.17; $p = 0.008$). Income, education, age of menopause, type of menopause, BMI, cigarette smoking, exercise or measures of depressive symptoms, anxiety and perceived stress did not demonstrate an association with glucose control. Age of diabetes diagnosis (r = -0.33; $p = <0.001$), a diabetes diagnosis before menopause (r = -0.17; $p = 0.004$) and insulin use (r = -0.18; $p = 0.01$) were negatively associated with HbA_{1c} concentrations.

Glucose control (HbA_{1c}) values were positively associated with the total, global and most of the subscale scores of the DSC-R (data not shown), but did not demonstrate a relationship with the psychological subscales. The total MSL (r = 0.17; $p = 0.02$) and MSL psychological factor (r = 0.16; $p = 0.02$) severity scores were positively associated with HbA_{1c} . There was no association between glucose control values and the somatic or vasomotor factor severity scores. The only individual menopause symptom specific severity scores to demonstrate a relationship with HbA_{1c} levels were those for mood (r = 0.17; $p = 0.01$) and sleep (r = 0.18; $p = 0.01$).

Diabetes Symptoms

Global and Subscale Scores

Women with and without Diabetes. Higher (greater perceived burden) Diabetes Symptoms Checklist – Revised (DSC-R) global scores were noted in women with diabetes compared to those without diabetes. With the lone exception of higher burden scores for hyperglycemia related symptoms demonstrated in women with diabetes, all DSC-R subscale burden scores were *similar* between the groups of women (Table 4.23)

Women with and without Diabetes by Glucose Control Status. When diabetes symptoms scores were examined using the three study groups (Table 4.24), higher global DSC-R scores (greater perceived burden) were observed in women veterans with poorly controlled DM compared to their controlled peers and the non-diabetic cohort (Figure 4.3). Of the eight DSC-R subscales, the psychological symptoms related to fatigue were perceived as most troublesome by all the respondents and noted to be similar among the groups (Table 4.24). Women with poor glucose control reported greater burden of hyperglycemia symptoms than women without diabetes, but had similar levels as their counterparts with controlled levels of glucose. Women with poorly controlled diabetes reported greater burden of cardiovascular symptoms compared to their diabetic peers but had similar scores as the non-diabetic cohort. While ophthalmologic complaints more troublesome in women with poorly controlled diabetes, the perceived burden of hypoglycemia, psychologic-cognitive complaints, and neurologic symptoms of altered sensation and pain were similar among the study groups.

By ANOVA, w*omen with controlled DM and women without DM* demonstrated similar scores on all diabetes symptoms scales. Examined by *t*-test, all DSC-R scores were similar between the groups, except for higher hyperglycemia scores detected in women with controlled diabetes (Table 4.24).

Women with Controlled DM and Women with Poorly Controlled DM. Higher global DSC-R scores were noted in women with poorly controlled DM compared to their controlled peers (Table 4.24). The perceived burden of hypoglycemia, cardiovascular, ophthalmologic and psychological-fatigue symptoms was also greater for those with poor glucose control, while both groups reported similar scores for hyperglycemia, neurologic pain and sensation, and psychologic – cognitive symptoms.

Diabetes Symptoms Scores and Menopause Symptom Severity

Correlational analyses demonstrated menopause severity scores (total, factor, symptom specific) were positively associated to all diabetes symptom scores (data not shown). Pearson r values for most of these relationships were very high (r = 0.43-0.66) and reflects the common measurement items on both instruments. Hot flash and vaginal dryness severity scores (the symptoms most distinctly associated with estrogen loss), demonstrated the lowest r values (0.3) but the relationships were still significant. Number of years postmenopause and a diagnosis of DM in the reproductive years were positively associated with all DSC-R scores, while age of menopause demonstrated an inverse relationship. No association between diabetes symptoms scores and type of menopause (natural, surgical) was detected. Table 4.25 presents the correlation matrix with the DSC global scores.

Correlates of Diabetes Symptoms

Correlational analyses between the DSC-R global score and clinical and demographic variables of interest were conducted. With the exception of self monitored blood glucose, diabetes self care management behaviors were inversely related to DSC-R global scores. HbA1c values and insulin use were positively associated with the DSC-R global score, but the number of prescribed diabetes medications, duration of diabetes and age of diabetes diagnosis did not demonstrate a relationship (Table 4.26).

No relationship between current age, education level, employment or relationship status and the DSC-R global score was detected (Table 4.26). BMI and cigarette use were positively associated with the global burden score while income levels, alcohol use, and exercise demonstrated an inverse relationship. Altered mood diagnosis and measures of perceived stress, anxiety and depressive symptoms were positively associated with the diabetes symptoms global score.

Health Status

This last section addresses research question five and considers the influence of both diabetes and menopause symptoms on perceived health status in midlife women.

The summative composite scores for physical and mental health of the Short Form 12 Health Survey (SF-12) were used as the indicators of health status.

Health Status Scores by Study Group

Overall, women veterans rated their general health status as good (mean 3.0 ± 0.06), on a scale from 1 (poor) to 5 (excellent). Women without DM reported higher general health scores compared to both groups of women with DM who demonstrated similar ratings (Figure 4.4). Table 4.27 presents the major summative scale measures of SF-12. Mental Component Summary health scores (MCS) were similar among the study groups and consistent with other data regarding the mental health of the sample. Physical Component Summary (PCS) health scores were higher in women without diabetes compared to women with controlled diabetes as well as those with poorly controlled DM. Both groups of women with diabetes demonstrated similar PCS scores.

Perceived Health Status, Menopause and Diabetes

Correlational analyses demonstrated the PCS and MCS scores were inversely associated with the MSL total severity score, factor scores and all item specific symptom severity scores with the exception of vaginal dryness severity (data not shown). Age of menopause was positively related to PCS and MCS scores while number of years postmenopause was inversely associated (Table 4.28). Type of menopause was negatively associated with the PCS score but did not demonstrate a relationship with the mental health composite score.

Diabetes group status (no diabetes, controlled diabetes, poorly controlled diabetes; Table 4.28) was inversely associated with the PCS score but not associated with the mental health composite score. All DSC-R checklist scores (global, subscales) were negatively associated with the PCS and MCS summary measures (data not shown).

Correlates of Perceived Health Status

Age was inversely related to both the PCS and MSC scores (Table 4.28). BMI was negatively associated with PCS score but had no relationship with MCS score. Cigarette smoking was inversely related to both composite measures, while exercise (walking, aerobic) and employment status were positively related. Income was positively associated with the PCS score. No relationship was demonstrated between the health status scores and alcohol use, education, relationship status and any race/ethnicity group.

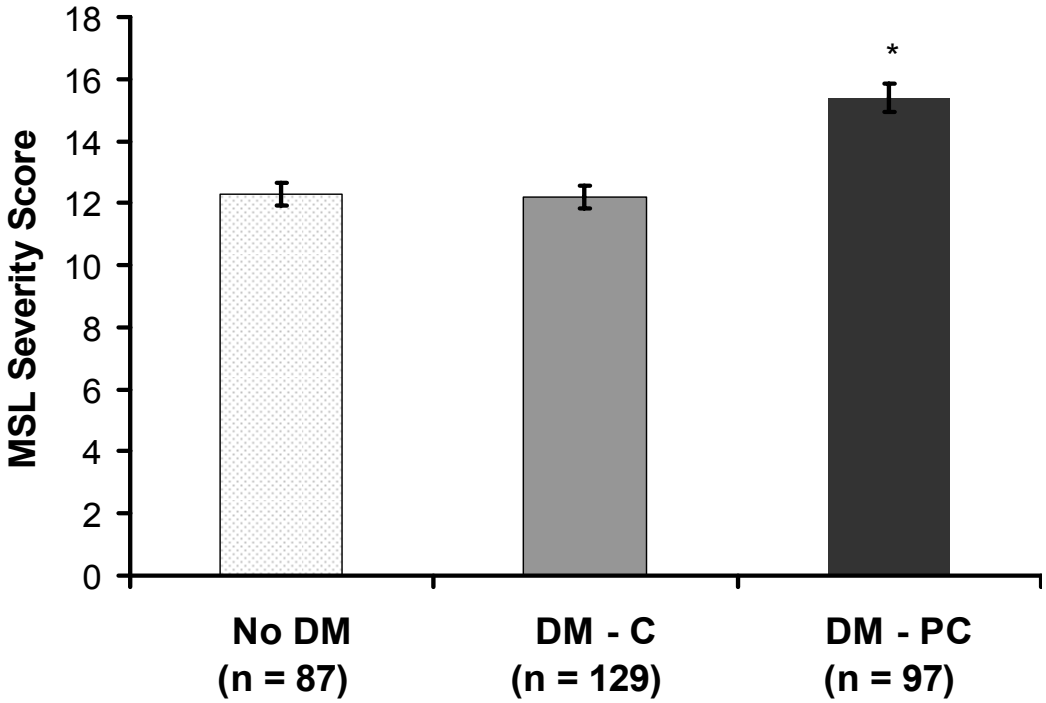
Multivariate Analysis: Health Status, Menopause Symptom Severity, Diabetes

Physical Health Composite Summary Score. Perceived menopause symptom severity (β = -0.28; $p < 0.001$), but not diabetes or glucose control status, was statistically significant and negatively associated with the physical health composite score (Table 4.29), adjusting for age, BMI, ethnicity, tobacco use, diagnosis of altered mood, employment and age of menopause. BMI (β = -0.30; $p < 0.001$), age (β = -0.13; $p = 0.02$), and cigarette smoking (β = -0.128; $p = 0.02$), demonstrated statistically significant negative associations with the PCS score while employment status (working) was positively associated (β = 0.24; $p < 0.001$).

In women with diabetes, both perceived menopause symptom severity (β = -0.24; $p < 0.001$), and poor glucose control (β = -0.13; $p = 0.03$) were negatively associated with physical health status (Table 4.29) controlling for BMI, age, cigarette use, altered mood, age of menopause, ethnicity and employment. While age did not demonstrate an independent relationship, BMI (β = -0.33; $p < 0.001$), and tobacco use (β = -0.17; $p = 0.008$) were negatively associated and employment positively related (β = 0.29; $p < 0.001$) with the PCS score after taking into account the other variables in the model.

Mental Health Composite Summary Score. Few variables demonstrated associations with the MCS score. Controlled or poorly controlled diabetes were not statistically significantly associated with the mental health composite score in any of the models tested with the full sample or the diabetic cohort. Controlling for ethnicity, BMI, employment, cigarette smoking and diabetes, both perceived menopause symptom severity (β = -0.42; $p < 0.001$) and altered mood (β = -0.34; $p < 0.001$) were negatively associated with the MCS score (Table 4.30), while age (β = 0.12; $p = 0.02$) was positively related. Among women with diabetes, perceived menopause symptom severity score (β = -0.43; $p < 0.001$), and an altered mood diagnosis (β = -0.36; $p < 0.001$) demonstrated a statistically significant negative association with the mental health composite score adjusting for BMI, age, smoking behavior, ethnicity, age of menopause, employment and glucose control.

Figure 4.1. Menopause Symptom Severity by Diabetes Groups



DM, Diabetes Mellitus (n = 87); DM-C, Diabetes Controlled (n = 129); DM-PC, Diabetes Poorly Controlled (n = 97).
ANOVA with post hoc bonferroni. *$p < 0.05$ versus No DM and DM-C

Figure 4.2. Menopause Symptom Severity: Women with Controlled and Poorly Controlled Diabetes

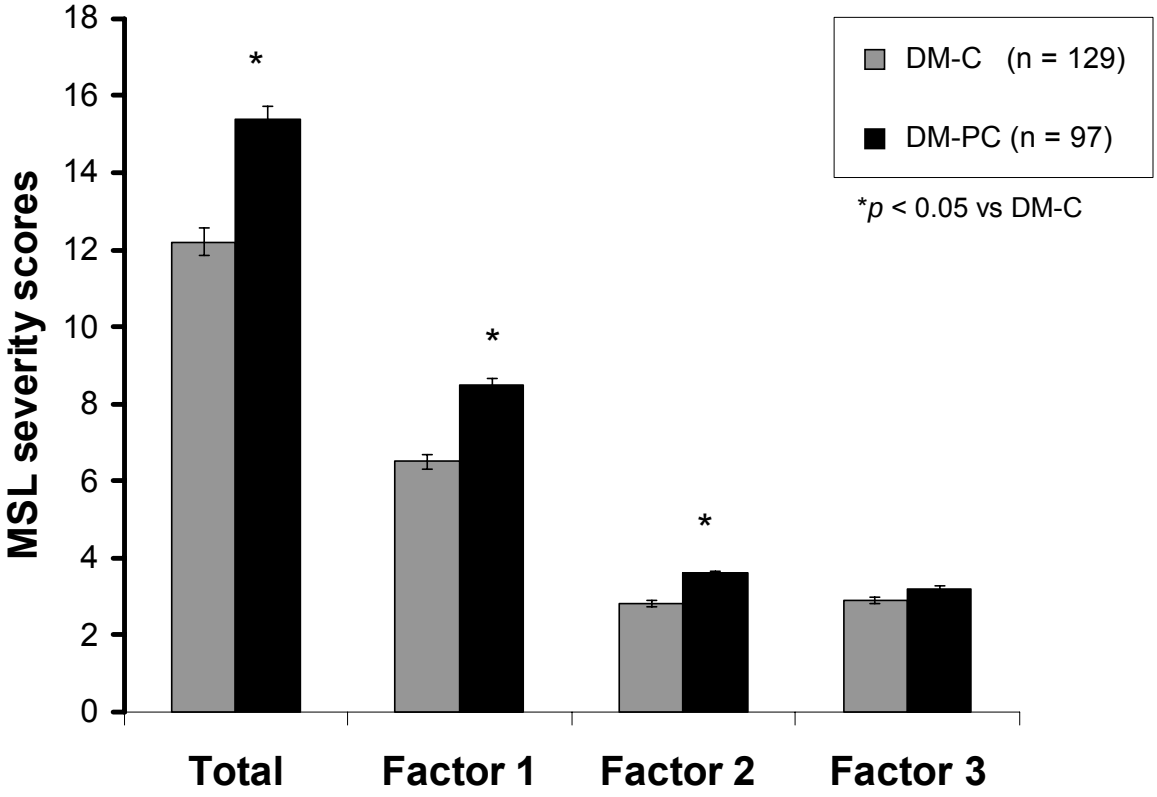


Figure Legend:
DM-C, Diabetes Controlled (n = 129); DM-PC, Diabetes Poorly Controlled (n = 97).
MSL, Menopause Symptom List severity score
ttest. *$p < 0.05$ compared to DM-C
Total: MSL total severity score, range 0-36.
Factor 1: Psychological symptoms severity score, range 0-21.
Factor 2: Somatic symptoms severity score, range 0-9.
Factor 3: Vasomotor symptoms severity score, range 0-6.

Figure 4.3. DSC-R Global Score by Diabetes Groups

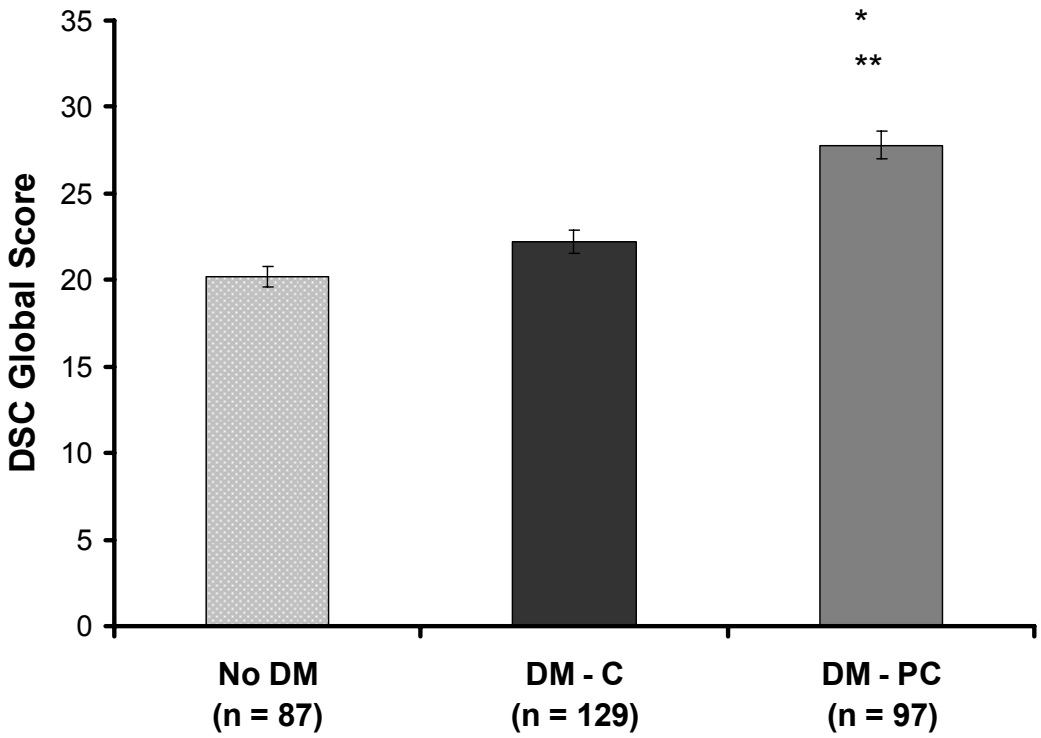


Figure 4 Legend.
DM, Diabetes Mellitus; DM-C, controlled DM; DM-PC, poorly controlled DM.
DSC-R Global, Diabetes Symptom Checklist – Revised Global Score.
ANOVA with post hoc bonferroni.
*$p < 0.02$ versus women without DM. **$p < 0.04$ versus women with controlled DM

Figure 4.4

Self-Reported General Health by Diabetes Groups

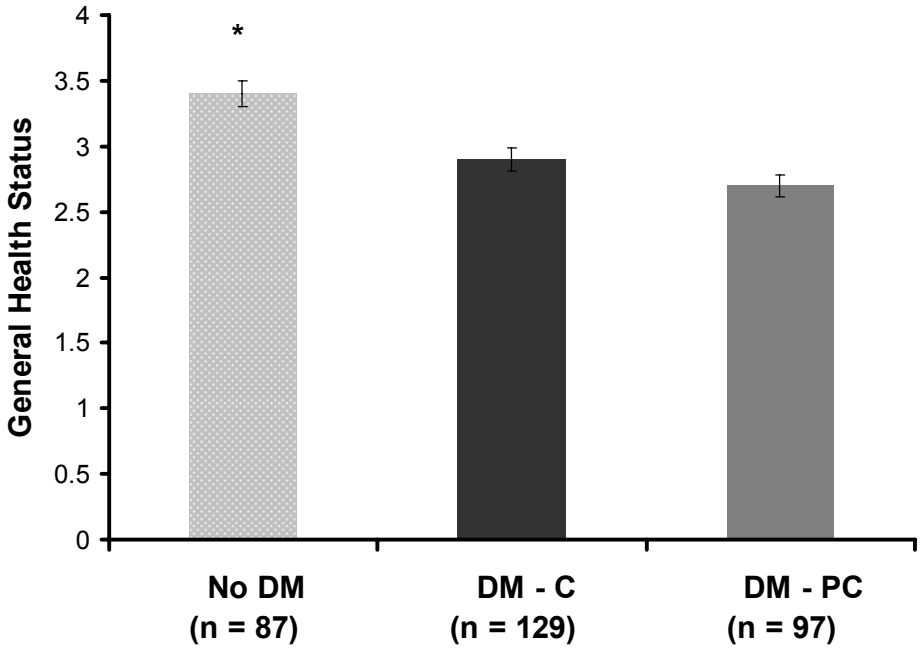


Figure 4 Legend.
DM, Diabetes Mellitus; DM-C, controlled DM; DM-PC, poorly controlled DM.
ANOVA with post hoc bonferroni
*$p < 0.05$ versus women with controlled DM and women with poorly controlled DM

Table 4.1 Clinical Characteristics by Diabetes Groups

	Total Sample (n =327)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 135)	Women with Poorly Controlled Diabetes (n = 102)
Age (years)[a,b]	55.0 ± 0.2	53.6 ± 0.5	55.5 ± 0.4	55.5 ± 0.5
Years Postmenopause[b]	11.3 ± 0.2	8.9 ± 0.8	11.6 ± 0.8	13.0 ± 0.9
BMI (kg/m^2)[#a,b]	33.9 ± 0.4	30.8 ± 0.6	34.8 ± 0.6	35.9 ± 0.7
Chronic medical conditions (number)[a,b]	4.7 ± 0.1	2.8 ± 0.2	5.3 ± 0.2	5.5 ± 0.3
HbA_{1c} (%)[#c]			6.4 ± 0.05	8.9 ± 0.2
Cholesterol (mg/dL)[#a,b]	182.5 ± 2.9	201.1 ± 5.3	172.7 ± 3.4	185.2 ± 6.3
LDL (mg/dL)[#a,b]	104.6 ± 2.5	122.7 ± 4.4	98.0 ± 3.0	104.1 ± 5.1
HDL (mg/dL)[#a,b]	46.2 ± 0.7	51.7 ± 2.0	45.1 ± 0.9	44.6 ± 1.3
Triglycerides(mg/dL)[#]	168.6 ± 8.6	137.3 ± 10.3	160.8 ± 8.6	196.7 ± 21.7
Lipid lowering medication use (%)[d]	200 (61)	22 (24.2)	100 (74.1)	78 (76.5)
SSRI, SSNI, or Gabapentin use (%)[e,f]	94(28.7)	18 (19.8)	43 (31.9)	33 (32.4)
PSS – 10	15.2 ± 0.4	14.8 ± 0.8	14.6 ± 0.7	16.4 ± 0.8
GAD – 7	5.2 ± 0.3	5.2 ± 0.6	5.0 ± 0.5	5.4 ± 0.5
CESD – 10	9.8 ± 0.4	9.0 ± 0.7	9.5 ± 0.6	10.8 ± 0.7

Values are mean ± SEM or n (%).
[#]Normality ensured by logarithmic transformation
BMI, body mass index; CESD-10, Center for Epidemiologic Studies Short Depression scale (0-30 scale); GAD-7, Generalized Anxiety Disorder-7 scale (0-21 scale); HbA_{1c}, Hemoglobin A1c; LDL, low density lipoprotein; HDL, high density lipoprotein; PSS-10,

Perceived Stress Scale-10 (0-40 scale); SSRI, selective serotonin reuptake inhibitor, SSNI, selective serotonin-norepinephrine reuptake inhibitor.
ANOVA with post hoc bonferroni.
[a]$p \leq 0.01$ women without diabetes vs. women with controlled diabetes
[b]$p \leq 0.01$ women without diabetes vs. women with poorly controlled diabetes
t-test.
[c]$p \leq 0.01$ women with controlled diabetes vs. women with poorly controlled diabetes
X^2 with Fisher's exact test: [d]$p \leq 0.05$. [e]$p = 0.08$ (all groups). [f]$p = 0.03$ (DM vs non-DM).

Table 4.2. Comorbid Medical Conditions by Diabetes Groups

	Total Sample (n =327)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 135)	Women with Poorly Controlled Diabetes (n = 102)
Hypertension[a]	234 (73)	47 (53)	109 (82)	78 (80)
Hyperlipidemia[a]	208 (65)	38 (43)	98 (74)	72 (73)
Arthritis/DJD[a]	155 (48)	32 (36)	75 (56)	48 (49)
Mood disorder	106 (33)	22 (25)	48 (36)	36 (37)
CVD*[a]	92 (29)	16 (18)	42 (32)	34 (35)
Neuropathy[a]	83 (26)	11 (12)	34 (26)	38 (39)
Lung disease	64 (20)	18 (20)	28 (21)	18 (18)
Thyroid disease	56 (17)	9 (10)	29 (21)	18 (18)
Retinopathy[a]	23 (7)	0 (0)	8 (6)	15 (15)
Renal disease[a]	18 (6)	3 (3)	4 (3)	11 (11)
Liver disease	10 (3)	1 (1)	4 (3)	5 (5)

Values are n (%).
CVD, cardiovascular disease; DJD, degenerative joint disease.
*CVD = all cardiac conditions: coronary artery disease, stroke, heart failure, rhythm disturbances, conduction disturbances, valvular disease, peripheral vascular disease
X^2 with Fisher's exact test $^a p \leq 0.05$

Table 4.3. Demographic Characteristics by Diabetes Groups

	Total Sample (*n* =327)	Women without Diabetes (*n* = 90)	Women with Controlled Diabetes (*n* = 135)	Women with Poorly Controlled Diabetes (*n* = 102)
Ethnicity				
White	187 (58)	57 (65)	80 (60.2)	50 (50)
Black	91 (28)	24 (27)	36 (27)	32 (32)
Hispanic	22 (7)	4 (5)	9 (6.8)	9 (9)
Other*	21 (7)	3 (3)	8 (6)	9 (9)
Relationship status				
Partner	156 (48)	45 (51)	59 (44)	52 (52)
No partner	166 (52)	44 (49)	74 (56)	48 (48)
Education[a]				
HS graduate or less	42 (13)	7 (8)	12 (9)	23 (23)
College, AA or Technical degree	186 (58)	50 (57)	83 (62)	53 (53)
BA degree or higher	93 (29)	31 (35)	38 (29)	24 (24)
Income[a]				
Above US median[#]	128 (41)	46 (52)	52 (41)	30 (31)
Below US median	183 (59)	42 (48)	74 (59)	67 (69)
Income[a]				
≤ $19,999	94 (30)	20 (23)	42 (33)	32 (33)
$20,000-50,000	153 (49)	39 (44)	65 (52)	49 (51)
> $50,000	64 (21)	29 (33)	19 (15)	16 (16)
Employment				
Working	178 (56)	57 (64)	74 (56)	47 (47)
Not working	142 (44)	32 (36)	58 (44)	52 (52)

Values are n (%).
HS, high school; AA, associate's degree; BA, bachelor's degree; US, United States
*Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian)
[#]United States Census Bureau (2006) data
X^2 with Fisher's exact test. [a]$p < 0.03$

Table 4.4 Lifestyle Behaviors by Diabetes Groups

	Total Sample (n =327)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 135)	Women with Poorly Controlled Diabetes (n = 102)
Tobacco use[a]	45 (14)	15 (17)	11 (8)	19 (19)
Alcohol use[b]	104 (32)	47 (53)	38 (29)	19 (19)
Exercise: Walking				
None	77 (24)	26 (28)	29 (23)	22 (23)
< 30 minutes	57 (18)	18 (19)	19 (15)	20 (20)
30-59 minutes	76 (24)	20 (22)	33 (26)	23 (23)
1-3 hours	73 (23)	17 (18)	33 (26)	23 (23)
>3 hours	37 (11)	12 (13)	14 (10)	11 (11)
Exercise: Aerobic				
None	242 (75)	72 (80)	98 (74)	72 (73)
< 30 minutes	26 (8)	4 (4)	10 (8)	12 (12)
30-60 minutes	21 (7)	6 (7)	8 (6)	7 (7)
1-3 hours	20 (6)	7 (8)	7 (5)	6 (6)
>3 hours	12 (4)	1 (1)	9 (7)	2 (2)

Values are n (%).
X^2 with Fisher's exact test.
[a]$p = 0.04$ [b]$p < 0.0001$

Table 4.5. Characteristics of Women with Diabetes Mellitus (DM)

	Women with DM (n =227)	Women with DM diagnosis before menopause (n = 74)	Women with DM diagnosis after menopause (n = 155)	Women with Controlled DM (n = 135)	Women with poorly Controlled DM (n = 102)
Age (years)	55.5 ± 0.5	55.1 ± 0.5	55.6 ± 0.3	55.5 ± 0.4	55.5 ± 0.4
BMI (kg/m^2)*	35.9 ± 0.7	34.4 ± 0.8	35.6 ± 0.6	34.7 ± 0.6	35.6 ± 0.7
Age of DM diagnosis[a,b]	47.9 ± 0.5	42.7 ± 0.9	50.4 ± 0.4	49.8 ± 0.5	45.4 ± 0.8
DM duration (years)[a,b]	7.6 ± 0.4	12.2 ± 0.9	5.5 ± 0.4	5.7 ± 0.5	10.1 ± 0.7
Diabetes Medications (number)[a,b]	1.5 ± 0.06	1.7 ± 0.1	1.4 ± 0.07	1.1 ± 0.07	1.9 ± 0.09
HbA_{1c} (%)*[a,b]	7.5 ± 0.1	7.9 ± 0.2	7.2 ± 0.1	6.4 ± 0.05	8.9 ± 0.2

Values are mean ± SEM.
*Logarithmic transformation to ensure normality
BMI, body mass index; DM, diabetes mellitus; HbA_{1c}, Hemoglobin A1c
*t*test.
[a]$p \leq 0.01$ women with DM before menopause vs. women with DM after menopause.
[b]$p \leq 0.001$ women with controlled DM vs. women with poorly controlled DM

Table 4.6. Diabetes Self Care Management Behaviors

	Women with Diabetes (n =227)	Women with Controlled Diabetes (n = 135)	Women with Poorly Controlled Diabetes (n = 102)
Diabetes treatments			
Check glucose	212 (92)	118 (91)	94 (94)
Oral medications	181 (78)	100 (77)	81 (80)
Diet[a]	151 (65)	95 (73)	56 (55)
Exercise[a]	102 (44)	65 (50)	37 (37)
Insulin use[a]	76 (33)	20 (15)	52 (52)
Other injections	3 (1)	2 (1.5)	1 (1)
Insulin Use			
Once daily	15 (20)	15 (20)	15 (20)
Twice daily	48 (63)	48 (63)	48 (63)
3-4 times/day	11 (15)	11 (15)	11 (15)
Continuous	1 (1)	1 (1)	1 (1)
As needed	1 (1)	1 (1)	1 (1)
Diabetes self care[*b]			
Weight control	2.3 ± 0.08	2.4 ± 0.1	2.2 ± 0.1
Take medications	4.5 ± 0.05	4.5 ± 0.08	4.5 ± 0.08
Follow diet plan	3.5 ± 0.06	3.5 ± 0.08	3.4 ± 0.1
Exercise regularly	2.8 ± 0.08	2.8 ± 0.1	2.6 ± 0.1
Check feet	4.5 ± 0.06	4.6 ± 0.08	4.5 ± 0.1
Check glucose as ordered	3.9 ± 0.08	4.0 ± 0.1	3.8 ± 0.1

Values are n (%) or mean ± SEM

[*] reported adherence on a 1-5 scale from 'none of the time' to 'all of the time'.

X^2 with Fisher's exact test. [a] $p \leq 0.01$

t-test.

[b] p = NS; women with controlled diabetes vs. women with poorly controlled diabetes

Table 4.7. Type of Menopause by Diabetes Groups

	Entire Sample (n = 327)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 133)	Women with Poorly Controlled Diabetes (n = 102)
Type of Menopause				
Natural[a]	146 (44.9)	43 (47.8)	60 (45.1)	43 (42.2)
Induced*	179 (55.1)	47 (52.2)	73 (54.9)	59 (57.8)
Surgical	172 (52.9)	46 (51.1)	69 (51.9)	57 (55.9)
Other	7 (2.2)	1 (1.1)	4 (3.0)	2 (1.9)
Surgical Causes[b]				
TAH-BSO	89 (51.7)	25 (54.3)	41 (59.4)	23 (40.4)
Hysterectomy	83 (48.3)	21 (45.7)	28 (40.6)	34 (59.6)

Values are n (%).
TAH-BSO, total abdominal hysterectomy with bilateral salpingoopherectomy.
*includes TAH-BSO, hysterectomy (uterus with or without one ovary removed), exposure induced causes (drug, trauma, procedural).
X^2 with Fisher's exact test.
[a]p = NS (Natural/Induced by group).
[b]p = 0.09 (Surgical causes by group).

Table 4.8. Type of Menopause: Women with Diabetes Pre- or Postmenopause

Type of Menopause	Women with Diabetes (n = 222)	Women with Premenopause Diabetes Diagnosis (n = 72)	Women with Postmenopause Diabetes Diagnosis (n = 150)
Natural[a]	100 (45.1)	48 (66.7)	52 (34.7)
Surgical	122 (54.9)	24 (33.3)	98 (65.3)
Surgical Type[b]			
TAH-BSO	61(50.0)	15 (62.5)	46 (46.9)
Hysterectomy	61(50.0)	9 (37.5)	52 (53.1)

Values are n (%).
TAH-BSO, total abdominal hysterectomy with bilateral salpingoopherectomy.
*includes TAH-BSO, hysterectomy (uterus with or without one ovary removed),
X^2 with Fisher's exact test.
[a]$p < 0.0001$ (Natural/Surgical by group).
[b]p = NS (Surgical types by group)

Table 4.9. Age of Menopause by Diabetes Groups

	Entire Sample (n = 326)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 133)	Women with Poorly Controlled Diabetes (n = 102)
Age of Menopause	43.7 ± 0.4	44.7 ± 0.8	43.9 ± 0.7	42.5 ± 0.9
Natural Menopause	49.2 ± 0.3	49.7 ± 0.5	48.8 ± 0.6	49.3 ± 0.7
Induced Menopause	39.2 ± 0.6	40.2 ± 1.1	39.8 ± 0.9	37.7 ± 1.0
Surgical Menopause	39.1 ± 0.6	40.1 ± 1.2	39.6 ± 0.9	37.6 ± 1.0
TAH-BSO	41.4 ± 0.8	40.2 ± 1.7	41.7 ± 1.1	42.1 ± 1.6
Hysterectomy[a,b]	36.5 ± 0.8	40.0 ± 1.6	36.5 ± 1.3	34.4 ± 1.0

Values are mean ± SEM.
TAH-BSO, total abdominal hysterectomy with bilateral salpingoopherectomy
ANOVA with post hoc bonferroni
[a]p = 0.01 women with poorly controlled diabetes vs. women without diabetes.
[b]p = 0.06 women with poorly controlled diabetes vs. women with controlled diabetes

Table 4.10. Years Postmenopause by Diabetes Groups

	Entire Sample (n = 326)	Women without Diabetes (n = 90)	Women with Controlled Diabetes (n = 133)	Women with Poorly Controlled Diabetes (n = 102)
Years postmenopause[a]	11.3 ± 0.2	8.9 ± 0.8	11.6 ± 0.8	13.0 ± 0.9
Postmenopause Stage[b*]				
I. Early Postmenopause 0 - 5 years	97 (31)	34 (39.1)	39 (29.3)	24 (24.5)
IIa. Late Postmenopause 6 -10 years	88 (28)	28 (32.2)	34 (25.6)	26 (26.5)
IIb. Late Postmenopause 11 - 20 years	77 (24)	16 (18.4)	37 (27.8)	24 (24.5)
IIc. Late Postmenopause > 20 years	56 (17)	9 (10.3)	23 (17.3)	24 (24.5)

Values are n (%) or mean ± SEM
*Postmenopause Stage derived using the Stages of Reproductive Aging Workshop criteria but modified to reflect sample distribution
ANOVA with post hoc bonferroni.
[a]$p < 0.01$ women without diabetes vs. women with poorly controlled diabetes
X^2 with Fisher's exact test.
[b]p = NS (0.08) for group differences in postmenopause stage.

Table 4.11. Menopause Difficulty

	Menopause Difficulty*
Women without DM (n = 85)[a]	4.6 ± 0.3
Women with DM (n = 221)	4.8 ± 0.2
Women without DM (n = 85)[b]	4.6 ± 0.3
Women with controlled DM (n = 127)	4.6 ± 0.3
Women with poorly controlled DM (n = 94)	4.9 ± 0.3
Natural Menopause (n = 141)[c]	4.4 ± 0.2
Surgical Menopause (n = 158)	5.1 ± 0.2

Values are mean ± SEM.
*menopause difficulty on 0-10 scale from not difficult to very difficult.
t test. [a]*p* = NS. [c]*p* = 0.05 vs. surgical menopause
ANOVA. [b]*p* = NS

Table 4.12. Menopause Symptom Prevalence: Women with and without Diabetes.

	Entire Sample (n = 313)	Women without Diabetes (n = 87)	Women with Diabetes (n = 226)
Muscle/Joint aches	245 (78.6)	68 (78.2)	177 (78.7)
Hot Flashes	233 (74.4)	66 (75.9)	167 (73.9)
Trouble sleeping	214 (68.6)	60 (69.0)	154 (68.4)
Memory	203 (65.0)	57 (65.5)	146 (64.9)
Irritable	199 (64.2)	55 (63.2)	144 (64.6)
Sad or blue	191 (61.2)	50 (57.5)	141 (62.7)
Decreased libido	178 (58.4)	52 (60.5)	126 (57.5)
Leaking urine	179 (57.2)	45 (51.7)	134 (59.3)
Mood Swings	169 (54.2)	44 (50.6)	125 (55.6)
Anxiety	165 (52.9)	48 (55.2)	117 (52.0)
Headaches	147 (47.0)	37 (42.5)	110 (48.7)
Vaginal dryness	141 (45.2)	42 (48.3)	99 (44.0)

Values are n (%).
X^2 with Fisher exact test.
p = NS.

Table 4.13. Menopause Symptom Prevalence by Diabetes Groups.

	Entire Sample (n = 313)	Women Without Diabetes (n = 87)	Women with controlled Diabetes (n = 129)	Women with poorly controlled Diabetes (n = 97)
Muscle/Joint aches	245 (78.6)	68 (78.2)	100 (77.5)	77 (80.2)
Hot Flashes	233 (74.4)	66 (75.9)	90 (70.0)	77 (79.4)
Trouble sleeping[b]	214 (68.6)	60 (69.0)	81 (62.3)	73 (76.0)
Memory[b]	203 (65.0)	57 (65.5)	76 (58.9)	70 (72.9)
Irritable	199 (64.2)	55 (63.2)	79 (61.7)	65 (68.4)
Sad or blue	191 (61.2)	50 (57.5)	78 (60.5)	63 (65.7)
Decreased libido[b]	178 (58.4)	52 (60.5)	66 (52.0)	60 (65.2)
Leaking urine	179 (57.2)	45 (51.7)	71 (55.0)	63 (65.0)
Mood Swings	169 (54.2)	44 (50.6)	66 (51.2)	59 (61.2)
Anxiety[a,b]	165 (52.9)	48 (55.2)	58 (45.0)	59 (61.5)
Headaches[a,b]	147 (47.0)	37 (42.5)	52 (40.3)	58 (59.8)
Vaginal dryness	141 (45.2)	42 (48.3)	52 (40.3)	47 (50.0)

Values are n (%).
X^2 with Fisher exact test.
[a]$p < 0.05$ (comparisons between women without diabetes, women with controlled diabetes, women with poorly controlled diabetes)
[b]$p < 0.05$ (comparisons between women with controlled diabetes and women with poorly controlled diabetes)
p = NS (comparisons between women without diabetes and women with controlled diabetes).

Table 4.14. Menopause Symptom Severity: Women with and without Diabetes

	Entire Sample (n = 313)	Women without Diabetes (n = 87)	Women with Diabetes (n = 226)
MSL severity score*	13.2 ± 0.5	12.3 ± 0.8	13.5 ± 0.6
MSL factor 1 score (psychological)	7.1 ± 0.3	6.5 ± 0.5	7.4 ± 0.4
MSL factor 2 score (somatic)	3.1 ± 0.1	3.0 ± 0.3	3.1 ± 0.2
MSL factor 3 score (vasomotor)	3.0 ± 0.1	2.9 ± 0.2	3.0 ± 0.1
Muscle/Joint aches	1.7 ± 0.06	1.6 ± 0.1	1.7 ± 0.07
Trouble sleeping	1.4 ± 0.07	1.4 ± 0.1	1.5 ± 0.08
Hot Flashes	1.3 ± 0.05	1.3 ± 0.1	1.3 ± 0.07
Decreased libido	1.3 ± 0.07	1.2 ± 0.1	1.3 ± 0.09
Irritable	1.1 ± 0.06	1.0 ± 0.1	1.1 ± 0.07
Memory	1.0 ± 0.05	0.9 ± 0.09	1.0 ± 0.06
Sad or blue	1.0 ± 0.06	0.9 ± 0.1	1.1 ± 0.07
Leaking urine	1.0 ± 0.06	0.9 ± 0.1	1.0 ± 0.07
Mood Swings	0.9 ± 0.06	0.8 ± 0.1	1.0 ± 0.07[a]
Anxiety	0.8 ± 0.05	0.8 ± 0.09	0.9 ± 0.07
Vaginal dryness	0.8 ± 0.06	0.9 ± 0.1	0.8 ± 0.06
Headaches	0.8 ± 0.06	0.7 ± 0.1	0.8 ± 0.07
Hot Flash score	9.8 ± 0.7	10.5 ± 1.4	9.5 ± 0.9

Values are mean ± SEM.
*symptom severity on 0-3 scale from none to severe for each symptom.
MSL range 0-36; Factor 1 range 0-21; Factor 2 range 0-9; Factor 3 range 0-6.
*t*test. [a]$p < 0.05$

Table 4.15. Menopause Symptom Severity by Diabetes Groups

	Women Without DM (n = 87)	Women with controlled DM (n = 129)	Women with poorly controlled DM (n = 97)
MSL total score* [a,b,c]	12.3 ± 0.8	12.2 ± 0.8	15.4 ± 0.8
MSL factor 1 score (psychological)[a,b,c]	6.5 ± 0.5	6.5 ± 0.4	8.5 ± 0.4
MSL factor 2 score (somatic)[c]	3.0 ± 0.3	2.8 ± 0.2	3.6 ± 0.2
MSL factor 3 score (vasomotor)	2.9 ± 0.2	2.9 ± 0.1	3.2 ± 0.1
Muscle/Joint aches	1.6 ± 0.1	1.7 ± 0.07	1.7 ± 0.07
Hot Flashes	1.3 ± 0.1	1.2 ± 0.07	1.4 ± 0.07
Trouble sleeping[b,c]	1.4 ± 0.1	1.3 ± 0.08	1.7 ± 0.08
Decreased libido[c]	1.2 ± 0.1	1.2 ± 0.09	1.5 ± 0.09
Irritable	1.0 ± 0.1	1.0 ± 0.07	1.2 ± 0.07
Memory	0.9 ± 0.09	0.9 ± 0.06	1.1 ± 0.06
Leaking urine	0.9 ± 0.1	0.9 ± 0.07	1.1 ± 0.07
Sad or blue	0.9 ± 0.1	1.0 ± 0.07	1.2 ± 0.07
Mood Swings[a]	0.8 ± 0.1	0.9 ± 0.07	1.1 ± 0.07
Anxiety[b,c]	0.8 ± 0.09	0.7 ± 0.07	1.1 ± 0.07
Vaginal dryness	0.9 ± 0.1	0.7 ± 0.06	0.9 ± 0.06
Headaches[a,b,c]	0.7 ± 0.1	0.7 ± 0.07	1.0 ± 0.07
Hot Flash score	10.5 ± 1.4	9.6 ± 0.9	9.5 ± 0.9

Values are mean ± SEM.
*symptom severity on 0-3 scale from none to severe for each symptom.
MSL range 0-36; Factor 1 range 0-21; Factor 2 range 0-9; Factor 3 range 0-6.
ANOVA with post-hoc bonferroni.
[a]$p < 0.05$ women with poorly controlled diabetes vs. women without diabetes.
[b]$p < 0.05$ women with poorly controlled diabetes vs. women with controlled diabetes
t-test.
p = NS; women without diabetes vs. women with controlled diabetes
[c]$p < 0.05$ women with poorly controlled diabetes vs. women with controlled diabetes

Table 4.16. Correlation Matrix: Menopause Symptom Severity Score

	MSL score All women (n = 313)	**MSL score** Women without DM (n = 87)	**MSL score** Women with DM (n = 226)
Age in years	-0.02	-0.06	-0.04
BMI[#]	0.11	0.07	0.01
Cigarette smoking	0.20*	0.20	0.20*
Alcohol use	-0.08	-0.17	-0.03
Exercise: Aerobic	-0.16*	-0.16	-0.16*
Exercise: Walking	-0.08	-0.008	-0.11
Ethnicity –White	-0.03	-0.02	-0.03
Ethnicity – Hispanic	0.02	0.02	0.02
Ethnicity – Black	0.02	0.01	-0.05
Ethnicity – Other**	0.15*	0.13	0.14*
Employment: working or not	-0.17*	-0.06	-0.21*
Income	-0.09	-0.13	-0.05
Education	-0.07	-0.15	-0.02
Relationship status	-0.08	-0.08	-0.08
Age of menopause	-0.17*	-0.14	-0.17*
Years postmenopause	0.15*	0.12	0.14*
Type of menopause	0.08	0.007	0.11
Altered mood diagnosis	0.29*	0.33*	0.28*
CESD-10 score	0.70*	0.78*	0.66*
GAD-7 score	0.65*	0.69*	0.65*
PSS-10 score	0.54*	0.55*	0.53*
DSC-R global score	0.70*	0.67*	0.70*
SSRI or SNRI use	0.22*	0.05	0.26*

BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale; DSC-R, Diabetes Symptom Checklist-Revised; GAD-7, Generalized Anxiety Disorder-7 scale; HbA1c, Hemoglobin A1c result; PSS-10, Perceived Stress Scale-10.
**Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander(n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian)
[#]Log transformed to ensure normality. Pearson r. $*p \leq 0.05$.

Table 4.17. Correlations: Menopause Symptom Severity and Diabetes

Glucose Related Variables	**MSL score** Women with DM (n = 226)	**MSL score** Women with DM-C (n = 129)	**MSL score** Women with DM-PC (n = 97)
HbA_{1c} result[#]	0.17*	0.04	0.02
Duration of diabetes	0.10	0.004	0.06
Age of diabetes diagnosis	-0.12	-0.14	0.03
DM diagnosis before/after menopause	0.03	-0.03	0.25*
Number of diabetes medications	0.03	-0.01	-0.11
Insulin use	0.14*	-0.01	0.14
Adherence to self care behaviors			
Weight control	-0.14*	-0.11	-0.16
Diet	-0.20*	-0.20*	-0.17
Exercise	-0.17*	-0.14	-0.19
Diabetes Symptom Checklist Scores			
DSC-R total	0.70*	0.66*	0.75*
DSC-R global	0.70*	0.67*	0.75*
DSC-R subscales			
Hypoglycemia	0.64*	0.64*	0.64*
Hyperglycemia	0.50*	0.42*	0.51*
Cardiovascular	0.45*	0.36*	0.53*
Ophthalmologic	0.53*	0.50*	0.61*
Neurologic – Sensory	0.42*	0.44*	0.47*
Neurologic – Pain	0.46*	0.38*	0.46*
Psychologic – Fatigue	0.59*	0.54*	0.65*
Psychologic – Cognition	0.62*	0.62*	0.63*

DM, diabetes mellitus; DM-C, diabetes mellitus - controlled; DM-PC, diabetes mellitus - poorly controlled; DSC-R, diabetes symptom checklist - revised; HbA1c, Hemoglobin A1c result. #Log transformed to ensure normality. Values are Pearson r. *$p < 0.05$.

Table 4.18 Multivariate Analysis: Menopause Symptom Severity Score

Variable	Standardized Beta	*p* value	R^2
Model 1 (All Women)			0.15
Uncontrolled Diabetes	0.12	0.09	
Controlled Diabetes	−0.02	0.68	
Altered Mood disorder	0.27	0.000	
Tobacco Use	0.16	0.008	
Age of menopause	−0.13	0.08	
Ethnicity - Black	0.02	0.64	
Ethnicity - Hispanic	0.06	0.35	
Ethnicity - Other$^{\Sigma}$	0.10	0.08	
BMI$^{\#}$	0.03	0.61	
Type of menopause	0.005	0.94	
Model 2 (Women with Diabetes)			0.14
Uncontrolled Diabetes	0.15	0.03	
Altered Mood disorder	0.25	0.000	
Tobacco Use	0.18	0.01	
Age of menopause	−0.11	0.19	
Ethnicity - Black	0.04	0.63	
Ethnicity - Hispanic	0.06	0.38	
Ethnicity – Other$^{\Sigma}$	0.10	0.14	
BMI$^{\#}$	0.04	0.53	
Type of menopause	0.02	0.80	

$^{\#}$Log transformed to ensure normality. BMI, Body Mass Index
$^{\Sigma}$Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).

Table 4.19 Correlation Matrix: MSL Factor Severity Scores

Variable	Factor 1 Severity (psychological)	Factor 2 Severity (somatic)	Factor 3 Severity (vasomotor)
HbA_{1c} result[#]	0.17*	0.11	0.05
Age	−0.02	0.03	−0.04
Diabetes Status	0.07	0.10	0.04
Cigarette smoking	0.18*	0.16*	0.10
Ethnicity - White	−0.06	0.04	−0.05
Ethnicity – Black	−0.007	−0.12*	0.04
Ethnicity - Hispanic	0.01	0.10	−0.09
Ethnicity - Other[Σ]	0.14*	0.10	0.02
BMI[#]	0.08	0.14*	0.05
Years postmenopause	0.14*	0.12*	0.08
Age of menopause	−0.16*	−0.11**	−0.11**
Type of menopause	0.06	0.08	0.03
Exercise: Walking	−0.05	−0.13*	−0.05
Exercise: Aerobic	−0.16*	−0.14*	−0.04
Alcohol use	−0.09	−0.03	−0.04
Employment: work or not	−0.21*	0.06	−0.06
Income	0.11*	0.01	−0.05
Education	−0.10	0.01	−0.03
Relationship: partner or not	−0.06	0.17*	−0.005
Mood disorder diagnosis	0.34*	0.14*	0.13*
PSS-10 score	0.60*	0.26*	0.40*
GAD-7 score	0.70*	0.33*	0.50*
CESD-10 score	0.74*	0.32*	0.30*

[#]Log transformed to ensure normality.
[Σ]Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).

BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale;GAD-7, Generalized Anxiety Disorder-7 scale; HbA1c, Hemoglobin A1c result; PSS-10, Perceived Stress Scale-10.
Values are Pearson r. *$p \leq 0.05$. **$p = 0.06$.

Table 4.20. Multivariate Analysis: Factor 1 Psychological Severity Score

Variable	Standardized Beta	*p* value	R^2
Model 1 (All Women)			0.18
Uncontrolled Diabetes	0.13	0.07	
Controlled Diabetes	−0.03	0.70	
Altered Mood disorder	0.33	0.000	
Tobacco Use	0.13	0.02	
Ethnicity – Black	0.07	0.25	
Ethnicity – Hispanic	0.05	0.35	
Ethnicity – Other$^{\Sigma}$	0.13	0.02	
Age of menopause	−0.12	0.10	
Type of menopause	−0.02	0.80	
BMI$^{\#}$	0.02	0.80	
Model 2 (Women with Diabetes)			0.16
Uncontrolled Diabetes	0.15	0.03	
Altered Mood disorder	0.32	0.000	
Tobacco Use	0.14	0.04	
Ethnicity - Black	0.09	0.25	
Ethnicity - Hispanic	0.05	0.41	
Ethnicity – Other$^{\Sigma}$	0.11	0.08	
Age of menopause	−0.09	0.27	
Type of menopause	−0.02	0.90	
BMI$^{\#}$	0.01	0.73	

$^{\#}$Log transformed to ensure normality.
BMI, Body Mass Index
$^{\Sigma}$Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).

Table 4.21. Multivariate Analysis: Factor 2 Somatic Severity Score

Variable	Standardized Beta	*p* value	R^2
Model 1 (All Women)			0.20
Uncontrolled Diabetes	0.03	0.70	
Controlled Diabetes	−0.03	0.65	
Relationship status	0.19	0.001	
Tobacco Use	0.14	0.01	
Ethnicity - Black	−0.07	0.25	
Ethnicity - Hispanic	0.12	0.04	
Ethnicity - Other$^{\Sigma}$	0.02	0.46	
Anxiety (GAD-7 score)	0.19	0.02	
Depressive symptoms (CESD-10)	0.16	0.04	
BMI$^{\#}$	0.14	0.05	
Age of menopause	−0.03	0.72	
Type of menopause	0.12	0.08	
Model 2 (Women with Diabetes)			0.17
Uncontrolled Diabetes	0.07	0.34	
Relationship status	0.20	0.003	
Tobacco Use	0.16	0.02	
Ethnicity - Black	−0.02	0.81	
Ethnicity - Hispanic	0.13	0.05	
Ethnicity - Other$^{\Sigma}$	0.04	0.53	
Anxiety (GAD-7 score)	0.19	0.05	
Depressive symptoms (CESD-10)	0.10	0.30	
BMI$^{\#}$	0.11	0.09	
Age of Menopause	−0.50	0.63	
Type of Menopause	0.94	0.35	

[#]Log transformed to ensure normality.
BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale; GAD-7, Generalized Anxiety Disorder-7 scale.
[Σ]Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).

Table 4.22. Multivariate Analysis: Factor 3 Vasomotor Severity Score

Variable	Standardized Beta	*p* value	R^2
Model 1 (All Women)			0.19
Uncontrolled Diabetes	0.03	0.71	
Controlled Diabetes	0.02	0.76	
Tobacco Use	0.03	0.60	
Ethnicity - Black	0.02	0.78	
Ethnicity - Hispanic	−0.08	0.19	
Ethnicity - Other$^{\Sigma}$	0.00	0.99	
Anxiety (GAD-7 score)	0.12	0.15	
Depressive symptoms (CESD-10)	0.36	0.000	
BMI$^{\#}$	0.02	0.68	
Age of menopause	−0.05	0.94	
Type of menopause	0.04	0.50	
Model 2 (Women with Diabetes)			0.16
Uncontrolled Diabetes	0.01	0.93	
Tobacco Use	0.003	0.96	
Ethnicity - Black	0.02	0.85	
Ethnicity - Hispanic	−0.07	0.31	
Ethnicity - Other$^{\Sigma}$	0.03	0.69	
Anxiety (GAD-7 score)	0.10	0.29	
Depressive symptoms (CESD-10)	0.35	0.000	
BMI$^{\#}$	0.02	0.67	
Age of menopause	−0.05	0.92	
Type of menopause	0.10	0.25	

[#]Log transformed to ensure normality.
[Σ]Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).
BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale; GAD-7, Generalized Anxiety Disorder-7 scale.

Table 4.23 Diabetes Symptoms: Women with and without Diabetes

	Women without Diabetes (*n* = 87)	Women with Diabetes (*n* = 226)
DSC-R global score[a]	20.2 ± 1.7	24.5 ± 1.2
DSC-R subscales		
Psychologic–Fatigue	36.4 ± 2.8	41.2 ± 1.8
Psychologic–Cognition	26.5 ± 2.3	27.6 ± 1.6
Hypoglycemia	19.2 ± 2.2	22.8 ± 1.4
Hyperglycemia[a]	19.9 ± 2.4	29.9 ± 1.7
Cardiovascular	18.1 ± 2.0	18.5 ± 1.3
Neurologic–Sensory	18.9 ± 2.1	22.5 ± 1.6
Neurologic–Pain	15.2 ± 2.4	16.7 ± 1.4
Ophthalmologic[b]	11.7 ± 1.9	16.1 ± 1.3

Values are mean ± SEM.
DSC-R, Diabetes Symptom Checklist-Revised- all scores standardized to a 0-100 scale
*t*test. [a]$p < 0.05$ [b]$p = 0.06$

Table 4.24. Diabetes Symptoms by Diabetes Study Groups

	Women without Diabetes (n = 87)	Women with controlled DM (n = 129)	Women with poorly Controlled DM (n = 97)
DSC-R total [a,d]	19.9 ± 1.7	21.9 ± 1.4	27.4 ± 2.1
DSC-R global [a,b,d]	20.2 ± 1.7	22.2 ± 1.4	27.8 ± 2.1
DSC-R subscales			
Psychologic–Fatigued[d]	36.4 ± 2.8	37.9 ± 2.4	45.7 ± 2.6
Psychologic–Cognition	26.5 ± 2.3	25.4 ± 1.9	30.8 ± 2.7
Hypoglycemia[d]	19.2 ± 2.2	20.3 ± 1.7	26.1 ± 2.4
Hyperglycemia[a,c]	19.9 ± 2.4	27.5 ± 2.3	33.2 ± 2.7
Cardiovascular [b,d]	18.1 ± 2.0	15.3 ± 1.5	22.9 ± 2.4
Neurologic–Sensory	18.9 ± 2.1	20.9 ± 1.9	24.8 ± 2.7
Neurologic–Pain	15.2 ± 2.4	14.8 ± 1.8	19.4 ± 2.5
Ophthalmologic[a,b,d]	11.7 ± 1.9	13.3 ± 1.6	20.0 ± 2.3

Values are mean ± SEM.
DSC-R, Diabetes Symptom Checklist-Revised standardized to a 0-100 scale
ANOVA with post hoc bonferroni
[a] $p < 0.02$ women with poorly controlled diabetes vs. women without diabetes
[b] $p < 0.04$ women with poorly controlled diabetes vs. women with controlled diabetes
t-test
[c] $p \leq 0.05$ women with controlled diabetes vs. women without diabetes
[d] $p \leq 0.05$ women with poorly controlled diabetes vs. women with controlled diabetes

Table 4.25. Correlation Matrix: DSC-R Global Scores and Menopause Variables

	DSC-R Global Score
MSL Severity Scores	
Total	0.70*
Factor 1 psychological	0.67*
Factor 2 somatic	0.47*
Factor 3 vasomotor	0.50*
Hot flashes	0.31*
Vaginal dryness	0.32*
Memory loss	0.58*
Irritability	0.50*
Mood swings	0.52*
Sad or Blue	0.48*
Anxiety	0.52*
Sleep trouble	0.43*
Muscle/Joint aches	0.49*
Headaches	0.42*
Urinary leak	0.38*
Decreased libido	0.31*
Menopause Related Variables	
Age of Menopause	−0.24*
Years Postmenopause	0.22*
Menopause Difficulty	0.34*
Diabetes diagnosis before menopause	0.14*
Type of menopause (natural, surgical)	0.08

Values are Pearson r. *$p \leq 0.05$.
DSC-R, Diabetes Symptoms Checklist-Revised; MSL, Menopause Symptom List

Table 4.26. DSC-R Global Scores and Clinical/Demographic Variables

	Diabetes Symptom Checklist Global Score
Diabetes Variables	
HbA_{1c}[#]	0.20*
Duration of diabetes	0.12
Age of diabetes diagnosis	−0.07
Number of diabetes meds	0.03
Insulin use	0.18*
Diabetes Self Care Management	
Weight control	−0.21*
Take medications	−0.22*
Manage diet	−0.30*
Exercise	−0.35*
Check feet	−0.14*
Check glucose as ordered	−0.10
Demographic Variables	
Age (years)	0.003
BMI[#] (kg/m^2)	0.14*
Education	−0.07
Income	−0.13*
Employment	0.07
Relationship status	0.004
Health Behaviors	
Cigarette smoking	0.18*
Alcohol use	−0.15*
Walking exercise	−0.12*
Aerobic exercise	−0.25*
Mood related variables	
Altered mood diagnosis	0.37*
CESD-10 score	0.66*
GAD-7 score	0.60*
PSS-10 score	0.57*

Values are Pearson r. *$p \leq 0.05$.
[#]Log transformed to ensure normality.
BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale; DSC-R, Diabetes Symptom Checklist-Revised; GAD-7, Generalized Anxiety Disorder-7 scale; HbA_{1c}, Hemoglobin A1c value, PSS-10, Perceived Stress Scale.

Table 4.27. Health Status by Diabetes Groups

	Women without Diabetes (n = 87)	Women with controlled DM (n = 129)	Women with poorly controlled DM (n = 97)
General Health[a,b]	3.4 ± 0.1	2.9 ± 0.9	2.7 ± 0.1
PCS score[a,c]	43.3 ± 1.3	38.6 ± 1.1	39.1 ± 1.2
MCS score	43.8 ± 1.2	44.9 ± 1.0	41.7 ± 1.2

Values are mean ± SEM.
General Health: reported on a scale of 1 (poor) to 5 (excellent)
PCS, normed Physical Component Summary health score; MCS, normed Mental Component Summary health score.
ANOVA with post hoc bonferroni
[a]$p < 0.05$ women without diabetes compared to women with poorly controlled DM.
[b]$p < 0.05$ women without diabetes compared to women with controlled DM
[c]$p = 0.06$ women without diabetes compared to women with poorly controlled DM

Table 4.28. Correlation Matrix: Short Form -12 Composite Scores

	Physical Health Composite score	Mental Health Composite score
Major Variables		
MSL severity score	−0.39*	−0.50*
DSC-R global score	−0.54*	−0.51*
Diabetes group status	−0.12*	−0.08
Demographic Variables		
Age (years)	−0.20*	−0.12*
BMI[#] (kg/m^2)	−0.35*	−0.004
Education	0.02	0.08
Income	0.20*	0.11
Employment	0.41*	0.15*
Relationship status	−0.07	0.06
Ethnicity/Race		
White	−0.05	0.05
Black	0.02	0.007
Hispanic	0.07	−0.03
Other[Σ]	−0.07	−0.07
Health Behaviors		
Cigarette smoking	−0.18*	−0.15*
Alcohol use	0.23	−0.05
Walking exercise	0.18*	0.12*
Aerobic exercise	0.22*	0.22*
Menopause related variables		
Years postmenopause	−0.26*	−0.06
Age of menopause	0.18*	0.12*
Type of menopause	−0.15*	0.006
Mood related variables		
Altered mood diagnosis	−0.21*	−0.46*
CESD-10 score	−0.26*	−0.72*
GAD-7 score	−0.14*	−0.66*
PSS-10 score	−0.14*	−0.75*

[Σ]Other: Native American Indian (n = 4), Asian (n = 2), Hawaiian Pacific Islander (n = 1), Multiracial women (n =14; 10 of whom identified as Native American Indian).
A1c, Hemoglobin A1c values, BMI, Body Mass Index; CESD-10, Center for Epidemiologic Studies Short Depression scale; DSC-R, Diabetes Symptoms Checklist-Revised; GAD-7, Generalized Anxiety Disorder-7 scale.
[#]Log transformed to ensure normality.
Values are Pearson r. *$p \leq 0.05$.

Table 4.29. Multivariate Analysis: Physical Health Composite Score

	Standardized Beta	*p* value	R^2
Model 1(All Women)			0.36
Uncontrolled Diabetes	0.05	0.42	
Controlled Diabetes	−0.06	0.32	
MSL severity score	−0.28	0.000	
BMI[#]	−0.30	0.000	
Tobacco Use	−0.12	0.02	
Altered Mood	−0.05	0.38	
Employment	0.24	0.000	
Age of Menopause	0.09	0.09	
Age	−0.13	0.02	
Ethnicity - Black	−0.05	0.39	
Ethnicity - Hispanic	0.06	0.25	
Ethnicity - Other[Σ]	−0.002	0.97	
Model 2 (Women with Diabetes)			0.38
Uncontrolled Diabetes	−0.13	0.03	
MSL severity score	−0.24	0.000	
BMI[#]	−0.33	0.000	
Tobacco Use	−0.17	0.008	
Altered Mood	−0.03	0.59	
Employment	0.29	0.000	
Age of Menopause	0.10	0.12	
Age	−0.07	0.23	
Ethnicity - Black	−0.05	0.42	
Ethnicity - Hispanic	0.05	0.41	
Ethnicity - Other[Σ]	−0.02	0.76	

[#]Log transformed to ensure normality
BMI, Body Mass Index; MSL, Menopause Symptom List.
[Σ]Other: Native American Indian, Asian, HPI and multiracial women.

Table 4.30. Multivariate Analysis: Mental Health Composite Score

	Standardized Beta	*p* value	R^2
Model 1(All Women)			0.37
Uncontrolled Diabetes	−0.02	0.70	
Controlled Diabetes	0.05	0.43	
MSL severity	−0.42	0.000	
BMI[#]	0.10	0.06	
Age	0.12	0.02	
Altered mood diagnosis	−0.34	0.000	
Cigarette smoking	0.006	0.89	
Age of menopause	−0.03	0.61	
Ethnicity - Black	0.02	0.73	
Ethnicity - Hispanic	−0.01	0.88	
Ethnicity - Other[Σ]	−0.002	0.99	
Employment	0.07	0.18	
Model 2(Women with Diabetes)			0.40
Uncontrolled Diabetes	−0.06	0.27	
MSL severity	−0.43	0.000	
BMI[#]	0.04	0.50	
Age	0.12	0.06	
Altered mood diagnosis	−0.36	0.000	
Cigarette smoking	−0.01	0.87	
Age of Menopause	−0.02	0.76	
Ethnicity - Black	0.02	0.77	
Ethnicity - Hispanic	−0.004	0.94	
Ethnicity - Other[Σ]	0.03	0.55	
Employment	0.06	0.30	

[#]Log transformed to ensure normality
BMI, Body Mass Index; MSL, Menopause Symptom List.
[Σ]Other: Native American Indian, Asian, HPI and multiracial women

Chapter 5

Discussion

Overview of Main Findings

This study describes for the first time, the menopause symptom experience of women veterans with and without type 2 diabetes receiving care in the Veteran's Affairs (VA) Healthcare system. Participants (n = 327) were recruited from an ethnically diverse postmenopausal sample (n = 536) who responded to a national mailed survey (n = 900) and consented to clinical data access. As a group, the women were primarily obese, of low income with more than one chronic illness. On average, menopause symptom prevalence rates were higher compared to those observed in previous community-based investigations of ethnically diverse non-veteran cohorts. However, despite higher BMI and increased disease-related co-morbidities, diabetic participants experienced menopause at the same age and report similar menopause symptoms (hot flashes, muscle/joint aches, trouble sleeping) as the non-diabetic cohort.

Among respondents with diabetes, glucose control was an important clinical correlate of menopause symptom severity, independent of the well-known influence of obesity, surgical menopause, and non-European ethnicity. With the exception of vasomotor symptoms, women veterans with poor glucose control demonstrated higher menopause symptom severity scores (total score, psychological factor scores, somatic factor scores) than their controlled peers of comparable body size, years postmenopause and psychological status. Further, both menopause symptom severity and glucose control were significant correlates of perceived physical health in the diabetic cohort. These findings substantiate the importance of addressing menopause health issues in the clinical management of women veterans with diabetes using services in the VA healthcare system. For this group already in poor health, intervention efforts targeting glucose control may also improve their menopause symptom experience. Future studies are

warranted to better understand the relationship between military service and the menopause experience of women veterans, as well as confirm these findings in non-veteran diabetic populations

Menopause Symptom Prevalence.

Despite a higher BMI, greater number of years postmenopause, and higher incidence of disease-related co-morbidities, women veterans with diabetes reported similar menopause symptoms as those without diabetes. In all study groups, symptoms of muscle and joint aches, hot flashes and trouble sleeping were the most common, while vaginal dryness was the least prevalent. This is an important finding as women with chronic illness have typically been excluded from investigation and little is known about their menopause experience. These data support the view that women with diabetes should be considered women 'first' in terms of health care needs.

While the most frequently reported menopause symptoms by women veterans are consistent with those documented in community-based cohort studies of healthy and ethnically diverse women (Avis et al., 1994; Dennerstein et al., 2000; Gold et al., 2000; Freeman et al., 2001; Woods & Mitchell, 2005), higher prevalence rates of all symptoms were noted in this unique population regardless of diabetes status (Table 5.1). Approximately 69% of respondents had trouble sleeping, compared with 43.2-50% in other studies of postmenopausal women (Gold et al., 2000; Dennerstein et al., 2000; Freeman et al., 2001). Muscle and joint aches, hot flashes and sad mood were reported at rates up to 79%, 75% and 61% in this study compared with 55%, 49% and 22% respectively in postmenopausal women of the SWAN study (Gold et al., 2001). Vaginal dryness was the least prevalent symptom (45.2%), but these rates were also higher compared to those (21.2%) reported by the ethnically diverse SWAN study participants and comparable to those (47%) noted in the Melbourne Women's Midlife Project of Australian born women (Dennerstein et al., 2000).

The high levels of symptom reporting are noteworthy and may be related to characteristics of the sample. The women veterans were obese and physically inactive with low incomes and high rates of surgical menopause (53%), all clinical and demographic factors previously associated with increased reporting of vasomotor, sleep, somatic, genitourinary and altered mood symptoms with menopause (Freeman et al.,

2008; Gold et al., 2001; Li et al., 2000; Kuh et al., 1997; Hardy & Kuh, 2002; Harlow et al., 2003; Pastore et al., 2004). Increased symptom reporting has also been documented in women of African American and Hispanic ethnicity (Gold et al., 2001; Gold et al., 2006; Freeman et al., 2001; Pastore et al., 2004; Miller et al., 2005), groups well represented (35%) in this sample.

The high symptom prevalence rates may have also been manifestations of the poor physical and mental health status that was characteristic of the sample. Increased reporting of somatic symptoms in persons with mood disorders and traumatic experiences is well described (Kroenke, Jackson, & Chamerlin, 1997; Eisendrath & Lichtmacher, 2008; Simon, VonKorff, Piccinelli, Fullerton & Ormel, 1999, Stein, Lang, Laffaye, Satz, Lennox & Dresselhaus, 2004). Cross-sectional menopause investigations have documented an inverse relationship between perceived health and menopause symptom reporting (Ferriera et al., 2007; Miller et al., 2005) and well-designed longitudinal studies demonstrated women with previous mood disorder or stressful life experiences are more likely to suffer mood and other behavioral or somatic symptoms with menopause (Hardy & Kuh, 2002; Kuh et al., 2002, Freeman et al., 2004; Freeman et al., 2006).

One third of the women veterans in this sample reported a diagnosis of altered mood (depression, anxiety or post traumatic stress disorder) and while most of the sample was comprised of women with diabetes, a group at high risk for depression (Anderson, Freedland, Clouse & Lustman, 2001), the prevalence rates (33%) for altered mood were *similar* across all study groups. These rates for altered mood are consistent with the high rates of post-traumatic stress disorder (32.5%-36%) and depression (21.3%-75%), described in the women using VA healthcare services (Dobie et al., 2002; Dobie et al., 2006; Polusny, Dickinson, Murdoch & Thuras, 2008). Moreover, the mean CESD-10 score of 9.8 in this population approached the cut-off of 10, indicative of depressive symptoms.

The physical and mental health status in this sample of women veterans was poor and may also explain the increased menopause symptomatology. Benchmarked to the standardized SF-12 physical and mental health norms for age and co-morbid conditions (Table 5.2), the women veterans in this sample demonstrated lower physical health scores compared to all other norms and lower mental health scores for all norms except for

persons with major depression. These data are consistent with previous investigations that documented male and female users of VA care are sicker on average and have worse physical and mental health than the general population (Frayne et al., 2006; Polusny et al., 2008; Kazis, Miller & Clark, 1998).

Traumatic life events are another strong correlate of menopause symptoms (Miller et al., 2005), and women veterans, a trauma-exposed group (Dobie et al., 2004), may be more likely to have a magnified symptom response. The nature of military service imposes risk for traumatic experiences related to deployment, but women soldiers are also at risk for other high-stress events, such as sexual assault or harassment from male comrades (Murdoch, Bradley, Mather, Klein, Turner & Yano, 2006). In cross-sectional data, up to 80% of women veterans described some form of sexual harassment (Miller, 1997; Murdoch et al., 2006), 23-30% reported an episode of rape during military service (Hankin, Skinner, Sullivan, Miller, Frayne & Tripp, 1999; Coyle, Wolan, & Van Horn, 1996; Skinner, Kressin, & Frayne, 2000), and almost half (48%) of the women in one study reported an episode of assaultive violence (Sadler, Booth, Nielson, & Doebbling, 2000). Beyond these military incidents, many women veterans (over 50%) have suffered other violent experiences pre- and post military service (Sadler et al., 2004) that can culminate in a life trajectory of traumatic stress (Dobie et al., 2006). In this study, details of the military service experience and other unrelated traumatic life events were not explored but should be included in future studies of women veterans.

The symptom prevalence rates observed among the women veterans are higher than those described in the major cohort studies of healthy women, but consistent with rates reported in the few studies of women with chronic illness (Table 5.3). Kalpakjian and associates (2005) demonstrated high prevalence rates in the 80% range for vasomotor, sleep, mood, sexual and cognitive symptoms in post polio survivors compared to ranges of 37-79%, 43-45%, 6-34%, 27% and 42% respectively in other studies of healthy postmenopausal women. In a study of HIV infected women (Ferreira et al., 2007), frequencies of psychological symptoms (97.9%) and genitourinary symptoms (73%) were higher than rates of 34% and 57% observed in ethnically diverse but healthy women (Gold et al., 2001; Freeman et al., 2007). High rates of decreased libido (79.5%), muscle and joint stiffness (85.2%) and cognitive symptoms (80.7%) were

described in postmenopausal women with the metabolic syndrome compared to rates of 27%, 42% and 55-57% respectively in other studies of healthy women (Chedaraui, Hidalgo, Chavez, Morocho, Alvardado & Huc, 2007a; Woods & Mitchell, 2005). These findings suggest that co-morbid chronic illness, an inherent characteristic in this sample, may have been an important contributor to the high symptom rates.

Variation in the patterns of most common symptoms was also demonstrated in women with chronic illness. Vasomotor complaints, the most commonly reported menopause concern (Avis et al., 2005; NIH State of the Science Panel, 2005; Freedman, 2005a) were *not* the most frequently reported symptom in the women veterans with diabetes or other samples of chronically ill women. Complaints of muscle and joint aches (78.6%) were most prevalent and vaginal dryness the least prevalent among the women veterans with diabetes, while HIV-infected women most frequently reported psychological concerns and least frequently reported somatic symptoms (Ferreira et al., 2007). Polio survivors with physical disabilities reported the greatest prevalence of somatic symptoms (Kalpakjian, 2005) and Ecuadorian women with the metabolic syndrome most frequently complained of dry skin and muscle/joint aches and least frequently reported vasomotor symptoms (Chedaraui et al., 2007a). Methodological differences in design and instrumentation limit the ability to accurately compare these findings, but they suggest chronic illness is an important modifier of menopause symptom presentation and worthy of continued inquiry. Further, these findings also remind us that there is not a universal menopausal syndrome (Avis et al., 2005); rather variation in symptom presentation is normative, reinforcing the need to consider the unique experience of every woman.

Menopause Symptom Severity and Glucose Control

The findings provide evidence that glucose control is an important clinical correlate of menopause symptom severity in women veterans with diabetes, independent of an altered mood state and the well-established influence of obesity, surgical menopause, and non-European ethnicity. With the exception of vasomotor symptoms, women veterans with poor glucose control demonstrated higher menopause symptom severity scores on all major parameters (total severity scores, psychological and somatic factor severity scores) than their controlled peers of comparable body size, years

postmenopause and psychological status. Moreover, all major menopause symptom severity scores were similar between women with controlled diabetes and the non-diabetic cohort, despite differences in BMI and disease-related co-morbid conditions. These data reinforce the message that 'control matters' and suggests interventions targeting glucose control may improve the menopause symptom experience for women with diabetes mellitus (DM).

Only three cross-sectional studies have described the menopause symptom experience of women with diabetes. In a community sample of age- and BMI-matched diabetic and non-diabetic Mexican women (n = 100), those with diabetes demonstrated higher scores for depressive symptoms and the 'empty nest syndrome' but similar levels of anxiety and disturbed sleep compared to non-diabetics (Malacara et al., 1997). Although the study used six different symptom scales, only one was psychometrically sound and none of them evaluated hot flashes, the most commonly reported menopause symptom. In another study of 400 age- and BMI-matched obese Mexican women with and without type 2 diabetes, vasomotor symptom rates were similar between the groups but were the only symptom investigated (Lopez-Lopez et al., 1999). Glucose values were measured in this research but only in healthy controls to confirm the absence of diabetes. Using the menopause quality of life questionnaire, Chedraui and colleagues (2007b) observed higher psychological and physical symptom scores, but similar vasomotor and sexual symptom scores in postmenopausal Ecuadorian women with the metabolic syndrome (n =135) compared to non-affected peers (n =190). Only a small portion (16%) of those diagnosed with the metabolic syndrome demonstrated impaired fasting glucose, suggesting the other features of the condition were more common, precluding a clear assessment of the relationship between the symptoms and glucose values.

To date, this is the first US study to examine the menopause experience of women veterans with diabetes. The results from this investigation extend the previous findings in Mexican and Central American women and demonstrate for the first time that among women with diabetes, glucose control is an important correlate of menopause symptom severity. Our null results for differences in vasomotor symptoms confirm the observations of others and extend those data, demonstrating the continued similarity in vasomotor symptom severity at higher levels of glucose dysfunction. While the similar

sexual domain scores (decreased libido, vaginal dryness) observed between women with the metabolic syndrome and healthy controls corroborates the similar somatic scores (libido, vaginal dryness, urinary leaking) among non-diabetics and those with controlled diabetes in our study, we extend these findings demonstrating the increased severity of these complaints among women with poor glucose regulation. We also clarify the findings of increased psychological symptom severity reported by others (Chedraui et al., 2007b; Malacara et al., 1997), again identifying the influence of glucose control status. Taken together, the collective data suggest glucose control plays a role in the manifestation of some but not all menopause symptoms in women with diabetes.

Two day recall hot flash scores were also similar among the respondents and further confirm the null findings for vasomotor symptoms in our data. These results are consistent with those from other investigations of women with diabetes (Lopez-Lopez et al., 1999), the metabolic syndrome (Chedraui et al., 2007b) and HIV (Miller et al., 2005; Ferriera et al., 2007). In the current investigation, the absence of group differences in vasomotor symptom severity might be explained by the greater proportion of women with diabetes (32.3% vs. 19.8% no diabetes; $p < 0.0001$) taking psychoactive medications such as SSRI's, SNRI's and gabapentin, all known to relieve vasomotor symptoms. The later postmenopausal status of the participants might also explain the findings. Only one-third of the sample was in the early postmenopause, the peak time for vasomotor symptoms (NAMS, 2007), with most women in late postmenopause (on average 11 years) when these symptoms are expected to be less frequent and severe.

There is little literature to explain how vasomotor symptoms are related to diabetes pathophysiology but there are several neuroendocrine mechanisms hypothesized to be responsible for hot flashes in healthy women. The most promising model asserts the hot flash is the result of a narrowing in the thermoneutral zone that triggers a central autonomic reaction and an associated peripheral cutaneous response (Freedman, 2000). In this sample, women with diabetes reported greater rates of neuropathy (39% of poorly controlled; 26% of controlled) than the non-diabetic cohort (12%). This high degree of neurological impairment may have dampened the intensity of the hot flash response centrally or diminished peripheral awareness of the symptoms and could explain the similar severity scores.

Another model proposes hot flashes may result from transient declines in central nervous system glucose transport (Dormire & Reame, 2003) and conversely hot flashes may be prevented with elevations in glucose levels (Bishop & Simpkins, 1992; Simpkins, Katovich & Millard, 1990). In a pilot study of healthy women (Dormire & Reame, 2003), hot flash symptom frequency was significantly higher in the fasting state (glucose < 110 mg/dl) compared to an induced postprandial state (glucose 130-140 mg/dl). These data suggest glucose concentrations may affect hot flash symptomatology and could have implications for women with diabetes, but to date has not been studied in this population. Future studies in women with diabetes using objective measures of hot flashes and glucose levels with skin conductance devices and continuous glucose monitors would provide opportunity to more accurately assess these symptoms.

In multivariate analysis, depressive symptoms were the only variable to demonstrate an independent relationship with vasomotor symptoms. Depressed mood history has been identified as a strong covariate of menopausal symptoms (Freeman et al., 2007) including vasomotor symptoms (Joffe et al., 2002; Freeman et al., 2005; Gold et al., 2006), with one study identifying it as the single most important factor (Dennerstein, 1996). Glucose control and other well-established correlates of vasomotor symptoms such as BMI (Greendale & Gold, 2005; Freeman et al., 2001), tobacco use (Gold et al., 2006; Guthrie et al., 2005; Freeman et al., 2001), African American ethnicity (Grisso et al., 1999; Freeman et al., 2001), were not associated with vasomotor symptom severity in this study. Yet, along with glucose control several of these characteristics were highly correlated with depressed mood (increased BMI, cigarette smoking). This could suggest the depressive symptoms were the dominant characteristic and 'overshadowed' or subsumed the influence of the other correlates.

Muscle and joint aches were reported with the greatest prevalence (78.6%) and also perceived as the most severe symptom by the entire sample. These complaints are consistently reported in major longitudinal menopause investigations (Dugan et al., 2006; Dennerstein et al., 2000; Freeman et al., 2007), but have been difficult to distinctly link with menopause, as they are common to both midlife men and women (Woods & Mitchell, 2005). The National Institutes of Health State of the Science Panel (2005) concluded that most studies showed no association between menopause and these

symptoms. However, there is a growing body of evidence that musculoskeletal symptoms are associated with menopause transition. A cross-sectional analysis of SWAN data (Dugan et al., 2006) documented significantly higher prevalence rates and severity scores for aches and joint pain in postmenopausal women compared to those premenopause. Increased muscle aches and joint stiffness were observed across the menopause transition in a longitudinal study of Australian women (Dennerstein et al., 2000) and recently, another well-designed prospective cohort study demonstrated a robust association of musculoskeletal symptoms with both menopause stage and reproductive hormone changes, independent of age, depressed mood and other known risk factors (Freeman et al., 2007).

In this cross-sectional sample of later postmenopausal (mean 11.2 years) women veterans, it is difficult to determine without longitudinal assessment and more detailed data collection, if the high rates of muscle and joint aches are menopause-related, age-related, or service-connected. Military service is physically challenging with intensive training requirements (i.e., 10 km road marches with 36kg loads) and demanding on the job duties that stress muscles and joints. Musculoskeletal injuries are a major problem among military personnel (Kauffman, Brodine & Shaffer, 2000) and the leading cause of disability (Songer & LaPorte, 2000). The knee is the most common site for injury, followed by the back (Lauder, Baker, Smith & Lincoln, 2000).

Women have twice the injury rates of men; almost half sustain a musculoskeletal injury in initial training (Shaffer, Brodine, Ito & Le, 1999). Stress fractures are common in women, with pelvic and femoral fractures most frequent (Friedl, 2005; Shaffer et al, 1999; Kelly, Jonson, Cohen & Shaffer, 2000). And until recently, women were using ill-fitting equipment designed for men and experienced more shoulder and hip complaints from shoulder straps on their more narrow shoulders and pistol belts over small waists that fell onto hips (Freidl, 2005).

It may not be unexpected that the most commonly reported symptoms among the women veterans were muscle aches and joint pains. Almost half of the sample (48%) reported a diagnosis of osteoarthritis (OA) and degenerative joint disease (DJD) on the health history section of the survey, raising the question that the high severity scores for muscle and joint complaints among the women veterans may not be menopause-related

but rather a function of aging or previous injury. Future studies in women veterans should include a more thorough assessment of the musculoskeletal system and injury related disorders.

Factor scores for psychological symptoms were higher in women with poorly controlled diabetes, but similar between women with controlled diabetes and those without diabetes. This was notable as the prevalence rates of altered mood and the standardized scores for anxiety (GAD-7) and depressive symptoms (CESD-10) were *similar* among the three groups. The range of other psychological-related symptoms included in this factor likely explains these higher scores. In addition to anxiety and sadness, the factor total included the severity scores for the symptoms of irritability, mood swings, memory difficulty, trouble sleeping and headaches. Of these symptoms, the individual severity scores for headaches, mood swings, trouble sleeping and anxiety were higher in women with poor glucose control and accounts for this finding.

In prior studies, increased psychological symptoms have been documented in both women with diabetes and the metabolic syndrome compared to their non-affected peers of similar menopause status (Malacara et al., 1997; Cheraui et al., 2007b). While it is difficult to compare these findings due to differences in instrumentation, it is clear that some degree of increased psychological symptoms are noted in postmenopausal women with a metabolic chronic illness. Our data corroborates these findings and documents the key contribution of glucose dysfunction to the manifestation of these symptoms in postmenopausal women with diabetes, but may also be reflective of the strong association of mood symptoms in persons with diabetes.

Described as "one of the most psychologically demanding chronic medical illnesses" (Ciechanowski, Katon & Russo, 2000, p. 3278), it is not surprising that both depression and anxiety are highly prevalent co-morbid conditions in persons with diabetes. Depressed mood occurs in 15-30% of adults with diabetes (Anderson, Freedland, Clouse & Lustman, 2001) and has been associated increased risk of diabetic complications (deGroot, Anderson, Freedland, Clouse & Lustman, 2000) and greater burden of diabetes symptoms (Ludman et al., 2004). Generalized anxiety disorder occurs in approximately 14% of persons with diabetes, but up to 40% of diabetic patients experience some degree of elevated anxiety symptoms, with women more often affected

than men (Grigsby, Anderson, Freedland, Clouse & Lustman, 2002). Both depression and anxiety have been strongly associated with poor glycemic control (Lustman, Anderson, Freedland, deGroot, & Carney, 2000; Grigsby et al. 2002) and treatment of these conditions improves control (Anderson et al., 2001; Grigsby et al., 2002).

The strong association of depression with diabetes makes it difficult to determine if the greater severity of mood symptoms observed in the women with poorly controlled diabetes in this sample are menopause or diabetes-related or a function of the interaction between both conditions. This is the major challenge in evaluating symptoms in midlife women with a chronic illness: differentiating whether symptoms are related to menopause or the co-morbid chronic condition. The cross-sectional design of this study and others (Malacara et al., 1997; Chedraui et al., 2007a) makes it difficult to disentangle these relationships and precludes the ability to make such a determination. Future longitudinal studies that can monitor changes over time are warranted.

Besides anxiety and depressed mood, the other symptoms in the psychological factor score, sleep, headache, memory trouble, irritability, and mood swings have all been associated with both menopause and diabetes. Headache, irritability and difficulty concentrating are known symptoms associated with acute hypoglycemia (Zammit & Frier, 2005). Population-based studies have demonstrated diabetes is a risk factor for cognitive impairment, most often memory deficits (Whitmer, 2007; Huber, 2008). These decrements in cognitive function have also been correlated with poor glucose control (Awad, Gagnon & Messier, 2004) and longer duration of illness (Coker & Shumaker, 2003). An increased prevalence of sleep disorders has been described in persons with diabetes (Sridhar & Madha, 1994). Both poor glucose control and diabetic complications have been associated with sleep disruption, particularly difficulty initiating and maintaining sleep (Lamond, Tiggeman & Dawson, 2000). Yet, while the association of these symptoms with diabetes is fairly well documented, few studies have specifically examined these symptoms in midlife women, *much less in the context of estrogen loss at menopause* (Zausniewski et al., 2002).

Until recently, the evidence for an association of the symptoms reflected in the psychological factor score (depressed mood, sleep difficulties, headache, irritability, mood swings, anxiety, memory troubles) with menopause has been limited (NIH State of

the Science Panel, 2005). The most recent data from longitudinal studies of ethnically diverse healthy women (Freeman et al., 2007; Hardy & Kuh, 2005; Bromberger et al., 2007) provide strong evidence of an association between depressed mood symptoms with the menopause transition, with one investigation corroborating the increase in these symptoms with changes in reproductive hormone measures (Freeman et al., 2007). There are little data evaluating the association of anxiety, irritability, mood swings and headache with the menopause transition. In the only cohort study to investigate these complaints, headache was significantly associated with menopause stage, initially increasing in the late reproductive stage and then gradually decreasing over the transition (Freeman et al., 2008). Anxiety, irritability, and mood swings demonstrated a similar pattern of decline over time but did not demonstrate a significant association with menopause stage (Freeman et al, 2005; Freeman et al., 2008).

The association of sleep disturbance with menopause remains controversial. Population-based studies have documented the increase in sleep complaints over the menopause transition (Dennerstein et al., 2000; Young et al., 2003; Ohayon, 2006; Freeman et al., 2007; Kravitz et al., 2008) and suggest these symptoms are associated with menopause (Lee, Baker, Newton & Ancoli-Israel, 2008). However, in the two major longitudinal menopause studies with clinical measures of reproductive hormones, one documented a corroborating association between changes in the reproductive hormones and sleep complaints (Kravitz et al, 2008; Sowers et al, 2008), while the other noted only a minimal increase in sleep complaints compared to the magnitude of change in reproductive hormones over time, concluding that poor sleep was likely not menopause-related (Freeman et al., 2007). In a more detailed assessment of the latter study, the menopause symptoms of hot flashes and depressed mood were shown to be the stronger predictors of disturbed sleep rather than menopause stage (Pien, Sammel, Freeman, Lin & DeBlassis, 2008).

While neuroimaging studies have documented several effects of estrogen on brain function (McEwen & Alves, 1999; McEwen, 2002; Markou, Duka, & Prelevic, 2005; Craig & Murphy, 2007), and cognitive complaints are prevalent among midlife women (Mitchell & Woods, 2001), the evidence regarding the association of these symptoms is limited. Limitations of previous studies have precluded a clear answer, primarily due to

great variation in measurement of cognition, ranging from memory testing, to verbal fluency to fine motor skills (Sherwin, 2003). Early population based studies have reported conflicting results (Woods & Mitchell, 2005), but the most recent data from the SWAN study did not demonstrate a relationship between cognitive performance with menopause stage or measures of reproductive hormones (Luetters et al., 2007). Similarly, another longitudinal cohort study of ethnically diverse women also documented no change in cognitive symptoms across the menopause transition, suggesting these symptoms are likely not menopause related (Freeman et al., 2008).

Well-designed longitudinal studies have provided strong evidence that the psychological-related symptoms of depressed mood and headaches are associated with the menopause transition in healthy women, while at present little data support a relationship between anxiety, irritability, mood swings and cognition. Sleep symptoms are likely related to the menopause but whether that relationship is independent or secondary to vasomotor symptoms remains unclear to date. These cumulative data suggest the higher psychological factor scores in the poorly controlled women could be either menopause or diabetes related. The evidence, to date, reflects the menopause symptom experience of primarily healthy women and there are few studies describing menopause symptoms in women with diabetes. All have been cross-sectional investigations and preclude the ability to determine whether these symptoms during the menopause in women with diabetes are truly diabetes or menopause related, or even if they are modified or accelerated in some way with menopause. Future longitudinal studies that can monitor changes over time are warranted.

The higher somatic scores (urinary incontinence, vaginal dryness, decreased libido) in women with poorly controlled diabetes are consistent with previous reports of genitourinary and sexual symptoms in women with altered glucose metabolism. A cross-sectional analysis of the Women's Health Initiative data, found increased prevalence of vaginal irritation and dryness complaints in postmenopausal women with diabetes (Pastore et al., 2004). Higher glucose values and BMI were associated with recurrent vaginitis in one case control study (Donders, Prenen, Verbeke & Reybrouck, 2002) and intensive glucose control was associated with a reduction of vaginitis in the Diabetes Control and Complications Trial (Adverse Events, 1995).

Diabetes has been documented as a strong risk factor for urinary incontinence (UI) symptoms in postmenopausal women in the Women's Health Initiative (Pastore et al., 2004) and the SWAN study participants (Sampselle et al., 2002; Waejten et al., 2007). Data from the National Health and Nutrition Examination Survey (NHANES) extended these findings to demonstrate increased UI prevalence not only in women with diabetes but also those with impaired fasting glucose (Brown, Vittinghoff, Lin, Nyberg, Kusek, Kanaya, 2006). While glucose control has not been associated with UI severity to date, the duration of diabetes and the presence of diabetes-related complications, such as neuropathy have been associated with the severity of these urinary symptoms (Jackson, Scholls, Boyko, Abraham & Fihn, 2005).

Symptoms of sexual dysfunction such as decreased sexual desire, lubrication and dyspareunia with sexual activity have been documented in women with type 1 and 2 diabetes with varying degrees of glucose control in several investigations (Basson et al., 2001; Doruk et al., 2005; Enzlin et al, 2002). However, most study participants were younger women and few midlife women or postmenopausal women with diabetes were included. Glucose control did not show a relationship with these sexual symptoms in the previous investigations, which suggests the symptoms may be a function of other clinical factors associated with diabetes, such as altered mood or neuropathic complications.

Again, without longitudinal assessment, it is difficult to evaluate the interaction of these genitourinary and sexual symptoms at menopause in women with diabetes to ascertain if they are diabetes or menopause related. While the literature indicates women with diabetes are vulnerable to increase genitourinary and sexual symptoms, evidence of such a relationship between these symptoms and menopause is varied. Observational studies have provided strong evidence of the increase in the symptoms of vaginal dryness and dyspareunia across the menopause transition (Dennerstein et al., 2000; Gold et al., 2000; NIH State of the Science Panel, 2005) that could suggest these symptoms may worsen for women with diabetes. There is limited support for an association with menopause for the symptoms of decreased libido in healthy women. Menopause has been reported as a risk factor for decreased libido and sexual dysfunction in two cross-sectional studies (Valadares et al., 2008; Gracia et al., 2007) but among longitudinal investigations the data are mixed. Dennerstein and colleagues (2004) demonstrate an

increase in sexual dysfunction over the menopause transition in Australian women, while Freeman et al (2008) did not detect an association between decreased libido and the menopause transition despite changes in reproductive hormones. To date, evidence from prospective cohort studies have not established a temporal relationship for the symptoms of urinary incontinence with menopause (Dennerstein et al., 2000; Waetjen et al., 2008).

Important covariates of these somatic symptoms were identified in this study. Relationship status (partner or not), anxiety and tobacco use were independent correlates of the somatic factor severity score among women with diabetes, consistent with previous data linking these characteristics to decreased libido (Gracia et al., 2004; Gracia et al., 2007; Valadares et al., 2008), UI (Gold et al., 2001; Sherburn et al., 2001; Waejten et al., 2007; Waejten et al., 2008) and vaginal dryness (Gold et al., 2000) in healthy women. In multivariate analysis using the full sample, BMI was an independent correlate of somatic symptoms consistent with previous reports of the relationship between BMI and UI (Sampselle et al., 2002; Brown et al., 2006; Waejten et al., 2007), vaginitis (Donders et al., 2002) and decreased libido (Gracia et al., 2007). Only a trend for a relationship with BMI was observed in the multivariate model of women with diabetes, likely due to the reduced variation in BMI among the participants in that group. While somatic severity scores were higher among women with poor glucose control, in multivariate assessment an independent association with either controlled or uncontrolled diabetes was not detected and might be due to the strong influence of the other covariates, particularly relationship status and anxiety symptoms.

Hispanic ethnicity demonstrated an independent association with somatic symptom severity, which also is consistent with previous reports. In the WHI data, Hispanic ethnicity was an independent risk factor for increased urinary and vaginal symptoms (Pastore et al., 2004). Hispanic women reported more UI symptoms in the baseline SWAN assessment (Gold et al., 2000). In a later SWAN evaluation, while the Hispanic women were noted to report less prevalence of 'any' UI (42%) symptoms than Caucasian women (66%) they were more likely to identify these symptoms as bothersome (Sampselle et al., 2002). In a recent report, Waejten and colleagues (2008) documented Hispanic ethnicity was associated with increased odds for worsening stress and urge incontinence across the menopause transition.

Besides the race/ethnicity effect noted in the somatic severity score, few associations between race/ethnicity and menopause symptom severity were observed in this study. The previously described association between African American race and vasomotor symptoms (Freeman et al., 2001; Gold et al., 2004) was not detected in this study. Homogeneity among all the study participants for covariate characteristics associated with increased vasomotor symptoms, such as BMI (Gold et al., 2006), depressive symptoms (Joffe et al., 2002) and socioeconomic status could explain the absence of this relationship.

In multivariate analysis, non-white, non-black, non-Hispanic ethnicity was an independent correlate of the psychological factor score and demonstrated a trend for a significant association with the overall menopause severity score. This eclectic group was comprised of Native American Indian (n = 4), Asian (n = 3) and multiracial (n =14) women, with ten of the fourteen multiracial women self-identifying as Native Americans. In sub-analyses, the Native American Indian and multiracial women demonstrated higher MSL severity scores (23.5 $\pm$ 2.1 and 18.1 $\pm$ 2.3 respectively) than the two central Asian (5.0 $\pm$ 1.5) and the lone Hawaiian Pacific Islander (5.5 $\pm$ 1.0), suggesting women of Native American ethnicity were the group generating this effect. This was a novel finding not previously described in the literature and presents an opportunity for future investigation.

In this study, the group of Native American multiracial women had highest scores in the sample for perceived stress and depressive symptoms (13.9 on the CESD-10) with 45% of the group reporting a diagnosis of altered mood (depression, anxiety, post-traumatic stress disorder). These findings are consistent with the high rates of depressive disorder and traumatic life events observed in Native Americans. National survey data indicate Native Americans have the highest lifetime prevalence of major depressive disorder (19.2%) compared to whites (14.58%), Hispanics (9.64%), blacks (8.93%) and Asians (8.7%) (Grant et al., 2005). In another study, high rates of depression up to 50% and physical or sexual abuse (87%) were reported among Native American women (Bohn, 2003). While these data likely explain the high severity scores observed in this investigation it also suggests the Native American Indians are a high-risk group among

the women veterans and detailed evaluation of both their mental and physical health at menopause is indicated.

Prominent Covariates

Tobacco use was independently associated with menopause symptom severity and consistent with previous evidence linking this behavior with menopause symptoms (Gold et al., 2000; Waejten et al., 2007; Freeman et al., 2001; Ford et al., 2005; Bosworth et al., 2001; Malacara et al., 2002). *Mood related measures* were significant covariates of perceived menopause symptom severity in this sample. A diagnosis of altered mood was a strong independent correlate of menopause symptom severity, demonstrating an association with the total menopause symptom severity score and the psychological factor score. Depressive symptoms were the primary correlate of vasomotor symptom severity and demonstrated an association with somatic symptom severity. Anxiety was an independent correlate of somatic symptom severity.

The associations of altered mood, anxiety or depressive symptoms with menopause symptom severity were not unexpected, given the high prevalence of mood disorder reported by the participants, but are also consistent in the literature. Several cross-sectional (Grisso et al., 1999; Miller et al., 2005; Joffe et al., 2005; Waejten et al., 2007) and well-designed longitudinal studies (Freeman et al., 2007; Dennerstein et al., 2004; Hardy & Kuh, 2005; Gracia et al., 2007; Gold et al., 2006) have documented the association between depressed mood and menopause symptoms including hot flashes (Joffe et al., 2005), UI (Waejten et al., 2007), decreased libido (Enzlin et al., 2002), sleep (Freeman et al., 2007; Kravitz et al., 2003), mood swings (Freeman et al., 2008) and anxiety (Freeman et al., 2008). Anxiety has been documented as a covariate for vasomotor symptoms (Freeman et al., 2005; Gold et al., 2006) and decreased libido (Gracia et al., 2004; Gracia et al., 2007; Valadares et al., 2008). The pervasive association of these covariates with menopause symptom severity in these data and other investigations suggests a careful assessment for altered mood be conducted when evaluating such symptoms in women veterans with diabetes.

Health Status

Women veterans rated their general health status as good and as expected, women without diabetes reported higher health scores than those with diabetes. Despite their

differences in glucose control and perceived menopause symptom severity, both groups of women with diabetes rated their general health to be similar. These are important findings when placed in the context of the poor mental and physical health scores documented among the women veterans; scores that fell below the national norms for women of similar age and co-morbid conditions. Despite these data, the women with diabetes perceived their overall health as good.

Hooker and Siegler (1992) advise self-rated health status reflects more than the individual's opinion about their physical health; rather it represents an integrated perception of biological, psychological and social dimensions that shape this perception of 'health'. Several studies have documented the importance of perceived health as a predictor of mortality (Idler & Benyamini, 1997) and functional ability (Idler, 1992), but little research has examined how this perception is related to other health experiences or outcomes (Bosworth, Butterfield, Stechuchak & Bastian, 2000).

This similar perception of good health in spite of the co-morbid illness, reminds us that women's assessments about themselves in the context of their lives are critical determinants that may also influence their view of menopause and its associated symptoms. Qualitative studies in healthy midlife women of diverse ethnicities demonstrate most women perceive the physical changes of menopause as a normal developmental phase, often viewing this life stage as a time of freedom or personal development (Carolan, 2000; Bertero, 2003; Sampselle et al., 2002), but to date, no studies have considered the experience of women with chronic illness.

Woods & Mitchell (2005) propose individuals similarly appraise symptoms in the context of the personal and sociocultural milieu, and reach a judgment regarding the meaning of the symptom that determines the individual's response. In an exploratory study of healthy midlife women's perceptions of memory changes, Mitchell and Woods (2001) observed that women attribute these menopause symptoms to a variety of other factors rather than their health such as emotional factors, stress, social roles, family history and getting older (Woods & Mitchell, 2003). These attributions and perceptions about health and symptoms are meaningful data that inform and guide symptom management strategies. As there is a modicum of data regarding the experience of healthy women, this is an important opportunity for inquiry among the women veterans

and those with chronic illness that might also assist in disentangling the symptoms as menopause or diabetes-related.

Mental health composite scores were similar among the study groups and consistent with the other measures of mental health. The only independent correlates of mental health scores were an altered mood diagnosis and the menopause symptom severity score, which measured a significant number of mood-related complaints. These are intriguing findings, as despite the diabetes, the mental health status of all three groups was similar and considerably lower than national norms.

This is an important issue to the VA healthcare system as it adapts to meeting both the mental and physical health needs of this growing portion of their patient population. Frayne and colleagues (2006) recently surveyed 28,000 women veterans using the SF-36 to characterize their health status compared to men. Mean mental health composite scores were 43.8 for women aged 45-64 year and strikingly similar to those in this study (mean score 43.6). Our data confirm and extend those findings to a group of exclusively menopausal women and further suggest our sample is representative of the population of women veterans using the VA healthcare system.

Menopause symptom severity and glucose control were significant correlates of perceived physical health among women with diabetes. These findings substantiate the importance of addressing menopause symptoms in the clinical management of women veterans and also suggest that intervention efforts targeting glucose control may not only benefit physical health status but also improve menopause symptom experience. BMI and cigarette smoking were correlates of the physical health score and also demonstrated associations with some of the menopause symptom severity scores, suggesting smoking cessation and interventions targeting diet and exercise to reduce BMI, may also improve both physical health and menopause symptom severity of the women veterans.

Other Issues

Women with Poorly Controlled Diabetes. Several clinical characteristics of these women may have influenced their glucose control status and the increased symptom severity. Women in this group had the earliest age of menopause (42.5 yrs) and the greatest duration postmenopause (13 yrs), placing them at risk for the adverse metabolic changes associated with menopause. Estrogen loss has been associated with decreased

skeletal muscle uptake of glucose (Bishop & Simpkins, 1992), and increased abdominal adiposity (Poehlman et al., 1995). Over time these changes are associated with insulin resistance and impaired glucose function, increasing the risk for the metabolic syndrome, diabetes and cardiovascular disease (Carr, 2003; Otsuki et al., 2007; Hu et al., 1999).

Most (58%) women in this group were diagnosed with DM during their reproductive years at an early age 45.4 years and had the condition for an average of 10.1 years, compared to those with controlled DM who were (65%) diagnosed postmenopause at a later age 50.4 year and had diabetes only 5.5 years. The earlier age of a diabetes diagnosis and the greater duration of the illness increased risk for diabetic complications that were apparent in their medical histories. Women of poor glucose control had higher prevalence rates of renal disease, neuropathy, and retinopathy.

All of these characteristics likely affected the greater symptom presentation and perception in this group. Without longitudinal tracking, it is difficult to determine which of the two conditions, menopause or diabetes were the likely contributors to the greater symptom severity reported. Is this the manifestation of menopause symptoms in women with premenopausal diabetes? Are these symptoms more severe because of the pre-existing diabetes? Or did the prolonged years of menopause contribute to worsening diabetes that increased the symptom severity? Future longitudinal studies that follow women with a premenopausal diabetes diagnosis and with healthy controls through the menopause, corroborated with clinical measures would contribute to a more complete understanding of the menopause experience of these women.

Diabetes Symptoms Checklist-Revised (DSC-R). The DSC-R is a reliable, valid instrument that was developed and tested in persons with type 2 diabetes. It has been used extensively in behavioral and pharmaceutical intervention trials to measure the changes in diabetes symptom burden with these interventions. In this study, the DSC-R was measured in all respondents but did not discriminate well between the study groups in this unique population, likely due to the co-morbid obesity, high rates of altered mood and common chronic medical problems (hypertension, hyperlipidemia) present in all participants. For example, the rates of cardiovascular symptoms were higher in those with poorly controlled diabetes compared to women with controlled diabetes but *similar* to those without diabetes.

While women with diabetes had higher total DSC-R scores compared to those without diabetes, only one of the eight subscale scores demonstrated a difference between the groups. Hyperglycemia scale scores were higher in those with diabetes compared to those without diabetes, but with analysis of variance, women with poorly controlled and controlled diabetes had similar scores. Several subscales were similar among all three of the study groups including ones expected to discriminate complications related to diabetes, such as neuropathy and cognition. A few symptoms overlapped between the menopausal symptoms list and the diabetes instrument (memory loss, aches in the legs) that may have affected the ability to clearly discriminate menopause related symptoms from those related to the diabetes.

Age of Menopause. The average age of natural menopause in the sample was approximately 2 years earlier than the mean of 51 years common to western women in industrialized nations (Birkhauser et al., 2002). This younger age of menopause is of concern as early menopause is associated with increased risk for osteoporosis (Fritz-Silverstein & Barrett-Connor, 1993), cognitive decline (Kok et al., 2006) and cardiovascular disease (Hu et al., 1999), the leading cause of mortality in women.

The earlier age of natural menopause among women veterans may be a function of their co-morbidities and is comparable to earlier ages of menopause reported in women with chronic illnesses. Cross-sectional investigations of women with HIV reported median ages of menopause at 46 years (Schoenbaum, 2005) and 47.5 years (Ferreira et al 2007), and in Hispanic women with diabetes, mean ages of menopause at 49.8 (Lopez-Lopez et al, 1999) and 45.7 years (Malacara et al., 1997) were documented. In contrast, Kalpakjian and colleagues (2005) reported natural menopause at 50.5 years in a sample of primarily white well-educated polio survivors with physical disabilities.

Environmental stress, exposure to violence or abuse and a history of depression are life experiences hypothesized to affect the hypothalamic-pituitary-ovarian axis (HPO) and compromise ovarian function leading to an early menopause. Working from this hypothesis and corroborated with measures of gonadatropins and estrogen in one study (Harlow et al., 2003), prospective cohort studies have demonstrated independent associations between social stress in early childhood (Hardy & Kuh, 2005) and adulthood

(Lawlor et al., 2003), lifetime history of depressive symptoms (Harlow et al., 2003) and exposure to abuse or violence (Allsworth et al., 2004) with an earlier age of menopause.

Military service, a characteristic of this sample, can be considered a source of significant stress that compromises HPO axis function and could induce an earlier age of natural menopause. Higher prevalence rates (22-30%) of post-traumatic stress disorder are documented in veterans than the general population (Kukla et al., 1990) with even higher rates (44-50%) observed in women veterans (Bell, Roth & Weed, 1998; Furey, 1991; Paul, 1985; Schnair, 1986) especially those who have served in active war zones (Kang, Natelson, Mahan, Lee & Murphy, 2003; Magruder et al., 2004; Proctor et al., 1998). Women veterans also report unique and significant sources of stress as part of the military experience including sexual harassment or discrimination (Miller, 1997; Murdoch et al., 2006), assaultive violence from male peers (Sadler et al., 2000), and parental guilt at leaving children during periods of active duty (Bell et al, 1998; Pierce, 1997). To date, no studies have investigated the long-term effects of these stressors on menstrual function and age of menopause, but as the numbers of women in the military increase, such inquiry should be considered.

Environmental chemical exposures to endocrine disruptive toxins during military service may also affect women's reproductive health and menopause age. The most notable of these toxins, dioxin (Agent Orange), used during the Vietnam era has been linked with diabetes mellitus and exposure to this chemical is now considered a service-connected illness (Panangala, 2008). In addition to diabetes, other endocrine-related reproductive effects of dioxin have been observed. In vitro studies of human ovarian and endometrial tissue have demonstrated dioxin-induced opposing actions, either anti-estrogenic effects (Safe et al., 1998) or estrogen-like responses (Eskenazi et al., 2007). In several studies, dioxin has been associated with medley of female related reproductive issues including reduced fertility, antenatal mortality, endometriosis, high rates of miscarriage, uterine fibroids and lengthening of the menstrual cycle (Bullan et al., 2000; Eskenazi et al., 2002; Eskenazi et al., 2007; Tuyet & Johansson, 2001). One epidemiologic investigation documented a dose-related association with increasing risk for early menopause in Italian women exposed to dioxin during a chemical plant explosion (Eskenazi et al., 2005). While a detailed assessment of the military service

experience or chemical exposures was not part of this study, future studies should consider these factors in evaluating women veteran's menopause experience.

Military Service may be considered an important covariate that not only affects age of menopause but also could affect the prevalence rates of symptoms and perceptions of health status documented in this study of postmenopausal women veterans. There are several aspects of the military experience that were not assessed and merit consideration in future studies. Dimensions of the service commitment that may be of importance include years of service, branch served, rank, service status as active or reserve and deployment (location, length, frequency).

Previous studies that examined the symptom experiences of veterans have primarily assessed symptom prevalence rates and subsequent health outcomes in relationship to combat exposure and adjustment post-deployment. Most investigations have evaluated the male veterans of the Vietnam, Persian Gulf and Iraqi wars, with few studies exclusively considering the experience of women soldiers. In retrospective observational studies, poorer health status and increased symptom prevalence rates were observed in male and female veterans with a history of deployment to an active war zone compared to non-deployed soldiers or those deployed to non-combat areas (Barrett, Doebbeling, Schwartz, Voelker, Falter, & Woolson et al, 2002a; Hotopf, Hull, Fear, Browne, Horn, & Iverson et al., 2006; Kang, Natelson, Mahan, Lee & Murphy, 2003; Pierce, 1997; Proctor, Heeren, White, Wolfe, Borgos, & Davis et al., 1998; Steele, 2000; Unwin, Hotopf, Hull, Ismail, Davis & Weasley, 2002; Wolfe, Schnurr, Brown & Furey, 1994). Mental health concerns were most commonly reported (Hotopf et al., 2006; Hoge et al., 2006; Proctor et al., 1998) with one recent study of Iraqi veterans noting higher rates of these concerns in women veterans (Felker, Hawkin, Dobie, Gutierrez & McFall, 2008). The most frequently reported symptoms include headache, fatigue, cognitive disturbances, pain and sleep difficulties (Barrett, Gray, Doebbling, Clauw & Reeves, 2002b; Steele, 2000). Additionally, musculoskeletal and dermatological symptoms were commonly noted by deployed Gulf war veterans (Spencer, McCauley, Joos, Laserev, Schuell & Bourdett et al., 1998; Barrett et al., 2002b) and gynecological symptoms frequently reported among deployed Vietnam and Gulf war women veterans (Pierce, 1997; Unwin et al., 2002; Wolfe, Schnurr, Brown & Furey, 1994). Greater symptom

prevalence rates were noted in female Gulf war veterans in some (Steele, 2000; Proctor et al., 1998; Kipen, Hallman, Kang, Fiedler & Natelson, 1999) but not all studies (Unwin et al., 2002). In a population-based survey of 3,956 Gulf war veterans that examined health related quality of life, poorer quality of life scores were also detected in deployed veterans compared to non-deployed participants (Voelker, Saag, Schwartz, Chrischilles, Clarke & Woolson et al., 2002)

Few studies have documented the influence of branch of service on either post-deployment symptoms or health concerns. Kipen and colleagues (1999) observed no effects of branch of service, duty status or rank on symptom reporting or medical problems in 68,000 Gulf war veterans. Yet, in other studies of Gulf war veterans, higher rates of post-traumatic stress disorder (Barrett et al., 2002a), poorer physical and mental health status scores (Voelker et al., 2002) and higher prevalence rates of chronic symptoms (Steele, 2000) were observed in Army personnel compared to Air Force, Navy, Marines or Coast Guard veterans. In another population-based survey of Gulf war veterans, Kang and colleagues (2003) detected higher prevalence rates of chronic fatigue syndrome in Army and Marine veterans than those who served in the Air Force or Navy.

Military rank (enlisted, officer) and duty status (active, reserve) are other dimensions to consider when evaluating symptoms in women veterans. Lower rates of post-traumatic stress disorder symptoms (Barrett et al., 2002a) and higher perceived physical and mental health scores (Voelker et al., 2002) were observed in Gulf war veterans who were officers than enlisted personnel, yet another investigation observed no differences by rank (Kipen et al., 1999). Higher symptom prevalence rates and greater mental health concerns were observed in deployed reservists compared to active duty personnel in several studies (Barrett 2002a; Hotopf et al., 2006; Voelker et al., 2002), but one study of Air Force women documented greater general health problems among those in active duty (Pierce, 1997) and another observed no differences in symptoms or health problems on the basis of military status (Kipen et al., 1999). While it is difficult to draw conclusions from the current literature due to variations in study design and sample populations, these findings suggest future investigations evaluating symptoms in postmenopausal women should control for dimensions of the military service experience, particularly data regarding deployment, rank, branch of service and duty status.

The Theory of Unpleasant Symptoms

The Theory of Unpleasant Symptoms (TOUS) guided this study and permitted the multifactorial assessment of physiologic, psychologic and situational variables that were key contributors to perceived menopause symptom severity in this cohort of women veterans. In particular, the influence of glucose control on perceived menopause symptom severity in women with diabetes was demonstrated (Figure 5.1). The theory also recommends the assessment of symptom consequences, which provided important data of the impact of the symptoms on both mental and physical health. The assessment of severity, also guided by the conceptual framework, presented a new dimension in understanding the relative impact of the symptom on women's health and extends the work of previous investigations. This was clearly demonstrated, as while prevalence rates for symptoms were often similar among the groups, severity scores differed identifying either symptoms that were more critical than others or groups of women that were more affected by these symptoms. Dimensions and characteristics of the military service experience were not assessed in this study of women veterans but are an important situational variable affecting the menopause symptom experience of women veterans that can be easily operationalized in future studies guided by the TOUS.

Limitations

There are several important limitations and sources of bias to consider in this study. The use of a cross-sectional design does not allow for tracking symptom change over time and precludes assessment of the temporal relationship of these symptoms to one another, both between the diabetes symptoms and menopause symptoms, but also between the individual menopause symptoms. For example, hot flashes may precipitate poor sleep or vaginal dryness may predicate decreased libido. With the exception of the extracted clinical data, most of the study findings are based on respondent's retrospective self-reports of symptom severity and are vulnerable to bias.

Several characteristics of the participants were not measured in the survey instrument that might have permitted more thorough assessment of relationships among the variables. This would include data regarding military service (years of service, branch, rank, type of deployment, combat exposure) and reproductive and gynecological history (reason for hysterectomy, parity). Selection bias may have been introduced, as

the subjects who elected to participate may possess traits or characteristics that possibly influence the variables of interest. The findings are from a national sample of women veterans receiving care in the VA healthcare system and are not generalizable to other groups.

Conclusions and Implications

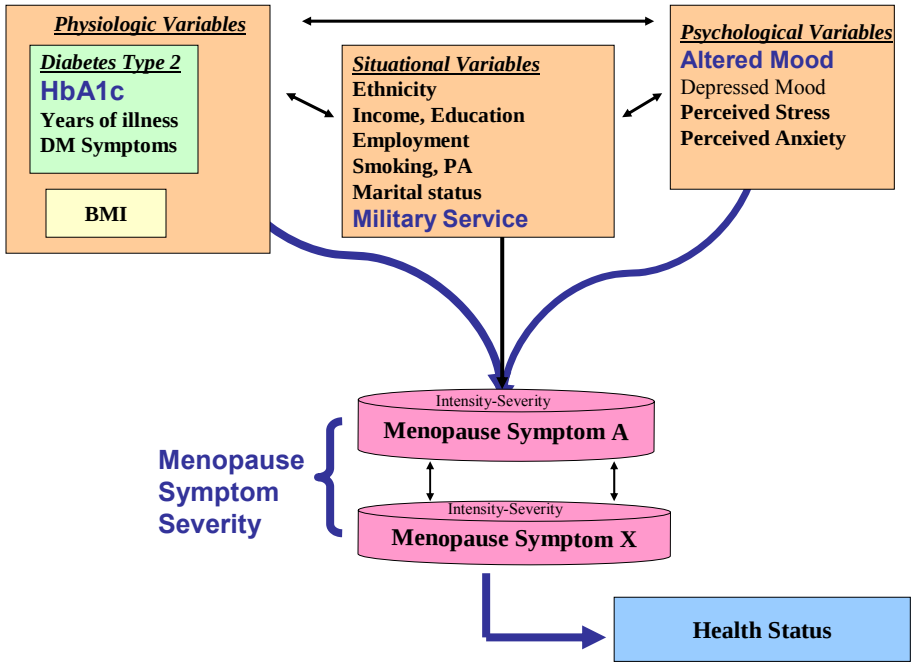
This is the first US study to examine the menopause symptom experience in women veterans with diabetes. We demonstrated that women veterans with diabetes experienced menopause at the same age and report similar symptoms (hot flashes, muscle/joint aches, trouble sleeping) as their non-affected peers. Among women with diabetes, glucose control was an important correlate of menopause symptom severity and perceived physical health status. These findings substantiate the importance of addressing menopause symptoms in the clinical management of women veterans with diabetes using services in the VA healthcare system. The data also suggest interventions targeting glucose control may improve the menopause symptom experience of women with diabetes as well as benefit physical health status.

BMI and cigarette smoking were important correlates of the physical health score and efforts aimed at smoking cessation or diet and exercise interventions to reduce BMI, may also improve both physical health and menopause symptom severity of the women veterans. Altered mood was a prominent covariate of overall menopause symptom severity, depressive symptoms were the primary correlate of vasomotor symptom severity and perceived anxiety demonstrated a strong relationship with somatic symptom severity among all the women veterans. The strong association of these covariates with menopause symptom severity, along with previous documentation of the risk for new onset of mood disorder at menopause in other investigations (Freeman et al., 2007; Hardy & Kuh, 2005; Bromberger et al., 2007) and the high risk for psychiatric disorder in women veterans (Dobie et al., 2002; Dobie et al., 2006), suggest careful and thorough assessment for altered mood be considered when evaluating menopause symptoms in women veterans.

Details regarding the military service experience, in particular deployment history, the branch of service, military rank and status, chemical exposures, assaultive violence, and musculoskeletal injury or trauma should be included in future studies of

women veterans to evaluate the relationship of these variables with menopause symptom severity. Prospective studies are also recommended to determine the temporal relationship among specific menopause symptoms such as vasomotor and sleep symptoms and to disentangle the association between diabetes and menopause symptoms over the course of the menopause transition. Qualitative studies that investigate women veterans' perceptions of their menopause symptoms as menopause or diabetes related and the perceived impact of these symptoms on health status are also warranted. The findings from this study should also be confirmed in non-veteran populations.

Figure 5.1. Theory of Unpleasant Symptoms: SWIM Study Findings



BMI, Body Mass Index; DM, Diabetes Mellitus, HbA1c, Hemoglobin A1c levels; PA, Physical Activity; SWIM, Study of Women veterans in Menopause.

Table 5.1: Postmenopause Symptom Prevalence: Comparisons with Longitudinal Investigations*

Symptom Group	SWIM	SWAN[a]	MWMHP[b]	POA[c.d,]	Manitoba Project[f,g]	Healthy Women[h]	MA-WHS[i,j]
Vasomotor	74.4%	48.8%	52%	73-79%	41.5%	43%	
Muscle/joint pain	78.6%	54.8%	45%	72%			
Sleep disturbances	68.6%	43.2%	45%	50%[d]			
Altered Mood symptoms	Sad or blue: 61.2% Irritable: 64.2% Anxiety: 52.9% Mood swings: 54.2%	22%	26% 26%	40%[d]	23%	5.9%	33.8%
Memory, trouble concentrating	65%	42%	26%				
Decreased libido	58.4%			37%			
Urinary incontinence	57.2%	57%[e]	16%				
Headaches	47%		42%				
Vaginal Dryness	45.2%	21.2%	47%	20%[d]			

SWIM, Study of Women veterans in Menopause; SWAN, Study of Women's Health Across the Nation; MWMHP, Melbourne Women's Midlife Health Project; POA, Penn Ovarian Aging study; MA-WHS, Massachusetts Women's Health Study;
*Adapted from Woods & Mitchell (2005). *American Journal of Medicine 118*(128), 14S-24S.

[a]Gold, E. B. et al. (2000). *American Journal of Epidemiology 152*, 463-473.
[b]Dennerstein, L. et al. (2000). *Obstetrics & Gynecology 96,* 351-358. Women were 3 years postmenopause
[c]Freeman, E. W. et al. (2001). *Menopause 8,* 33-42.
[d]Approximated from the graphs in Freeman E. W. et al. (2007). *Obstetrics & Gynecology 110*(2), 230-240.
[e]Sampselle C.M. et al. (2002). *Obstetrics & Gynecology 100*, 1230-1238. Pre and peri-menopausal women
[f]Kaufert, P. A. et al. (1992). *Maturitas 14*, 143-155.
[g]Kaufert, P. & Syrotuik, J. (1981). *Social Science & Medicine 151*, 173-184.
[h]Matthews, K. A. et al. (1990). *Journal of Consultation in Clinical Psychology 58*, 345-351.
[i]Avis, N. E. et al. (2001). *Climacteric 4*, 243-249.
[j]Avis, N. E. et al. (1994). *Annals of Epidemiology 4*, 214-220.

Table 5.2. Mental and Physical Health Summary Scores: Women Veterans Healthcare Service users and National Norms*

	Women Veterans	Women Veterans with Diabetes	Norms: Females Age 45-54	Norms: Females Age 55-64	Norms: Diabetes Mellitus	Norms: Major Depression	Norms: HTN	Norms: OA, DJD
Mental Health	43.6 ± 0.7	43.5 ± 0.8	49.64	50.14	47.28	37.40	49.11	47.53
Physical Health	40.0 ± 0.7	38.8 ± 0.8	48.20	46.28	41.52	45.55	43.68	38.91

*Ware J. E. et al. (2007). *User's Manual for the SF-12v2 Health Survey*. Boston, MA: Quality Metric Incorporated.
Values are mean ± SEM
DJD, Degenerative Joint Disease; HTN, Hypertension; OA, Osteoarthritis.

Table 5.3. Menopause Symptom Prevalence: Comparisons among Women with Chronic Illness

Menopause Symptom	**SWIM** (*n* = 328)	**Polio Survivors**[a] (*n* = 190)	**HIV**[b] (*n* = 536)	**HIV**[c] (*n* = 251)	**Metabolic Syndrome**[d] (*n* = 325)	**Healthy Women**[e-n] **Averages**
Vasomotor	74.4%	80.0%	64%	78.1%	52.3%	41.5-79%
Muscle/joint pain	78.6%		64.9%		85.2%	45-72%
Sleep disturbances	68.6%	88.9%	51.9%	66.7%		43-50%
Altered Mood	Sad or blue: 61.2% Irritable: 64.2% Anxiety: 52.9% Mood swings: 54.2%	Depressed: 81.6% Irritability: 87.4% Excitable: 85.3% Moodiness: 82.5%	90%	97.9%	Sadness: 71.9%	6-34%
Memory loss	65%	84.2%			80.7%	26-42%
Decreased libido	58.4%	81.8%			79.5%	37%
Urinary Incontinence	57.2%		48.4%	73.0%		16-57%
Headaches	47%	78.4%				42%
Vaginal Dryness	45.2%	39.6%	48.4%	73.0%		20-47%
Sample						
Age (years)	55.0	52.9-56.2	44-51	48.9-51.0	55.9	
Ethnicity	41% non-white	93% white	90% non-white	30% non-white	Ecuadorian	
Reproductive status	Postmenopause Natural & Surgical	1/3 perimenopause, 2/3 PM Natural only	Pre, Peri, PM Natural & Surgical	Pre, Peri, PM Natural & Surgical	All PM Natural only	

[a]Kalpakjian, C. Z. et al., (2005). *Menopause 12*(1), 78-87.
[b]Ferreira, C. E. et al. (2007). *Gynecological Endocrinology 23* (4), 198-205.
[c]Miller, S. A. et al. (2005). *Menopause 12* (3), 348-356.
[d]Chedraui, P. et al. (2007b). *Archives of Gynecology & Obstetrics 275,* 161-168.
[e]Gold, E. B. et al. (2000). *American Journal of Epidemiology 152*, 463-473.
[f]Dennerstein, L. et al. (2000). *Obstetrics & Gynecology 96,* 351-358.
[g]Freeman, E. W. et al. (2001). *Menopause 8,* 33-42.
[h]Freeman E. W. et al. (2007). *Obstetrics & Gynecology 110*(2), 230-240.
[i]Sampselle C.M. et al. (2002). *Obstetrics & Gynecology 100*, 1230-1238.
[j]Kaufert, P. A. et al. (1992). *Maturitas 14*, 143-155.
[k]Kaufert, P. & Syrotuik, J. (1981). *Social Science & Medicine 151*, 173-184.
[l]Matthews, K. A. et al. (1990). *Journal of Consultation in Clinical Psychology 58*, 345-351.
[m]Avis, N. E. et al. (2001). *Climacteric 4*, 243-249.
[n]Avis, N. E. et al. (1994). *Annals of Epidemiology 4*, 214-220.

Appendix A

Study of Women Veterans In Menopause

STUDY OF WOMEN VETERANS IN MENOPAUSE

This is a survey about menopause symptoms in women veterans with and without type 2 diabetes (high blood sugars). Your answers will help us understand what women veterans after menopause experience so that we can provide women with the best possible health care during this time in their lives.

This survey asks questions about you, your health, and your menopause. **If you have type 2 diabetes**, there are some extra questions about your diabetes at the end of the survey. Please answer each question as best you can. Be careful not to skip any. There are no right or wrong answers.

All your answers will be kept completely private and confidential.

When you complete the survey, please return it and the informed consent form in the enclosed self-addressed stamped envelope. Thank you in advance for your help. If you have any questions about anything in this survey or are not sure how to answer an item, please feel free to contact us via phone or email:

Sarah Krein: 734-845-3621 or sarah.krein@va.gov
Patricia Rouen: 734-845-3502 or prouen@umich.edu

Your participation is completely voluntary. If you choose not to fill out the survey, please return it to us in the enclosed envelope.

The survey takes about 20 to 30 minutes to complete. Please read each question and using a pen, Place an **"X"** in the one box that best describes your experience. There is only one answer for each question.

Example:

What color is the sun?

1☒ Yellow

2☐ Purple

3☐ Blue

SECTION A: YOUR MENSTRUAL CYCLE & MENOPAUSE

These questions are about your menstrual periods, your menopause and symptoms or feelings women may have during this time in their lives.

M1. What is your current age? _____ years old

M2. Are you still having menstrual periods or menstrual bleeding?

1☐ Yes (If Yes, please stop here and return the survey in the enclosed self- addressed stamped envelope. Thank you for your time.)

2☐ No (If No, please continue to fill out the survey.)

M3. Has it been **at least 12 months** since your last period?

1☐ Yes (If Yes, please continue to fill out the survey)

2☐ No (If No, please stop here and return the survey in the enclosed self-addressed stamped envelope. Thank you for your time.)

M4. How old were you when your periods permanently stopped?

_____ years old

M5. How did your periods stop? Pick the answer that best describes you.

1☐ My periods stopped naturally (on their own).

2☐ My periods stopped when I had **both** my uterus (womb) **and** my ovaries removed

3☐ My periods stopped when I had my uterus (womb) **but not** my ovaries removed

4☐ My periods stopped when I was treated for breast cancer

5☐ My periods stopped for another reason. Please write in the reason:

_____

M6. If you had your uterus **but not your ovaries** removed in surgery, you stopped having periods but your ovaries continued to work.

Later in your life, when your ovaries stopped working, you would have experienced menopause. With menopause, you may have noticed symptoms such as hot flashes, sleeping problems, fatigue, or being irritable.

At what age did you enter menopause?

1☐ _____ years old

2☐ This does not apply to me.

3☐ I don't know.

M7. Please circle the number on the 0 to 10 scale that best describes **how problematic or difficult your overall experience** with menopause has been?

0 → **10**

Not difficult — **Very difficult**

No problems — **Many problems**

0	1	2	3	4	5	6	7	8	9	10

Comments: (feel free to write in)

M8. The next questions ask about symptoms women may have during menopause.

Please check "*Yes*" or "*No*" if you have had any of these symptoms **in the past 4 weeks**. If you answer, **"YES"** to any symptom, write in the number of days in the month you had the symptom and check how severe (bad) the symptom was.

Use these definitions to rate how severe (bad) the symptom was:
Mild: Bothered a little

Moderate: Bothered about half the time. Interferes with activity

Severe: Bothered a lot, most of the time, or enough to seek treatment

Symptom	Yes or No (check)	If YES, how many days in the month?	If YES, how severe (bad)? (check one)
Hot flashes or night sweats	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Vaginal dryness or discomfort	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Concentration or memory problems	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Irritability	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Mood swings	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Feeling sad, down or blue	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Feeling anxious, on edge or nervous	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Trouble sleeping	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Aches, joint pains or stiffness	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Headaches	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Losing or leaking urine	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐
Decreased interest in sex (libido)	Yes 1☐ No 2☐		Mild 1☐ Moderate 2☐ Severe 3☐

M9. The next questions are about **HOT FLASHES and NIGHT SWEATS only.**

The sensation of being flushed can occur at any time of day or night.

For these questions, use the words: ***hot flashes*** for symptoms that occurred during daytime (awake hours) and the words ***night sweats*** for symptoms that occurred during the nighttime (sleep hours).

Thinking back over the past 2 days,

1. Write in the number of hot flashes or night sweats you had each day or night.

2. Next, mark how many of the hot flashes or night sweats on that day or night were mild, moderate or severe.

3.If you did not have any symptoms, write "0" in the 1st box and skip the 2nd box.

Example:

	HOT FLASHES Total Number in the past 2 days	**HOT FLASHES Number that were Mild, Moderate or Severe**
Day 1	**5**	**3** mild **1** moderate **1** severe
Day 2	**0**	___ mild ____ moderate ___ severe

A. **HOT FLASHES**: Use these definitions to rate how severe (bad) the *hot flashes* were

Mild: Feeling warm but no sweating. Your face may have gotten red. You were able to continue your activities.

Moderate: Feeling hot with or without sweating. Your head, neck, ears or whole body felt hot. You were able to continue your daily activities.

Severe: Feeling very hot with sweating. You had to stop what you were doing and take action such as opening a window, putting cold water on your face or changing your blouse.

	HOT FLASHES **Total Number in the past 2 days**	**HOT FLASHES** **Number that were Mild, Moderate or Severe**
Day 1		**___ mild ___ moderate ___ severe**
Day 2		**___ mild ___ moderate ___ severe**

B. **NIGHT SWEATS**: Use these definitions to rate how severe (bad) the *night sweats* were

Mild: They don't wake you up, but you notice damp sheets or a damp nightgown when wake up or get up for other reasons

Moderate: They wake you up because you're hot and/or sweating, but no action is needed other than removing blankets or sheets

Severe: You wake up hot and/or sweating and you need to take action, such as removing your nightgown, opening the window or getting out of bed.

	NIGHT SWEATS **Total Number in the past 2 nights**	**NIGHT SWEATS** **Number that were Mild, Moderate or Severe**
Night 1		**___ mild ___ moderate ___ severe**
Night 2		**___ mild ___ moderate ___ severe**

M10. The next set of questions asks about feelings women may have with menopause. How often **during the past week**, have you felt this way?

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me	0☐	1☐	2☐	3☐
2. I had trouble keeping my mind on what I was doing	0☐	1☐	2☐	3☐
3. I felt depressed	0☐	1☐	2☐	3☐
4. I felt that everything I did was an effort	0☐	1☐	2☐	3☐
5. I felt hopeful about the future	0☐	1☐	2☐	3☐
6. I felt fearful	0☐	1☐	2☐	3☐
7. My sleep was restless	0☐	1☐	2☐	3☐
8. I was happy	0☐	1☐	2☐	3☐
9. I felt lonely	0☐	1☐	2☐	3☐
10. I could not get "going"	0☐	1☐	2☐	3☐

M11. **Over the last 2 weeks**, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0☐	1☐	2☐	3☐
2. Not being able to stop or control worrying	0☐	1☐	2☐	3☐
3. Worrying too much about different things	0☐	1☐	2☐	3☐
4. Trouble relaxing	0☐	1☐	2☐	3☐
5. Being so restless that it is hard to sit still	0☐	1☐	2☐	3☐
6. Becoming easily angered or irritable	0☐	1☐	2☐	3☐
7. Feeling afraid as if something awful might happen	0☐	1☐	2☐	3☐

M12. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
0☐	1☐	2☐	3☐

M13. **In the last month**, how often have you

	Never	Almost Never	Sometimes	Fairly often	Very Often
1. Been upset because of something that happened unexpectedly	0☐	1☐	2☐	3☐	4☐
2. Felt that you were unable to control the important things in your life	0☐	1☐	2☐	3☐	4☐
3. Felt nervous and "stressed"	0☐	1☐	2☐	3☐	4☐
4. Felt confident about your ability to handle your personal problems	0☐	1☐	2☐	3☐	4☐
5. Felt that things were going your way	0☐	1☐	2☐	3☐	4☐
6. Found that you could not cope with all the things that you had to do	0☐	1☐	2☐	3☐	4☐
7. Been able to control irritations in your life	0☐	1☐	2☐	3☐	4☐
8. Felt that you were on top of things	0☐	1☐	2☐	3☐	4☐
9. Been angered because of things that were outside of your control	0☐	1☐	2☐	3☐	4☐
10. Felt difficulties were piling up so high that you could not overcome them	0☐	1☐	2☐	3☐	4☐

SECTION B: YOUR HEALTH

These questions ask about your health and how well you are able to do your usual activities.

H1. Please mark if you have been told by a doctor or a nurse that you have any of the health conditions below. (**Please check all that apply**.)

1☐	A. Chronic heart failure (also called congestive heart failure)
1☐	B. Other heart disease (such as heart attack, coronary artery disease, angina)
1☐	C. Stroke or Transient Ischemic attack (TIA or 'mini-stroke')
1☐	D. Hypertension or High Blood Pressure
1☐	E. Peripheral Vascular Disease (poor circulation in your legs)
1☐	F. Cancer (what body parts: _____)
1☐	G. Kidney disease (kidney failure, protein in your urine)
1☐	H. Liver disease
1☐	I. Diabetes or high blood sugar
1☐	J. Eye disease (diabetic retinopathy)
1☐	K. Eye disease (cataracts or macular degeneration)
1☐	L. Lung disease (such as COPD, asthma, emphysema, or chronic bronchitis)
1☐	M. Depression, anxiety, or post-traumatic stress disorder (PTSD)
1☐	N. Neuropathy (nerve problems causing tingling, numbness, burning sensations)
1☐	O. Arthritis or degenerative joint disease ("DJD")
1☐	P. High Cholesterol
1☐	Q. Foot ulcers or gangrene
1☐	R. Other (Please write in _____)
1☐	S. Other (Please write in _____)

H2. Have you had any surgery or a recent injury in the past 4 weeks?

1☐ Yes 2☐ No

H3. Are you currently taking **or** have taken in the past 6 months ON A DAILY BASIS any of these medications? **Check all that apply**

1☐ Birth control pills
1☐ Hormone replacement therapy
1☐ Estrogen
1☐ Progesterone
1☐ Testosterone
1☐ Nolvadex (Tamoxifen)
1☐ Anastrozole (Arimidex)
1☐ Prednisone (Deltasone)
1☐ Methylprednisone (Medrol)
1☐ Decadron (Dexamethasone)
1☐ Divalproex (Depakote)
1☐ Citalopram (Celexa)
1☐ Escitalopram (Lexapro)
1☐ Sertraline (Zoloft)
1☐ Fluoxetine (Prozac, Serafem)
1☐ Paroxetine (Paxil)
1☐ Venlafaxine (Effexor)
1☐ Duloxetine (Cymbalta)
1☐ Lithobid (Lithium)
1☐ Bupropion (Wellbutrin)
1☐ Trazadone (Desyrel)
1☐ Lamotrigine (Lamictal)

1☐ Fluphenazine (Prolixin)
1☐ Risperidine (Risperdal)
1☐ Quetiapine (Seroquel)
1☐ Olanzapine (Zyprexa)
1☐ Symbyax
1☐ Aripiprazole (Abilify)
1☐ Clozapine (Clozaril)
1☐ Ziprasidone (Geodon)
1☐ Thioridazine (Mellaril)
1☐ Protriptyline (Vivactil)
1☐ Imipramine (Tofranil)
1☐ Amitriptyline (Elavil, Endep)
1☐ Doxepin (Sinequan)
1☐ Nortriptyline (Pamelor)
1☐ Phenelzine (Nardil)
1☐ Tranylcypromine (Parnate)
1☐ Mirtazapine (Remeron)
1☐ Busprinone (Buspar)
1☐ Clonazepam (Klonipin)
1☐ Lorazepam (Ativan)
1☐ Alprazolam (Xanax)
1☐ Oxazepam (Serax)

H4. Do you take any **over the counter** (non-prescription) products for menopause symptoms (for example: herbal supplements, soy products, vitamins)

1☐ No 2☐ Yes→ If "***YES***", please list those products you are taking:

_____

H5. How **tall** are you without shoes? _____ feet, _____inches

H6. How much do you **weigh** without clothes? _____ pounds

H7. Do you currently smoke cigarettes?

1☐ Yes

2☐ No

H8. At present, do you drink alcoholic drinks at all (such as beer, wine, gin, vodka, other hard liquor)?

1☐ No

2☐ Yes → If "***YES***", how many <u>days in a week</u>, do you have an alcoholic drink?

0☐ 0 1☐ 1 2☐ 2 3☐ 3 4☐ 4 5☐ 5 6☐ 6 6☐ 7

On the days that you drink, <u>how many drinks</u> do you usually have?

0☐ 0 1☐ 1 2☐ 2-3 3☐ 4-5 4☐ 6 or more 5☐ Doesn't apply to me

H9. During the **past week** (even if it was not a typical week for you), how much total time (for the entire week) did you <u>walk for exercise</u>?

1☐ <u>None</u>

2☐ **Less than 30 minutes** during the week

3☐ **30-59 minutes** during the week

4☐ **1-3 hours** during the week

5☐ **More than 3 hours** during the week

H10. During the **past week** (even if it was not a typical week for you), how much total time (for the entire week) did you do other aerobic exercise (e.g., swimming and bicycling including stationary bike)?

1☐ None

2☐ **Less than 30 minutes** during the week

3☐ **30-59 minutes** during the week

4☐ **1-3 hours** during the week

5☐ **More than 3 hours** during the week

H11. These questions ask about symptoms you may have had **in the past 4weeks.** Have you had any….

Symptom	Yes or No (check)	If "YES", how troublesome?
1. Lack of energy?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
2. Aching calves when walking?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
3. Numbness (loss of sensation) in the feet?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
4. An overall sense of fatigue?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
5. Shortness of breath at night?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
6. Sleepiness or drowsiness?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐
7. Difficulty concentrating?	Yes 1☐ No 2☐	Not at all 0☐ A little 1☐ Moderately 2☐ Very 3☐ Extremely 4☐

Symptom	Yes or No (check)	If "YES", how troublesome?				
8. Moodiness?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
9. Numbness (loss of sensation) in the hands?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
10. Persistently blurred vision (even with glasses on)?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
11. Tingling sensations in arms or legs at night?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
12. Being very thirsty?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
13. Palpitations or pounding in the heart region?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
14. Deteriorating vision?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
15. Burning pain in the calves at night?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
16. Dry mouth?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
17. Increasing fatigue during the course of the day?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
18. Flashes or black spots in the field of vision?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐
19. Irritability just before a meal?	Yes $_1$☐ No $_2$☐	Not at all $_0$☐	A little $_1$☐	Moderately $_2$☐	Very $_3$☐	Extremely $_4$☐

Symptom	Yes or No (check)	If "YES", how troublesome?
20. Fatigue in the morning when getting up?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
21. Shooting pains in the legs?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
22. Alternating clear and blurry vision?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
23. Frequent need to urinate?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
24. Pains in the chest or heart region?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
25. Burning pain in the legs during the day?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
26. Tingling or prickling sensation in hands or fingers?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
27. Easily irritated or annoyed?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
28. Sudden deterioration of vision?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
29. Odd feeling in lower legs or feet when touched?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐
30. Shortness of breath during physical exertion (walking, chores)?	Yes ₁☐ No ₂☐	Not at all ₀☐ A little ₁☐ Moderately ₂☐ Very ₃☐ Extremely ₄☐

Symptom	Yes or No (check)	If "YES", how troublesome?				
31. Fuzzy feeling in your head (difficulty thinking clearly)?	Yes ☐1 No ☐2	Not at all ☐0	A little ☐1	Moderately ☐2	Very ☐3	Extremely ☐4
32. Drinking a lot (all sorts of beverages)?	Yes ☐1 No ☐2	Not at all ☐0	A little ☐1	Moderately ☐2	Very ☐3	Extremely ☐4
33. Difficulty paying attention?	Yes ☐1 No ☐2	Not at all ☐0	A little ☐1	Moderately ☐2	Very ☐3	Extremely ☐4
34. Tingling or prickling sensations in lower legs or feet?	Yes ☐1 No ☐2	Not at all ☐0	A little ☐1	Moderately ☐2	Very ☐3	Extremely ☐4

H12. In general, would you say your health is:

☐1 Excellent ☐2 Very Good ☐3 Good ☐4 Fair ☐5 Poor

H13. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Moderate activities</u> such as moving a table, pushing a vacuum cleaner, bowling, playing golf	☐1	☐2	☐3
b. Climbing <u>several</u> flights of stairs	☐1	☐2	☐3

H14. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like?	0☐	1☐	2☐	3☐	4☐
b. Were limited in the kind of work or other activities?	0☐	1☐	2☐	3☐	4☐

H15. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like?	0☐	1☐	2☐	3☐	4☐
b. Did work or other activities less carefully than usual?	0☐	1☐	2☐	3☐	4☐

H16. During the **past 4 weeks**, how much did pain interfere with your normal work, (including both work outside the home and housework)?

1☐ Not at all 2☐ A little bit 3☐ Moderately 4☐ Quite a bit 5☐ Extremely

H17. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
0☐	1☐	2☐	3☐	4☐

H18. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the past 4weeks…..

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	0☐	1☐	2☐	3☐	4☐
b. Did you have a lot of energy?	0☐	1☐	2☐	3☐	4☐
c. Have you felt downhearted and depressed?	0☐	1☐	2☐	3☐	4☐

SECTION C

These are a few questions about you. It is very important that the study represents the views of all people. For this reason, please answer to the following questions. **Remember all of your answers are confidential**

C1. Are you of Hispanic of Latino origin?

1☐ Yes 2☐ No

C2. What is your **ethnic origin/race?**

1☐ Black or African American

2☐ White, European or Caucasian

3☐ Hispanic or Latino

4☐ American Indian or Alaskan Native

5☐ Native Hawaiian or Other Pacific Islander

6☐ Central / South Asian

7☐ Middle Eastern or Arab American

8☐ Other (write in): _____

C3. What is your **current relationship status?**

1☐ Married

2☐ Never Married

3☐ Separated

4☐ Widowed

5☐ Divorced

6☐ Living with Partner

7☐ Have Partner, not living together

C4. How much **schooling** have you had? (check one box)

1☐ 8th grade or less

2☐ Some high school

3☐ High school graduate or GED

4☐ Some college or technical school

5☐ 2 year college degree

6☐ 4 year college degree (bachelor's degree)

7☐ More than a 4-year college degree

C5. Which best describes your **current employment** status? (check one box)

1☐ Working full time or part time

2☐ Not employed for health reasons

3☐ Not employed and looking for work

4☐ Retired

5☐ Full time Homemaker

6☐ Student

7☐ Something else? (Please write in):

_____

C6. What is your total **family income**?

This information is important for describing the women in the study as a group and is like all other questions, kept confidential.

1☐ Less than $10,000

2☐ $10,000 to $19,999

3☐ $20,000 to $34,999

4☐ $35,000 to $49,999

5☐ $50,000 to $74,999

6☐ $75,000 to $99,999

7☐ $100,000 or more

C7. How many **dependents** are in your household? _____
(A dependent is an adult or child that you provide financial support to.)

C8. Have you ever been told by a health care provider (doctor, nurse) that you have **diabetes or high blood sugar**?

1☐ Yes (If **Yes**, **please continue to fill out the survey**)

2☐ No (If No, please stop here and return the survey in the enclosed self-addressed stamped envelope. **Thank You** very much for your time)

SECTION D: DIABETES

D1. At what **age** were you told you had diabetes? _____ years old

D2. How **long** have you had diabetes?

1☐ _____ years (write in)

2☐ Less than 12 months

3☐ Don't know

D3. Was your diabetes found **before or after you reached menopause**?

1☐ Before 2☐ After

D4. How do you currently manage or control your diabetes? (Check all that apply).

1☐ Diet

2☐ Exercise

2☐ Oral medications

3☐ Insulin (either injected or inhaled)

4☐ Other (please write in): _____

D5. Do you now use **insulin (either inhaled or injected)**?

1☐ No 2☐ Yes → If **"**YES**",** how often do you use insulin? (check one box)

1☐ Once a day (taken in the morning)

2☐ Once a day (taken in the evening)

3☐ Twice a day

4☐ Three times a day

5☐ Four or more times a day

6☐ I use an infusion pump

D6. At present, do you take any of these diabetes medicines?
CHECK ALL THAT APPLY

1☐ Glucotrol (Glipizide)

1☐ Amaryl (Glimepiride)

1☐ Glyburide (Micronase, Glynase, Diabeta)

1☐ Tolinase (Tolazamide)

1☐ Glucophase (Metformin)

1☐ Diabinese (Chloroproamide)

1☐ Precose (Acarbose)

1☐ Prandin (Repaglinide)

1☐ Avandia (Rosiglitazone)

1☐ ACTOS (Pioglitazone)

1☐ Symlin (Pramlintide)

1☐ Byetta (Exenatide)

1☐ Januvia (Sitagliptin)

1☐ Other: _____

D7. Do you **check your own blood sugar**?

0☐ No 1☐ Yes → If "**YES**", how often do you usually check your blood sugar?

1☐ Once a month

2☐ Every other week (twice a month)

3☐ Once a week

4☐ A couple of times during the week

5☐ Once a day

6☐ Twice a day

7☐ Three times a day

7☐ Four or more times a day

D8. Over the past 6 months, how controlled (near the normal range of 80-130) would you say your blood sugars have been?

All of the time (100%)	Most of the time (75%)	Some of the time (50%)	A little of the time (25%)	None of the time (0%)
0☐	1☐	2☐	3☐	4☐

D9. When was the last time you had a **Hemoglobin A1c test** done? This is a blood test that measures your overall average blood sugar.

1☐ Within the past 3 months

2☐ Within the past 6 months

3☐ Within the past 12 months

4☐ 1-2 years ago

5☐ 2-3 years ago

6☐ Don't remember

D10. What was your last **Hemoglobin A1c value**?

Write in (if known): _____

1☐ 4-7%

2☐ 7-10%

3☐ Greater than 10%

4☐ I don't know

D11. In the **past 6 months**, how much of the time have you been able to…..

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Keep your weight under control	0☐	1☐	2☐	3☐	4☐
b. Take your medicines (pills or insulin) as ordered	0☐	1☐	2☐	3☐	4☐
c. Follow your diabetic eating plan	0☐	1☐	2☐	3☐	4☐
d. Exercise regularly	0☐	1☐	2☐	3☐	4☐
e. Check your blood sugar as ordered	0☐	1☐	2☐	3☐	4☐
f. Check your feet for wounds or sores	0☐	1☐	2☐	3☐	4☐

END OF QUESTIONNAIRE! Thank you very much for taking the time to complete this survey. Please return in the self-addressed envelope provided.

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