THE ROLE OF FAMILY HISTORY OF DEPRESSION IN THE DEVELOPMENT OF MAJOR DEPRESSION IN WOMEN DURING MIDLIFE

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Depression is associated with increased morbidity and mortality and is highly prevalent, particularly in women. Studies indicate increased risk for onset of new and recurrent episodes of major depression in women during midlife. To improve understanding of the etiology of depression in midlife women and to inform prevention and treatment efforts, the risk and protective factors that influence the occurrence and course of depression in midlife women should be determined. In particular, the role of family history of depression in the development of depression among midlife women is unknown. This dissertation explores associations between family history and major depression in midlife women in the context of other risk and protective factors.

First, the relationship between family history and major depression was examined in 303 midlife women. Results showed that family history of depression is a significant predictor of midlife major depression, particularly in women with a history of depression prior to midlife.

Second, data from the same cohort of midlife women showed that family history of depression is associated with midlife major depression, after controlling for the menopausal transition and relevant time-varying covariates. Furthermore, menopausal status is associated with major depression among midlife women without a family history of depression but not among those with a family history.

Third, potential mediators of the relationship between family history and the onset of major depression during midlife were explored in 103 midlife women with a lifetime history of depression. Mediation analyses provided evidence that childhood abuse, trait anxiety, and life events mediate the effect of family history on the onset of depression during midlife.

In conclusion, family history of depression continues to play an important role in the development of depression in women during midlife, particularly for women with a prior history

of depression. The public health relevance of our findings is that clinicians may be able to improve the emotional health of midlife women by assessing family history and lifetime history of depression to identify those at risk and by closely monitoring mood among women found to have such histories, thus allowing for implementation of appropriate interventions in a timely manner.

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PREFACE

I would never have been able to finish my dissertation without the guidance and support of my committee members, friends, and family.

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1.0 INTRODUCTION AND OVERVIEW

1.1 OVERVIEW

Recent epidemiologic studies indicate increased risk for the onset of new as well as recurrent episodes of clinical depression among midlife women. However, little is known about the risk and protective factors that influence the occurrence, severity, and course of depression in women during midlife. In particular, the role of family history of depression in the development of incident and recurrent depression in women during midlife is unknown.

This dissertation will address these gaps in knowledge by examining the relationship between family history of depression and the occurrence and course of major depression in midlife women using data collected from the Pittsburgh Mental Health cohort of the Study of Women's Health Across the Nation (SWAN). In brief, the aims of the project are as follows: 1) To determine whether family history of depression is a significant risk factor for major depression in midlife women; 2) To evaluate whether family history of depression remains a significant predictor of major depression among midlife women after adjusting for changes in menopausal status and other time-varying covariates; 3) To explore whether women who have both a family and a lifetime history of depression are at greater risk of major depression during midlife than women who have a lifetime history of depression only and to examine potential explanatory factors for the increased risk. Knowledge gained through this work will increase understanding of risk factors for depression in women during midlife and inform prevention and treatment efforts.

1.2 DEPRESSION

Major depression is a psychiatric disorder characterized by low mood and/or loss of interest or pleasure (anhedonia). According to the fourth edition of the American Psychiatric Association's

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994), major depression is defined as the presence of at least five of the following symptoms during a 2-week period: 1) depressed mood, 2) loss of interest or pleasure, 3) significant weight gain or weight loss, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) diminished ability to think, concentrate, or make decisions, 9) recurrent thoughts of death, suicidal ideation, or suicide attempt or plan. In addition, reported symptoms must include depressed mood or anhedonia, and symptoms must be clinically significant in terms of impairment and distress to the individual.

Depression is often a chronic condition, and it is estimated that 50-80% of those who experience a depressive episode will suffer from one or more additional episodes in their lifetime (Kessler, Zhao, Blazer, & Swartz, 1997). Furthermore, depression is a complex disorder that is multifactorial in origin (Belmaker & Agam, 2008). A number of social, biological, and psychological factors, as well as interactions between these factors and chronic and acute stressors, appear to influence the development of depression (aan het Rot, Mathew, & Charney, 2009; Accortt, Freeman, & Allen, 2008; Colman & Ataullahjan, 2010).

1.2.1 Morbidity, Mortality, and Costs

Associated with increased morbidity and mortality, depression is a significant public health problem (Cassano & Fava, 2002; Neugebauer, 1999). Depression is estimated to be the third leading cause of disability across the world and is the leading cause of health-related disability in women (World Health Organization, 2008). In addition, depression has been linked to increased risk for cardiovascular disease and diabetes, as well as a greater likelihood of engaging in poor health behaviors (i.e., smoking, sedentary lifestyle, poor diet) (Aneshensel & Huba, 1983; Cassano & Fava, 2002; Faith, Matz, & Jorge, 2002; Musselman, Evans, & Nemeroff, 1998; Stephens, 1988). Depression is also associated with enormous financial burden, with an estimated cost of $83.1 billion per year in the United States alone (Greenberg et al., 2003).

1.2.2 Prevalence, Gender, and Midlife

Depression is highly prevalent, particularly in women. The National Comorbidity Survey (NCS), a large-scale community-based study conducted in the United States, estimated the overall current (30-day) and lifetime prevalence of major depression to be 4.9% and 17.1%, respectively (Blazer, Kessler, McGonagle, & Swartz, 1994). When the results were stratified by gender, 3.8% of men and 5.9% of women reported current major depression, while 12.7% of men and 21.3% of women had experienced lifetime major depression. The gender difference in prevalence was evident across different racial/ethnic groups. Furthermore, additional large-scale studies conducted in the United States and internationally have confirmed that depression affects approximately twice as many women as men (Kessler et al., 2003; Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Kessler, McGonagle, Zhao, et al., 1994; Weissman et al., 1996).

Gender differences in prevalence become apparent at ages 11-14 corresponding with the onset of puberty and then persist through adulthood (Kessler et al., 1993). This timing has led to speculation that fluctuations in reproductive hormones may, in part, explain gender differences in prevalence. In addition, a number of epidemiologic studies have consistently shown that approximately 25% to 30% of midlife women report significant depressive symptoms (Bosworth et al., 2001; Bromberger, Harlow, Avis, Kravitz, & Cordal, 2004; Bromberger et al., 2007; Dennerstein, Guthrie, Clark, Lehert, & Henderson, 2004; Gallicchio, Schilling, Miller, Zacur, & Flaws, 2007; Y. Li, Yu, Ma, Sun, & Yang, 2008; Maartens, Knottnerus, & Pop, 2002; Woods & Mitchell, 1997). Recent studies also indicate that incidence of first onset or recurrent episodes of clinical depression in women during midlife ranges from 20-30% (Cohen, Soares, Vitonis, Otto, & Harlow, 2006; Kessler, McGonagle, Nelson, et al., 1994; Kessler et al., 1993; Schmidt, Haq, & Rubinow, 2004). Women in this age group are likely to be undergoing the menopausal transition, which is also a time of significant hormonal fluctuation.

1.3 RISK FACTORS FOR DEPRESSION IN WOMEN

1.3.1 Psychosocial Factors

Associations between depression and multiple psychosocial factors, including stressful life events, chronic stressors, and low social support, are seen across the lifespan. For example, job loss and widowhood have been linked with the development of depression (Paykel, 1994), and marital disruption has been associated with an increased risk of experiencing significant depressive symptoms (Aseltine & Kessler, 1993; Menaghan EG & Lieberman MA, 1986), or a depressive episode (Bulloch, Williams, Lavorato, & Patten, 2009; Rotermann, 2007).

In females of all ages, those with depression show higher rates of life events at depression onset when compared to psychologically healthy controls (Friis, Wittchen, Pfister, & Lieb, 2002; Paykel, 1994). A dose-response relationship has also been fairly consistently reported, with more severe events showing a stronger relationship with depression than events perceived to be non-severe (Kessler, 1997). Several recent studies in both clinical and community samples indicate that depressed individuals may actually increase their likelihood of experiencing stressful life events, primarily interpersonal events, through their personality characteristics and behavior (Daley, Stokes-Lampard, & Macarthur, 2009; Hammen, 2006; Hammen & Brennan, 2002; Harkness, Monroe, Simons, & Thase, 1999; Rudolph & Hammen, 1999), thereby promoting recurrent depressive episodes. Furthermore, better social support is related to decreased risk of depression and depressive symptoms (Billings & Moos, 1981; Kawachi & Berkman, 2001; Paykel, 2001; Wildes, Harkness, & Simons, 2002) and is thought to be an important moderator of the effects of stressful life events on mood (Billings & Moos, 1981).

Major depression and depressive symptoms are more prevalent in women with lower socioeconomic status (Bruce, Takeuchi, & Leaf, 1991; Stansfeld & Marmot, 1992). A number of studies have found an inverse relationship between both education and income and depression in younger adulthood through later life (Berkman LF & Breslow L, 1983; Chang-Quan, Zheng-Rong, Yong-Hong, Yi-Zhou, & Qing-Xiu, 2010; Kaplan, Roberts, Camacho, & Coyne, 1987; Roberts, Stevenson, & Breslow, 1981). A recent meta-analysis reported that those with low

socioeconomic status were 1.8 times more likely to be depressed as compared to those in the highest socioeconomic status category (Lorant et al., 2003). It is important to note that there was some inconsistency in the results from the studies examined which may be due to differences in study populations and the measurement of depression and socioeconomic status.

For many women, midlife in particular brings numerous changes in terms of social roles and circumstances. For example, midlife women may be faced with caring for aging parents, children leaving or returning to the home, financial strain, marital disruption, and the death of loved ones (Rasgon, Shelton, & Halbreich, 2005). According to the psychosocial theory of midlife depression, these changes are thought to lead to depression. Indeed, experiencing stressful life events has been consistently linked with high depressive symptom levels in women during midlife (Amore et al., 2004; Bromberger et al., 2007; Bromberger et al., 2010; Cohen et al., 2006; Dennerstein et al., 2004; Kaufert, Gilbert, & Tate, 1992; Maartens et al., 2002; Schmidt, Murphy, Haq, Rubinow, & Danaceau, 2004; Timur & Sahin, 2010). Several studies of midlife women have specifically indicated that financial strain and unemployment (Bosworth et al., 2001; Freeman et al., 2004; Y. Li et al., 2008), as well as marital disruption (Y. Li et al., 2008; McKinlay, McKinlay, & Brambilla, 1987) are associated with depressed mood. Furthermore, changes in social networks in midlife may lead to reduced social support, which in turn is related to increased risk of significant depressive symptoms (Y. Li et al., 2008).

In addition to current social stressors, several studies have shown that being exposed to early life adversities, such as child abuse and childhood poverty, may increase the risk of developing depression not only at the time of the exposure but also in later adolescence and adulthood (Bernet & Stein, 1999; Bifulco, Brown, & Adler, 1991; Diaz, Simantov, & Rickert, 2002; Gilman, Kawachi, Fitzmaurice, & Buka, 2002; Hovens et al., 2010; Johnson, Cohen, Dohrenwend, Link, & Brook, 1999; Melchior et al., 2010; Najman et al., 2010; Springer, Sheridan, Kuo, & Carnes, 2007; Weiss, Longhurst, & Mazure, 1999). This also appears to be true for midlife women. Women who were physically and/or sexually abused or had a lower childhood socioeconomic status have been reported to be at increased risk for depression in midlife compared to women with no such history of childhood adversity (Gilman et al., 2002; Rohde et al., 2008; Wise, Zierler, Krieger, & Harlow, 2001).

1.3.2 Health Status and Health Behaviors

Depression is associated with both chronic health conditions and poor health behaviors in women. These relationships are largely thought to be bi-directional, with health risk behaviors and chronic medical conditions leading to increased risk for depression, and depression in turn leading to increased risk of poor health behaviors and the development of medical problems (Katon, 2011). For example, there is good evidence that depression is associated with diabetes (Anderson, Freedland, Clouse, & Lustman, 2001; Eaton, 2002; Lloyd & Brown, 2002; Peyrot & Rubin, 1997), the metabolic syndrome (McIntyre et al., 2009), cardiovascular disease (Hayes, 2009; Kinder, Carnethon, Palaniappan, King, & Fortmann, 2004; Nemeroff, Musselman, & Evans, 1998; Rugulies, 2002; Wulsin & Singal, 2003), and arthritis (Vali & Walkup, 1998).

Some, but not all, cross-sectional and prospective general population studies suggest a significant relationship between obesity and depression in children, adolescents, and adults (Faith et al., 2011; Luppino et al., 2010). Associations between obesity and depression appear to be particularly strong in women (Bjerkeset, Romundstad, Evans, & Gunnell, 2008; Herva et al., 2006; Kasen, Cohen, Chen, & Must, 2008; Roberts, Deleger, Strawbridge, & Kaplan, 2003). Multiple biological mechanisms have been proposed to explain observed obesity and depression associations, such as inflammation, altered cortisol secretion, poor health behaviors, and obesity-related health conditions (Faith et al., 2002; Jorm et al., 2003; Stunkard, Faith, & Allison, 2003).

A number of studies in both community and clinical samples of adult women indicate a significant inverse relationship between physical activity and depression (Blumenthal et al., 1999; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Strohle, 2009; Teychenne, Ball, & Salmon, 2008). While studies show that physical activity improves depression, the exact mechanism responsible for exercise-related improvements in depressive symptoms is still unknown. However, potential psychological explanations include distraction from negative thoughts and development of a sense of mastery through meeting physical activity goals (Paluska & Schwenk, 2000). A number of physiological factors may be involved as well, such as changes in the hypothalamic adrenocortical system (Droste et al., 2003), and increased central norepinephrine neurotransmission, endorphin secretion, and serotonin synthesis and metabolism (Dunn & Dishman, 1991).

According to the health theory of midlife depression, changes in health status and health behaviors may particularly contribute to depressed mood among midlife women. Self-reported poor health (Dennerstein et al., 2004; Gallicchio et al., 2007; Kaufert et al., 1992) and chronic illnesses that become more common with age, such as cardiovascular disease and cancer, (Krishnan et al., 2002) have been found to be significantly associated with depressive symptoms and major depression at midlife (Alexander et al., 2007; Gallicchio et al., 2007). Furthermore, midlife women are likely to experience weight gain and decreases in physical activity (Matthews et al., 2001; D. F. Williamson, Kahn, Remington, & Anda, 1990), and, as noted above, the literature strongly suggests that both obesity (Freeman et al., 2004; Simon et al., 2008; Timur & Sahin, 2010) and physical inactivity (Bosworth et al., 2001; W. J. Brown, Ford, Burton, Marshall, & Dobson, 2005; Gallicchio et al., 2007; Lee & Kim, 2008; Mirzaiinjmabadi, Anderson, & Barnes, 2006; Slaven & Lee, 1997) are associated with depressive symptoms in midlife.

1.3.3 Comorbid Psychiatric Disorders

Anxiety disorders have been found to be highly comorbid with major depression. It is estimated that 50-60% of those with major depression have a lifetime history of anxiety disorder (Kaufman & Charney, 2000; Kessler et al., 1996). Comorbidity of anxiety disorders and depression has been found in both adults and youths (Axelson & Birmaher, 2001; D. E. Williamson, Forbes, Dahl, & Ryan, 2005), and there is evidence from clinical and community samples of all ages that anxiety often precedes the development of depression (Goodwin, 2002; Kovacs, Gatsonis, Paulauskas, & Richards, 1989; Lewinsohn, Gotlib, & Seeley, 1995; Wittchen, Beesdo, Bittner, & Goodwin, 2003). In addition, twin and family studies indicate a shared genetic vulnerability for the two conditions (Middeldorp, Cath, Van Dyck, & Boomsma, 2005).

Substance use disorders are also highly prevalent in those with major depression. Clinical samples report substance use disorders in approximately one third of those with major depression (Abraham & Fava, 1999; Melartin et al., 2002; Zimmerman, Chelminski, & McDermut, 2002). In the general population, prevalence of current substance use disorder in

those with major depression ranges from 8-21%, and lifetime prevalence ranges from 27-40% (Grant, 1995; Grant & Harford, 1995; Kessler et al., 2003; Regier et al., 1990). Of those with current major depression, 14% have alcohol use disorder and 5% have drug use disorder. Among those with lifetime major depression, 40% report alcohol use disorder, while 17% have a drug use disorder (Hasin, Goodwin, Stinson, & Grant, 2005). There is evidence that substance use disorder leads to depression, as well as evidence that depression increases the risk of substance use disorders (L. Davis, Uezato, Newell, & Frazier, 2008).

1.3.4 Personality Characteristics

Several studies have explored the link between the development of depression and certain personality traits such as neuroticism (the persistent tendency to experience negative emotional states such as sadness, irritability, and anxiety), conscientiousness, and positive emotionality (Klein, Kotov, & Bufferd, 2011). While there is only moderate evidence for relationships between depression and conscientiousness and positive emotionality, numerous cross-sectional and prospective studies have reported that higher levels of neuroticism are strongly associated with depression (De Graaf, Bijl, Ravelli, Smit, & Vollebergh, 2002; Fanous, Neale, Aggen, & Kendler, 2007; Kendler, Gatz, Gardner, & Pedersen, 2006; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Kotov, Gamez, Schmidt, & Watson, 2010). Furthermore, interactions between stressful life events and neuroticism have been found to predict first episodes of major depression (Kendler, Kuhn, & Prescott, 2004; Ormel, Oldehinkel, & Brilman, 2001).

On the other hand, dispositional optimism has been linked with psychological well-being (Scheier M & Carver C, 1992) and may be a protective factor for depression. For example, a small cross-sectional study of middle-aged adults reported that optimism was associated with lower depressive symptoms (Chang & Sanna, 2001), and prospective studies in adolescents and older adults indicate that optimism may protect against the development of depressive symptoms (Giltay, Zitman, & Kromhout, 2006; Patton et al., 2011).

1.3.5 The Menopausal Transition

Recent epidemiologic research has explored whether the menopausal transition is an independent risk factor for increased risk of depression during midlife, with studies focusing on relationships between depressed mood and menopausal status, fluctuating reproductive hormones, and menopausal symptoms. Although results from cross-sectional research examining depressed mood and the menopausal transition have been inconsistent, with several studies reporting increased depressive symptoms in perimenopausal women (Amore et al., 2004; Steinberg et al., 2008; Tangen & Mykletun, 2008; Timur & Sahin, 2010) and a number of others failing to replicate these results (Baker, Simpson, & Dawson, 1997; Bosworth et al., 2001; Gallicchio et al., 2007; Juang, Wang, Lu, Lee, & Fuh, 2005; Y. Li et al., 2008; Lu, Tseng, Lin, Luh, & Shu, 2009; McKinlay et al., 1987; Woods & Mitchell, 1997), recent longitudinal studies have provided strong evidence of increased risk of depressed mood among women undergoing the menopausal transition.

For example, Maartens et al. (2002) sought to determine whether depressive symptoms were independently associated with the menopausal transition in a population-based sample of 2,103 middle-aged women from the Netherlands. Compared to women whose menopausal status did not change, women who transitioned from premenopause to perimenopause and from perimenopause to postmenopause had significantly higher odds of depressive symptoms (OR=1.8, 95% CI: 1.1-3.3; OR=1.8, 95% CI: 1.5-2.7, respectively) after adjustment for age, marital status, prior depression, financial strain, employment, and major life events.

Freeman et al. (2004) found that reporting of high depressive symptoms (Center for Epidemiologic Studies Depression Scale (CES-D) $\geq$16) increased significantly during the transition (OR=2.89, 95% CI: 1.29-6.45) and decreased during the postmenopausal period (OR=0.78, 95% CI: 0.10-6.17) in an urban community sample of US women. Woods et al. (2008) analyzed 15 years of follow-up data from 302 women participating in the Seattle Midlife Women's Health Study and determined that the late menopausal transition (defined as missing at least one menstrual period in the past 12 months) was significantly associated with depressed mood (p=.03) even after controlling for age, antidepressant use, stress, body mass index (BMI), parity, and history of postpartum blues.

Bromberger et al. (2007) explored the longitudinal relationship between changes in menopausal status and risk of depressive symptoms in 3,302 middle-aged US women participating in the Study of Women's Health Across the Nation (SWAN). Women were more likely to report significant depressive symptoms (CES-D ≥16) when they were early perimenopausal (OR=1.30, 95% CI: 1.09-1.55), later perimenopausal (OR=1.71, 95% CI: 1.27-2.30), or postmenopausal (OR=1.57, 95% CI: 1.15-2.15) than when they were premenopausal.

In one of the few longitudinal studies to focus on diagnosed depression, Bromberger et al. (2011) found that women were two to four times more likely to have a major depressive episode when they were perimenopausal (OR=1.98, 95% CI: 1.00-3.92) or early postmenopausal (OR=3.86, 95% CI: 1.36-10.92) compared to when they were premenopausal.

Three longitudinal studies specifically explored incident major depression in midlife women. Both Cohen et al. (2006) and Freeman et al. (2006) determined that women undergoing the menopausal transition who had no prior history of depression were at significantly increased risk for significant depressive symptoms and a first depressive episode. Conversely, Bromberger et al. (2009) reported that neither menopausal status nor reproductive hormones were predictors of incident depression. Instead, lifetime anxiety disorder (HR=2.2, 95% CI: 1.11-4.33), low role functioning due to physical problems at baseline (HR=1.9, 95% CI: 0.95-3.72), stressful life events (HR=2.2, 95% CI: 1.13-4.47), and psychotropic medication use (HR=2.5, 95% CI: 1.18-5.42) were the strongest predictors of first onset depression in a subset of the SWAN cohort.

In contrast, a few longitudinal studies failed to find evidence of an association between changes in menopausal status and depressive symptoms. Busch et al. (1994) concluded that depression was not related to the menopausal transition in a large US national sample. However, this study only included two participant interviews spaced ten years apart, and the length of the follow-up interval would make it extremely difficult to obtain an accurate understanding of associations between changes in depressed mood and menopausal status. A prospective study by Kaufert et al. (1992) showed similar negative results, but it is important to note that they did not take hormone therapy use into account in the analyses. In addition, although a study conducted by Avis et al. (1994) reported that change in menopausal status itself was not related to depression, the authors did find a significant association between depressive symptoms and experiencing a long perimenopausal period, which appeared to be mediated by menopausal symptoms.

Two mechanisms have been proposed to explain the association between depressed mood and the menopausal transition. The neurobiological theory asserts that menopause-related fluctuations in reproductive hormones lead to changes in levels of neurotransmitters associated with emotional pathways (Rasgon et al., 2005). For example, the brain has numerous estrogen receptors, and changes in estrogen impact levels of serotonin, dopamine, and norepinepherine through degradation of catabolic enzymes, unblocking of binding sites, and enhancement of neurotransmitter transport (Spinelli, 2005; Studd & Panay, 2004). Clearly, despite the fact that all women undergoing menopause experience hormonal changes, not all develop depressed mood. The ability to maintain optimal physical and psychological functioning in response to changing levels of hormones may be modified by factors such as genetics, health, stress, or social support, thus potentially making certain subsets of women more vulnerable to depression during the menopause (Deecher, Andree, Sloan, & Schechter, 2008; Harsh, Meltzer-Brody, Rubinow, & Schmidt, 2009).

A second, the domino theory, states that the hormonal fluctuations experienced by women during the menopause are only indirectly related to depressed mood. It is thought that experiencing menopausal symptoms associated with hormonal changes, such as hot flashes, night sweats, and insomnia, leads to depression. A number of studies have provided evidence in support of the domino theory, reporting significant associations between depressed mood and vasomotor symptoms (Avis, Crawford, Stellato, & Longcope, 2001; Bromberger et al., 2007; J. P. Brown, Gallicchio, Flaws, & Tracy, 2009; Joffe et al., 2002; Juang et al., 2005; Y. Li et al., 2008), poor sleep (Avis et al., 2001; Baker et al., 1997; J. P. Brown et al., 2009; Freeman et al., 2004), and experiencing a greater number of menopausal symptoms overall (Bosworth et al., 2001; Gallicchio et al., 2007; McKinlay et al., 1987).

1.4 DEPRESSION AND FAMILY HISTORY OVERVIEW

1.4.1 Familiality of Depression

A number of studies have provided evidence for the familial nature of depression (Bierut et al., 1999; Janzing et al., 2009; Kendler, Pedersen, Neale, & Mathe, 1995; X. Li, Sundquist, & Sundquist, 2008; Sullivan et al., 1996; Timko et al., 2008; Weissman, Kidd, & Prusoff, 1982). Findings are remarkably consistent despite differences in samples and methodologies, with the majority of family studies reporting that depressed individuals are two to three times more likely to have a family history of depression than those without depression (Janzing et al., 2009; Sullivan, Neale, & Kendler, 2000; Weissman et al., 1982).

Heritability estimates for depression obtained from twin studies range from 39% to 75% (Bierut et al., 1999; Kendler et al., 1995; Kendler & Prescott, 1999; McGuffin, Katz, Watkins, & Rutherford, 1996), with a recent meta-analysis reporting an overall heritability estimate of 37% (95% CI=31% - 42%) (Sullivan et al., 2000). Similar results have been found in both clinical and community samples of twins. Twin studies indicate familiality of depression is mostly a result of genetic influences, rather than shared environment (Sullivan et al., 2000), and there is statistically significant evidence for major depression susceptibility genes (Lopez-Leon et al., 2008), particularly polymorphisms in the promoter region of the serotonin transporter (5-HTT) gene (Caspi et al., 2003).

1.4.2 Clinical Characteristics Associated with Family History

In terms of clinical characteristics, family history has been consistently associated with a more recurrent course of depression and significantly worse impairment (Gershon, Weissman, Guroff, Prusoff, & Leckman, 1986; Janzing et al., 2009; Kendler, Gardner, & Prescott, 1999; Lieb, Isensee, Hofler, & Wittchen, 2002; Timko et al., 2008). Comorbid anxiety disorders, dysthymia,

and alcohol use disorders are also more prevalent among those with familial major depression (Verhagen et al., 2008).

The influence of family history has been most strongly linked with early-onset depression, with studies showing family history to be significantly associated with onset of depression in probands before age 20 or 30 (Janzing et al., 2009; Klein et al., 1999; Kupfer, Frank, Carpenter, & Neiswanger, 1989; X. Li et al., 2008; McGuffin, Katz, & Bebbington, 1987; Tozzi et al., 2008; Weissman et al., 1984). Furthermore, a Swedish national twin study reported increased risk of depression in individuals whose monozygotic twin had early-onset of major depressive disorder ($p<.0001$) (Kendler, Gatz, Gardner, & Pedersen, 2005).

Results from studies of family history of depression and mid- and later-life onset of depression are not as consistent, with some researchers reporting stronger associations between depression and environmental and physical health factors than between depression and family history (Tozzi et al., 2008). The role of family history in the development of depression during the menopausal transition is even less clear. At present, only two studies have examined this relationship in midlife women (Schmidt, Haq, et al., 2004; Woods et al., 2008).

1.5 DEPRESSION AND FAMILY HISTORY IN MIDLIFE WOMEN

1.5.1 Findings from Current Research

Schmidt et al. (2004) conducted a small longitudinal study of predictors of clinical depression, including family history of depression, in a community sample of 29 US midlife women. Depression was assessed annually with the Structured Clinical Interview for DSM-IV (SCID) over an average of five years. The method of obtaining family history of depression was not specified. The study found no difference in reporting of family history of depression between those with and without depression during the 24 months surrounding the final menstrual period. It is important to note that all women identified with depression during the study met criteria for minor depression only and not major depressive disorder.

Woods et al. (2008) also examined family history of depression as a potential risk factor for depressed mood in a population-based cohort of 302 US women 35 to 55 years of age. Participants completed the CES-D annually during the 15-year study. Family history of depression was obtained by asking participants if they had a first degree relative who was ever diagnosed with clinical depression (yes/no). In bivariate analysis, family history of depression predicted an average CES-D score increase of 2.05 ($p=.046$). However, once the analysis was adjusted for menopausal transition stage, age, antidepressant use, BMI, parity, and a history of postpartum blues, family history of depression was no longer significantly related to depressive symptoms.

1.5.2 Limitations and Gaps in Knowledge

Both the Schmidt et al. (2004) and Woods et al. (2008) studies have a number of limitations. First, results from the Schmidt et al. study should be interpreted with caution given the small sample size. There was insufficient power to test hypotheses, and only bivariate analyses were conducted. While the Woods et al. study had ample power, it is important to note that they did not assess clinical depression, measuring self-reported depressive symptoms only. Furthermore, depressive symptoms were only obtained for a 1-week period during each year of the study, and periods of depressed mood experienced outside of this window of data collection would not have been captured.

In terms of the assessment of family history of depression, Schmidt et al. (2004) did not provide the methods for obtaining family mental health history from participants. Therefore, it is not possible to speak to the accuracy and quality of the family history data used in this study. Woods et al. determined family history of depression by asking participants one yes/no question about depression in first degree relatives. This method has been shown to underestimate depression in relatives (Andreasen, Endicott, Spitzer, & Winokur, 1977), and this may have somewhat affected the results.

Finally, neither study was able to explore associations of family history of depression with specific patterns of midlife depression, such as incident or recurrent depression. Thus,

given the discussed limitations, it is clear that more prospective studies focused on the occurrence, course and predictors of clinical depression in midlife should be conducted. Specifically, longitudinal studies with sufficient power and a more detailed assessment of family history are needed to better characterize the role of family history of depression in the development of clinical depression in midlife women.

1.5.3 Potential Pathways to Midlife Depression

There are a number of pathways that could explain how family history of depression may be related to depression in women during midlife. While there is evidence that genetic factors are directly associated with depression in adult women, there are also several potential mediators for this relationship (Kendler, Gardner, & Prescott, 2002; Kendler, Kessler, Neale, Heath, & Eaves, 1993). For example, family history of depression has been linked with greater reporting of social impairment, stressful life events and more severe stressors and traumas in childhood and adulthood (Hammen & Brennan, 2001; Hammen, Shih, Altman, & Brennan, 2003; Timko, Cronkite, Swindle, Robinson, Sutkowi, et al., 2009; Timko et al., 2008; Weissman, Warner, Wickramaratne, Moreau, & Olfson, 1997; Weissman et al., 2006), which may in turn lead to depression in midlife. Higher neuroticism has been associated with family history of depression (Kendler et al., 2002; Kendler, Kessler, et al., 1993) and appears to be related to depression in adults both directly and through associations with stressful life events (Bolger & Schilling, 1991; Poulton & Andrews, 1992). Family depression is also a strong risk factor for child sexual and physical abuse (Chaffin, Kelleher, & Hollenberg, 1996; Conron, Beardslee, Koenen, Buka, & Gortmaker, 2009; Walsh, MacMillan, & Jamieson, 2002), and a history of child abuse is associated with increased risk of developing major depression in adulthood (Springer et al., 2007; Weich, Patterson, Shaw, & Stewart-Brown, 2009). Finally, poor health behaviors and chronic health conditions may be important mediators of the relationship between family history of depression and depression during midlife. Maternal depression has been associated with low physical activity and obesity in children (M. Davis, Young, Davis, & Moll, 2008; Fernald, Jones-Smith, Ozer, Neufeld, & DiGirolamo, 2008; McConley et al., 2011; Surkan, Kawachi, &

Peterson, 2008), which may lead to poor health behaviors in adulthood and subsequent depression, although this has not been examined in any study to date. Furthermore, those with a family history of depression are more likely to experience pain and to report a greater number of medical conditions in adulthood, particularly cardiovascular disease, which may increase the risk for depression at midlife (Sobieraj, Williams, Marley, & Ryan, 1998; Timko, Cronkite, Swindle, Robinson, & Moos, 2009; Timko et al., 2008; Weissman et al., 2006).

1.6 SPECIFIC AIMS AND HYPOTHESES

The objective of this dissertation is to examine associations between family history of depression and the occurrence and course of major depression in midlife women in the context of other potential risk and protective factors. This dissertation will address the following specific aims:

1a. Determine whether family history of depression is a significant risk factor for major depression in midlife women independent of lifetime history of depression and other baseline characteristics.

1b. Evaluate whether the relationship between family history of depression and major depression in midlife women differs by lifetime history of depression prior to midlife.

2a. Determine whether family history of depression is a risk factor for major depression in midlife women after adjusting for changes in menopausal status and other potential time-varying covariates.

2b. Evaluate whether the relationship between family history of depression and major depression in midlife women differs by menopausal status.

3a. Explore whether women who have both a lifetime and family history of depression are at greater risk of major depression during midlife than women who have a lifetime history of depression only.

3b. Examine potential explanatory factors for the increased risk.

1.6.1 Is Family History of Depression Associated with Major Depression in Midlife Women: Study of Women's Health Across the Nation

First, it is hypothesized that family history of depression will be a significant risk factor for depression in midlife women over 10 years of follow-up. It is expected that family history of depression will remain an important predictor of depression after adjusting for relevant baseline covariates. Potential covariates measured at baseline will be assessed in bivariate analyses, and results from these analyses as well as results from prior literature will determine appropriate covariates to include in the statistical models.

It is further hypothesized that family history of depression will be a significant predictor of major depression for midlife women who have a history of depression prior to midlife but not for women without such a history. Given there is a strong relationship between lifetime history of depression and family history of depression at other points in the lifespan, it is expected that this association will also be evident at midlife. It is postulated that stressful life events and changes in health status and health behaviors will be more important predictors of first onset depression than family history among midlife women. This aim will be addressed by repeating the analyses discussed above stratified by lifetime history of depression.

Thus, the purpose of the first paper is to evaluate whether family history of depression is a significant risk factor for the development of major depression over 10 years of follow-up in a sample of 303 midlife women from the SWAN cohort. Multivariable logistic regression models will be used to test the significance of family history of depression adjusting for relevant baseline covariates.

1.6.2 The Role of Family History of Depression and the Menopausal Transition in the Development of Major Depression in Midlife Women

It is hypothesized that family history of depression will remain a significant predictor of depression in midlife women even after accounting for the menopausal transition and other time-varying covariates. The covariates will be selected based on the literature and results from

bivariate analyses. It is also hypothesized that the relationship between family history of depression and depression in midlife will differ by menopausal transition stage, with risk for depression being greater during perimenopause and postmenopause compared with premenopause among women with a family history but not among those without family history.

Thus, the purpose of the second paper is to evaluate whether family history of depression is a significant risk factor for depression during the menopausal transition compared to premenopause after adjusting for and key time-varying covariates over 10 years of follow-up in the sample of 303 midlife women from the SWAN cohort. Longitudinal random effects multivariable logistic regression models will be constructed to address this question.

1.6.3 Major Depression in Midlife Women: Associations with Both Family and Personal Histories of Depression and an Examination of Potential Explanatory Factors

The overall question to be addressed by the third paper is how does family history of depression increase the risk of major depression in midlife among women who have a lifetime history of depression. Both pre-midlife factors (childhood abuse, trait anxiety) and factors occurring in midlife (menopausal symptoms, health-related variables, and stressful life events) will be evaluated as potential mediators of the relationship between family history of depression and midlife major depression among women with a history of depression prior to midlife.

Both childhood abuse and trait anxiety have been strongly associated with family history of depression and linked with major depression in midlife. Thus, it is hypothesized that childhood abuse and trait anxiety will, in part, explain the relationship between family history of depression and major depression during midlife. Furthermore, given there is evidence from the literature that stressful life events and chronic medical conditions are significantly associated with both family history of depression and major depression in midlife, it is posited that these two midlife factors will also mediate the relationship between family history of depression and midlife major depression.

Thus, the goal of the third paper is to examine participant characteristics that may explain why women who have both a lifetime and family history of depression are more vulnerable to

experiencing depression during midlife than women who have a lifetime history of depression only. Cox proportional hazard regression, Baron and Kenny's method, and a product-of-coefficients test will be used to assess possible mediation of the relationship between family history of depression and midlife depression by pre-midlife and midlife factors among 103 midlife women who have a lifetime history of depression.

2.0 IS FAMILY HISTORY OF DEPRESSION ASSOCIATED WITH MAJOR DEPRESSION IN MIDLIFE WOMEN: STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

Manuscript in preparation

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2.1 ABSTRACT

Objective. To evaluate the relationship between family history of depression and major depression in midlife women.

Methods. Data for the current study were obtained from 303 African American and Caucasian women (42-52 years at baseline) who were participants at the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation (SWAN) at baseline. Women provided sociodemographic, physical, and psychosocial information, and trained interviewers administered the Structured Clinical Interview for DSM-IV (SCID) to obtain both lifetime history of major depression and current depressive episodes at baseline and annually. At the 9th or 10th year of follow-up (2005-2007) participants completed an assessment of family history of depression. Multivariable logistic regression was used to determine whether family history of depression was associated with experiencing a major depressive episode from baseline through visit 10, after adjusting for relevant baseline covariates.

Results. The odds of experiencing a major depressive episode during the study were approximately three times greater for those with a family history of depression than for those without a family history of depression (OR=3.22, 95% CI=1.95-5.31). Family history of depression remained a significant predictor of major depression in midlife (OR=2.67, 95% CI=1.50-4.78) after adjusting for lifetime history of major depression, age, trait anxiety, chronic medical conditions, and stressful life events. When analyses were stratified by lifetime history of major depression, family history of depression was significantly associated with major depression among midlife women with a lifetime history of depression but not among those without such a history.

Conclusions. Family history of depression is associated with major depression in midlife women, particularly in those with a lifetime history of depression prior to midlife.

Key Words: family history of depression, major depression, menopause, midlife women

2.2 INTRODUCTION

Depression is a significant public health problem. It is associated with increased morbidity and mortality (Cassano & Fava, 2002; Neugebauer, 1999) and is estimated to be the third leading cause of disability across the world and the leading cause of health-related disability in women (World Health Organization, 2008). Depression is also highly prevalent, particularly in women. The estimated lifetime prevalence of major depression is 17%, affecting twice as many women as men (Kessler et al., 2003; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kessler, McGonagle, Zhao, et al., 1994).

Recent epidemiologic studies indicate that incidence of first onset or recurrent episodes of clinical depression in women during midlife ranges from 20-30% (Cohen et al., 2006; Kessler, McGonagle, Nelson, et al., 1994; Kessler et al., 1993; Schmidt, Haq, et al., 2004). However, little is known about the risk and protective factors that influence the occurrence, severity and course of depression in women during midlife. In particular, the role of family history of depression in the development of incident and recurrent depression in midlife women is unknown.

While a number of studies have provided evidence for the familial nature of depression (Bierut et al., 1999; Janzing et al., 2009; Kendler et al., 1995; X. Li et al., 2008; Sullivan et al., 1996; Timko et al., 2008; Weissman et al., 1982), the influence of family history has been most strongly linked with early-onset depression. Results from studies of family history of depression and mid- and later-life onset of depression are less clear, with some researchers reporting stronger associations between depression and environmental and physical health factors than between depression and family history (Tozzi et al., 2008). Furthermore, it is unknown whether family history is independently associated with recurrent major depression during midlife.

At present, only one study has explored this relationship specifically in midlife women (Woods et al., 2008). Woods et al. examined family history of depression as a potential risk factor for depressed mood in a population-based cohort of 302 U.S. women 35 to 55 years of age. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) annually during the 15-year study. In bivariate longitudinal analysis, family history of depression predicted an average increase in CES-D score of 2.05 ($p=.046$). Once the analysis was adjusted for menopausal stage, age, antidepressant use, body mass index, parity, and a

history of postpartum blues, family history of depression was no longer significantly related to depressive symptoms. However, it is important to note that this study did not assess clinical depression, family history of depression was determined by asking participants one yes/no question about depression in first degree relatives, and the study was not able to explore associations of family history of depression with specific patterns of midlife depression, such as incident or recurrent depression.

Thus, the overall aim of the current study is to address gaps in knowledge and limitations of the prior literature by examining whether family history of depression is a significant risk factor for major depression in midlife women using detailed diagnostic psychiatric and family history data collected from a community-based cohort. Specifically, the study will focus on the following questions: 1) Is family history of depression a significant risk factor for major depression in midlife women, adjusting for a lifetime history of major depression and other relevant baseline covariates; and 2) Does the relationship between family history of depression and major depression in midlife women differ by lifetime history of depression?

Given there is a strong relationship between major depression and family history of depression at earlier points in the lifespan, it is expected that this association will also be evident in midlife. Therefore, we hypothesize that family history of depression will be significantly associated with major depression in midlife women, even after adjusting for lifetime history of depression and other potential confounders. It is also expected that the relationship between family history of depression and major depression will differ for women who are experiencing recurrent vs. first-onset depression during midlife. Family history of depression has consistently been associated with an earlier onset and more recurrent course of depression (Janzing et al., 2009; Kendler et al., 1999; Lieb et al., 2002; Timko et al., 2008), while mid- and later life onset of depression may be more influenced by current psychosocial factors and changes in physical health (Alexander et al., 2007; Bromberger et al., 2007; Freeman et al., 2004; Gallicchio et al., 2007; Timur & Sahin, 2010; Tozzi et al., 2008). Thus, it is also hypothesized that family history of depression will be associated with major depression only in women with a history of lifetime depression prior to midlife. Among women without a history of depression, it is postulated that factors occurring during midlife, such as stressful life events and changes in health status and health behaviors, will be more important predictors of major depression.

2.3 METHODS

2.3.1 Participants and Procedures

Study data were collected from women participating in the Study of Women's Health Across the Nation (SWAN) Menopausal Transition, Mental Health and Ethnicity Study (MHS) at the Pittsburgh SWAN site. SWAN is a multi-center longitudinal study of the natural history of the menopausal transition. The SWAN MHS is an ancillary project designed to capture diagnostic psychiatric interview data from the SWAN Pittsburgh participants. Eligible women were: aged 42-52 years, had an intact uterus, were not using hormones, had at least one menstrual period in the last 3 months, and self-identified as non-Hispanic White or African American. A total of 463 women were recruited into the Pittsburgh SWAN sample through random digit dialing and voter registration lists. Of these, 443 (96%) SWAN Pittsburgh women agreed to participate in the SWAN MHS.

Family history of depression was obtained from 303 women still actively participating in the SWAN MHS during annual visits 9 and 10 (2005-2007); these women comprise the sample for the current study. Reasons for non-participation in the family history assessment were as follows: withdrew from SWAN before the ninth annual visit (n=92, 59.7%), missed the study visit (n=30, 19.5%), completed the study visit but not the assessment of family history of depression (n=25, 16.3%), and deceased (n=7, 4.5%). Compared to women who completed the family history assessment, non-completers were younger ($p=.009$), more likely to be African American ($p=.02$), less educated ($p=.005$), more likely to be experiencing financial strain ($p<.0001$), and less likely to be married ($p=.03$).

The University of Pittsburgh Institutional Review Board approved this study, and all participants provided informed consent. Participants have been followed annually since 1996 with a core protocol that includes biological, medical, and psychosocial measures. At baseline and at each visit, participants answered questions about their medical and menstrual history, symptoms, and lifestyle and psychosocial factors. Standardized protocols were used to measure weight and height. Psychiatric interviews were conducted at baseline and annually using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer, Williams, Gibbon, & First, 1992).

The independent variables analyzed in the current study were collected at the baseline SWAN visit unless otherwise indicated.

2.3.2 Measures

Assessment of Major Depression: The main outcome for the study was the occurrence of any major depressive episode from baseline through annual visit 10. Lifetime history of major depression was obtained at baseline and defined as the occurrence of a major depressive episode prior to enrollment in the SWAN. Diagnoses of lifetime and current major depression were obtained from the SCID, a semi-structured diagnostic psychiatric interview that has frequently been used in research and has demonstrated good reliability in a number of studies (Segal DL, Hersen M, Van Hasselt VB, Kabacoff RI, & Roth L, 1993; Skre, Onstad, Torgersen, & Kringlen, 1991; Spitzer et al., 1992; Williams et al., 1992).

SCID interviewers were required to hold a Masters or a PhD in a mental health field and to have prior clinical experience. J.T.B. supervised all interviewers at the Pittsburgh site. To maintain consistency in SCID administration across interviewers and over annual visits, all interviewers were required to participate in an initial training conducted by Biometrics Research and Development, New York State Psychiatric Institute, as well as an annual re-certification process. Participant interviews were audiotaped, and these tapes were used to assess individual interviewing skills and inter-rater reliability. Within the SWAN, follow-up reliability has been quite good for both lifetime (k=0.81) and past year major depression (k=0.76-0.89).

Family History of Depression: Trained interviewers obtained family history of depression in first degree relatives using the family history method and a modified version of the depression module from the Family Interview for Genetic Studies (FIGS) (Maxwell ME, 1992; Nurnberger et al., 1994). The family history method, in which an informant is queried about the history of mental illness in relatives, has been used in numerous studies of psychiatric disorder, and data from prior research indicate the family history method has acceptable reliability and validity (Andreasen et al., 1977; Weissman et al., 2000). In brief, the FIGS consisted of three interviewer administered questionnaires. Participants were first screened with a Family Mental Health History form. Those who endorsed a first degree relative with depression and/or

attempted/completed suicide were then administered a second questionnaire to collect more detailed information about their relative's symptoms. Finally, participants completed the Depression Symptoms Checklist, which confirmed whether or not their relative met the DSM-IV criteria for major depression. Participants completed the FIGS at their ninth or tenth annual SWAN visit.

Menopausal Status: The categorization of menopausal status was based on self-reported menstrual bleeding patterns. At baseline, women were either premenopausal (menstrual bleeding in the past 3 months with no change in cycle regularity in the past 12 months) or early perimenopausal (menstrual bleeding in the past 3 months accompanied by changes in cycle regularity).

Socioeconomic Indicators: Difficulty paying for basic necessities and level of educational attainment were included in the analyses as indicators of socioeconomic status. Sociodemographic variables included age, ethnicity, and marital status.

Health-related Factors: Health-related variables included chronic medical conditions, perceived overall health, and vasomotor symptoms. Chronic medical conditions were assessed by asking participants whether a medical professional had ever told them that they had any of the following: diabetes, hypertension, arthritis/osteoarthritis, under or overactive thyroid, cardiovascular disease, or cancer. The total number of chronic medical conditions reported was categorized into: none vs. one or more conditions. Perceived overall health was assessed by asking participants to rate their overall health as excellent, very good, good, fair, or poor. For the current analyses, overall health was dichotomized into excellent/very good/ good vs. fair/poor. Vasomotor symptoms data were collected as part of a symptom checklist that has been used in numerous menopause studies (Matthews et al., 1990; Neugarten & Kraines, 1965). Women were asked to indicate how often they had experienced hot flashes and night sweats in the past two weeks (not at all, 1-5 days, 6-8 days, 9-13 days, and every day). Women who reported experiencing hot flashes and/or night sweats at least six out of 14 days were classified as having frequent vasomotor symptoms.

Lifestyle: Height and weight measurements collected by the study were used to calculate body mass index (BMI) as weight (kg) / height $(m)^2$. A modified version of the Baecke (Baecke, Burema, & Frijters, 1982) physical activity questionnaire was administered to participants to obtain information on the intensity, duration, and frequency of activity related to the domains of

daily living, exercise/sports, and home/child care. A total physical activity score was calculated to reflect activity across all three domains.

Psychosocial Variables: In order to assess life stress, women were asked whether they had 1) experienced any of 18 negative life events in the past year and 2) how upsetting each of the events was for them (Dohrenwend et al., 1987). Women were categorized as having experienced at least one very upsetting life event in the past year or having experienced no such event. Women also reported whether they had any of the following 9 chronic difficulties for 12 months or longer: own health problems, health problem with partner or child, substance abuse in a family member, work difficulties, financial strain, housing problems, problem with a close relationship, helping sick family member or friend on a regular basis, any other ongoing problem. Each of the chronic difficulties was rated in terms of how upsetting it was to the participant. Women were categorized as having experienced at least one very upsetting chronic difficulty in the past year or having experienced no such difficulty. A social support score was created by summing responses to the 4-item Medical Outcomes Study Social Support Survey (Sherbourne & Stewart, 1991), with higher scores indicating more social support.

Optimism was measured at the first annual follow-up visit with the 6-item Life Orientation Test. Items were scored and summed to create a total optimism score as per Scheier and Carver (1985). Higher scores indicate greater optimism. Trait anxiety was also assessed at visit 1 with a 10-item version of the Spielberger Trait Anxiety Inventory (Spielberger C, Gorsuch R, & Lushene R, 1970); higher scores reflect higher levels of trait anxiety.

2.3.3 Statistical Analysis

The SAS system version 9.3 was used for all statistical analyses. Preliminary analyses included descriptive plots and statistics (means, standard deviations, ranges, frequencies), as well as an examination of the correlation between predictors. Differences in baseline characteristics between women with and without a family history of depression were assessed using chi square tests for comparison of categorical variables and t-tests or Wilcoxon rank-sum tests for unadjusted comparisons of continuous variables.

To address the question of whether or not family history of depression is associated with major depression in midlife women, an unadjusted logistic regression model was first run with any major depression during midlife as the outcome and family history of depression as the sole independent variable. Next, in order to determine whether the effect of family history of depression is independent of a lifetime history of depression, a second logistic regression model was run including lifetime history of depression as a predictor.

Multivariable models to examine the influence of family history of depression on major depression in midlife in the context of other important baseline covariates were then constructed. Potential covariates were assessed in bivariate logistic regression analyses, and results from these analyses, as well as results from prior literature, informed which variables to include in the multivariable model building process. Covariates identified in bivariate analyses at $p<.15$ were entered into the logistic regression model, and manual backwards elimination was used (retaining variables significant at $p <.10$) to obtain a final parsimonious multivariable model.

Finally, to explore whether the relationship between family history of depression and major depression during midlife differs by lifetime history of depression, multivariable logistic regression models stratified by lifetime history of depression were run using the model building process described above.

2.4 RESULTS

Descriptive data for the study participants are presented in Table 2-1. At baseline, the participants were 42-52 years of age with a mean age of 46. Thirty-one percent of the participants were African American, and 34% had a family history of depression. Participants with a family history of depression were more educated (χ^2 (2, N=303) =7.01, p=.03), were more likely to have experienced a very upsetting chronic difficulty in the past year (χ^2 (1, N=284) =5.61, p<.01), and more likely to have a lifetime history of major depression (χ2 (1, N=303) =14.00, p<.001) compared to those with no family history.

Table 2-1: Baseline Characteristics by Family History of Major Depression (MD)

	Total	No Family History of MD	Family History of MD	
	N=303	*n*=199 (65.7%)	*n*=104 (34.3%)	p value
Age (years), mean (SD)	46.3 (2.6)	46.4 (2.6)	46.1 (2.4)	.51
African American, *n* (%)	95 (31.3)	62 (31.2)	33 (31.7)	.91
Education, *n* (%)				
Less than High School	70 (23.1)	55 (27.6)	15 (14.4)	**.03**
High School/ Some College	102 (33.7)	65 (32.7)	37 (35.6)	
College/More than College	131 (43.2)	79 (39.7)	52 (50.0)	
Marital Status, *n* (%)				
Married	208 (69.1)	141 (70.8)	67 (65.7)	.45
Never married	37 (12.3)	25 (12.6)	12 (11.8)	
Separated / Widowed / Divorced	56 (18.6)	33 (16.6)	23 (22.5)	
Somewhat/very hard to pay for basics, *n* (%)	84 (27.8)	55 (27.8)	29 (27.9)	.98
Menopausal Status, *n* (%)				
Premenopausal	165 (54.5)	114 (57.3)	51 (49.0)	.17
Early Perimenopausal	138 (45.5)	85 (42.7)	53 (51.0)	
Vasomotor Symptoms: at least 6/14 days, *n* (%)	28 (9.3)	14 (7.1)	14 (13.5)	.07
Any Chronic Medical Condition, *n* (%)	110 (36.3)	68 (34.2)	42 (40.4)	.28
Overall Health, *n* (%)				
Good/Very Good/Excellent	258 (85.7)	171 (86.4)	87 (84.5)	.66
Poor/Fair	43 (14.3)	27 (13.6)	16 (15.5)	
Body Mass Index (kg/m^2), mean(SD)	28.6 (6.6)	28.3 (6.5)	29.2 (6.9)	.25
Physical Activity Score (range: 0-14), mean (SD)	7.9 (1.7)	7.9 (1.7)	7.8 (1.7)	.65
Very Upsetting Life Event in past year, *n* (%)	157 (52.0)	98 (49.5)	59 (56.7)	.23
Very Upsetting Chronic Difficulty in past year, *n* (%)	72 (25.4)	40 (21.0)	32 (34.0)	**<.01**
Social Support (range: 0-16), mean (SD)	12.9 (2.8)	13.0 (2.8)	12.8 (2.7)	.27
Optimism (range: 0-18), mean (SD)	13.0 (3.8)	13.0 (3.7)	13.1 (4.0)	.63
Trait Anxiety (range: 10-40), mean (SD)	15.9 (4.7)	15.6 (4.6)	16.5 (5.0)	.12
Lifetime History of MD, *n* (%)	103 (34.0)	53 (26.6)	50 (48.1)	**<.001**

Total percentages may not equal to 100 due to rounding

Forty-eight percent of the participants had neither a family nor a personal history of depression, while 16% of the sample reported both a family and lifetime history of depression. Approximately 18% of women had a family history of depression but no lifetime depression history, and the remaining 18% reported a lifetime history of depression but no family history (Figure 2-1).

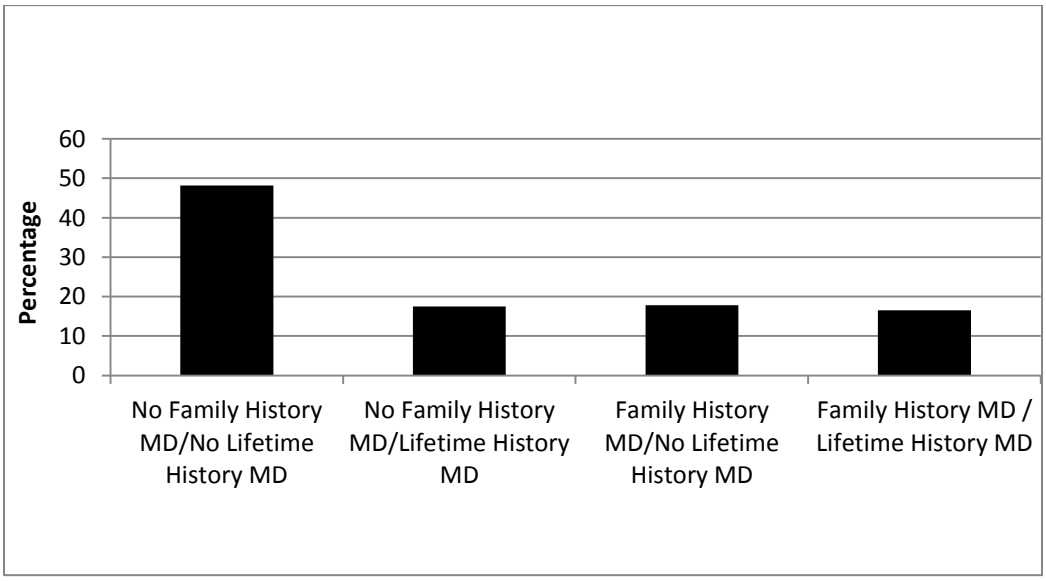

Figure 2-1: Family History of Depression by Lifetime History of Major Depression (MD)

In the total sample, 104 (34.3%) reported having at least one major depressive episode during the study. This represented a first onset of depression for 41% of the women who experienced a major depressive episode during the study and a recurrent major depressive episode for the remaining 59%. Of those with a family history of depression, 54 (52%) experienced major depression during the study, while 50 (25%) of those without a family history reported a major depressive episode.

Table 2-2 shows the unadjusted and adjusted associations of family history of depression with experiencing major depression during the study. The odds of experiencing a major depressive episode during the study were approximately three times greater for those with a

family history of depression than for those without a family history (Model A: OR=3.22, 95% CI=1.95-5.31, p<.0001). The relationship between family history of depression and major depression in midlife remained significant even after adjusting for lifetime history of depression (Model B: OR=2.61, 95% CI=1.53-4.45, p=<.001).

Table 2-2: Association of Family History of Depression with Major Depression (MD), N=303

	Model A OR (95% CI)	**Model B OR (95% CI)**	**Model C OR (95% CI)**
Family History of MD	3.22 (1.95-5.31)	2.61 (1.53-4.45)	2.67 (1.50-4.78)
Lifetime History of MD		4.64 (2.73-7.89)	3.76 (2.10-6.70)
Age (years)			0.87 (0.78-0.98)
Trait Anxiety			1.11 (1.05-1.17)
Any Chronic Medical Condition			2.37 (1.32-4.25)
Very Upsetting Life Event in past year			1.85 (1.04-3.29)

OR, odds ratio; CI, confidence interval
Model A: Family history of depression
Model B: Addition of lifetime history of depression
Model C: Final multivariable model

Model C shows the association between family history of depression and experiencing any major depression during the study adjusted for additional variables that remained in the final model. After adjusting for confounders, family history of depression was still a significant predictor of major depression in midlife (Model C: OR=2.67, 95% CI=1.50-4.78, p<.001). Other factors significantly associated with major depression were a lifetime history of major depression (OR=3.76, 95% CI=2.10-6.70, p<.0001), younger age (OR=0.87, 95% CI=0.78-0.98, p=.02), higher trait anxiety (OR=1.11, 95% CI=1.05-1.17, p<.001), having one or more chronic medical conditions (OR=2.37, 95% CI=1.32-4.25, p=.004), and experiencing a very upsetting life event in the past year (OR=1.85, 95% CI=1.04-3.29, p=.04).

Analyses stratified by lifetime history of depression showed different patterns of association between family history of depression and major depression during midlife (Tables 2-3 and 2-4). Table 2-3 shows bivariate associations of major depression with family history of depression and other covariates (associated at p≤.15) in women with and without a lifetime history of depression prior to midlife. There was a significant bivariate relationship between family history of depression and major depression in the lifetime history of depression group

(OR=4.13, 95% CI=1.77-9.63, p=.001), but not in the group that reported no lifetime history of depression (OR=1.86, 95% CI=0.91-3.81, p=.09). Age, ethnicity, vasomotor symptoms, chronic medical conditions, overall health, physical activity, very upsetting life events, chronic difficulties, optimism, and trait anxiety were all associated with major depression at p≤.15 in women who had no lifetime history of major depression prior to midlife. These variables were considered in the final multivariable modeling process for the no lifetime history of depression group. Among women with a lifetime history of depression, variables significant at p≤.15 included difficulty paying for basics, very upsetting life events, chronic difficulties, optimism, and trait anxiety.

Table 2-3: Bivariate Associations of Family History with Major Depression (MD) by Lifetime History of Depression

	No Lifetime History of MD (N=200)		**Lifetime History of MD (N=103)**	
	OR (95% CI)	p value	OR (95% CI)	p value
Family History of MD	1.86 (0.91-3.81)	.09	4.13 (1.77-9.63)	**.001**
Age (years)	0.91 (0.79-1.04)	.15	---	NS
Ethnicity				
Caucasian (REF)	REF	.08	**---**	NS
African American	1.85 (0.93-3.70)			
How hard to pay for basics				
Not hard (REF)	---	NS	REF	.07
Somewhat / very hard			2.22 (0.93-533)	
Vasomotor Symptoms: at least 6/14 days	3.60 (1.22-10.57)	**.02**	**---**	NS
Chronic Medical Condition(s)	3.46 (1.72-6.95)	**<.001**	**---**	NS
Overall Health				
Good/Very Good/Excellent (REF)	REF	.15	**---**	NS
Poor/Fair	1.91 (0.79-4.59)			
Physical Activity Score	0.74 (0.58-0.94)	**.01**	**---**	NS
Very Upsetting Life Event in Past Year	1.87 (0.94-3.69)	.07	2.30 (0.99-5.35)	**.05**
Very Upsetting Chronic Difficulty in Past Year	2.00 (0.88-4.56)	.10	2.64 (1.11-6.29)	**.03**
Optimism	0.90 (0.82-0.99)	**.05**	0.91 (0.83-1.01)	.08
Trait Anxiety	1.12 (1.05-1.19)	**<.001**	1.11 (1.02-1.20)	**.02**

OR, odds ratio; CI, confidence interval; REF, reference category; NS, not significant (p≤.15)

In the final multivariable models (Table 2-4), family history of depression continued to be significantly associated with major depression among midlife women who had a lifetime

history of depression (OR=3.45, 95% CI=1.39-8.57, p=.008) but not among those who did not have a lifetime depression history (OR=2.08, 95% CI=0.90-4.79, p=.09). While there was a significant relationship between trait anxiety and major depression in both groups of women, age and chronic medical conditions were only significantly associated with major depression in those without a lifetime history of depression.

Table 2-4: Adjusted Association of Family History with Major Depression (MD) by Lifetime History of Depression

	No Lifetime History of MD (N=200)		**Lifetime History of MD (N=103)**	
	OR (95% CI)	p value	OR (95% CI)	p value
Family History of MD	2.08 (0.90-4.79)	.09	3.45 (1.39-8.57)	**.008**
Age (years)	0.86 (0.73-1.01)	.07	---	NS
Trait Anxiety	1.14 (1.05-1.23)	**<.001**	1.12 (1.02-1.22)	**.02**
Chronic Medical Condition(s)	3.51 (1.61-7.68)	**.002**	**---**	NS

OR, odds ratio; CI, confidence interval; REF, reference category; NS, not significant (p≤.10)

2.5 DISCUSSION

The current study shows that family history of depression is associated with major depression in women during midlife. Specifically, in this community sample of midlife women, the odds of experiencing a major depressive episode during the study were approximately two and one half times greater for those with a family history of depression than for those without a family history of depression. Importantly, the effects of family history were independent of lifetime history of depression, age, trait anxiety, chronic medical conditions, and stressful life events.

These results confirm previous studies that have demonstrated an important relationship between family history of depression and major depression in general (Janzing et al., 2009; Sullivan et al., 2000; Weissman et al., 1982). However, the current study is the first to show that family history of depression is associated with major depression specifically in women during

midlife. This is in contrast with the study conducted by Woods et al. (2008), which reported that family history of depression was not a significant predictor of depressive symptoms in a similar community sample of midlife women. They found that menopausal stage, age, antidepressant use, body mass index, parity, and a history of postpartum blues were more significant predictors of midlife depression than family history.

The results from the current study and the Woods et al. study may differ because of the differences in depression and family history assessments. Woods et al. did not assess clinical depression, measuring self-reported depressive symptoms only. Depressive symptoms were only obtained for a 1-week period during each year of the study, and periods of depressed mood experienced outside of this window of data collection would not have been captured. Furthermore, Woods et al. determined family history of depression by asking participants one yes/no question about depression in first degree relatives. This method has been shown to underestimate depression in relatives (Andreasen et al., 1977), and this may have affected the results.

The design of the Woods et al. study did not allow for the exploration of associations of family history of depression with specific patterns of midlife depression, such as incident or recurrent depression. In the current study, we were able to stratify our analyses by lifetime history of depression, and we determined that family history of depression was associated with recurrence of major depression during midlife. This is consistent with the majority of the literature which has demonstrated a strong relationship between family history and depression recurrence across the lifespan (Gershon et al., 1986; Janzing et al., 2009; Kendler et al., 1999; Lieb et al., 2002; Timko et al., 2008).

However, in our sample of midlife women, the relationship between family history of depression and incident depression was not significant. Twin studies indicate familiality of depression is mostly a result of genetic influences, rather than shared environment (Sullivan et al., 2000), with heritability estimates for depression ranging from 39% to 75% (Bierut et al., 1999; Kendler et al., 1995; Kendler & Prescott, 1999; McGuffin et al., 1996) and a recent meta-analysis reporting an overall heritability estimate of 37% (95% CI=31% - 42%) (Sullivan et al., 2000). A number of studies, including the current study, have found that a family history of depression is less common among those with mid- and later onset of depression than those with an earlier age of depression onset (Kupfer et al., 1989; Lyons et al., 1998; Weissman et al.,

1986). Furthermore, there is evidence that earlier onset depression is significantly more heritable than mid- and later onset depression and that factors other than genetic vulnerability become more important predictors of depression in mid- and later life (Baldwin & Tomenson, 1995; Lyons et al., 1998).

For example, Tozzi et al. (2008) reported that family history of depression was not associated with major depression onset in either mid- or later life in a clinical sample of 1,022 men and women undergoing depression treatment. They concluded that environmental and physical health problems were potentially more important risk factors for mid- to later onset depression. A number of other community and clinical studies have supported these results in mixed gender and age samples (Gallagher et al., 2010; Korten, Comijs, Lamers, & Penninx, 2012; Sneed, Kasen, & Cohen, 2007), reporting significant associations between depression and stressful life events and poor health in those with mid- and later onset depression but no relationship with family history or other earlier life factors.

Indeed, the current study found that chronic medical conditions were associated with depression in the total sample and particularly in women reporting first onset of depression during midlife. This is consistent with other studies that have found self-reported poor health (Dennerstein et al., 2004; Gallicchio et al., 2007; Kaufert et al., 1992) and chronic illnesses that become more common with age, such as cardiovascular disease and cancer, (Krishnan et al., 2002) to be significantly associated with depressive symptoms and major depression in women at midlife (Alexander et al., 2007; Gallicchio et al., 2007).

Stressful life events have been linked with high depressive symptom levels in women during midlife (Amore et al., 2004; Bromberger et al., 2007; Bromberger et al., 2010; Cohen et al., 2006; Dennerstein et al., 2004; Kaufert et al., 1992; Maartens et al., 2002; Schmidt, Murphy, et al., 2004; Timur & Sahin, 2010). The current study also found evidence for the relationship between stressful life events and depression among midlife women. However, the smaller sample size did not allow for an exploration of the relative importance of different types of stressful life events (interpersonal, health-related, work-related, etc.) in the development of midlife depression.

Trait anxiety was associated with midlife depression overall, as well as with both first-onset and recurrent major depression. Numerous cross-sectional and prospective studies have reported that higher levels of neuroticism are strongly associated with depression (De Graaf et

al., 2002; Fanous et al., 2007; Kendler et al., 2006; Kendler, Neale, et al., 1993; Kotov et al., 2010). However, some studies have shown that personality characteristics, including neuroticism, are only associated with early-onset major depression (Korten et al., 2012; Sneed et al., 2007), while others have indicated that neuroticism is also an important risk factor for depression in mid- and later life (Steunenberg, Beekman, Deeg, & Kerkhof, 2006; Steunenberg, Braam, Beekman, Deeg, & Kerkhof, 2009). The inconsistency in results may be due to differences in samples, study designs, age cut-offs for early, mid- and later life depression, and the assessment of major depression or depressive symptoms.

The current study has a number of strengths. Previous epidemiologic studies of depression in midlife women have generally relied on the assessment of depressive symptoms rather than a formal diagnosis of depression. The study had access to 11 years of clinical depression data obtained by semi-structured clinical interviews, allowing not only for more accurate classifications of depression but also for an examination of the course and patterns of depression during midlife. Despite this, it is possible that some misclassification could have occurred.

An additional strength of the current study is that it includes an assessment of family history of depression based on DSM-IV criteria. However, due to time and financial constraints, family history of depression was collected through participant self-report instead of direct family interviews. It is possible that participants may have incorrectly recalled the psychopathology of their relatives and that depressed women may be more likely to remember their relatives as being depressed than women without a history of depression. However, it is important to note that the family history method has been used in numerous studies of psychiatric disorder and has established validity and reliability.

The study was also somewhat limited due to the smaller sample size. While there was adequate power to address the main study aims, it was not possible to conduct more complex analyses to adequately explore interactions between explanatory variables.

2.6 CONCLUSIONS

The relationship between family history of depression and the occurrence and course of midlife major depression has not been well studied. The current study is important because it is the first to evaluate the influence of family history of depression on the development of both incident and recurrent clinical depression in women during midlife, using longitudinal data from one of the few well-characterized cohorts of midlife women. We found that family history of depression is strongly associated with major depression in midlife women, particularly in those with a lifetime history of depression prior to midlife. These results suggest that women with a family history of depression may benefit from closer monitoring of their mood during midlife. By recognizing the importance of family history of depression in the recurrence of major depression during midlife and implementing appropriate interventions in a timely manner, we may be able to improve the emotional health of women in midlife.

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3.0 THE ROLE OF FAMILY HISTORY OF DEPRESSION AND THE MENOPAUSAL TRANSITION IN THE DEVELOPMENT OF MAJOR DEPRESSION IN MIDLIFE WOMEN

Manuscript in preparation

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3.1 ABSTRACT

Objective. To determine whether family history of depression is a risk factor for major depression in midlife women after adjusting for relevant time-varying covariates and whether the relationship between family history of depression and major depression in midlife women differs by menopausal status.

Methods. 303 African American and Caucasian (42-52 years at baseline) women participating in the Study of Women's Health Across the Nation at the Pittsburgh site completed an assessment of family history of depression at the 9th or 10th year of follow-up (2005-2007). Trained interviewers administered the Structured Clinical Interview for DSM-IV (SCID) to participants to obtain lifetime history of major depression and major depressive episodes at baseline and annually. Multivariable random effects logistic regression was used to determine the relationship between family history of depression and major depression in midlife women after adjusting for time-varying covariates. To determine if the menopausal transition is a particularly vulnerable time for women with a family history of depression, we added an interaction term, family history by menopausal status, to the fully adjusted model.

Results. Family history of depression was significantly associated with major depression in midlife even after adjusting for lifetime history of major depression (OR=2.24, 95% CI=1.17-4.29, p=.02), trait anxiety and age at baseline, and changes over time in menopausal status, body mass index, very upsetting chronic difficulties, and very upsetting life events. In the total sample, higher odds of major depression were found when women were late perimenopausal or postmenopausal relative to when they were pre- or early perimenopausal (OR=3.01, 95% CI=1.76-5.15, p<.0001). However, when analyses were stratified by family history of depression, menopausal status was significantly associated with major depression among midlife women without a family history of depression but not among those with a family history.

Conclusions. Family history of depression is an important predictor of major depression in midlife women, even after adjusting for menopausal status and other time-varying covariates. Furthermore, the menopausal transition appears to be associated with major depression only among women without a family history of depression.

Key Words: family history of depression, major depression, menopause, midlife women

3.2 INTRODUCTION

Depression is associated with increased morbidity and mortality and is highly prevalent, particularly in women (Cassano & Fava, 2002; Kessler et al., 2003; Kessler et al., 2005; Neugebauer, 1999). Recent studies indicate that incidence of first onset or recurrent episodes of clinical depression in women during midlife ranges from 20-30% (Cohen et al., 2006; Kessler, McGonagle, Nelson, et al., 1994; Kessler et al., 1993; Schmidt, Haq, et al., 2004). Despite this, little is known about the risk and protective factors that influence the occurrence, severity and course of depression in women during midlife.

Several theories have been proposed to explain risk of depression among midlife women. First, midlife can bring numerous changes in terms of social roles and circumstances, such as caring for aging parents, children leaving or returning to the home, financial strain, marital disruption, and the death of loved ones, and these changes may lead to depression (Rasgon et al., 2005). Indeed, experiencing stressful life events has been consistently linked with high depressive symptom levels in women during midlife (Amore et al., 2004; Bromberger et al., 2007; Bromberger et al., 2010; Cohen et al., 2006; Dennerstein et al., 2004; Kaufert et al., 1992; Maartens et al., 2002; Schmidt, Murphy, et al., 2004; Timur & Sahin, 2010). Furthermore, changes in social networks in midlife may lead to reduced social support, which in turn is related to increased risk of significant depressive symptoms (Y. Li et al., 2008).

Changes in health status and health behaviors may also contribute to depressed mood among midlife women. Both self-reported poor health (Dennerstein et al., 2004; Gallicchio et al., 2007; Kaufert et al., 1992) and chronic illnesses that become more common with age, such as cardiovascular disease and diabetes, (Krishnan et al., 2002) have been found to be significantly associated with depressive symptoms and major depression at midlife (Alexander et al., 2007; Gallicchio et al., 2007). Furthermore, midlife women are likely to experience weight gain and decreases in physical activity (Matthews et al., 2001; D. F. Williamson et al., 1990), and the literature strongly suggests that obesity (Freeman et al., 2004; Simon et al., 2008; Timur & Sahin, 2010) and physical inactivity (Bosworth et al., 2001; W. J. Brown et al., 2005; Gallicchio et al., 2007; Lee & Kim, 2008; Mirzaiinjmabadi et al., 2006; Slaven & Lee, 1997) are associated with depressive symptoms in midlife.

Finally, recent epidemiologic research has explored whether the menopausal transition is an independent risk factor for increased risk of depression during midlife. Results from cross-sectional research examining depressed mood and the menopausal transition have been inconsistent, with several studies reporting increased depressive symptoms in perimenopausal women (Amore et al., 2004; Steinberg et al., 2008; Tangen & Mykletun, 2008; Timur & Sahin, 2010) and a number of others failing to replicate these results (Baker et al., 1997; Bosworth et al., 2001; Gallicchio et al., 2007; Juang et al., 2005; Y. Li et al., 2008; Lu et al., 2009; McKinlay et al., 1987; Woods & Mitchell, 1997). Recent longitudinal studies have provided strong evidence of increased risk of depressed mood and major depression among women undergoing the menopausal transition (Bromberger et al., 2011; Bromberger et al., 2007; Cohen et al., 2006; Freeman et al., 2006; Freeman et al., 2004; Maartens et al., 2002).

Two mechanisms have been proposed to explain the association between depressed mood and the menopausal transition. The neurobiological theory asserts that menopause-related fluctuations in reproductive hormones lead to changes in levels of neurotransmitters associated with emotional pathways (Rasgon et al., 2005). For example, the brain has numerous estrogen receptors, and changes in estrogen impact levels of serotonin, dopamine, and norepinepherine through degradation of catabolic enzymes, unblocking of binding sites, and enhancement of neurotransmitter transport (Spinelli, 2005; Studd & Panay, 2004). A second, the domino theory, states that the hormonal fluctuations experienced by women during the menopause are only indirectly related to depressed mood. It is thought that experiencing menopausal symptoms associated with hormonal changes, such as hot flashes, night sweats, and insomnia, leads to depression (Avis, Crawford, Stellato, & Longcope, 2001; J. P. Brown et al., 2009 Gallicchio et al., 2007).

While recent research has examined the importance of psychosocial factors, changes in health and health behaviors, and the menopausal transition in the development of depression in midlife women, the role of family history of depression in this process is currently unknown. A number of studies have provided evidence for the familial nature of depression (Bierut et al., 1999; Janzing et al., 2009; Kendler et al., 1995; X. Li et al., 2008; Sullivan et al., 1996; Timko et al., 2008; Weissman et al., 1982). However, the influence of family history has been most strongly linked with early-onset depression, with studies showing family history to be significantly associated with onset of depression in probands before age 20 or 30 (Janzing et al.,

2009; Klein et al., 1999; Kupfer et al., 1989; X. Li et al., 2008; McGuffin et al., 1987; Tozzi et al., 2008; Weissman et al., 1984). Results from studies of family history of depression and mid- and later-life onset of depression are not as consistent, with some researchers reporting stronger associations between depression and environmental and physical health factors than between depression and family history (Tozzi et al., 2008). The role of family history in the development of depression during midlife and the menopausal transition is even less clear.

At present, only one study has explored the role of family history of depression in the development of depressed mood specifically in midlife women undergoing the menopausal transition (Woods et al., 2008). Woods et al. examined family history of depression as a potential risk factor for depressed mood in a population-based cohort of 302 U.S. women 35 to 55 years of age. Participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) annually during the 15-year study. In bivariate longitudinal analysis, family history of depression predicted an average increase in CES-D score of 2.05 ($p=.046$). Once the analysis was adjusted for menopausal stage, age, antidepressant use, body mass index, parity, and a history of postpartum blues, family history of depression was no longer significantly related to depressive symptoms. It is important to note that this study did not capture clinical depression, measuring depressive symptoms only.

Thus, to address gaps in knowledge and limitations of the prior literature, the current study will primarily focus on determining whether family history of depression is a risk factor for clinical depression in midlife women after taking changes in menopausal status and other important time-varying covariates, such as stressful life events and health conditions and behaviors, into account. Given that there is a strong relationship between family history of depression and major depression at earlier points in the lifespan, it is hypothesized that family history of depression will remain a significant predictor of depression in midlife women, even after adjusting for the menopausal transition and other time-varying factors.

The study will also address the question of whether the relationship between family history of depression and major depression in midlife women differs by menopausal status. Despite the fact that all women undergoing menopause experience hormonal changes, not all develop depressed mood. Maintaining homeostasis in response to changing levels of hormones may be modified by genetic factors, thus potentially making certain subsets of women, such as those with a family history of depression, more vulnerable to depression during the menopause

(Deecher et al., 2008; Harsh et al., 2009). Therefore, it is postulated that stronger associations between menopausal status and midlife major depression will be found in women with a family history of depression compared to women without a family history.

3.3 METHODS

3.3.1 Participants and Procedures

This study used data collected from women participating in the Study of Women's Health Across the Nation (SWAN) Menopausal Transition, Mental Health and Ethnicity Study (MHS) at the Pittsburgh SWAN site. SWAN is a multi-center longitudinal study of the biological, social, and psychological changes associated with the menopausal transition. The SWAN MHS is an ancillary project designed to obtain diagnostic psychiatric interview data from SWAN Pittsburgh participants. Women eligible for the study were: aged 42-52 years, had an intact uterus, were not using hormones, had at least one menstrual period in the last 3 months, and self-identified as non-Hispanic White or African American. A total of 463 women were recruited into the Pittsburgh SWAN sample through random digit dialing and voter registration lists. Of these, 443 (96%) SWAN Pittsburgh women agreed to participate in the SWAN MHS.

Three hundred and three women still actively participating in the SWAN MHS completed an assessment of family history of depression during annual visits nine or ten (2005-2007); these women comprise the sample for the current study. Reasons for non-participation in the family history assessment were as follows: withdrew from SWAN before the ninth annual visit (n=92, 59.7%), missed the study visit (n=30, 19.5%), completed the study visit but not the assessment of family history of depression (n=25, 16.3%), and deceased (n=7, 4.5%). Compared to women who completed the family history assessment, non-completers were younger ($p=.009$), more likely to be African American ($p=.02$), less educated ($p=.005$), more likely to be experiencing financial strain ($p<.0001$), and less likely to be married ($p=.03$).

The University of Pittsburgh Institutional Review Board approved this study, and all participants provided informed consent. Participants have been followed annually since 1996

with a core protocol that includes biological, medical, and psychosocial measures. At each visit, participants answered questions about their medical and menstrual history, symptoms, and lifestyle and psychosocial factors. Standardized protocols were used to measure weight and height. Psychiatric interviews were conducted at baseline and annually using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992). Non-time-varying independent variables analyzed in the current study were collected at baseline unless otherwise indicated, while time-varying independent variables such as marital status, menopausal status, vasomotor symptoms, chronic medical conditions, body mass index, stressful life events, and social support were collected annually from baseline through visit 10.

3.3.2 Measures

Assessment of Major Depression: Participants were assessed for current or past-year major depression at each annual visit from baseline through visit 10. Lifetime history of major depression was collected at baseline and defined as the occurrence of a major depressive episode prior to enrollment in the SWAN. The SCID, a semi-structured diagnostic psychiatric interview that has frequently been used in research and has demonstrated good reliability in numerous studies (Segal DL et al., 1993; Skre et al., 1991; Spitzer et al., 1992; Williams et al., 1992), was used to obtain diagnoses of lifetime and current or past year major depression.

All SCID interviewers held a Masters or a PhD in a mental health field and had prior clinical experience. Interviewers at the Pittsburgh site were supervised by J.T.B. To maintain consistency in SCID administration across interviewers and over annual visits, all interviewers were required to participate in an initial training conducted by Biometrics Research and Development, New York State Psychiatric Institute, as well as an annual re-certification process. Participant interviews were audiotaped, and these tapes were used to assess individual interviewing skills and inter-rater reliability. Follow-up reliability has been good for both lifetime (k=0.81) and past year major depression (k=0.76-0.89) within the SWAN.

Family History of Depression: Trained interviewers assessed family history of depression in first degree relatives using the family history method and a modified version of the depression module from the Family Interview for Genetic Studies (FIGS) (Maxwell ME, 1992; Nurnberger

et al., 1994). The family history method, in which an informant is queried about the history of mental illness in relatives, has been used in numerous studies of psychiatric disorder, and data from prior research indicate the family history method has acceptable reliability and validity (Andreasen et al., 1977; Weissman et al., 2000). In brief, the FIGS consisted of three interviewer administered questionnaires. Participants were first screened with a Family Mental Health History form. Those who endorsed a relative with depression and/or attempted/completed suicide were administered a second questionnaire to collect more detailed information about their relative's symptoms. Participants then completed the Depression Symptoms Checklist, which confirmed whether or not their relative met the DSM-IV criteria for major depression. Participants completed the FIGS at either SWAN visit nine or ten.

Menopause: The categorization of menopausal status was based on self-reported menstrual bleeding patterns. Women were classified as follows: premenopausal (menstrual bleeding in the past 3 months with no change in cycle regularity in the past 12 months), early perimenopausal (menstrual bleeding in the past 3 months accompanied by changes in cycle regularity), late perimenopausal (menstrual bleeding within the past 12 months but no bleeding in the past 3 months), postmenopausal (no menstrual bleeding within the past 12 months). Women who underwent a hysterectomy were excluded from the current study from the time of the surgery forward. Hormone therapy users, including postmenopausal hormone therapy users, were excluded from the current study for the duration of their hormone use. If a participant stopped using hormone therapy during the study, her data were included from the time her menopausal status could once again be reliably determined forward. In analyses, menopausal status categories were combined into pre-/early perimenopause and late perimenopause/postmenopause because there were relatively few late perimenopausal observations overall and very few women were premenopausal at visits 5 through 10.

Socioeconomic Indicators: Sociodemographic variables included age, ethnicity, and marital status. Difficulty paying for basic necessities and level of educational attainment were collected at baseline and included in the analyses as indicators of socioeconomic status.

Health-related Factors: At each visit, the presence of chronic medical conditions was determined by asking participants whether a medical professional had ever told them that they had any of the following: diabetes, hypertension, arthritis/osteoarthritis, under or overactive thyroid, cardiovascular disease, or cancer. The total number of chronic medical conditions

reported was categorized into: none vs. one or more conditions. Perceived overall health was assessed by asking participants to rate their overall health as excellent, very good, good, fair, or poor. For the current analyses, overall health was dichotomized into excellent/very good/good vs. fair/poor. Information about vasomotor symptoms was collected as part of a symptom checklist (Matthews et al., 1990; Neugarten & Kraines, 1965). Women were asked to indicate how often they had experienced hot flashes and night sweats in the past two weeks (not at all, 1-5 days, 6-8 days, 9-13 days, and every day). Women who reported experiencing hot flashes and/or night sweats at least six out of 14 days were classified as having frequent vasomotor symptoms.

Lifestyle: Height and weight measurements were taken annually and were used to calculate body mass index (BMI) as weight (kg) / height $(m)^2$. A modified version of the Baecke (Baecke et al., 1982) physical activity questionnaire was used to obtain information on the intensity, duration, and frequency of activity related to the domains of daily living, exercise/sports, and home/child care at baseline. A total physical activity score was calculated to reflect activity across all three domains.

Psychosocial Variables: To assess stressful life events, women were asked whether they had 1) experienced any of 18 negative life events in the past year and 2) how upsetting each of the events was for them (Dohrenwend et al., 1987). Thus, at each visit women were categorized as having experienced at least one very upsetting life event in the past year or having experienced no such event. Women also reported whether they had any of nine chronic difficulties for 12 months or longer, such as their own health problem, health problem with partner or child, work difficulties, or any other ongoing problem. Each of the chronic difficulties was rated in terms of how upsetting it was to the participant. Women were categorized as having experienced at least one very upsetting chronic difficulty in the past year or having experienced no such difficulty. Responses from the 4-item Medical Outcomes Study Social Support Survey (Sherbourne & Stewart, 1991) were summed to create a social support score, with higher scores indicating more social support.

Optimism was measured at the first annual follow-up visit with the 6-item Life Orientation Test. Items were scored and summed to create a total optimism score as per Scheier and Carver (1985). Higher scores indicate greater optimism. Trait anxiety was also collected at

the first annual visit with a 10-item version of the Spielberger Trait Anxiety Inventory (Spielberger C et al., 1970), and higher scores reflect higher levels of trait anxiety.

3.3.3 Statistical Analysis

The STATA system version 12 was used for all statistical analyses. Preliminary analyses included descriptive plots and statistics (means, standard deviations, ranges, frequencies), as well as an examination of the correlation between predictors. Differences in baseline characteristics between women with and without a family history of depression were assessed using chi square tests for comparison of categorical variables and t-tests or Wilcoxon rank-sum tests for unadjusted comparisons of continuous variables.

To address the question of whether family history of depression is associated with major depression in midlife women after adjusting for changes in menopausal status and other potentially important time-varying covariates, multivariable random effects logistic regression models were constructed (xtlogit procedure). This modeling approach accounts for the correlation of repeated observations from each woman resulting from the longitudinal design. These models allow women to contribute different numbers of observations and to remain in the model even if they do not have complete data for all follow-up visits. Women are treated as the random effect (i.e., woman-specific intercept).

Time-invarying covariates included baseline age, ethnicity, education, financial strain, physical activity, optimism, trait anxiety, and lifetime history of major depression. Marital status, menopausal status, vasomotor symptoms, chronic medical conditions, overall health, body mass index, stressful life events, chronic difficulties, and social support were included as time-varying covariates. All potential covariates were assessed in bivariate repeated measures random effects logistic regression analyses, and results from these analyses, as well as results from prior literature, informed which variables were included in the multivariable model building process. Covariates identified in bivariate analyses at $p<.15$ were entered into the logistic regression model, and manual backwards elimination was used (retaining variables significant at $p<.10$) to obtain a final parsimonious multivariable model. To explore whether the relationship between

family history of depression and major depression during midlife differs by menopausal status, an interaction term was added to the final multivariable model.

3.4 RESULTS

Descriptive data for the study participants are presented in Table 3-1. At baseline, the participants were 42-52 years of age with a mean age of 46. Thirty-one percent of the participants were African American and 34% had a family history of depression. Participants with a family history of depression were more educated (χ^2 (2, N=303) =7.01, p=.03), were more likely to have experienced a very upsetting chronic difficulty in the past year (χ^2 (1, N=284) =5.61, p<.01), and more likely to have a lifetime history of major depression (χ2 (1, N=303) =14.00, p<.001) compared to those with no family history.

Table 3-1: Baseline Characteristics by Family History of Major Depression (MD)

	Total	No Family History of MD	Family History of MD	
	N=303	*n*=199 (65.7%)	*n*=104 (34.3%)	p value
Age (years), mean (SD)	46.3 (2.6)	46.4 (2.6)	46.1 (2.4)	.51
African American, *n* (%)	95 (31.3)	62 (31.2)	33 (31.7)	.91
Education, *n* (%)				
Less than High School	70 (23.1)	55 (27.6)	15 (14.4)	**.03**
High School/Some College	102 (33.7)	65 (32.7)	37 (35.6)	
College/More than College	131 (43.2)	79 (39.7)	52 (50.0)	
Marital Status, *n* (%)				
Married	208 (69.1)	141 (70.8)	67 (65.7)	.45
Never married	37 (12.3)	25 (12.6)	12 (11.8)	
Separated/Widowed/Divorced	56 (18.6)	33 (16.6)	23 (22.5)	
Somewhat/very hard to pay for basics, *n* (%)	84 (27.8)	55 (27.8)	29 (27.9)	.98
Menopausal Status, *n* (%)				
Premenopausal	165 (54.5)	114 (57.3)	51 (49.0)	.17
Early Perimenopausal	138 (45.5)	85 (42.7)	53 (51.0)	
Vasomotor Symptoms: at least 6/14 days	28 (9.3)	14 (7.1)	14 (13.5)	.07
Any Chronic Medical Condition, *n* (%)	110 (36.3)	68 (34.2)	42 (40.4)	.28
Overall Health, *n* (%)				
Good/Very Good/Excellent	258 (85.7)	171 (86.4)	87 (84.5)	.66
Poor/Fair	43 (14.3)	27 (13.6)	16 (15.5)	
Body Mass Index (kg/m^2), mean(SD)	28.6 (6.6)	28.3 (6.5)	29.2 (6.9)	.25
Physical Activity Score (range: 0-14), mean (SD)	7.9 (1.7)	7.9 (1.7)	7.8 (1.7)	.65
Very Upsetting Life Event in past year, *n* (%)	157 (52.0)	98 (49.5)	59 (56.7)	.23
Very Upsetting Chronic Difficulty in past year, *n* (%)	72 (25.4)	40 (21.0)	32 (34.0)	**<.01**
Social Support (range: 0-16), mean (SD)	12.9 (2.8)	13.0 (2.8)	12.8 (2.7)	.27
Optimism (range: 0-18), mean (SD)	13.0 (3.8)	13.0 (3.7)	13.1 (4.0)	.63
Trait Anxiety (range: 10-40), mean (SD)	15.9 (4.7)	15.6 (4.6)	16.5 (5.0)	.12
Lifetime History of MD, *n* (%)	103 (34.0)	53 (26.6)	50 (48.1)	**<.001**

Total percentages may not equal to 100 due to rounding

Table 3-2 shows the number of observations for the 303 participants overall and by visit year and menopausal status. The number of major depressive episodes reported by participants during each visit and menopausal stage are also provided. Out of the total 2,574 visits, 241 major depressive episodes were diagnosed during the study. Major depressive episodes were identified during 115 (8.1%) of the 1,412 pre-/early perimenopause visits and 126 (10.8%) of the 1,162 late perimenopause/postmenopause visits.

Table 3-2: Number of Women with Major Depression (MD) by Visit and Menopausal Status

Visit	Total N	Total MD	Pre / E. Peri N	Pre / E. Peri MD	L. Peri / Post N	L. Peri / Post MD
Baseline	303	9	303	9	0	0
V01	256	22	243	19	13	3
V02	240	23	211	20	29	3
V03	226	16	178	13	48	3
V04	208	20	142	13	66	7
V05	207	24	107	14	100	10
V06	202	25	83	10	119	15
V07	216	17	59	3	157	14
V08	240	24	43	7	197	17
V09	244	31	30	5	214	26
V10	232	30	13	2	219	28
Total Obs.	2,574	241	1,412	115	1,162	126
Percent of Visits with MD = 9.4%			**Percent of Visits with MD** = 8.1%		**Percent of Visits with MD** = 10.8%	

Pre, premenopausal; E. Peri, early perimenopausal; L. Peri, late perimenopausal; Post, postmenopausal; Obs, observations

Table 3-3 shows the association of family history of depression and major depression during the study adjusted for menopausal status and other covariates. The odds of major depression were approximately 2.2 times greater for those with a family history of depression than for those without a family history (OR=2.24, 95% CI=1.17-4.29, p=.02). Menopausal status was also significantly associated with major depression in midlife women, with higher odds of major depression found when women were late perimenopausal or postmenopausal relative to when they are pre- or early perimenopausal (OR=3.01, 95% CI=1.76-5.15, p<.0001). In addition, baseline age, trait anxiety, lifetime history of major depression, and annual body mass index and very upsetting chronic difficulties were significantly related with major depression

during the study. The adjusted relationship between major depression and very upsetting life events was marginally statistically significant (OR=1.71, 95% CI=0.98-2.98, p=.06).

Table 3-3: Random Effects Logistic Regression Analyses for Odds of Major Depression (MD) among 285 Women (1,513 Observations)

	OR	95% CI	p value
Family History of MD	2.24	1.17-4.29	**.02**
Age at Baseline (years)	0.80	0.69-0.92	**.003**
Menopausal Status			
Pre-/Early Perimenopausal (REF)	REF	REF	**<.0001**
Late Perimenopausal/Post	3.01	1.76-5.15	
BMI (kg/m^2)	1.07	1.03-1.11	**.001**
Trait Anxiety	1.14	1.07-1.20	**<.0001**
Lifetime History of MD	2.92	1.50-5.66	**.002**
Very Upsetting Life Event in past year	1.71	0.98-2.98	.06
Very Upsetting Chronic Difficulty in past year	1.85	1.08-3.15	**.02**

BMI, body mass index; OR, odds ratio; CI, confidence interval; REF, reference category.

In order to determine whether the relationship between family history of depression and major depression during midlife differed by menopausal status, an interaction term was added to the model shown in Table 3-3. A statistically significant interaction between family history of depression and menopausal status was observed (OR=0.46, 95% CI=0.22-0.99, p=.04). To illustrate this interaction, adjusted models stratified by family history of depression are presented in Table 3-4. Menopausal status was not significantly associated with major depression in midlife among women with a family history of depression (OR=1.36, 95% CI=0.84-2.20, p=.21). However, for women without a family history of depression, the odds of reporting major depression during the study were higher when they were late perimenopausal or postmenopausal compared to when they were pre- or early perimenopausal (OR=3.36, 95% CI=1.79-6.32, p<.0001).

Table 3-4: Random Effects Logistic Regression for Odds of Major Depression (MD) by Family History

	No Family History of MD N=199 (1710 observations)		**Family History of MD N=104 (864 observations)**	
	OR (95% CI)	p value	OR (95% CI)	p value
Menopausal Status				
Pre- / Early Perimenopausal (REF)	REF	**<.0001**	REF	0.21
Late Perimenopausal / Post	3.36 (1.79-6.32)		1.36 (0.84-2.20)	

OR, odds ratio; CI, confidence interval; REF, reference category. Model adjusted for Baseline Age, Trait Anxiety, Lifetime History of MD, Annual Body Mass Index and Very Upsetting Life Events

3.5 DISCUSSION

This is the first prospective study to show that family history of depression is a risk factor for major depression in midlife women after taking changes in menopausal status and other important time-varying covariates, such as health conditions and behaviors and psychosocial factors, into account. Specifically, the odds of experiencing a major depressive episode were approximately 2.2 times greater for those with a family history of depression than for those without a family history even after adjusting for menopausal status, age, BMI, trait anxiety, very upsetting chronic difficulties and stressful events, and lifetime history of depression.

While the results confirm our primary hypothesis, they are not consistent with findings from the only other study to examine the importance of family history of depression in the development of depressed mood during the menopausal transition conducted by Woods et al. (2008). Woods et al. found a significant unadjusted association between depressive symptoms and family history of depression, but the relationship became non-significant in the final multivariable model which was adjusted for antidepressant use, stress, BMI, age, menopausal stage, history of postpartum depression, and parity. The inconsistency in results between the current study and the Woods et al. study may be due to differences in the method of ascertaining family history, the evaluation of depressive symptoms vs. clinical depression, and the inclusion

of different variables in the final multivariable models. In additional analyses (results not shown), we explored the effects of parity and history of postpartum depression but did not find that either variable was significantly related to major depression in our cohort of midlife women.

In the total sample, higher odds of major depression were found when women were late perimenopausal or postmenopausal relative to when they were pre- or early perimenopausal. This is consistent with recent longitudinal studies, including the Woods et al. study, which have provided strong evidence of increased risk of depressed mood among women undergoing the menopausal transition. Freeman et al. (2004) showed that reporting of high depressive symptoms (CES-D ≥16) increased significantly during the transition (OR=2.89, 95% CI= 1.29-6.45) and decreased during the postmenopausal period (OR=0.78, 95% CI= 0.10-6.17) in an urban community sample of US women, and Bromberger et al. (2011) reported that women were two to four times more likely to have a major depressive episode when they were perimenopausal (OR=1.98, 95% CI= 1.00-3.92) or early postmenopausal (OR=3.86, 95% CI= 1.36-10.92) compared to when they were premenopausal.

We hypothesized that the relationship between menopausal status and midlife major depression would be stronger in women with a family history of depression compared to women without a family history. However, we found the opposite to be the case. Menopausal status was significantly associated with major depression in those without a family history of depression, but not in those with a family history. Twin studies have reported that familiality of depression is mostly a result of genetic and individual environmental influences (Sullivan et al., 2000) and, therefore, women with a family history of depression may be more vulnerable to depression across the lifespan and less affected by factors specific to midlife, such as the menopausal transition.

Consistent with the Woods et al. study, we found that BMI was significantly associated with major depression in women during midlife. Some, but not all, cross-sectional and prospective general population studies suggest a significant relationship between obesity and depression in adults (Faith et al., 2011; Luppino et al., 2010), particularly in women (Bjerkeset et al., 2008; Herva et al., 2006; Kasen et al., 2008; Roberts et al., 2003). Multiple biological mechanisms have been proposed to explain observed obesity and depression associations, such as inflammation, altered cortisol secretion, poor health behaviors, and obesity-related health conditions (Faith et al., 2002; Jorm et al., 2003; Stunkard et al., 2003).

We also found a significant relationship between stressful life events and depression among midlife women, as has been shown in other studies of women in midlife (Amore et al., 2004; Bromberger et al., 2007; Bromberger et al., 2010; Cohen et al., 2006; Dennerstein et al., 2004; Kaufert et al., 1992; Maartens et al., 2002; Schmidt, Murphy, et al., 2004; Timur & Sahin, 2010). Trait anxiety was associated with midlife depression in the current study as well, independent of family history of depression, age, menopausal status, BMI, lifetime history of depression, and stressful life events and chronic difficulties. Cross-sectional and prospective studies have reported that higher levels of neuroticism are strongly associated with depression (De Graaf et al., 2002; Fanous et al., 2007; Kendler et al., 2006; Kendler, Neale, et al., 1993; Kotov et al., 2010). However, some research has shown that neuroticism is only a risk factor for early-onset major depression (Korten et al., 2012; Sneed et al., 2007), while others have found that neuroticism is also an important risk factor for depression in mid- and later life (Steunenberg et al., 2006; Steunenberg et al., 2009).

The main limitation of the current study is the method used to ascertain family history of depression. Due to time and financial constraints, direct family interviews were not conducted, and family history was instead collected through participant self-report. Participants may have incorrectly reported the psychopathology of their relatives, and it is possible that women who have experienced depression may be more likely to remember their relatives as being depressed than women without a history of depression. Thus, the results may have been affected by both limited knowledge of relatives' emotional health and recall bias. However, the family history method has established validity and reliability and has often been used in studies of psychiatric disorders. In addition, rather than relying on a simple yes/no question to obtain family history information, the assessment used in the current study was based on DSM-IV criteria which may have helped to limit the amount of misclassification.

The study also has a number of strengths. While most epidemiologic studies of depression in midlife women have examined depressive symptoms, we had access to 11 years of clinical depression data collected with a semi-structured diagnostic interview which allowed for a more accurate classification and examination of depression. In addition, SWAN has collected a wealth of longitudinal data from one of the few community cohorts of menopausal women, and we were able to use these data to determine the importance of the relationship between family

history of depression and major depression during midlife in the context of other risk factors, including the menopausal transition, and changes in biological, psychosocial and medical factors.

3.6 CONCLUSIONS

In conclusion, the current study is important because it is the first to show that family history of depression is a risk factor for major depression in midlife women after taking changes in menopausal status and other important time-varying covariates, such as health conditions and behaviors and psychosocial factors, into account. This suggests that clinicians should be aware that while physical health and environmental factors are associated with depression in midlife women, family history of depression continues to play an important role in the development of depression in women during midlife, particularly for women with a prior history of depression. On the other hand, it is also important to recognize that women without a family history of depression may be more vulnerable to the effects of the menopausal transition than women with such a history and that this group of women may benefit from increased monitoring for signs of depression during midlife as well.

Thus, it is recommended that both collection of family mental health history and depression screening become a routine part of primary care for women in midlife. This would allow clinicians to identify women who are at increased risk for depression during midlife and to initiate prevention measures, such as educating patients about depression risk, symptoms, and treatments. Furthermore, depression screening would facilitate early interventions, including the introduction of pharmacotherapy or psychotherapy and/or the provision of referrals to mental health professionals as appropriate.

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4.0 MAJOR DEPRESSION IN MIDLIFE WOMEN: ASSOCIATIONS WITH BOTH FAMILY AND PERSONAL HISTORIES OF DEPRESSION AND AN EXAMINATION OF POTENTIAL EXPLANATORY FACTORS

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4.1 ABSTRACT

Objective. Previous analyses have shown that women with both a lifetime and a family history of depression are at greater risk of major depression during midlife than women who have a lifetime history of depression only. The purpose of the current study is to examine participant characteristics that may explain why this group of women is more vulnerable to experiencing depression during midlife.

Methods. Data for the current study were collected from 103 African American and Caucasian women (42-52 years at baseline) participating in the longitudinal Study of Women's Health Across the Nation (SWAN) at the Pittsburgh site. To be included in the current study, women had to have a lifetime history of depression prior to the SWAN baseline visit. The Structured Clinical Interview for DSM-IV (SCID) was administered by trained interviewers to diagnose both lifetime history of major depression and major depressive episodes at baseline and annually. Participants completed an assessment of family history of depression at the 9th or 10th year of follow-up (2005-2007). Cox proportional hazard regression, Baron and Kenny's method, and a product-of-coefficients test were used to assess possible mediation of the relationship between family history of depression and midlife depression by pre-midlife and midlife factors.

Results. As expected, family history of depression was significantly associated with the onset of major depression during midlife (HR=2.15, 95% CI = 1.21-3.83, p=.009). Simple mediation analyses provided evidence that childhood abuse, trait anxiety, and the total number of life events mediated the effect of family history on the onset of depression during midlife. In multiple mediation analysis, the effect of family history of depression was reduced to non-significance by trait anxiety and the total number of life events (HR=1.52, 95% CI=0.82-2.82, p=.18), which together accounted for 52.7% of the effect of family history of depression.

Conclusions. Among women with a lifetime history of depression, the relationship between family history of depression and the onset of major depression during midlife may, in part, be explained by trait anxiety and exposure to more life events.

Key Words: family history of depression, major depression, menopause, midlife women

4.2 INTRODUCTION

A significant public health problem, depression is associated with increased morbidity and mortality and is estimated to be the third leading cause of disability across the world and the leading cause of health-related disability in women (World Health Organization, 2008). Affecting twice as many women as men, the lifetime prevalence of depression in women is estimated to be approximately 21% (Blazer et al., 1994; Kessler et al., 2003).

Depression is a complex disorder that is multifactorial in origin (Belmaker & Agam, 2008). Numerous social, biological, and psychological factors, as well as interactions between these factors and chronic and acute stressors, appear to influence the development of depression (aan het Rot et al., 2009; Accortt et al., 2008; Colman & Ataullahjan, 2010). A number of studies have provided evidence for the familial nature of depression (Bierut et al., 1999; Janzing et al., 2009; Kendler et al., 1995; X. Li et al., 2008; Sullivan et al., 1996; Timko et al., 2008; Weissman et al., 1982). Family studies have reported that depressed individuals are two to three times more likely to have a family history of depression than those without depression (Janzing et al., 2009; Sullivan et al., 2000; Weissman et al., 1982), and family history has been consistently associated with a more recurrent course of depression.

In a prior analysis (Colvin et al., manuscript in preparation), we found a significant relationship between family history of depression and major depression during midlife only among women who had a lifetime history of depression prior to midlife. Furthermore, we determined that women who had both a family history and a lifetime history of depression were at greater risk of depression in midlife than women who only had a lifetime history of depression.

There are a number of potential pathways that may explain this finding. For example, family history of depression has been linked with greater reporting of stressful life events and more severe stressors in childhood and adulthood (Hammen & Brennan, 2001; Hammen et al., 2003; Timko, Cronkite, Swindle, Robinson, Sutkowi, et al., 2009; Timko et al., 2008; Weissman et al., 1997; Weissman et al., 2006) which may be associated with depression in midlife. Family depression is also a strong risk factor for child sexual and physical abuse (Chaffin et al., 1996; Conron et al., 2009; Walsh et al., 2002), which is associated with increased risk of developing major depression in adulthood (Springer et al., 2007; Weich et al., 2009). Higher neuroticism

has been associated with family history of depression (Kendler et al., 2002; Kendler, Kessler, et al., 1993) and appears to be related to depression in adults both directly and through associations with stressful life events (Bolger & Schilling, 1991; Poulton & Andrews, 1992). Finally, poor health behaviors and chronic health conditions may be important mediators of the relationship between family history of depression and depression during midlife. Those with a family history of depression are more likely to experience pain and to report a greater number of medical conditions in adulthood, particularly cardiovascular disease, which may increase the risk for depression at midlife (Sobieraj et al., 1998; Timko, Cronkite, Swindle, Robinson, & Moos, 2009; Timko et al., 2008; Weissman et al., 2006).

In order to better understand the relationship between family history of depression and major depression in women during midlife, the current study aims to identify participant characteristics that may help explain why women who have both a lifetime and family history of depression are more vulnerable to experiencing depression during midlife than women who have a lifetime history of depression only. Specifically, we will address the following questions among midlife women with a lifetime history of depression: 1) Do pre-midlife factors (childhood abuse, trait anxiety) explain the relationship between family history of depression and major depression?; 2) Do factors occurring in midlife (health-related variables, stressful life events, menopausal symptoms) explain the relationship between family history of depression and major depression?; 3) When both pre-midlife and midlife factors are considered, which factors remain significant mediators of the relationship between family history of depression and major depression?

Both childhood abuse and trait anxiety have been strongly associated with family history of depression and linked with major depression in midlife. Thus, it is hypothesized that childhood abuse and trait anxiety will, in part, explain the relationship between family history of depression and major depression during midlife. Furthermore, given there is evidence from the literature that stressful life events and chronic medical conditions are significantly associated with both family history of depression and major depression in midlife, it is posited that these two midlife factors will also mediate the relationship between family history of depression and midlife major depression.

4.3 METHODS

4.3.1 Participants and Procedures

Data for the current study were collected from women participating in the Study of Women's Health Across the Nation (SWAN) Menopausal Transition, Mental Health and Ethnicity Study (MHS) at the SWAN Pittsburgh site. SWAN is a multi-center longitudinal study of the biological and psychological sequelae associated with the menopausal transition, and the SWAN MHS is an ancillary project designed to obtain diagnostic psychiatric interview data from the SWAN Pittsburgh participants. In order to be eligible for SWAN, women had to be between 42 and 52 years old, have an intact uterus, not be taking hormones, have had at least one menstrual period in the last 3 months, and self-identify as non-Hispanic White or African American. A total of 463 women were recruited into the Pittsburgh SWAN sample through random digit dialing and voter registration lists. Of these, 443 (96%) SWAN Pittsburgh women agreed to participate in the SWAN MHS.

Family history of depression was obtained from 303 women still actively participating in the SWAN MHS during annual visits 9 or 10 (2005-2007). Reasons for non-participation in the family history assessment were as follows: withdrew from SWAN before the ninth annual visit (n=92, 59.7%), missed the study visit (n=30, 19.5%), completed the study visit but not the assessment of family history of depression (n=25, 16.3%), and deceased (n=7, 4.5%). Compared to women who completed the family history assessment, non-completers were younger ($p=.009$), more likely to be African American ($p=.02$), less educated ($p=.005$), more likely to be experiencing financial strain ($p<.0001$), and less likely to be married ($p=.03$). Of the 303 women who completed the family history assessment, 103 reported a lifetime history of major depression prior to the SWAN baseline visit, and these women comprise the sample for the current study.

Biological, medical, and psychosocial measures have been collected from participants annually since 1996. Standardized protocols were used to obtain anthropometric measures. Psychiatric interviews were conducted at baseline and annually using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992). Time-invariant independent variables

included in the current study were collected at baseline, and time-varying variables were obtained each year from baseline through visit 10 unless otherwise indicated. The University of Pittsburgh Institutional Review Board approved this study, and all participants provided informed consent.

4.3.2 Measures

Assessment of Major Depression: The main outcome for the study was time to the first occurrence of major depression during the study. Lifetime history of major depression was determined at the baseline visit and defined as the occurrence of a major depressive episode prior to enrollment in the SWAN. Diagnoses of lifetime and current major depression were diagnosed using the SCID, a semi-structured diagnostic psychiatric interview that has frequently been used in research and has demonstrated good reliability in a number of studies (Segal DL et al., 1993; Skre et al., 1991; Spitzer et al., 1992; Williams et al., 1992).

SCID interviewers were required to have prior clinical experience and hold a Masters or a PhD in a mental health field. J.T.B. provided supervision to all interviewers at the Pittsburgh site. Interviewers were also required to participate in an initial training conducted by Biometrics Research and Development, New York State Psychiatric Institute, as well as an annual re-certification process to maintain consistency in SCID administration across interviewers and over annual visits. Participant interviews were audiotaped, and these tapes were reviewed to assess interviewing skills and inter-rater reliability. Follow-up reliability has been quite good for both lifetime (k=0.81) and past year major depression (k=0.76-0.89) within the SWAN.

Family History of Depression: Family history of depression in first degree relatives was assessed by trained interviewers at the ninth or tenth annual SWAN visit using the family history method and a modified version of the depression module from the Family Interview for Genetic Studies (FIGS) (Maxwell ME, 1992; Nurnberger et al., 1994). The family history method, in which a participant is asked about the history of mental illness in relatives, has been used in numerous studies of psychiatric disorder, and data from prior research indicate the family history method has acceptable reliability and validity (Andreasen et al., 1977; Weissman et al., 2000). The FIGS consisted of three interviewer administered questionnaires. Participants were first

screened with a Family Mental Health History form. Those who endorsed a relative with depression and/or attempted/completed suicide completed a second questionnaire to supply more detailed information about their relative's depressive symptoms. Finally, participants completed the Depression Symptoms Checklist, which confirmed whether or not their relative met the DSM-IV criteria for major depression.

Socioeconomic Indicators: Indicators of socioeconomic status included difficulty paying for basic necessities and level of educational attainment. Age, ethnicity, and marital status were included in the analyses as sociodemographic variables.

Health-related Factors: Health-related factors examined in the analyses were chronic medical conditions, vasomotor symptoms, and role limitations due to physical health. Chronic medical conditions were assessed by asking participants whether a medical professional had ever told them that they had any of the following: diabetes, hypertension, arthritis/osteoarthritis, under or overactive thyroid, cardiovascular disease, or cancer. The total number of chronic medical conditions reported was categorized into none or one or more conditions.

Vasomotor symptoms data were collected as part of a symptom checklist which has been used in numerous menopause studies (Matthews et al., 1990; Neugarten & Kraines, 1965). Women were asked to indicate how often they had experienced hot flashes and night sweats in the past two weeks (not at all, 1-5 days, 6-8 days, 9-13 days, and every day). Women who reported experiencing any hot flashes and/or night sweats were classified as having vasomotor symptoms.

Role limitations due to physical health were obtained at baseline and annual visits 1-3, 6, 8, and 10 from the 36-item Short-Form Health Survey (SF-36). Scores were transformed to range from 0-100 as per Ware and Sherbourne (1992) and were then dichotomized as follows according to criteria developed by Rose et al. (1999): good functioning (> 75% of the distribution) and low functioning (≤ 25%).

Lifestyle: Height and weight measurements collected by the study were used to calculate body mass index (BMI) as weight (kg) / height $(m)^2$. A modified version of the Baecke (Baecke et al., 1982) physical activity questionnaire was administered to participants to obtain information on the intensity, duration, and frequency of activity related to the domains of daily living, exercise/sports, and home/child care. A total physical activity score was calculated to reflect activity across all three domains.

Psychosocial Variables: In order to assess life stress as cumulative burden or perception of stressfulness, life events were examined as follows: 1) the total number of life events experienced in the past year, 2) the total number of very upsetting life events experienced in the past year, and 3) whether or not women had experienced at least one very upsetting life event in the past year (Dohrenwend et al., 1987). Women also reported whether they had any of the following 9 chronic difficulties for 12 months or longer: own health problem, health problem with partner or child, substance abuse in a family member, work difficulties, financial strain, housing problems, problem with a close relationship, helping sick family member or friend on a regular basis, any other ongoing problem. Each of the chronic difficulties was rated in terms of how upsetting it was to the participant. Women were categorized as having experienced at least one very upsetting chronic difficulty in the past year or having experienced no such difficulty.

History of childhood abuse was obtained from the 28-item short form of the Childhood Trauma Questionnaire (Bernstein et al., 2003) at visit 8. The questionnaire is divided into five subscales (emotional abuse, physical abuse, emotional neglect, physical neglect, and sexual abuse), and participants rate items for each subscale from 1 (never) to 5 (very often true). Scores for each subscale range from 5-25, and items across all subscales were summed to create a continuous total childhood abuse score.

Trait anxiety was assessed at annual visit 1 with a 10-item version of the Spielberger Trait Anxiety Inventory (Spielberger C et al., 1970). Higher scores reflect higher levels of trait anxiety. Trait anxiety is a measure of individual differences in anxiety proneness that are relatively stable across time and a variety of circumstances (Spielberger C.D., Reheiser E.C., Ritterband L.M., Synderman S.J., & Larger K.K., 1995). The Spielberger Trait Anxiety Inventory has demonstrated excellent test-retest reliability (average r=.88) over multiple time intervals (Barnes, Harp, & Jung, 2002).

4.3.3 Statistical Analysis

The SAS system version 9.3 was used for all statistical analyses. Preliminary analyses included descriptive plots and statistics (means, standard deviations, ranges, frequencies), as well as an examination of the correlation between predictors. Differences in baseline characteristics

between women with and without a family history of depression were assessed using chi square tests for comparison of categorical variables and t-tests or Wilcoxon rank-sum tests for unadjusted comparisons of continuous variables.

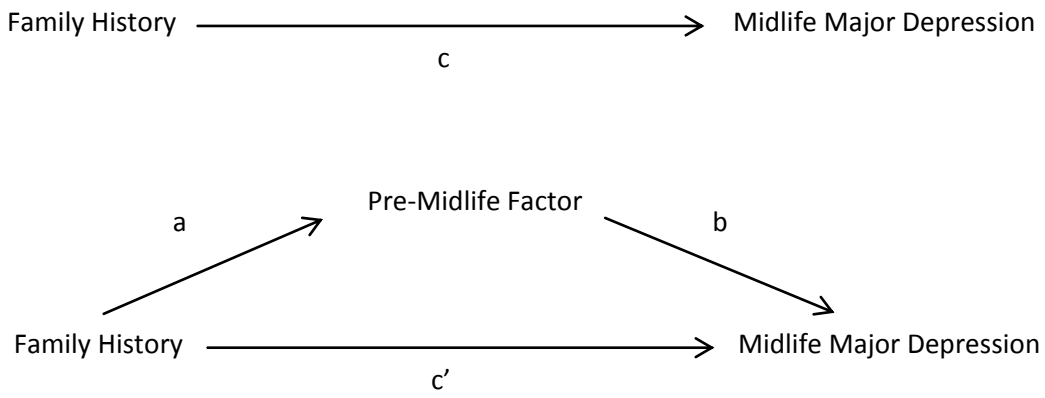
Cox proportional hazard models were used to obtain hazard ratios and 95% confidence intervals for time to first occurrence of major depression during the study. Women who experienced a major depressive episode were censored from the following visit forward. Women who did not report a major depressive episode for the duration of the study (through visit 10) or were lost to follow-up were censored at their last completed visit. Time-invarying variables included in the models were baseline age, ethnicity, education, financial strain, trait anxiety, and childhood abuse. Marital status, vasomotor symptoms, chronic medical conditions, limitations in physical functioning, BMI, and stressful life events were assessed as time-varying variables.

Potential mediators of the relationship between family history of depression and midlife major depression among women with a lifetime history of depression were identified using the four step process developed by Baron and Kenny (1986). According to their criteria, a variable is a mediator if (1) the independent variable significantly predicts the outcome, (2) the independent variable significantly predicts the mediator, (3) the mediator significantly predicts the outcome controlling for the independent variable of interest, and (4) the mediator reduces the relationship between the independent variable and the outcome either partially or to non-significance.

Mediators to be tested were separated into pre-midlife and midlife factors. Trait anxiety and childhood abuse were considered to be pre-midlife factors, while midlife factors included life events, health-related factors, and menopausal symptoms. All of the models included in the mediation analyses were adjusted for age, ethnicity, education, and marital status. Figure 4-1 shows the conceptual models tested in the simple mediation analyses. In step 1, a Cox proportional hazards model was run to test whether family history was a significant predictor of time to first major depression during the study (path c). In step 2, linear and logistic regressions, as appropriate, were constructed to determine which potential mediators were significantly predicted by family history of depression (path a). A Cox proportional hazards model was run to assess step 3, whether the mediator in question significantly predicted time to first major depression in midlife controlling for family history of depression (path b), and step 4, whether or not the potential mediator reduced the effect of family history (path c'). A product-of-

coefficients test (PRODCLIN) developed by MacKinnon et al. (2007) was then used to formally assess the significance of the indirect effect for each potential mediator. Specifically, the PRODCLIN approach creates asymmetric confidence intervals based on the distribution of the product of a and b to test the statistical significance of the indirect effect. The indirect effect is considered to be significant if the confidence interval does not include zero. This approach has been shown to have more power and more accurate Type 1 error rates with small samples than tests which assume a normal distribution for the indirect effect (MacKinnon et al., 2007). The proportion of the effect of family history of depression due to a mediator was calculated as follows: (ab/c) *100. A final multiple mediation model was constructed and tested using the process described above.

A



B

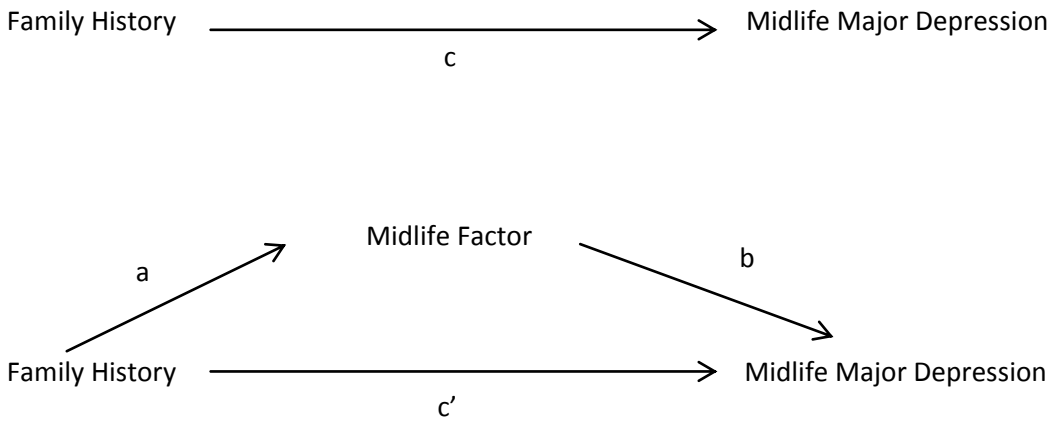


Figure 4-1: Diagrams of the Theoretical Models Used in Mediation Analyses

4.4 RESULTS

Table 4-1 shows baseline characteristics of the sample of 103 women with a lifetime history of depression by family history. At baseline, the participants were 42-52 years of age with a mean age of 46. Twenty-eight percent of the participants were African American, and 48% had a family history of depression. Participants with a family history of depression were more likely to report vasomotor symptoms (χ^2 (1, N=103)=8.09, p=.004) and low role physical functioning (χ^2 (1, N=103) =9.27, p=.002), experienced more life events in the past year (t (101) =-2.66, p<.008), and scored higher on measures of trait anxiety (t (101)=-2.32, p=.02) and childhood abuse (t (100)=-2.58, p=.01) compared to those with no family history.

Table 4-1: Baseline Characteristics by Family History of Major Depression (MD) among Women with a Lifetime History of Depression

	Total (N=103)	**No Family History of MD (*n*=53)**	**Family History of MD (*n*=50)**	**p value**
Age (years), mean (SD)	46.2 (2.4)	46.0 (2.5)	46.5 (2.4)	.31
Ethnicity, *n* (%)				
African American	29 (28.2)	16 (30.2)	13 (26.0)	.64
Education, *n* (%)				
Less than High School	15 (14.6)	11 (20.7)	4 (8.0)	.11
High School/Some College	32 (31.1)	13 (24.5)	19 (38.0)	
College/More than College	56 (54.3)	29 (54.7)	27 (54.0)	
Marital Status, *n* (%)				
Married	59 (57.8)	30 (56.6)	29 (59.2)	.96
Never married	13 (12.7)	7 (13.2)	6 (12.2)	
Separated/Widowed/Divorced	30 (29.4)	16 (30.2)	14 (28.6)	
Somewhat or very hard to pay for basics, *n* (%)	68 (66.0)	37 (69.8)	31 (62.0)	.40
Any Vasomotor Symptoms	47 (45.6)	17 (32.1)	30 (60.0)	**.004**
Any Chronic Medical Condition, *n* (%)	44 (42.7)	20 (37.7)	24 (48.0)	.29
Low Role Physical Functioning, *n* (%)	44 (42.7)	15 (28.3)	29 (58.0)	**.002**
Body Mass Index (kg/m^2), mean(SD)	29.5 (7.6)	28.7 (7.3)	30.4 (8.0)	.27
Physical Activity Score (range: 0-14), mean(SD)	7.9 (1.9)	8.3 (1.9)	11.1 (7.6)	.07
Very Upsetting Chronic Difficulty in past year, *n* (%)	39 (40.6)	18 (35.3)	21 (46.7)	.26
No. Life Events in past year, mean (SD)	4.1 (2.5)	3.4 (2.4)	4.6 (2.5)	**.008**
No. Very Upsetting Life Events in past year, mean (SD)	1.7 (1.7)	1.4 (1.6)	2.0 (1.8)	.07
Any Very Upsetting Life Event in past year, *n* (%)	70 (68.0)	32 (60.4)	38 (76.0)	.09
Trait Anxiety (range: 10-40), mean (SD)	18.3 (5.6)	17.1 (5.1)	19.6 (5.9)	**.02**
Childhood Abuse Score, mean (SD)	57.8 (8.5)	55.7 (7.2)	59.9 (9.2)	**.01**

When midlife major depression was compared by family history of depression among the 103 participants with a lifetime history of depression, women with both a family and a lifetime history of depression were significantly more likely to report depression during midlife than those with a lifetime history of depression only (Figure 4-2, χ^2 (1, N=103) =11.32, p=.0008).

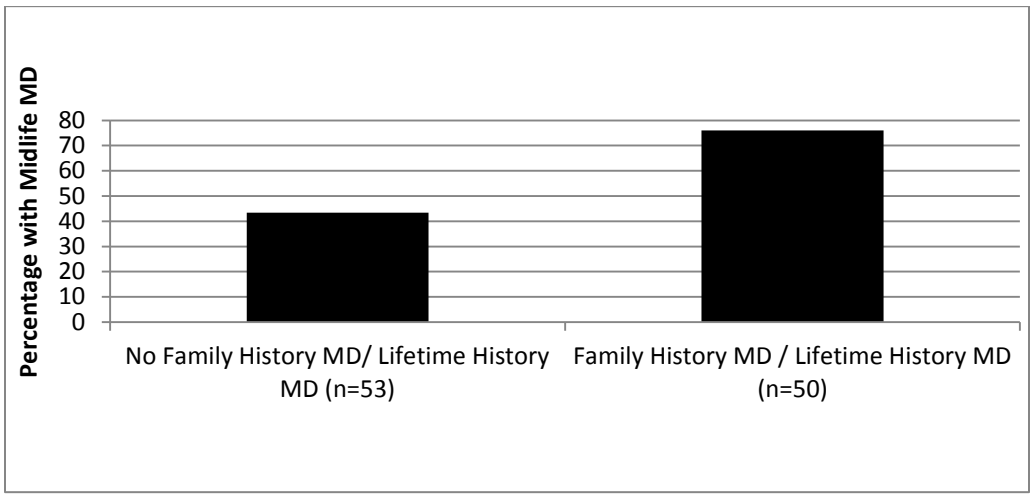


Figure 4-2: Percentage with Midlife Major Depression (MD) by Family and Lifetime History of MD

Pre-midlife factors, trait anxiety and childhood abuse, were tested first as potential mediators for the relationship between family history of depression and midlife depression among women with a lifetime history of depression (Table 4-2) using the adjusted model. Family history of depression was significantly associated with the onset of major depression during midlife (HR=2.15, 95% CI = 1.21-3.83, p=.009), fulfilling step (1) of the Baron and Kenny criteria. Both trait anxiety and childhood abuse met the remaining Baron and Kenny criteria. Family history of depression significantly predicted trait anxiety and childhood abuse, while trait anxiety and childhood abuse each significantly predicted the onset of midlife major depression controlling for family history (HR=1.08, 95% CI=1.03-1.13, p=.001; HR=1.04, 95% CI=1.01-1.07, p=.02, respectively). Finally, the effect of family history was partially reduced

when trait anxiety was added to the model (HR=1.89, 95% CI=1.04-3.40, p=.04) and also with the addition of childhood abuse (HR=1.95, 95% CI=1.07-3.57, p=.03). The proportion of the effect of family history due to childhood abuse was 21.5%, and the proportion of the effect of family history due to trait anxiety was 27.3%. According to the product-of-coefficients test, both trait anxiety (product of coefficients=0.21, 95% CI=0.02-0.50) and childhood abuse (product of coefficients=0.16, 95% CI=0.02-0.42) were significant mediators of the relationship between family history of depression and midlife depression.

Table 4-2: Mediation of Associations between Family History and the Onset of Major Depression in Midlife among 103 Women

Models[†]	**HR**	**95% CI**	**p-value**
Independent Variable: Family History			
HR for Family History on Major Depression	2.15	1.21-3.83	**.009**
Mediator 1: Childhood Abuse			
HR for Family History on Major Depression by Childhood Abuse	1.95	1.07-3.57	**.03**
Proportion of Family History Effect Due to Mediator: 21.5%			
Product of Coefficients=0.16, 95% CI=0.02-0.42			
Mediator 2: Trait Anxiety			
HR for Family History on Major Depression by Trait Anxiety	1.89	1.04-3.40	**.04**
Proportion of Family History Effect Due to Mediator: 27.3%			
Product of Coefficients=0.21, 95% CI=0.02-0.50			
Mediator 3: Total Number of Life Events			
HR for Family History on Major Depression by Total Life Events	1.77	0.96-3.27	.07
Proportion of Family History Effect Due to Mediator: 25.7%			
Product of Coefficients=0.20, 95% CI=0.01-0.50			

HR, hazards ratio; CI, confidence interval.
[†]All models adjusted for baseline age, education, ethnicity, and marital status

Next, several midlife factors were tested for mediation. Physical activity, chronic medical conditions, vasomotor symptoms, low role physical functioning, any very upsetting life events, and the total number of very upsetting life events did not meet step (2) of the Baron and Kenny procedure, and therefore no further testing was performed with these variables. The total number of life events met step (2) and the remaining Baron and Kenny criteria. Family history of depression significantly predicted the total number of life events, and the total number of life

events significantly predicted the onset of midlife major depression controlling for family history (HR=1.19, 95% CI=1.06-1.35, p=.005). The effect of family history became non-significant when the total number of life events was added to the model (HR=1.77, 95% CI=0.96-3.27, p=.07). The proportion of the effect of family history due to the total number of life events was 25.7%. The product-of-coefficients test was also significant (product of coefficients=0.20, 95% CI=0.01-0.50).

A final multiple mediation model was constructed using the Baron and Kenny method and the product-of-coefficients test (Table 4-3). When childhood abuse, trait anxiety, and the total number of life events were tested simultaneously, only trait anxiety and the total number of life events met the Baron and Kenny criteria. Trait anxiety significantly predicted time to the onset of major depression after controlling for family history of depression, the total number of life events, and the relevant covariates (HR=1.08, 95% CI=1.02-1.14, p=.004). Likewise, total number of life events significantly predicted time to onset of major depression after controlling for family history, trait anxiety, and the included covariates (HR=1.20, 95% CI=1.06-1.35, p=.003). When both trait anxiety and the total number of life events were added to the model with family history of depression, the effect of family history of depression was reduced to non-significance (HR=1.52, 95% CI=0.82-2.82, p=.18).

The proportion of the effect of family history due to trait anxiety controlling for life events was 26.7%, and the proportion of the effect of family history due to life events controlling for trait anxiety was 26.0%. Thus, trait anxiety and the total number of life events together accounted for 52.7% of the effect of family history of depression. The product-of-coefficients test reached statistical significance for both trait anxiety (product of coefficients=0.20, 95% CI=0.02-0.51) and total number of life events (product of coefficients=0.19, 95% CI=0.01-0.50).

Table 4-3: Multiple Mediation of Associations between Family History and the Onset of Major Depression in Midlife among 103 Women

Models[†]	HR	95% CI	p-value
Model 1			
Family History of Depression	2.15	1.21-3.83	**.009**
Model 2			
Family History of Depression	1.52	0.82-2.82	.18
Trait Anxiety	1.08	1.02-1.14	**.004**
Total Number of Life Events	1.20	1.06-1.35	**.003**
Proportion of Family History Effect Due to Trait Anxiety: 26.7% Product of Coefficients=0.20, 95% CI=0.02-0.51 Proportion of Family History Effect Due to Number of Life Events: 26.0% Product of Coefficients=0.19, 95% CI=0.01-0.50			

HR, hazards ratio; CI, confidence interval.
[†]All models adjusted for baseline age, education, ethnicity, and marital status

4.5 DISCUSSION

The current study found that, among women with a lifetime history of depression the relationship between family history of depression and the onset of major depression during midlife may, in part, be explained by childhood abuse, trait anxiety, and exposure to more life events. Furthermore, when both pre-midlife and midlife factors were tested in multiple mediation analysis, the effect of family history of depression was reduced to non-significance by trait anxiety and the total number of life events.

This is consistent with the literature that has shown that child sexual and physical abuse is strongly associated with both family history of depression (Chaffin et al., 1996; Conron et al., 2009; Walsh et al., 2002) and increased risk of developing major depression in adolescence and adulthood (Springer et al., 2007; Weich et al., 2009). In our sample of midlife women, we found that those with a family history of depression had significantly higher scores on the Childhood Trauma Questionnaire than those without a family history, and prior research has shown that women who were physically and/or sexually abused are at increased risk for depression in midlife compared to women with no such history of childhood adversity (Gilman

et al., 2002; Rohde et al., 2008; Wise et al., 2001). However, while we found evidence that childhood abuse is a partial mediator of the effect of family history of depression on the onset of midlife major depression in simple mediation analysis, we could no longer show mediation by childhood abuse in multiple mediation models including trait anxiety and the total number of life events experienced in the past year.

Trait anxiety appears to be an important mediator of the relationship between family history of depression and major depression in women during midlife. This is consistent with numerous cross-sectional and prospective studies that have reported that higher levels of neuroticism are strongly associated with depression and family history (De Graaf et al., 2002; Fanous et al., 2007; Kendler et al., 2002; Kendler et al., 2006; Kendler, Kessler, et al., 1993; Kendler, Neale, et al., 1993; Kotov et al., 2010). Higher neuroticism has been associated with family history of depression both directly and through associations with stressful life events (Bolger & Schilling, 1991; Poulton & Andrews, 1992). In the current study, we determined that the mediating effect of trait anxiety remained even after controlling for the effect of the total number of life events.

Interestingly, we found that while the overall number of life events was a significant mediator for the effect of family history on midlife depression, the number of events perceived to be very upsetting did not have a mediating effect on this relationship. This is in contrast with studies that have shown a stronger relationship between both family history and depression and more stressful events than with events perceived to be non-stressful or less severe (Hammen & Brennan, 2001; Kessler, 1997; Timko, Cronkite, Swindle, Robinson, Sutkowi, et al., 2009; Weissman et al., 2006). However, several recent studies in both clinical and community samples indicate that depressed individuals may actually increase their likelihood of experiencing life events, primarily interpersonal events, through their personality characteristics and behavior (Daley et al., 2009; Hammen, 2006; Hammen & Brennan, 2002; Harkness et al., 1999; Rudolph & Hammen, 1999), thereby promoting recurrent depressive episodes. According to a study conducted by Kendler et al. (1997), this may be especially true for women with a family history of depression. They found that women with a family history of depression had a significantly increased probability of experiencing life events, particularly interpersonal events. This may help to explain the results of the current study. Unfortunately, given our smaller sample size, we were unable to separate life events into categories to test this theory.

The main limitation of the current study is the method used to ascertain family history of depression. Family history of depression was obtained through participant self-report rather than direct family interviews. Participants may have incorrectly reported the psychopathology of their relatives, and it is possible that women who have experienced depression may be more likely to remember their relatives as being depressed than women without a history of depression. However, the family history method has established validity and reliability and has often been used in studies of psychiatric disorders. In addition, the assessment used in the current study was based on DSM-IV criteria, which may have helped to limit the amount of misclassification.

The current study was also somewhat limited by small sample size. While we were able to formally test several important potential mediators using the product-of-coefficients method, we were not able to conduct a more complete investigation of covariates, interactions, and mediating variables. For example, a larger sample would have allowed for the exploration of more complex potential pathways for the relationship between family history of depression and midlife depression using structural equation models for time-varying data.

However, the study has a number of strengths. While most epidemiologic studies of depression in midlife women have examined depressive symptoms, we were able to evaluate 11 years of clinical depression data collected with a semi-structured diagnostic interview, which allowed for a more accurate classification and examination of depression. In addition, SWAN has collected a wealth of longitudinal data from one of the few community cohorts of midlife women, including data on earlier life factors such as childhood abuse, and we were able to use these data to examine a number of potential pre-midlife and midlife mediating variables.

4.6 CONCLUSIONS

In conclusion, the current study found evidence that both pre-midlife and midlife factors may help to explain why women who have both a family and lifetime history of depression are more vulnerable to experiencing depression during midlife than women who have a lifetime history of depression only. Specifically, among women with a lifetime history of depression, the

relationship between family history of depression and midlife major depression may, in part, be explained by trait anxiety and exposure to more life events during midlife.

Our results suggest that, in addition to assessing midlife women for family and lifetime history of depression, administering brief evaluations of trait anxiety and recent life events may help clinicians to identify women who are at greatest risk for depression during midlife. Furthermore, clinicians could also potentially use this information to determine appropriate prevention and treatment strategies. For example, women with high trait anxiety may benefit from interventions focused on anxiety reduction, while those experiencing life events may benefit from learning effective coping techniques or by increasing their social support.

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5.0 DISCUSSION AND CONCLUSIONS

5.1 OVERVIEW OF FINDINGS

The following is a review of the main findings from the papers presented in Chapters 2-4. A brief synopsis of the results from each paper is provided below.

5.1.1 Is Family History of Depression Associated with Major Depression in Midlife Women: Study of Women's Health Across the Nation

In the first paper, we evaluated the relationship between family history of depression and major depression in midlife women using data collected from 303 African American and Caucasian women who were participants at the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation (SWAN). Starting with bivariate logistic regression models, we found that the odds of experiencing a major depressive episode during the study were approximately three times greater for those with a family history of depression than for those without a family history of depression. Multivariable logistic regression was used to determine that family history of depression remained a significant predictor of major depression in midlife after adjusting for lifetime history of major depression, age, trait anxiety, chronic medical conditions, and stressful life events. When analyses were stratified by lifetime history of major depression, family history of depression was significantly associated with major depression among midlife women with a lifetime history of depression but not among those without such a history.

While our results confirm previous studies that have demonstrated an important relationship between family history of depression and major depression in general (Janzing et al., 2009; Sullivan et al., 2000; Weissman et al., 1982), they contrast with the study conducted by

Woods et al. (2008), which reported that family history of depression was not a significant predictor of depressive symptoms in a similar community sample of midlife women. Differences in the assessment of family history and depression may account for the inconsistency of results.

In the current study, we were also able to show that family history of depression was associated with recurrence of major depression during midlife, which is consistent with the majority of the literature conducted in mixed age and gender samples (Gershon et al., 1986; Janzing et al., 2009; Kendler et al., 1999; Lieb et al., 2002; Timko et al., 2008). Our findings that the relationship between family history of depression and incident depression was not significant in midlife women was also consistent with the literature. Numerous studies have reported that a family history of depression is less common among those with mid- and later onset of depression than those with an earlier age of depression onset (Kupfer et al., 1989; Lyons et al., 1998; Weissman et al., 1986) and that factors other than genetic vulnerability, such as environmental and physical health problems, become more important predictors of depression in mid- and later life (Baldwin & Tomenson, 1995; Lyons et al., 1998). This is also in agreement with our finding that chronic medical conditions and stressful life events were associated with depression in women reporting first-onset of depression during midlife.

Given our results, we conclude that family history of depression is strongly associated with major depression in midlife women, particularly in those with a lifetime history of depression prior to midlife. These results suggest that women with a family history of depression may benefit from closer monitoring of their mood during midlife.

5.1.2 The Role of Family History of Depression and the Menopausal Transition in the Development of Major Depression in Midlife Women

In the second paper, we sought to determine whether family history of depression is a risk factor for major depression in midlife women after adjusting for relevant time-varying covariates and whether the relationship between family history of depression and major depression in midlife women differs by menopausal status. We addressed this question using data from the same cohort of 303 midlife women evaluated in the analyses for Paper 1. Multivariable random

effects logistic regression was used to assess the relationship between family history of depression and major depression in midlife women after adjusting for time-varying covariates. We found that family history of depression was significantly associated with major depression in midlife even after adjusting for lifetime history of major depression, trait anxiety and age at baseline, and changes over time in menopausal status, body mass index, very upsetting chronic difficulties, and very upsetting life events. We also reported that higher odds of major depression were found when women were late perimenopausal or postmenopausal relative to when they were pre- or early perimenopausal. However, when analyses were stratified by family history of depression, menopausal status was significantly associated with major depression among midlife women without a family history of depression but not among those with a family history.

As discussed above in Paper 1, our main results are not consistent with the study conducted by Woods et al. (2008). However, our findings that late perimenopausal or postmenopausal women have higher odds of major depression relative to when they are pre- or early perimenopausal is consistent with recent longitudinal studies (Bromberger et al., 2011; Freeman et al., 2004), including the Woods et al. study, which have provided strong evidence of increased risk of depressed mood among women undergoing the menopausal transition. We also hypothesized that the relationship between menopausal status and midlife major depression would be stronger in women with a family history of depression compared to women without a family history. However, we found that menopausal status was significantly associated with major depression in those without a family history of depression, but not in those with a family history. Other studies have reported that familiality of depression is mostly a result of heritable influences and individual environmental exposures (Sullivan et al., 2000), and it may well be that women with a family history of depression may be more vulnerable to depression across the lifespan and less affected by factors specific to midlife, such as the menopausal transition.

We conclude that family history of depression is an important predictor of major depression in midlife women, even after adjusting for menopausal status and other changes in other risk factors for depression. This suggests that women with a family history of depression may benefit from routine evaluations of their emotional health during midlife. Furthermore, the menopausal transition appears to be associated with major depression only among women without a family history of depression. Therefore, women without a family history of depression

may be more vulnerable to the effects of the menopausal transition than women with such a history, and this group of women may benefit from increased monitoring for signs of depression as well.

Specifically, it is recommended that both collection of family mental health history and depression screening become a routine part of primary care for women in midlife. This would allow clinicians to identify women who are at increased risk for depression during midlife and to initiate prevention measures, such as educating patients about depression risk, symptoms, and treatments. Furthermore, depression screening would facilitate early interventions, including the introduction of pharmacotherapy or psychotherapy and/or the provision of referrals to mental health professionals as appropriate.

5.1.3 Major Depression in Midlife Women: Associations with Both Family and Personal Histories of Depression and an Examination of Potential Explanatory Factors

Finally, in the third paper, we examined participant characteristics that may explain why women who have both a lifetime and family history of depression are more vulnerable to experiencing depression during midlife than women who have a lifetime history of depression only. We included 103 midlife women with a lifetime history of depression prior to midlife in our analyses. We assessed mediation of the relationship between family history of depression and midlife depression by both early and midlife factors using Cox proportional hazard regression, Baron and Kenny's method, and a product-of-coefficients test.

Simple mediation analyses provided evidence that childhood abuse, trait anxiety, and the total number of life events mediated the effect of family history on the onset of depression during midlife. In multiple mediation analysis, the effect of family history of depression was reduced to non-significance by trait anxiety and the total number of life events.

We conclude that among women with a lifetime history of depression, the relationship between family history of depression and the onset of major depression during midlife may, in part, be explained by trait anxiety and life events. Our results suggest that in addition to assessing midlife women for family and lifetime history of depression, administering brief

evaluations of trait anxiety and recent life events may help clinicians to identify women who are at greatest risk for depression during midlife. Furthermore, clinicians could also potentially use this information to determine appropriate prevention and treatment strategies. For example, women with high trait anxiety may benefit from interventions focused on anxiety reduction, while those experiencing life events may benefit from learning effective coping techniques or by increasing their social support.

5.2 STRENGTHS AND LIMITATIONS

This dissertation project has a number of strengths. Analyses evaluated lifetime and annual clinical depression data collected with a standardized interview from a well-characterized menopausal cohort. In addition, covariate data for the project were obtained from the SWAN core database, which contains a wealth of longitudinal biological, psychosocial, medical, and hormonal data. The main limitation of the study is the method of family history data collection. Due to time and financial constraints, family history of depression was collected through participant self-report instead of direct family interviews. It is possible that participants may incorrectly recall the psychopathology of their relatives and that depressed women may be more likely to remember their relatives as being depressed than women without a history of depression. However, the family history method has been used in numerous studies of psychiatric disorder and has established validity and reliability. The study was also somewhat limited due to the smaller sample size. While there was adequate power to address the aims of the dissertation in their final form, it was not possible to conduct more complex analyses to explore explanatory pathways involved in the relationship between family history of depression and depression in women during midlife.

5.3 PUBLIC HEALTH SIGNIFICANCE

The proposed dissertation project is the first to evaluate the influence of family history of depression on the development of major depression in women during midlife, using longitudinal data from one of the few well-characterized cohorts of midlife women. Specifically, the project was able to determine the significance of family history of depression in the development of depression in women during midlife, during the menopausal transition in particular, evaluate how the role of family history differs for women experiencing first onset or recurrent major depression during midlife, and explore potential explanatory factors for these relationships.

Previous epidemiologic studies of depression in midlife women have generally relied on the assessment of depressive symptoms rather than a formal diagnosis of depression. The proposed project had access to 11 years of clinical depression data obtained by semi-structured clinical interviews, allowing not only for more accurate classifications of depression but also for an examination of the course and patterns of depression during midlife. Furthermore, this is the only study of clinical depression in midlife women that includes an assessment of family history of depression based on DSM-IV criteria. Finally, SWAN has captured a wealth of longitudinal data on biological, psychosocial, medical, and hormonal factors that we were able to incorporate into our analyses. This project was therefore uniquely positioned to examine the relationship between family history of depression and course of clinical depression in the context of other known risk and protective factors. Knowledge gained through this work will increase understanding of the etiology of depression in women, encourage further research in this area, and inform prevention and treatment efforts.

For example, our results suggest that women with a family history of depression are at increased risk for depression during midlife. Thus, it is recommended that assessment of family mental health history becomes a routine part of primary care for midlife women. This would allow clinicians to identify women at risk and to initiate preventive measures as soon as possible, such as providing depression education to patients and their families.

Women with a family history of depression would also likely benefit from closer monitoring of their mood during midlife. Although many women receive the majority of their health care through a primary care physician, primary care practices typically do not have the resources available to conduct full diagnostic psychiatric interviews. However, there are several

brief standardized depression instruments which have good psychometric properties and can be administered quickly in a primary care setting by a physician or a nurse-educator, such as the 9-item Patient Health Questionnaire (Kroenke, Spitzer, & Williams, 2001) and the 6-item Hamilton Rating Scale for Depression (Hooper & Bakish, 2000). Depression screening would facilitate early interventions, including antidepressant therapy, psychotherapy, or referral to a mental health professional for more complex cases.

Finally, we found evidence that the relationship between family history of depression and the development of depression in midlife women is mediated by childhood abuse, trait anxiety, and life events. Therefore, the introduction of brief evaluations of childhood trauma, personality characteristics, and recent life events in primary care may also help to identify women at risk and to determine the most effective treatment strategy.

5.4 SUGGESTED FUTURE RESEARCH

Overall, given the lack of studies focused on family history and midlife depression in women, there is a need for more community-based research of the relationship between clinical depression and family history of depression in midlife women. Ideally, these studies would be longitudinal in design and have a reasonably large and diverse sample. This would allow for a more complete investigation of covariates, interactions, and mediating variables. For example, a logical extension of this work would be to explore potential pathways for the relationship between family history of depression and midlife depression using structural equation models that allow for time-varying data.

In addition, future work would benefit from assessment of family history data through family interviews. This would minimize the problems with participant recall associated with the family history method. It is also suggested that future research collect both genetic data and more complete data on the early family environment so that genetic vs. environmental effects can be examined.

Importantly, studies examining how family history interacts with and leads to multiple risk factors for depression in midlife would make a significant contribution to the literature. Specifically, research exploring issues of biologic vulnerability and environmental exposures, as well as how family history affects perceptions and lifestyle choices from early life through midlife is needed.

5.5 CONCLUSIONS

The overall aim of this dissertation was to improve understanding of the etiology of depression in midlife women by exploring associations between family history of depression and major depression in women during midlife. We were able to demonstrate that family history of depression plays an important role in the development of major depression in midlife women, particularly for women who have a history of depression prior to midlife. Furthermore, we showed that family history remains a significant predictor of depression in midlife women in the context of the menopausal transition and other relevant changing risk factors, such as stressful life events and health conditions and behaviors. Finally, we explored several potential mediators for the relationship between family history of depression and major depression in midlife women and found evidence that both pre-midlife (childhood abuse, trait anxiety) and midlife factors (life events) at least partially explain the effect of family history. We hope that the findings from this dissertation will help to inform prevention and treatment efforts and encourage further research in this area.

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