Published in final edited form as:
Arch Womens Ment Health. 2014 August ; 17(4): 269–278. doi:10.1007/s00737-014-0433-8.

Does Family History of Depression Predict Major Depression in Midlife Women? Study of Women's Health Across the Nation Mental Health Study (SWAN MHS)

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Abstract

Purpose—To determine whether family history of depression predicts major depression in midlife women independent of psychosocial and health profiles at midlife.

Methods—Participants were 303 African American and Caucasian women (42–52 years at baseline) recruited into the Study of Women's Health Across the Nation (SWAN) and the Women's Mental Health Study (MHS) in Pittsburgh. Major depression was assessed annually with the Structured Clinical Interview for DSM-IV. Family mental health history was collected at the 9th or 10th follow-up. Multivariable logistic regression was used to determine whether family history of depression predicted major depression in midlife, adjusting for covariates.

Results—The odds of experiencing major depression during the study were three times greater for those with a family history than for those without a family history (OR=3.22, 95% CI=1.95-5.31). Family history predicted depression (OR=2.67, 95% CI=1.50–4.78) after adjusting for lifetime history of depression, age, trait anxiety, chronic medical conditions, and stressful life events. In analyses stratified by lifetime history of depression, family history significantly predicted depression only among women with a lifetime history of depression.

Conclusions—Family history of depression predicts major depression in midlife women generally, but particularly in those with a lifetime history of depression prior to midlife.

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Ethical standards
This study was approved by the University of Pittsburgh Institutional Review Board. All participants provided informed consent prior to their inclusion in the study.

Conflict of interest
The authors declare that they have no conflict of interest.

Keywords

family history of depression; major depression; menopause; midlife women

Introduction

Depression is a significant public health problem. It is associated with increased morbidity and mortality (Neugebauer 1999; Cassano and Fava 2002) 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. 1994b; Kessler et al. 2003; Kessler et al. 2005).

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; Schmidt et al. 2004a; Kessler et al. 1994a; Kessler et al. 1993). However, little is known about the risk and protective factors that influence the occurrence 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 numerous studies have provided evidence for the familial nature of depression (Weissman et al. 1982; Timko et al. 2008; Li et al. 2008; Janzing et al. 2009; Bierut et al. 1999; Sullivan et al. 1996; Kendler et al. 1995), 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 associated with recurrent major depression during midlife independent of current psychosocial or health factors.

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). In analyses 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 could not explore associations of family history with incident vs. recurrent depression.

To improve understanding of the etiology of depression in midlife women, the influence of family history of depression on the occurrence of depression in midlife women in the

context of other risk and protective factors should be determined. Such knowledge would help clinicians to identify women at increased risk for experiencing a major depressive episode during midlife based on their family history, as well as presenting symptoms and risk factor profile, thus allowing for the timely implementation of preventive measures.

Therefore, the aim of this study is to address gaps in knowledge and limitations of the prior literature by examining whether family history of depression is a significant predictor of 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 predictor of 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 the strong relationship between major depression and family history of depression earlier in the lifespan, we expect that this association will also be evident in midlife. Therefore, we hypothesize that family history of depression will significantly predict major depression in midlife women, even after adjusting for lifetime history of depression and other potential confounders. We also expect 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; Timko et al. 2008; Kendler et al. 1999; Lieb et al. 2002), while mid- and later life onset of depression may be more influenced by current psychosocial factors and changes in physical health (Tozzi et al. 2008; Gallicchio et al. 2007; Freeman et al. 2004; Bromberger et al. 2007; Timur and Sahin 2010; Alexander et al. 2007). Thus, we hypothesize 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 depression.

Methods

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 obtain 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, 457 (98%) SWAN Pittsburgh women agreed to participate in the SWAN MHS.

Family history of depression was obtained from 303 women still participating in the SWAN MHS during annual visits 9 and 10 (September, 2005–November, 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 visit 9 (n=92), missed the visit (n=30), completed the visit but not the assessment of family history of depression (n=25), and deceased (n=7). Compared to women who completed the family history assessment (N = 303), non-completers (N = 154) 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 protocol that includes biological, medical, and psychosocial measures. Psychiatric interviews were conducted at baseline and annually from January of 1996 through December of 2007 using the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al. 1992). The independent variables analyzed in the current study were collected at the baseline SWAN visit (January, 1996 – December, 1997) unless otherwise indicated.

Measures

Assessment of Major Depression—The main outcome for the study was the occurrence of any major depressive episode 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. Diagnoses of lifetime and current major depression were obtained from the SCID, which has frequently been used in research and has demonstrated good reliability in a number of studies (Spitzer et al. 1992; Williams et al. 1992; Segal DL et al. 1993; Skre et al. 1991).

SCID interviewers were required to hold a Masters or a PhD in a mental health field and to have prior clinical experience. To maintain consistency in SCID administration across interviewers and over annual visits, all interviewers were trained by Biometrics Research and Development, New York State Psychiatric Institute, and re-certified annually. 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) (Nurnberger et al. 1994; Maxwell ME 1992). 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 (Weissman et al. 2000; Andreasen et al. 1977). In brief, the FIGS consisted of three interviewer administered questionnaires. Participants were 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 additional 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.

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—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 (Ware and Sherbourne 1992). 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 (Neugarten and Kraines 1965; Matthews et al. 1990). Women indicated 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 were measured by trained staff according to a standard protocol 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 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 experienced any of the following 9 chronic difficulties for 12 months or longer: 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 a sick family member or friend on a regular basis, any other ongoing difficulty. Women rated how upsetting each of the chronic difficulties was for them on a 3 point scale (not upsetting, somewhat upsetting, or very upsetting). 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 and Stewart 1991), with higher scores indicating more social support.

Optimism was measured at follow-up visit 1 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 et al. 1970); higher scores reflect higher levels of trait anxiety.

Statistical Methods

The SAS system version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. Preliminary analyses included descriptive plots and statistics, 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 a predictor of 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 predictors 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 to omit any irrelevant predictors (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.

Results

Descriptive data for the study participants are presented in Table 1. At baseline, 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), 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.

Forty-eight percent of the participants had neither a family nor a personal history of depression at baseline, 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 1).

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 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).

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 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 candidates for inclusion in the final multivariable modeling process for the group without a lifetime history of depression. 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.

In the final multivariable models (Table 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.

Discussion

This study shows that family history of depression is a significant predictor of 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. 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 are consistent with those of 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.

Results from the current study and the Woods et al. (2008) study may differ because of the differences in depression and family history assessments. Woods et al. (2008) measured self-reported depressive symptoms. Depressive symptoms were 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.

Our findings are also consistent with the majority of the literature which has demonstrated a strong relationship between family history and depression recurrence across the lifespan (Kendler et al. 1999; Janzing et al. 2009; Timko et al. 2008; Gershon et al. 1986; Lieb et al. 2002). Importantly, 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 and Prescott 1999; McGuffin et al. 1996; Kendler et al. 1995) 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 midlife and later onset of depression than those with an earlier age of depression onset (Lyons et al. 1998; Kupfer et al. 1989; Weissman et al. 1986). Furthermore, there is evidence that earlier onset depression is significantly more heritable than midlife- and later onset depression and that factors other than genetic vulnerability become more important predictors of depression in mid- and later life (Lyons et al. 1998; Baldwin and Tomenson 1995).

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 more important risk factors for midlife- to later-onset depression than family history or other earlier life factors. Several community and clinical studies have supported these results in mixed gender and age samples (Gallagher et al. 2010; Sneed et al. 2007; Korten et al. 2012).

Indeed, we found that chronic medical conditions were associated with depression in the total sample and particularly in women reporting incident depression during midlife. This is consistent with other studies that have found self-reported poor health (Dennerstein et al. 2004; Kaufert et al. 1992; Gallicchio et al. 2007) 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 (Gallicchio et al. 2007; Alexander et al. 2007).

It is well established that stressful life events are associated with depression in women of all ages, including midlife (Maartens et al. 2002; Dennerstein et al. 2004; Bromberger et al. 2007; Bromberger et al. 2010; Kaufert et al. 1992; Cohen et al. 2006; Timur and Sahin 2010; Schmidt et al. 2004b; Amore et al. 2004). Unsurprisingly, the current study also found evidence for this relationship. 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 (Kotov et al. 2010; De Graaf et al. 2002; Fanous et al. 2007; Kendler et al. 1993; Kendler et al. 2006). 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 et al. 2006; Steunenberg et al. 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.

This 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. We had access to 11 years of clinical depression data obtained by semi-structured clinical interviews, allowing for more accurate classifications of depression. Despite this, it is possible that 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.

In summary, this study is the first to evaluate the influence of family history of depression on the development of incident and recurrent clinical depression in women during midlife. We found that family history of depression is a strong predictor of 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.

Acknowledgments

The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and the NIH Office of Research on Women's Health (ORWH) (Grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. Funding from The National Institute of Mental Health for the Mental Health Study is gratefully acknowledged. University of Pittsburgh, Pittsburgh, PA – Joyce T. Bromberger, PI (R01 MH59689); Psychiatric Epidemiology Training Grant Fellowship – Gale A. Richardson, Program Director (T32 MH015169).

Participating institutions and principal staff were as follows. *Clinical Center:* University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI. *NIH Program Office:* National Institute on Aging, Bethesda, MD – Winifred Rossi 2012 - present; Sherry Sherman 1994 – 2012; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Program Officers. *Central Laboratory:* University of Michigan, Ann Arbor – Daniel McConnell (Central Ligand Assay Satellite Services). *Coordinating Center:* University of Pittsburgh, Pittsburgh, PA – Maria Mori Brooks, PI 2012 - present; Kim Sutton-Tyrrell, PI 2001 – 2012; New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001. *Steering Committee:* Susan Johnson, Current Chair, Chris Gallagher, Former Chair. We thank the study staff and all the women who participated in SWAN.

References

Alexander JL, Dennerstein L, Woods NF, Kotz K, Halbreich U, Burt V, Richardson G. Neurobehavioral impact of menopause on mood. Expert Rev Neurother. 2007; 7(11 Suppl):S81–S91. [doi]. [PubMed: 18039071]

Amore M, Di Donato P, Papalini A, Berti A, Palareti A, Ferrari G, Chirico C, De Aloysio D. Psychological status at the menopausal transition: an Italian epidemiological study. Maturitas. 2004; 48(2):115–124. [doi]. [PubMed: 15172085]

Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. Arch Gen Psychiatry. 1977; 34(10):1229–1235. [PubMed: 911222]

Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982; 36(5):936–942. [PubMed: 7137077]

Baldwin RC, Tomenson B. Depression in later life. A comparison of symptoms and risk factors in early and late onset cases. Br J Psychiatry. 1995; 167(5):649–652. [PubMed: 8564322]

Bierut LJ, Heath AC, Bucholz KK, Dinwiddie SH, Madden PA, Statham DJ, Dunne MP, Martin NG. Major depressive disorder in a community-based twin sample: are there different genetic and environmental contributions for men and women? Arch Gen Psychiatry. 1999; 56(6):557–563. [PubMed: 10359473]

Bromberger JT, Matthews KA, Schott LL, Brockwell S, Avis NE, Kravitz HM, Everson-Rose SA, Gold EB, Sowers M, Randolph JF Jr. Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). J Affect Disord. 2007; 103(1–3):267–272. doi:S0165-0327(07)00054-7 [pii]. [PubMed: 17331589]

Bromberger JT, Schott LL, Kravitz HM, Sowers M, Avis NE, Gold EB, Randolph JF Jr, Matthews KA. Longitudinal change in reproductive hormones and depressive symptoms across the menopausal transition: results from the Study of Women's Health Across the Nation (SWAN). Arch Gen Psychiatry. 2010; 67(6):598–607. doi: 67/6/598 [pii]. [PubMed: 20530009]

Cassano P, Fava M. Depression and public health: an overview. J Psychosom Res. 2002; 53(4):849–857. doi:S0022399902003045 [pii]. [PubMed: 12377293]

Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry. 2006; 63(4): 385–390. doi: 63/4/385 [pii]. [PubMed: 16585467]

De Graaf R, Bijl RV, Ravelli A, Smit F, Vollebergh WA. Predictors of first incidence of DSM-III-R psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand. 2002; 106(4):303–313. doi: 1o397 [pii]. [PubMed: 12225498]

Dennerstein L, Guthrie JR, Clark M, Lehert P, Henderson VW. A population-based study of depressed mood in middle-aged, Australian-born women. Menopause. 2004; 11(5):563–568. doi: 00042192-200411050-00011 [pii]. [PubMed: 15356410]

Dohrenwend BP, Levav I, Shrout PE, Link BG, Skodol AE, Martin JL. Life stress and psychopathology: progress on research begun with Barbara Snell Dohrenwend. Am J Community Psychol. 1987; 15(6):677–715. [PubMed: 3326408]

Fanous AH, Neale MC, Aggen SH, Kendler KS. A longitudinal study of personality and major depression in a population-based sample of male twins. Psychol Med. 2007; 37(8):1163–1172. doi:S0033291707000244 [pii]. [PubMed: 17407614]

Freeman EW, Sammel MD, Liu L, Gracia CR, Nelson DB, Hollander L. Hormones and menopausal status as predictors of depression in women in transition to menopause. Arch Gen Psychiatry. 2004; 61(1):62–70. [doi]. [PubMed: 14706945]

Gallagher D, Mhaolain AN, Greene E, Walsh C, Denihan A, Bruce I, Golden J, Conroy RM, Kirby M, Lawlor BA. Late life depression: a comparison of risk factors and symptoms according to age of onset in community dwelling older adults. Int J Geriatr Psychiatry. 2010; 25(10):981–987. [PubMed: 19998316]

Gallicchio L, Schilling C, Miller SR, Zacur H, Flaws JA. Correlates of depressive symptoms among women undergoing the menopausal transition. J Psychosom Res. 2007; 63(3):263–268. doi:S0022-3999(07)00069-4 [pii]. [PubMed: 17719363]

Gershon ES, Weissman MM, Guroff JJ, Prusoff BA, Leckman JF. Validation of criteria for major depression through controlled family study. J Affect Disord. 1986; 11(2):125–131. [PubMed: 2948985]

Janzing JG, de Graaf R, ten Have M, Vollebergh WA, Verhagen M, Buitelaar JK. Familiality of depression in the community; associations with gender and phenotype of major depressive disorder. Soc Psychiatry Psychiatr Epidemiol. 2009; 44(12):1067–1074. [doi]. [PubMed: 19319457]

Kaufert PA, Gilbert P, Tate R. The Manitoba Project: a re-examination of the link between menopause and depression. Maturitas. 1992; 14(2):143–155. doi: 0378-5122(92)90006-P [pii]. [PubMed: 1565022]

Kendler KS, Gardner CO, Prescott CA. Clinical characteristics of major depression that predict risk of depression in relatives. Arch Gen Psychiatry. 1999; 56(4):322–327. [PubMed: 10197826]

Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression: a Swedish longitudinal, population-based twin study. Arch Gen Psychiatry. 2006; 63(10):1113–1120. doi: 63/10/1113 [pii]. [PubMed: 17015813]

Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. A longitudinal twin study of personality and major depression in women. Arch Gen Psychiatry. 1993; 50(11):853–862. [PubMed: 8215811]

Kendler KS, Pedersen NL, Neale MC, Mathe AA. A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. Behav Genet. 1995; 25(3):217–232. [PubMed: 7598665]

Kendler KS, Prescott CA. A population-based twin study of lifetime major depression in men and women. Arch Gen Psychiatry. 1999; 56(1):39–44. [PubMed: 9892254]

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003; 289(23):3095–3105. [doi]. [PubMed: 12813115]

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62(6):617–627. [PubMed: 15939839]

Kessler RC, McGonagle KA, Nelson CB, Hughes M, Swartz M, Blazer DG. Sex and depression in the National Comorbidity Survey. II: Cohort effects. J Affect Disord. 1994a; 30(1):15–26. [PubMed: 8151045]

Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord. 1993; 29(2–3):85–96. doi:0165-0327(93)90026-G [pii]. [PubMed: 8300981]

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994b; 51(1):8–19. [PubMed: 8279933]

Korten NC, Comijs HC, Lamers F, Penninx BW. Early and late onset depression in young and middle aged adults: differential symptomatology, characteristics and risk factors? J Affect Disord. 2012; 138(3):259–267. [PubMed: 22370067]

Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. Psychol Bull. 2010; 136(5):768–821. doi: 2010-17510-004 [pii]. [PubMed: 20804236]

Krishnan KR, Delong M, Kraemer H, Carney R, Spiegel D, Gordon C, McDonald W, Dew M, Alexopoulos G, Buckwalter K, Cohen PD, Evans D, Kaufmann PG, Olin J, Otey E, Wainscott C. Comorbidity of depression with other medical diseases in the elderly. Biol Psychiatry. 2002; 52(6):559–588. doi:S0006322302014725 [pii]. [PubMed: 12361669]

Kupfer DJ, Frank E, Carpenter LL, Neiswanger K. Family history in recurrent depression. J Affect Disord. 1989; 17(2):113–119. [PubMed: 2527886]

Li X, Sundquist J, Sundquist K. Age-specific familial risks of depression: a nation-wide epidemiological study from Sweden. J Psychiatr Res. 2008; 42(10):808–814. doi:S0022-3956(07)00149-5 [pii]. [PubMed: 17983628]

Lieb R, Isensee B, Hofler M, Wittchen HU. Parental depression and depression in offspring: evidence for familial characteristics and subtypes? J Psychiatr Res. 2002; 36(4):237–246. doi:S0022395602000158 [pii]. [PubMed: 12191628]

Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Toomey R, Faraone SV, Merla-Ramos M, Tsuang MT. A registry-based twin study of depression in men. Arch Gen Psychiatry. 1998; 55(5):468–472. [PubMed: 9596050]

Maartens LW, Knottnerus JA, Pop VJ. Menopausal transition and increased depressive symptomatology: a community based prospective study. Maturitas. 2002; 42(3):195–200. doi:S0378512202000385 [pii]. [PubMed: 12161043]

Matthews KA, Wing RR, Kuller LH, Meilahn EN, Kelsey SF, Costello EJ, Caggiula AW. Influences of natural menopause on psychological characteristics and symptoms of middle-aged healthy women. J Consult Clin Psychol. 1990; 58(3):345–351. [PubMed: 2365898]

Maxwell, ME. Intramural Research Program NIMH. Clinical Neurogenetic Branch; 1992. FIGS: Family Interview for Genetic Studies.

McGuffin P, Katz R, Watkins S, Rutherford J. A hospital-based twin register of the heritability of DSM-IV unipolar depression. Arch Gen Psychiatry. 1996; 53(2):129–136. [PubMed: 8629888]

Neugarten BL, Kraines RJ. "Menopausal Symptoms" in women of various ages. Psychosom Med. 1965; 27:266–273. [PubMed: 14327878]

Neugebauer R. Mind matters: the importance of mental disorders in public health's 21st century mission. Am J Public Health. 1999; 89(9):1309–1311. [PubMed: 10474543]

Nurnberger JI Jr, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry. 1994; 51(11):849–859. discussion 863-844. [PubMed: 7944874]

Scheier MF, Carver CS. Optimism, coping, and health: assessment and implications of generalized outcome expectancies. Health Psychol. 1985; 4(3):219–247. [PubMed: 4029106]

Schmidt PJ, Haq N, Rubinow DR. A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. AJ Psychiatry. 2004a; 161(12):2238–2244. doi: 161/12/2238 [pii].

Schmidt PJ, Murphy JH, Haq N, Rubinow DR, Danaceau MA. Stressful life events, personal losses, and perimenopause-related depression. Arch Womens Ment Health. 2004b; 7(1):19–26. [doi]. [PubMed: 14963729]

Segal DL, Hersen M, Van Hasselt VB, Kabacoff RI, Roth L. Reliability of diagnosis in older psychiatric patients using the structured clinical interview for DSM-III-R. J of Psychopathology and Behav Assess. 1993; 15(4):347–356.

Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med. 1991; 32(6):705–714. [PubMed: 2035047]

Skre I, Onstad S, Torgersen S, Kringlen E. High interrater reliability for the Structured Clinical Interview for DSM-III-R Axis I (SCID-I). Acta Psychiatr Scand. 1991; 84(2):167–173. [PubMed: 1950612]

Sneed JR, Kasen S, Cohen P. Early-life risk factors for late-onset depression. Int J Geriatr Psychiatry. 2007; 22(7):663–667. [PubMed: 17173352]

Spielberger, C.; Gorsuch, R.; Lushene, R. STAI Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists Press; 1970.

Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry. 1992; 49(8):624–629. [PubMed: 1637252]

Steunenberg B, Beekman AT, Deeg DJ, Kerkhof AJ. Personality and the onset of depression in late life. J Affect Disord. 2006; 92(2–3):243–251. [PubMed: 16545466]

Steunenberg B, Braam AW, Beekman AT, Deeg DJ, Kerkhof AJ. Evidence for an association of the big five personality factors with recurrence of depressive symptoms in later life. Int J Geriatr Psychiatry. 2009; 24(12):1470–1477. [PubMed: 19382138]

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. AJ Psychiatry. 2000; 157(10):1552–1562.

Sullivan PF, Wells JE, Joyce PR, Bushnell JA, Mulder RT, Oakley-Browne MA. Family history of depression in clinic and community samples. J Affect Disord. 1996; 40(3):159–168. doi: 0165032796000560 [pii]. [PubMed: 8897115]

Timko C, Cronkite RC, Swindle R, Robinson RL, Turrubiartes P, Moos RH. Functioning status of adult children of depressed parents: a 23-year follow-up. Psychol Med. 2008; 38(3):343–352. doi:S0033291707002073 [pii]. [PubMed: 17988421]

Timur S, Sahin NH. The prevalence of depression symptoms and influencing factors among perimenopausal and postmenopausal women. Menopause. 2010; 17(3):545–551. [doi]. [PubMed: 20400922]

Tozzi F, Prokopenko I, Perry JD, Kennedy JL, McCarthy AD, Holsboer F, Berrettini W, Middleton LT, Chilcoat HD, Muglia P. Family history of depression is associated with younger age of onset in patients with recurrent depression. Psychol Med. 2008; 38(5):641–649. doi:S0033291707002681 [pii]. [PubMed: 18272011]

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36)I. Conceptual framework and item selection. Med Care. 1992; 30(6):473–483. [PubMed: 1593914]

Weissman MM, Kidd KK, Prusoff BA. Variability in rates of affective disorders in relatives of depressed and normal probands. Arch Gen Psychiatry. 1982; 39(12):1397–1403. [PubMed: 7149900]

Weissman MM, Merikangas KR, Wickramaratne P, Kidd KK, Prusoff BA, Leckman JF, Pauls DL. Understanding the clinical heterogeneity of major depression using family data. Arch Gen Psychiatry. 1986; 43(5):430–434. [PubMed: 3964021]

Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. Arch Gen Psychiatry. 2000; 57(7):675–682. doi:yoa8214 [pii]. [PubMed: 10891038]

Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, Howes MJ, Kane J, Pope HG Jr, Rounsaville B, et al. The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Arch Gen Psychiatry. 1992; 49(8):630–636. [PubMed: 1637253]

Woods NF, Smith-DiJulio K, Percival DB, Tao EY, Mariella A, Mitchell S. Depressed mood during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. Menopause. 2008; 15(2):223–232. [doi]. [PubMed: 18176355]

World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: WHO Press; 2008.

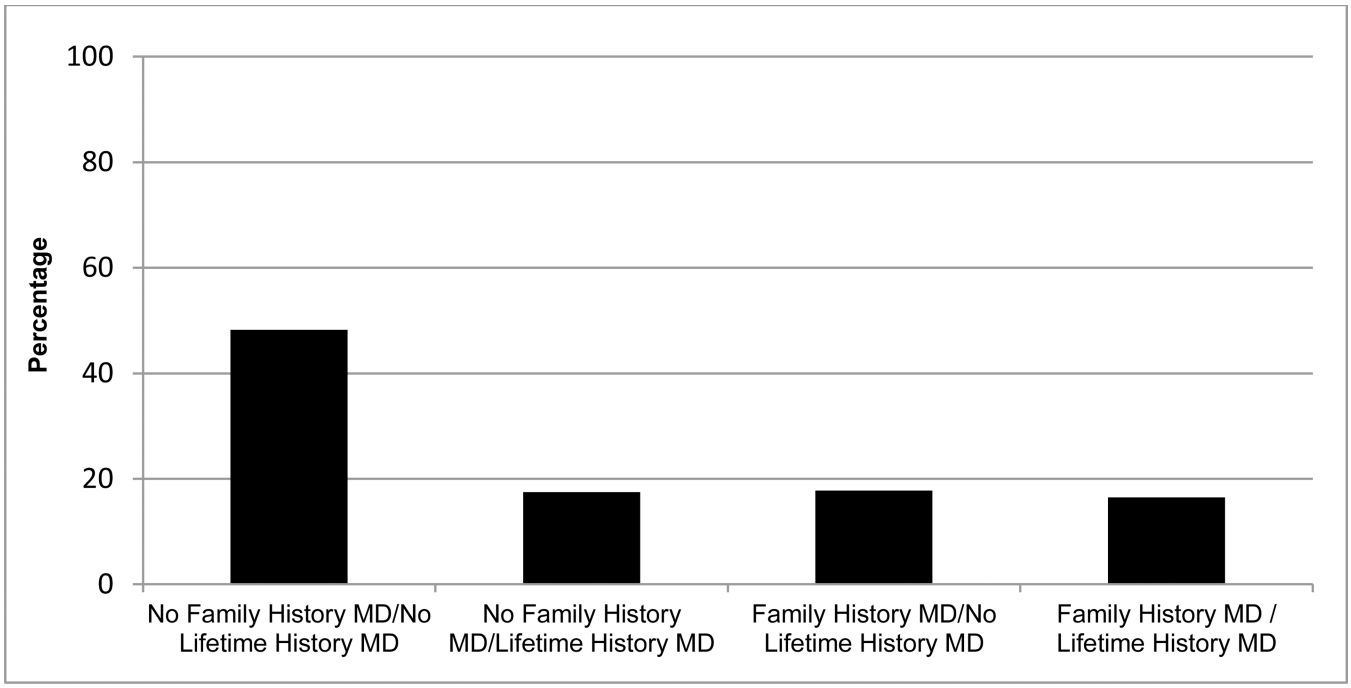

Fig. 1.
Family History of Depression by Lifetime History of Major Depression (MD)

Table 1

Baseline Characteristics by Family History of Major Depression (MD)

	Total N=303	No Family History of MD *n*=199 (65.7%)	Family History of MD *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.

Table 2

Association of Family History of Depression with Major Depression (MD), N=303

	Model A	Model B	Model C
	OR (95% CI)	OR (95% CI)	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

Table 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 (0.93–5.33)	
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)

Table 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) baseline	0.86 (0.73–1.01)	.07	---	NS
Trait Anxiety baseline	1.14 (1.05–1.23)	<.001	1.12 (1.02–1.22)	.02
Chronic Medical Condition(s) baseline	3.51 (1.61–7.68)	.002	---	NS

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