Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN)

J. T. Bromberger[1]*, H. M. Kravitz[2], Y.-F. Chang[3], J. M. Cyranowski[4], C. Brown[4] and K. A. Matthews[5]

[1] *Departments of Epidemiology and Psychiatry, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA*

[2] *Departments of Psychiatry and Preventive Medicine, Rush University Medical Center, Chicago, IL, USA*

[3] *Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA*

[4] *Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA*

[5] *Departments of Psychiatry, Epidemiology, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA*

Background. It is unclear whether risk for major depression during the menopausal transition or immediately thereafter is increased relative to pre-menopause. We aimed to examine whether the odds of experiencing major depression were greater when women were peri- or post-menopausal compared to when they were pre-menopausal, independent of a history of major depression at study entry and annual measures of vasomotor symptoms (VMS), serum levels of, or changes in, estradiol (E2), follicular stimulating hormone (FSH) or testosterone (T) and relevant confounders.

Method. Participants included the 221 African American and Caucasian women, aged 42–52 years, who were pre-menopausal at entry into the Pittsburgh site of a community-based study of menopause, the Study of Women's Health Across the Nation (SWAN). We conducted the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) to assess diagnoses of lifetime, annual and current major depression at baseline and at annual follow-ups. Psychosocial and health factors, and blood samples for assay of reproductive hormones, were obtained annually.

Results. Women were two to four times more likely to experience a major depressive episode (MDE) when they were peri-menopausal or early post-menopausal. Repeated-measures logistic regression analyses showed that the effect of menopausal status was independent of history of major depression and annually measured upsetting life events, psychotropic medication use, VMS and serum levels of or changes in reproductive hormones. History of major depression was a strong predictor of major depression throughout the study.

Conclusions. The risk of major depression is greater for women during and immediately after the menopausal transition than when they are pre-menopausal.

Introduction

In the first half of the twentieth century, the common wisdom based on clinical and anecdotal reports was that menopause conferred an increased risk of depression. Indeed, DSM-II included a mood disorder called Involutional Melancholia, a diagnosis specific to menopause, which was subsequently removed from DSM-III because of the lack of data to support its existence (Weissman, 1979). In the past two decades,

numerous, mostly cross-sectional, studies have reported inconsistent findings, with the majority reporting either no association or an association between the menopausal transition and depressive symptoms (Matthews *et al.* 1990; Hunter, 1992; Kaufert *et al.* 1992; Avis *et al.* 1994; O'Connor *et al.* 1994; Kuh *et al.* 1997; Maarten *et al.* 2002; Freeman *et al.* 2004). Specifically, we have moved from the 'belief' that women were particularly susceptible to depression after the menopausal transition to the current empirically supported conclusion that middle-aged women are at a greater risk for depression during the transition than before (Maarten *et al.* 2002; Freeman *et al.* 2004; Cohen *et al.* 2006; Bromberger *et al.* 2007). Three limitations in the literature to date are important. First, the conclusions

* Address for correspondence: Dr J. T. Bromberger, Ph.D., University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, USA.

(Email: brombergerjt@upmc.edu)

are based primarily on longitudinal studies of depressive symptoms, not depression diagnoses, albeit using standard instruments such as the Center for Epidemiological Studies of Depression Scale (CES-D). Second, the longitudinal data on the risk for depression immediately after the transition (post-menopause) are inconclusive because few studies follow women beyond the final menses for any length of time. Third, it is unclear whether any effects obtained are due to a lifetime history of elevated risk for depression as most studies do not have data with regard to past history.

It is also unclear whether the reproductive hormones that change markedly during the menopausal transition (i.e. gonadotropins and ovarian hormones) are associated with major depression. Increased odds of high depressive symptoms were associated with variability in serum estradiol (E2) and follicle-stimulating hormone (FSH) levels in one study (Freeman et al. 2006) and with declines in serum E2 and large increases in FSH levels in another (Schmidt et al. 2002). Neither study found a significant association between odds of depressive symptoms and absolute hormone levels.

The Study of Women's Health Across the Nation (SWAN) Pittsburgh site provides an opportunity to address three questions: (1) Does the risk for a major depressive episode (MDE) increase during the menopausal transition or immediately thereafter and is the risk independent of a history of major depression at study entry and upsetting events at annual visits? (2) Do annually measured reports of 'frequent' vasomotor symptoms (VMS) or circulating levels of, or changes in, reproductive hormones, E2, FSH or testosterone (T), account for or attenuate the association of menopausal status and major depression? (3) If the risk for an episode during the post-menopause increases, how long is the period of increased risk? We also explored whether risk for an MDE varies by race (African Americans and Caucasians).

Method

Subjects and procedures

This study was conducted among participants in the Pittsburgh site of SWAN, a multi-site community-based cohort investigation of the menopause and aging. Of the 463 women enrolled in the Pittsburgh SWAN, 443 participated in the SWAN ancillary study, the Mental Health Study (MHS). At study entry, about half of the women were pre-menopausal and half were early peri-menopausal. The sample for the current analyses consisted of the 77 African American and 144 Caucasian women, aged 42–52 years, who were pre-menopausal at study entry. We selected this subset to

provide a more conservative estimate of the relative odds of experiencing an MDE during and after the menopausal transition compared to pre-menopause. In the MHS, psychiatric interviews were conducted to obtain information on lifetime and current psychiatric disorders in addition to the extensive data collected as part of the larger SWAN study, which tracks a variety of health parameters in a multi-ethnic community-based sample of women as they transition through menopause.

The sampling procedures and design of the SWAN have been described previously (Sowers et al. 2000). Each site recruited Caucasian women and a sample of a predetermined minority group. Pittsburgh participants were recruited using random digit dialing that was supplemented by a voter's registration list and enrolled 162 African American women and 301 Caucasian women. Eligibility criteria for the SWAN included being aged between 42 and 52 years, having an intact uterus, having had at least one menstrual period and no use of reproductive hormones in the previous 3 months, and self-identifying with one of the site's designated race/ethnic groups. In Pittsburgh, 3540 telephone numbers called were of unknown usability (e.g. busy signals, never home, moved), 2148 contacts yielded unknown cohort eligibility (e.g. incomplete screening interview, refusal to be screened), 12 027 women were ineligible to be screened (e.g. out of age range, no period in past 3 months), and 2604 completed the screening interview. Of the latter, 1050 were eligible and 463 of those eligible entered the SWAN study in Pittsburgh. Participants and those who were eligible but did not participate did not vary by ethnicity, marital status, parity, quality of life, social support, perceived stress or reports of feeling 'blue or depressed' in the prior 2 weeks measured during the screener. There were no significant differences between the 443 MHS participants and the 20 non-participants with respect to sociodemographic factors and CES-D scores ⩾16.

At the beginning of the study all participants signed an informed consent in accordance with the University of Pittsburgh Institutional Review Board guidelines. The women provided extensive health, psychosocial, lifestyle and biologic data at baseline and at annual follow-up visits as part of the larger SWAN study. Height and weight were measured using a common protocol and body mass index (BMI) was calculated (kg/m²). Women were scheduled for venipuncture for assays of reproductive hormones prior to 1000 h on days 2–5 of a spontaneous menstrual cycle occurring within 60 days of recruitment at the baseline visit, and annually thereafter. If a timed sample could not be obtained after two attempts, a random fasting sample was taken within a 90-day

window of the anniversary of the baseline visit. The Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) was administered 2–9 months after the SWAN baseline assessment and annually within 3 months of the annual SWAN visit.

Measures

Assessment of psychiatric disorders

Diagnoses of lifetime and current major depressive disorders were determined from interviews conducted by trained clinicians using the SCID (Spitzer *et al.* 1992). The SCID has been used with many different ethnic groups and field testing has demonstrated its suitability for research purposes; adequate reliability has been demonstrated in numerous studies (Williams *et al.* 1992). All interviewers had extensive clinical experience and at least a master's degree in a relevant field, such as social work or psychology. Interviewers were supervised by the first author (J.T.B.).

Extensive training and qualitative procedures were used to ensure and monitor consistency of SCID administration, symptom elicitation, and diagnostic decision making. These included central training conducted by biometrics, follow-up practice with community volunteers, and ongoing supervision by the principal investigator (J.T.B.). All interviews with study participants were audiotaped. Tapes were used for supervision, to monitor rater drift and to estimate inter-rater reliability. Using a systematic sampling procedure, 24–36 audiotapes were selected and reviewed by all interviewers and the supervisor (J.T.B.) and consultant (H.M.K.) to estimate inter-rater reliability for lifetime diagnoses of selected disorders and subsequent follow-up diagnoses. Inter-rater reliability was very good to excellent for lifetime major depressive disorder ($\kappa = 0.81$) and for major depression in the past year ($\kappa = 0.76-0.89$, reliability at several follow-ups).

A history of major depression was defined as the occurrence of major depression prior to the SWAN baseline assessment. Annual SCIDs assessed MDEs that occurred in the previous year or were current at the baseline or annual assessment.

Participants with current major depression were asked by the interviewer whether they were receiving treatment or had considered seeking help for the distress/depression they were experiencing. If treatment had not been obtained, information regarding resources available in the community was offered. The presence of current suicidal ideation is assessed as part of the Mood Disorders module of the SCID. The SCID *Manual of Operations* includes procedures to

intervene and arrange for emergency referrals if women report suicidal thoughts during the interview.

Independent variables

Menopausal status

Menopausal status was based on menstrual bleeding patterns in the previous 12 months and was categorized as follows: (*a*) pre-menopausal: menstrual period in the past 3 months with no change in regularity in the past 12 months; (*b*) menopausal transition/peri-menopausal: menstrual period in the past 3 months with change in regularity over the previous 12 months or no menstrual period within the past 3 months, but some menstrual bleeding within the past 12 months; (*c*) post-menopausal: no menstrual period within the past 12 months. The classifications are similar to those recommended by the World Health Organization (WHO, 1996). Based on SWAN eligibility requirements, all women were pre-menopausal or early peri-menopausal at baseline. As noted, the women in the current analyses were all pre-menopausal at baseline.

VMS

Data on VMS (hot flashes or night sweats) were obtained with a self-report checklist of symptoms commonly included in studies of the menopause (Neugarten & Kraines, 1965; McKinlay *et al.* 1974; Matthews *et al.* 1994). At each visit, women were asked how often they had experienced hot flashes and night sweats in the past 2 weeks: not at all, 1–5 days, 6–8 days, 9–13 days, daily. We defined frequent VMS as those occurring at least 6 days in the past 2 weeks.

Reproductive hormones

The fasting blood draw was targeted to days 2–5 of the follicular phase of the menstrual cycle in menstruating women and within 90 days of the anniversary of the baseline examination date. If a timed sample could not be obtained after two attempts, a random fasting sample was taken within a 90-day window of the annual visit. Blood was refrigerated within 1–2 h after phlebotomy. All samples were maintained at 4 °C until separated; following centrifugation, the serum was aliquotted, frozen at −80 °C, and shipped on dry ice to the central laboratory, the SWAN Endocrine Laboratory at the University of Michigan, Ann Arbor, where all assays were performed using an ACS-180 automated analyzer (Bayer Diagnostics Corporation, USA). The assays involved a chemiluminescent immunoassay with a solid-phase anti- (Ig)G immunoglobulin conjugated to paramagnetic particles, anti-ligand antibody, and competitive ligand labeled

with dimethylacridinium ester. E2 assays were conducted in duplicate and FSH and T in singlicate. The respective intra- and interassay coefficients of variation were 8.5% and 13.8% for E2, 12.0% and 6.0% for FSH and 9.7% and 11.3% for T (Randolph *et al.* 2005).

Covariates

Demographic factors relevant to the current analyses included baseline marital status, level of educational attainment and age at annual visit. Marital status was categorized as single, married/partnered, or separated/divorced/widowed. Educational attainment was classified in three categories: completed high school or less, high school plus some college, or completed college or more. Race/ethnicity was self-identified based on the participant's response to the question 'What is your primary racial or ethnic group?' At each visit, women completed a checklist of 18 negative life events indicating whether any of these had occurred in the past year and, if so, to rate these according to how upsetting they were: not at all, somewhat, or very upsetting. Women were categorized as having experienced at least one 'very upsetting' event *versus* none/somewhat upsetting event since their last study visit. Psychotropic medication use in the past year and BMI at each visit were also considered for inclusion to account for potential confounding with depression.

Statistical analysis

The analytic sample consisted of 221 pre-menopausal women for whom we had 1698 person-years of observations, 89% of a possible 1913, over the 10 years of assessments. The possible number of observations was based on the number of women expected at each visit and whose data were eligible for inclusion. For example, pre- or peri-menopausal women who were using hormone therapy (HT) at a visit were not considered as possible observations because their data from that visit were excluded, as noted below. However, a missed visit would have been included as a possible person-year of observation.

We used repeated-measures random effects logistic regression models to examine whether the menopausal transition was associated with an increased odds of meeting criteria for an MDE in the past year or currently at each annual visit. The inclusion of a (woman-specific) random intercept allows for the correlation between all observations from a given woman to be modeled and enables us to ascribe a 'woman-specific' interpretation to model parameters. Random effects logistic regression models are rela-

tively robust to missing data and make use of all available data across all visits. Data from women who reported a surgical menopause were censored at that visit forward and data from those who were pre- or peri-menopausal and were using HT were excluded at the visit at which they reported its use because HT use affects bleeding patterns and obfuscates menopausal status. The data from these HT users were included at subsequent visits when they had not been using HT for 1 year and menopausal status could be determined. Data from post-menopausal women using HT were included.

We first used random effects logistic regression analyses to examine the odds of an MDE for each of the variables marital status and education individually, and for the time-dependent variables: upsetting life events, psychotropic medication use, BMI, HT use (during post-menopause), VMS and levels of natural log transformed hormones and change in log hormones from baseline. Variables associated with MDE at $p < 0.10$ in these univariate analyses were candidates for inclusion in the multi-variable models. To examine our first aim, we modeled the odds of having an MDE at any given annual assessment or in the previous year as a function of the participant's menopausal status, age, race, and history of major depression at study entry. Race was included as an independent variable because of the study design. We next added the covariates associated with an MDE at $p < 0.10$ in the univariate analyses to control for their confounding with depression. To address our second aim, we added to the model, individually, frequent VMS and endogenous hormones that were significant at $p < 0.10$ in the univariate analyses. For our third aim, we divided post-menopause into early ($\leqslant 2$ years amenorrheic) and late (> 2 years amenorrheic) post-menopause and conducted analyses as described above. Analyses were run using SAS version 8 (SAS Institute, Inc., USA) and Stata version 7 (StataCorp LP, USA).

Results

All women had at least one peri-menopause visit and 131 had at least one post-menopause visit, with the numbers of visits for each participant during each stage of menopause ranging from 1 to 10. Among those who reached post-menopause during the study, the average number of visits was 8.98 out of 10 possible visits.

Figure 1 shows the total number of actual person-years of observations and the numbers of observations during each menopausal stage for the 221 participants. The total number of MDEs and the number diagnosed during each stage are also shown. It can be seen that there were a total of 146 MDEs diagnosed during 1698
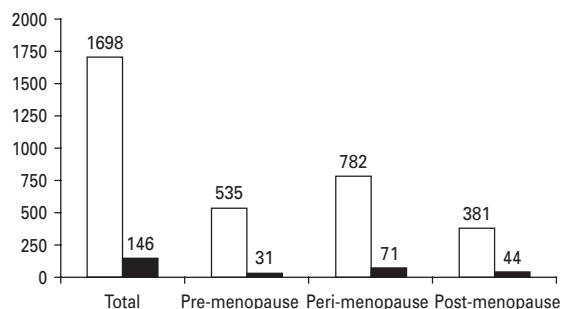
Fig. 1. Number of person-years of observations (visits) for total sample (maximum possible = 1913) and for pre-, peri- and post-menopause visits. □, Number of observations; ■, number of major depressive episodes.

annual visits: 31 occurred during a pre-menopause visit, 71 during a peri-menopause visit, and 44 during a post-menopause visit. Thus, MDEs were diagnosed during 5.8% ($n = 31$) of 535 pre-menopause visits, 9.1% ($n = 71$) of 782 peri-menopause visits, and 9.8% ($n = 44$) of 381 post-menopause visits. Over the 10 years of the study, 69 (23.8%) women had at least one MDE: 33.8% of African Americans and 29.9% of Caucasians. Of these, 15 (21.7%) had three or more episodes: six (14.0%) Caucasian women and nine (34.6%) African American women.

At baseline, women with and without at least one MDE over the study did not differ by race, marital status or education. Nor did they vary by prevalence of frequent VMS, log E2 or log FSH. A significantly higher proportion of women who ever had an MDE had very upsetting life events in the past year, current use of psychotropic medications, a history of major depression and a lower mean log T compared with those who never had an MDE (Table 1). Because reproductive hormone levels have been shown to vary with BMI (Burger *et al.* 1999), analyses for each hormone were also adjusted for BMI. This did not change substantively the association of hormones with MDE.

In the univariate repeated-measures analyses (Table 2), being peri- or post-menopausal, compared to being pre-menopausal, was associated with a significantly greater odds of experiencing an MDE over time. Also significant were age, history of major depression, use of psychotropic medications, very upsetting life events, BMI and frequent VMS. One reproductive hormone, log FSH, showed only a non-significant trend ($p = 0.08$); HT use and race were not significant.

Table 3 presents the results of the three multi-variable models. Model A shows that being peri- or post-menopausal compared to being pre-menopausal was significantly associated with an increased odds of

experiencing an MDE and that the odds ratios (ORs) increased as women progressed through the transition to post-menopause, independent of age, race and history of major depression. Model B shows that peri- and post-menopause remained significantly related to the development of a new MDE independent of covariates. Having a history of major depression at baseline, psychotropic medication use, higher BMI, and very upsetting life events annually were each associated with odds of an MDE. Model C shows that frequent VMS were marginally significant as 95% confidence intervals (CIs) included 1.0 and reduced the ORs for peri- and post-menopause compared with pre-menopause by 4.8% and 10.6% respectively. However, peri- and post-menopause remained significant predictors of MDEs (ORs 1.98 and 3.86 respectively). Log FSH was not significant (data not shown).

When the post-menopause period was divided into early (⩽2 years amenorrheic) and late (>2 years amenorrheic), the multi-variable analyses showed that the early post-menopause posed a significantly greater risk for MDEs than did pre-menopause (OR 5.01, 95% CI 1.66–15.17) whereas late post-menopause did not (OR 2.93, 95% CI 0.92–9.36). Frequent VMS was marginally significant (OR 1.76, 95% CI 0.99–3.13), as was peri-menopause (OR 1.91, 95% CI 0.99–3.72).

Discussion

In longitudinal analyses that spanned 10 years, we found that the odds of experiencing an MDE were significantly greater when women were peri- and post-menopausal than when they were pre-menopausal, independent of a baseline history of major depression and annually measured very upsetting life events, use of psychotropic medications, reproductive hormone characteristics, BMI and frequent VMS. These findings are consistent with previous results in the entire SWAN cohort ($n = 3296$) showing that the odds of high depressive symptoms (CES-D score ⩾16) were significantly greater as women progressed through the menopausal transition (Bromberger *et al.* 2007).

In the past three decades, epidemiological studies of menopause have found no relationship between depressive symptoms and menopausal status (Kaufert *et al.* 1992; Matthews *et al.* 1994; McKinlay *et al.* 1994), or in some cases, higher levels of symptoms during peri-menopause (Hunter, 1992; Avis *et al.* 1994; Kuh *et al.* 1997). These studies were mostly cross-sectional and had numerous methodological limitations, including select or small samples, non-standard measures of depressive symptoms, and inconsistent definitions of menopausal status. The results of more

Table 1. *Baseline characteristics of women who never or ever had an episode of major depression across 10 years*

	MDE: never (n = 152)	MDE: ever (n = 69)	p value
Age (years), mean (S.D.)	45.7 (92.6)	45.1 (2.3)	0.10
Ethnicity, *n* (%)			
African American	51 (33.6)	26 (37.7)	0.55
Caucasian	101 (66.5)	43 (62.3)	
Married, *n* (%)			
No	44 (29.0)	24 (34.8)	0.38
Yes	108 (71.1)	45 (65.2)	
Education, *n* (%)			
⩽High school	31 (20.4)	17 (24.6)	0.72
Some college	55 (36.2)	22 (31.9)	
⩾College	66 (43.4)	30 (43.5)	
Very upsetting life events, *n* (%)			
No	91 (59.9)	21 (30.4)	<0.0001
Yes	61 (40.1)	48 (69.6)	
Psychotropic medication use, *n* (%)			
No	142 (93.4)	54 (78.3)	0.001
Yes	10 (6.6)	15 (21.7)	
History of MDE, *n* (%)			
No	113 (74.3)	34 (49.3)	<0.0001
Yes	39 (25.7)	35 (50.7)	
Frequent VMS (⩾6 days/past 2 weeks)[a], *n* (%)			
No	139 (91.4)	59 (85.5)	0.13
Yes	12 (7.9)	10 (14.5)	
BMI (kg/m²), mean (S.D.)	28.1 (5.7)	28.9 (7.6)	0.35
Hormones, mean (S.D.)[b]			
log T	3.7 (0.5)	3.6 (0.5)	0.04
log FSH	2.7 (0.5)	2.8 (0.7)	0.75
log E2	4.2 (0.5)	4.1 (0.7)	0.51

MDE, Major depressive episode; VMS, vasomotor symptoms; BMI, body mass index; T, testosterone; FSH, follicle-stimulating hormone; E2, estradiol; S.D., standard deviation.

[a] One woman was missing complete data on VMS.

[b] The results for hormones were similar when adjusted for BMI.

recent longitudinal studies (Maarten *et al.* 2002; Freeman *et al.* 2004; Cohen *et al.* 2006) have more consistently found that the odds of high depressive symptoms were greater during peri-menopause than pre-menopause. Compared to the earlier studies, these recent studies had larger or more diverse samples, longer and more frequent follow-up, more consistent, careful definitions of menopausal status and used sophisticated analyses that utilized fully the longitudinal data. With one exception (Maarten *et al.* 2002), these studies did not find an increased risk for depressive symptoms post-menopause. The null findings may have been due to insufficient power because of the relatively small numbers of women followed through post-menopause. For example, the Penn Ovarian Aging (POA) study (Freeman *et al.* 2004) reported an increase in depressive symptoms in the peri-menopause and a subsequent decline post-menopause over 4 years of follow-up. However, in that study 73% of the 332 participants remained pre-menopausal over the 4 years of follow-up.

Three longitudinal studies of menopause have assessed depressive disorders (Freeman *et al.* 2004; Schmidt *et al.* 2004; Cohen *et al.* 2006). The POA study found that depressive disorders were not more likely to occur during the menopausal transition than pre-menopausal (Freeman *et al.* 2004). However, the study was limited by having only 4 years of data collection, only 3% of the sample had reached post-menopause, and the assessment of MDE covered only the past month, making the numbers for post-menopause and MDE too small to determine statistical significance.

Table 2. *Univariate repeated-measures associations of baseline and annual measures with odds of a major depressive episode (MDE) from baseline to visit 9*

	OR	95% CI	*p* value
Baseline characteristics			
Age	1.10	1.03–1.17	0.005
African American	1.62	0.76–3.46	0.21
History of major depressive disorder	4.51	2.20–9.25	<0.0001
Annual measures			
Menopausal status (referent category: pre-menopause)			
Peri-menopause	2.17	1.23–3.81	0.007
Post-menopause	3.43	1.79–6.56	<0.0001
HT use	1.20	0.38–3.73	0.76
VMS ⩾6 days/past 2 weeks	2.50	1.48–4.22	0.001
BMI	1.08	1.02–1.13	0.004
log E2[a]	0.82	0.63–1.06	0.13
log T[a]	1.04	0.62–1.74	0.90
log FSH[a]	1.25	0.97–1.62	0.08
Change in E2 from baseline[b]	1.00	1.00–1.00	0.57
Change in T from baseline[b]	1.01	1.00–1.03	0.10
Change in FSH from baseline[b]	1.00	0.99–1.01	0.90

HT, Hormone therapy; VMS, vasomotor symptoms; BMI, body mass index; E2, estradiol; T, testosterone; FSH, follicle-stimulating hormone; OR, odds ratio; CI, confidence interval.

[a] The results for hormones were similar when adjusted for BMI.

[b] Adjusted for baseline value.

Table 3. *Results of random effects logistic regression analyses for odds of a major depressive episode (MDE) from baseline to visit 9 by menopausal status*

	OR (95% CI)		
Variable	Model A	Model B	Model C
Age	0.99 (0.90–1.09)	0.96 (0.86–1.06)	0.95 (0.86–1.05)
Menopausal status (referent category: pre-menopause)			
Peri-menopause	2.20 (1.17–4.16)	2.08 (1.06–4.08)	1.98 (1.00–3.92)
Post-menopause	3.57 (1.35–9.39)	4.32 (1.54–12.13)	3.86 (1.36–10.92)
African American	1.96 (0.96–3.97)	1.64 (0.82–3.29)	1.56 (0.78–3.15)
History of major depression at baseline		3.02 (1.57–5.80)	2.98 (1.55–5.72)
Psychotropic medication use		4.71 (2.65–8.38)	4.55 (2.55–8.09)
Very upsetting life event		2.66 (1.59–4.47)	2.62 (1.56–4.40)
BMI continuous		1.04 (0.99–1.09)	1.04 (1.00–1.09)
Frequent VMS (⩾6 days/past 2 weeks)			1.76 (1.00–1.09)

BMI, Body mass index; VMS, vasomotor symptoms.

Model A: adjusted for age and race. Model B: addition of history of major depression at baseline, annual psychotropic medication, annual very upsetting life events, and BMI. Model C: final model with addition of annual frequent VMS.

The POA study and the Harvard Study of Moods and Cycles reported an increased risk of first-onset depressive disorder during peri-menopause compared to pre-menopause over 8 years (Cohen *et al.* 2006). Importantly, neither study included women who had ceased menstruating and both examined a only subset of women.

Our findings of an increased risk of MDE during post-menopause and particularly during the first 2 years after the final menstrual period are similar to those reported in a small longitudinal study (5 years) that followed 29 regularly cycling women in their forties through 1 year after their last menses (Schmidt *et al.* 2004). In that study, detailed measures of

menstrual cycles, symptoms and depression, and also plasma FSH, were collected every 3–6 months and the SCID was conducted to obtain data on episodes of minor and major depression. The results indicated that women were significantly more likely to experience an episode of clinical depression (primarily minor depression) during the year before or after their final menstrual period than when they were pre-menopausal.

In our sample, the increased vulnerability to an MDE during and after the menopausal transition was not accounted for by frequent VMS or by levels of or changes in reproductive hormones. Lack of a statistically significant association between frequent VMS and MDE may be due to the short time-frame over which we assessed VMS (i.e. the past 2 weeks). It is possible that a measure of VMS frequency over a longer period of time may have been more strongly related to major depression onset in the multivariate analysis and may have attenuated the association between menopausal status and MDE, particularly because VMS can wax and wane across a period of time. Nonetheless, future studies should continue to examine the role of VMS in the development of MDEs.

We found no significant associations between any reproductive hormone and MDEs, which is consistent with the literature showing no direct associations between depression and serum E2 levels (Schmidt *et al.* 2002). However, single annual hormone samples have limited ability to provide information about the underlying hormonal dynamics that occur during the menopausal transition. Reproductive hormone secretion, especially that of E2, is subject to great variability during the menopausal transition. It has been hypothesized that the fluctuations in reproductive hormones in susceptible women pose a risk for depression. However, we found no association between change or variability in hormones over time with major depression. By contrast, the POA study of first-onset depression did report an association between the variability of E2 and FSH measured at two consecutive monthly assessments with high depressive symptoms or depressive disorder (Freeman *et al.* 2006). Our null result for T was in contrast to our previously reported associations between high depressive symptom scores (CES-D $\geqslant 16$) and T levels and changes in these over the first 8 years of the SWAN in the entire cohort. The conflicting findings may be due to the relatively small sample of women in the current analysis ($n = 221$) compared to the SWAN cohort of more than 3000 women. Perhaps T is more likely to be associated with the level of depressive symptoms than with the syndromal cluster represented by an MDE.

It is noteworthy that the odds of an MDE were nearly tripled in those with a history of major depression at baseline or at least one very upsetting event at the annual visits (OR 2.83 and 2.93 respectively), indicating that, in addition to and independent of menopausal status, lifetime depression history and the experience of recent life stressors made significant contributions to the risk of an MDE. Both factors are known to be consistently related to major depression (Kendler & Gardner, 2010) but prior studies of menopause have not assessed their importance relative to the menopausal transition.

In addition to the limitations concerning the measures of VMS and hormones described above, other limitations of the current report are important. Because of the small size of the sample, we were limited in our ability to examine racial/ethnic differences in major depression according to menopausal status and/or history of major depression at study entry. However, in a future paper encompassing a longer period of follow-up we will focus on the characteristics and subgroups of midlife women who may be particularly vulnerable to an MDE. Furthermore, structured interviews, although they improve diagnostic reliability and validity, are subject to subjective recall and interpretation of symptoms.

Finally, we do not know the potential bias introduced by the absence of data on women whom we could not contact or who refused to complete the initial telephone screener. If this group of women included more who were depressed at the time of contact than did the group who participated, there would probably be more cases of major depression during the study. Because our sample is not large enough to determine whether women with a prior history of depression would be more likely to experience a subsequent MDE when they were peri- or post-menopausal than when they were pre-menopausal, we cannot know how our current findings would be affected.

The current study is unique in its ability to assess major depression annually in midlife African American and Caucasian women as they transitioned through peri-menopause and post-menopause. We used a standard semi-structured interview to assess MDEs during the time between visits and currently, which allowed us to account for episodes for the entire 10-year period. The current findings confirm the greater risk for MDEs during the menopausal transition than before. Although our data also indicate that the years immediately after the transition are a high-risk period for MDEs, these findings warrant confirmation when all SWAN participants become late post-menopausal. Many questions remain regarding the factors that contribute to the elevated risk of MDEs during the menopausal transition and after, including the role of reproductive hormone changes and the

characteristics of the subgroup of vulnerable women. When all women enrolled in our study complete the menopausal transition, we will be able to address these important questions in further detail.

Declaration of Interest

None.

References

Avis NE, Brambilla D, McKinlay SM, Vass K (1994). A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. *Annals of Epidemiology* **4**, 214–220.

Bromberger JT, Matthews KA, Schott LL, Brockwell S, Avis N, Kravitz HM, Everson-Rose SA, Gold EB, Sowers M, Randolph Jr. J (2007). Depressive symptoms during the menopausal transition: the Study of Women's Health Across the Nation (SWAN). *Journal of Affective Disorders* **103**, 267–272.

Burger HG, Dudley EC, Hopper JL, Groome N, Guthrie JR, Green A, Dennerstein L (1999). Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. *Journal of Clinical Endocrinology and Metabolism* **84**, 4025–4030.

Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL (2006). Risk for new onset of depression during the menopausal transition. The Harvard Study of Moods and Cycles. *Archives of General Psychiatry* **63**, 385–390.

Freeman EW, Sammel MD, Lin H, Nelson DB (2006). Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Archives of General Psychiatry* **63**, 375–382.

Freeman EW, Sammel MD, Lui L, Gracia CR, Nelson DB, Hollander L (2004). Hormones and menopausal status as predictors of depression in women in transition to menopause. *Archives of General Psychiatry* **61**, 62–70.

Hunter M (1992). The southeast England longitudinal study of the climacteric and postmenopause. *Maturitas* **14**, 117–126.

Kaufert PA, Gilbert P, Tate R (1992). The Manitoba Project: a re-examination of the link between menopause and depression. *Maturitas* **114**, 143–155.

Kendler KS, Gardner CO (2010). Dependent stressful life events and prior depressive episodes in the prediction of major depression. *Archives of General Psychiatry* **67**, 1120–1127.

Kuh DL, Wadsworth M, Hardy R (1997). Women's health in midlife: the influence of the menopause, social factors and health in earlier life. *British Journal of Obstetrics and Gynaecology* **104**, 923–933.

Maarten LW, Knottnerus JA, Pop VJ (2002). Menopausal transition and increased depressive symptomatology: a community based prospective study. *Maturitas* **42**, 195–200.

Matthews KA, Bromberger JT, Egland G (1990). Behavioral antecedents and consequences of the menopause. In *The Menopause* (ed. S. G. Korenman), pp. 1–15. Serono Symposia: Norwell, MA.

Matthews KA, Wing RR, Kuller LH, Leilahn EN, Plantinga P (1994). Influence of the perimenopause on cardiovascular risk factors and symptoms of middle-aged healthy women. *Archives of Internal Medicine* **20**, 2349–2355.

McKinlay SM, Jefferys M (1974). The menopausal syndrome. *British Journal of Preventive and Social Medicine* **28**, 108–115.

Neugarten BL, Kraines RJ (1965). 'Menopausal symptoms' in women of various ages. *Psychosomatic Medicine* **27**, 266–273.

O'Connor VM, Del Mar CB, Sheehan M, Siskind V, Fox-Young S, Cragg C (1994). Do psychosocial factors

contribute more to symptom reporting by middle-aged women than hormonal status? *Maturitas* **20**, 63–69.

Randolph JF, Sowers MF, Bondarenko I, Gold EB, Greendale GA, Bromberger JT, Brockwell SE, Matthews KA (2005). The relationship change in reproductive hormones and vasomotor symptoms during the menopausal transition. *Journal of Clinical Endocrinology and Metabolism* **90**, 6106–6112.

Schmidt PJ, Murphy JH, Haq N, Danaceau MA, St Clair LS (2002). Basal plasma hormones levels in depressed perimenopausal women. *Psychoneuroendocrinology* **27**, 907–920.

Schmidt PJ, Nazli H, Rubinow DR (2004). A longitudinal evaluation of the relationship between reproductive status and mood in perimenopausal women. *American Journal of Psychiatry* **161**, 2238–2244.

Sowers MF, Crawford S, Sternfeld B, Morganstein D, Gold EB, Greendale GA, Evans D, Neer R, Matthews KA, Sherman S, Lo A, Weiss G, Kelsey J (2000).

SWAN: a multi-center, multi-ethnic, community-based cohort study of women and the menopause. In *Menopause: Biology and Pathobiology* (ed. R. Lobo, J. Kelsey and R. Marcus), pp. 175–178. Academic Press: San Diego, CA.

Spitzer RL, William JB, Gibbon M, First MB (1992). The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Archives of General Psychiatry* **49**, 624–629.

Weissman M (1979). The myth of involutional melancholia. *Journal of the American Medical Association* **242**, 742–744.

WHO (1996). *Research on the Menopause in the 1990s*. WHO Technical Report Series: 866. World Health Organization: Geneva, Switzerland.

Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, Howes MJ, Kane J, Pope Jr. HG, Rounsaville B (1992). The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. *Archives of General Psychiatry* **49**, 630–636.