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Does childhood maltreatment or current stress contribute to increased risk for major depression during the menopause transition?

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Abstract

Background.—The menopausal transition (MT) poses an increased risk for major depression (MD), but not for all women. Current and past stress are toxic risk factors for depression throughout life. The MT may be a time of increased sensitivity to stress, especially among women with a lifetime history of major depressive disorder (MDD). We evaluated whether women who experienced childhood maltreatment (CM) or current stressful events or ongoing problems were at increased risk for MD during the MT.

Methods.—At the Pittsburgh site of the Study of Women's Health Across the Nation, 333 midlife women were interviewed approximately annually over 15 years with the Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders and provided health and psychosocial data including the Childhood Trauma Questionnaire. Repeated measures logistic regression analyses were conducted separately for women with and without lifetime MDD at study entry.

Results.—Among women with lifetime MDD, CM, but not current stress, interacted with menopausal status to increase risk for MD during postmenopause (ORs ranged from 2.71 to 8.04). All stressors were associated with increased odds of MD. Among women without lifetime MDD, current stress was related to risk for MD, but the effect did not vary by menopausal status.

Conclusions.—Women with MDD prior to midlife and who experienced CM were at greatest risk for MD after the MT. Women without prior MDD were at increased risk for MD during peri- and postmenopause. Healthcare providers should monitor women at risk for MD even after the MT.

The menopause transition (MT) is a period of vulnerability to unipolar major depression (Bromberger et al., 2011; 2015; Freeman et al., 2004; Soares, 2017; see Maki et al., 2019

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for a review). The prevalence of major depressive episodes (MDEs) during the transition is 2–4 times higher than prior to it (Bromberger et al., 2011). Yet, most menopausal women do not report levels of depressive symptoms or impairment sufficient to be diagnosed with a MDE. Although it has been hypothesized that alterations of reproductive hormones during the MT account for susceptibility to a MDE, studies indicate this is not the case (Schmidt et al., 2002). It may be that vulnerable women are sensitive to the “normal” changes in the hormonal milieu that occur during the MT (Soares, 2017). The question then is: what renders a woman vulnerable to depression during the MT? This is an important question as depression can be a debilitating illness.

Many psychosocial, health, and life course factors are associated with risk for depression in women during their lives. A particularly toxic risk factor for depression throughout the life span is stress, in the form of discrete life events or chronic and ongoing negative situations (Kessler, 2003; Harkness, 2008). Hormonal changes of the MT are hypothesized to increase a woman’s sensitivity to stress (Parry, 2016), suggesting that exposure to stressful events during the MT may confer increased vulnerability to depression. We extend this work by examining longitudinally whether community women exposed to stressful events would be more likely to experience MDE during the MT or early postmenopause than during premenopause.

The stress literature has focused primarily on stressors proximate or concurrent with the MT. Nevertheless, numerous studies have shown a relationship between childhood maltreatment (CM), such as child abuse or neglect, and later mental health (Comjis et al., 2013; Wise et al., 2001), and one study reported that CM was associated with risk of depression during the MT (Epperson et al., (2017). Therefore, we also examined the impact of CM on risk for depression during the MT and compared whether current or childhood stressors would be more likely to be associated with midlife depression. We also evaluated whether CM would predict depression particularly when other stressors in adulthood are occurring (Comijs et al., 2007; Korkeila et al., 2005). Such information about the contribution of past and current psychosocial exposures to the occurrence of clinical depression during the MT may help to identify vulnerable women.

Risk for a MDE in midlife is much greater for women with a MDD history which is the most robust predictor of later depression (Bromberger et al, 2011) and must be accounted for when assessing MDE risk factors in a group of women with and without prior MDD. Furthermore, we previously found in the current sample that at study entry women with prior MDD compared to women without a MDD history, reported fewer close friends, more health problems, a history of psychiatric disorders other than MDD, and greater trait anxiety (Bromberger et al., 2015). Therefore, because exposures and characteristics may vary in women with a history of MDD and those without such a history, we addressed the study objectives separately for the two groups.

The objectives of the present study were three-fold. The primary aim was to test the hypothesis that women who experienced current (stressful events that occurred within the previous year, chronic events that lasted 12 months or longer) or past stressful circumstances, i.e., CM, would be more likely to experience MDE during the MT or

early postmenopause than during premenopause. Second, we assessed the relative effect of current versus childhood stressors. Third, we evaluated whether CM would predict MDE particularly when other stressors in adulthood are occurring.

METHODS

Sample and procedures

The current report is based on data collected at the Pittsburgh site of a large multi-site, multi-racial/-ethnic community-based study of the MT and aging, the Study of Women's Health Across the Nation (SWAN), and an ancillary study, the Mental Health Study (MHS). In SWAN, each site recruited White women and a predetermined minority group (Black at the Pittsburgh site). Eligibility criteria included being aged 42–52 years, having an intact uterus and at least one ovary, having had at least one menstrual period, no use of reproductive hormones, and not pregnant or breastfeeding/lactating in the previous 3 months. The Pittsburgh site enrolled 162 Black and 301 White women using random digit dialing and a voter's registration list. Of these 463 women enrolled, 443 participated in the SWAN ancillary MHS, which began concurrent with the SWAN parent study in 1996. The 443 MHS participants (95.7%) and the 20 non-participants (4.3%) did not differ significantly on sociodemographic variables or percentage with the Center of Epidemiological Studies Depression Scale (CES-D: Radloff, 1977) scores ≥16, which has been typically used to distinguish potentially clinically significant depressive symptoms (Boyd et al, 1982). Written informed consent was obtained from all participants in accordance with the University of Pittsburgh Institutional Review Board guidelines.

Women were evaluated at study entry and approximately annually with similar protocols. Women provided extensive health, psychosocial, lifestyle, and psychological symptom and biologic data for the Core SWAN. As part of the MHS, the Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) was conducted 2 to 9 months after the SWAN baseline assessment and within three months of each follow-up core SWAN visit. The current analyses used the Core SWAN and the MHS psychiatric diagnostic data collected at baseline and at annual follow-up assessments. Because the current analyses were based on unipolar depression, 14 women with a diagnosis of bipolar disorder prior to study entry or during the course of SWAN MHS were excluded, as were 27 women with only 1 SCID assessment, for a total of 402 participants. Of these 402 participants, the analytic sample is comprised of 333 women who also completed the Childhood Trauma Questionnaire (CTQ).

Measures

With the exception of information about CM (obtained at follow-up 7 or 8 and 15) and the baseline data for race and paying for basics, we used time-varying independent and covariate variables from baseline through visit 12.

Assessment of Psychiatric Disorders—The SCID (Spitzer et al., 1992) is a semi-structured psychiatric interview for which we (Bromberger et al., 2011) and others (Williams et al., 1992) have found substantial reliability for depressive disorders (kappa=.81-.82).

SCID interviews for diagnoses of lifetime MDD (APA, DSM-IV, 2005), and other psychiatric disorders were conducted at study entry by trained mental health clinicians. Current and past year disorders occurring in the intervening year were diagnosed at each follow-up assessment.

Measures of Stress—Stressful events experienced in the previous 12 months were assessed with a checklist of 18 life events from the Psychiatric Epidemiology Research Interview scale, (Bromberger et al, 2011) modified to include events relevant to midlife women or those living in low socioeconomic environments. Women checked the life event(s) they experienced since the last study visit and rated them according to how upsetting each was with 4-level responses: not at all, somewhat, or very upsetting. Life events rated as "very upsetting" were totaled and categorized as one or more very upsetting event versus none (Bromberger et al., 2011).

Ongoing problems were assessed using a questionnaire (Bromberger and Matthews, 1996) asking participants whether they had experienced any of the following chronic problems for 12 months or longer: your own health problems, health problems with partner or child, substance abuse in a family member, work difficulties, financial strain, housing problems, problem with a close relationship, helping sick family member or friend on a regular basis, any other ongoing problem An endorsed problem was rated by participants as not upsetting, somewhat upsetting, or very upsetting. Ongoing problems were coded as at least one very upsetting ongoing problem versus none.

Childhood maltreatment was determined by the Childhood Trauma Questionnaire (CTQ: Bernstein et al., 2003) which was administered at the 7^{th} or 8^{th} visit and in visit 15. The CTQ is a 28-item self-report instrument that assesses five types of maltreatment experienced during childhood. Participants rate items from each of five subscales (emotional abuse, physical abuse, emotional neglect, physical neglect, and sexual abuse) from 1 (never) to 5 (very often true); subscale scores range from 5–25. Validated clinical cutoff points have sensitivity and specificity at 0.85 relative to clinical interview (therapists' ratings of CM) (Bernstein et al., 2003; Walker et al., 1999). Scores for each subscale that were at or above these thresholds were classified as positive. If subscale scores were all below cutoff points, an individual was classified as not exposed to abuse or neglect. The CTQ has strong test-retest reliability and convergent validity with clinical interview and therapist ratings (Bernstein et al., 1994). Responses from SWAN participants showed that the CTQ had strong internal consistency, Cronbach's α ranged from 0.80–0.94 for the subscales in this investigation. Intraclass correlations across visits 7 or 8 and 15 for the 241 Pittsburgh women who had completed the questionnaire at both time points were 0.82 for emotional, 0.85 for physical, and 0.86 for sexual abuse.

Menopausal status was based on menstrual bleeding patterns in the previous 12 months. Similar to World Health Organization recommended classifications (World Health Organization, 1996), "premenopause" was defined as no change in menstrual bleeding regularity and "perimenopause" as menses in the preceding 3 months with an increase in bleeding irregularity or no menses in the past 3–11 months. "Postmenopause" was defined as no menstrual period for at least 12 months or a hysterectomy and bilateral salpingectomy

(BSO). Eight women had a hysterectomy without BSO. All hysterectomies took place before women had a final menstrual period.

Covariates included from baseline, race and paying for basics (very or somewhat hard versus not very hard, indicating the presence/absence of financial strain) and lifetime MDD at study entry in analyses of the total sample. Time-varying covariates were self-reports of use of medications for nervous conditions in the past 3 months, vasomotor symptoms *(VMS*; hot flashes/flushes, cold sweats, and/or night sweats*)* in the past 2 weeks, and hormone therapy use at least two times per week for the last month.

Statistical analyses

Distributions of baseline variables were examined using means (standard deviations) and crosstabs as appropriate and of time-varying variables including menopausal status at each visit. We also examined the distribution of MDEs for each stressor according to menopausal visit status. We tested interactions between stressors and lifetime history of MDD (yes/no) at study entry among all women to determine whether the effect of stressors on occurrence of MDEs differed significantly according to this history. Subsequent analyses were conducted on the entire sample and also stratified by history of MDD at study entry. As noted above, we report here primarily the results for the two separate samples. If a woman reported having had a hysterectomy without an oophorectomy, her data were censored from that visit forward. Women who had an oophorectomy were retained in the analyses and were grouped with the postmenopausal women at the relevant follow-up(s). Bivariate associations of each independent variable (stressor) and then each potential covariate with MDE from follow-up 1 through follow-up 12 were conducted. Covariates that were significant at a $p<0.10$ were included in initial multivariable analyses, General Estimating Equations (GEE models). In the multivariable GEE model building a covariate with a p-value >0.10, was removed and the model was run again in order to identify main effects in the most parsimonious model as the sample was relatively small for testing subsequent interactions. Repeated measures logistic regression GEEs were conducted to test the hypothesized interactions between a stressor and menopausal status. These analyses included covariates from the initial repeated logistic regression models and the interaction of age and stressor to account for the potential variation of the effect of the stressor on odds of a MDE by age. Significant interactions of menopausal status and each stressor were followed by analyses of the stressor in separate models for premenopause, perimenopause and postmenopause/BSO women with relevant covariates. The final analyses examined the relative importance of a current stressor and a CM type by including both together as main effects and the interaction of the two. The latter was considered to determine if the multiplicative effect of a current and early childhood stressor was greater than each individually.

RESULTS

Characteristics of sample

Table 1 shows the baseline and CM characteristics of the total sample and those without (n=222) and with (n=111) lifetime MDD at study entry. Those who had a previous MDD had a higher proportion of women with an elevated CES-D (score > 16: 41.4%), a very hard

time paying for basics, a chronic ongoing problem, a very upsetting life event in the past year, and all types of CM. Over the course of the study a total of 129 women met criteria for a new MDE: 58 (26.1%) among women without lifetime MDD and 71 (64%) with lifetime MDD. Multiple episodes were experienced by 41.4% of the former and 71.8% of the latter. (See Supplement Table 1 for details.)

Initial statistical tests of the interactions between stressors and lifetime history of MDD (yes/no) at study entry on odds of a MDE over the study visits among all women were all nonsignificant. These data indicate that stressors did not vary significantly in their association with MDE according to lifetime MDD history.

The unadjusted distribution of visits with a MDE by stressor and menopausal status within each group showed that among women without lifetime MDD at baseline, those with a chronic problem had a higher prevalence of MDE when they were perimenopausal (16.7%) or postmenopausal (19.0%) than premenopausal (4.35%). This was also the case for women reporting physical abuse: 4.1% had MDE when premenopausal, 10.5% when perimenopausal and 11.4% when postmenopausal. There were no cases of MDE during premenopause among women with emotional abuse, sexual abuse or emotional or physical neglect.

Among women with lifetime MDD at baseline, those with a chronic problem, had a higher prevalence of an MDE during perimenopausal (33.3%) and postmenopausal visits (38.5%) than during premenopausal visits (21.4%). Among women with CM, the prevalence of MDEs during premenopause and perimenopause were similar for women with emotional (11/53, 20.8%; 35/155, 22.6%, respectively) or physical abuse (10/37, 27.0%; 49/67, 29.3%, respectively) and emotional (6/24, 25.0%; 15/49, 30.6%, respectively) or physical neglect (9/40, 22.5%; 25/96, 26.0, respectively). Prevalence of MDEs during postmenopause was much higher for these types of maltreatments (emotional abuse: 76/242, 31.4%; physical abuse: 70/185, 37.8%; emotional neglect: 35/58, 60.3%; physical neglect: 53/134, 39.6%). For sexual abuse, the prevalence of MDs was similar during all 3 stages of the transition (premenopause: 13/40, 32.5%; perimenopause: 40/148, 27.0%; postmenopause: 48/158, 30.4%).

Influence of stress or menopausal status on risk for a MDE among women with and without lifetime history of MDD at study entry

Table 2 displays the results of the initial main effects models adjusted for relevant covariates (see footnotes). In the group of women without lifetime MDD at baseline, a stressful chronic ongoing problem and at least one stressful event in midlife, each quadrupled or more than tripled the odds of MDE in separate analyses. None of the CM types was significant. In general, their odds of a MDE were greater when they were perimenopausal and postmenopausal compared to when they were premenopausal.

In contrast, among women with lifetime MDD at baseline, all seven stressors were significant predictors, at least doubling the odds of a MDE during the study. However, when compared to premenopause, perimenopause status was not significant and postmenopause

status was significant only in the analyses with emotional or physical neglect in childhood (ORs=2.63 and 2.19, respectively.)

Varying impact of stress by menopause status.

Among women without lifetime MDD at baseline, there were no significant interactions between a stressor and menopausal status. However, interaction analyses of status with emotional or sexual abuse or with emotional or physical neglect could not be conducted due to zero events in some cells. Among women with lifetime MDD at baseline, three interactions with menopausal status were significant: emotional abuse (p=.022), emotional neglect (p=.002) and physical neglect (p=.038). Follow-up analyses showed that each of these three types of maltreatments more than doubled the odds of a MDE when women were postmenopausal/BSO but not when they were pre- or perimenopausal (Table 3).

Relative effects of current versus childhood stressor

A series of analyses included various combinations of a current midlife stressor (stressful event or stressful chronic ongoing problem) with a type of CM. Among women without lifetime MDD, a current stressor was consistently significant, tripling or quadrupling the odds of MDE (p's <.01) whereas no type of CM was significant possibly due to small numbers in CM cells. Additionally, compared to premenopause, perimenopause consistently significantly increased the odds of an MDE by approximately four times. (See supplement Table 2a)

Among women with lifetime MDD at baseline, in all analyses, a current stressor was significant, more than doubling or tripling the odds of MDE and with the exception of emotional abuse, all types of CM were also significant. None of the analyses that assessed the interaction of a current stressor with a type of CM was significant, suggesting the effects of current adult stressors and specific types of childhood abuse/neglect were additive. (See supplement Table 2b)

DISCUSSION

We addressed three sets of hypotheses in a community sample of black and white women. First, we evaluated the hypothesis that current and childhood stressors would each interact with menopausal status to increase risk for MDE across 15 years of approximately annually collected data. Results showed that among the women with lifetime MDD at study entry, the experience of CM significantly increased the risk for MDE during the postmenopause, not during the MT as we had hypothesized. Specifically, in this group, women reporting childhood emotional abuse, emotional neglect, or physical neglect had a significantly greater likelihood of experiencing a MDE when postmenopausal than when pre- or perimenopausal, accounting for age, race/ethnicity, and when relevant, financial strain, psychotropic medications, vasomotor symptoms, or hormone use. These unexpected results indicate that among the SWAN midlife women with a history of MDD, the perturbations of the MT had no greater effect on risk for MDE for women with childhood emotional or physical neglect or emotional abuse than those without such experiences. Rather, these adverse childhood exposures increased risk for recurrent MDE after the MT

(i.e., postmenopause) and into older age. This suggests that early CM may be a particularly toxic risk factor for MDE during older ages in women who have experienced MDD in young or middle adulthood prior to the MT. Among women without lifetime MDD, adult stress leads to increased MDE risk irrespective of MT stage.

Our results do not support the hypothesis that the MT increases sensitivity to current or past stressful experiences and, thereby, increases risk for depression during the MT. Limited evidence for the hypothesis was reported by Epperson and colleagues (Epperson et al., 2017) who found that midlife women with two or more adverse childhood experiences (included abuse, neglect and household dysfunction) were more than twice as likely as those without such exposures to have incident MDE during the MT. However, current stressors were not assessed and the analyses were based on a subsample of premenopausal women (n=232) followed for 14 years who had not reported a history of depression prior to study entry or who had prior depression and depression during follow up. Women with prior depression but no episodes during follow up were excluded. This approach limited conclusions about the relative impact of CM on women with or without MDD prior to the MT and the effect of concurrent stress on risk for depression.

Results for the association between various types of CM and later depression are consistent with previous studies (Bifulco et al., 1998; Danese et al., 2009; Hovens et al., 2010), demonstrating the long lasting effects on mental health throughout an individual's life (Jones et al., 2018; Kendler et al., 2000; Kessler, 1997; Wise et al., 2001) but only among women with earlier MDD. Indeed, CM is considered one of the strongest risk factors for major depression (Lancet; Li et al., 2016, Opel et al., 2019). We found that among women with lifetime MDD, emotional abuse, physical abuse, sexual abuse, emotional or physical neglect individually increased the odds of MDE. However, among women without lifetime MDD, as noted above, no type of CM was a risk factor for incident MDE.

We also found that when a current stressor and a type of CM were simultaneously included in analyses as main effects, only the current stressor was a significant predictor of MDE among women without lifetime MDD. Among women with lifetime MDD, both current stressors and CM types were significant. These findings are consistent with data from the National Comorbidity Survey Replication I (Green et al., 2010) and II (McLaughlin et al., 2010) which showed that childhood physical and sexual abuse and neglect were more strongly associated with early MDE onsets than later ones. A study of participants in the Netherlands Study of Depression in Older Persons found that childhood abuse was most strongly associated with early-onset clinical depression (OR=13.73) and less so with middle age-onset (OR=5.36) and late-onset (OR=4.74) (Comijs et al., 2013), although the risk for later depression remained substantial in this study. These studies suggest that CM may be directly associated with early depression which may be an important link between maltreatment and later MDE.

CM may exert its effects through numerous pathways including via psychological vulnerabilities of helplessness and low self-esteem and experiences of adversity in adulthood, including economic disadvantage, low quality social support, and accumulation of adult stresses (Kessler, 2003). In addition, numerous and varied studies have shown that

many neurobiological mechanisms may explain how stress generally and CM in particular influence early brain development and alterations that may contribute to the development of depression (Li et al., 2016; Lupien et al., 2009; Opel et al., 2019). For example, childhood trauma (child abuse and neglect), has been associated with long lasting dysregulation of the hypothalamic-pituitary adrenal (HPA) axis, reductions in cortical surface areas in the hippocampus and the prefrontal cortex (Opel et al., 2019) and in hippocampal volume (Rao et al., 2010).

This study has several limitations. CM is self-reported retrospectively, raising questions about misclassification due to recall bias. Duration and severity of maltreatment which potentially can influence recall and associations with outcomes is unknown. Information on lifetime MDD is retrospectively reported. However, the SCID has been shown to have substantial reliability for depressive disorders (Williams et al., 1992) and in the current study (kappa=.81-.82: Bromberger et al., 2011). Also, only a small number of women without lifetime MDD reported CM, limiting the ability to conduct a number of interaction analyses and, thus, to reach any conclusions about the impact of CM on the risk for MDE during the MT or after in women who experience an incident MDE during the MT or postmenopause. The study sample size was small relative to that needed for detecting significant three-way interactions, i.e., history of MDD by menopausal stage by risk factor. Therefore, we relied on stratified results based on history of MDD for our primary conclusions even though interactions between lifetime MDD and each stressor on occurrence of MDEs over the twelve follow-ups were not significant. Finally, we could not examine variability of E2 because bioassay measures of E2 were only collected annually and during postmenopause, due to limited funding, we only obtained E2 data on 50% of women. To our knowledge, this is the first community study of midlife women to longitudinally evaluate whether a CM or current stressor interacted with menopausal status to increase the risk for major depression during the MT or early postmenopause. Furthermore, this is the first study of midlife women to examine the longitudinal impact of both CM and a current stressor, separately and together in the same analyses, on risk for a MDE during the MT. Finally, no study has considered depressive disorders prior to the MT as potentially influencing the impact of early or recent stress on vulnerability to depression during or after the MT. The current study has additional strengths including the collection of data over a 15-year period, psychiatric diagnostic data, and detailed information on the menopausal transition.

While a clinician should always be watchful for a recurrence among midlife patients with a MDD history, the increased risk of a recurrence for women with CM during postmenopause suggests that a clinician increase vigilance after the final menstrual period. Being watchful involves monitoring patients for signs of depression, including changes in mood and behavior/activities, and for exposures to stressful situations. Numerous screening tools such as the CES-D (Radloff, 1977) and the Patient Health Questionnaire (PHQ-9: Kroenke et al., 2001) are available to quickly screen for depressive symptoms. Importantly, we recently found that anxiety is a predictor of MDE (Kravitz et al, 2014) and can be screened with the General Anxiety Disorder-7 (GAD-7: Spitzer et al., 2006). A positive screen indicates the presence of depressive symptoms (or anxiety) and warrants an evaluation for clinical depression and treatment.

For women with no history of MDD, the risk for MDE is lower than that for those with prior MDD. However, risk does increase even for these women when they become perimenopausal suggesting that clinicians should pay more attention to signs and symptoms of depression as women progress through the MT. Optimal clinical care would include obtaining information about current stressful events (in the previous 12 months) and ongoing chronic situations (lasting longer than 12 months) as such stressors substantially increase risk for a first onset depression. Screening instruments as described above can be used to evaluate level of depression and anxiety symptoms. Such information could be used to determine whether a referral to other health care providers or to supportive services is appropriate. The latter may be able to assist with practical matters that are the source of stress.

In conclusion, the study presents a complex picture of the interrelationships among MDD prior to midlife, the MT, current stressors, early CM and incident and recurrent MDD during midlife. CM is a consistent predictor of MDE in women with prior MDD even after accounting for a concurrent stressor, but especially postmenopausally. However, among women without lifetime MDD, current stressors are strong predictors of MDE whereas CM is not. These findings highlight the importance of obtaining knowledge of a woman's psychiatric and early childhood history during her midlife health visits. Such information may help health care providers identify the relative risk of women for MDE or depressive symptoms that impair functioning.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Sample characteristics at baseline

	All N = 333	Without Lifetime MDD at baseline N=222	With Lifetime MDD at baseline N = 111	p-value
Age (mean ± sd)	45.7 ± 2.5	45.7 ± 2.5	45.7 ± 2.4	0.735
Race (n (%))				0.161
Black	110 (33.0)	79 (35.6)	31 (27.9)	
White	223 (67.0)	143 (64.4)	80 (72.1)	
CES-D ≥ 16 (n (%))	80 (24.0)	34 (15.3)	46 (41.4)	<0.0001
Medication for nervous condition (n (%))	44 (13.2)	19 (8.6)	25 (22.5)	0.0004
Paying for basic (n (%))				0.020
Very hard	17 (5.1)	7 (3.2)	10 (9.0)	
Somewhat hard	87 (26.2)	53 (24.0)	34 (30.6)	
Not hard	228 (68.7)	161 (72.9)	67 (60.4)	
Menopausal status (n (%))				0.436
Premenopause	184 (55.3)	126 (56.8)	58 (52.3)	
Perimenopause	149 (44.7)	96 (43.2)	53 (47.7)	
Current Stressor (n (%))				
Any Chronic ongoing problem	78 (24.5)	42 (19.8)	36 (33.6)	0.007
At least 1 stressful event	169 (50.9)	95 (43.0)	74 (66.7)	<0.0001
Childhood Maltreatment (n (%))				
Emotional abuse	67 (20.1)	27 (12.2)	40 (36.0)	<0.0001
Physical abuse	63 (19.0)	28 (12.6)	35 (31.8)	<0.0001
Sexual abuse	54 (16.2)	22 (9.9)	32 (28.8)	<0.0001
Emotional neglect	23 (6.9)	10 (4.5)	13 (11.7)	0.015
Physical neglect	60 (18.0)	35 (15.8)	25 (22.5)	0.131

CES-D = Center for Epidemiologic Studies of Depression Scale

Table 2.

Association of Stress (current stressor and childhood maltreatment) and MDE stratified by individuals with and without lifetime MDD at baseline

	Without Lifetime MDD at baseline OR (95% CI)		With Lifetime MDD at baseline OR (95% CI)	
Current stressor				
Any chronic ongoing event	4.86 (2.91, 8.11)	**	2.48 (1.73, 3.56)	**
Menopausal Status - Perimenopause	4.47 (1.56,12.84)	**	0.96 (0.50,1.85)	
Post/BSO	4.28 (1.02,17.98)	*	1.41 (0.60,3.35)	
At least one stressful event	3.26 (2.05, 5.17)	**	2.73 (1.90, 3.91)	**
Menopausal Status - Perimenopause	4.44 (1.47,13.39)	**	0.89 (0.49,1.65)	
Post/BSO	4.51 (1.02,20.01)	*	1.85 (0.82,4.16)	
Childhood Maltreatment				
Emotional abuse	1.69 (0.81, 3.52)		1.89 (1.13, 3.15)	*
Menopausal Status - Perimenopause	4.57 (1.57,13.24)	**	1.25 (0.70,2.23)	
Post/BSO	4.46 (1.06,18.87)	*	1.92 (0.93,3.98)	
Physical abuse	1.80 (0.81, 3.99)		2.49 (1.42, 4.36)	**
Menopausal Status - Perimenopause	4.76 (1.72,13.18)	**	1.12 (0.63,1.99)	
Post/BSO	4.64 (1.16,18.64)	*	1.78 (0.85,3.76)	
Sexual abuse	0.86 (0.33, 2.21)		2.23 (1.33, 3.77)	**
Menopausal Status - Perimenopause	4.69 (1.62,13.55)	**	1.06 (0.60,1.88)	
Post/BSO	4.56 (1.09,19.04)	*	1.67 (0.79,3.55)	
Emotional neglect	1.05 (0.25, 4.47)		3.86 (1.60, 9.33)	**
Menopausal Status - Perimenopause	4.66 (1.60,13.52)	**	1.49 (0.75,2.94)	
Post/BSO	4.52 (1.08,18.94)	*	2.63 (1.12,6.18)	*
Physical neglect	0.95 (0.42, 2.16)		2.11 (1.10, 4.07)	*
Menopausal Status - Perimenopause	4.67 (1.62,13.49)	**	1.34 (0.74,2.43)	
Post/BSO	4.57 (1.09,19.08)	*	2.19 (1.03,4.67)	*

* $P < 0.05$

** $p < 0.01$

Premenopause is the reference for perimenopause and postmenopause/biilateral salpingectomy

Covariates included age, race, medication for nervous condition

Among those with lifetime MDD at baseline, the following covariates were also included in the model

Any chronic ongoing event, sexual abuse

At least one stressful event – paying for basic, HT use

Table 3.

Odds Ratio stratified by menopausal status; separate analyses for odds ratio for type of childhood maltreatment in analyses for each menopausal status – follow up of interaction analyses
Participants: women **with lifetime MDD** at baseline

Childhood Maltreatment	Menopausal status	OR (95% CI)
Emotional abuse	Premenopause Perimenopause Postmenopause/BSO	0.55 (0.20, 1.54) 1.32 (0.63, 2.76) 2.71 (1.40, 5.22) *
Emotional neglect	Premenopause Perimenopause Postmenopause/BSO	0.54 (0.14, 2.13) 3.15 (0.69, 14.35) 8.04 (3.40, 19.04) *
Physical neglect	Premenopause Perimenopause Postmenopause/BSO	0.65 (0.21, 2.04) 1.73 (0.68, 4.40) 3.06 (1.44, 6.53) *

* $P < 0.01$

Covariates were Age, race, medication for nervous condition.

Table 4.

Results of Analyses of Three Aims
History of Major Depression at Study Entry

Hypothesis/Aim	Yes	No
#1 Does either adult stress or childhood maltreatment lead to greater risk for major depression during the menopause transition (MT) relative to their risk during premenopause?	During postmenopause relative to premenopause, Significant increase in risk for emotional abuse (OR=2.71), emotional neglect (OR=8.04), physical neglect (OR=3.06). No effects of adult stress. No increased risk for CM or adult stress during MT.	No
#2 Do both a concurrent stress and a childhood maltreatment lead to greater risk for major depression?	Yes, Significant increase in risk for stressful event (OR range 2.64–2.85) and for CM type (OR range 1.59–3.27). Significant increase in risk for ongoing problem (OR range 2.41—2.49) and for CM type (except emotional abuse) (OR range 1.78–3.54).	Significant increase in risk for stressful event (OR range 3.15–3.28). Significant increase in risk for ongoing problem (OR range 4.74–5.09). No effect of CM.
#3 Are the effects of adult stress and childhood maltreatment synergistic, i.e. more than additive?	No	No

Note: CM=childhood maltreatment