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- Assess all women in perimenopause for adverse childhood experiences, a known risk factor for psychiatric disorders

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Adverse Childhood Experiences and Risk for First-Episode Major Depression During the Menopause Transition

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ABSTRACT

Objective: Stress exposures may have a differential impact on risk and resilience for depression depending on their timing across development. We sought to determine whether adverse childhood experiences (ACEs) and their onset with respect to puberty contribute to the increased risk observed in first-episode major depressive disorder (MDD) during the menopause transition.

Methods: Participants were from the Penn Ovarian Aging Study cohort, which is composed of women from Philadelphia County, Pennsylvania, who underwent behavioral, cognitive, and endocrine evaluations approximately yearly from 1996 to 2012 and completed the Adverse Childhood Experiences Questionnaire at study end point (n = 243). ACEs that first occurred 2 or more years before menarche were considered prepubertal. Incident menopause MDD was defined as first observed onset of the disorder in the perimenopause to postmenopause transition using the Structured Clinical Interview for DSM-III-R and the Primary Care Evaluation of Mental Disorders.

Results: Incident menopause MDD occurred in 48% of the 100 women who reported lifetime MDD. Women reporting ≥ 2 total ACEs were at significantly greater risk for lifetime MDD (adjusted odds ratio [aOR] = 2.05, P = .034) and incident menopause MDD (aOR = 2.58, P = .03) compared to those reporting 0 ACEs; women with ≥ 2 postpubertal ACEs were 2.3 times more likely to experience incidence menopause MDD (P = .024) after controlling for race, smoking, body mass index, and employment. Experiencing only 1 ACE in the prepubertal window, regardless of additional ACEs in postpuberty, was associated with reduced risk for lifetime and incident menopause MDD.

Conclusions: Timing and number of adverse experiences with respect to puberty differentially impacted risk and resilience for MDD across the female life span and during the menopause transition in this community cohort.

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Research confirms multiple sex differences in affective disorders, with women experiencing major depression, dysthymia, rapid-cycling bipolar, seasonal affective, posttraumatic stress, and panic disorders more often than men.¹ Moreover, women experience sex-specific affective disorders such as premenstrual dysphoric disorder² and are at increased risk for major depressive disorder

- Although depression is common during the menopause transition, predictors for who will experience a first episode of major depressive disorder (MDD) during this period of hormonal fluctuation are not available.
- Childhood adversity, a known risk factor for psychiatric disorders, should be assessed in all midlife women, as our findings indicate that women with more than 2 types of childhood adversity are at risk for first-onset MDD during perimenopause.
- Timing of childhood adversity should be assessed, as events that first occurred between puberty and age 18 years appear to have particularly potent effects on risk for new-onset MDD during perimenopause.

(MDD) during certain reproductive events such as the menopause transition.³ Women with no previous history of depression are 2–3 times more likely to experience a first episode of depression during perimenopause and early postmenopause,^{4–8} although risk declines over the first few postmenopausal years,^{3,6} particularly among women who experienced their first episode of depression during perimenopause.³

Endocrine changes, associated physical symptoms, interpersonal conflicts, role changes, cognitive style, and early and recent stressful life events are purported to contribute to this sex bias in major affective disorders after puberty^{9,10} and to increased risk for depression during the menopause transition specifically.^{3–8} The relationship between early life stress reproductive hormones and risk for depression is complex, encompassing individual and aggregate effects on neurotransmitter systems, stress neural circuitry, and endocrine and immune function.^{11–16} Moreover, the impact of estradiol on the behavioral and endocrine sensitivity to psychosocial stress depends on reproductive status (premenopause vs postmenopause) of the individual.^{17,18}

Several studies have suggested that current psychosocial stressors contribute to risk for new-onset depression in adults¹⁹ and that childhood trauma is associated with earlier onset mood episodes and greater years of illness among adults with bipolar disorder.²⁰ Interestingly, childhood trauma is also associated with objective deficits in executive function domains in adults without a history of psychiatric disorders, suggesting that the negative sequelae of early life stress is enduring even among the relatively resilient.²⁰ To our knowledge, no studies have focused on the role of childhood adversity in onset of major depressive disorder (MDD) during the menopause transition. Moreover, preclinical research suggests that timing of childhood adversity with respect to puberty is likely to contribute to depression risk among menopausal women. A nonhuman primate model (subordination in social hierarchy) of prepubertal-onset stress provides support for an interactive effect of stress and estradiol with respect to enzymes critical for serotonin synthesis,^{21,22} hypothalamic-pituitary-adrenal axis function,²³ and sexual behavior.²⁴ Finally, rodent studies indicate that prepubertal and peripubertal exposures to stress

adversely impact cognitive aging and affect regulation,^{25–27} in part through effects on the prefrontal cortex and hippocampus.^{28,29}

We examined the impact of early life stress as assessed by the Adverse Childhood Experiences Questionnaire (ACE-Q)^{30,31} on the first episode of MDD during the menopause transition among participants in the 16-year, longitudinal Penn Ovarian Aging Study (POAS).^{3,4} We chose to examine childhood adversity instead of specific traumatic life events to more closely mimic the preclinical studies of chronic variable stress and social subordination, which reveal the importance of timing of adversity in relation to puberty with respect to aging outcomes.^{22,29} Furthermore, we explored whether adverse childhood experiences (ACEs) with onset prior to initiation of pubertal hormonal fluctuations more potentially contributed to MDD risk over the life-course in addition to the menopause transition than ACEs that occurred later in childhood; we also examined whether any degree of early life adversity contributed to resilience with respect to risk for MDD in adulthood.

METHODS

Cohort Description

Between June 2012 and August 2012, 243 women (83.8%) of the 293 women remaining active in the POAS cohort were contacted by telephone to obtain history regarding early-life adversity using the ACE-Q.³¹ The POAS cohort is a population-based cohort (n = 436) identified by random-digit dialing to households in Philadelphia County, Pennsylvania, in 1996–1997 and stratified to obtain equal numbers of white and African American women. At enrollment, the participants were between the ages of 35 and 47 years, were premenopausal with regular menstrual cycles in normal range (22–35 days), and had an intact uterus and at least 1 ovary. Exclusion criteria included the use of psychotropic medication or hormonal contraception, presence of a serious health problem, or alcohol or drug abuse in the previous year. Attrition since POAS inception has been acceptable at 33%, and the cohort (n = 243) remaining who provided ACE-Q data is consistent with the original sample (see Supplementary eTable 1 at PSYCHIATRIST.COM).^{32,33} The POAS study was approved by the University of Pennsylvania institutional review board (IRB), and written informed consent was obtained from participants. In 2012, IRB approval was granted to contact the women who remained in the POAS to obtain ACE history. Participants gave assent by phone and were interviewed by members of the research team who were blind to the participant's history of depression.

Assessment Periods for the POAS Cohort

Data were collected during 6 assessment periods at approximately 8-month intervals through year 5 and then yearly thereafter, with a 2-year gap between period 10 and period 11. Trained research interviewers administered a structured questionnaire and cognitive and mood

assessments, measured height and weight to determine body mass index (BMI), and collected blood samples for hormone assays at each assessment period. Information regarding demographics, menstrual cycle dates, reproductive history, general health status and behaviors, and common menopausal symptoms was obtained at each assessment during in-home evaluations until 2010 (the 14th study year). Between years 14 and 16, women were interviewed by phone to obtain information regarding menopause status. History of ACE was obtained in year 16.

Study Variables

Menopausal status. Menopausal status was determined from the data on menstrual bleeding, recorded using daily diaries, the number of menstrual periods between assessments, and cycle length. The definitions for the menopausal status groups were based on the staging system for reproductive aging in women,³⁴ with an added late-premenopause stage (Supplementary Methods).³²

Adverse Childhood Experiences Questionnaire. The ACE-Q has been utilized to assess the relationship between childhood adversity and adult health outcomes in a number of studies, with the best known the Adverse Childhood Experiences (ACE) Study³¹ conducted in collaboration with the Centers for Disease Control and Prevention (CDC) and Kaiser Permanente. Numerous publications from this study emphasize the graded impact of ACEs on risk for a range of adverse adult health outcomes. The ACE-Q focuses on 3 general categories of childhood adversity (abuse, neglect, and household/family dysfunction), which are broken down into subcategories (ie, physical, sexual, and emotional abuse; emotional and physical neglect; parental separation; household violence; parental substance abuse or psychiatric disorders; and household member in prison). With 10 items, scores range from 0 to 10 depending on the number of different types of experiences reported. To examine the differential impact of prepubertal versus postpubertal ACEs in the present study, the ACE-Q was modified to ask all participants to recall the age at which a given ACE first occurred. Adverse childhood experiences that were reported to have occurred or started at least 2 years prior to menarche were considered prepubertal, even if they extended into the postpubertal window. All other ACEs with onset up to age 18 years were considered postpubertal. For female participants in the large ACE study,³⁵ even having 2 ACEs was associated with a significant increased risk of lifetime MDD compared to having experienced no ACEs, but timing of the ACE with respect to puberty was not evaluated and neither was the impact of ACE on risk for new-onset menopause depression.

We also examined impact of ACEs on participant characteristics at study enrollment. Those who reported 0 or 1 ACE were in the “low ACE” group; those who reported 2 or more ACEs were in the “high ACE” group given our interest in ACE impact on MDD risk. For all other analyses, comparisons were made between 1 ACE or ≥ 2 ACEs versus 0 ACEs. We parceled out those with only 1 ACE in an effort to examine the impact of relatively limited degrees of stress and

to determine the possibility of a “stress inoculation” effect in humans that has been observed and reported in preclinical models.^{36,37}

Major depressive disorder diagnosis and depressive symptoms. At initial screening, women were asked whether they had ever been diagnosed with depression by a doctor. During assessment period 1, MDD diagnosis was determined using the depression section from the Structured Clinical Interview for *DSM-III-R* (SCID).³⁸ At each assessment from periods 2 to 6, trained researchers and interviewers administered the Primary Care Evaluation of Mental Disorders (PRIME-MD)³⁹ to determine MDD diagnosis. From period 7 to study end, the self-administered version of the PRIME-MD, the 9-item Patient Health Questionnaire (PHQ-9),^{40,41} was administered to obtain a SCID diagnosis of MDD. Specifically, women had to endorse 1 of the 2 key symptoms of depression (ie, depressed mood or decreased interest or pleasure) and a total of 5 symptoms to meet criteria for MDD diagnosis. For each woman, the menopausal status at the first assessment in which she reported MDD was used to define the study outcome of interest. Lifetime MDD refers to individuals with any MDD diagnosis during the 14-year study period, as women who reported a history of depression at screening but were not observed to have ever met MDD criteria were not included in these analyses. Incident menopause MDD was defined as follows: no history of MDD during premenopause when menstrual cycles were regular and new-onset MDD after the first occurrence of a ≥ 7 -day change in menstrual cycle length (stage 2). Women who had no history of MDD were considered as the reference group for analysis. The Center for Epidemiologic Studies Depression scale (CES-D),⁴² a 20-item self-report scale, was administered at each POAS assessment period to assess presence and severity of depressive symptoms. A score of ≥ 16 reflects a clinically meaningful level of depressive symptoms, while a score of ≥ 25 has greater specificity for a clinical diagnosis of MDD.⁴² We report here CES-D scores at study entry.

Hormone assessment. Blood samples for measurement of estradiol, follicle-stimulating hormone, and inhibin B were collected between days 2 and 6 of 2 consecutive menstrual cycles or 1 month apart in nonmenstruating women during each assessment period. The samples were prepared and stored at -80°C (-112°F). Methods for hormone quantification with interassay and intraassay coefficients of variation and lower limits of detection were conducted as described previously.^{4,32} We report baseline hormone levels in Tables 1 and 2 to demonstrate the sample’s premenopausal status.

Statistical Methods

Odds ratio estimates for the association between ACE groups and incident and lifetime MDD were estimated using logistic regression. Models for adjusted estimates included race, BMI (kg/m^2) > 30 , current smoking, and current employment (full time vs other). Two-sample *t* tests and Pearson χ^2 tests were used to compare demographics

Table 1. Baseline Subject Characteristics by Total Number of Adverse Childhood Experiences (ACEs)

Characteristic	Low ACE Group ^a (n = 150)		High ACE Group ^b (n = 93)		<i>P</i> ^c
	Mean	SD	Mean	SD	
Age, y	41.7	3.4	41.4	3.7	.497
Race	n	%	n	%	
White	87	58	41	44	.035
African American	63	42	52	56	
Education					
High school or less	65	43	33	35	.225
College	85	67	60	65	
CES-D ≥ 16	51	34	46	49	.020
CES-D ≥ 25	19	13	23	25	.018
MDD diagnosis	11	7	10	11	.329
Body mass index ≥ 30	45	30	47	54	.001
	Geometric		Geometric		
	Mean	95% CI	Mean	95% CI	
FSH, IU/L	6.76	6.3–7.2	7.08	6.5–7.7	.403
LH, IU/L	2.78	2.6–3.0	2.83	2.6–3.1	.755
Estradiol, pg/mL	36.60	33.8–39.5	34.81	31.5–39.0	.478
DHEA-S, µg/dL	92.76	85.6–101.5	94.63	83.9–105.6	.860
Inhibin B, pg/mL	68.03	61.6–75.9	57.97	50.9–66.7	.065

^aLow ACE Group includes women who report having 0 or 1 ACE prior to the age of 18 years. Percentages are shown for each factor within ACE group.

^bHigh ACE Group includes women who report having experienced 2 or more ACEs any time before the age of 18 years. Percentages are shown for each factor within ACE group.

^c*P* values represent unadjusted associations between each demographic, health, or hormonal factor and 2 ACE groups. Pearson χ^2 associations for categorical variables and 2-sample *t* tests for continuous variables. Boldface values indicate statistical significance.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale, DHEA-S = dehydroepiandrosterone sulfate, FSH = follicle-stimulating hormone, LH = luteinizing hormone, MDD = major depressive disorder.

between women with low (0 or 1) ACEs and those with high (2 or more) ACEs. The timing (prepuberty or postpuberty) of individual ACEs was compared using an exact binomial test of the hypothesis that the participants who report each individual ACE are equally likely to report the timing of the first occurrence to be prepuberty or postpuberty (see Table 4). Reproductive hormones were compared after natural log transformation. We report geometric mean hormone levels along with 95% confidence intervals in Tables 1 and 2.

We estimated, by using CDC reports, that 34.5% of the women would have no ACE history and that 41% would have ≥ 2 ACEs. Additional assumptions included a type I error with an α of 5% and 80% power. We computed that we would have sufficient statistical power to detect risk ratios on the order 2.4 or greater for incident MDD for women with ≥ 2 total ACEs compared to women without history of ACE. The statistical analysis was conducted using STATA version 13 (College Station, Texas); 2-tailed *P* values of .05 were considered statistically significant.

RESULTS

Participants and Assessments

Of the 293 women active in the POAS cohort at study end, ACE-Q data were obtained from 243 (82.9%). Each woman contributed a mean of 12.3 assessments for a total of 2,986 assessments. Comparison between the entire POAS cohort and those for whom ACE-Q data were collected revealed no

significant baseline differences with respect to race, age, BMI, employment, CES-D scores, or marital status (all *P* values > .05). Likewise, the proportion of women with lifetime or incident menopause MDD diagnoses at baseline did not differ (*P* > .05; Supplementary eTable 1). For the 243 women (128 white; 115 African American) who comprise the present group, mean (SD) age at enrollment in the POAS was 41.6 (3.5) years, and significant differences were found between the high and low ACE groups with respect to race (*P* = .035), with a greater proportion of the African American participants in the high versus low ACE groups. Similarly, the proportion of women with high levels of depressive symptoms and obesity as evidenced by CES-D scores ≥ 16 (*P* = .020) or ≥ 25 (*P* = .018) and BMI ≥ 30 (*P* = .001), respectively, was greater in the high versus low ACE groups (Table 1). Table 2 shows that baseline differences between high and low ACE groups are, in part, driven by whether the ACEs first occurred in the prepubertal or postpubertal period. Having ≥ 2 postpubertal ACEs is associated with having baseline CES-D scores ≥ 16 (*P* < .001) or ≥ 25 (*P* = .005), while having a prepubertal ACE score of ≥ 2 is associated with having a BMI ≥ 30 (*P* < .001). Interestingly, there were a greater proportion of college graduates among the group of women who reported ≥ 2 prepubertal ACEs (*P* = .025).

Lifetime and Incident Menopause Depression

At the time of enrollment, 95.5% of the cohort (232/243) was at risk of experiencing incident menopause MDD. Excluded from our analysis were 2 women who had no observed changes in cycle length and could therefore not be included because no menopause transition had yet transpired. An additional 9 women reported a history of depression at enrollment but were never observed to experience an episode of MDD over the 14 years that home visits were completed. Because their symptom severity and duration of their symptoms prior to study entry were not determined, they were also excluded. The cumulative incidence of lifetime MDD among the women who provided ACE-Q data was 43.1% (100/232). Fifty-two women (22.4%) were diagnosed with MDD during premenopause, while 48 women (20.7%) were found to have their first diagnosis of MDD after onset of menstrual irregularity (incident menopause MDD).

Number and Types of ACEs Reported

In this sample, 39.5%, 22.2%, and 38.3% of women reported having experienced 0, 1, or ≥ 2 ACEs, respectively. The number of individuals reporting each type of ACE is listed in Table 3 in total and by pubertal status. Overall, the most commonly reported adverse experiences were emotional abuse, parental separation or divorce, and living with someone with alcohol or substance abuse. Among the 54 women who reported

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Table 2. Baseline Subject Characteristics by Pubertal Status of Adverse Childhood Experiences (ACEs)

Characteristic	Prepubertal ACE ^a				Postpubertal ACE ^a				
	Low (n=177)		High (n=66)		Low (n=212)		High (n=31)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, y	41.5	3.5	41.5	3.6	41.7	3.5	40.6	3.4	
Age at menarche, y	Median	Min, Max	Median	Min, Max	Median	Min, Max	Median	Min, Max	
	12	8, 18	12.5	9, 17	12	8, 18	12.5	9, 16	
Race ^b	n	%	n	%	n	%	n	%	
	White	80	45	35	53	94	44	21	68
African American	97	55	31	47	118	56	10	32	
Education ^c	High school or less	79	45	19	29	83	39	15	48
	College	98	55	47	71	129	61	16	52
CES-D $\geq 16^d$	67	38 ^e	30	45	76	36 ^f	21	68	
CES-D $\geq 25^d$	26	15 ^e	16	24	31	15 ^f	11	35	
MDD diagnosis	12	7	9	14	19	9	2	6	
Body mass index $\geq 30^g$	56	32	36	56	77	37	15	50	
FSH, IU/L	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	
	6.89	6.5–7.3	6.9	6.2–7.6	6.80	6.4–7.2	7.44	6.3–8.8	
LH, IU/L	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	Geometric Mean	95% CI	
	2.82	2.6–3.0	2.74	2.5–3.1	2.78	2.6–3.0	2.91	2.4–3.6	
Estradiol, pg/mL	36.23	33.9–39.1	34.6	30.5–39.4	35.63	33.3–38.1	37.94	31.8–45.3	
DHEAS, $\mu\text{g/dL}$	94.54	87.4–102.2	91.19	79.4–104.8	91.65	85.4–98.4	108.09	87.1–134.0	
Inhibin B, pg/mL	65.04	58.7–72.0	61.62	53.1–71.5	66.67	61.1–72.6	50.25	38.3–66.0	

^aPrepubertal ACEs refer to those adverse childhood experiences that were reported to have had onset at least 2 years prior to menarche, while postpubertal ACEs refers to those which had their onset within the 2 years prior to menarche up to age 18 years. "High" refers to having 2 or more ACEs in that category, while "low" refers to having 0 or 1 ACE in that category. Percentages are shown for each factor within the ACE group. Prepubertal ACEs are considered without regard for the number of postpubertal ACEs and vice versa.

^bGreater proportion of African American women in the high versus low postpubertal ACE group ($P=.015$).

^cGreater proportion of women in the high versus low prepubertal ACE group with a college education ($P=.025$).

^dGreater proportion of women with CES-D scores ≥ 16 and ≥ 25 in the high versus low postpubertal ACE group ($P < .001$ and $P=.005$, respectively).

^eFor low prepubertal ACE group, $n=175$.

^fFor low postpubertal ACE group, $n=210$.

^gGreater proportion of women with body mass index ≥ 30 in the high versus low prepubertal ACE group.

Abbreviations: CES-D=Clinical Epidemiologic Depression scale, DHEA-S=dehydroepiandrosterone sulfate, FSH=follicle-stimulating hormone, LH=luteinizing hormone, Max=maximum, MDD=major depressive disorder, Min=minimum.

a single ACE, the most commonly experienced event was familial drug or alcohol abuse, followed by separation/divorce. Most ACEs had an onset in the prepubertal window (P values $< .05$), suggesting that adversity exposures typically began quite early in development.

Relationship Between ACEs and MDD

In models adjusted for race, smoking, BMI ≥ 30 , and employment status (Table 4), those with a total ACE of ≥ 2 were significantly more likely to experience a lifetime MDD (adjusted odds ratio [aOR]=2.05, $P=.034$) and incident menopause MDD (aOR=2.58, $P=.03$) compared to those with 0 ACEs. Women who were smokers at study entry had an elevated risk for incident menopause MDD (aOR=2.43, $P=.02$) and lifetime MDD (aOR=2.56, $P=.002$). Employment was associated with reduced risk for lifetime MDD (aOR=0.37, $P=.009$).

Pubertal Status and Risk for MDD

Again in adjusted models (Table 4), compared to those with no ACEs, women with ≥ 2 postpubertal ACEs were at greater risk of incident menopause MDD (aOR=2.26, $P=.02$) but not lifetime MDD ($P=.12$). On the basis of preclinical evidence that some types and degrees of stress

during development may induce resilience even in the face of future stressors,^{36,37} we examined the impact of varying number (0, 1, or ≥ 2) of prepubertal ACEs in the context of varying number (0, 1, or ≥ 2) of postpubertal ACEs on risk for lifetime MDD (Figure 1A) and incident menopause MDD (Figure 1B). Across the postpubertal ACE categories (x-axis), those reporting 1 (gray line) versus ≥ 2 (black line) prepubertal ACEs had significantly reduced MDD risk when there were no postpubertal ACEs ($P=.034$), with a trend toward significance ($P=.054$) observed for those with 1 prepubertal and 1 postpubertal ACE. The pattern was similar for incident MDD, although the relatively smaller sample size ($n=48$ vs $n=100$) was a limitation for statistical significance.

DISCUSSION

Early life adversity exerts a powerful influence on health outcomes across the life span. For women, the interplay between stress and reproductive hormonal shifts may be particularly relevant.^{11,43} Our findings add to the literature regarding the impact of childhood trauma and neglect^{15,16} and ACE history³⁵ on lifetime risk for MDD. However, our novel finding that experiencing ≥ 2 total or

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Table 3. Prevalence of Specific Adverse Childhood Experiences (ACEs) in the Penn Ovarian Aging Study Cohort: Total and By Pubertal Status at Onset (based on 243 subjects)

Experience	Total No. of ACEs (%)	Prepubertal, n	Postpubertal, n	P Value ^a
Abuse				
Physical	52 (21.4)	37	15	.003
Sexual	42 (17.3)	28	14	.044
Emotional	57 (23.5)	39	18	.008
Neglect				
Physical	23 (9.5)	15	8	.210
Emotional	41 (16.9)	26	15	.118
Household dysfunction				
Separation/divorce	54 (22.2)	31	23	.341
Violence toward mother or stepmother	41 (16.9)	33	8	<.001
Alcohol/substance abuse	53 (21.8)	35	18	.027
Mental illness	33 (13.6)	25	8	.005
Household member in prison	15 (6.2)	5	10	.302

^aBoldface values indicate statistical significance.

Table 4. Impact of Adverse Childhood Experiences (ACEs) on Risk for Major Depressive Disorder (MDD)

ACE Group	Unadjusted Odds Ratio	Adjusted Odds Ratio ^a	95% CI	P Value ^b
Lifetime MDD (n = 100) vs no MDD (n = 132)				
Total				
1 vs 0	0.95	1.12	0.53–2.38	.776
≥ 2 vs 0	2.00	2.05	1.05–3.97	.034
Prepubertal				
1 vs 0	0.49	0.65	0.29–1.50	.315
≥ 2 vs 0	1.78	1.74	0.88–3.42	.109
Postpubertal				
1 vs 0	1.50	1.46	0.72–2.93	.294
≥ 2 vs 0	2.66	2.06	0.84–5.08	.116
Covariates				
African American race	2.04	1.80	0.99–3.29	.055
Smoking	2.56	2.56	1.41–4.63	.002
Body mass index > 30	1.50	1.00	0.54–1.88	.989
Employment	0.33	0.37	0.18–0.78	.009
Incident menopause MDD (n = 48) vs no MDD (n = 132)				
Total				
1 vs 0	1.46	1.84	0.72–4.75	.203
≥ 2 vs 0	2.28	2.58	1.09–6.08	.030
Prepubertal				
1 vs 0	0.34	0.46	0.14–1.51	.200
≥ 2 vs 0	1.57	1.60	0.71–3.61	.257
Postpubertal				
1 vs 0	1.84	1.91	0.81–4.48	.137
≥ 2 vs 0	3.84	2.26	1.17–9.09	.024
Covariates				
African American race	1.82	1.57	0.75–3.30	.231
Smoking	2.24	2.43	1.15–5.11	.020
Body mass index > 30	1.49	1.05	0.49–2.25	.900
Employment	0.43	0.43	0.17–1.08	.071

^aAdjusted for race, smoking status, body mass index >30, and employment status.

^bBoldface values indicate statistical significance.

postpubertal, but not prepubertal, ACEs is associated with increased risk for incident menopause MDD suggests that the hormonal milieu of the perimenopause may unmask risk for depression in women who experienced childhood adversity, particularly when the onset of adversity occurred in the context of postpubertal hormonal cyclicality. Our

observation that postpubertal ACEs did not contribute significantly to risk for lifetime MDD may seem counter to the literature regarding history of childhood trauma and adversity and depression risk. It is important to note that a number of previous studies^{44–47} finding a relationship between childhood adversity and risk for lifetime MDD focused on maltreatment (abuse and/or neglect) or a specific type of trauma. Although age at onset of adversity has been considered, our focus on timing of events in relationship to puberty and impact of ACEs on MDD risk at menopause is unique.

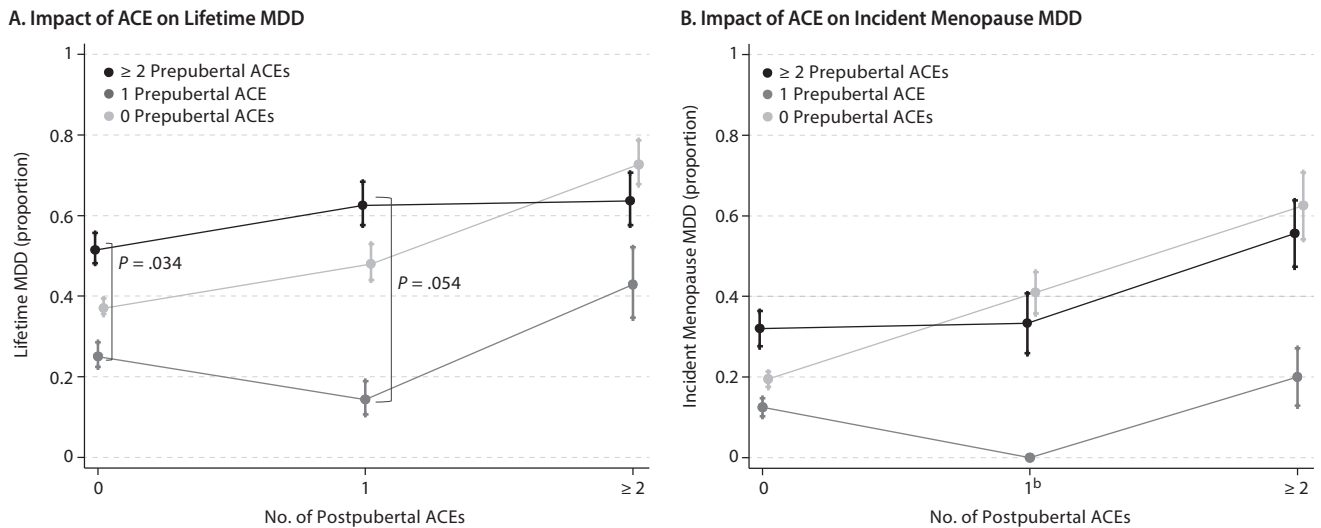
Plausible explanations for this observation include the unique impact that early versus late childhood onset of early life stress imparts on the development and function of limbic and executive brain regions. Onset of early life stress in late childhood, defined as ages 8–17 years, is associated with greater reduction in anterior cingulate and insula cortex volumes than stress occurring earlier in life.^{15,16} Peak sensitivity to childhood

maltreatment with respect to right amygdala volume has been previously observed in individuals whose experience of maltreatment occurred between ages 10 and 11 years.¹⁴ Postpubertal-onset early life stress occurs in the context of fluctuating estradiol, which itself alters neurochemistry and brain structure and function. Estradiol enhances enzymes critical to serotonin synthesis,²² monoamine oxidase inhibition,³⁸ prefrontal dopaminergic tone,³⁹ and neuronal dendrite density and morphology (reviewed by Shanmugan and Epperson¹¹). Both preclinical and human studies^{17,43} suggest an interactive effect of estradiol and timing of stress onset across development with respect to neurochemistry and behavior.

Given the graded effect of ACEs on adverse health outcomes and preclinical studies^{36,37} demonstrating the capacity for exposure to early life stress to promote resilience, we were intrigued by the observation that the experience of 1 prepubertal ACE was associated with decreased risk for both lifetime and incident menopause MDD, even in the context of postpubertal ACEs (Table 4). Although they were significant only when considering the larger group who experienced lifetime MDD (Figure 1A; ie, inclusive of those with incident menopause MDD), these findings suggest that stress inoculation models should be explored in the human laboratory. While the findings are compelling, cautious interpretation is warranted given the relatively small sample size within specific strata defined by the prepubertal and postpubertal ACE categories.

In the CDC-sponsored ACE Study,³¹ the most commonly reported adverse experiences were household substance, physical, and sexual abuse. Emotional abuse posed the largest risk for lifetime or recent depression among women.³⁵ Pubertal status was not reported and neither is it clear which ACE was the most common among those reporting only 1 type of adversity. In the present study, household substance abuse and separation/divorce were reported most frequently in those women who experienced only 1 prepubertal ACE. Whether our finding of relative resilience among the women

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It is illegal to post this copyrighted PDF on any website.**Figure 1. Impact of Prepubertal Adverse Childhood Experiences (ACEs) on Risk for Lifetime (A) and Incident Menopause (B) Major Depressive Disorder (MDD) by Number of Postpubertal ACEs^a**

^aThe figures illustrate the impact of varying combinations of prepubertal with postpubertal ACE scores with respect to risk for lifetime MDD (panel A) and incident menopause MDD (panel B). The sample size for women experiencing MDD in panel A ($n = 100$) is considerably larger than that in panel B ($n = 48$), and lifetime MDD is inclusive of incident menopause MDD. Those with a prepubertal ACE score of 1 and postpubertal ACE score of 0 were significantly less likely to experience lifetime MDD than those reporting ≥ 2 prepubertal ACEs and no postpubertal ACE ($P = .034$). Similarly, those reporting having experienced 1 prepubertal ACE versus 2 prepubertal ACEs were less likely to experience lifetime MDD even if they went on to experience 1 additional postpubertal ACE ($P = .054$), suggesting that the experience of 1 prepubertal ACE may be protective against the risk of lifetime depression. While a similar pattern was observed with incident menopause MDD, the sample size was a limitation.

^bThe SE for prepubertal and postpubertal ACE score of 1 had to be estimated, as no women in that level of prepubertal and postpubertal ACE experienced incident menopause depression.

with 1 prepubertal ACE would have been replicated had the 1 prepubertal ACE been physical, emotional, or sexual abuse could not be determined with this sample, but child abuse does not typically occur in isolation. Among women and men in the larger CDC study³¹ who experienced 1 ACE, 86.5% reported at least 1 other ACE and 38.5% reported 4 or more additional ACEs. For those individuals reporting childhood abuse or emotional neglect, the percentage reporting at least 1 additional ACE was even higher, at 98% and 93%, respectively.

The POAS is unique among the longitudinal studies of midlife women,⁶⁻⁸ as all participants were premenopausal, with regular menstrual cycles at the time of study enrollment, and standard instruments were administered yearly for the determination of MDD diagnosis. In addition, women underwent hormonal assessments and completed menstrual cycle calendars allowing for objective confirmation of menstrual cycle changes. Recruitment of all participants during the premenopause allowed us to examine the risk for incident MDD concurrent with the earliest changes in reproductive hormones leading to menstrual irregularity. While the prevalence of MDD in this study (43%) may appear high, it is important to remember that this proportion represents a cumulative incidence of MDD, as women were evaluated yearly. Epidemiologic studies^{1,6,8} reporting a 21% prevalence of lifetime MDD among women utilize a 1-time interview to determine past and current MDD. Moreover, a similar cumulative 13-year incidence of 39% was reported in the even larger longitudinal Study of Women's Health

Across the Nation.⁶ While we observed a greater percentage of African American women and obese women in the high ACE group, white women represented a greater proportion of those in the high postpubertal ACE group. These baseline differences, however, did not contribute significantly to risk for lifetime or incident MDD in analyses adjusted for race, BMI, smoking, and employment.

Although our findings are based on close to 3,000 observations among 243 women across 14 years, there are several important limitations to consider. A shortcoming of the ACE-Q is that it does not provide a granular assessment of the frequency and severity of given ACEs, such as sexual and physical abuse or the number of times an individual witnessed abuse against her mother. The benefit of the ACE-Q is that it provides a broader understanding of the impact of what the American Academy of Pediatrics refers to as "toxic stress" on adult health outcomes.⁴⁸ We also chose a cutoff for low ACE of 0 or 1 and a cutoff for high ACE of ≥ 2 based on previous research³⁵ examining ACE impact on MDD risk in women. In the current cohort, we conducted a sensitivity analysis for lifetime MDD (which includes incident menopause MDD) with respect to numbers of ACEs. Supporting our cutoff of ≥ 2 for high ACE (total, prepubertal, and postpubertal), we observed a significant increase in lifetime MDD risk between 1 and 2 ACEs for the prepubertal ACE score ($P = .026$) and a trend for the postpubertal ACE score ($P = .06$). The increase in MDD risk between 1 and 2 when considering total ACE score did not reach statistical significance ($P > .05$), perhaps due to the continued increase

in risk between 2 and 6 total ACEs (Supplementary eFigure 1). As most of the ACEs endorsed by this cohort of women were reported to have started in the prepubertal window, we may have had insufficient power to fully determine the impact of postpubertal onset of ACEs alone on MDD risk. However, our observation that ≥ 2 postpubertal ACEs were associated with a significant increased risk for MDD in the smaller incident menopause MDD group than the larger lifetime MDD group would suggest that power is not the primary reason for the relative importance of postpubertal ACEs to incident MDD.

Other potential limitations include the reliance on recall of age at menarche and timing of adverse events occurring decades before. Some studies, but not all,⁴⁹ suggest that recall for age at menarche is stable over time,⁵⁰ and even 30 years later the correlation between recalled age at menarche and medical records is quite robust.⁵¹ The allowance of a 2-year window prior to the first menstrual period increases the likelihood that women were not actually postpubertal when they reported an ACE as occurring in the prepubertal window. A subset of 106 women from the current cohort have been interviewed twice 2 years apart to determine reliability of recall of age at menarche, age at which an ACE first began, and number of ACEs endorsed (data not shown). Recall of age at menarche was exact in 83% of women and

within 1 year in 93%. With respect to total ACEs endorsed and timing of their onset, prepubertal ACE category switched from low to high in 4 individuals and from high to low in 1, a finding suggesting that, if anything, we have biased the outcome toward the null. We were also unable to examine the impact of hormone therapy by ACE group on risk for MDD, as relatively few women (approximately 15%) in the POAS reported using hormone therapy, with the majority of these individuals reporting use at only 1 assessment. We did not examine the interaction between vasomotor symptoms and depression, as we previously reported that depression typically precedes onset of hot flashes.⁵²

In summary, this study provides further evidence that childhood adversity exerts a powerful influence on MDD risk across the female life span and highlights the novel finding that risk is enhanced during the menopause transition, even among previously resilient women. Relatively low levels of adversity with onset prior to establishment of ovarian cyclicity may contribute to resilience in the face of postpubertal adversity, while postpubertal onset of adversity may enhance risk. Future research examining risk and resilience for psychopathology during adulthood after exposures to childhood adversity would benefit from considering the reproductive status of the child at the time exposures occur.

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Supplementary material: See accompanying pages.

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For the CME Posttest, see next page.

Supplementary material follows this article.

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POSTTEST

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to take this Posttest and complete the Evaluation. A nominal processing fee is required.

1. Women who have never experienced depression before are at increased risk of depression during the menopause transition.
 - a. True
 - b. False

2. Regarding adverse childhood experiences (ACEs), which of the following statements is true?
 - a. Experiencing 2 or more ACEs total is associated with a significantly increased risk of both lifetime major depressive disorder (MDD) and incident menopause depression.
 - b. Experiencing 2 or more ACEs before puberty is associated with a significantly increased risk of incident menopause depression.
 - c. Women must report having experienced at least 4 ACEs to be at significantly increased lifetime risk of MDD.
 - d. Only those with a body mass index > 30 and 2 or more ACEs were at increased risk for lifetime and incident menopause MDD.

3. Dr A is a 52-year-old, married mother of two teenaged daughters who presents with low mood, decreased interest in social activities, irritability, mood fluctuations, decreased sexual interest, and middle-of-the-night awakening. She has never experienced these symptoms before. Which of the follow questions/assessments seems *least* appropriate at this time?
 - a. Adverse Childhood Experiences Questionnaire
 - b. Menstrual cycle history
 - c. Review of menopausal symptoms such as night sweats, hot flashes, and vaginal dryness
 - d. Height and weight



Supplementary Material

Article Title: Adverse Childhood Experiences and Risk for First-Episode Major Depression During the Menopause Transition

Authors: Cynthia Neill Epperson, MD; Mary D. Sammel, ScD; Tracy L. Bale, PhD; Deborah R. Kim, MD; Sarah Conlin, BA; Stephanie Scalice, MA; Katharine Freeman, BA; and Ellen W. Freeman, PhD

DOI Number: <https://doi.org/10.4088/JCP.16m10662>

List of Supplementary Material for the article

1. [Supplemental Methods](#) Supplemental Methods
2. [eTable 1](#) Baseline Characteristics for Current Study Cohort Versus Those Who Dropped Out of the Penn Ovarian Aging Study
3. [eFigure 1](#) Proportion of Women With Lifetime MDD Based on Number of ACEs

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SUPPLEMENTAL METHODS:

Menopausal Status:

At every assessment period, each participant was assigned to one of the following categories based on bleeding patterns: Stage 1) pre-menopausal: regular menstrual cycles in the 22- to 35-day range; Stage 2) late pre-menopause: change in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 1 cycle; Stage 3) early transition: change in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 2 cycles up to 60 days of amenorrhea; Stage 4) late transition: 3–11 months of amenorrhea; and Stage 5) post-menopausal: 12 months or more of amenorrhea without hysterectomy.

Statistical Methods:

Students t test or chi square methods were utilized to determine whether women remaining in the POAS cohort and available for inclusion in this analysis were similar with respect to demographics, body mass index, baseline depression symptom severity and history of depression to the participants that comprised the original cohort (Supplemental Table 1).

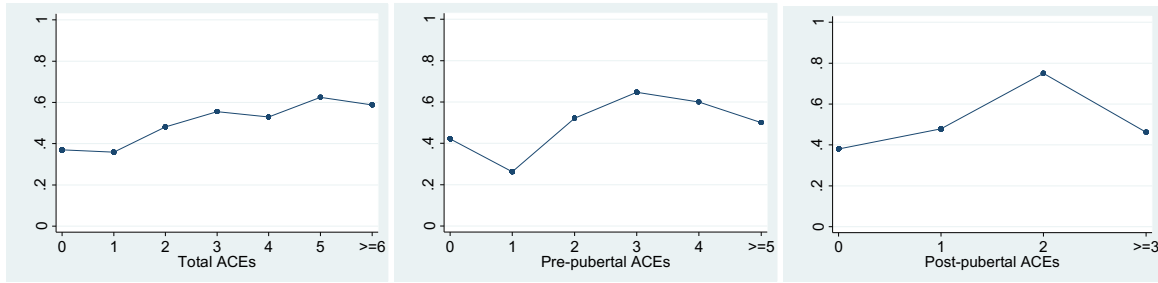
For the purposes of this study, we defined the high ACE group as those women with 2+ ACEs. A binomial test of proportions was used to compare lifetime prevalence of MDD in individuals with 1 ACE to 2 ACEs directly, considering total, prepubertal and postpubertal ACEs separately (Supplemental Figure 1).

SUPPLEMENTAL RESULTS

Supplemental Table 1. Baseline Characteristics for Current Study Cohort Versus Those Who Dropped Out of the Penn Ovarian Aging Study

VARIABLE	CURRENT STUDY COHORT (N=243)		DROP OUTS FROM POAS (N=195)		P VALUE
	Mean	SD	Mean	SD	
Age	41.6	3.5	41.3	3.4	0.422
Body Mass Index	29.3	8.3	29.1	7.3	0.776
	N	%	N	%	
Race					
Caucasian	128	52.7	89	46.1	0.174
African American	115	47.3	104	53.9	
Education					
High School or Less	98	40.3	94	48.7	0.080
College	145	59.7	99	51.3	
Employed	200	82.3	155	80.3	0.595
Marital Status (Married)	138	56.8	112	58.0	0.795
CES-D >=16	97	40.3	85	44.0	0.426
MDD Diagnosis (Yes)	23	9.5	24	12.4	0.321

LEGEND: Comparison between the entire POAS cohort and those for whom ACE-Q data was collected revealed no significant baseline differences with respect to race, age, BMI, employment, CES-D scores, smoking, or marital status (all $p > 0.05$). Likewise, the proportion with lifetime or incident menopause MDD diagnoses at baseline and across the study did not differ ($p > 0.05$).



Supplemental Figure 1: Proportion of Women With Lifetime MDD Based on Number of ACEs

LEGEND: Comparing lifetime incidence of major depressive disorder (MDD) between women with 1 ACE and women with 2 ACEs for each definition of ACE (total, prepubertal and postpubertal), there was a significant increase in MDD risk when considering pre-pubertal ACE [Pearson Chi-square (df=1) =4.95, p-value=0.026], but not for post-pubertal ACE [Pearson Chi-square (df=1) = 3.55, p-value= 0.060] or total ACE [Pearson Chi-square (df=1) = 1.27, p-value=0.261].