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Longitudinal patterns and group heterogeneity of depressive symptoms during menopausal transition in middle-aged Korean women

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Abstract

Aims. While depressive symptoms are common during menopausal transition, the relationship between the two remains unclear. Therefore, this study aimed to examine the longitudinal changes in depressive symptoms among middle-aged Korean women and identify those with elevated and worsening symptoms during this period.

Methods. A total of 1,178 participants who underwent comprehensive health examinations at Kangbuk Samsung Hospital in Korea were followed for a median of 10.8 years (IQR, 9.2–11.6; maximum, 12.7), including all women who reached natural menopause during follow-up, with only data prior to HRT initiation included. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), and menopausal stages were classified according to the STRAW + 10 criteria and final menstrual period (FMP). Linear mixed-effects models and group-based trajectory modelling (GBTM) were applied to evaluate longitudinal changes in depressive symptoms and to identify distinct trajectories in the severity and stability of depressive symptoms.

Results. The age-adjusted prevalence of CES-D ≥ 16 was 11.0%, 11.5%, 11.2% and 12.4%, with corresponding mean scores of 6.7, 6.6, 6.9 and 7.1 across stages. After adjusting for time-varying age and covariates, menopausal stage transitions were not significantly associated with higher levels of depressive symptoms, whether analysed as continuous or binary variables. For binary CES-D (≥16), the estimated coefficients (95% CI) were 0.10 (–0.20 to 0.41) for early transition, 0.09 (–0.21 to 0.39) for late transition and 0.26 (–0.09 to 0.61) for post-menopause. Similarly, time relative to the FMP (–11 to +9 years) showed no significant association with depressive symptoms. GBTM identified three distinct trajectories: most participants (75.5%) maintained consistently low depressive symptoms throughout the transition, whereas 5.8% showed worsening symptoms. Poor sleep quality (OR 5.83, 95% CI 3.25 to 10.45) and moderate-to-severe vasomotor symptoms (OR 2.95, 95% CI 1.30 to 6.70) were significantly associated with the worsening trajectory. Suicidal ideation was higher in this group (45.4% at baseline, increasing to 70.5% at follow-up).

Conclusions. Most women maintained low depressive symptoms during the menopausal transition; however, a subset experienced worsening symptoms linked to menopause-related physical symptoms. Medical visits for menopause-related symptoms may provide opportunities for screening depressive symptoms in higher-risk women, though the screening effectiveness requires further evaluation.

Introduction

Menopausal transition (MT) represents a critical period in women's health, marked by fluctuating and declining ovarian hormones that initiate broad physical and psychological changes (Gordon *et al.*, 2021; Jia *et al.*, 2024; Joffe *et al.*, 2020; Weber *et al.*, 2014). Estradiol variability, in particular, affects the frontolimbic emotion-regulation network, encompassing the prefrontal cortex and amygdala (Newhouse and Albert, 2015a). Both regions express estrogen receptors (ERα and Erβ in the prefrontal cortex; Erα in the amygdala), making them vulnerable to hormonal fluctuations (Hara *et al.*, 2015; Österlund *et al.*, 1999). During MT, heightened estradiol variability may impair synaptic function and neurotransmission, weakening prefrontal regulatory control (Motzkin *et al.*, 2015) and producing amygdala hyperreactivity (Hamilton *et al.*, 2012), thereby inducing a neurobiological vulnerability to depressive symptoms, particularly when compounded by concurrent midlife stressors.

Although biologically plausible, epidemiological findings remain inconsistent. Some studies showed no overall significant association between MT and depression (Hickey *et al.*, 2016; Woods *et al.*, 2006), while others identify increases in depressive symptoms during the transition (Badawy *et al.*, 2024; Bromberger *et al.*, 2010; Cohen *et al.*, 2006; Colvin *et al.*, 2017; Freeman *et al.*, 2006). Importantly, longitudinal studies demonstrate heterogeneous trajectories, revealing subgroups of women who differ in symptom severity and stability over time, with some showing persistent or worsening symptoms and others remaining stable (Hickey *et al.*, 2016; Musliner *et al.*, 2016). Symptom worsening has been associated with non-White race/ethnicity, those with lower income and education (Musliner *et al.*, 2016), and frequent stressful life events (Bromberger *et al.*, 2007; Musliner *et al.*, 2016), whereas greater perceived social support appears protective (Avis *et al.*, 2024).

Methodological heterogeneity complicates interpretation. Studies vary in how depressive symptoms are assessed and classified – employing different tools such as the Center for Epidemiologic Studies Depression Scale (CES-D) (An *et al.*, 2022) vs. the Patient Health Questionnaire-9 (PHQ-9) (Lee *et al.*, 2018), using continuous scores (Hickey *et al.*, 2016) vs. categorical cut points (Bromberger *et al.*, 2007); in population sampling – community-based (Bromberger *et al.*, 2007) vs. clinic-based cohorts (Schmidt *et al.*, 2015); in time-scale definitions – menopausal stages (Campbell *et al.*, 2017) vs. years relative to the final menstrual period (FMP) (Freeman *et al.*, 2014); and in modelling approaches – mixed-effects models (Woods *et al.*, 2008) vs. group-based trajectory or latent-class models (Hickey *et al.*, 2016; Musliner *et al.*, 2016).

Beyond depressive symptoms per se, worsening sleep quality and vasomotor symptoms (VMS), such as hot flashes, are common during MT and contribute to increased depressive symptoms (Brown *et al.*, 2009) and, in some cases, suicidal ideation (Sugawara *et al.*, 2012). Ethnic differences have also been observed, with Asian women experiencing more depressive symptoms during MT than White women (Avis *et al.*, 2024). However, most studies are derived from Western populations (Bromberger *et al.*, 2007; Freeman *et al.*, 2014; Woods *et al.*, 2006), leaving a gap in the research on Asian populations.

This study had three aims. First, we examined the longitudinal changes in depressive symptoms among middle-aged Korean women during MT, as defined by the Stages of Reproductive Ageing Workshop + 10 criteria (Harlow *et al.*, 2012), and in relation to their FMP (McKinlay, 1996). Second, we investigated the heterogeneity of symptom patterns to determine whether distinct trajectories reflecting differences in severity and stability emerged over time. Third, we sought to elucidate the features of high-risk groups to help identify them at baseline.

Methods

Study population

This prospective study recruited participants between 2014 and 2018 from the Kangbuk Samsung Health Study, a cohort of Korean adults undergoing comprehensive health examinations at Kangbuk Samsung Hospital. Written consent was obtained from all participants for longitudinal follow-up and the research use of pre-enrolment data, and the study period spanned 2011 to 2023 (Cho *et al.*, 2022; Choi *et al.*, 2024; Namgoung *et al.*, 2022).

Enrolment criteria included: (1) no history of oophorectomy, hysterectomy or hormone therapy; (2) at least one menstrual period within the past three months and no history of amenorrhea lasting ≥60 days (consistent with premenopausal or early transition stage per STRAW + 10 [Harlow *et al.*, 2012]); and (3) no history of malignancy, renal failure, hypothyroidism or hyperthyroidism that could influence the menstrual cycle.

To assess the changes in depressive symptoms over time from pre-menopause through post-menopause, we focused on women who had reached menopause ($n = 1{,}680$; 32.0% of the enrolled participants). We excluded women with induced menopause ($n = 40$), unclear FMP dates ($n = 8$) and non-premenopausal stage at baseline ($n = 92$). For women who initiated hormone therapy during follow-up, only pre-treatment observations were included in analyses. We further excluded participants with fewer than three CES-D assessments with at least two before and one after the FMP ($n = 355$, required for reliable group-based trajectory modelling [GBTM] analysis) (Nagin, 2009) and women who started hormone therapy but did not meet the minimum observation criteria before treatment initiation ($n = 7$) (Fig. 1). Final analytic sample comprised 1,178 women with observation windows ranging from 11 years before to 9 years after the FMP. Individual follow-up varied (e.g., −6 to +6 years or −11 to +1 year relative to FMP).

Measurement

Demographic and socioeconomic factors, lifestyle habits and reproductive, menstrual, medical, and medication history were assessed using standardised self-administered questionnaires. Body mass index was calculated from nurse-measured height and weight, categorised by Asian standards as normal (<23.0 kg/m^2), overweight (23.0–24.9 kg/m^2) and obese (≥25.0 kg/m^2) (Organization WH, 2000). Physical activity was assessed using the Korean short form of the International Physical Activity Questionnaire (Chun, 2012; Oh *et al.*, 2007), with total MET-minutes/week calculated from frequency, duration and intensity-specific MET values (3.3, 4.0, 8.0 METs for low, moderate and vigorous, respectively) and classified as inactive (<600 MET-minutes/week), minimally active (600–2,999) or health-enhancing physical activity (HEPA; ≥3,000). Smoking status was defined as ever smoker (>5 packs lifetime) or never smoker (Agaku *et al.*, 2014). Alcohol consumption was categorised using 10 g ethanol/day as the cutoff for light drinking (Chang *et al.*, 2019; Fernández-Solà, 2015). Employment status was defined as employed if a participant worked for pay for at least 1 hour or as an unpaid family worker for at least 18 hours

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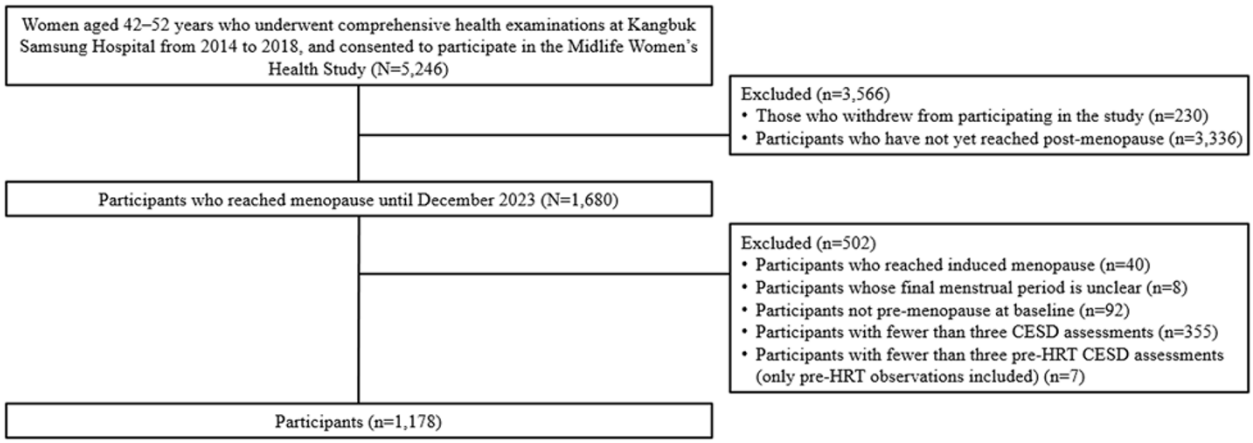

Figure 1. Flowchart of participant selection.

during the past 7 days; otherwise, the participant was classified as not employed (Kim *et al.*, 2024). Other covariates included marital status (married/cohabiting, unmarried or divorced/separated/widowed), parity (nulliparous/parous), age at menarche (<14, 14–16, ≥17 years) and educational attainment (high school graduate or below vs. college graduate or above). Sleep quality over the past month was assessed using the Pittsburgh Sleep Quality Index (PSQI), with poor sleep quality defined as PSQI ≥ 6 (Buysse *et al.*, 1989; Shin and Kim, 2020). Participants' VMS were assessed using the average score of three items (hot flashes, night sweats and sweating) from the Menopause-Specific Quality of Life questionnaire (Park *et al.*, 2020; Sydora *et al.*, 2016), allowing for one missing item, in which case, the average of the remaining two responses was used. Severity was rated on a scale of 1–8, with 1 indicating no symptoms, 1.1–3 indicating mild symptoms and values greater than 3 indicating moderate to severe symptoms (Choi *et al.*, 2024).

Depressive symptoms and suicidal ideation

Depressive symptoms over the past week were assessed using the Korean version of the CES-D, a validated 20-item instrument with each item rated on a 4-point scale from 0 to 3, yielding total scores ranging from 0 to 60 (Cho and Kim, 1998; Radloff, 1977). Participants were categorised into three groups: non-depressed (CES-D: < 8), subthreshold depressive symptoms (CES-D: 8–15) and clinically relevant depressive symptoms (CES-D: ≥ 16) (Cuijpers *et al.*, 2013; Hybels *et al.*, 2001; Vahia *et al.*, 2010).

Suicidal ideation was assessed using two items from the health screening self-questionnaire with yes/no responses: 'In the last year, have you ever thought about wanting to die?' and 'Have you attempted suicide in the last year?' If the response to either item was 'yes', the participant was categorised as having suicidal ideation (An *et al.*, 2022; Czyz *et al.*, 2019; Kleiman *et al.*, 2018).

Statistical analyses

Baseline characteristics are presented as mean (SD) for continuous variables and frequencies (percentages) for categorical variables. To examine the associations between MT and annual years from −11 to +9 relative to the FMP with depressive symptoms, a linear mixed-effects model was employed with random intercepts using participant IDs. Main exposures (menopausal stage transitions and years relative to the FMP (−11 to +9) and the outcome variable (CES-D scores) were treated as time-varying, with age as a time-varying covariate and others as time-fixed.

To address potential differences between women included (n = 1,178) and excluded (n = 502) among women who reached menopause (n = 1,680), inverse probability weighting (IPW) was applied (Chesnaye *et al.*, 2022). Predicted probabilities were estimated from a logistic regression model with inclusion status (included = 1, not included = 0) as the dependent variable and baseline characteristics as independent variables, including age, depressive symptoms (CES-D), VMS, sleep quality, smoking status, alcohol consumption, physical activity, BMI, age at menarche, parity, marital status, education, employment status and the maximum study visits. Because all participants were premenopausal at baseline, the menopausal stage was not included. The model fit was assessed using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) (Supplementary Table 1).

GBTM identified distinct patterns of depressive symptom change over time from −11 to +9 years relative to the FMP, with optimal functional form and group number determined using AIC, BIC, entropy and posterior probabilities (Supplementary Table 2). Model robustness was assessed by residual checks (Supplementary Figure 3) and sensitivity analyses (Supplementary Figure 4). Odds ratios (ORs) compared baseline characteristics across trajectory groups with the lowest levels of depressive symptoms as the reference, using multinomial logistic regression and three progressive adjustment models: age-only; additionally adjusted for socioeconomic factors, reproductive and menstrual history and lifestyle habits; and further adjusted for VMS and sleep quality. We evaluated multicollinearity using variance inflation factors, with all values < 3.5 in model 3, indicating no substantial collinearity, and the AIC was the lowest (Supplementary Tables 3 and 4). To further examine group differences, we estimated the prevalence of suicidal ideation in each group to determine whether the proportion of individuals who reported suicidal ideation during the study period differed across groups. Additional GBTM analysis used ordinal CES-D categories (minimal symptoms [<8], subthreshold depression [8–15] (Cho *et al.*, 2021), and clinically significant depression [≥16]) with the R package lcmm. Statistical significance was set at a two-sided P-value of 0.05. Statistical analyses were performed using Stata (version 18.0; StataCorp LLC, College Station, TX, USA) and R (version 4.4.2). Missing categorical values were

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Table 1. Baseline characteristics (n = 1,178)

Baseline characteristics	Frequency (%)
Age at baseline[a]	42.6 ± 2.9
Age at menarche	
<14 years old	437 (37.1)
14–16 years old	688 (58.4)
≥17 years old	47 (4.0)
Unknown	6 (0.5)
Smoking	
Never	987 (83.8)
Currently/formerly	151 (12.8)
Unknown	40 (3.4)
Alcohol consumption	
<10 g ethanol/day	1047 (88.9)
≥10 g ethanol/day	80 (6.8)
Unknown	51 (4.3)
Parity	
Nulliparous	75 (6.4)
Parous	1057 (89.7)
Unknown	46 (3.9)
Marital status	
Married/cohabitating	1101 (93.5)
Unmarried	38 (3.2)
Divorced/separated/widowed	22 (1.9)
Unknown	17 (1.4)
Employment status	
Not employed	510 (43.3)
Employed	576 (48.9)
Unknown	92 (7.8)
Education	
≤High school	248 (21.1)
≥College	911 (77.3)
Unknown	19 (1.6)
Body mass index	
<18.5 kg/m[b]	43 (3.7)
18.5–23.0 kg/m[b]	693 (58.8)
23.0–24.9 kg/m[b]	225 (19.1)
≥25.0 kg/m[b]	216 (18.3)
Unknown	1 (0.1)
Physical activity[b]	
Inactivity	526 (44.7)
Minimal activity	501 (42.5)
Health-enhancing physical activity	147 (12.5)
Unknown	4 (0.3)
Pittsburgh Sleep Quality Index	
Good sleep quality (PSQI < 6)	713 (60.5)
Poor sleep quality (PSQI ≥ 6)	285 (24.2)
Unknown	180 (15.3)
Vasomotor symptoms	
Absent ≤ 1	831 (70.5)
Mild > 1, ≤ 3	261 (22.2)
Moderate/severe > 3	84 (7.1)
Unknown	2 (0.2)
History of hypertension	
Yes	63 (5.4)
History of diabetes	
Yes	26 (2.2)
Medication for hyperlipidaemia	
Yes	11 (0.9)

[a]Age at baseline is presented as the mean and standard deviation.
[b]The Korean version of the short form of the International Physical Activity Questionnaire was used to assess physical activity.

handled using separate 'unknown' categories, with Stata's factor-variable notation ('i.' prefix) automatically generating dummy variables during estimation.

Results

Table 1 summarises the participants' characteristics (n = 1,178). Mean age was 42.6 years (±2.9), with a median follow-up of 10.8 years (IQR, 9.2–11.6; maximum, 12.7) across a median of 9 visits (IQR, 7–11; maximum, 13) at a median 1.0-year intervals (IQR, 0.9–1.4).

The age-adjusted prevalence of CES-D ≥ 16 was 11.0%, 11.5%, 11.2% and 12.4%, and the corresponding mean scores were 6.7, 6.6, 6.9 and 7.1 across stages (Table 2). After adjusting for time-varying age and fixed covariates (smoking status, age at menarche, parity, marital status, education and employment status) with IPW applied, MT was not significantly associated with higher levels of depressive symptoms as continuous variables. For binary CES-D scores (≥16 vs. < 16), estimated coefficients (95% CI) were 0.10 (95% CI: −0.20 to 0.41) for early transition, 0.09 (95% CI: −0.21 to 0.39) for late transition and 0.26 (95% CI: −0.09 to 0.61) for post-menopause, with consistent findings for continuous CES-D scores. Time-varying age showed a non-significant negative association with depressive symptom scores (Supplementary Figure 1; Table 2). In the analysis using time relative to the FMP (−11 to +9years), the overall association with depressive symptoms remained stable, with no significant changes over time (Supplementary Figure 2).

In GBTM, we identified three distinct patterns of depressive symptom change from −11 to +9 relative to the FMP (Fig. 2), consistent across both binary categories (Fig. 2-1) and continuous CES-D scores (Fig. 2-2). When using a CES-D cutoff of 16

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Table 2. Association between menopausal transition and CES-D over time ($n = 1{,}178$)

	CES-D binary (≥16, <16)			CES-D score		
	Coefficient (95% CI)	*P*-value	Age-adjusted prevalence (%) at each stage (95% CI) [a]	Coefficient (95% CI)	*P*-value	Age-adjusted mean scores at each stage (95% CI) [a]
Time-varying age (year)	−0.013 (−0.051–0.024)	0.486		−0.053 (−0.107–0.002)	0.057	
Menopausal transition over time						
Pre-menopause	Ref	-	11.0 (9.5–12.4)	Ref	-	6.7 (6.3–7.1)
Early transition	0.103 (−0.202–0.409)	0.508	11.5 (9.4–13.5)	−0.104 (−0.514–0.306)	0.620	6.6 (6.1–7.0)
Late transition	0.090 (−0.215–0.395)	0.562	11.2 (9.4–13.0)	0.232 (−0.187–0.651)	0.278	6.9 (6.4–7.3)
Post-menopause	0.260 (−0.088–0.607)	0.143	12.4 (10.4–14.4)	0.460 (−0.032–0.953)	0.067	7.1 (6.6–7.5)

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval.
Adjusted for smoking (never, formerly/currently, unknown), age at menarche (<14, 14–16, ≥17 years, unknown), parity (nulliparous, parous, unknown), marital status (married/cohabitating, unmarried, divorced/separated/widowed, unknown), education (≤ high school, ≥ college, unknown) and employment status (not employed, employed, unknown), with a random intercept for pseudonymised identifiers, by incorporating inverse probability weighting (IPW) into the model.
aAdjusted time-varying age with a random intercept for anonymised IDs.

as a binary outcome, Group 1 (75.5%, $n = 890$) maintained consistently low levels of depressive symptoms throughout the study period. Group 2 (18.7%, $n = 220$) had relatively higher baseline depressive symptoms that slightly decreased over time. Group 3 (5.8%, $n = 68$) started with higher baseline depressive symptoms and exhibited worsening trajectories with upward convex trends.

Baseline characteristic comparisons using Group 1 as reference revealed significant associations for poor sleep quality (PSQI ≥ 6): Group 2 had an OR of 2.73 (95% CI: 1.92 to 3.90) and Group 3 had an OR of 5.83 (95% CI: 3.25 to 10.45). Regarding VMS, Group 2 had an OR of 1.46 (95% CI: 1.02 to 2.10) for mild symptoms and 2.87 (95% CI: 1.70 to 4.85) for moderate-to-severe symptoms, while Group 3 had OR of 1.89 (95% CI: 1.05 to 3.43) for mild symptoms and 2.95 (95% CI: 1.30 to 6.70) for moderate-to-severe symptoms. Age was not significantly associated with group membership (Table 3). The baseline characteristics of each group are presented in Supplementary Table 7.

Age-adjusted prevalence of suicidal ideation at baseline was 6.0 (95% CI: 3.7 to 8.3) in Group 1, 25.4 (95% CI: 17.4 to 33.4) in Group 2 and 45.4 (95% CI: 25.4 to 65.3) in Group 3 (Table 4). The age-adjusted prevalence of suicidal ideation at least once from baseline through the follow-up period increased to 16.3 (95% CI: 13.9 to 18.7) in Group 1, 49.0 (95% CI: 42.4 to 55.6) in Group 2 and 70.5 (95% CI: 59.7 to 81.4) in Group 3. After further adjustment for other covariates, similar patterns were observed.

Comparison between women who reached menopause ($n = 1{,}680$) and those who did not ($n = 3{,}336$) showed no significant age-adjusted differences in depressive symptoms (CES-D), VMS and sleep quality (Supplementary Table 8). Within the menopausal subgroup, included ($n = 1{,}178$) versus excluded ($n = 502$) women showed no significant differences in depressive symptoms or sleep quality, though VMS scores were marginally higher among excluded women ($P = 0.061$) (Supplementary Table 9).

In sensitivity analysis using ordinal CES-D categories (Supplementary Figure 5; Supplementary Tables 5 and 6), we confirmed consistent patterns. Comparisons of baseline characteristics and suicidal ideation across these trajectory groups were also consistent with the primary findings.

Discussion

This study of middle-aged Korean women undergoing natural menopause without hormone replacement therapy demonstrated longitudinal changes in depressive symptoms from pre-menopause through the MT and into the postmenopausal period. Overall, menopausal stage transitions were not significantly associated with increased depressive symptoms, regardless of whether menopausal status was assessed by clinical staging or by time relative to the FMP, ranging from 11 years before to 9 years after. However, GBTM revealed three distinct patterns: a Low-Stable group, a High-Decreasing group characterised by with slight improvement in depressive symptoms, and a High-Increasing group with continuous worsening. Although the latter two groups had similar levels of depressive symptoms at baseline, their trajectories diverged over time. The High-Increasing group demonstrated significantly higher ORs for poor sleep quality and VMS at baseline than the Low-Stable group. These associations persisted after adjusting for age, socioeconomic factors and other confounders. Importantly, this high-risk group also showed a consistently higher prevalence of suicidal ideation throughout the follow-up period, suggesting implications for future investigation and supportive strategies.

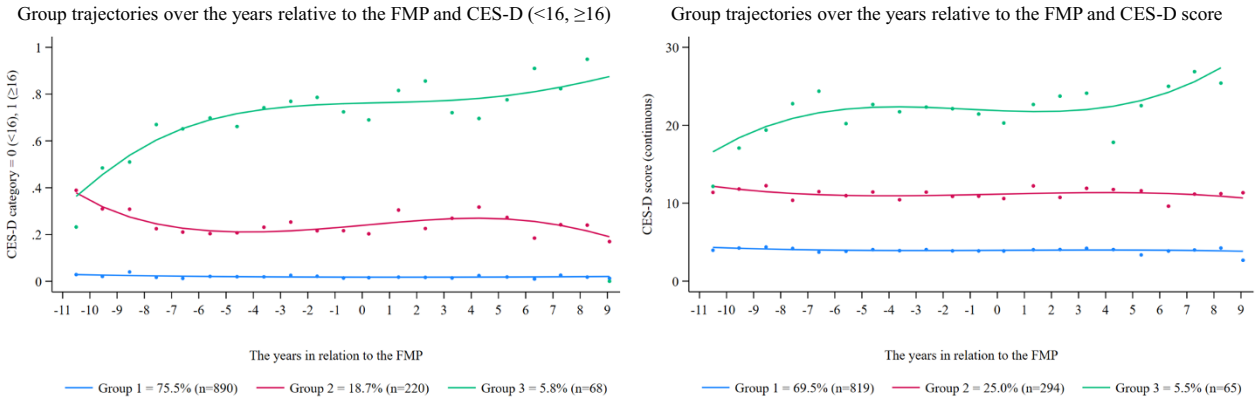

Figure 2. Group trajectories over the years relative to the FMP and CES-D (n = 1,178).
[1]Figure 2-1. Group trajectories over the years relative to the FMP and CES-D (<16, ≥16)
[2]Figure 2-2. Group trajectories over the years relative to the FMP and CES-D scores
Abbreviation: CES-D, Center for Epidemiologic Studies Depression Scale; FMP, final menstrual period

Table 3. Odds ratios of baseline characteristics for each group (n = 1,178)

Ref (Group 1)Variables	Group 2		Group 3	
	ORs (95% CI)	*P*-value	ORs (95% CI)	*P*-value
Age (year)	1.011 (0.957–1.069)	0.688	0.978 (0.889–1.075)	0.644
Pittsburgh Sleep Quality Index				
Good sleep quality (PSQI < 6)	Reference	–	Reference	–
Poor sleep quality (PSQI ≥ 6)	2.734 (1.918–3.898)	<0.001	5.827 (3.249–10.452)	<0.001
Vasomotor symptoms				
Absent ≤ 1	Reference	–	Reference	–
Mild > 1, ≤ 3	1.464 (1.020–2.101)	0.039	1.895 (1.048–3.426)	0.034
Moderate/severe > 3	2.871 (1.700–4.848)	<0.001	2.955 (1.303–6.701)	0.010

Abbreviations: ORs, odds ratios; CI, confidence interval.
Adjusted for smoking (never, formerly/currently, unknown), age at menarche (<14, 14–16, ≥17 years old, unknown), parity (nulliparous, parous, unknown), marital status (married/cohabitating, unmarried, divorced/separated/widowed, unknown), education (≤ high school, ≥ college, unknown) and employment status (not employed, employed, unknown).

Table 4. Prevalence (95% CI) of suicidal ideation by group (n = 1,178)

	Group 1 75.5% (n = 890)	Group 2 18.7% (n = 220)	Group 3 5.8% (n = 68)
Baseline prevalence of suicidal ideation			
Age-adjusted	6.0 (3.7–8.3)	25.4 (17.4–33.4)	45.4 (25.4–65.3)
Multivariable-adjusted	6.2 (3.8–8.6)	25.8 (17.6–33.9)	43.4 (22.7–64.2)
Prevalence of suicidal ideation at least once[a]			
Age-adjusted	16.3 (13.9–18.7)	49.0 (42.4–55.6)	70.5 (59.7–81.4)
Multivariable-adjusted	16.4 (14.0–18.8)	48.6 (42.0–55.3)	69.5 (58.3–80.6)

The covariates include smoking status (never, current/former, unknown), education level (≤ high school, ≥ college, unknown), parity (nulliparous, parous, unknown), age at menarche (<14, 14–16, ≥17 years old, unknown), marital status (married/cohabitating, unmarried, divorced/separated/widowed, unknown) and employment status (not employed, employed, unknown).
[a]Prevalence of suicidal ideation at least once during baseline and follow-up visits during the study period.

A recent meta-analysis of 17 cohort studies supports a heightened vulnerability, showing that perimenopausal women have a significantly higher risk for depressive symptoms and diagnoses compared to premenopausal women (Badawy *et al.*, 2024); however, findings on the association between menopausal stages and depressive symptoms vary across studies (Campbell *et al.*, 2015; Vivian-Taylor and Hickey, 2014). Some studies observed no significant association between MT and depressive symptoms (Campbell *et al.*, 2017; Mitchell and Woods, 2017; Tang *et al.*, 2019; Woods *et al.*, 2006), whereas others did (Bromberger *et al.*, 2010; Cohen *et al.*, 2006; Colvin *et al.*, 2017; Freeman *et al.*, 2006). Some studies have used the FMP time approach to observe changes in depressive symptoms before and after the FMP (Avis *et al.*, 2023, 2024; Freeman *et al.*, 2014). The average depressive symptoms tended to increase before the FMP and decrease thereafter (Avis *et al.*, 2023, 2024; Freeman *et al.*, 2014).

In the Australian Longitudinal Study on Women's Health, nearly 6,000 women aged 45–50 were followed up for over 15 years (Hickey *et al.*, 2016). Four distinct trajectories of depressive symptom changes were identified over time using latent class analysis. While the majority of women (80%) maintained consistently low

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levels of depressive symptoms, 9% exhibited an increasing pattern and 2.5% showed persistently high levels (Hickey *et al.*, 2016). In the group with increasing symptoms, there was a higher proportion of women who had undergone bilateral oophorectomy or were in the perimenopausal stage at baseline compared with the other groups (Hickey *et al.*, 2016). Furthermore, the Study of Women's Health Across the Nation (SWAN) followed approximately 3,300 women aged 42–52 for over 15 years and identified 5 distinct trajectories of depressive symptom changes over time using GBTM (Bromberger *et al.*, 2019). The majority of women (79%) maintained either very low or low symptoms, whereas 5% exhibited persistently high symptoms, and another 5% showed an increasing pattern (Bromberger *et al.*, 2019). A time-varying increase in depressive symptoms is associated with sleep problems, and social support is associated with a reduction in depressive symptoms (Bromberger *et al.*, 2019).

Our study identified three distinct depressive symptom trajectories using GBTM. Most of the participants (Group 1, 75.5%) maintained consistently low depressive symptoms, consistent with findings from previous studies (Bromberger *et al.*, 2019; Hickey *et al.*, 2016). Group 2 (18.7%) showed subthreshold depressive symptoms (Cuijpers *et al.*, 2013; Hybels *et al.*, 2001; Vahia *et al.*, 2010) that remained stable or slightly decreased over time. Group 3 (5.8%) exhibited a worsening trend despite a similar prevalence of clinically relevant depressive symptoms as Group 2 at baseline. The ORs for VMS and poor sleep quality were significantly higher in Group 3 than in Group 1. These findings are consistent with those of previous studies (Bromberger *et al.*, 2019; Caruso *et al.*, 2019; Luo and Lin, 2024; Zeleke *et al.*, 2017), including the SWAN study (Bromberger *et al.*, 2019). We also found that the prevalence of suicidal ideation was notably higher in Group 3 than in the other two groups. Given the close association between depressive symptoms, their worsening and suicidality (Jahn *et al.*, 2011), Group 3 potentially demonstrated a higher risk of more severe outcomes beyond depression, thereby necessitating careful monitoring.

A systematic review has shown that menopausal symptoms are more pronounced during MT, when estrogen fluctuations are greater, compared with post-menopause, when estrogen levels stabilise at consistently low levels (Zhang *et al.*, 2023). This supports our findings, wherein depressive symptoms in the high-risk group intensified before the FMP and continued on a mild upward trajectory thereafter. Estrogen fluctuations are closely linked to brain networks that regulate emotional sensitivity (Albert and Newhouse, 2019; Newhouse and Albert, 2015b), and previous research has suggested that affective dysregulation may increase when reproductive hormones fluctuate before the FMP (Albert and Newhouse, 2019). Additionally, midlife is a period when women assume central roles in their families and communities, which often leads to increased exposure to stressors and may contribute to elevated depressive symptoms (Lachman, 2004).

This study has several limitations. First, key exposures, outcomes and covariates – including menopausal stage, FMP, depressive symptoms, sleep quality and VMS – were assessed using self-administered structured questionnaires, though this approach is widely used in population-based studies. The CES-D screening tool, while validated for depression screening (sensitivity 0.87, specificity 0.70), may misclassify some participants (Vilagut *et al.*, 2016). Second, the analysis was restricted to women who reached menopause (32% of the original cohort), though the mean age at menopause (51.4 years) aligned with Korean population norms (HA *et al.*, 2010; Park *et al.*, 2002; Shin *et al.*, 2017). Among these women, 70.1% were included in final analyses with generally similar baseline characteristics, though VMS were marginally higher among excluded participants. Although IPW was applied to account for potential attrition bias, this bias cannot be entirely eliminated. Third, socioeconomic variables including income, employment changes and marital status transitions were not incorporated as time-varying covariates, representing a significant limitation given that socioeconomic disadvantage is an established depression risk factor. Consequently, some residual bias in the point estimates may still remain due to potential unmeasured confounding (Schneeweiss, 2006), given that socioeconomic disadvantages are established risk factors for depressive symptoms (Korous *et al.*, 2022). Finally, our occupational health screening sample likely underrepresents women with unstable employment, limiting generalizability to socioeconomically vulnerable groups. Future studies should incorporate longitudinal socioeconomic measures to assess confounding and effect modification.

Conclusion

Overall, menopausal stage transitions were not significantly associated with increased depressive symptoms, regardless of whether menopausal status was assessed by clinical staging or by time relative to the FMP. However, we identified three distinct trajectories of depressive symptom changes ranging from 11 years before to 9 years after the FMP. While most participants maintained low depressive symptoms, 5.8% experienced worsening depressive symptoms over time. This high-risk subgroup had a higher prevalence of VMS and poor sleep at baseline, as well as a markedly higher prevalence of suicidal ideation throughout the follow-up period. Given that depressive symptoms are frequently underreported in clinical settings, clinical encounters for menopause-related complaints may provide valuable screening opportunities for identifying women at higher risk. Future research should evaluate the effectiveness and feasibility of such targeted screening strategies.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796025100334.

Availability of data and materials. The data supporting the findings of this study are not publicly available at present, but the analytical methods and dataset are available from the corresponding author upon request.

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Ethical standards. This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (IRB No. KBSMC 2023-05-036). All research procedures were performed strictly according to the applicable protocols and regulations.

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