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Review article

The risk of depression in the menopausal stages: A systematic review and meta-analysis

Yasmeen Badawy, Aimee Spector *, Zishi Li, Roopal Desai

Department of Clinical Health Psychology, University College London, 1-19 Torrington Place, London WC1E 7HB, United Kingdom of Great Britain and Northern Ireland

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ABSTRACT

Introduction: For many women, menopause transition can be a period of emotional and physical changes, with different menopausal stages associated with varied risk for depressive symptoms and diagnosis. This review aimed to conduct a systematic review and meta-analyses to provide an estimate for the risk of developing a) clinical depression and b) depressive symptoms at different menopausal stages.

Methods: We searched Medline, PsycInfo, Embase and Web of Science from inception to July 2023. Seventeen prospective cohort studies with a total of 16061 women were included in the review, and risk of bias was assessed using the Quality in Prognosis Studies tool (QUIPS). Seven papers with a total of 9141 participants were included in meta-analyses, using random effects models and pooled odds ratios (OR) calculated for depressive symptoms and diagnoses.

Results: Perimenopausal women were found to be at a significantly higher risk for depressive symptoms and diagnoses, compared to premenopausal women (OR = 1.40; 95 % CI: 1.21; 1.61, $p < .001$). We did not find a significantly increased risk for depressive symptoms or diagnoses in post-menopausal, compared to pre-menopausal women.

Limitations: Studies used different criteria to classify the menopausal stages and different measures for depression, which may have contributed to the heterogeneity seen in some models. We were unable to include a model that compared *peri* to post-menopause, due to a lack of longitudinal studies comparing the two stages.

Conclusions: The risk of depression in perimenopause, shown in an ethnically diverse sample; highlights the clinical need for screening and support in this potentially vulnerable group.

1. Introduction

Menopause describes the reproductive stage where menstruation stops due to loss of ovarian follicular activity (Gyllstrom et al., 2007). The average age of menopause is 49 to 52 years, coinciding with the highest rates of depression in women as reported by epidemiological research (Takahashi and Johnson, 2015; Infurna et al., 2020). The menopause transition is characterized by fluctuating and eventually decreased levels of estrogen and progesterone as well as high levels of Follicle Stimulating Hormone (FSH) (Soares and Zitek, 2008).

A global consensus regarding the definition of menopausal stages was reached in 2001 with the development of the Stages of Reproductive Aging Workshop (STRAW) criteria, based on self-reported bleeding patterns (Soules et al., 2001). Prior to this, criteria used to define the stages of menopause varied between studies; making it difficult to determine the true effect of menopause on the development of depressive symptoms (de Kruif et al., 2016). The STRAW criteria included three phases: the reproductive stage, the menopausal transition, and the post-menopause, further divided to indicate early and late phases. These were later developed into the STRAW+10 criteria, which were more generalizable to multiethnic populations and women with physical health issues (Harlow et al., 2012).

The bio-psycho-social nature of menopause (Hunter and Rendall, 2007) demonstrates the need to understand how menopausal stage may affect the development of depression. The increased risk of depression during menopause has been attributed to biological vulnerability, with studies finding an association between greater variation in estradiol and FSH levels and higher depressive symptoms (Freeman et al., 2004). A previous meta-analysis (Weber et al., 2014), found that perimenopausal women were twice as likely to get a depression diagnosis or experience symptoms compared to pre-menopausal women. Of note, only four longitudinal studies were included in this meta-analysis, all from the

* Corresponding author.
E-mail address: a.spector@ucl.ac.uk (A. Spector).

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USA; hence reducing generalizability to other populations. More recently, de Kruif et al. (2016) pooled the results from both cross-sectional and longitudinal studies to determine the risk of depressive symptoms during menopausal stages, finding that there was a trend towards risk of clinical depression during the perimenopause, with results not statistically significant. A key limitation noted was that more studies using the STRAW criteria were needed.

This study aimed to update the review of Weber et al. (2014), synthesizing evidence from existing prospective cohort studies on the relationship between menopausal stage and depression. The key research question was: Is there is an association between menopausal stage and risk of (a) depressive symptoms and (b) depression diagnosis?

2. Methods

This systematic review was registered with PROSPERO (CRD42023426139). The search was performed in accordance with the PRISMA 2020 guidelines for systematic reviews (Page et al., 2021)

2.1. Search and selection of relevant studies

We searched four databases: Medline, PsycInfo, and Embase separately on Ovid and Web of Science from inception to 12th July 2023. All combinations of the following terms were used "premenopaus*", "postmenopaus*", and "perimenopaus*" in combination with "depression" or "depressive symptoms" or "mood" in combination with "stage*" in adjacency with "menopause*" searched in the title and abstract. This search was replicated in Web of Science with the necessary adjustments. Additional limits included the English language and humans. For the Embase and Medline search, the MeSH terms for "depression" and "mood change" were used. Reference lists of other meta-analyses on the topic (Weber et al., 2014; de Kruif et al., 2016) were examined to identify other relevant studies.

Studies were included if they were (1) peer reviewed (2) longitudinal prospective cohort (3) used a population of females over 18 who were pre, *peri*, or postmenopausal (4) assessed the difference between pre, peri, or postmenopausal stages or any of those combinations (5) used standard depression inventories for symptoms or standardized interviews for a depression diagnosis (6) published in the English language. Excluded studies were: (1) systematic reviews (2) intervention studies (3) studies using participants who underwent surgical menopause or psychiatric populations. In a situation where more than one study had reported data from the same cohort, we included the study using the largest sample size.

The results were deduplicated and titles, abstracts, and full texts were screened by one reviewer (YB), with 10 % screened by a second independent reviewer (ZL) using Rayyan. Inter-rater reliability for both stages was calculated using Cohen's kappa. Disagreements were resolved in discussion with a third reviewer (RD) in a consensus meeting.

2.2. Quality assessment

The quality of the studies was assessed using the Quality of Prognosis Studies in Systematic Reviews (QUIPS) tool (Hayden et al., 2013). This is based on six domains divided into subdomains. Based on previous research, eight subdomains were chosen (Hayden et al., 2013): (i) baseline characteristics were provided; (ii) inclusion criteria were specified; (iii) at least 70 % participation rate; (iv) no difference at baseline between participants and drop-outs; (v) menopausal stages identified using STRAW criteria (Harlow et al., 2012); (vi) outcomes assessed using standardized scales with validated cut-off scores; (vii) potential confounders taken into consideration; (viii) statistical model presented was sufficient. Each study was given an overall risk of bias rating: 'low' where 6–8 criteria were met, 'moderate' where 3–5 items were met, or 'high' where 0–2 items were met. Only studies with moderate or low risk were included in this review.

2.3. Data extraction

Data extraction was conducted by two reviewers (YB and RD) who identified relevant statistics and study characteristics from each paper, presented in Table 1. All studies reported both depressive symptoms and diagnoses as binary outcomes. The least adjusted odds ratios (OR) and 95 % confidence intervals (CI) for depressive symptoms or diagnosis were extracted for each menopausal stage reported. The least adjusted model was used to optimise comparability between studies. For studies that did not report effect sizes, raw frequency data was extracted and the OR and 95 % CI calculated. All comparisons used the premenopausal group as the reference group. Where a study reported insufficient data, study authors were contacted to obtain the raw data.

2.4. Meta-analyses

Random effects meta-analyses were conducted using the inverse variance weighted method to pool the effect sizes. The analyses were conducted using the metafor package (Viechtbauer, 2010) in R studio (version 4.2.2).

3. Results

3.1. Search results

The search yielded 2094 studies, reducing to 1296 after removing duplicates. After screening the titles and the abstracts, 34 studies were excluded because they were cross-sectional. During the full text screening stage, 23 studies were excluded for either not meeting the inclusion criteria or having insufficient data. Seventeen longitudinal studies (Avis et al., 1994; Bromberger et al., 2010; Bromberger et al., 2007; Bromberger et al., 2011; Cohen et al., 2006; Campbell et al., 2017; Colvin et al., 2017; Dennerstein et al., 2004; Freeman et al., 2006; Freeman et al., 2004; Freeman et al., 2014; Hickey et al., 2016; Maartens et al., 2002; Mulhall et al., 2018; Rössler et al., 2016; Tang et al., 2019; Tang et al., 2020) were eligible for the review. The study by Dennerstein et al. (2004) was identified through examination of de Kruif et al.'s (2016) reference list. Four studies were eligible for the review but not the meta-analyses because they did not report sufficient data (Campbell et al., 2017; Mulhall et al., 2018; Dennerstein et al., 2004; Hickey et al., 2016). Seven studies (Tang et al., 2020; Bromberger et al., 2007; Bromberger et al., 2011; Colvin et al., 2017; Freeman et al., 2014; Freeman et al., 2006) were included in the review but excluded from the meta-analyses due to reporting data from the same cohort as another study included in the analysis. The PRISMA flow diagram for study selection is presented in Fig. 1.

3.2. Characteristics of the studies

The study characteristics are presented in Table 1. Year of publication ranged from 2001 to 2022. Sample sizes ranged from 116 to 5895, with a total of 16061 included; and follow-up periods ranging from three to thirty years. The mean age of the participants ranged from 35 to 50 years at baseline. Ethnicity was not reported in all studies, but showed variation where it was reported. The Penn Ovarian Aging Study sample consisted of around 43 % African American and 57 % White participants (Freeman et al., 2006; Freeman et al., 2004; Freeman et al., 2014). The studies that used data from the SWAN cohort included a sample of diverse participants including 46 % White, 26 % African American, 5 % Hispanic, 11 % Chinese, and 12 % Japanese (Bromberger et al., 2007; Bromberger et al., 2010; Colvin et al., 2017; Bromberger et al., 2011). The Australian Longitudinal Study of Women's Health included refugees and migrants and reported the country of birth of participants: 73 % were Australian born, 17 % were from another English-speaking

Table 1
Characteristics of studies included in the review.

Author/Year	Study/location	Entry Criteria/Exclusion Criteria	Follow-up period (Years)	N	Age mean (SD)/ range (Years)	Statistic Reported	Menopausal Stages and Criteria/ Effect Size (95% CI)	Outcome Measure (Cut-off score)	Main Findings	Covariates	Risk of Bias rating
*Campbell et al. 2016	Women's Health Aging Project, originally Melbourne Women's Midlife Health Project, Australia	Australian born women at baseline who menstruated in the last 3 months/ Taking HT or contraceptives.	11	273	45-55	Mean (SD)	**STRAW+10 criteria** Menopausal transition 8.47 (6.09) Stage 1a 6.75 (5.66) Stage 1b 8.24 (5.27) Stage 1c 6.81(5.61) Late menopause (after 1c) 5.7 (5.73)	CESD-10 (≥10)	**Depressive symptoms:** CES-D-10 scores were higher in the menopausal transition compared with other periods during the stages of reproductive aging and were lowest in the late post-menopause.	Age and years of education	Low
*Dennerstein et al. 2004	The Melbourne Women's Midlife Health Project, Australia	See study criteria above for Melbourne Women's Midlife Health Project.	11	314	59.9 (2.5)	Mean (SD)	**STRAW criteria** Early/late Peri At 10th Year 8.9 (5.9) Post 6.7 (4.2)	CES-D (≥10)	**Depressive symptoms:** The few women in the cohort who remained in the menopause transition had higher depressed mood scores than women who had become postmenopausal.	Demographic variables Lifestyle factors Health status Menopause symptoms Medication	Low
*Mulhall et al. 2018	Personality and Total Health through life project waves 1-3, Australia	Women who were premenopausal at Wave 1/ Women who had undergone a hysterectomy, oophorectomy, current HT or contraceptive use, and those with an indeterminable menopausal stage at wave 3	8	711	50.6(1.5)	Adjusted IRR	**Questionnaire Drew upon STRAW+10** Pre vs Peri 1.32 (1.08, 1.60) Pre vs Post 1.27 (1.02, 1.56)	GDS (NR)	**Depressive symptoms**: perimenopause was associated with increased risk independent of the effect of covariates.	Age and education	Moderate
Avis et al. 1994	Massachusetts Women's Health Study From census lists, USA	Women from the census lists who had menstruated in the previous 3 months, had a uterus and at least one ovary intact. Six telephone calls consisting of 30-minute interviews were conducted 9 months apart over the follow-up period.	5	2356	45-55	OR	**Study's Interview** Pre vs Peri 1.56 (0.72, 3.40) Pre vs Peri/Post 1.62 (0.81, 3.24)	CES-D (≥16)	**Depressive symptoms:** Perimenopause is associated with a slight increase in depression, but this association can be explained by increased menopausal symptom reporting and appears to be transitory **(NS)**.	History of depression Demographic variables Vasomotor symptoms HRT	Low
*Bromberger et al. 2007	SWAN cohort study, USA	Eligible women had an intact uterus, were not using Hormones, had at least one menstrual period in the last three months, and self-identified as non-Hispanic White or African American Interviewers were required to hold a Masters or PhD in a mental health field or have relevant prior clinical experience.	5	2885	46.5(2.7)	Adjusted OR	**STRAW criteria** Pre vs Early Peri 1.3 (1.09, 1.55) Pre vs Late Peri 1.71 (1.27, 2.30) Pre vs Post 1.57 (1.15, 2.15)	CES-D (≥16)	**Depressive symptoms:** The risk was significantly higher when a woman was early peri, late peri or postmenopausal relative to when she was premenopausal after controlling for other covariates.	Ethnicity Economic status Hot flashes Attitudes Psychotropic medication Social support and life stressors	Low
*Bromberger et al. 2010	SWAN Cohort study, USA	See SWAN cohort study criteria above.	8	3292	45.8(2.7)	Adjusted OR	**STRAW criteria** Pre vs Early Peri 1.35 (1.14, 1.61) Pre vs Late Peri 1.68 (1.28, 2.2) Pre vs Post 1.83 (1.40, 2.42)	CES-D (≥16)	**Depressive symptoms:** Peri and post-menopause continued to be significantly independently associated with odds of high depressive symptoms after adjusting for covariates.	Demographic variables Smoking Medication Vasomotor symptoms Social support Upsetting life events Study site	Low
Bromberger et al. 2011	SWAN Cohort study (Pittsburgh), USA	See SWAN cohort study criteria above.	10	221	42-52	Adjusted OR	**STRAW criteria** Pre vs Peri 2.17 (1.23. 3.81) Pre vs Post 3.43 (1.79, 6.56)	SCID	**Depressive disorder:** The peri and post-menopause remained significantly Related to the development of a new major depressive episode independent of covariates.	History of depression Age, race and BMI Frequent vasomotor symptoms Medication Life events	Low
Cohen et al. 2006	The Harvard Study of Moods and Cycles, USA	Women residing in Boston, Metropolitan area Without a lifetime history of major depression/ Pregnancy, menopausal status, mania or psychosis.	3	460	36-45	OR	**STRAW criteria** Pre vs Peri (First any depressive symptoms onset) 1.80 (1.10, 3.20) Pre vs Peri (Severe first onset) 1.90 (0.89, 4.0)	CES-D (≥16) CES-D (≥24)	**Depressive symptoms and disorder**: The study suggests an increased risk of depressive symptoms and clinical depression in the perimenopause compared to the pre-menopause.	Vasomotor symptoms Negative life experiences Age at study enrollment No history of depression at baseline	Low
*Colvin et al. 2017	SWAN cohort study (Pittsburgh), USA	See SWAN cohort study criteria above.	10	443	40-44	Adjusted OR	**STRAW+10 criteria** Pre/early peri vs Late peri/post 3.01 (1.76, 5.15)	SCID	**Depressive disorder:** Menopause status was significantly associated with major depression in those without and with family history of depression.	Trait anxiety History of major depression Upsetting life events	Low
Freeman et al. 2004	POAS, USA	Women who Premenopausal at enrollment and reached natural menopause during the follow up period, had an intact uterus and at least one ovary/ use of hormone or psychotropic medication, alcohol or drug abuse, major psychiatric disorder, pregnancy or any health problems affecting ovarian function. Sampling was stratified to have equal numbers of White and African American women.	4	332	35-47	OR OR	**STRAW criteria** Pre vs Early Peri 1.33(0.95, 1.86) Pre vs Late Peri 1.79(0.90, 3.56) Pre vs Post 0.36 (0.09, 1.39) Pre vs Early Peri 1.12 (0.75, 1.67) Pre vs Late Peri/Post 0.33 (0.08, 1.44)	CES-D (≥16) PRIME-MD	**Depressive symptoms:** Symptoms significantly increased during the transition to menopause and decreased after menopause after controlling for other covariates. **Depressive disorder:** New cases of MDD were more likely to occur in the early transition phase but small numbers in the MDD group were insufficient to reach statistical significance. **(NS)**	History of depression Demographic variables PMS Hot flashes Sleep	Low
*Freeman et al. 2006	POAS, USA	See POAS study criteria above.	8	231	42.2 (NR)	OR OR	**STRAW Criteria** Pre vs Peri 4.29 (2.39, 7.72) Pre vs Peri 2.50 (1.25, 5.02)	CES-D (≥16) PHQ-9/PRIME-MD (≥10)	**Depressive symptoms**: ≥4 times more likely to occur in the menopausal transition vs premenopausal period in unadjusted analyses. Five times more likely after adjusting for other covariates. **Depressive disorder:** twice as likely to occur in menopausal transition vs premenopausal status.	BMI Hot flashes Smoking status PMS Mean Estradiol No history of depression at baseline	Low

***Freeman et al. 2014**	POAS, USA	See POAS study criteria above.	14	NR	42.77 (3.12)	OR	**STRAW+10 Criteria** Pre/Peri vs Post (8 yrs after FMP) 0.85 (0.81, 0.89)	CES-D (≥16)	**Depressive symptoms:** There was a risk of depressive symptoms for those who first experienced the symptoms in the menopause transition continued for several years after the FMP but then sharply decreased.	History of depression Age BMI Smoking status Race	Low
Hickey et al. 2016	Australian Longitudinal Study of Women's Health, Australia	Women who are permanent residents of Australia including refugees and migrants/ women using oral contraceptive pills, had missing data on depressive symptoms or menopause status or covariates.	15	5895	49.5(1.5)	Parameter estimates	**STRAW+10 criteria** Pre vs Peri 0.18 (0.01, 0.29) Pre vs Post —0.06 (—0.28, 0.17)	CESD-10 (≥10)	**Depressive symptoms:** Those in the perimenopausal stage had significantly higher CES-D than those who were post or perimenopausal even after adjustment for covariates.	Demographic variables Night sweats History of depression Lifestyle factors	Low
Maartens et al. 2002	Eindhoven Perimenopausal Osteoporosis Study, Netherlands	Only Dutch Caucasian women Not using HRT and not having undergone a hysterectomy or ovariectomy	3.5	2103	47-54	Adjusted OR	**Menstrual patterns** Pre vs Peri 1.8 (1.12, 3.33) Peri vs Post 1.81 (1.25, 2.56)	EDS (≥12)	**Depressive symptoms:** The perimenopause showed an independent relation to a high increase of depressive symptoms.	Age Marital status Employment Occurrence of major life events	Low
Rössler et al. 2016	Zurich Study, Switzerland	Women who participated consistently until 2008 and were still menstruating in 1999.	30	168	49.8(2.6)	beta OR	**Study Interview** Pre vs Peri 0.09 (—0.131, 0.311) Pre vs Post 0 (—0.22, 0.22) Pre vs Peri 0.71 (0.34, 1.51) Pre vs Post 0.57(0.24, 1.37)	SCL-90-R (NR) DSMIII depression diagnosis	**Depressive symptoms and disorder:** No symptom score increased or decreased significantly over time in relation to menopause status. **(NS)**	Preceding psychological vulnerability Duration of reproductive period Age at menopause	Moderate
Tang et al. 2019	PALM study, China	Female residents of the TieEr community in Beijng China who Have an intact uterus, at least one ovary and no history of HRT in past 3 months, not pregnant r lactating in past 6 months, no reproductive disorders.	10	430	52.5(6.4)	OR	**STRAW+10 criteria** Pre vs Early Peri 1.17 (0.68, 2.02) Pre vs Late Peri 0.98 (0.57, 1.68) Pre vs Post (Stage +1a) 1.06 (0.58, 1.95) Pre vs Post (Stage +1b) 1.25(0.69, 2.28) Pre vs Post (Stage 1+c) 1.37(0.8, 2.37) Pre vs Post (Stage +2) 1.34(0.77, 2.34)	HADS-D (≥8)	**Depressive symptoms:** The association between menopausal stage and depression was not statistically significant. **(NS)**	BMI Physical health status Education and income Night sweats Hot flashes	Low
***Tang et al. 2020**	PALM cohort study, China	See PALM study criteria above	10	430	52.5(6.4)	Adjusted OR	**STRAW+10 criteria** Pre vs Early Peri 1.58 (0.9, 2.78) Pre vs Late Peri 3.19 (1.75, 5.84) Pre vs Post, Stage 1a 6.28 (3.17, 12.44)	HADS-D (≥8)	**Depressive symptoms:** The prevalence of symptoms of anxiety and depression was higher during the pre- and post-menopausal stage than during the premenopausal stage.	BMI General health status Demographic variables Log FSH and log estradiol	Moderate

Note. All reported odds ratios are unadjusted and used the premenopausal group as a reference unless specified otherwise. * Excluded from the meta-analyses because of insufficient data or repeated cohort with smaller sample size. Abbreviations. N: sample size included in the analyses; NR: Not reported; OR: Odds ratios; CI: Confidence intervals; NS: non-significant association, BMI: Body Mass Index; PMS: Premenstrual Syndrome; STRAW: Stages of Reproductive Aging Workshop SWAN: Study of Women's Health Across the Nation; POAS: Penn Ovarian Aging Study; PALM: Peking Union Medical College Hospital Aging Longitudinal Cohort of Women in Midlife; CES-D: Center for Epidemiological Studies Depression scale; CESD-10: short 10-item form of the CES-D; PHQ-9: Patient Health Questionnaire; HADS-D: Hospital Anxiety and Depression Scale; SCID is the Structured Clinical Interview for DSM-5; GDS is the Goldberg Depression Scale; MDD: Major Depressive Disorder Diagnosis; EDS: Edinburgh Depression Scale; PRIME-MD is the Primary Care Evaluation of Mental Disorders; HRT: Hormone Replacement Therapy; Pre: Premenopausal stage; Peri: Perimenopausal stage; Post: Postmenopausal stage.

background, 6.4 % from Europe, 2.5 % from Asia, and 1 % were from another country (Hickey et al., 2016). Nine studies did not report ethnicity.

Nine studies took place in the USA (Freeman et al., 2006; Cohen et al., 2006; Bromberger et al., 2007; Bromberger et al., 2010; Bromberger et al., 2011; Colvin et al., 2017; Freeman et al., 2004; Avis et al., 1994; Freeman et al., 2014), four in Australia (Hickey et al., 2016; Campbell et al., 2017; Dennerstein et al., 2004; Mulhall et al., 2018), two in Europe (Rössler et al., 2016; Maartens et al., 2002), and two in Asia (Tang et al., 2020; Tang et al., 2019).

Seven of the studies reporting depressive symptoms used the Center for Epidemiological Studies Depression Scale (CES-D) which is a 20-item rating scale with a cut-off score of ≥16. This cut-off score is used to indicate high depressive symptoms which may develop into major depression (Lewinsohn et al., 1997). Three studies (Campbell et al., 2017; Hickey et al., 2016; Dennerstein et al., 2004) used the CESD-10 brief version with a cut-off score of ≥10 (Shrout and Yager, 1989). Four studies (Tang et al., 2019; Mulhall et al., 2018; Rössler et al., 2016; Maartens et al., 2002) used other standardized scales to measure depressive symptoms (Table 1). Six studies (Freeman et al., 2004; Rössler et al., 2016; Bromberger et al., 2011; Freeman et al., 2014; Colvin et al., 2017) used standard interview questions to determine a depression diagnosis.

All the included studies in the review used each woman in the cohort as her own control, following her up prospectively from pre/early *peri*-menopause until late peri or post-menopause. Thirteen studies used the STRAW criteria (Harlow et al., 2012) for defining menopausal stages. Four studies used other ways of defining menopausal stages (Rössler et al., 2016; Avis et al., 1994; Maartens et al., 2002; Mulhall et al., 2018).

The POAS study in 2006 (Freeman et al., 2006) and the Harvard Study of Moods and Cycles (Cohen et al., 2006) used a sample of participants with no history of depression. The study by Rössler et al. (2016) included preceding psychological vulnerability as a covariate. Seven studies (Bromberger et al., 2011; Colvin et al., 2017; Hickey et al., 2016; Avis et al., 1994; Freeman et al., 2014; Freeman et al., 2004) adjusted for depression at baseline or history of depression in the analyses. The remaining seven studies did not take history of depression into consideration.

Three studies (Tang et al., 2020; Mulhall et al., 2018; Rössler et al., 2016) were rated to have a moderate risk of bias and the remaining fourteen a low risk of bias according to the QUIPS criteria.

3.3. *Meta-analyses*

3.3.1. *Pre-menopause vs perimenopause*

Pooling the results from seven studies (Avis et al., 1994; Bromberger et al., 2010; Cohen et al., 2006; Freeman et al., 2004; Maartens et al., 2002; Rössler et al., 2016; Tang et al., 2019), we found that compared to the pre-menopausal stage, women in the perimenopausal stage were at significantly increased risk (OR = 1.40, 95 % CI: 1.21; 1.61, $p < .001$) of elevated depressive symptoms or receiving a diagnosis of depression (Fig. 2). There was low heterogeneity in this model ($\chi^2 = 6.87$, df = 6, $p = .33$, $I^2 = 0.01$ %).

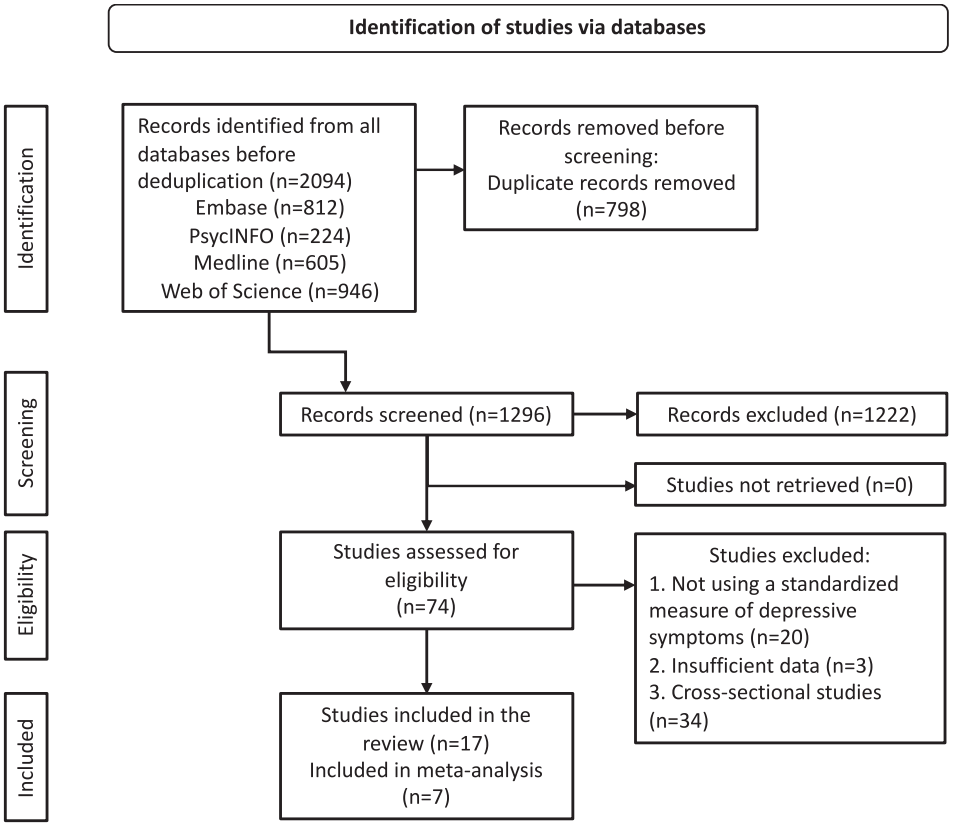

Fig. 1. PRISMA Flow Chart *from* Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Aki, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLOS Medicine*, *18*(3), Article e1003583. doi:10.1371/journal.pmed.1003583.

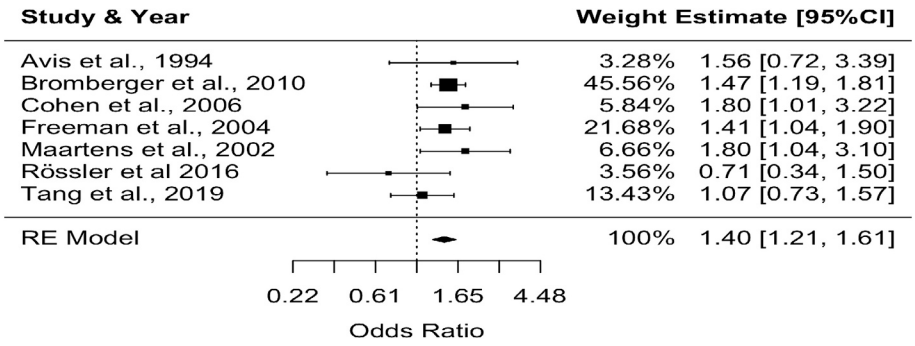

Fig. 2. Forest plot of the random effects model comparing the odds of depressive symptoms and diagnosis in the perimenopausal versus premenopausal period.

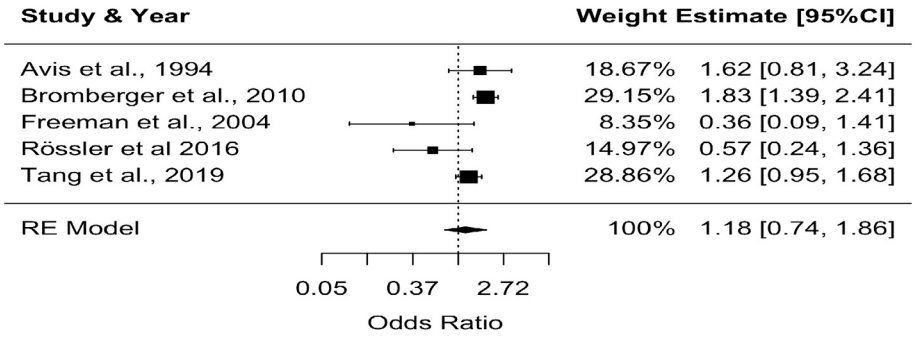

Fig. 3. Forest plot for the random effects model comparing the odds of depressive symptoms and diagnosis in the postmenopausal versus premenopausal period.

3.3.2. Pre-menopause vs post-menopause

Pooling the results from five studies (Rössler et al., 2016; Bromberger et al., 2010; Freeman et al., 2004; Tang et al., 2019; Avis et al., 1994) there was no significant (OR = 1.18, 95 % CI: 0.74; 1.86; $p = .48$) increase in risk of a depression diagnosis or depressive symptoms in the post-menopausal compared to the premenopausal period. There was significant heterogeneity ($\chi^2 = 12.28$, df = 4, $p = .02$, $I^2 = 74.59$ %) in the model. Pooling depressive symptoms and diagnoses as an outcome in this model may account for some of the heterogeneity, so two separate models were conducted for each outcome (Fig. 3).

For depressive symptoms as an outcome, three studies (Bromberger et al., 2010; Freeman et al., 2004; Tang et al., 2019) were included in the model and the results remained non-significant (OR = 1.25, 95 % CI: 0.69; 2.26, $p = .46$) with significant heterogeneity ($\chi^2 = 7.63$, df = 2, $p = .02$, $I^2 = 83.15$ %). For depression diagnosis as an outcome, three studies (Avis et al., 1994; Rössler et al., 2016; Freeman et al., 2004) were included and the results remained non-significant (OR = 0.77, 95 % CI: 0.31; 1.93, $p = .58$) with heterogeneity being slightly reduced ($\chi^2 = 5.65$, df = 2, $p = .05$, $I^2 = 63.98$ %) (Figs. 4 and 5).

4. Discussion

4.1. Main findings

This review and meta-analyses found that women are at significantly greater risk of depressive symptoms and diagnoses when in the perimenopausal compared to the pre-menopausal stage. These results are consistent with previous findings from cross-sectional and longitudinal studies from the USA and Asia (Juang et al., 2005; Bromberger et al., 2011; Tang et al., 2020) as well as Weber et al.'s review (2014). However, there was no difference found in depressive symptoms or diagnoses when comparing post-menopause to pre-menopause. Consistent with those findings, the Australian Longitudinal Study of Women's Health (consisting of 5895 participants) did not find a statistically significant increased risk of clinical depression in the postmenopausal compared to the premenopausal stage (Hickey et al., 2016). In contrast, Gibson et al. (2011) found that depressive symptoms actually decreased in the years following menopause. These inconsistent findings for depressive symptoms and diagnoses post-menopause suggest that more research is needed focusing on that stage.

4.2. Possible mechanisms

The neurobiological or estrogen withdrawal theory speculates that reduced estrogen or dramatic fluctuation of hormones triggers the onset or worsening of pre-existing depressive symptoms in women who are at risk (Schmidt and Rubinow, 1991). Estrogen has been found to affect the metabolism of neurotransmitters (dopamine, norepinephrine, β-endorphin, and serotonin), all of which influence emotional states (Rasgon et al., 2005). This supports the idea that the perimenopausal stage acts as a "window of vulnerability", since it involves significant decline in circulating estrogen which is associated with increased depressive symptoms (Soares and Zitek, 2008; Clayton and Ninan, 2010). The domino hypothesis posits that vasomotor symptoms such as night sweats lead to sleep problems, which result in depressed mood (Freeman, 2015). However, this hypothesis has conflicting evidence since three studies in our review (Bromberger et al., 2007; Bromberger et al., 2010; Tang et al., 2020) found that the risk for depressive symptoms remained high in the perimenopausal stage, even after adjusting for vasomotor symptoms.

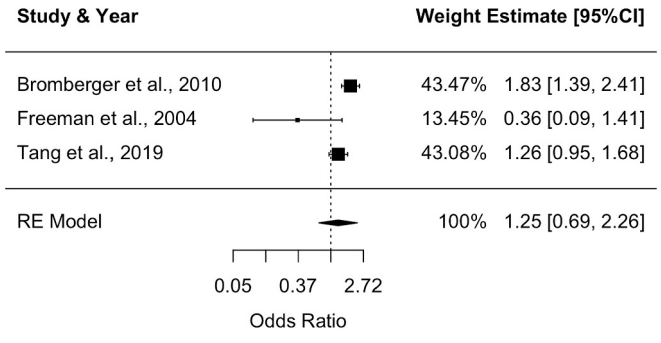

Fig. 4. Forest plot for the random effects model comparing the odds of depressive symptoms only in the postmenopausal versus premenopausal period.

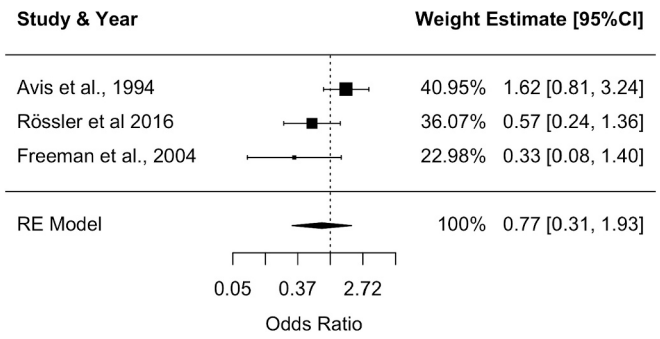

Fig. 5. Forest plot for random effects model comparing the odds of depressive diagnosis only in the postmenopausal versus premenopausal period.

Previous history of depression has also been associated with depression in the menopause transition and the findings are relatively consistent across cohort studies (Freeman et al., 2006; Bromberger et al., 2015). Of note, the Harvard Study of Moods and Cycles was conducted on a population of women with no history of depression, finding that they were still twice as likely to experience depressive symptoms even after adjusting for life events and vasomotor symptoms (Cohen et al., 2006). In contrast, the Penn Ovarian Aging Study suggested that women with a history of depression were thirteen times more at risk of depressive symptoms in the perimenopause compared to women with no history of depression (Freeman et al., 2004).

The bio-psycho-socio-cultural model (Hunter and Rendall, 2007) posits that difficult events experienced during this period including caring for both aging of parents and children may increase biological vulnerability (Hunter and Rendall, 2007). Cultural attitudes towards aging and menopause have been speculated to increase vulnerability, with Western cultures found to hold more negative views about this period and experience worse symptoms (Minkin et al., 2015).

4.3. Strengths and limitations

This is to our knowledge the only meta-analysis conducted on this topic in the past decade, a period when several new studies have been published. This includes a study from China, increasing generalizability to non-Western populations. The samples of the studies included were also ethnically diverse including White, African American, Asian, Hispanic, Chinese, and Japanese women.

We included seventeen cohort studies in our review and seven in the meta-analyses, with previous meta-analyses (Weber et al., 2014; de Kruif et al., 2016) only including four and six longitudinal studies respectively.

In terms of limitations, studies used different criteria to classify the menopausal stages and different measures for depression, which may have contributed to the increased the heterogeneity seen in some of our models.

It is important to note that our analyses included unadjusted effect sizes when possible since each study adjusted for different covariates which would have affected our results. However, this meant that some relevant covariates were excluded from the meta-analyses, the most significant not taken into consideration being history of depression,

which has been found to be of relevance, as discussed above.

We were unable to include a model that compared the peri- to the post-menopause due to the lack of studies that compared the two stages. This could have been a useful comparison since the meta-analyses by de Kruif et al. (2016) found that the risk of depressive symptoms during the perimenopause doubled when compared to the post-menopause.

Including only prospective cohort studies, which allowed within-woman comparisons, might have also limited our findings since including cross-sectional studies would have given us more data. A final limitation is that there is some overlap between menopausal symptoms and depressive symptoms which might have attenuated the risk found for depression during the perimenopause found in our analyses (Soares and Taylor, 2007).

4.4. Research implications

Our study shows the need for more research exploring the exact mechanisms through which depression during the menopause occurs and identification of specific risk factors. More longitudinal studies are needed that assess whether the long-term trajectories of women who develop depressive symptoms during the perimenopause are different from those who do not. Future research should consider cultural differences in the experience of depressive symptoms.

4.5. Clinical implications

Negative attitudes and stigma towards menopause highlight the need for public awareness around the menopause, its implications, and possible interventions (Alblooshi et al., 2023). Early recognition and treatment of depressive symptoms in women during midlife is necessary to prevent the possible negative social and physical consequences of depressive disorder (Clayton and Ninan, 2010).

5. Conclusion

Depressive symptoms and diagnosis are twice as common in women than in men and are more likely to occur during midlife; highlighting depression as a public health problem with a bias in disease burden for women (de Kruif et al., 2016). Our study further solidifies the existing evidence on the association between the perimenopausal stage and the risk for depressive symptoms, including a significantly larger number and more diverse studies than in previous meta-analyses. However, the post-menopausal stage was not found to be associated with an increased risk for depressive symptoms or diagnoses, consistent with previous literature. Our findings highlight the need for early screening and treatment for depression in midlife women and further research into potential risk factors.

CRediT authorship contribution statement

Yasmeen Badawy: Data curation, Formal analysis, Investigation, Writing – original draft. **Aimee Spector:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **Zishi Li:** Formal analysis, Writing – review & editing. **Roopal Desai:** Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

Nothing to declare.

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