Menopause 3

Promoting good mental health over the menopause transition

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The potential risk for mental health conditions over the menopause transition shapes women's expectations and informs putative physiological mechanisms regulating women's mental health. We review evidence from prospective studies reporting on associations between mental health conditions and the menopause transition. Major depressive disorder and the more prevalent subthreshold depressive symptoms are the most common conditions studied. We reviewed 12 prospective studies reporting depressive symptoms, major depressive disorder, or both over the menopause transition and found no compelling evidence for a universal increased risk for either condition. However, specific subgroups of participants, primarily defined by menopause-related risk factors (ie, vasomotor symptoms that are severe or disturb sleep, a long duration of the transition, or reproductive hormone dynamics) and psychosocial risk factors (eg, stressful life events), were vulnerable to depressive symptoms. The increased risk of major depressive disorder over the menopause transition appears predominantly in individuals with previous major depressive disorder. Greater focus on recognising risk factors in primary care is warranted. On the basis of scarce data, we found no compelling evidence that risk of anxiety, bipolar disorder, or psychosis is universally elevated over the menopause transition. Potential misattribution of psychological distress and psychiatric disorders to menopause could harm women by delaying accurate diagnosis and the initiation of effective psychotropic treatments, and by creating negative expectations for people approaching menopause. A paradigm shift is needed. We conclude with recommendations for the detection and treatment of depressive symptoms or major depressive disorder and strategies to promote good mental health over the menopause transition, while responsibly preparing and supporting those at risk.

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Introduction

The menopause transition usually starts around age 47 years with the onset of menstrual changes and ends at the final menstrual period.[1] Perimenopause is a related term. Perimenopause includes the menopause transition and the 12 months following the final menstrual period (early postmenopausal stage). The attribution of psychological distress to the menopause in high-income countries is long-standing. In 1816, Charles-Pierre-Louis de Gardanne included "hysteria, or nervous affection of the uterus" as a typical symptom of the menopause.[2] In 1959, Kupperman, Wetchler, and Blatt described the menopause as a "rather unpleasant and possibly dangerous"[3] period of life, and developed the first widely used menopause symptom checklist.[4] Notably, this scale, the 11-item Blatt–Kupperman Index, includes psychological symptoms such as melancholia and nervousness, informing the inclusion of psychological symptoms in contemporary menopause rating scales.[5,6] Although this approach has raised the profile of mental health conditions requiring care, it might also have contributed to the widespread belief that the menopause transition is universally associated with poor mental health. Anxiety,[7,8] paranoid thinking,[9] schizophrenic psychosis,[10] and even suicidality[11,12] have been attributed to the menopause, yet the empirical evidence to support these claims has not been subject to rigorous scientific review.

This Series paper has three objectives. First, we review findings from prospective studies investigating the association between the menopause transition and risk of mental health symptoms and disorders, including depression, anxiety, bipolar disorder, psychosis, and suicide risk. Second, since most research has focused on the relationship between the menopause transition and the risk of depressive symptoms and major depressive disorder, we contextualise these findings and explore vulnerability factors that help explain why some subgroups of people are at risk of depressive symptoms

Key messages

- Concerns about increased risks of anxiety and depression may shape expectations and experiences of menopause.
- However, women are not universally or uniformly at risk of psychological symptoms over the menopause transition.
- Risk factors for depressive symptoms at this time include severe and prolonged vasomotor symptoms, chronic sleep disturbance, and stressful life events, and women with previous depressive disorder might be at increased risk of recurrence of a new depressive episode during the menopause transition.
- The menopause transition often coincides with important life stressors, health conditions, and role transitions that increase vulnerability to depression.
- Clinicians should not assume that psychological symptoms during the menopause transition are always attributable to hormonal changes and should offer evidence-based treatments; menopausal hormone therapy can improve concurrent depressive symptoms for patients with troublesome vasomotor symptoms.

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or major depressive disorder over the menopause transition. Third, we conclude with recommendations for the detection and treatment of depressive symptoms or major depressive disorder and strategies to promote mental health over the menopause transition.

Menopause happens to all people with typically functioning ovaries who reach the relevant age. We recognise that this population includes some transgender men and other gender-diverse people; therefore, in this Series, we sometimes refer to "people" rather than "women" in order to be as accurate and inclusive as possible. However, since much published work refers to people experiencing menopause collectively as women and does not clarify how findings might apply to the specific needs of gender-diverse people, we have also used "women" in some instances, to avoid inappropriate generalisation. More information is needed about the experience of menopause in transgender men and gender-diverse people.[13]

Search strategy and selection criteria

We searched the databases MEDLINE, Embase, and PsycInfo from Jan 1, 1990, to July 1, 2023. Key terms were customised for individual sections and included "menopaus*", "perimenopause*", and "postmenopaus*" combined with "depression", "depressive disorder*", "anxiety", "bipolar", "bi-polar", "psychosis", "psychotic", "schizophren*", and "suicid*". For sections reporting on the absolute and relative risk of mental health symptoms or disorders over the menopause transition, we limited our review a priori to cohort studies with more than 100 participants for whom prospective data on the risk of mental health symptoms or disorders in the menopause transition compared with before the menopause transition (ie, premenopause) were available. When a prospective study reported data in more than one paper, we have reported findings from the most comprehensive study with the largest sample size or longest follow-up period. Findings were cross-checked against relevant meta-analyses, systematic reviews, and clinical guidelines. In sections reporting on risk factors and recommendations, we prioritised findings from prospective studies, clinical guidelines, and recent randomised controlled trials (RCTs).

Findings from prospective studies

Depression

An association between the menopause and depression is widely promoted. Highly cited papers state a doubled to quadrupled risk of depressive symptoms or depressive disorders over the menopause transition.[7,14,15] However, most papers report the relative risk rather than the absolute risk. Furthermore, studies have often not adequately distinguished between depressive symptoms and depressive disorder. Generally, depressive symptoms are more prevalent, less debilitating, and do not constitute a clinical depressive disorder, the most common and burdensome of which is major depressive disorder (table 1).[18] The presence of depressive symptoms does not necessarily imply that a person is experiencing a depressive episode.[19] Self-report scales typically include generic symptoms, such as sleep problems, appetite disturbance, and fatigue, that have a range of physical, psychological, and social causes that are not limited to depression. For example, during the menopause transition, vasomotor symptoms (hot flushes and night sweats) might cause sleep disturbance, which could elevate scores on a depressive symptom scale even without core depressive symptoms (ie, low mood and anhedonia). Definitive diagnosis of major

	Major depressive disorder	Depressive symptoms
Method of assessment	Typically assessed by a trained health professional through a clinical interview	Assessed through a self-administered questionnaire
Prevalence	Global 12-month prevalence of approximately 6%[16]	Prevalence is established with a cutoff score to represent the presence or absence of clinically significant symptoms; on the 20-item CES-D, a cutoff score of ≥16 is commonly used to indicate the presence of clinically significant depressive symptoms
Symptoms	Nine symptoms including two core symptoms of depressed mood and anhedonia; symptoms can be remembered with the SIGECAPS mnemonic: depressed mood and sleep changes (insomnia or hypersomnia), interest (markedly diminished pleasure in all or almost all activities), guilt (excessive guilt or feelings of worthlessness), energy loss or fatigue, concentration disturbance, appetite or weight changes, psychomotor retardation or agitation, and suicidal ideation or thoughts of death that are recurrent	The CES-D measures symptoms of depression on a frequency scale ranging from 0 (rarely or none of the time) to 3 (most or all the time)
Diagnosis	Requires co-occurrence of at least five of the nine symptoms, including at least one core symptom; symptoms must be sustained and clearly present nearly every day and must represent a change from previous functioning; symptoms must cause clinically significant distress or impairment in daily life functioning	The CES-D is not diagnostic of major depressive disorder; meta-analysis[17] indicates that a cutoff of ≥16 on the CES-D has a specificity of only 0·70 for major depressive disorder in the general population or primary care settings
Timeframe	Symptoms must persist over at least 2 weeks	Symptoms can ebb and flow and might not be sustained; the CES-D measures symptoms over the past week

CES-D=Center for Epidemiologic Studies Depression Scale.

Table 1: **Differences between major depressive disorder and depressive symptoms**

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
Major depressive disorder*							
Study of Women's Health Across the Nation (SWAN)†[20–22]	USA	443	47% White; 28% African American; 25% Chinese, Hispanic, or Japanese	Premenopausal or perimenopausal women aged 42–52 years at baseline with an intact uterus and no use of MHT	13 years and 13 assessments	SCID	The most recent publication (13 years of follow-up) with the largest sample size[20] found that the menopause transition was associated with an increased risk of recurrence of major depressive disorder (HR 2·67, 95% CI 1·04–6·86, p=0·04 in perimenopause; 4·03, 1·15–14·15, p=0·03 in early postmenopause) but not new onset major depressive disorder
Zurich Study‡[23]	Switzerland	168	Not reported	Women aged 21 years at baseline	29 years and seven assessments (menopause data measured at two timepoints)	SPIKE	Women who transitioned to perimenopause (OR 0·71, 95% CI 0·34–1·51) or postmenopause (0·57, 0·24–1·37) were not at increased risk of major depressive disorder
Depressive symptoms							
Penn Ovarian Aging Study (POAS)§[15,24,25]	USA	436	Stratified sample: 50% African American and 50% White	Premenopausal women aged 35–47 years at baseline	8 years and ten assessments	CES-D (cutoff of 16)	At 8-year follow-up, the menopause transition was associated with a quadrupled risk of new onset depressive symptoms in a subsample without a personal history (n=231) relative to the premenopausal baseline (OR 4·29, 95% CI 2·39–7·72), and the effect was stronger (5·44, 2·56–11·59) when adjusting for covariates; however, data at 14 years of follow-up[24] show evidence of declining depressive symptom prevalence from 10 years before to 7 years after the menopause
Study of Women's Health Across the Nation (SWAN)§[26,27]	USA	3302	47% White; 28% African American; and 25% Chinese, Hispanic,or Japanese	Premenopausal or perimenopausal women aged 42–52 years at baseline with an intact uterus and no use of MHT	13 years and 13 assessments	CES-D (cutoff of 16)	The early and late menopause transitions were associated with elevated risk of depressive symptoms, with the highest risk in the late menopause transition (adjusted OR 1·68, 95% CI 1·28–2·20) and early postmenopause (1·83, 1·40–2·42)
Australian Longitudinal Study of Women's Health (ALSWH)†[28]	Australia	5895	73% Australian-born; 17% from another English-speaking background; 6% European; and 3·5% Asian or other	Women aged 45–50 years at baseline; women reporting use of an oral contraceptive pill were excluded from analysis	15 years and seven assessments	CES-D (continuous)	In longitudinal analyses, entering the menopause transition did not increase the risk of depressive symptoms (adjusted B 0·03, 95% CI –0·29 to 0·35); remaining in the menopause transition at consecutive study timepoints was associated with increased depressive symptoms: women in the menopause transition scored 0·29 points higher on the CES-D 10 compared with women remaining in postmenopause (95% CI 0·02 to 0·61); overall, women in the menopause transition scored 0·19 points higher on the CES-D compared with those in postmenopause (–0·02 to 0·31)
Eindhoven Perimenopausal Osteoporosis Study†[29]	Netherlands	2103	100% Dutch	Women aged between approximately 47 years and 54 years; women who used hormone therapy or who had undergone hysterectomy or oophorectomy were excluded from analyses	3·5 years and two assessments	EDS (cutoff of 12)	Entering the menopause transition was potentially a risk factor for depressive symptoms in multivariate modelling, but the effect was sensitive to the statistical methodology used; with the step-wise method of logistic regression, transition from premenopause to perimenopause (OR 1·80, 95% CI 1·12–3·33) and perimenopause to postmenopause (1·81, 1·25–2·26) were associated with a significantly increased risk of depressive symptoms; with the enter method of logistic regression, the transition from premenopause to perimenopause did not increase the risk of depressive symptoms (1·14, 0·64–2·02)

(Table 2 continues on next page)

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
(Continued from previous page)							
Harvard Study of Mood and Cycles†[14]	USA	460	Not reported	Premenopausal women aged 36–45 years at baseline with no lifetime diagnosis of major depressive disorder	6 years and seven assessments (six assessments in the first 3 years, and the seventh at 6 years)	CES-D (cutoff of 16), SCID, or at least one positive response to three questions about mood symptoms	Overall, the menopause transition was associated with increased risk of depressive symptoms at borderline statistical significance (OR 1·8, 95% CI 1·0–3·2); women with both vasomotor symptoms and stressful life events were at increased risk of depressive symptoms during the menopause transition (adjusted OR 2·5, 95% CI 1·2–5·2); for women with one or neither of these risk factors, risk of depressive symptoms was not increased over the menopause transition
Massachusetts Women's Health Study†[30]	USA	2565	Not reported	Premenopausal and perimenopausal women aged 45–55 years at baseline with a uterus and at least one ovary intact	5 years and six assessments	CES-D (cutoff of 16)	Risk of depressive symptoms was independent of reproductive stage, but women experiencing a long menopause transition (>27 months) were twice as likely to report depressive symptoms; this effect was accounted for by including vasomotor symptoms and the presence of menstrual problems in multivariate modelling
Personality and Total Health Through Life (PATH)†[31]	Australia	711	Not reported	Premenopausal women aged 40–44 years at baseline; women using MHT and women who had had an oophorectomy or hysterectomy were excluded from analyses	8 years and two assessments	GDS (symptom count)	Women in the menopause transition at follow-up were at greater risk of experiencing depressive symptoms relative to women who remained premenopausal (IRR 1·29, 95% CI 1·10–1·52); in subgroup analyses, the effect was only seen in women without a probable history of major depressive disorder (1·35, 1·08–1·68); depressive symptoms were independent of reproductive stage among women with a personal history of probable major depressive disorder
Seattle Midlife Women's Health Study†[32]	USA	302	77% White; 11% African American; and 8·3% Asian American, or Pacific Islander	Women aged 35–55 years at baseline; women taking hormones were excluded from analyses	9 years and annual assessments	CES-D	Risk of depressive symptoms was independent of reproductive stage; reproductive stages were not significant predictors of depressive symptoms when entered simultaneously in a multivariable model but were included in the final model because they were the major research focus of the paper; in the final model, the late menopause transition was associated with elevated depressive symptoms (β 1·37, p=0·03)
The Manitoba Project†[33]	Canada	477	Not reported	Women aged 45–55 years who had either menstruated in the past 3 months or had previously had a hysterectomy	3 years and six assessments (depressive symptoms measured at five timepoints)	CES-D (cutoff of 16)	The menopause transition was not associated with an increased risk of depressive symptoms compared with remaining premenopausal; however, among women without depressive symptoms at baseline, women who had a hysterectomy were more likely to develop depressive symptoms than premenopausal women (OR 1·7, 95% CI 1·15–2·6)
Midlife Women's Health Study‡[34]	USA	264	51% White; 26% African American; and 23% Latina	Regularly menstruating individuals aged 40–50 years; women taking hormone therapy or antidepressants, or who had a history of major chronic illness were excluded from enrolment	3 years and six assessments	CES-D	At 36 months, only 64 women (24%) had transitioned to being in the menopause transition; menopausal stage was not a significant predictor of CES-D scores or risk of depression (score ≥16); women who were in the menopause transition had a non-significantly higher mean score on the CESD (mean 12·6) compared with women who remained premenopausal (10·9)

(Table 2 continues on next page)

	Country	Participants (n)	Ethnicity	Inclusion criteria	Duration of follow-up	Outcome measure	Effect of the menopause transition on risk of depressive symptoms
(Continued from previous page)							
PALM Study‡[35]	China	430	Not reported	Women aged 35–64 years with an intact uterus and at least one ovary; women who had had a hysterectomy or were taking hormone therapies were excluded from analyses	9 years and annual assessments	HADS-D (cutoff of ≥8)	There was no evidence of increased risk of depressive symptoms during the menopause transition; the prevalence of depressive symptoms was 14·5% in women with premenopause, 18·2% during the menopause transition, and 19·6% in postmenopause; these differences were not statistically significant
Zurich Study‡[23]	Switzerland	168	Not reported	Women aged 21 years at baseline	29 years and seven assessments (menopause data measured at two timepoints when women were aged 41 years and 50 years)	SCL-90-R	The transition to perimenopause or postmenopause was not associated with increased risk of depressive symptoms (transition to perimenopause: b 0·090, 95% CI –0·13 to 0·31; transition to postmenopause: 0·00, –0·22 to 0·22)

The self-report tools were either not valid measures of major depressive disorder[14] or used the Patient Health Questionnaire, which has been found to greatly overestimate the prevalence of major depressive disorder.[36] CES-D=Centre for Epidemiologic Studies Depression Scale. DSM=Diagnostic and Statistical Manual of Mental Disorders. EDS=Edinburgh Depression Scale. GDS=Goldberg Depression Scale. HADS-D=Hospital Anxiety and Depression Scale–depression subscale. HR=hazard ratio. IRR=incidence rate ratio. MHT=menopausal hormone therapy. OR=odds ratio. SCID=Structured Clinical Interview for DSM-IV. SCL-90-R=Symptom Checklist-90-Revised. SPIKE=Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology. *Major depressive disorder is uniformly diagnosed with a structured clinical interview. The Harvard Study of Mood and Cycles and the Penn Ovarian Aging Study were excluded from this section because they used a combination of clinical interviews and self-report screening tools to assess for major depressive disorder. †The study reported mixed findings or evidence of an effect limited to some women with risk factors. ‡The study did not find evidence of increased risk of depressive symptoms or disorders over the menopause transition compared with the premenopausal baseline. §The study found uniform increased risk of depressive symptoms or disorders over the menopause transition compared with the premenopausal baseline.

Table 2: **Findings from prospective studies investigating the relationship between reproductive stage and depressive symptoms and disorders**

depressive disorder requires clinician-rated interviews. Of the 12 prospective studies investigating the association between the menopause transition and depression (table 2), only two[20,23] have uniformly diagnosed major depressive disorder with clinician-rated interviews, probably due to the expense of implementing this assessment. Hence, our understanding of the risk of major depressive disorder over the menopause transition assessed uniformly by clinical interviews is limited to data from 600 women globally.

Major depressive disorder

Major depressive disorder affects approximately 6% of the global population each year and is diagnosed twice as often in women as in men.[16] The mechanisms underlying this sex difference are poorly understood, but changes in endogenous sex steroid hormones have been identified as a contributory factor.[1] The menopause transition is marked by changes in circulating sex steroids compared with before the menopause transition (premenopause).[37] Specifically, oestradiol variability is more marked during the early menopause transition, and then progesterone production reduces then stops as ovulation ceases in the late menopause transition.[1] The menopause transition often coincides with substantial midlife stresses, health conditions, and role transitions, which increase individuals' vulnerability to depression.[20]

One prospective study suggests that women with a previous history of major depressive disorder are at increased risk of recurrence over the menopause transition. The Study of Women's Health Across the Nation (SWAN) Mental Health substudy (n=425)[20] reported a 2·67-fold increased risk of major depressive disorder recurrence over the menopause transition (95% CI 1·04–6·86; p=0·04).[20] However, there was no increased risk of first lifetime episodes of major depressive disorder. First-onset major depressive disorder was predicted by risk factors unrelated to the menopause transition, such as trait anxiety, low physical functioning, and physical illness. Over 30 years, the longitudinal Zurich Study (n=168)[23] measured the prevalence of major depressive disorder at age 41 years and again at age 50 years. They found no increase in major depressive disorder in people who became perimenopausal or postmenopausal over this period, although only 27% of the sample group had reached postmenopause at follow-up and, unlike SWAN, this study did not include annual assessments of reproductive stage and mood.

In summary, the few available prospective data suggest that the menopause transition might be a vulnerable period for the recurrence of major depressive disorder but not for first lifetime onset of this condition. Future research is needed to clarify menopause-related factors that might increase the risk of first lifetime onset major depressive disorder during the menopause transition.

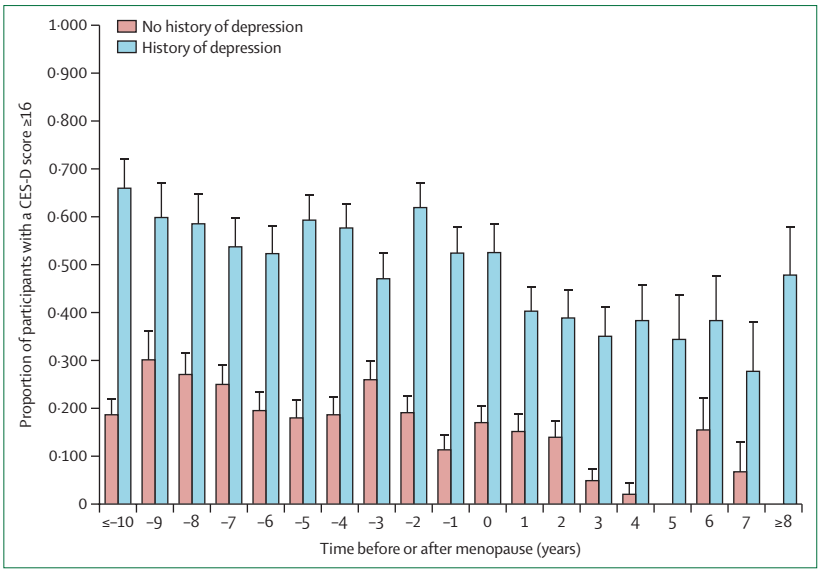

Figure 1: **Proportion of participants with a score of 16 or higher on the CES-D in each study year, grouped by history of depression at study enrolment**
Reproduced from Freeman and colleagues,[24] by permission of the American Medical Association. Error bars indicate SE. CES-D=Center for Epidemiologic Studies Depression Scale.

Depressive symptoms

Four prospective studies have measured the prevalence of depressive symptoms over the menopause transition for groups with and without previous major depressive disorder.[28,29,35,38] These studies report prevalences of between 16·5%[29] and 27·8%,[38] which are slightly higher than those seen in the late premenopause (between 14·3%[29] and 20·9%).[38] However, a 13-year prospective study over the menopause transition reported that depressive symptoms were much higher (50–65%) in people with previous major depressive disorder.[24] These data suggest that for people without previous major depressive disorder, the absolute risk of depressive symptoms is not markedly elevated over the menopause transition.

Less is known about the prevalence of depressive symptoms during the menopause transition in low-income and middle-income countries. Of the 12 prospective studies tracking changes in depressive symptoms across the menopause transition, only one, the PALM study from China,[35] was not conducted in a high-income country. The remaining studies were conducted in the USA (n=6), Europe (n=2), Australia (n=2), and Canada (n=1). The PALM study found a prevalence of depressive symptoms of 14·5% in the premenopause (baseline), which rose slightly to 18·2% during the menopause transition and to 19·6% in the postmenopause. These differences were not statistically significant.

Of the 12 prospective studies that have considered the relative risk of depressive symptoms during the menopause transition compared with the premenopause, two[15,26] reported increased depressive symptoms, and three[23,34,35] found no association. The remaining seven studies reported mixed results. Four identified specific subgroups as being at risk of depressive symptoms, including people with a combination of vasomotor symptoms and adverse life events in the 6 months before assessment,[14] people with a hysterectomy,[33] people without a history of probable major depressive disorder,[31] and people with a longer duration of the menopause transition.[30] One study found an association contingent on time spent in the menopause transition.[28] Women who remained perimenopausal across recurrent surveys had a higher risk of depressive symptoms. Two studies found evidence of a possible association between depressive symptoms and the menopause, but this association was sensitive to the statistical approach used (table 2).[29,32]

SWAN[26,27] and the Penn Ovarian Aging Study (POAS)[15,25] reported an increased risk of depressive symptoms over the menopause transition compared with the premenopause. SWAN[26,27] followed over 3000 women in the USA for more than 13 years and found an increase in depressive symptoms during the menopause transition (adjusted odds ratio [OR] 1·68, 95% CI 1·28–2·20).[26] At the 8-year follow-up in women who were aged 35–47 years and premenopausal at baseline,[15] POAS[15,25] found that the menopause transition more than quadrupled the risk of depressive symptoms (OR 4·29, 95% CI 2·39–7·72). Taken in isolation, this result suggests a substantial risk of depressive symptoms that could be alarming for women and their clinicians. However, in women with no previous depressive disorder, a minority (10–30%) reported clinically significant depressive symptoms across both the late premenopause and menopause transition, with no obvious increase in depressive symptoms in the years preceding the final menstrual period (figure 1).[24] By contrast, 45–65% of women with previous major depressive disorder reported depressive symptoms over late premenopause and the menopause transition. POAS found the risk of depressive symptoms reduced after menopause,[24] whereas SWAN found evidence of ongoing risk, especially in women with a history of depressive symptoms.[39]

Five prospective studies did not find a universally increased risk of depressive symptoms over the menopause transition, but their findings offer clarification about at-risk subgroups.[14,28,30] The Harvard Study of Mood and Cycles[14] in the USA found a marginally significant association overall (OR 1·8, 95% CI 1·00–3·20), but subgroup analyses showed that only women with both vasomotor symptoms and stressful life events in the 6 months before assessment were at risk of depressive symptoms (adjusted OR 2·5, 95% CI 1·20–5·20). The duration of the menopause transition varies substantially between individuals. Both the Massachusetts Women's Health Study (n=2565, USA)[30] and the Australian Longitudinal Study of Women's Health (ALSWH; n=5,895)[28] reported that

longer time spent in the menopause transition was associated with significantly increased risk of depressive symptoms. In the Massachusetts Study, increasing depressive symptoms associated with a long menopause transition were explained by vasomotor symptoms and menstrual symptoms in multivariable modelling.[30] In agreement, ALSWH found that women who remained perimenopausal across recurrent surveys had a higher risk of depressive symptoms (a Center for Epidemiologic Studies Depression Scale [CES-D] score of 0·29 points higher, 95% CI 0·02–0·61) than those who remained postmenopausal. PATH[31] found an association overall, but in subgroup analyses only individuals without a history of probable major depressive disorder were at increased risk of more symptoms of depression during the menopause transition (incidence rate ratio 1·35, 95% CI 1·08–1·68). The Manitoba Project[33] found no association between reproductive stage and risk of depressive symptoms overall, but participants with a hysterectomy who did not have depressive symptoms at baseline were more likely to develop depressive symptoms than those who were premenopausal (OR 1·7, 95% CI 1·15–2·6).

The Eindhoven Perimenopausal Osteoporosis Study (EPOS)[29] and Seattle Midlife Women's Health Study[32] found a possible increased risk of depressive symptoms over the menopause transition, but the association was sensitive to the statistical analysis used (table 2). For example, EPOS found evidence of increased symptoms of depression during the menopause transition with the stepwise method but not with the enter method of logistic regression.[29]

The Zurich study,[23] PALM study,[35] and Midlife Women's Health study[34] found no increased risk of depressive symptoms over the menopause transition. In the Midlife Women's Health study, just 64 participants (24%) had entered the menopause transition at the endpoint of the study, which limited the study's statistical power to detect an association.

In summary, on the basis of mixed findings from prospective studies, we found no compelling evidence for a universal or uniform increased risk of depressive symptoms over the menopause transition. Greater awareness of risk factors might inform an understanding of the mechanisms underlying depressive symptoms in subgroups of women and provide new opportunities for prevention and treatment.

Anxiety

Associations between the menopause transition and anxiety are poorly understood.[40] One prospective study measuring anxiety disorders found no increase over the menopause transition.[23] Four prospective studies have measured changes in anxiety symptoms over the menopause transition, with mixed results (appendix p 1). Two studies found no increase in anxiety symptoms over the menopause transition.[23,35] In contrast, the SWAN[41] and PATH[31] studies found that people with low anxiety in the premenopause were at risk of increased anxiety symptoms during the menopause transition. The SWAN study controlled for vasomotor symptoms, which is important since symptoms of menopause can overlap with symptoms of anxiety, such as sweating, a racing heart, and rapid breathing.

Findings from POAS suggest that anxiety exacerbates vasomotor symptoms. Women with physical symptoms of anxiety were at increased risk of developing moderate or severe vasomotor symptoms over the menopause transition.[42] In China, the PALM study[43] found a bidirectional longitudinal relationship between symptoms of anxiety and bother due to vasomotor symptoms, suggesting that anxiety could be both a cause and consequence of vasomotor symptoms.

In summary, there is no consistent evidence that anxiety increases over the menopause transition. However, somatic anxiety might predict moderate or severe vasomotor symptoms, suggesting that reducing anxiety might reduce bother from vasomotor symptoms and is a potential target for intervention.

Other mental health disorders

Bipolar disorder

No prospective studies have investigated psychiatric symptoms over the menopause transition in people with bipolar disorder. One small study (n=47) found that depressive episodes (but not mood elevation) measured prospectively over the menopause transition were increased compared with retrospective self-reports of premenopausal depressive episode frequency.[44] A systematic review of nine cross-sectional or retrospective studies reported an increase in symptoms of bipolar disorder over the menopause transition, largely on the basis of retrospective self-reports.[45] The largest of these studies found that 25·9% (57 of 220) of participants with bipolar 1 disorder retrospectively self-reported having "perimenopausal mood symptoms", compared with 12·5% (7 of 56) of their relatives without a diagnosed mood disorder.[46]

Schizophrenia spectrum and other psychotic disorders

It has been widely suggested that the menopause transition is a vulnerable period for new onset or recurrent episodes of schizophrenic psychosis,[10] however empirical evidence supporting this claim is scarce. We found no prospective studies investigating rates of psychotic symptoms or disorders over the menopause transition.

A meta-analysis of 83 studies found that women but not men experience a small increase in first lifetime onset psychosis after age 45 years.[47] These data informed the oestrogen hypothesis, which suggests that a decline in oestrogens across the menopause transition might trigger psychosis in women.[10] A large (n=61 889) Finnish study[48] found that women with schizophrenia-spectrum

See Online for appendix

disorders were more often hospitalised for psychosis after age 45 years than men were.[48] However, oestrogen withdrawal does not occur uniformly at this age and circulating oestradiol concentrations in the early menopause transition can be markedly elevated in a woman's late 40s.[49] The mean age of onset of schizophrenic psychosis is 20–40 years when oestradiol concentrations are generally high (appendix p 4).

Suicidality and the menopause transition

The risk of suicide is higher in men than in women across the lifespan, and midlife is a time of elevated suicide risk for both sexes.[50,51] Recent media reports have suggested that women are at elevated risk of suicide over the menopause transition.[11,12] However, there is no substantive evidence of an association between attempted or completed suicide and the menopause transition. One cross-sectional study from Korea (n=45 177)[52] showed increased suicidal ideation (thoughts about wanting to die in the past year) during the menopause transition (prevalence of 7·2% compared with a premenopause prevalence of 5·73%). Although the study measured self-reported rates of suicide attempts, no relationship between these rates and reproductive stage was reported.[52] A US study of 298 women in treatment for mood disorders found no association between reproductive stage and suicidal ideation or attempts.[53]

One longitudinal study (n=291709) in US veterans[54] found that use of menopausal hormone therapy (MHT) was associated with significantly increased risk of attempted and completed suicide over the next 4·5 years. These associations with death by suicide remained significant after accounting for psychiatric comorbidity and psychoactive medications.[54]

In summary, despite claims that the menopause transition is associated with increased risk of suicide, empirical data to support these claims are scarce. However, some evidence suggests that use of MHT is associated with suicide attempts and completion. The reasons for this association are uncertain.

Who is at risk of experiencing depressive symptoms or disorders over the menopause transition?

Large prospective studies report that a small subgroup of about 5–9%[28,55] of women experience increasing depressive symptoms over midlife, whereas a similar proportion (8·5–11%)[28,55] report decreasing depressive symptoms. Menopause-specific and general risk and resilience factors might help explain why a subgroup of women could be at risk of depressive symptoms or disorders over the menopause transition.

Established psychosocial risk factors for depressive symptoms

Prospective studies confirm that established psychosocial stressors such as financial problems,[29] unemployment,[29] poor social support,[26] and stressful life events[29,32] are important predictors of depressive symptoms during the menopause transition.[23,29,26] Similarly, adverse childhood experiences,[56] being from a minority ethnic group,[25] higher BMI,[15,29] neuroticism,[23] and lifestyle behaviours (eg, smoking and lack of physical activity)[26] are also associated with increased risk of depressive symptoms.

Emerging evidence suggests that psychosocial factors can interact with sex steroid hormones to modify mood. A prospective study (n=52)[57] found that greater variability in serially measured oestradiol over 14 months predicted greater depressive symptoms, but only in individuals with very stressful life events in the 6 months before baseline assessment, suggesting an interaction between established risk factors for depression and endocrine changes over the menopause transition.

Menopause-related factors

Type and timing of menopause

The type (natural or surgical) and timing of menopause might influence the risk of depressive symptoms. Prospective studies show that surgical menopause (ie, from bilateral oophorectomy before natural menopause) confers greater risk[58–60] than hysterectomy alone.[58,59] However, the effects might be transitory. A prospective controlled study of depressive symptoms and anxiety following surgical menopause showed a doubling in new-onset depressive symptoms at 12 months, which had resolved by 24 months.[61] Abrupt changes in sex steroid hormones following oophorectomy might contribute to this effect. However, women undergoing surgical menopause commonly have other risk factors for depression, such as adverse childhood experiences, abuse, and chronic pelvic pain.[62] Similarly, women with spontaneous premature[63] or early[64] menopause are at increased risk of depressive symptoms, but are more likely to have experienced cancer treatment, infertility, and gynaecological pathology than women who have menopause at the average age. Hence, factors other than endocrine changes might influence mood for these subgroups. Longer duration of the menopause transition has also been associated with increased risk of depressive symptoms,[28,30,60] potentially explained by extended time with vasomotor symptoms.[30]

Vasomotor symptoms and sleep disturbance

A systematic review of 33 publications[65] reported that the presence and frequency of vasomotor symptoms were bidirectionally associated with depressive symptoms.[65] Some women are more bothered by vasomotor symptoms than others and this variability might relate to mood, stress, and the degree of sleep disturbance. The extent to which vasomotor symptoms are problematic or interfere with daily life predicts mood disturbance and quality of life more than vasomotor symptom frequency does.[66] A pooled analysis of longitudinal data from over 20 000 women found that sleep disturbance largely

accounted for the association between vasomotor symptoms and depressed mood.[67] In an experimental ovarian suppression model of menopause, vasomotor symptoms at night but not during the day contributed to depressed mood independent of their effect on sleep.[68] Effective management of nocturnal vasomotor symptoms and sleep disturbance might play an important part in the prevention and management of mood disturbances over the menopause transition.

Sex steroids

Oestradiol variability,[15,57,69,70] low progesterone concentration,[70] and change in the ratio of testosterone concentration to oestradiol concentration[71] have been associated with an increased risk of depressive symptoms, but findings vary and these associations have not been consistently replicated.[26,32,72,73] Prospective studies with annual measures of oestradiol concentration and mood found no associations with depressive symptoms,[26,32,73] and cross-sectional studies report no differences in oestradiol concentrations in perimenopausal women with a depressive disorder compared with those without.[74] However, epidemiological[15,57] and repeated-measures[69,70] studies with more frequent assessments report that greater oestradiol variability is associated with worse mood. Circulating progesterone is reduced over the menopause transition. One study found that low progesterone concentrations were associated with worse mood.[70] Some women might be more mood-sensitive to changes in oestradiol concentrations than others,[75,76] as was shown for women with previous major depressive disorder during the menopause transition who experienced a relapse of symptoms when MHT was withdrawn.[75] Together, these data suggest that greater oestradiol variability and possibly a decline in progesterone might increase the risk of depressive symptoms, especially in vulnerable women. However, there are no established ways of predicting vulnerability to depressed mood following fluctuations in ovarian sex steroids.

Psychosocial and cultural aspects of menopause

Psychosocial and cultural factors shape mental health over the menopause transition. Negative expectations and attitudes towards menopause (eg, "[d]uring the menopause or the change of life, I became, or expect to become, irritable or depressed")[27] and ageing[60] (eg, worry about physical decline) predict subsequent depressive symptoms. Most women experience vasomotor symptoms. Together with predisposing factors such as anxiety, people with more negative attitudes towards menopause might have unhelpful cognitive appraisals of vasomotor symptoms (eg, thinking that people will notice their hot flashes or that their symptoms will never end), which might increase their distress and amplify the effects of these symptoms on their mood and functioning.[77] By contrast, positive coping strategies might minimise the effect of vasomotor symptoms on mood. There are marked global differences in attitudes towards menopause, which might help to explain the variation in attributed symptoms across different cultures.[78] For example, White Australians report higher rates of depressive symptoms together with fears of ageing than Laotian women, who position menopause as a positive event.[79]

Optimising mental health at menopause

Identifying modifiable factors is essential to inform preventive interventions. Managing troublesome vasomotor symptoms and sleep disturbance might reduce the risk of depressive symptoms and possibly major depressive disorder. Effective pharmacological and non-pharmacological interventions for vasomotor symptoms are widely available.[80] Evidence-based information promoting more positive or neutral attitudes towards ageing and menopause might be helpful (panel). Increasing social support and physical activity are other potentially modifiable targets.[55] Furthermore, a systematic review has identified psychological resources including optimism, healthy self-image, and perceived control as being protective of mental health across the menopause transition.[81] Cognitive behaviour therapy (CBT) is a proven intervention for depression and anxiety across life stages and is effective for sleep disturbance and for vasomotor symptoms. CBT is specifically recommended by UK National Institute for Health and Care Excellence (NICE) guidelines for depressed mood during menopause.[82] The North American Menopause Society 2023 guidelines also recommend CBT for bothersome vasomotor symptoms.[83]

In summary, women with previous major depressive disorder might be at elevated risk of recurrence over the menopause transition. Vulnerability to depressive symptoms includes both established psychosocial risk factors and menopause-specific factors, which might interact (figure 2).

Detection and treatment of depressive symptoms and major depressive disorder over the menopause transition

A US survey of trainee physicians[84] found that only 6·8% felt adequately prepared to address menopause, despite recognising the importance of this life stage.[84] Understanding the associations between menopause and mental health and evaluating and managing mental health disorders and symptoms are essential aspects of midlife care.

Detection

The approach to diagnosis and management of depressive symptoms and major depressive disorder over the menopause transition should mirror that at other life stages.[85] Because the menopause transition is a risk period for recurrence of major depressive disorder, women with previous experience of this condition require

Panel: Promoting mental health over the menopause transition

Key findings from prospective data

Depressive symptoms or depressive disorder

- Risk of first lifetime major depressive disorder is not increased over the menopause transition, but individuals with previous major depressive disorder might be at increased risk of recurrence
- Women are not universally or uniformly at risk of depressive symptoms over the menopause transition; only a minority experience depressive symptoms, and these symptoms are more common in people with previous major depressive disorder
- Vulnerability to depressive symptoms over the menopause transition is due to established and menopause-related risk factors (figure 2)
- The type and timing of menopause might contribute to risk; surgical menopause might be more likely than natural menopause to increase depressive symptoms
- Frequent, severe, or nocturnal vasomotor symptoms can be associated with increased risk of depressive symptoms
- Fluctuations in oestradiol concentrations might contribute to vulnerability to depressive symptoms in some individuals, especially those who are mood-sensitive to oestradiol; however, findings are mixed and there are no established biomarkers

Other symptoms or disorders

- Scarce evidence suggests that the risk of anxiety disorders does not increase over the menopause transition;[17] women are not universally or uniformly at risk of experiencing symptoms of anxiety over the menopause
- The onset or trajectory of psychosis has not been shown to be affected by the menopause transition
- No studies have found that the menopause transition increases risk of suicide attempt or completion

Recommendations for clinicians

- Provide individuals with evidence-based information about menopause, including clear statements that most individuals are not at risk of mental health problems
- Be aware of who is at risk of depressive symptoms and major depressive disorder; consider treating modifiable risk factors such as severe vasomotor symptoms and sleep problems when these are present
- Do not automatically assume that psychological symptoms over the menopause transition are attributable to menopause; investigate and manage these symptoms as at any other life stage
- Be cautious about discontinuing active treatments for major depressive disorder (eg, antidepressants or psychotherapy) over the menopause transition due to the possible increased risk of recurrence

Social change to improve mental health over the menopause transition

- Challenge assumptions that the menopause transition confers universal risk for depression, anxiety, and other mental health symptoms or disorders, since these assumptions are inaccurate and potentially harmful
- Learn from societies in which ageing in women confers status and in which views of menopause are more affirming
- Model empowered views of the menopause and women's ageing to cultivate more positive attitudes at the societal level
- Promote gender equity and safety across the lifespan since early adversity increases the risk of poor mental health at midlife

vigilant monitoring during this life stage. Although the menopause transition is not a risk period for first lifetime onset major depressive disorder, UK guidelines[86] recommend being alert to depression across adulthood and considering screening. During the menopause transition, clinicians should consider risk factors for mental illness, including previous history, and both established psychosocial and menopause-related risk factors (figure 2).

Prevention

RCTs have considered psychosocial[87,88] and hormonal interventions[76] for the primary prevention of depressive symptoms or disorders over the menopause transition. Mindfulness based stress reduction (MBSR) is an 8-week group intervention designed to ameliorate stress through mindfulness meditation and yoga techniques. Two RCTs investigated the efficacy of MBSR to prevent depressive symptoms[88] and cope with severe vasomotor symptoms.[89] In 104 euthymic women in menopause, MBSR effectively prevented the development of depressive symptoms while also promoting higher levels of resilience and lower levels of stress and anxiety relative to participants who were on the waiting list for treatment.[88] These benefits were particularly evident in participants with previous major depressive disorder, stressful life events in the 6 months before assessment, and increased mood sensitivity to oestradiol fluctuations.

In an RCT of 172 euthymic women in perimenopause and early postmenopause,[76] high-dose MHT (100 µg transdermal oestradiol with progesterone every 3 months) halved the risk of emergent depressive symptoms compared with placebo over 12 months (incidence 17·3% *vs* 32·3%), particularly in those with stressful life events in the 6 months before assessment. However, MHT was not specifically effective in preventing major depressive disorder in women who had already experienced this condition, who are a group more

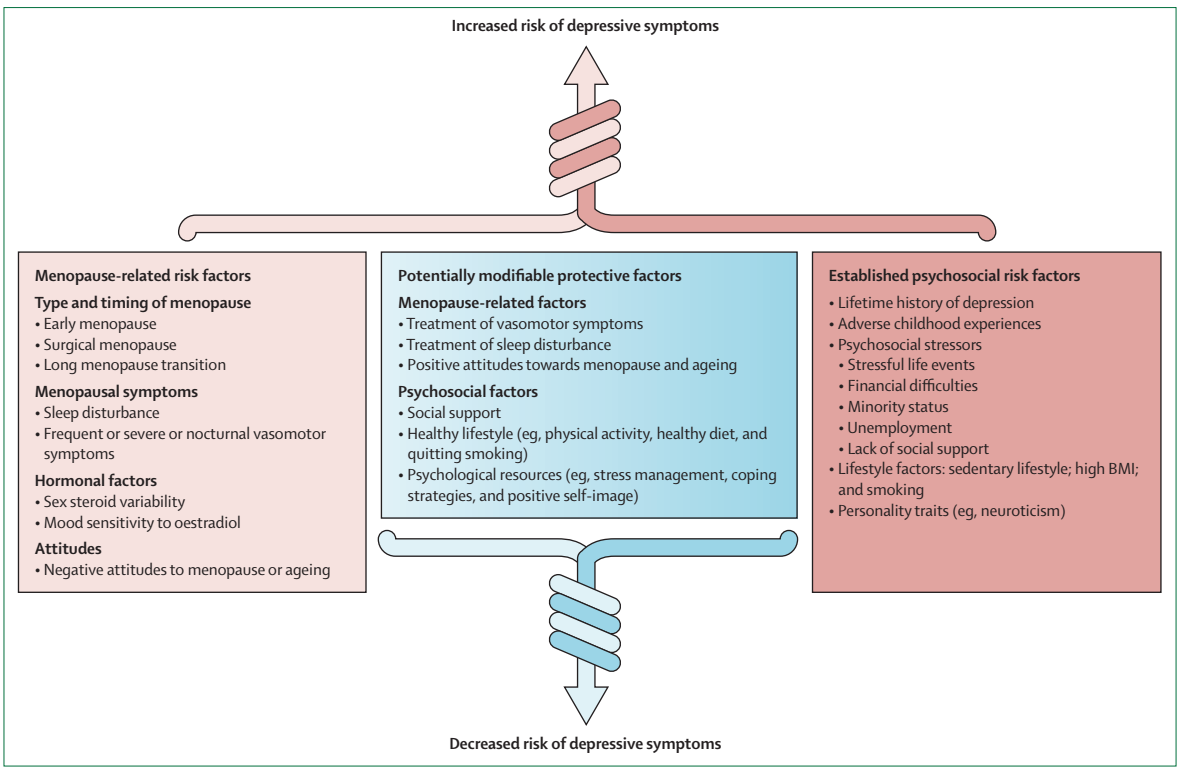

Figure 2: **Interactions between menopause-specific and established psychosocial risk factors for depression and potentially modifiable protective factors that predict increased risk or resilience to depressive symptoms during the menopause transition**
The intertwined arrows indicate that risk and resilience factors can interact with each other to elevate or reduce the overall risk of depressive symptoms.

at risk of depression over the menopause transition. Also, this regimen did not contain adequate dose and duration of progesterone to prevent endometrial hyperplasia.[90]

In summary, emerging evidence suggests that, among women at elevated risk, psychosocial interventions might prevent depressive symptoms over the menopause transition. Overall, the evidence does not support MHT to prevent depressive symptoms or major depressive disorder over the menopause transition.

Treatment

Depressive disorders over the menopause transition should be treated as at any other life stage, within a personalised framework that considers previous history, hormone sensitivity, and psychosocial and menopause-related factors in the cause, recurrence, and maintenance of symptoms.[91] Effective options for major depressive disorder include psychotherapy, antidepressants, and interventional psychiatric approaches. Psychotherapy might be particularly helpful when symptoms are caused or exacerbated by exogenous stressors, including life events and role transitions common in midlife women. Selected antidepressants including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors might confer additional benefits by treating both depression and vasomotor symptoms.[92] The duration of antidepressant treatment for major depressive disorder during the menopause transition has not been studied and standard treatment duration guidelines are therefore advised. For people experiencing major depressive disorder as they approach the menopause transition, consideration should be given to continuing antidepressants due to the increased risk of recurrence.[93]

MHT is not an approved treatment for depressive symptoms or major depressive disorder by regulatory agencies in Europe or the USA due to insufficient evidence for efficacy. Trials of MHT as a treatment for major depressive disorder have had small sample sizes (combined n=222 on MHT and a placebo) and shown mixed results.[94–97] Two RCTs (combined n=84) found that transdermal oestradiol was superior to a placebo in women with perimenopause and early postmenopause over 3 weeks[94] and 12 weeks[95] of administration. Two other RCTs (combined n=138) of transdermal oestradiol for major depressive disorder and other unipolar depressive disorders in women in perimenopause[96] or a mixed cohort of women in perimenopause and postmenopause[97] reported no benefits over a placebo.

MHT improves concurrent depressive symptoms for patients with bothersome vasomotor symptoms,[98] but it is not a primary approach for depressive symptoms in the absense of vasomotor symptoms. A meta-analysis of

12 RCTs found that bioidentical oestrogen was ineffective in reducing depressive symptoms in women in perimenopause and postmenopause.[99] Despite this result, some organisations suggest considering MHT to treat depressive symptoms during the menopause transition.[100]

Promoting good mental health over the menopause transition

WHO defines health promotion as a "process of enabling people to increase control over, and to improve, their health".[101] Information resources for people transitioning the menopause might contain mixed messages about what to expect and fail to identify at-risk groups. For example, the UK National Health Service and Mayo Clinic websites list mood changes as symptoms of menopause, whereas Johns Hopkins University emphasises that the association between menopause and mental health is inconclusive. Our findings support enhanced awareness of groups and individuals at risk for poor mental health over the menopause transition and caution against automatically attributing depressed mood or other mental health symptoms or disorders to menopause. This assumption is potentially harmful, as it creates negative expectations that reinforce stereotypes about the menopause and ageing. A survey of more than 7000 European and Australian midlife women[102] found that about half (48% of European respondents and 56% of Australian respondents) were concerned about managing menopause and that most did not feel "very well supported" in terms of their symptoms during the menopause transition.[102] Women and their clinicians need access to accurate and consistent information about what to expect, who is at risk for poor mental health, and when to seek help (panel).

For people at risk of depressive symptoms over the menopause transition (figure 2), addressing modifiable risk factors, such as sleep disturbance, troublesome vasomotor symptoms, and stress exposures, while promoting more positive attitudes towards menopause and ageing, might be beneficial. According to UN data, 90% of people hold gender biases against women.[103] Outdated views about menopause might be both a cause and a consequence of gender bias. Promoting gender equity and safety across the lifespan is relevant, since early life adversity is a powerful predictor of midlife mental health.[56] Midlife is often a period of low wellbeing for both men and women,[104] and, therefore, a potential window of opportunity to prioritise mental health optimisation. Psychological interventions such as MBSR show promise for prevention,[88] and CBT can reduce anxiety and depressed mood, together with vasomotor symptoms.[82] Primary care providers and community health educators can contribute to improving care with helpful health messaging and evidence-based practices that empower women and promote mental health over the menopause transition.

For more on the **UK National Health Service overview of menopause** see https://www.nhs.uk/conditions/menopause/

For more on the **Mayo Clinic overview of menopause** see https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397

For more on the **Johns Hopkins Introduction to Menopause** see https://www.hopkinsmedicine.org/health/conditions-and-diseases/introduction-to-menopause

Contributors

MH and LB conceived and designed this Series paper. LB wrote the initial draft and was responsible for revising this draft on the basis of comments from all other authors. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH made substantial contributions to the conception or design of this Series paper; or to the acquisition, analysis, or interpretation of data. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH made substantial contributions to drafting this Series paper or revising it critically for important intellectual content; and gave their final approval of the submitted version. MSH, RC, CJC, JLG, GDM, VR, HJ, and MH agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

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