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Cognition and mood in perimenopause: A systematic review and meta-analysis

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Abstract

Objective—It is suggested that declines in estrogen around menopause are associated with declines in cognitive functioning as well as increased risk of depressive symptoms and depressive disorders. Existing studies of objective cognitive function and mood have differed in the criteria used to stage the menopausal transition and in the outcome measures used. The purpose of this review was to synthesize the existing studies of the relationship between menopausal stage and neuropsychological performance and depression.

Design—A search of the literature of observational studies was performed using PubMed. Four cross-sectional studies on menopausal transition stage and cognitive function and four longitudinal studies on menopausal transition stage and risk of depression, as measured by symptom inventories and structured clinical interviews, were selected. For the cognitive outcomes, fixed effects models were used to estimate overall standardized effect sizes. For the depression outcomes, the results of group comparisons were summarized using the log odds ratio and its estimated standard error.

Results—Postmenopausal women performed significantly worse than pre- and perimenopausal women on delayed verbal memory tasks, and significantly worse than perimenopausal women on phonemic verbal fluency tasks. Peri- and postmenopausal women were at significantly increased risk of depression, as measured by standard symptom inventories and structured clinical interviews, than premenopausal women.

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Conclusions—The menopausal transition is a time of increased vulnerability to cognitive declines and increased risk of depressive symptoms and depressive disorders. However, these results cannot necessarily be generalized beyond the studies included in this review.

Keywords

Perimenopause; menopausal transition; cognition; memory; depression

1. Introduction

Perimenopause is commonly defined as the period of time in which the first endocrine, biological and clinical features of approaching menopause begin, up through one year after the final menstrual period (FMP). Menstrual cycle changes may be seen as early as four to eight years prior to menopause [1], though the average duration of perimenopause is four years [2]. The latest consensus criteria for staging reproductive aging (STRAW+10) [3] are based on self-reported bleeding patterns. *Perimenopause* is defined as encompassing three stages*: early menopausal transition* (−2): persistent cycle irregularity, defined as ≥7 day difference in length of consecutive cycles at least twice over the prior 10 cycles; *late menopausal transition* (−1): an interval of amenorrhea of ≥ 60 days in the prior 12 months, and *early postmenopause* (+1a): the first year following the final menstrual period (FMP). STRAW+10 further delineates *early postmenopause* as encompassing the first 6 years following the FMP and *late postmenopause* as encompassing the remaining lifespan; however only the first year following the FMP is part of *perimenopause*.

Most large-scale epidemiological studies of midlife women that have informed our understanding of perimenopause, including the Study of Women's Health Across the Nation (SWAN) and the Seattle Midlife Women's Health Study, were initiated prior to the initial publication of the original STRAW guidelines [4], and each study uses somewhat different staging criteria. For instance, the SWAN defines the late perimenopausal stage as no menses for 3-11 months [5], and the Seattle Midlife Women's Health Study defines an early, middle and late transition [6]. Most studies have utilized 12 months of amenorrhea as defining postmenopause. This transitional period is commonly associated with cognitive and affective changes, though the actual severity and mechanisms of such reported changes are not well understood.

Reproductive aging in women is associated with a decrease in ovarian estrogens (estradiol and estrone) and progesterone and an increase in serum follicle stimulating hormone (FSH) [7,8]. These changes are most pronounced in the two years prior to, and the two years after, the FMP [9]. Within individual women, however, perimenopause is characterized by widely fluctuating levels of estrogen, as opposed to a steady decrease [10,11]. The relationship between these hormonal changes, cognition, and affect has yet to be fully elucidated.

It is suggested that declines in estrogen around menopause are associated with declines in cognitive functioning as well as increased risk of depressive symptoms and depressive disorders [see 12-15 for reviews]. Estrogen promotes neuronal growth and survival [16] and acts on the cholinergic system, which is closely linked to cognitive functioning, particularly memory [17,18]. Several studies suggest that cognitive function supported by the prefrontal

cortex may be particularly sensitive to estrogen [19,20,21,22,23]. Estrogen also has a role in neurotransmitter systems involved in depression. For instance, estrogen acts as a serotonergic agonist/modulator by increasing receptor binding sites, synthesis and uptake in animal models [24] and post-menopausal women [25]. Estrogen therapy (ET) improves mood in women with perimenopausal–related depression [26, 27] as well as in surgical and naturally post-menopausal women who report depressive symptoms [28, 29]. ET also has beneficial effects when combined with selective serotonin reuptake inhibitor (SSRI) treatment [30].

The majority of women report forgetfulness and concentration difficulties during the menopausal transition [31]; however, few studies have examined objective cognitive functioning in women as they transition through menopause. The Melbourne Women's Midlife Health Project was the first to investigate the relationship between reproductive aging stage and measured memory performance [32]. This cross-sectional study found no differences between women in the early perimenopause, late perimenopause and postmenopausal stages on objective memory tests; however, there was no premenopausal group used for comparison. Our understanding of the relationship between menopausal stage and cognition was heightened with the publication of longitudinal data from the SWAN [33]. Those data showed that perimenopausal women did not show the expected improvements in verbal memory and processing speed with repeated test administration that pre- and postmenopausal women did. Despite the strengths of design and follow-up, the study was limited by a small cognitive battery and the use of a verbal memory test with a low ceiling. In all, six cross-sectional and three longitudinal studies have examined whether cognitive function varies by menopausal transition stages. Of these nine studies, two cross-sectional studies and one longitudinal study report no differences across stages, whereas four cross-sectional and two longitudinal studies report small, but significant differences. Differences in staging criteria and cognitive batteries may account for some of these discrepancies.

Perimenopause is also associated with affective changes, ranging from an increase in depressive symptoms to diagnosed Major Depressive Episode. The Massachusetts Women's Health Study was one of the first studies to utilize a randomly sampled, community-based cohort of midlife women, standardized definitions of menopausal status, and a valid and reliable symptom inventory. In their cross-sectional analysis of midlife women, they found no relationship between reproductive aging stage and depressive symptoms [34]; however, a longitudinal follow-up revealed that those women who experienced a long perimenopause (over 27 months) were twice as likely to develop elevated depressive symptoms [35]. Since then, numerous longitudinal studies have demonstrated an increased risk of depressed mood in the menopausal transition compared to the premenopausal stage.

The purpose of this review was to synthesize the existing studies of the relationship between menopausal stage and neuropsychological performance and depression. We required that studies include a premenopausal comparison group as a referent group that represented cognitive or affective function prior to the menopausal transition, since studies lacking that control group might underestimate the association between reproductive aging and cognition or mood. While a prospective, longitudinal design is optimal, there were only three

longitudinal studies on cognition [33, 36, 37], and only two met our criteria [33, 36]. Both of these were from the SWAN; one from the Chicago site [36] and the other from the entire cohort [33]. Given the lack of longitudinal data on other cognitive domains besides working memory, processing speed and verbal memory, we undertook a meta-analysis of cross-sectional studies. Such an analysis also addresses the generalizability of the SWAN findings to other cohorts. Given the abundance of reports on menopausal status and mood, and the advantages of longitudinal studies compared to cross-sectional studies, we focused on large-scale longitudinal cohort studies of the association between menopausal status and mood.

2. Methods

In conducting this review, we followed the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [38]. Specific details are described below.

2.1 Search and selection of relevant studies

2.11 Cognitive—Data for this meta-analysis were initially identified by searches in PubMed using the MeSH terms “menopause” and “perimenopause” in combination with the terms “cognition” and “memory” with additional limits of “human subjects”, “English language”, “females”, and “adult age 19+”. The focus of the review was the natural history of cognition in the menopausal transition. Inclusion criteria included 1) use of premenopausal, perimenopausal and postmenopausal participants for comparison and 2) use of standard neuropsychological measures as dependent variables. Exclusion criteria included 1) intervention studies, 2) surgical menopause, and 3) special populations, such as individuals with breast cancer or psychiatric disorders. The search yielded 311 abstracts, 36 of which were reviews and 88 of which were randomized controlled trials. The first author (MW) read each of the remaining 276 abstracts and identified 12 that were relevant to the topic of this review. Of these, six did not include three stages of transition, one did not include standardized neuropsychological outcomes, and four were from the SWAN. One study did not provide adequate data about each group or the specific cognitive tests used to allow comparison to other studies, thus was not included in the meta-analysis [39]. One relevant study was familiar to the first author, but was not identified by the search [40]. Examination of reference lists from relevant primary papers and reviews did not yield any additional studies. Ideally, we would have focused the meta-analysis on longitudinal cognitive studies where each woman serves as her own control; however, the SWAN was the only longitudinal study to meet criteria and since the SWAN has published cross-sectional findings [41], we further restricted inclusion to cross-sectional studies. One study [42] included both experimental and standard neuropsychological tasks; we included only the latter in the meta-analysis. One study that is currently in press [43] was also included. Thus, data from four studies were utilized in the meta-analysis [40-43].

2.12 Mood—Data for this meta-analysis were initially identified by searches in PubMed using the MeSH terms “menopause”, and “perimenopause” in combination with the terms “depression”, “depressive symptoms”, and “mood” with additional limits of “human subjects”, “English language”, “female”, and “adult age 19+”. The focus of this review was

the natural history of psychological changes in the menopausal transition. Inclusion criteria included 1) use of premenopausal and perimenopausal subjects for comparison, 2) use of standard depression inventories with a validated cut-off score to indicate "depressed symptoms" or the use of a structured clinical interview to indicate "diagnosed clinical depression", and 3) the availability of an odds ratio and 95% confidence interval or sufficient raw data to allow calculation of such. Exclusion criteria were 1) intervention studies, 2) surgical menopause, and 3) psychiatric populations. The search yielded 721 abstracts, 71 of which were reviews and 129 of which were randomized controlled trials. The first author (MW) read each of the remaining 521 abstracts and identified 53 that were relevant to the topic of this review. Of these, 21 did not include premenopausal and perimenopausal stages of transition, 14 did not include a reliable and valid measure of depressive symptoms, and 10 did not utilize a cut-off score to indicate depression or provide enough data to allow calculation of an odds ratio. One study did not adequately define menopausal stages to allow comparison to other studies. Of the remaining seven abstracts, two studies were cross-sectional [43, 44] and five were from three separate longitudinal cohorts (two from the SWAN [46, 47], two from the Penn Ovarian Aging Study[48, 49], and one from the Harvard Study of Mood and Cycles [50]). Examination of reference lists from relevant primary papers and reviews did not yield any additional studies.

Given the availability of prospective longitudinal studies that are optimally designed to investigate the relationship between menopausal transition stage and depression, we excluded the cross-sectional studies. Five published longitudinal studies of the menopausal transition and depression from three cohorts were identified. Of these, two reported on depression as measured by symptoms inventories [47, 49], two reported on depression as measured by structured clinical interview [46, 50], and one reported on both [48]. We performed separate analyses on each of these outcomes. As the SWAN paper on depressive symptoms [47] divided perimenopause into early and late categories, we chose to use the Penn paper that did as well [48], rather than a later publication from that cohort that used only one perimenopausal group [49]. Two papers on diagnosis of Major Depression used only one perimenopausal group [46, 50]; the third used early and late perimenopause groups [48]. As there was no way to pool those odds ratios into one perimenopause category, we were unable to use data from the Penn study [48] in that analysis. Thus, four studies were included in the meta-analysis [46-48, 50].

2.2 Data extraction

2.21 Cognitive—Data extraction was independently conducted by two reviewers (MW and PM) who each identified relevant statistics from each paper and agreed on the obtained values, including calculated values (e.g., standard error and pooled standard error). We first identified means and standard deviations/standard errors for each cognitive outcome for each of the three reproductive aging stages (pre-, peri- and postmenopause) in the studies. In two of the four cross-sectional cognitive studies, data were provided for a single perimenopausal group. In the other two studies, data were provided separately for early and late perimenopausal groups, so these were pooled for analysis. In the SWAN, means for pre- and early perimenopausal women tested within the early follicular phase (EFP) were reported separately from those seen outside of the EFP. Thus, we first pooled the data across

in EFP and out of EFP for both premenopause and early perimenopause, and then pooled the data across early and late perimenopause. In the cognitive studies, the analyses of the relationship between transition stage and cognition adjusted for relevant covariates (Table 1). However, adjusted means and standard deviations were not available in two of the studies [40, 43], thus unadjusted values were used in the meta-analysis for these studies. In these studies, the differences in mean age between the premenopause and postmenopause groups were four [43] and seven years [40].

To enable comparison across studies despite the use of disparate neuropsychological tests, we identified common domains of cognitive function according to standard practice [51]. *Working memory* is the ability to hold information for brief periods of time and manipulate it. Common tests of working memory include presenting participants with increasing series of digits and having them repeat them backward, presenting participants with increasing series of letters and numbers and having them sequence them in numerical and alphabetical order, or presenting participants with timed arithmetic problems. Working memory was assessed in two studies. Weber et al. [43] analyzed group performance on a composite working memory domain comprised of two tests, but the authors were able to provide raw data on Digit Span backward to allow direct comparisons to SWAN. Only one study examined each of the following cognitive functions: set-shifting [40], attention/vigilance [43], fine motor speed [43] and visual memory [40]. Two studies examined visual-spatial function [42, 43], but differed in the components assessed (construction versus perceptual organization). Thus, we were unable to include these in the meta-analysis.

Executive functions refer to a number of cognitive processes, including selective attention, set-shifting, reasoning, judgment, planning, problem solving, as well as behavioral processes such as initiation, inhibition, and monitoring. There are a host of commonly used tests that assess different aspects of executive functions. In this review, executive functions were divided into verbal fluency and processing speed. Two studies reported on semantic (letter) verbal fluency [40, 43] and three on phonemic (category) fluency [40, 42, 43]. Only the SWAN [41] reported data on processing speed, as measured by the Symbol Digit Modalities Test [52]. However, Weber et al. [43] had raw data on group performance on a similar task, the Digit-Symbol Coding subtest of the Wechsler Adult Intelligence Scale [53], and provided them for the meta-analysis.

The most commonly assessed domain was *verbal episodic memory*. In tests of verbal episodic memory, subjects are exposed to verbal stimuli such as lists of words, word pairs, or paragraphs and asked to recall them immediately and/or after a delay. The SWAN [41] utilized a paragraph recall test, and two others utilized a list learning task [40, 43]. Two studies reported results for the encoding trial (Immediate Memory), and three reported results for delayed free recall (Delayed Memory) (confirmed via Berent-Spillson, personal communication, October 29, 2012).

2.22 Mood—We extracted data (odds ratios and 95% confidence intervals) for depressive symptoms and depression diagnosis by menopausal stage, with premenopause being the referent group in all cases. The estimated odds ratios for all of these studies were adjusted for relevant covariates (Table 2).

Both of the longitudinal cohort studies utilized a cut-off score of ≥16 on the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item measure used to assess the frequency of current depressive symptoms [54]. This cut-off score is frequently used to define high depressive symptoms and to identify potential clinical depression [55]. Both of the longitudinal cohort studies conducted the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [56] to diagnose major depression. The Harvard Study of Mood and Cycles used the SCID at baseline and the first three years of follow-up. After 36 months, assessment was based on clinical criteria, until the final follow-up, at which a cut-off score of ≥ 16 on the CES-D was used. The estimated odds ratios were based on meeting criteria for Major Depression by any of these three criteria over the course of the study.

2.3 Statistical analysis

For the cognitive outcomes, since the instruments used were not necessarily identical across studies the results of a group comparison were summarized using the standardized effect size (SES), i.e., the difference between the group means divided by the pooled standard deviation, multiplied by a bias correction factor [57]. The standard error of the SES was estimated using a standard formula [57]. For the depression outcomes (depressive symptoms; diagnosis of major depression), the results of a group comparison (peri- or postmenopause vs. premenopause) were summarized using the log odds ratio and its estimated standard error [57], the latter derived from the reported 95% confidence interval.

Fixed effects models were used to estimate overall SES values and log odds ratios summarized across the different studies. These were computed as weighted averages of the individual study estimates, with the weights being inversely proportional to the variance of the estimated quantity of interest (SES or log odds ratio) [57]. Ninety-five percent confidence intervals for these quantities were also computed. The overall log odds ratios (and associated confidence limits) were exponentiated in order to report the results on the odds ratio scale. The small number of studies contributing to each overall estimate (2-3) and consequent unreliability of the estimate of study-to-study variation precluded consideration of a random effects model [57]. Hence, the reported results apply to the studies that were included in this analysis and cannot necessarily be generalized [57].

3. Results

3.1 Relationship between Menopausal Transition Stage and Cognition

Four cross-sectional studies compared neuropsychological test performance in pre-, peri- and postmenopausal women (Table 1). Two of these are population-based [41, 42], one is a sub-sample from a population-based study [40], and one is a sample of convenience [43]. All excluded women who were using hormone therapy (HT). The study samples were similar in terms of mean age and years of education. The mean age of the women in the studies ranged from 49 to 52 years, and the mean years of education ranged from 13.5-16 years. The studies differed in their racial and ethnic make-up. The SWAN sample was 46% white, 26% African American, 5% Hispanic, 11% Chinese, and 12% Japanese. In contrast, the Weber et al. [43] sample was 91% white, 6% African American, 2% Hispanic, and 2% Asian. Two studies did not report data about race or ethnicity of the sample [40, 42],

although the Herlitz et al. [42] sample was based in Umea, Sweden and excluded non-native Swedish speakers.

Seventeen different cognitive tests were used in these studies; only two of the studies used a comprehensive neuropsychological test battery [40, 43]. We extracted data to enable comparisons across six domains of cognition. Details of each study and which cognitive domains were assessed are shown in Table 1. Details of group comparisons are summarized in Table 3.

3.11 Working Memory—Two of the studies in the meta-analyses examined working memory performance [41, 43]. Only Weber et al. [43] found an association with transition stage, wherein postmenopausal women performed significantly worse than late perimenopausal women on a composite domain of attention/working memory. In the meta-analysis, two studies provided data on Digit Span backward [53] performance [37,40]. There was a trend for perimenopausal women to perform worse than premenopausal women, but this did not reach statistical significance (estimated SES = −0.147, p=0.07; Table 3).

3.12 Executive Functions—The studies in this review utilized measures of processing speed and verbal fluency. Two studies utilized a digit-symbol substitution test [52, 53], and neither found an association between transition stage and processing speed [41, 43]. Two studies reported on semantic (category) verbal fluency and neither found an association with transition stage [40, 43]. Three studies examined phonemic (letter) fluency [40, 42, 43], and only one found an association with transition stage [40]. In the meta-analysis, postmenopausal women performed significantly worse than perimenopausal women on phonemic verbal fluency tasks (estimated SES = −0.333, p = 0.02; Table 3). There were no significant differences between groups in performance on any other the executive functions.

3.13 Verbal Memory—Three of the studies examined verbal episodic memory using a standard neuropsychological test [40, 41, 43]. Only Weber et al. [43] found an association between transition stage and verbal episodic memory, with postmenopausal women performing significantly worse than women in the pre- and late perimenopausal stages on both immediate and delayed verbal memory. In the meta-analysis, postmenopausal women performed significantly worse than premenopausal and perimenopausal women on measures of delayed memory (Table 3). There was a trend for postmenopausal women to perform worse than perimenopausal women on immediate memory, but this did not reach statistical significance (estimated SES = −0.118, p = 0.06; Table 3).

3.2 Relationship between Menopausal Transition Stage and Depressive Symptoms

Two longitudinal studies compared the proportions of subjects with depression as measured by symptom inventory in pre-, early peri-, late peri-, and postmenopause (Table 2). Both of the studies were population-based and racially diverse. The mean age of the Penn Ovarian Aging Study sample was 40.6 years at baseline, 50% were white and 50% African-American, and 59% of the sample had an education beyond high school. The mean age of the sample from the SWAN was 46.4 years at baseline, 27% were African-American, 9%

Chinese, 5% Hispanic, and 10% Japanese, and nearly 77% of subjects had an education beyond high school.

Details of each contributing study are shown in Table 2. The SWAN found that the odds of having a CES-D score ≥ 16 were significantly higher when a woman was early peri-, late peri-, or postmenopausal compared to when she was premenopausal. The Penn Ovarian Aging Study found that the odds of having a CES-D score ≥ 16 were significantly higher when a woman was in early or late perimenopause compared to when she was premenopausal, and when she was in late perimenopause compared to early perimenopause. There was no increased risk in postmenopause; however, only 3% of the cohort was menopausal by study end, thus this finding must be seen as preliminary. A later publication from the Penn study that had only one perimenopausal group found that the odds of having a CES-D score ≥ 16 increased 4.3 times in perimenopause compared to premenopause[49]. In the meta-analysis, the odds of have a CES-D score ≥ 16 increased 1.3 times in early perimenopause, 1.8 times in late perimenopause, and 1.5 times in postmenopause compared to premenopause (Table 4).

3.3 Relationship between Menopausal Transition Stage and Diagnosis of Clinical Depression

Two longitudinal, population-based studies compared the proportions of subjects with depression as measured by structured clinical interview in pre-, peri-, and postmenopause (Table 2). As discussed above, the SWAN is racially and ethnically diverse, and in this study, 78% were educated beyond high school [46]. The Harvard Study of Mood and Cycles cohort is 93% white [59], and 93% were educated beyond high school (Table 2).

Both studies found that the odds of experiencing a major depressive episode increased two times in perimenopause compared to premenopause. The SWAN found that the odds of experiencing a major depressive episode increased four times in postmenopause compared to premenopause. The Harvard study did not have a postmenopausal group for comparison. In contrast, the Penn study [48] found no significantly increased rate of depression, as measured by the Primary Care Evaluation of Mental Disorders [60] structured interview, in early or late perimenopause compared with premenopause [48]. This study was not included in the meta-analysis as it contained two perimenopausal groups. In the meta-analysis, the odds of having a diagnosis of Major Depression, as measured by structured clinical interview, increased 1.9 times in perimenopause and 4.3 times in postmenopause compared to premenopause (Table 4).

4. Discussion

In this meta-analysis, we analyzed the results of several observational studies on the relationships between menopausal transition stage and cognition and mood in midlife women. The data suggest that the peri- and postmenopausal stages are associated with decreases in delayed verbal memory compared to premenopause. Additionally, the postmenopausal stage is associated with decreases in phonemic verbal fluency compared to perimenopause. The data also suggest that women are at a significantly increased risk of

developing depression, as measured either by symptom inventory or structured clinical interviews, in the peri- and postmenopausal stages than in premenopause.

The cognitive results are in contrast to a majority of cross-sectional studies that have failed to find an association between transition stage and verbal memory. However, they are consistent with two longitudinal studies, the SWAN [33] and the Kinmen Women's Health Investigation (KIWI) [37], which demonstrated associations between menopausal stage and delayed verbal memory [33] and verbal fluency [37]. They are also consistent with a vast literature that suggests that estrogen may mediate cognitive functions subserved by the hippocampus and the prefrontal cortex [23, 61-63].

It is important to note that the estimated standardized effect sizes for cognitive outcomes in the current study were quite small. This is consistent with the SWAN, which found that declines in verbal memory in perimenopause were evident as a failure to improve over repeated administrations of the same task, rather than a decline from prior performance. This failure to demonstrate a practice effect is a common focus of longitudinal cognitive studies and recognizes the considerable improvements on tests that emerge with practice. Practice effects result from increased familiarity with a test, or "learning" the test. Similarly, the decline in verbal fluency seen in the KIWI [37], an average of 1.3 fewer items, was quite small. This suggests that cognitive declines in the menopausal transition are quite modest. The high prevalence of self-reported memory complaints in perimenopausal women [31, 39, 64], however, suggests that a subtle decline is still quite bothersome and clinically significant.

There are several limitations to this study. First, there were few studies included in the meta-analysis. Thus, the reported results apply only to the studies that were included in this analysis and cannot necessarily be generalized. Our inability to include all relevant studies due to differences in menopausal transition staging and data reporting likely impacted some of our results. For instance, inclusion of the Penn study in the meta-analysis of depression as measured by structured interview would likely have attenuated the odds ratio for the Peri vs. Pre comparison. The small number of studies reflects that fact that although there is much discussion of estrogen effects on cognition, there are few studies of neuropsychological test performance in perimenopause, and even fewer that compare women in the pre-, peri-and postmenopausal stages. Furthermore, not all of the analyses in the different studies adjusted for covariates, and even when they did, the covariates differed across studies. Perhaps the most significant covariate is age, as verbal episodic memory is well-known to decrease with age. However, the age range between the studies was quite similar, and the age differences between menopausal stage groups were not large. In the two studies that contributed unadjusted means, the differences in mean age between the premenopause and postmenopause groups were four [43] and seven years [40]. Also, in these two studies the group differences in cognitive test performance remained significant after adjusting for age. Depression is another important covariate that was not consistently considered in the different studies of cognition. Depression is known to be associated with worse cognitive function, although deficits in executive function are most prominent [65, 66]. Only two of the four studies adjusted for depressive symptoms, and they reported conflicting findings on the association between menopausal transition stage and verbal memory. It is possible that

the group differences in verbal memory were due to depressive symptoms. Both the Weber et al. [43] study and the longitudinal analysis of the SWAN data [33] found that the association with menopausal stage was not accounted for by depression. A final limitation is the differences in criteria used to define menopausal stage. The Weber et al. [43] study was the only one to define postmenopause according to STRAW+10 as occurring after the FMP. The other three studies defined postmenopause as 12 months after the FMP. It is thus possible that many perimenopausal women in these studies would be in early postmenopause according to STRAW+10. Longitudinal data from the SWAN demonstrate that estradiol levels decline and FSH levels rise from two years prior to the FMP up to two years after the FMP and then plateau [9]. If the cognitive declines during perimenopause are due to declines in estrogen, then a failure to differentiate early and late postmenopause may mask a true difference. Large-scale prospective studies of midlife women are needed to better demonstrate the trajectory of cognition across all phases of the transition, including early and late postmenopause.

The findings of significantly increased odds of depression in peri- and postmenopause, as measured by symptom inventories and structured clinical interviews, are consistent with many prior cross-sectional and longitudinal studies. While the three studies in this analysis were similar in age range, they differed in their racial and ethnic make-up. The SWAN is a multiethnic cohort that includes a large percentage of African American, Chinese, Hispanic, and Japanese women and the Penn Ovarian Aging Study is 50% African American. In contrast, the Harvard Study of Mood and Cycles is 93% white. The results from SWAN were adjusted for race. The Penn Ovarian Aging Study did not include race as a covariate, and found that the odds of having depression (as measured both by the CES-D and structured clinical interview) was increased two times in African-American women compared to white women. Cross-sectional studies of cohorts in Asia and the Middle East report an increased risk of depression in the perimenopause compared to premenopause [44, 45, 67], suggesting that this risk is not confined to the Western world. Future studies are needed to clarify if a perimenopausal-associated risk of depression differs across ethnic, racial, and cultural groups.

The magnitudes of the increased odds of depression found in this meta-analysis are consistent with those seen in both cross-sectional and longitudinal studies. The risk of depression in the perimenopause seems fairly clear, but the specific risk factors for perimenopausal depression, and the trajectory over the late postmenopausal period remain to be clarified.

While our understanding of cognitive and affective changes in the menopausal transition is improving, several issues remain. Several of the studies we reviewed are limited by a restricted range in the categorization of menopausal stage. For instance, many studies use only one perimenopausal stage, but there is evidence to suggest that there are important differences in early versus late perimenopause [33, 48]. Further, most studies thus far have not differentiated between early and late postmenopausal stages. Given that the hormonal milieu continues to change after the FMP this may be important. Data from SWAN demonstrating an increased likelihood of Major Depressive Episode in the first two years of postmenopause but not beyond [46], suggests that finer tuned differentiations of the

postmenopausal period are warranted. It may also be important to examine the length of time a woman remains in a stage as a possible risk for cognitive declines and depression. Future studies should follow-up on the finding of increased risk of depression with longer time spent in perimenopause (> 27 months) [25] to see if this can be replicated in another sample, and if it is true for cognitive function as well. Finally, future studies are needed to identify the specific risk factors for development of depression in perimenopause, and to determine if the long-term trajectories of mood and cognition differ in women who develop perimenopausal depression from those who do not.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We performed a meta-analysis of studies of cognition and depression across stages of the menopausal transition
- Postmenopausal women perform worse than perimenopausal women on phonemic verbal fluency and delayed verbal memory tests
- Perimenopausal and postmenopausal women are more likely to have significant depressive symptoms compared to premenopausal women
- Perimenopausal and postmenopausal women are more likely to meet criteria for a diagnosis of Major Depression than premenopausal women

Table 1

Cross-sectional studies of cognition across menopause transition stages

Study	Demographics			Stage					Cognitive Domain					
	N	Mean Ed	Mean Age	Pre	Early Peri	Late Peri	Peri	Post	Working Memory	Executive Functions			Verbal Memory	
										PS	PVF	SVF	Imm	Delay
Luetters et al. 2007[a] [41]	1567	14.5[b]	49.8[c]	X	X	X		X	ns	ns			ns	ns
Herlitz et al. 2007[d] [42]	242	13.5 [c]	49.4 [c]	X			X	X			ns			
Berent-Spillson, et al. 2012[e][40]	67	14	52.0	X			X	X			↓	ns	ns	ns
Weber et al. 2013[f][43]	117	16	48.7	X	X	X		X	↓	ns	ns	ns	↓	↓

↓ indicates decreased performance in postmenopause relative to premenopause, ns indicates no significant difference. Ed-years of education, PS-processing speed, SVF-semantic verbal fluency, PVF-phonemic verbal fluency, Imm-Immediate memory, Delay-delayed memory

[a] adjusted for site, age, race, education, BMI, self-reported poor health, vasomotor symptoms, poor sleep, somatic symptoms, and dysphoric mood symptoms

[b] Education was reported as post-college, college, some college, HS, and < HS. We assigned respective years of 18, 16, 13, 12, and 9, and derived a pooled mean.

[c] pooled mean

[d] adjusted for age and education

[e] adjusted for age

[f] adjusted for age, education, vasomotor symptoms , sleep disturbance, depressive symptoms, anxiety symptoms, estradiol, and follicle-stimulating hormone

Table 2

Longitudinal studies of risk of depression in the menopausal transition

Study	N	Baseline Mean Age	Stage				
			Pre	Early Peri	Late Peri	Peri	Post
Depressive Symptoms							
Bromberger et al, 2007[a][47]	2885	46.4[b]	X	↑	↑		↑
Freeman et al, 2004[c][48]	436	44.6[d]	X	↑	↑		ns
Depression Diagnosis							
Cohen et al, 2006[e] [50]	460	36-46[f]	X			↑	
Bromberger et al, 201[g] [46]	221	45.5 [b]	X			↑	↑

↑ indicates increased risk compared to premenopausal stage, ns indicates no significant difference

[a] adjusted for site, baseline age, overall health and smoking status

[b] pooled mean

[c] adjusted for history of depression, severe premenstrual syndrome, poor sleep, age, race, employment status, hot flashes and FSH

[d] age at end of 4 year follow-up

[e] adjusted for age and proximate Life Experience Survey score

[f] age reported in age-bands only

[g] adjusted for age, race, history of major depression, annual psychotropic medication, annual very upsetting life events, and BMI

Table 3

Standardized effect sizes for comparisons of cognitive outcomes between different stages of menopause

Variable	Comparison	Estimated SES	95% CI	P-value
Working Memory	Peri – Pre	−0.147	(−0.308, 0.013)	0.07
	Post – Pre	−0.122	(−0.310, 0.067)	0.21
	Post – Peri	0.028	(−0.094, 0.150)	0.66
Processing Speed	Peri – Pre	−0.022	(−0.185, 0.142)	0.80
	Post – Pre	−0.125	(−0.317, 0.066)	0.20
	Post – Peri	−0.087	(−0.210, 0.035)	0.16
Phonemic Verbal Fluency	Peri – Pre	0.146	(−0.087, 0.379)	0.22
	Post – Pre	−0.185	(−0.439, 0.068)	0.15
	Post – Peri	−0.333	(−0.612, −0.054)	0.02
Semantic Verbal Fluency	Peri – Pre	0.092	(−0.259, 0.442)	0.61
	Post – Pre	−0.217	(−0.635, 0.202)	0.31
	Post – Peri	−0.302	(−0.727, 0.123)	0.16
Immediate Verbal Memory	Peri – Pre	−0.018	(−0.179, 0.143)	0.83
	Post – Pre	−0.148	(−0.337, 0.040)	0.12
	Post – Peri	−0.118	(−0.240, 0.004)	0.06
Delayed Verbal Memory	Peri – Pre	−0.042	(−0.199, 0.114)	0.60
	Post – Pre	−0.224	(−0.404, −0.045)	0.01
	Post – Peri	−0.174	(−0.294, −0.054)	0.004

Estimates obtained from a fixed-effects meta-analysis; see text for details

SES = Standardized effect size; CI = Confidence Interval; Pre = Pre-menopausal; Peri = Peri-menopausal; Post = Post-menopausal

Table 4

Odds ratios for comparisons of depression outcomes between different stages of menopause

Variable	Comparison	Summary Odds Ratio	95% CI	P-value
Depressive	Early Peri – Pre	1.34	(1.14, 1.57)	0.0004
Symptoms	Late Peri – Pre	1.82	(1.38, 2.41)	< 0.0001
	Post – Pre	1.54	(1.14, 2.10)	0.006
Depression	Peri – Pre	1.92	(1.23, 2.98)	0.004
Diagnosis	Post – Pre[a]	4.32	(1.54, 12.12)	0.005

Estimates obtained from a fixed-effects meta-analysis; see text for details

CI = Confidence Interval; Pre = Pre-menopausal; Early Peri = Early peri-menopausal; Late Peri = Late peri-menopausal; Post = Post-menopausal

[a]Based only on Bromberger et al., 2011