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Abstract

Cognitive and mood changes are frequently mentioned as complaints before, during and after menopausal transition. There is substantial biological evidence for such associations to occur, as there are many mechanisms through which estrogens can affect the brain, by regulating metabolism, increasing cerebral blood flow and dendritic outgrowth, by acting on nerve growth factors through co-localisation of receptors, via neurotransmitters synthesis and turn-over and many more. However, the evidence for objective and longer term changes in cognitive function and mental health over the menopausal transition and beyond is less clear. While hormone treatment including estrogens could potentially reverse these psychological issues, the evidence of long-term benefit is also inconclusive. However, for women with severe menopausal complaints, and particularly for those who undergo early menopause, including women with Premature Ovarian Insufficiency, personalised hormone treatment at least up to the natural age of menopause around 50 should be considered, which is probably safe up to 10 years of treatment, unless contraindicated. This paper reviews the evidence for changes in psychological health related to menopausal transition and hormone treatments.

Word count abstract 175

Keywords: cognition; memory; mood; estrogen, menopause; hormone treatment, POI

MENOPAUSAL COMPLAINTS: DATA FROM SURVEYS

Self-report surveys show that between 50-75% of women experience symptoms during menopause [1]**.** The 2019 UK Chartered Institute of Personnel and Development (CIPD) research survey [2] of 1409 working women between 45 and 55 years of age suggested that menopausal complaints most reported were hot flushes (72%), sleep disturbances (64%) and night sweats (58%). Of the 6 in 10 women affected by menopausal symptoms at work, 65% said they were less able to concentrate and more than half had experienced more stress and less patience with colleagues. A recent review [3] also suggested that complaints of concentration, memory, planning and other cognitive impairments including 'brain fog' are common, seen in 62-67% of women during menopausal transition, with an earlier age at menopause resulting in a higher frequency of complaints. According to the Nuffield Health Survey (2014) of 3,725 UK women aged between 40 and 65 [4], almost half (47%) of menopausal women also reported feeling depressed and 37% suffered with anxiety. These mood symptoms could affect concentration and memory. Our previous review suggested that there was insufficient evidence to link menopausal transition to global cognitive dysfunction, but that specific cognitive functions may objectively show change [5].In this paper, we provide an update of current evidence with data derived from recent systematic reviews, meta-analyses and novel papers to further investigate objective changes in cognitive function and mood over the menopause, and effects of hormone treatment (HT).

METHODS

We included the following keywords in our search: 'review' or 'meta-analyses' AND 'hormone near treatment' or 'estrogen near treatment' AND 'cognition' or 'memory' or 'depression' AND 'menopause' which rendered 84 publications in Pubmed since 2020. This search rendered 81 citations in Google Scholar on 27/7/2021.

We excluded reviews and studies with a focus on phytoestrogens, exercise or testosterone. We did not include studies of women who had been treated for specific morbidity, such as psychotic disorders, HIV, hypertension or breast or ovarian cancer with tamoxifen or other estrogen antagonists, or papers which focused on genetics associated with estrogen metabolism or on older women (with an average age >60). We selected 11 reviews from Google Scholar and 12 from Pubmed and scrutinised these for relevant references We also searched for papers not included in our previous review [5] using keywords individually (e.g. surgical menopause AND memory; complaints AND menopause) to find novel studies to provide a narrative overview of the literature.

COGNITIVE COMPLAINTS AND OBJECTIVE COGNITIVE FUNCTION

A recent review of 19 studies [3] concluded that cognitive complaints were associated with menopausal transition, but also with specific areas of objective cognitive decline, affecting verbal memory, attention and working memory. However, not all studies they reviewed reported these outcomes. For instance, the review mentioned two neuroimaging studies where cognitive complaints were associated with medial temporal lobe functioning (which declines early in Alzheimer's disease or AD, the most common type of dementia), but not with objective verbal (or word) learning and recall performance. A meta-analyses [6] of 4 cross sectional studies of women not using HT concluded that delayed verbal recall was most clearly different between women at different menopausal stages, but only one study [7] stated this to be significantly affected by stage, whereas 2 others included in the meta-analyses did not [8] [9]. Three studies (see Table 1) not included in the meta-analyses (as these had not excluded women who had used HT) also did not show an effect of menopausal stage on verbal recall [10, 11] [12]. The meta-analyses also reported that (phonemic) verbal fluency was only different between peri- and postmenopausal women, which was significant in one study [9].

Our systematic review done around the same time [5] investigating hormone levels and cognitive change over the menopausal transition suggested that perhaps effects were most apparent on complex cognitive tests, which could benefit from using strategies (e.g. to improve recall of learned material, such as needed for word lists or for verbal fluency, or on executive function tests) [5]. The difference reported in verbal fluency performance [9] between the menopausal stages in the rather small study (n=67) in the review was associated with lower estradiol levels (E2, the most potent estrogen) and brain imaging data, and was independent of differences in age between the cohorts. No effects were found on executive function in this study. Our updated review (Table 1) suggested that the majority of other cross-sectional studies [7, 10] [8] [12] [13] did not report differences comparing groups of women of different menopausal status on verbal fluency performance. Two studies that included women using HT reported effects of menopausal status on executive function [10, 12], but the other studies did not report significant associations with complex psychomotor speed [7] [8] 9] [10] or executive tests [9], although one study did report an effect of different menopausal stages on attention/working memory [7] (see Table 1)

Differences in how menopausal status was determined between studies could explain some of the differences in findings (e.g. self-report vs. hormonal levels, pre- vs. post-menopausal status or investigating different stages of menopausal transition and distinguishing further by including early and late peri- or postmenopausal stage etc). This may be important as one of the studies [7] suggested that cognitive function does not change linearly across the menopausal stages. The authors reported lower performance on tasks sensitive to prefrontal areas, such as verbal learning and memory, fine motor skills, and attention/working memory, which were most clearly affected in the first year after the final menstrual period [7]. This non-linearity could result in not identifying transient effects of menopausal transition on cognitive change and is also reflected in other more recent longitudinal studies (see below).

In addition, including or excluding women who had undergone surgical menopause and/or hysterectomy, and/or those who were using HT [12] increases variability (see below). The ability to analyse and control for these variables within cohorts depends on group size, which may have precluded entry of essential covariates in some of the smaller studies (see Table 1) and could explain differences in findings, as would using different cognitive tests or versions of tests which may be less sensitive to change. Furthermore, cross-sectional studies by their nature compare cohorts of women of different ages and did not always take into account the effect of chronological age on cognition. Different cohorts also have different life histories[1], which could all further confound associations between menopausal transition and change in cognitive function and are difficult to control for statistically.

Therefore, longitudinal studies carry scientific precedence when reviewing evidence, as they follow the same women over the transitional period. However, they can be affected by attrition and be susceptible to 'healthy survivor bias' or other confounds related to retention (e.g. motivation or education), which can affect performance. In our previous review, two longitudinal studies [14] [15] showed a decline in the verbal recall of a word list. In a Taiwanese longitudinal study of perimenopausal women all cognitive tests improved over time, except for verbal memory, which declined. However, at 18 month follow-up, only verbal fluency performance was significantly different between women who became perimenopausal (33% of the cohort), as compared to those who remained premenopausal, when controlling for age, education and baseline cognitive scores [14]. A Swedish longitudinal study [15] also found that verbal fluency showed a decline across years since the final menstrual period (FMP, i.e. menopause), which was independent of chronological age. However, verbal memory and

[1] Including exposure to anti-biotics in childhood vs. surviving childhood morbidity without anti-biotics, living through war and famine, other medical support changes, including exposure to different types of contraceptives, attitudes towards childbirth/abortion, indications for hysterectomy, etc. and lifestyles, e.g. with more smoking and alcohol use, being more sedentary with less physically demanding housekeeping and more use of motorised transport in more recent female cohorts

visuospatial abilities only showed a decline in women who had normal weight, but not in overweight and obese (body mass index or BMI>25) women. The authors suggested that estrogen turn-over in fat tissue may have protected women with a higher BMI, but they may have insufficiently controlled for wasting disease (e.g. cancer). Our updated review included several other longitudinal studies (see Table 1). The effect of perimenopausal transition on more complex cognitive tests becomes most apparent when using the same tests. This phenomenon was also mentioned in a large longitudinal US based study, the Study of Women's Health Across the Nation (SWAN). Here effects of menopausal transition were seen on 'learning how to do the' complex speed of information processing test by using the same instrument (Symbol Digit Modalities Test or SDMT). The SDMT requires speed of visual stimuli (or symbol) processing, searching and matching to numbers (or digits) using a key which can benefit from working memory capacity. No effect of menopausal stage was seen on a non-speeded less complex attention and working memory test (Digit Span Backward or DSB) over a 4 year follow-up [16]. In this study, there was also no learning effect over the perimenopausal stages for verbal memory performance (which is complex and can benefit from speed of information processing and use of strategies, such as visualisation, chunking of stimuli or rehearsal). The authors suggested that these effects were transient, as these were no longer observed post menopause. Whereas women using HT (usually consisting of estrogens, with an added progestogen for women with an intact uterus) performed better in this study, this effect was not seen when HT was initiated post-menopause. Verbal fluency was not assessed in this study. A cross-sectional analyses of this large cohort had found no difference in cognition between women at different stages of the menopause or of E2 levels on cognition after control for covariates [8]. An earlier follow-up study, which had restricted analyses of this cohort using only the Chicago site had also shown no decline from pre- to perimenopause on the DSB and SDMT, but instead only reported small improvements (i.e. learning effects) over time [17].

A later report [18] of the SWAN cohort with a 6.5 year follow-up found that, when adjusting for these learning or practice effects (which were strong on the SDMT) by excluding the first couple of testing sessions, processing speed on the SDMT actually declined over the years since FMP and verbal delayed recall also did marginally so, after adjustment for many factors (see Table 1). Those women who stayed in the study for longer ('retention') had better cognitive scores, reflecting practice effects, which could be due to implicit learning effects and/or deliberate application of learned strategies to improve performance. Importantly, there was no sharp acceleration of cognitive decline during or after menopause. Another US based cohort, the Penn Ovarian Aging Study (POAS), using different verbal word lists to reduce these learning effects, found a pre- to postmenopausal decline in verbal recall (seen early in menopausal transition) over a 14-year follow-up, but reported no effects on speed of performance on the Digit Symbol Substitution Test (DSST), which is similar to the SDMT. Gonadotropin levels in this study were negatively associated with verbal recall and speed performance, but this was no longer significant when analyses were adjusted for age, race, education and BMI [19]. A recent large UK study [20] with a 4 year follow-up and 3 yearly assessments, also controlling for learning effects, found that the increase in verbal fluency scores over menopausal stages was associated with chronological age, rather than time since FMP. They looked at practice effects (by using the slope of change in performance over time), but this did not significantly interact with menopausal stage, unlike the SWAN study [18]. They did report a decline in processing speed on the DSST (but not in verbal memory) between the different menopausal stages at baseline, when controlling for age at testing and learning effects. [16]. In this study [20] perimenopausal women who had lower baseline scores had greater improvement in performance over time than premenopausal women on the complex speed and verbal recall tests. This suggests possible regression to the mean effects and/or that those who had the greatest baseline cognitive deficits showed the largest improvements. The

study showed that a raise in gonadotropin levels was associated with a decline in verbal recall, and this decline was independent of menopausal symptoms. However, effects of time since FMP on lowered scores in verbal memory -when chronological aging and learning effects were taken into account- were small. Importantly, recent analyses [21] suggested that only 20% of women show objective lower verbal memory scores when going through the menopausal transition, which was associated with sleep disturbances and less hormonal variation, but that the majority of women did not experience significant objective cognitive decline.

Associations between estrogen levels with cognitive change are inconclusive. Estrogen levels are liable to be affected by BMI and can fluctuate during menopausal transition, especially in the pre- and perimenopausal stages. The use of insensitive estrogen assays can also significantly affect hormone levels reported [22]. Furthermore, the amount of free or bioavailable estrogen relies largely on sex hormone binding globulin (SHBG). Some studies suggested that SHBG might be a more reliable predictor of cognitive impairment over time than sex steroid hormones, including risk for dementia [23] [24]. However, SHBG levels, apart from being affected by sex steroid levels and oral estrogen hormone treatment use, also increase with loss of body mass index (frailty), in subclinical hyperthyroidism and with persistent alcohol abuse [25]. Given that these are all risk factors or predictors for dementia in themselves, SHBG may therefore act as an 'umbrella variable' explaining most of the variance in regression models predicting dementia[23]. High levels of gonadotropins are perhaps more reliable indicators of menopausal status and are seen to occur ~2 years before and after the FMP. They occur in response to lower bioavailable estrogen and testosterone, and are associated with pathology in the brain, including in the hippocampus, which is affected early in AD [26]. Gonadotropin levels have been found to be increased in patients with AD [23]. Some studies reported no associations between gonadotropins and cognitive decline after adjustment for covariates over the menopausal transition (see Table 1). However, different methodologies

(number of participants, assays, control for covariates or in/exclusion criteria related to HT use etc.) may explain these differences.

In conclusion, the results from the current review (see Table 1) concur with that of a recent review of longitudinal studies [27], with verbal memory identified as most impacted by menopausal transition, and processing speed, verbal fluency, and attention/working memory demonstrating a less consistent and less marked impact. Similarly, we found strongest effects of menopausal transition in women on verbal memory, with variable findings on processing speed (reported in 3 of our 5 reviewed studies, but only in half of included cohorts), and verbal fluency (reported in 2 of 3 cohorts). We did not find effects on attention/working memory in our included studies, because of differences in inclusion criteria for studies (not including studies of women with HIV).

Improved performance which is normally seen after repeated engagement with the same complex cognitive test over time seems to be decreased in the perimenopausal stage. When controlling for learning effects on cognitive tests, reductions in verbal memory (in around 1 in 5 women) and probably in speed of processing information (which can also affect verbal learning ability) can be detected. This effect is transitory and seems reduced by the postmenopausal stage. Verbal memory has long been thought to be most affected by menopause [28]. These types of tests are sensitive to gender differences and are affected early in AD [29]. Risk for AD is also higher in women than in men in many cohorts [30]. Many studies showed a reduced risk of AD with HT use [31]. However, observational studies are susceptible to systematic bias (e.g. higher educated and more affluent women are more likely to use HT, which demographic factors in themselves could protect against AD[32] and are not easy to control for). 'Recall bias' can also occur, as women with AD (because of the nature of their disease) are more likely not to recall HT use, which -when compared to prescription data- resulted in the 50% ('risk') reduction for AD with HT use compared to controls [33]. Once

women develop dementia, clinicians may be reluctant to prescribe HT, fearing reduced adherence due to forgetfulness, leading to reverse causality in data.

SURGICAL MENOPAUSE AND COGNITIVE DECLINE

The effect of loss of sex hormones on verbal memory and executive function is possibly most pronounced in women undergoing surgical menopause, particularly if this is induced before the natural age of menopause without HT (FMP is usually around 50/51 years of age). Compared with the gradual decline in hormone levels due to natural menopause, surgical menopause is characterised by an abrupt decline in sex steroids. This perhaps better reflects the animal studies using ovariectomy and add-back estrogen treatment showing strong biological plausibility of benefits of estrogens on the aging brain, by regulating brain metabolism, counteracting oxidative stress, increasing cerebral blood flow and dendritic outgrowth, by acting on nerve growth factors through co-localisation of receptors, via neurotransmitters synthesis and turn-over and many more [34].

Several small prospective studies showed that surgical menopause had an acute detrimental effect on cognitive (in particular verbal memory and executive) function [35] [36]. The negative effect on verbal memory was worse when surgery occurred at a younger age [36]. Another small (n=53) prospective 6- month follow-up study of women (with an average age of 41 years) undergoing surgical menopause indicated a decline in global cognitive function, whereas controls had stable function over time [37]. In a Chinese observational study, unilateral oophorectomy (with or without hysterectomy) performed before age of natural menopause was also associated with worse verbal recall [38]. In a Nationwide Historical Cohort Study in Denmark, hysterectomy with or without oophorectomy was shown to increase the risk for early onset dementia: hysterectomy by itself by 38%, but this risk more than doubled when performed with unilateral (OR= 2.10) or bilateral oophorectomy (OR= 2.33)

[39]. In a recent meta-analysis [40] which did not include the above- but most of the- studies mentioned below and some earlier studies, surgical menopause initiated before age 45 resulted in an overall increased dementia risk of 70% and worse semantic memory.

A large US-based longitudinal study investigated older women of two cohorts without dementia at baseline (n=1884, mean age 78 years, of whom n=607 had undergone surgical menopause) with a follow-up of up to 18 years. Each year of earlier surgical menopause equated to the cognitive effects associated with 6 months of aging. An earlier age at time of surgical menopause also significantly decreased verbal memory and AD neuropathology, including neuritic plaques. In this study, there was no association between age at natural menopause and cognition at follow-up and data on type of surgery or HT use and duration of use were not reported [41].

HORMONE USE AND SURGICAL MENOPAUSE

Rocca et al. [42] reported that an earlier age at surgical menopause had a dose dependent effect on cognitive impairment. His data analyses from the Mayo clinic and other cohorts also suggested that if women were treated with HT up to the natural age at menopause, the risk for was no longer significant [43]. Another analyses [40] combining three US based studies reported that those women who had undergone bilateral oophorectomy after age 45 (but before FMP) had worse verbal memory and more visual memory decline. When surgery was done before age 45, women had worse decline in semantic memory and global cognition, but not an increased risk for dementia. HT users showed less global cognitive decline, but duration of treatment was not a factor in this study. The large three Cities Study in France suggested that an early menopause before age 40 was associated with a 40% higher risk for worse performance on verbal fluency and on a visual memory test sensitive to dementia, regardless of surgery or this being due to premature ovarian insufficiency (POI). Over a 7-year follow-up, women (>

age 65), who had undergone early menopause had a 35% increased risk for lower global cognitive function and psychomotor speed, but again not an increased risk for dementia. However, taking long term HT[2] in this study increased risk for worse verbal fluency, but reduced risk for visual memory dysfunction. [44]. Another study showed that if oophorectomized women were treated with E2 implants for a long period (10 years), their executive and verbal memory performance was worse than non-treated women, but no effects were found on verbal fluency or sustained attention [45]. In contrast, a Thai study (n=164, aged 56 years) of surgical menopausal women (with surgery performed on average 11 years before assessment) suggested that duration of hormone treatment at a younger age at surgery did not affect frontal lobe dysfunction [46], but the test used (MoCA) may have not been sensitive enough. Here, in women with late induced menopause, HT use >10 years was associated with a 47% lower prevalence of Mild Cognitive Impairment, a risk factor for AD [47]. However, only education had independent effects on both outcomes in multivariate analyses.

Reasons for discordance are unclear. Perhaps mainly more highly educated women used HT and/or these educated women were better protected against oophorectomy effects with more cognitive reserve against abrupt protective loss of estrogens. The Thai study women were also relatively young when assessed. Education is associated with the 'healthy user bias'. Cardiovascular disease (CVD) risk factors are largely similar to those for AD and conversely women with healthy lifestyles have less risk of either morbidity [48]. A US based study [32] had shown that women who would choose to use HT 8 years later already had fewer other risk factors for dementia (they were more active and had less CVD risk, including lower body weight and blood pressure, better blood lipid profiles, less insulin resistance, etc) and were better educated.

[2] HT for at least 1 year and initiated within 2 years of menopause, with mean HT use of 10 years, and an IQ range between 4 and 15 years

In contrast, while women undergoing surgical menopause were more likely to use HT, a Canadian study found that these women had higher Framingham Risk Scores (for CVD, e.g. obesity, smoking) before surgery, than those undergoing natural menopause and also tended to have had less education [49]. This aligns with data [50] from the large British birth cohort longitudinal study (n=1315) which followed women from midlife (average age 43) with four assessments to an average age of 69, and showed that better verbal memory function was associated with an older age at natural menopause. This association was not maintained for surgical menopause, which was attenuated in adjusted analyses by childhood IQ and other covariates associated with this, such as education. However, Bove et al [41] also adjusted analyses for age, education and smoking, which did not attenuate results. Possibly subject selection (some of Bove's cohort were from religious orders) may be responsible for differences in findings. In the British cohort study, in surgically (but not natural) menopausal women, use of HT was again associated with lower verbal memory functions. On the other hand, better speed of information processing over time was seen in women using HT who had undergone bilateral oophorectomy [50].

Taken together these data suggest that surgical menopause can increase risk for verbal recall impairment, particularly when performed early (<45 years of age), but that its association with dementia risk may be confounded or exacerbated by other associated risk factors (e.g., having had lower education, more CVD risk factors before surgery etc.). HT given up to the average age at FMP may be protective, but when given to older women (>age 60), and/or when prescribed for over 10 years after surgery this may increase risk for some cognitive impairments, but studies show mixed and inconsistent results. Age at time of cognitive testing, timing, i.e when surgery was induced (before FMP or after) and/or duration of hormone treatment and prior health status and education of women may all play modifying roles [29].

HORMONE USE AND AGE AT TREATMENT

Cochrane meta-analyses had earlier reported benefits of HT in women with dementia, but similar to younger women, this was only seen for a couple of months of treatment [51]. In contrast, in the Women's Health Initiative (WHI) randomised controlled trial study, in older women (>65 years) at risk for CVD, an increased risk of dementia was seen with combination HT use already after 1 year [52] [53]. An adverse effect was also seen on verbal fluency after combination HT use for 4 years in the Heart and Estrogen/Progestin Replacement Study (HERS) study with a similar group of older women (71 years) with existing CVD [54] [53]. It was posited that HT possibly increased risk of cognitive impairment through CVD risk factor pathways (e.g. atherosclerosis), and WHI also showed an increased risk for CVD [55]. However, later analyses of WHI suggested no increased risk for CVD or stroke in women using HT for < 10 years, and it was suggested that HT may even be protective for CVD [56]. Larger and longer term studies of older women with dementia showed no benefits or a reversal of cognitive benefits, also already after 1 year of HT [57] [51]. In line with these findings, a recent large Finnish observational study showed increased AD risk with HT which was dependent on HT duration (>10 years in women < 60 of age) or age of women (>60 years, where duration was not important for increased risk) [58].

These data fit with two theories. The 'window of opportunity theory' suggests that taking HT around the age of menopause carries benefit or little risk for cognitive impairment, perhaps for up to 10 years [57]. The 'healthy cell bias' theory outlines how effects of estrogens might be beneficial when given close to menopause (the 'window of opportunity theory') and help maintain healthy neurons, but that HT could accelerate cell damage in older women at risk. In vitro studies showed that estrogen can accelerate intracellular damage related to cognitive impairment and dementia when disruption in intracellular calcium homeostasis or

dysfunction of mitochondria is present. This could be responsible for the negative effects found of HT use with an older age and/or in women at risk for AD [59] [60].

While our earlier Cochrane analyses showed no overall effect and only a short-lived beneficial effect (2-3 months) of estradiol on verbal memory in surgical menopausal women [61], several later large randomised controlled studies overall showed no favourable, but also no adverse effects of longer-term estrogen treatment (for 4 [51] or 5 years [52]) on cognition or cardiovascular risk parameters in early [51, 52], but also in late [52] natural or surgical menopausal women. The Kronos Early Estrogen Prevention Study or KEEPS [62] investigated conjugated equine estrogen against transdermal estradiol or placebo. The Early (within 6 years after menopause) vs Late (> 10 years after menopause) Intervention Trial with Estradiol (ELITE, n=567) investigated oral estradiol vs placebo [63]. In these studies, a different progestogen (micronized progestin not known for adverse effects) was used compared to WHI (which had used medroxy progesterone acetate or MPA, previously described to have potential negative cardiovascular outcomes [64]). This difference may have also been responsible for not finding negative effects of HT in the late intervention group in ELITE. We had earlier found a reversal of beneficial effects of oral estradiol and a progesterone on verbal memory which started after 6 months to return to baseline by a year of treatment in highly symptomatic recently menopausal women [65]. As the first assessments in KEEPS and ELITE were after 2 to 5 years of treatment, this may have been after potential very brief benefits could have been detected, which might have been optimal by 2-4 months as the Cochrane analyses suggested. So if there are positive effects of current HT on cognition, these are very short lived, regardless of age, and possibly other strategies should be used to maintain its benefits on memory function[66]. Harm to brain function- if seen - may be present in older women at risk for CVD or AD and/or with longer duration (>10 years) of treatment and may depend on type of progesterone for combination therapy, as negative effects of estrogen only treatment were not

seen in the large trials in older women [56]. However, estrogen only long-term therapy was seen to have negative effects on some cognitive functions in studies of surgically menopausal women with treatment >10 years, as discussed above.

MENOPAUSE, HORMONE USE AND MOOD

Interestingly, in the KEEPS study beneficial effects of 48 months treatment with conjugated equine estrogens (but not transdermal E2) were detected on reducing anxiety and depression [62]. However, while women who have had a previous mental health disorder may show an increased risk for depression in perimenopausal transition [43], clinical depression is not generally seen to develop in women during menopausal transition [67] [43]. Similar to cognition, symptoms of depression and severity of symptoms may be worse peri- vs. pre- but not vs. post-menopause [67]. Treatment with antidepressants such as Selective Serotonin Reuptake Inhibitors (SSRI) may be advised for severe mood symptoms [43] and if women have bothersome hot flushes, additional HT is recommended, although SSRI have some effect in reducing flushes too and should be tried first [56]. Risks and benefits of HT require personalised treatments. Most guidelines do not suggest giving HT as a first line treatment for mental health disorders (e.g. [43] [56]). Psychosocial factors (empty nest syndrome, work stress, care for parents and teenagers) can also affect mood, concentration and sleep and should be considered for psychological treatments, such as lifestyle changes, counselling and/or cognitive behavioral therapy [43] [56].

SUMMARY

While menopausal complaints of psychological health issues such as brain fog and depressive symptoms are common, there is less evidence for an objective long-term accelerated decline in functioning after menopause. For cognitive issues, these transient effects seem most

clear on verbal memory and learning, perhaps related to some extent to a slight slowing of complex information processing, with less improvement (i.e. learning) on these tests over a limited period of time. HT has not shown long term beneficial effects on cognition in randomised controlled trials. Older women (>65) who are at increased risk for dementia or CVD may show decrements in some cognitive functions, possibly depending on the progesterone used, but this is not clear. This is in sharp contrast to animal studies showing strong biological plausibility for estrogens to protect the aging brain. Observational data suggest that surgical menopause in women better approximates this sharp decline in sex steroids and concomitant drop in cognitive functions, with verbal memory again being most clearly affected. Treatment with HT for this group is probably recommended at least until the natural age at menopause around 50/51, perhaps not for longer than 10 years after FMP [56], but this needs further investigation. Similarly, while mood changes are commonly reported during menopausal transition, these do not normally reflect clinical disorders, unless women had previous depressive episodes. Most guidelines do not recommend HT for cognitive or mood disorders, which should not be considered unless women have early onset menopause (< age 45), are otherwise at risk for osteoporosis, and/or have very severe menopausal symptoms and there are no counterindications, such as risk for breast, endometrium or ovarian cancer [56]. The role of vasomotor symptoms (VMS) and sleep deprivation in both memory and mood needs to be more closely investigated. The 'domino hypothesis' [68] asserts that VMS, with hot flushes and perspiration, are worse at night and lead to disrupted sleep, which could mediate effects on cognitive and mood complaints. VMS are most effectively treated by HT [56].

Wordcount 5272

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CONFLICT OF INTEREST

None

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Table 1 Observational studies of menopausal transition, hormone levels and cognitive function in middle-aged women

Author	Country	Year	N	Subjects	Age	Outcome	Adjusted	VF	VL	SP	EX
cross-sectional											
Henderson [11]	Australia	2003	326	women in different stadia menopause, HT included	52-63	no difference in episodic verbal memory transition or early postmenopausal or in women who never received HT	menopausal status, time from final menstrual period, HT use, serum estradiol concentration, and other indices. Memory did not vary significantly with most exposures.		no		
Lokken [12]	USA	2006	48	women in different stadia menopause, no surgical menopause, including HT users	18-62	No effect verbal Fluency (category or COWAT) but worse TMTB in postmenopausal women not using HT. No effect visual or verbal memory (Logical Memory)	age, vocabulary levels, and education	no	no		yes
Herlitz [13]	Sweden	2007	242	women in different stadia menopause not using HT	49.3	No effect of menopausal stage on verbal fluency (phonemic and semantic). No association E2	adjusted for age and education	no			
Luetters [8]	USA	2007	1657	women in different stadia menopause SWAN study. Differences in premenopausal, early perimenopausal, late perimenopausal, and postmenopausal stages were defined based on menstrual patterns. Not taking HT	49.7	no significant difference menopausal stage on digit span, processing speed (SDMT) or East Boston Memory test (EBMT, recall. No association with E2 or FSH, age, race/ethnicity, education, symptoms, self-rated general health, and body mass index (BMI). A second set of models, stratified by menopause status, examined the possible relations between each cognitive test and either E2 or FSH, adjusted for age, race/ethnicity, education, symptoms, self-related general health, and BMI.	adjusted for site, age, race, education, BMI, self-reported poor health, vasomotor symptoms, poor sleep, somatic symptoms, and dysphoric mood symptoms. These were additionally adjusted for FSH and E2. A second set of models, stratified by menopause status, examined the possible relations between each cognitive test and either E2 or FSH, adjusted for age, race/ethnicity, education, symptoms, self-related general health, and BMI.	no	no	no	(SDM
Elsabagh [10]	UK	2009	189	early menopause (<5 years) vs late menopause (> 5 years) not taking HT no illness	49-67	No effect verbal Fluency (phonemic, animals), attention (PASAT) or verbal (story recall)/visual (pictures) episodic memory but worse planning and mental flexibility	age and sleepiness (after tests, was worse in postmenopausal women)	no	no	no	yes
Berent-Spillson [9]	USA	2012	67	women in different stadia menopause, no use HT 3 months	52 average (42-61)	Verbal Fluency (phonemic, trend semantic) worse postmenopause compared to pre/peri, associated with E2 and FSH level and activation brain regions on fMRI (prefrontal for verbal encoding task). TMTA (not B, speed of search) also different between groups. Not effect on verbal or visual recall, pattern comparison (perceptual speed) or TMTB. TMTA search speed affected (but not pattern comparison) and effect not in adjusted age analyses	Similar education, intelligence quotient, body mass index, sleep quality, testosterone, and SHBG. FSH and estradiol differed between groups.Controlled for age	yes	no	no	no
Weber [7]	USA	2013	117	perimenopause (40-60) intact uterus, no HT	48.7	In the first year of postmenopause performed significantly worse than women in the late reproductive and late menopausal transition stages on measures of verbal learning (RAVLT) and fne motor skills, attention/working memory (late menopausal stage) (no effect on verbal fluency composite score_ Higher E2 and high! FSH associated with fine motor skills. Symptoms not associated with cognition.	adjusted for age, education, vasomotor symptoms , sleep disturbance, depressive symptoms, anxiety symptoms, estradiol, and follicle-stimulating hormone	no	yes	no	

Author	Country	Year	N	Subjects	Age	Outcome	Adjusted	VF	VL	SP	EX
longitudinal											
Fu [14]	Taiwan	2006	495	114 (33%) perimenopause. premenopausal and no HT or hysterectomy. FU 18 months	40-54	verbal fluency (animals) different pre vs perimenopausal, vsual recognition better (but ns in controlled analyses)RAVLT (trend) declined in perimenopausal women (others improved). No effect TMT or Digit Span	controlled for age, education and baseline cognition	yes	trend		no
Thilers [15]	Sweden	2010	193	women various menopausal stages, no HT, only 5 OVX, average FU 5.6 years	40-65	Verbal Fluency less improvement over menopausal transition. Episodic verbal memory and visuospatial function (block design) only in women with normal BMI, less or no decline in women BMI>25 (no control cancer). E2 associated with BMI	adjusted for age, education, BMI	yes	yes		
Meyer [17]	USA (Chica	2003	803	SWAN premenopausal/early perimenopausal, no HT in the past 3 months, and no hysterectomy. 4 years FU	42-52	Over menopausal transition SDMT and Digit span backward improved, no detrimental effect transition	chronological age, education, family income, ethnicity, or baseline self-perceived health.			no	
Greendale [16]	USA SWAN	2009	2362	SWAN, 4 year FU, at least one ovary (no hysterectomy), no HT	42-52	In perimenopausal stage little or no learning effect on processing speed (SDMT) and verbal memory (EBMT). No effect on Digit Span Backward (DSB)	age, education, deprivation, ethnicity, testing language (English or non-English), site, retention in study		yes	yes	
Karlamanga [18]	USA SWAN	2017	2017	SWAN, 6.5 year FU (3rd visit as baseline to control for learning effect) Majority was postmenopausal, half 2 years from menopause. At least one	54	When controlling for learning effects, processing speed and verbal delayed recall declined relative to final menstrual period (FMP). No effect Digit Span Backward. No acceleration of decline after menopause	adjusted for retention and practice effects (number of assessments), menopause symtoms (depressive, anxiety, vasomotor, and sleep disturbance), age at FMP and covariates (education, financial hardship,		yes	yes	
Epperson [19]	USA	2013	403	POAS study, 14 year FU, no HT, at least 2 FU and no ovarian disease: at least one ovary intact	41->54	Immediate/delayed recall on BSRT declined from the pre- to postmenopausal stages (different versons to reduce learning effect). No effect processing speed. High E2 and Low FSH associated with better performance but not after adjustment for age, race, education, BMI, and baseline performance.	baseline cognitive task scores, age, menopausal stage (ordinal), race, education, and BMI. Hormone models were adjusted for cognitive task scores, age, race, education, and BMI		yes	no	
Kilpi [20]	UK	2020	2411	ALSPAC birth cohort, exclusion HT or surgical menopause, 3 yearly tests over 4 year FU	51 first test	Verbal memory declined over menopausal transition when controlled for chornological age and this was associated with high FSH and LH (less robust with sex steroids). Processing speed (DSST, similar to SDMT) decreased over menopausal transition but was not associated with FSH or LH. Verbal Fluency and verbal Intelligence improved over menopausal stages which was explained by chronological age	education, chronological age, practice effects , fieldworker effects, and age at first pregnancy. Suggested practice effects are not affected by menopausal transition. Rather chronological age explains improvement in verbal fluency	no	yes	yes	

Abbreviations N=number of participants, VF=verbal fluency VL=verbal learning or recall SP=speed EX=executive function BMI=body mass index

fu=follow-up, cs=cross sectional, pos=positive association, neg=negative, nill=no association, E2=estradiol, E1=estrone, T=testosterone HT=hormone therapy

F=free or B=bioavailable not bound to SHBG=sex hormone binding globulin, FSH=follicle stimulating hormone, LH=luteinizing hormone, exec(utive)=excutive function

conc=concentration, wm=working memory, educ=education, MMSE=mini mental status examination,global cognition like camcog. neg=age means is explained by age

SDMT=symbol digit modalities test TMT=trail making test, DSST=Digit Symbol Substitution Test, EBMT=East Boston memory test PASAT=paced auditory serial addition test