Age at Natural Menopause and Memory Function: Modification by Education and Genotype

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Age at Natural Menopause and Memory Function: Modification by Education and Genotype

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Abstract

Meta analyses show that positive effects of estrogen treatment on cognition are most apparent in women who have recently undergone surgical menopause. Observational data suggested that a) undergoing surgical menopause at an early age increases dementia risk; b) if surgically menopausal women are treated with hormones up to the natural age of menopause, risk for dementia is reduced; c) however, if estrogen treatment is continued up to a decade after induced menopause, there may be a risk of worse cognitive function when compared to not having had estrogen treatment.

We analyzed the association between a natural early age at menopause and cognitive tests sensitive to dementia, including genetic risk factors which could mediate the association between age at menopause and cognition in 173 Indonesian postmenopausal women, who had not undergone ovariectomy and were not using hormone treatment.

Age at menopause at 50 years or over was associated with better memory (beta=0.15, p=0.03) and better global cognition (beta=0.22, p=0.002) in linear regression analyses, although education explained this association fully. However, worse memory was associated with an early age at menopause of 47 years or younger independent of confounds and mediators. ESR1 genotypes associated with age at menopause and dementia in other studies did not mediate these relationships. However, the P allele of the ESR1 PvuII polymorphism was associated with better memory function (p<0.05). Data suggested the converse may be the case for older (>65 years of age) women.

These data link in with cell culture, treatment and observational studies suggesting that estrogen and estrogen sensitivity (ESR1 PvuII P allele) may confer protective effects on cognition in midlife, but not in elderly women. Whether and how long women who undergo an early natural or surgical menopause should be treated with hormones to maintain optimal cognitive function in old age needs further study (300 words).

Keywords: Estrogen; Memory; Cognition; Age at menopause; Genetics

Introduction

In the last century, most available evidence of basic sciences data, observational studies and small treatment studies seemed to advocate the use of estrogen treatment after menopause to protect against dementia and cognitive decline [1]. Larger and better controlled treatment trials were subsequently started as a result, mainly in older (65+ years) women for whom normally estrogen treatment would not have been indicated [2-5]. Results of these trials (using an estrogen which had not shown beneficial an effect on cognition before and which was combined with a progestagen which is known to confer vascular risk) suggested increased risks for dementia and stroke with hormone treatment [6]. This hormone treatment also did not prevent cognitive decline in women with dementia [2,4]. Furthermore, several studies have shown that during natural menopause there is actually not that much cognitive decline, which would further negate the need for estrogen treatment to increase cognitive function in women closer to the menopause [7]. Enthusiasm for estrogen treatment with regards to its previously believed propensity to promote health and better cognitive function in middle-aged and older women has shown a marked drop since the turn of the century. The consensus seems to be not to treat older women with estrogens for a prolonged period of time to prevent dementia and cardiovascular disease.

However, the question remains whether there is a subgroup of middle-aged women for whom estrogen treatment would help reduce dementia risk in later life. This is largely based on the abundance of basic sciences data suggesting the propensity of estrogens to be able to do so [8]. In contrast to undergoing natural menopause, undergoing surgical menopause-by having the ovaries removed-is associated with a sharp drop in cognitive functions, especially when this occurs prematurely [9-11]. This quite drastic effect can be reversed by administration of estradiol [9]. Animal data providing convincing evidence for estradiol’s protective effect on brain function also included only ovariectomised animals [12]. Moreover, ovariectomy in women may also have longer lasting effects on brain function, especially if surgery occurs before the normal age of menopause (around 50 years of age) and is not treated with estrogens [13]. Observational data from the Mayo Clinic and a Danish study reported that the younger women were when they underwent the surgery, the higher the risk for later life cognitive impairment and dementia [13-14]. When these ovariectomized women had been treated with estrogens up to the natural age at menopause (at age 50) this risk was no longer significant [13]. However, not all observational studies have reported that undergoing surgical menopause increases the risk for dementia [15], i.e. there is a lack of consistency in the data. This could be related to differences in data collection (self-report or...
medical records) and design. Retrospective data collection is affected by recall, which is often impaired long before women develop other clear clinical symptoms of dementia, and this can act as a confound when assessing risk and protective factors for dementia [16].

The Mayo Clinic and Danish data (which showed that an earlier age at surgical menopause affected risk for earlier cognitive impairment) could give further indications for the timing of hormone treatment for women who undergo an early natural menopause. Several studies investigating this association reported that an early natural menopause was also associated with increased risk for dementia and cognitive impairment [17-19]. In a Chinese study [19] a doubled risk was found for Alzheimer’s disease (AD, the most common form of dementia) if natural menopause occurred before 47 years of age. Two studies found that in women with Down’s syndrome age at menopause was also independently associated with an earlier onset of dementia [20,21], where age at menopause before 46 years of age increased the risk of AD by almost a factor 3. However, not all studies found an early menopause to be a significant risk factor for AD [22-24] and in the Rotterdam Aging Study even the reverse was found [25].

Others investigating cognitive functions using tests that are sensitive to dementia reported that the association between lower performance on these tests and an early age at menopause was fully (or at least partially) explained by childhood IQ (which-in turn-is strongly associated with education) [26]. In another study, this association between natural age at menopause and cognition was explained by education, adversity and previous cognitive function [27]. Again, educational level mediating the association between age at menopause and later life cognition was not always replicated [28]. The latter study found associations of early age at menopause with lower cognitive scores which were independent from education, life course socioeconomic status (SES, associated with adversity), parity, alcohol use and smoking. Differences in cut-offs for what was considered ‘early age at menopause’, differences in the assessment of cognition and dementia, systematic differences in education and/or SES/lifetime adversity experienced between cohorts, and associated risk factors (alcohol abuse, smoking frequency, etc.) may explain differences in findings between cohorts. Analyses combining data from the Aberdeen cohort [26] and the British Birth cohort study [27] only found a weak attenuation of the association between age at menopause and midlife cognition by lifetime SES, parity and smoking [29]. The authors suggested that early environmental and/or genetic programming may alternatively be related to age at menopause and subsequent rate of cognitive decline and/or earlier onset of dementia risk, either through setting differential lifelong patterns of exposure to hormones or by causing transient hormonal changes during sensitive periods of development.

Two studies found that particular variants of the estrogen receptor (ER) alpha gene (ESR1 PvuII P allele) were associated with an earlier age at menopause [30] and an increased risk for surgical menopause [30,31]. This single nucleotide polymorphism (SNP4, rs2234693 or PvuII) when carrying the P (C>T) allele is thought to produce the functional estrogen binding site, whereas the p allele is probably associated with less effective estrogen signalling and is thus associated with ER which are less sensitive to estrogen. The ESR1 PvuII P allele was also found to increase the risk for dementia in several studies. One group [31] reviewed 14 studies and concluded that this association was mainly driven by results in women but that the direction of the effect (P or p as risk allele) also varied between studies. In contrast, Talbot reported in his meta-analyses of 16 studies that the PvuII P allele increased the risk for AD by a factor 1.3 to 1.5, but mainly in Asian cohorts [32]. This would mean that the more sensitive ER is associated with an increased dementia risk. Another often studied ESR1 SNP variant (SNP5, rs9340799 or XbaI), when carrying the more sensitive X allele (A>G) is thought to have minor contributions (but no main effects) to either age at menopause or dementia risk and is therefore also included in the present analyses.

To further investigate these associations between cognition, childhood education, both ER alpha genotypes and age at menopause, we carried out a study in urban middle aged and elderly postmenopausal Indonesian women who had not undergone ovariectomy and were not using hormone treatment at the time of testing for at least 12 months. We earlier reported that age at menopause, independent of age at testing, predicted worse performance on two tests sensitive to early dementia [33]. As age at menopause is associated with education and possibly ER alpha genotypes, these data were investigated in this paper as potential mediators of the association found.

**Methods**

**Participants**

Participants were 173 postmenopausal women who had undergone natural menopause (as defined by the last menses having occurred one year ago) and who were, at the time of testing between 45 to 80 years of age. These women had been selected at random from a census list of women of this age group living in the East Bekasi subdistrict, West Java, Indonesia. This study was part of a larger study to investigate risk factors for osteoporosis. Ethical approval was obtained from the University of Indonesia prior to onset of the study and informed consent was obtained in writing.

Participants fulfilled the following inclusion criteria: being of the Deutero-Malay race, not having undergone ovariectomy, having good physical health without any other systemic disorders, not using medication thought to affect bone health and endocrinology for the last 12 months at the time of study (e.g. any hormone use), and not participating in any kind of dietary program.

**Procedure and other assessments**

Body mass index was established using weight and height measurements with the standard formulae (weight/height squared). Subjects were tested for non fasting blood glucose and cholesterol levels using a standard finger prick test, had their blood pressure taken sitting down, and were then interviewed, after which the cognitive tests were done. The interview included questions about their educational level (‘0’ primary school, ‘1’ secondary school, ‘2’ more than secondary school’) and to establish previous use of contraceptives (duration of use and type of contraceptive), and age at- and years since- menopause. We included the Mini-Mental State Examination (MMSE) which is a well known dementia screening test which has good sensitivity and specificity in combination with the Hopkins Verbal Learning Test (HVLT [34]). The modified HVLT [35] is a 5-10 min memory test. Verbal memory is one of the earliest functions to decline in dementia and is sensitive to hormone effects [1]. Trained research assistants administered the tests. Validation of these tests after (back) translation in Bahasa Indonesia had been carried out and psychometrics for the Indonesian slightly modified versions are described in detail elsewhere [36].

Examination of estrogen levels was performed by measuring estradiol levels in serum using a micro particle enzyme immuno assay (MEIA) method. Sensitivity levels of this assay are 15 pg/ml (55 pmol/L). Bone density was measured using the Sonos T 3000 Osteosys ultrasound device. The sample for DNA was taken from venous blood.
ESR1 *PvuII* and *XbaI* genotypes were analyzed using the restriction fragment length polymorphism (RFLP) technique.

**Statistical analyses**

Descriptive analyses were carried out using Mann Whitney U tests for continuous variables and Chi Square tests for categorical variables to assess differences between those with normal (age 50 and over) versus an earlier age at menopause. In subsequent analyses, an early age at menopause was defined as 47 years or younger based on two earlier studies (see introduction). Linear regression analyses and general linear models (to investigate the interactions) were used to investigate whether level of education and the ESR1 genotypes mediated the association between cognition and age at menopause while controlling for age at testing and, in secondary analyses, for body mass index and blood levels of estradiol, total non fasting glucose and cholesterol, as well as systolic and diastolic blood pressure. All analyses were done in PASW 17.0 using a significance level of 0.05. Trends were analysed as p<0.10, given the exploratory character of the analyses.

**Results**

Descriptive analyses showed that mean age at testing of this cohort was 56 (SD=7, median age 54) years and that most participants (80%) were younger than 60 years of age. The median age at menopause was 50 years of age (ranging from 28 to 58 years). We identified those with normal age at menopause to have had their last menses at 50 years and above, but half of the sample underwent menopause before this age.

Table 1 shows that there were no differences in health indicators previously associated with lower cognitive function between the two groups, with similar blood pressure, blood glucose and cholesterol levels. There were also no significant differences in estradiol levels or previous contraceptive use (a third had used a spiral, a third nothing, 5% had been sterilised and the rest had used the contraceptive pill or hormone injections, p=0.55, using Chi Square analyses). Those who were younger than 50 years of age at menopause were younger at the time of testing (p<0.0001) and had a slightly higher body mass index, but there were no differences in activity levels (data not shown) or educational level obtained (p=0.18, with 29% of early and 22% of normal age at menopause having had primary education or less). Those who underwent menopause before age 50 recalled 1.5 word less on the HVLT total immediate recall, but this did not reach significance (p=0.15), nor was there a difference for age at menopause on the MMSE scores (p=0.29, data not shown).

There was no difference in ESR1 *PvuII* (p=0.75) or *XbaI* (p=0.51) genotype frequency between those who had experienced an earlier or normal age at menopause (see Table 2 and Figure 1). Hardy-Weinberg Equilibrium (HWE) analyses were carried out to test the consistency of the genotype frequencies within the population. The Chi-Square value for *PvuII* loci was 5.65 (p=0.05). *P Allele* 54, *p Allele* 44) and for *XbaI* was 1.47 (ns, X allele 66, x allele 34). This indicated that HWE was maintained for *XbaI*, but not for *PvuII*. However, allele frequencies for *PvuII* were similar to those of other studies. ESR1 genotypes did not explain age at menopause (p=0.92, for the interaction effect between *PvuII* and *XbaI*, also see Figure 1) using general linear models.

Using a linear regression model stepwise backward model to predict HVLT total immediate recall performance included only an older age (beta = -0.16, p = 0.03), lower education (beta = -0.38, p = 0.0001) and a trend for the ESR1 *PvuII* genotype (beta = -0.12, p = 0.09, but not *XbaI*, p = 0.77) to be associated with total immediate recall performance (see Table 3). These variables together only explained 18% of the variance. Age at menopause did not contribute to this model (p = 0.23) when education was added.

For the MMSE (using stepwise backward regression) only education explained performance (beta = 0.53, p = 0.0001) with age at menopause (beta = 0.13, p = 0.07) and age (beta = 0.13, p = 0.06) not quite reaching significance, nor did the genotypes (*PvuII*, p = 0.49, *XbaI*, p = 0.58) contribute to this model.

To investigate interactions, we used general linear analyses which revealed that HVLT total immediate recall showed a significant independent main effect of age at testing [F(1,169) = 8.52, p = 0.004] and an independent main effect of an earlier or normal age at menopause [F(1,169) = 3.94, p = 0.05]. Body mass index was not significant in these models (p = 0.25). ESR1 genotypes when entered in this model were also

| Table 1: Descriptive analyses. | | |
|---|---|---|---|---|
| | *PvuII* | *XbaI* | | |
| Age 50< yrs | 35% | 39% | XX | XX |
| Age 50 or > yrs | 36% | 42% | 22% | 9% |
| p=74 | p=52 |

Table 2: Age at menopause and ESR1 genotype frequency.

<table>
<thead>
<tr>
<th>ESR1 <em>PvuII</em></th>
<th>Mean</th>
<th>Std. Error</th>
<th>95% Confidence Interval</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
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<tbody>
<tr>
<td>PP</td>
<td>20.87</td>
<td>.69</td>
<td>19.52</td>
<td>22.33</td>
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<tr>
<td>Pp</td>
<td>20.42</td>
<td>.64</td>
<td>19.14</td>
<td>21.69</td>
<td></td>
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<tr>
<td>pp</td>
<td>18.95</td>
<td>.86</td>
<td>17.25</td>
<td>20.65</td>
<td></td>
</tr>
</tbody>
</table>

Dependent Variable: HVLT total immediate recall Covariates appearing in the model are evaluated at the following values: age at menopause = 48.72, age = 55.94, educational level = .85

Table 3: Estimates of the full regression model: ESR1 *PvuII* genotypes explaining memory function, while controlling for age at menopause, age at testing and educational level.

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not significant, but did partially explain the association between age at menopause (p=0.057) and recall performance. Only ESR1 PvuII had a trend (p=0.09) main effect on the HVLT total immediate recall (but the interaction or main effect of XbaI was not significant). When XbaI was removed from the analyses, PvuII no longer had a significant main effect (p=0.57) and age at menopause again had an independent main effect (p=0.05) from age at testing (p=0.004) in predicting memory performance.

However, when educational level obtained was entered as a covariate [F(1,66)=25.52, p=0.0001], this variable fully explained the association of age at menopause with memory recall [F(1,66)=1.58, p=0.21], although age at testing independently remained significant in this model [F(1,66)=5.09, p=0.03]. Body mass index, estradiol, total non fasting glucose and cholesterol, systolic and diastolic blood pressure did not contribute to these models when entered. For the MMSE, similarly only education remained in the analyses (p=0.0001) with only trends for age at testing (p=0.08) and age at menopause (p=0.07) to predict performance, but not genotypes (p>.50).

When analyses were split for age at menopause, overall the interaction of PvuII x XbaI polymorphisms showed a trend in the analyses [F(4,76)=2.21, p=0.07] to predict memory performance in those who had a normal age at menopause, independent of age (ns) and education (p=0.005). Estimated marginal means tests showed that those carrying PPXX had better memory performance (21.43, SE=2.37) than those carrying the p allele (variance in performance from 17.7 to 18.4, see fig 2). Only educational level obtained explained MMSE and HVLT performance in both earlier and normal/late menopausal women (p=0.0001).

About a third of women (34%) underwent natural age at menopause at age 47 years or younger. Having an early age at menopause at 47 years of age or younger versus an older age at menopause was also not predicted by genetic polymorphisms (p>.20). Those who underwent menopause before age 47 recalled 1.77 words less, which was trend significant (p=0.06). On the MMSE there was no difference in performance (p=0.47). However, women who had menopause at age 47 or younger had lower total immediate recall memory function (p=0.05), which remained independent from age at time of testing and educational level, and in secondary analyses: body mass index, estradiol levels, blood pressure (systolic and diastolic), blood glucose and cholesterol, bone density measures, duration since menopause (in years) and contraceptive use (which were all non significant). Only education (p=0.0001) and having an age at menopause of 47 years or younger (p<0.05) remained significant in these analyses. Similar associations were seen for the MMSE.

Discussion

We reported lower memory and global cognitive performance to be associated with an earlier than median age at menopause. However, in the analyses including education and genotypes, for a lower than median age at menopause (50 years of age), this association was fully explained by differences in educational levels obtained. This is in line with earlier findings [26]. Scottish women who had an earlier menopause were also more likely to have had lower childhood IQs [26] which is – in turn- related to lower levels of education, low SES and more life time adversity. Lifetime adversity was also found to be associated with an earlier age at menopause in another developing country [36]. Both low education and low SES are major independent risk factors for cognitive impairment and dementia [37].

However, similar to other studies (see introduction), for women who had an earlier natural age at menopause of 47 years or younger, the association remained independent of education and many other variables previously associated with lower cognitive function. These data tie in with those of surgically menopausal women [13,14] where the younger the age at menopause, the stronger the association with risk for later life lower cognitive function. As stated in the introduction and supported by our data, part of the discrepancies between studies could thus be explained by when an ‘early age at menopause’ is defined. Using menopause at age 50 (the median split) and beyond as ‘normal’, versus analyses using age at menopause at 47 or less as ‘early’ gives different outcomes. In addition, cohorts will have different distributions of educational levels and adversity experienced. It has been argued that age at menopause is a marker of accelerated (brain) ageing, which is at least partially explained by less childhood brain reserve capacity (as indicated by IQ) which is in turn strongly related to education and childhood environments. However, in this and other cohorts education and/or lifetime adversity only partially explained...
the association between age at menopause and cognition [18,23,28]. In addition, having low childhood- and subsequently less adult- brain reserve capacity does not necessarily indicate that these women would not benefit from hormone treatment.

Estrogens can act to boost brain reserve capacity by promoting dendritic outgrowth and synaptic contacts as well as neurotransmitter levels and reduction of toxic insults, such as oxidative stress and other factors thought to be important in dementia and age-related cognitive decline. Its biological plausibility was once called its strongest suit [38]. In the eighties and nineties, women who would go on to use hormones for menopause were found to already be better educated and healthier before they made this choice [7]. This ‘healthier user bias’ was said to have confounded previous observational data linking hormone use to reduced risk for dementia and better cognitive performance. However, as many observational studies still found independent protective associations of hormone treatment in reducing risk for dementia, while controlling for education and many of these health related variables, this could indicate that using hormones around the age of menopause-particularly when this is an early menopause- further acts to increase brain reserve capacity. In fact, women who had obtained little education were seen to benefit most from hormone treatment in our earlier review [1].

Interestingly, we also found that women who had normal age at menopause and who carried at least one P allele had better immediate memory capacity than those carrying both pp alleles. Best performance was seen in women who carried the PP and XX genotype. Similar results were found on a test for global cognition (Mini Mental State Examination, data not shown). This is in line with earlier data from another US based cohort where the p allele increased risk for global cognitive decline on a similar test sensitive to dementia [39]. However, as H-W equilibrium was not maintained for the PvuII genotype in our study, results need to be regarded with caution. On the other hand, allele frequencies were similar to those of other cohorts who often had similarly small numbers. The small sample size of studies investigating genetics is a major limitation, however, which must be addressed.

Our result seems at odds with findings of this particular genotype to be associated with an almost doubled risk for dementia in other studies [32]. For instance, a recent study [40] found that the ER alpha P allele increased risk of AD in women by a factor 1.6. However, while several studies reported increased risk (usually of the combination of PvuII P with Xba1 X genotype in Italian, US (Down Syndrome) and Japanese AD case-control cohorts [3, 41-45]), others did not find this in Dutch and Swedish cohorts [46]. It was thus suggested that ethnic differences may have played a role. One study [47] found no association in whites from the UK, and although there was no significant difference between Japanese cases and controls, 36% of Japanese AD cases carried the P allele versus 41% of controls (48 versus 46% in UK cases and controls, respectively). Similarly, but also in contrast to the earlier studies, another Swedish [48] and Italian cohort [49] reported that the p allele in combination with the AD genetic risk factor APOEe4 increased AD risk. In another Italian study, only the Xba1 x x genotype doubled AD risk, but not the PvuII genotype, alone or in interaction with APOE genotypes [50]. Hence, ethnic differences cannot alone explain differences in results found between cohorts.

To explain our current results, with the possibly more responsive ER alphas (P and X alleles) being associated with better cognitive function, it could be speculated that within this particular age range, with the majority of women being younger than 60 years of age, hyper-responsiveness of ER to estrogens may still convey protective effects for the brain. However, at a later age this particular genotype may reverse to exert negative effects on brain function and increase the risk for dementia. Professor Brinton Diaz, in explaining her ‘healthy cell bias’ hypothesis [51], showed that estrogens normally exert positive effects on healthy neurons. However, in neurons undergoing pathological change (which is more likely in older neurons and people who are at increased risk for earlier age at onset of dementia, such as those carrying the APOE e4 risk allele), estrogens can exert negative effects and accelerate the pathway towards neuronal death. This might explain why the P genotype was found to be associated with later life dementia risk in older women.

Indeed, when we did post hoc analyses, the 3 way interaction of age x Xba1 x PvuII was significant in predicting MMSE performance [F(4,152)=2.91, p=0.02], as well as the 2 way between genotypes [F(4,152)=2.91, p=0.02] and age at menopause [F(1,152)=7.28, p=0.008]. There was a similar trend for memory, including the 3 way interaction (p=0.09) which was independent of age at menopause (p=0.03). Stratifying analyses for age at menopause, for women who had undergone early menopause again only low education predicted MMSE and HVLT performance, whereas for women who had undergone normal or late menopause the 3 way interaction for age with both genotypes (for HVLT p=0.008, for MMSE p=0.06) and 2 way for genotypes (HVLT p=0.002 and MMSE p=0.05) independently predicted performance from education (p=0.001) and age (ns). Graphs indicated that indeed the P variant was associated with better cognition before age 65, whereas it was associated with worse cognition after this age. The X variant showed similar associations. So it may be that age differences between cohorts, as well as ethnic variation and differences in diagnostics/tests used can explain differences in results between studies (e.g. P conferring risk or protecting against cognitive impairment).

This phenomenon could also tentatively explain the link between undergoing surgical menopause (in two studies found to be associated with this P genotype [30,31]) and later life dementia. Furthermore, surgical menopausal women who were still using hormone therapy a decade after menopause (around age 60) had worse memory function than those not treated with hormones in two observational studies [53,54]. This would follow if high estrogens combined with increased ER sensitivity (P allele) confers risk for cognitive impairment but only at an older age. Accordingly, women undergoing premature natural or surgical menopause may benefit from estrogen treatment, but hormone treatment should be discontinued before age 60, particularly if women carry other of the above mentioned risk factors for dementia (obesity, carrying the APOE e4 risk allele, etc.).

In our study estradiol did not contribute to the analyses, but the assay used may have been insufficiently sensitive. Sex hormone binding globulin levels were also not measured to assess bio-available estrogenic effects. In subsequent analyses with an increased sample size we will investigate dementia risk as genotypes, bio-available estradiol and age at menopause may have different associations for this group. Another limitation of the present study is that no data on menopausal symptoms or subjective cognitive complaints were available. However, symptoms did not explain cognition function after hormone treatment in meta analyses. In addition, East Asian women, possibly because of high soy (which contains phytoestrogens) consumption [35] have been reported to have fewer menopausal symptoms. We also had no data on parity which in other cohorts was found to be associated with age at menopause. Lastly, there was no formal diagnosis of dementia and women of this cohort were overall too young to form a substantial group who was at risk for dementia. However, the type
of verbal episodic memory test used in this study has been shown in several studies to show reduced performance long before other clinical symptoms of dementia have become apparent [35].

Despite these limitations, preliminary results from these analyses are intriguing and fit other data. This again calls for a re-evaluation of estrogen treatment for women who are at an earlier than average age when they reach menopause, either naturally as the current data suggest, or surgically, as the Mayo Clinic and Danish cohort data suggest. These data also reflect those of other health related interventions, where cessation of smoking, treating high blood pressure and high cholesterol may also be indicated in early middle age at the latest to reduce the risk of cognitive decline and dementia in later life [52]. We believe that hormone treatment in midlife for a particular subgroup of women could still be part of this.

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