International IMS Menopause Society
Promoting education and research on midlife women's health

International Menopause Society Statement

Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study

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A new publication in BMJ linking Alzheimer's Disease to menopausal hormone therapy use. Should this warrant a change in prescribing practices for MHT?

The simple answer is no.

This recent publication in the BMJ reports a case-control study from Finland comparing the use of menopausal hormone therapy (MHT) among Finnish women with and without Alzheimer's disease (AD). The researchers report that systemic MHT ever-use was higher among women with AD (18.6%) compared with those without AD (17.0%). They conclude, "Use of postmenopausal systemic hormone therapy is accompanied with an increase in the risk of Alzheimer's disease in postmenopausal women" and that, "[this] data should be implemented into information for present and future users of hormone therapy".

The IMS does not agree with either concluding statements. This is because an *association* between MHT and AD *is not evidence for cause and effect*. There are many instances in medicine where research observations have not stood the test of subsequent randomized clinical trials[1,2]. Unfortunately, in this case the chance of an appropriately powered randomised trial ever being done is vanishingly small.

The study was based on the Finnish drug registries, so the sample is large. However, the study has a number of important limitations, acknowledged by the authors, that necessitate caution in interpreting these findings. Like all registry studies there was lack of information about key confounding factors, including other established dementia risk factors, and the timing of initiation of MHT. As an observational study, it is limited by ascertainment bias. Cases of AD were identified via a national reimbursement register. Whereas the Finnish Drug Reimbursement Register has a high positive predictive value for AD (most people identified will actually have AD), the sensitivity is in the order of 65%. This means that up to 35% of people with AD may not be identifiable by this process, and potentially some included as 'controls'. Such an ascertainment bias may have influenced the study findings either way.

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The study collected data on the use of MHT from 1994. Through the nineties, and until the first outcomes of the Women's Health Initiative Trials, MHT was thought to prevent cardiovascular disease and cognitive decline, such that women at increased risk for both vascular dementia and AD may have been preferentially prescribed MHT. Hence, the finding of a small excess in the present study could simply reflect this bias. As suggested by the authors, women may have been prescribed MHT once they started to develop early signs of cognitive dysfunction, so that at least part of the association could be "reverse causality". Also, in this study, some women classified as having AD may have had vascular dementia or mixed AD/vascular dementia, both of which may have been worsened by MHT.

The paper acknowledges that 90% of estrogen use was oral therapy, and when progestogen was prescribed it was primarily as norethisterone acetate or medroxyprogesterone acetate. Thus, the findings can only be considered to relate to these formulations.

But the greatest limitation of the study is that it is a real-life study, where women using or not using MHT may have been by default different, in that users were bothered by vasomotor symptoms, such that they were prescribed MHT, in some instances for many years. Vasomotor symptoms can affect cognitive function. A number of studies have shown that women with hot flushes have poorer scores in memory tests as compared with non-flushers, among other differences[3].

With respect to the use of MHT for the treatment of vasomotor symptoms in the early postmenopausal years, the available data for the effects on cognitive function is reassuring[4-6]. The evidence includes a trial of 1326 participants in the Women's Health Initiative (WHI) studies, aged 50-54 years randomly allocated to oral MHT (conjugated equine estrogen with or without medroxyprogesterone acetate; CEE±MPA) or placebo and then assessed approximately 7 years after cessation of treatment in the WHI intervention studies, at an average age of 67.2 years[5]. Treatment with MHT resulted in no overall apparent benefit or risk compared with placebo, although as the study was not large, a small effect of treatment, either positive or negative, cannot be ruled out[5].

CEE+MPA was reported to be associated with doubling of the dementia risk in women aged 65 years and older at randomisation in the larger WHI Memory Study, a sub-study of the WHI[7]. The 18-year follow-up of over 27,000 WHI participants revealed a decreased risk of death from AD and other dementias among women randomised to CEE compared with those randomised to placebo (HR, 0.74 [95% CI, 0.59-0.94]; p = 0.01) and no increased risk of death from AD and other dementias among those randomized to CEE+MPA vs placebo (HR, 0.93 [95% CI, 0.77-1.11]; p = 0.42)[8].

In summary, the potential adverse effects of MHT suggested by this publication are small and should be considered in the context of the findings from randomised controlled trials. The conclusions, as they have been presented, have the potential to arouse concerns and mislead those who are not experts. The study findings are insufficient to infer changes should be made to practice guidelines or policy.

The IMS recommendations are that:

1. The primary indication for the initiation of MHT is for the treatment of bothersome vasomotor symptoms
2. MHT should not be used for the prevention or treatment of cognitive difficulties in midlife women.
3. No clinical trial has yet specifically studied the long-term effects of MHT on cognitive function in women with moderate-to-severe vasomotor symptoms.
4. Available data from three randomised, placebo-controlled clinical trials of MHT[4-6] provide reassurance that MHT initiated in the early postmenopausal years does not result in early adverse effects on cognitive function.

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