BMJ 2019;364:l877 doi: 10.1136/bmj.l877 (Published 6 March 2019)

EDITORIALS

Menopausal hormone therapy and cognition

Evidence is reassuring for women needing a few years' treatment for menopausal symptoms

Pauline M Maki *professor*[1], Lucille M Girard *patient representative*[2], JoAnn E Manson *professor*[3 4]

[1]Departments of Psychiatry, Psychology, and Obstetrics & Gynecology, University of Illinois at Chicago, Chicago, IL, USA; [2]Participant, Women's Health Initiative, West Warwick, RI, USA; [3]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MI 02215, USA; [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MI, USA

A linked study (doi:10.1136/bmj.l665) by Savolainen-Peltonen and colleagues in this week's *The BMJ* explores associations between menopausal hormone therapy and risk of Alzheimer's disease.[1] Two thirds of patients with Alzheimer's disease are women.[2] Given the lack of effective treatments for the disease and estimates that prevalence will triple by 2050, medical and public health efforts focus on primary prevention, including risk factors and preventive strategies that pertain especially to women.[2] Among these factors, considerable attention has been given to the role of menopausal hormone therapy, which was associated with a 29% reduction in Alzheimer's disease in meta-analyses of observational studies[3] but with a doubling of the risk of all cause dementia with estrogen plus progestin in the Women's Health Initiative Memory Study (WHIMS),[4] the only randomised trial of postmenopausal hormone therapy for prevention of Alzheimer's disease.

These opposing findings have been the focus of much research and discussion. A key consideration is the age at initiation of menopausal hormone therapy, which in the general population is around 52 years but in WHIMS was 65 years and older. The timing hypothesis, which was proposed because of failed trials of hormone therapy in patients with Alzheimer's disease,[5] states that the use of hormone therapy in early menopause confers benefit whereas later use does not and may even be harmful. A parallel hypothesis applies to hormone therapy and cardiovascular health. Although available evidence suggests that the overall health benefits outweigh the risks in younger postmenopausal women without contraindications,[6] should these women be concerned about an increased risk of dementia, as the case-control study by Savolainen-Peltonen and colleagues suggests?[1]

A definitive large scale randomized trial of menopausal hormone therapy on incidence of Alzheimer's disease in younger postmenopausal women is unlikely to occur because of feasibility, costs, and competing funding priorities. Instead, insights are gained from observational studies, translational studies, and randomized trials of its effects on cognition and surrogate outcomes such as biomarkers for Alzheimer's disease and neuroimaging findings.

Reassurance that hormone therapy does not adversely influence cognition in young postmenopausal women comes from three high quality, randomized trials,[7-9] including one of WHIMS participants randomized to hormone therapy at ages 50-55,[8] showing neutral cognitive effects. The findings of WHIMS nevertheless raise concerns about adverse cognitive effects in older women who initiate menopausal hormone therapy, especially estrogen plus progestin, and in women who continue therapy long term. A critical knowledge gap is whether hormone therapy confers cognitive benefit to women with moderate to severe vasomotor symptoms, the key indication for treatment.

Should the Finnish case-control study by Savolainen-Peltonen and colleagues change the view that hormone therapy is generally safe for younger postmenopausal women? There are many advantages to examining hormone use and Alzheimer's disease in Finland, including a large sample size of 84 739 women, availability of national drug registries that document hormone therapy prescriptions and purchases, long follow-up, and well validated dementia diagnoses. These strengths, however, are countered by the substantial limitations common to all registry studies, including the lack of information on potential confounding factors, including hysterectomy/oophorectomy, cardiovascular risk factors, diabetes, apolipoprotein E4 genotype, and other risk factors for dementia. Additionally, age at the start of treatment was not consistently available. The drug reimbursement registry has a sensitivity of 65.2% for detecting Alzheimer's disease; thus, many undiagnosed cases could be missed among the controls.[10]

Ascertainment bias, confounding by indication, and other inherent limitations of observational studies that lead to residual confounding also apply to this case-control study. This study considered diagnoses of Alzheimer's disease during 1999-2013 and use of hormone therapy beginning in 1994. Before the 2004 WHIMS publication, women with memory difficulties might have been encouraged to start or continue hormone therapy because of expectation for cognitive improvement, whereas after WHIMS, women using hormone therapy might have been screened more for cognitive problems than other women because

Correspondence to: J E Manson jmanson@rics.bwh.harvard.edu

For personal use only: See rights and reprints http://www.bmj.com/permissions Subscribe: http://www.bmj.com/subscribe

BMJ: first published as 10.1136/bmj.l877 on 6 March 2019. Downloaded from http://www.bmj.com/ on 1 July 2022 by guest. Protected by copyright.

of expectation of adverse cognitive effects and close interactions with the healthcare system.

Additionally, in such a large sample, statistical significance can be observed for small, clinically insignificant associations. For instance, most women using estradiol therapy in the study initiated treatment before age 60 and continued for at least 10 years. That group showed a small but statistically significant 7% increased odds of Alzheimer's disease compared with controls. In contrast, for estrogen plus progestin therapy, most women initiated treatment before age 60 and continued for more than 10 years, with a clinically more meaningful increase (roughly 20%) in odds of Alzheimer's disease compared with controls.

For shorter treatment durations, the risk of Alzheimer's disease was not increased among those who initiated either estrogen therapy or estrogen plus progestin therapy before age 60.

Finally, correlation cannot infer causation. Considering the totality of the evidence, these findings should not influence clinical decision making about the use of hormone therapy for symptom management. For women in early menopause with bothersome vasomotor symptoms, no compelling evidence exists of cognitive concern from randomized trials and instead there is reassurance about cognitive safety. Concerns about longer term use of estrogen plus progestin on cognitive outcomes remain.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: PMM has received honorariums from Mylan for talks unrelated to the topic of this editorial. Further details of *The BMJ* policy on financial interests is here https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf

Provenance and peer review: commissioned; not peer reviewed.

1 Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, etal . Use of postmenopausal hormone therapy and risk for Alzheimer's disease in Finland: nationwide case-control study. *BMJ* 2018;364:l665.
2 Alzheimer's Association. 2018 Alzheimer's disease facts and figures. *Alzheimers Dement* 2018;14:367-42910.1016/j.jalz.2018.02.001
3 Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998;279:688-95. 10.1001/jama.279.9.688 9496988
4 Shumaker SA, Legault C, Kuller L, etal. Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-58. 10.1001/jama.291.24.2947 15213206
5 Marder K, Sano M. Estrogen to treat Alzheimer's disease: too little, too late? So what's a woman to do?*Neurology* 2000;54:2035-7. 10.1212/WNL.54.11.2035 10851358
6 The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2018;25:1362-87. 10.1097/GME.0000000000001241 30358733
7 Gleason CE, Dowling NM, Wharton W, etal . Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. *PLoS Med* 2015;12:e1001833, discussion e1001833. 10.1371/journal.pmed.1001833 26035291
8 Espeland MA, Shumaker SA, Leng I, etal. WHIMSY Study Group. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med* 2013;173:1429-36. 10.1001/jamainternmed.2013.7727 23797469
9 Henderson VW, St John JA, Hodis HN, etal . Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. *Neurology* 2016;87:699-708. 10.1212/WNL.0000000000002980 27421538
10 Solomon A, Ngandu T, Soininen H, Hallikainen MM, Kivipelto M, Laatikainen T. Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. *Alzheimers Dement* 2014;10:303-9. 10.1016/j.jalz.2013.03.004 23849592

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to http://group.bmj.com/group/rights-licensing/permissions

BMJ: first published as 10.1136/bmj.l877 on 6 March 2019. Downloaded from http://www.bmj.com/ on 1 July 2022 by guest. Protected by copyright.