



# Menopausal hormone therapy and dementia

## A causal link remains unlikely

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In a linked paper, Pourhadi and colleagues (doi:10.1136/bmj-2022-072770) investigated the associations of menopausal hormone therapy with dementia later in life.<sup>1</sup> Their observational study of data from Danish national registries reported that hormone treatment was associated with an increased risk of dementia with either short term or long term use (risk of all cause dementia associated with exposure to oestrogen plus progestin v never use: hazard rate ratio of 1.24 (95% confidence interval of 1.17 to 1.35)). Alzheimer's disease is twice as common in women than in men; therefore, midlife exposures that might influence its risk in women are of considerable interest.<sup>2</sup>

Menopausal hormone therapy has been in the spotlight as a potential risk factor contributing to this disparity in Alzheimer's disease. Treatment was widely prescribed before the 2003 Women's Health Initiative Memory Study (WHIMS)—a randomised trial—reported that oestrogen plus progestin treatment was associated with a twofold increase in the risk of dementia among women older than 65 years.<sup>3</sup> Risk did not increase among women starting hormone therapy aged 50-55 years in the WHIMS of Younger Women (WHIMS-Y) published in 2013.<sup>4</sup> Two other randomised trials tested the effects of oestrogen and progestogen treatment on cognitive function in women who started treatment shortly after menopause; in both trials, cognitive function was not affected by hormone therapy compared with placebo.<sup>5,6</sup>

Age at initiation of hormone treatment appears to be a crucial factor for cognitive outcomes based on these earlier clinical trials. Pourhadi and colleagues' new study reported an association with increased risk of dementia even in women using menopausal hormone therapy before the age of 55 years for less than or equal to five years, which is within the age range recommended by the North American Menopause Society.<sup>7</sup> Their findings contradict those of the WHIMS-Y trial and other trials that reported no effect on cognitive function among women who were randomly assigned to hormone therapy in early menopause.<sup>5,6</sup> Although, longer follow-up is needed to determine participants' dementia risk later in life.

Confounding factors could be producing a spurious signal for higher dementia risk in younger women using hormone therapy for either a short or long duration. In particular, increased dementia risk with less than one year of hormone treatment is not biologically plausible, further supporting the presence of confounding factors. Approximately two thirds of women have subjective cognitive difficulties during the menopausal transition and may experience a temporary decline in cognitive processing speed.<sup>8</sup>

Women with subjective cognitive complaints, vasomotor symptoms, and sleep disturbances would likely seek hormone therapy more often than those who do not experience these symptoms. During the early years of this study, before WHIMS results were available, hormone treatment was perceived as a strategy for slowing cognitive decline and was even prescribed for that purpose.<sup>7</sup> Additionally, women who were prescribed hormone therapy would potentially remain in the health system longer and therefore be diagnosed with dementia earlier than women who were not treated and did not seek medical attention. Moreover, after the results from WHIMS suggested a link between hormone treatment and dementia in 2003, women already taking hormone therapy, and their doctors, might have been more vigilant for signs of cognitive decline. Confounding by indication may also affect observational findings because vasomotor symptoms, particularly during sleep, are associated with a higher volume of white matter hyperintensity—a marker for poor brain vascular health.<sup>9</sup>

Pourhadi and colleagues' study has several strengths. The records from the entire population of Denmark were available, including detailed ascertainment of hormone treatment prescriptions, which distinguishes this study from most other observational studies. Furthermore, the authors were able to investigate cyclic and continuous oestrogen plus progestogen formulations separately, as well as age at initiation of menopausal hormone therapy and length of treatment, which allowed for secondary analyses of exposure of women younger than 55 years of age, according to treatment duration.

Previous observational studies have reported conflicting findings on the risks and benefits of hormone therapy with respect to cognitive function and dementia. Although Pourhadi and colleagues' study was done carefully using national registries, the observed associations could be artefactual and should not be used to infer a causal relationship between hormone therapy and dementia risk. These findings cannot inform shared decision making about use of hormone therapy for menopausal symptoms. Randomised clinical trials provide the strongest evidence on the effect of hormone therapy on dementia risk. Furthermore, brain imaging biomarkers might help to identify the effects of hormone treatment on dementia pathophysiology at an earlier stage, making assessment of its influence on dementia risk in trials of recently postmenopausal women feasible.<sup>10,11</sup>

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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>.

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