

# What is the association of menopausal HT use and risk of Alzheimer disease?

Women with Alzheimer disease (AD) were **more likely to have used postmenopausal systemic hormone therapy (HT)** than controls (**18.6% vs 17.0%,  $P<.001$** ), according to results of an observational study that used national records to match 84,739 women with a diagnosis of AD with an equal number of controls. Use of vaginal estrogen was not associated with an increased risk of AD (odds ratio, 0.99). **Small elevations in AD risk with systemic HT use, however, do not imply causation—and they should not impact clinical practice.**

## EXPERT COMMENTARY

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*Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ. 2019;364:1665.*

**A**lzheimer disease represents the most common cause of dementia. Although sex hormones may play a role in the etiology of AD in women, studies addressing the impact of menopausal HT on risk of AD have conflicting findings.

Finnish researchers Savolainen-Peltonen

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and colleagues aimed to compare postmenopausal HT use in women with and without AD. They used national drug and population registries to identify patients with AD, control women without a diagnosis of AD, and data on postmenopausal HT use.

## Details of the study

In Finland, reimbursement for treatment related to AD requires cognitive testing, brain imaging, and a statement from a specialist physician. Using national records, the study investigators identified 84,739 women with a diagnosis of AD during the years 1999–2013 and the same number of control women (without AD) during the same period. A national drug reimbursement registry was used to identify HT use from the year 1994.

**Findings.** Women diagnosed with AD were more likely to have been current or former users of systemic HT than controls (18.6% vs 17.0%,  $P<.001$ ). The odds ratios (ORs) for AD were 1.09 for the estradiol-only group and 1.17 for the estrogen-progestin group ( $P<.05$  for both comparisons).

## FAST TRACK

*According to an observational study, 84,739 women with AD were more likely to have used systemic HT than an equal number of controls without a diagnosis of AD*

CONTINUED ON PAGE 18

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

Alzheimer disease is more prevalent in women, and women are more likely to be caregivers for individuals with AD than men, making AD an issue of particular concern to midlife and older women. Current guidance from The North American Menopause Society and other organizations does not recommend use of systemic HT to prevent AD.<sup>1</sup> As Savolainen-Peltonen and colleagues note in their observational study, the small risk increases for AD with use of HT are subject to bias. Editorialists agree with this concern and point out that a conclusive large randomized trial assessing HT's impact on AD is unlikely to be performed.<sup>2</sup> I agree with the editorialists that the findings of this Finnish study should not change current practice. For recently menopausal women who have bothersome vasomotor symptoms and no contraindications, I will continue to counsel that initiating systemic HT is appropriate.

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### FAST TRACK

*The study authors noted that the small risk increases for AD with use of HT are subject to bias—and editorialists agree with this concern*

Initiation of HT prior to age 60 was less common among AD cases than controls ( $P = .006$ ). As a continuous variable, age was not a determinant for disease risk in estradiol-only users (OR, 1.0), estrogen-progestin users (OR, 1.0), or any HT use (OR, 1.0).

The exclusive use of vaginal estrogen therapy was not associated with an elevated risk of AD (OR, 0.99).

### Study strengths and limitations

This study on the association between HT and AD included a very large number of par-

ticipants from a national population registry, and the use of HT was objectively determined from a controlled registry (not self-reported). In addition, AD was accurately diagnosed and differentiated from other forms of dementia.

Limitations of the study include the lack of baseline demographic data for AD risk factors for both HT users and controls. Further, an increased risk of AD may have been a cause for HT use and not a consequence, given that initial cognitive impairments may occur 7 to 8 years prior to AD diagnosis and the possibility exists that such women may have sought help for cognitive symptoms from HT. In addition, the lack of brain imaging or neurologic examination to exclude AD might also account for undiagnosed disease in controls. The authors noted that they were unable to compare the use of oral and transdermal HT preparations or the use of cyclic and continuous estrogen-progestin therapy. ●

### References

1. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24:728-753.
2. Maki PM, Girard LM, Manson JE. Menopausal hormone therapy and cognition. *BMJ*. 2019;364:1877.