EDITORIAL

# HRT may increase the risk of Alzheimer's disease

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**POSTMENOPAUSAL WOMEN WHO TAKE SYSTEMIC HORMONE REPLACEMENT THERAPY (HRT) ARE** more likely to develop Alzheimer's disease, although the increase in risk is modest, a Finnish nationwide case-control study has found.[1]

Overall, 84,739 women who received a clinically verified diagnosis of Alzheimer's disease between 1999 and 2013 were identified from a treatment cost reimbursement register. An equal number of control women without a diagnosis were identified from the national population register. Controls were matched by age and hospital district. HRT use was identified from a national drug register.

The vast majority (98.8%) of the Alzheimer's disease cases were aged ≥ 60 years at the time of diagnosis, and 47,239 (55.7%) were aged ≥ 80. Compared with non users, users of systemic HRT were 9-17% more likely to develop Alzheimer's disease. The risk of Alzheimer's disease in oestradiol-only users, odds ratio (OR) 1.09 (95% CI: 1.05-1.14) did not differ significantly from the risk in oestrogen-progestogen users OR 1.17 (95% CI: 1.13-1.21). Exclusive use of vaginal oestradiol did not increase the risk of Alzheimer's disease OR 0.99 (95% CI: 0.96-1.01).

**'The researchers estimate an extra 9-18 cases of Alzheimer's disease per 10,000 women aged 70-80 years per annum'**

When those women aged under 60 at the time of HRT initiation were compared with those aged 60 and over, there was no significant difference in the risk of Alzheimer's disease. However, HRT use for less than 10 years in those aged under 60 did not increase the risk, whereas the risk increased after 3-5 years' use in those aged 60 and over.

Unfortunately, it was not possible to adjust for known Alzheimer's disease risk factors due to a lack of baseline demographic data. However, the authors cite another study from the same population where these risk factors were evenly distributed between cases and controls.

Most previous observational studies have suggested that HRT may in fact reduce the risk of Alzheimer's disease, but these studies have been criticised on account of potential recall bias (cognitively impaired women are less likely to remember previous HRT use) and confounding by the healthy user effect.[2] An important strength of the current study was the objective assessment of HRT use from a reliable national register. However, the study was still potentially prone to healthy user bias, although this would have been expected to lessen the observed association between HRT and Alzheimer's disease.

This is an observational study and cannot demonstrate causation. Moreover, the mechanism whereby HRT might increase the risk of Alzheimer's disease is unclear. However, the findings are consistent with those from a large primary prevention trial, the Women's Health Initiative Memory Study (WHIMS), which found that HRT significantly increased the risk of all cause dementia HR 1.76, (95% CI: 1.19-2.60).[3] Participants in the WHIMS trial were aged 65-79 at entry and it has been suggested that HRT might be beneficial only in younger women. However, the findings of the present study do not support this idea of a critical window.

The authors conclude that 'hormone therapy users should be informed of a possible risk of the disease with prolonged use' but emphasise that the absolute risk is low - they estimate an extra 9-18 cases of Alzheimer's disease per 10,000 women aged 70-80 years per annum.

In conclusion, women aged under 60 can be reassured that short-term HRT does not appear to increase the risk of dementia. However, for women aged 60 and over and younger women wishing to continue treatment beyond 10 years, it is now necessary to include the possibility of a small increase in the risk of dementia in the HRT benefit-risk discussion.

**REFERENCES**
**1** 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
**2** Henderson VW. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol* 2014 Jul;142:99-106
**3** Shumaker SA, Legault C, Kuller L et al. Conjugated equine oestrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-58

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