

Timing and Menopause Type Matter but HRT Linked to Lower Dementia Risk

A large study published found that [hormone replacement therapy](#) (HRT) use was associated with a modest reduction in dementia risk. The association was more marked in certain subgroups.



Study

The study included 183,450 postmenopausal women from the UK Biobank with a mean follow-up of 13.3 years. The authors used multivariable [Cox regression](#) models to identify associations between HRT use for at least 1 year or current use and all-cause dementia and dementia subtypes. This type of analysis accounts for measured potential confounding factors.

They also conducted subgroup analyses to assess whether the associations were modified by the type of menopause (natural versus surgical), estrogen exposure, [apolipoprotein E](#) (APOE) ϵ 4 genotype, and the age at which HRT was initiated.

The study covered over 2.43 million person-years of follow-up, during which 3,948 cases of dementia were diagnosed. These included 1,993 and 1,955 diagnoses of Alzheimer's dementia (AD) and non-AD or unspecified forms of [dementia](#), respectively.

The findings suggested that HRT use was associated with a 10% reduction in the risk of all-cause dementia. The association was stronger in surgical menopause, with a 26% lower risk, and in women with less than 37 years between menarche and natural or [surgical menopause](#), which the researchers used as a measure of natural estrogen exposure, with a 16% lower risk. Similarly, the association showed a 13% lower risk among APOE ϵ 4 carriers, although the overall interaction between HRT and APOE ϵ 4 status was not statistically significant.

Findings

Women with natural menopause did not show any statistically significant association between HRT and [dementia risk](#). However, among women classified as having surgical menopause, HRT use was associated with a 28% lower dementia risk in APOE ϵ 4-positive women and a 20% lower risk in APOE ϵ 4-negative women.

This must be considered along with the known differences in HRT for natural versus surgical menopause. With natural menopause, combined [estrogen-progestogen](#) HRT is typically prescribed to prevent endometrial hyperplasia. Conversely, estrogen-only HRT is commonly prescribed after hysterectomy, including in many women with surgical menopause.

Prior research has consistently shown the association of estrogen-only formulations with a lower dementia risk compared with combined HRT, but the current study did not include [information](#) on the HRT type or protocol used.

The risk of dementia was reduced when HRT was initiated between the ages of 46 and 56 years, but not after 56 years. The overall association was stronger (23% reduction in [risk](#)) for initiation at 51-56 years than for initiation at 46-50 years (13%).

However, for women with natural menopause, the risk was reduced by 18% only when HRT was started at 51-56 years. With surgical menopause, HRT was associated with a progressively larger decrease in dementia risk with later [initiation](#). When started before 46 years, the risk was reduced by 15%, compared with 31% and 43% at 46-50 years and 51-56 years, respectively.

The authors suggest that this supports the “[window of opportunity](#)” hypothesis, even as they note that reverse causation or confounding by indication cannot be excluded at older ages.

HRT use was also associated with a reduced risk of AD, with the association being stronger among those with surgical menopause compared to natural menopause (32% versus 11% reduction in risk, respectively). There was little difference in the estimated associations across APOE ϵ 4 [genotypes](#), while shorter natural estrogen exposure of less than 37 years was associated with a 19% lower risk.

There was no statistically significant association between HRT use and non-AD dementia overall. However, women with surgical menopause had a 21% reduction in non-AD risk associated with HRT, and a borderline association was observed among women with a shorter endogenous [estrogen exposure](#).

Further analyses that excluded women diagnosed with dementia within 2, 4, 6, or 8 years after baseline, examined [surgery type](#), and tested other possible modifiers supported the robustness of the original results.

Conclusion

The authors present this study as the most comprehensive prospective analysis to date of the association between HRT and dementia risk, and its [potential modifiers](#). The findings show that HRT use is associated with a 10% reduction in dementia risk.

The relationship varied by type of menopause and duration of exposure to endogenous estrogen, and appeared stronger among [APOE \$\epsilon\$ 4 carriers](#), although the formal HRT-by-APOE ϵ 4 interaction was not significant. While lower dementia risk was observed overall with HRT when initiated at 46-56 years, this was seen only in the latter half of this window among women with natural menopause. For surgical menopause, an increasingly strong association with lower dementia risk was seen with HRT initiation before 46 years, at 46-50 years, and at 51-56 years.

The researchers suggest that different subgroups of women may respond differently to HRT, justifying future randomized controlled trials to provide evidence that could help frame more tailored [HRT prescribing guidelines](#) in order to reduce dementia risk.

Source:

<https://www.news-medical.net/news/20260827/HRT-linked-to-lower-dementia-risk-but-timing-and-menopause-type-matter.aspx>