

Age at Menopause and Risk of Dementia: A Real-World Evidence Study

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INTRODUCTION

Age at menopause marks a critical neuroendocrine transition that may influence later-life cognitive health. Earlier estrogen deprivation has been linked to increased neuronal vulnerability, yet large-scale population-based data remain scarce.

Objective: to investigate the association between age at menopause and dementia risk using real-world data from the TriNetX Global Research Network.

METHODS

Retrospective cohort study of women aged ≥ 18 years with a menopause diagnosis (ICD-10 N95), grouped as early (<45 years) or typical/late (≥ 45 years) menopause. Women with prior dementia, multiple sclerosis, Parkinson's disease, epilepsy, or severe brain injury were excluded. The outcome was incident dementia. Crude and age-matched propensity-score analyses estimated hazard ratios (Cox regression, Kaplan–Meier).

RESULTS

The crude cohort comprised 2,681,006 women. After 1:1 age matching, 130,740 women were analysed per group. Two complementary analyses tested whether the association between age at menopause and dementia was confounded by current age.

In the crude (unmatched) analysis of 2,681,006 women, dementia incidence was 3.9% among those with menopause at ≥ 45 years versus 0.3% among those with menopause before 45 years (HR 11.2; 95% CI 10.4–12.0).

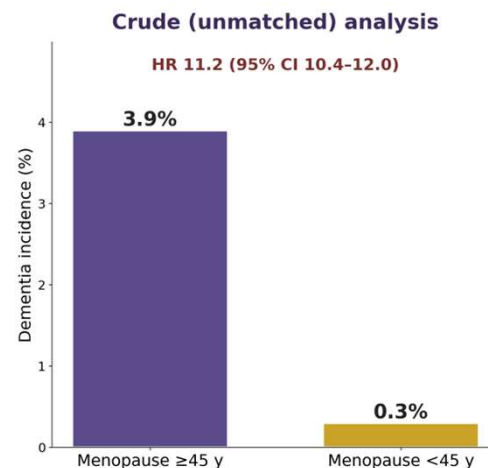


Figure 1. Crude (unmatched) analysis. Dementia incidence by age at menopause ($n = 2,681,006$). HR 11.2 (95% CI 10.4–12.0); estimate confounded by current age.

This apparent protective effect of early menopause was an artefact of age: younger women have both earlier menopause and far less accrued dementia, fully confounding the crude estimate. Age-matched analysis: after matching on current age (130,740 per group), the association reversed.

Early menopause (<45 years) was associated with a higher dementia risk than menopause at ≥ 45 years (0.6% vs. 0.4%; HR 2.95; 95% CI 2.6–3.3).

After controlling for age, early menopause independently predicted dementia — nearly a threefold higher risk than menopause after age 45.

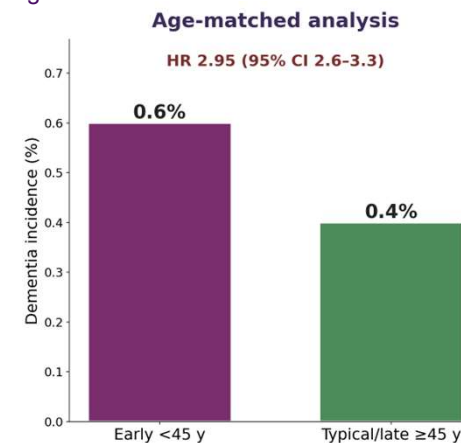


Figure 2. Age-matched analysis. Dementia incidence by age at menopause (130,740 per group). Early menopause (<45 y) independently associated with higher risk: HR 2.95 (95% CI 2.6–3.3).

These findings highlight the need for gender-focused dementia prevention strategies and reinforce the relevance of reproductive history in cognitive aging. After controlling for current age, early menopause independently predicted dementia, with nearly a threefold higher risk than menopause after age 45. Earlier estrogen deprivation may heighten neuronal vulnerability, supporting reproductive history as a relevant factor in cognitive aging. The reversal of the crude estimate after age matching underscores the importance of accounting for current age in observational research, and the value of large real-world databases such as TriNetX for studying sex-specific dementia risk.

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CONCLUSIONS

Early menopause (<45 years) is associated with nearly a threefold higher risk of dementia than menopause after age 45, after controlling for age.

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