Estrogen therapy's effect on Alzheimer's needs more study, say researchers

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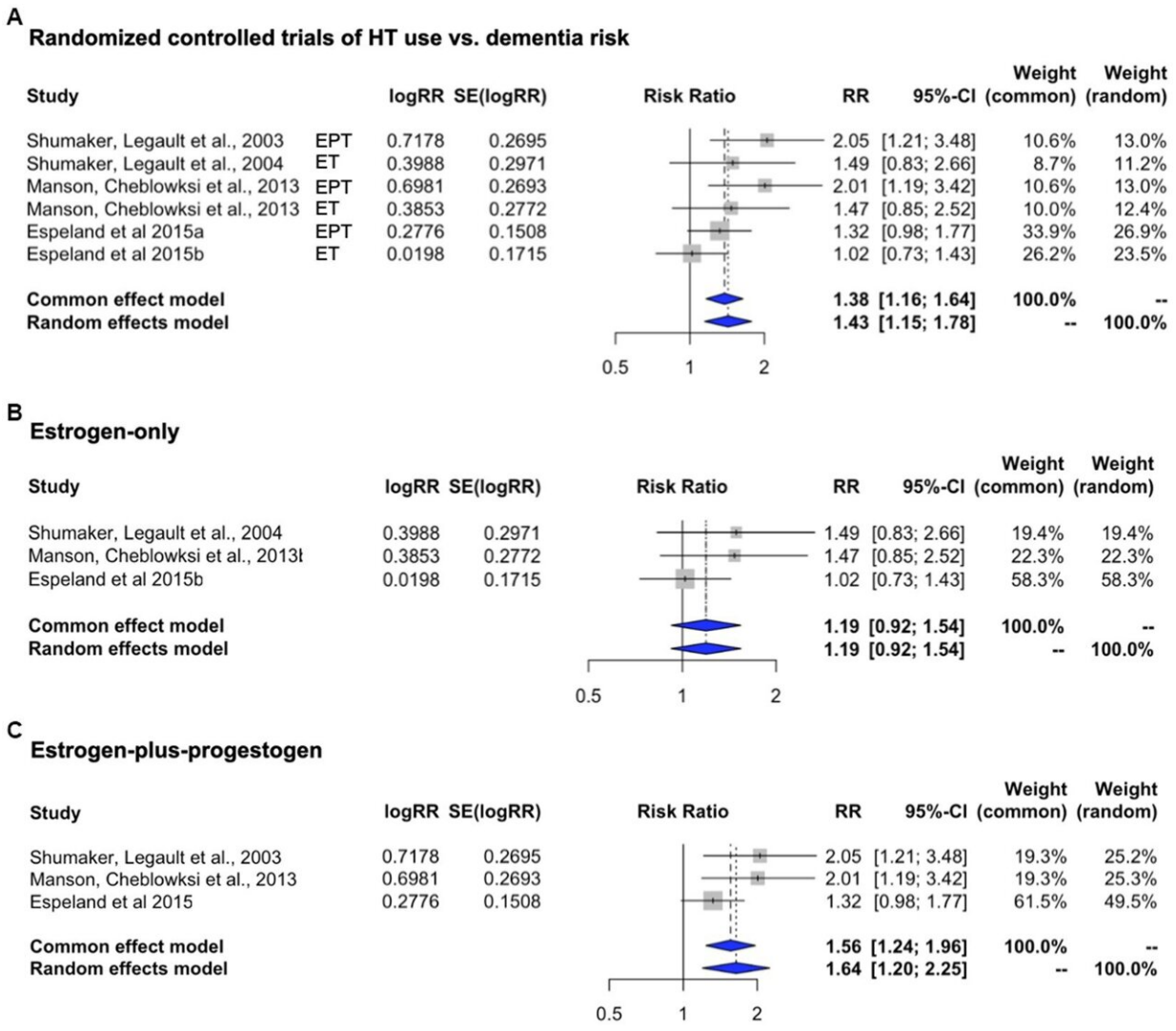

Meta-analysis of randomized, placebo-controlled trials of HT effects on dementia risk. Meta-analysis of randomized placebo-controlled trials investigating the risk of developing dementia with the use of systemic HT. Forest

plots display individual and pooled estimates of the association between HT use (A) and dementia risk expressed as relative risk (RR) and 95% confidence intervals (C.I.). HT includes (B) estrogen-only (ET, oral conjugated equine estrogens, CEE) and (C) estrogen-plus-progestogen therapy (EPT, oral CEE and medroxyprogesterone acetate, MPA). Studies are ordered by year of publication. Credit: *Frontiers in Aging Neuroscience* (2023). DOI: 10.3389/fnagi.2023.1260427

Estrogen-based menopause hormone therapy for women in midlife should be investigated more thoroughly as a potential strategy for preventing Alzheimer's disease, the most common form of dementia, according to a new analysis from researchers at Weill Cornell Medicine.

The researchers, whose findings appear Oct. 23 in *Frontiers in Aging Neuroscience*, performed a meta-analysis of six clinical trials and 45 observational studies, encompassing more than 6 million women, in which women were given estrogen-based therapy. The findings suggest that women who took hormones in midlife to treat their menopause symptoms were less likely to develop dementia than those who hadn't taken estrogen.

Women taking estrogen at ages 65 and older, however, did not have a lower chance of an eventual dementia diagnosis compared with peers who did not receive hormone therapy.

"These findings highlight the fact that we need more conclusive research on the possible Alzheimer's-preventing effect of menopause hormone therapy for women in midlife," said study senior author Lisa Mosconi, director of the Alzheimer's Prevention Program and of the Women's Brain Initiative and an associate professor in the department of neurology at Weill Cornell Medicine.

The study's first author is Dr. Matilde Nerattini, a visiting fellow in neurology at Weill Cornell Medicine.

The estimated lifetime risk for Alzheimer's disease for a 45- to 50-year-old woman is approximately 20%, compared with 10% for a man of the same age. The risks for both sexes are one percentage point higher for both at age 65.

Research suggests that estrogen has a protective effect on the brain, and the loss of this protection as estrogen production wanes during menopause may partly explain why females with Alzheimer's disease outnumber their male counterparts.

But does replacing estrogen reduce women's Alzheimer's risk? Studies in animal models suggest that it does, but the question has been difficult to answer conclusively in clinical research, because of the large time gap between menopause, usually in the early 50s, and the onset of Alzheimer's two to three decades later.

"It isn't really feasible to run a clinical trial of estrogen therapy for that length of time to look for a dementia-preventing effect," Mosconi said. "We need more clinical trials evaluating the effects of midlife hormone therapy on biological indicators of Alzheimer's disease, which we can now measure using brain imaging and fluids such as blood."

The clinical trials used to address this question have enrolled older women, and generally have found no protective effect of estrogen against dementia. But Mosconi notes that estrogen replacement may need to start much earlier, in midlife at the time of menopause, to be able to prevent or delay the Alzheimer's process.

In the new study, she and her team pooled the data from the 51 prior studies to compare estrogen therapy in midlife versus late life. While

midlife estrogen—administered alone—was associated with a 32% lower rate of dementia, there was no significant lowering of the dementia rate with late-life estrogen.

Estrogen-only therapy is typically used for women after a hysterectomy. However, in women with an intact uterus, estrogen is often combined with progesterone or progesterone-like hormones, to reduce uterine cancer risk. The analysis suggested that the inclusion of such "progestogens" blunts the preventive effect of midlife estrogen, lowering the apparent risk reduction from 32% to 23%, though, again, the data was varied, suggesting that further research is needed, Mosconi said.

In the hope of generating more conclusive data, Mosconi and her team have begun a clinical trial of estrogen therapy in midlife women, to see if this has an effect on some of the earliest biomarkers of Alzheimer's.

More information: Matilde Nerattini et al, Systematic review and meta-analysis of the effects of menopause hormone therapy on risk of Alzheimer's disease and dementia, *Frontiers in Aging Neuroscience* (2023). DOI: 10.3389/fnagi.2023.1260427

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