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doi: 10.12788/fjp.0594

## Q/ Does hormone replacement therapy prevent cognitive decline in postmenopausal women?

### EVIDENCE-BASED ANSWER

**A/ NO.** Hormone replacement therapy (HRT) does not prevent cognitive decline in postmenopausal women—and in fact, it may slightly increase risk (strength of recommendation, **A**; systematic review, meta-analysis of randomized controlled trials [RCTs], and individual RCT).

### Evidence summary

#### Multiple analyses suggest HRT worsens rather than improves cognition

A 2017 Cochrane review of 22 randomized, double-blind studies compared use of HRT (estrogen only or combination estrogen + progesterone therapies) with placebo in postmenopausal women (N = 43,637). Age ranges varied, but the average age in most studies was > 60 years. Treatment duration was at least 1 year. Various outcomes were assessed across these 22 studies, including cardiovascular disease, bone health, and cognition.<sup>1</sup>

Cognitive outcomes were assessed with the Mini-Mental Status Exam in 5 of the trials (N = 12,789). Data were not combined due to heterogeneity. The authors found no significant difference in cognitive scores between the treatment and control groups in any of these 5 studies.<sup>1</sup>

In the largest included study, the Women's Health Initiative (WHI) Memory Study (N = 10,739), participants were older than 65 years. Among those receiving estrogen-only HRT, there were no statistically significant differences compared to those receiving placebo. However, healthy postmenopausal women taking combination HRT had an increased risk for "probable dementia" compared to those taking placebo (relative risk [RR] = 1.97; 95% CI, 1.16-3.33). When researchers looked exclusively at women taking

HRT, the risk for dementia increased from 9 in 1000 to 18 in 1000 (95% CI, 11-30) after 4 years of HRT use. This results in a number needed to harm of 4 to 50 patients.<sup>1</sup>

Two notable limitations of this evidence are that the average age of this population was > 60 years and 80% of the participants were White.<sup>1</sup>

A 2021 meta-analysis of 23 RCTs (N = 13,683) studied the effect of HRT on global cognitive function as well as specific cognitive domains including memory, executive function, attention, and language. Mean patient age in the studies varied from 48 to 81 years. Nine of these studies were also included in the previously discussed Cochrane review.<sup>2</sup>

There was a statistically significant but small decrease in overall global cognition (10 trials; N = 12,115; standardized mean difference [SMD] = -0.04; 95% CI, -0.08 to -0.01) in those receiving HRT compared to placebo. This effect was slightly more pronounced among those who initiated HRT at age > 60 years (8 trials; N = 11,914; SMD = -0.05; 95% CI, -0.08 to -0.01) and among patients with HRT duration > 6 months (7 trials; N = 11,828; SMD = -0.05; 95% CI, -0.08 to -0.01). There were no significant differences in specific cognitive domains.<sup>2</sup>

In a 2017 follow-up to the WHI trial, researchers analyzed data on long-term cogni-

tive effects in women previously treated with HRT. There were 2 cohorts: participants who initiated HRT at a younger age (50-54; N = 1376) and those who initiated HRT later in life (age 65-79; N = 2880). Cognitive outcomes were assessed using the Telephone Interview for Cognitive Status-modified, with interviews conducted annually beginning 6 to 7 years after HRT was stopped.<sup>3</sup>

The investigators found no significant change in composite cognitive function in the younger HRT-treated group compared to placebo (estrogen alone: mean deviation [MD] = 0.014; 95% CI, -0.097 to 0.126; estrogen + progesterone: MD = -0.047; 95% CI, -0.134 to 0.04), or in the group who initiated HRT at an older age (estrogen alone: MD = -0.099;

95% CI, -0.202 to 0.004; estrogen + progesterone: MD = -0.022; 95% CI, -0.099 to 0.055). The authors state that although the data did not reach significance, this study also found a trend toward decreases in global cognitive function in the older age group.<sup>3</sup>

### Editor's takeaway

Abundant, consistent evidence with long-term follow-up shows postmenopausal HRT does not reduce cognitive decline. In fact, it appears to increase cognitive decline slightly. Renewed interest in postmenopausal HRT to alleviate menopausal symptoms should balance the risks and benefits to the individual patient.

JFP

### References

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