Womens Health Initiative Memory Study Suite of Studies – Extension Study

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Principal Investigators

RESNICK, SUSAN

Institution

National Institute on Aging

Contact information of lead PI
Country

USA

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Research Abstract

The Womens Health Initiative (WHI) randomized, placebo-controlled clinical trials of hormone therapy (HT) were designed to test the hypothesis that conjugated equine estrogens alone (CEE-Alone) or in combination with medroxyprogesterone acetate (CEE+MPA) protected

postmenopausal women against the development of heart disease. The WHI Memory Study (WHIMS) was an ancillary study to the WHI trials, which consisted of parallel placebo-controlled randomized clinical trials of 0.625 mg/day CEE therapy with and without 2.5 mg/day MPA in women with a uterus or post-hysterectomy, respectively. WHIMS investigated the effect of CEE-Alone and CEE+MPA on risk for probable dementia and mild cognitive impairment in women age 65 and older, as well as the effects of these treatments on global cognitive function. The WHI Study of Cognitive Aging (WHISCA), an ancillary study to WHIMS, was developed to investigate the effects of HT on domain-specific cognitive function in women without dementia. WHISCA enrolled 2305 women at 14 of the WHIMS sites, distributed across the two parallel trials. WHISCA was initiated on average 3 years after WHI randomization and the primary outcome was the effect of HT on rates of cognitive change, adjusted for time since randomization. The WHIMS CEE+MPA trial terminated earlier than planned (July, 2002) due to an adverse risk-to-benefit profile in the main WHI trial. Subsequently, the WHI CEE-Alone Trial also was terminated early (February, 2004). Results from the WHIMS trials showed that CEE-Alone or CEE+MPA increase the risk of dementia and have adverse effects on global cognition in women aged 65 years or older. HT also has been shown to increase the risk of clinical stroke in women 65 years and older. The initial report of WHISCA findings showed that CEE + MPA had a negative impact on verbal memory ($p < 0.01$) and a trend to a positive impact on figural memory ($p = 0.012$) over time compared with placebo with no effect on other cognitive domains. In addition, these effects were evident only after long-term therapy. CEE + MPA did not significantly influence positive affect, negative affect, or depressive symptoms. These findings suggest that HT may have different effects across different cognitive domains. The findings from the CEE-Alone Trial in women with prior hysterectomy who were randomized to CEE or placebo show that CEE alone did not affect domain-specific cognitive function over time. Participants in the WHISCA and WHIMS studies continue to be followed through telephone cognitive assessments as they pass through the risk period for cognitive decline. The WHIMS Suite of Studies also includes cognitive follow-up of women in the WHIMS-Younger (WHIMS-Y) study, who were randomized to hormone therapy through the WHI when aged 50-54 years. The WHIMS-Y study tested the hypothesis that hormone therapy around the time of the menopause may benefit cognitive function later in life. Initial results from the WHIMS-Y study were based on 1326 postmenopausal women studied with a validated telephone cognitive assessment battery an average of 7.2 years after the trials ended, when women had a mean age of 67.2 years. The initial report included the first two administrations of the cognitive battery and showed neither harm nor benefit of earlyHT on later cognitive function. The WHIMS Suite of Studies is conducted by Wake Forest University, which is also the site for the Southeast Regional Center for WHI and leads the Aging, Cognition and Functional Status interest group for the WHI. Over the last year, we have continued to perform cognitive follow-up evaluations through telephone assessments in the original WHIMS cohort (WHIMS extension study) and have closed out the WHIMS-Y study as sufficient data are available in the latter cohort to test the study hypotheses. Over the last year, we have continued to investigate factors that may modulate cognitive and brain outcomes in older women. Following on a previous paper that showed that presence of diabetes influence the effect of postmenopausal hormone therapy on brain volumes and ischemic lesion volumes, we examined interactions between prior hormone assignment and diabetes on cognitive outcomes. In older women, higher levels of estrogen may exacerbate the increased risk for cognitive impairment conveyed by diabetes. We examined whether the effect of postmenopausal HT on cognitive impairment incidence differed depending on type 2 diabetes. WHIMS participants ($N = 7,233$), aged 65-80 years, were classified according to type

2 diabetes status and followed for probable dementia and cognitive impairment (mild cognitive impairment or dementia). Through a maximum of 18 years of follow-up, women with diabetes had increased risk of dementia (hazard ratio HR 1.54 95% CI 1.16-2.06) and cognitive impairment (HR 1.83 1.50-2.23). The combination of diabetes and random assignment to HT increased their risk of dementia (HR 2.12 1.47-3.06) and cognitive impairment (HR 2.20 1.70-2.87) compared with women without these conditions, interaction P = 0.09 and P = 0.08. These interactions appeared to be limited to women assigned to unopposed conjugated equine estrogens. Our findings are consistent with a prior report that higher endogenous estrogen may exacerbate risks that type 2 diabetes poses for cognitive function in older women. We also investigated whether obesity influenced regional brain volumes and white matter lesion loads in WHIMS participants. While midlife obesity has been linked to age-related brain atrophy and risk of dementia, relationships are less clear for older individuals. We examined the associations that obesity (body mass index, BMI) and change in BMI over an average of 6.6 (1.0-9.1) years had with global and regional brain and white matter lesion volumes in a sample of 1,366 women aged 65-80. Both global obesity and increase in BMI were associated with lower cerebrospinal fluid and higher region-specific brain volumes, after controlling for diabetes and other cerebrovascular disease risk factors. Obesity, but not change in BMI, predicted lower lesion loads in some brain areas. Thus, contrary to predictions based on studies of midlife obesity, we found that higher BMI in late life was associated with less brain atrophy and lower ischemic lesion loads, perhaps reflecting weight loss during prodromal phases of neurodegenerative disease in older women. In a recent paper published as part of a series characterizing WHI participants who were 80 years or older, we investigated factors that predicted optimal or resilient cognitive aging in WHIMS participants. Two thousand two hundred twenty-eight women with a mean age of 85 years who participated in the WHIMS were classified as cognitively normal (85.5%), mild cognitive impairment (3.9%), dementia (5.4%) or other cognitive impairment (5.1%) by central adjudication. Global cognitive functioning was assessed using the TICS-M (telephone interview for cognitive status-modified). Backward stepwise logistic regression was used to select factors that were independently associated with cognitive status. Factors associated with preserved cognitive functioning were younger age, higher education and family incomes, being non-Hispanic white, better emotional wellbeing, fewer depressive symptoms, more insomnia complaints, being free of diabetes, and not carrying the APOE 4 Alzheimers disease risk allele. Cognitively normal women who demonstrated sustained high levels of cognition were younger, more educated, and endorsed better self-reported general health, emotional wellbeing, and higher physical functioning. These findings provide a broad overview of factors associated with maintenance of cognitive health at older ages and are motivating the next phase of the WHIMS follow-up.

Further information available at:

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