Women's Health Initiative Comments on FDA Panel on Menopause and Hormone Replacement Therapy for Women (Docket: FDA: 2025-N-2589)

For over 30 years, the Women's Health Initiative (WHI) has conducted groundbreaking research on the health of postmenopausal women. Prior to WHI, women were often excluded from health and medical research, and many pharmaceuticals were prescribed for women without rigorous testing for safety or efficacy. We are pleased to see renewed interest in the health of postmenopausal women, and we urge that any new medical recommendations for this age group be based on rigorous science.

During the FDA Expert Panel on Menopausal and Hormone Replacement Therapy for Women on July 17, 2025, the results of the WHI randomized controlled clinical trials of menopausal hormone therapy (MHT) were repeatedly cited in the panelists' presentations. In some instances, the WHI findings and their interpretation were presented accurately, but in other instances panelists' statements and the presentations were inaccurate, misleading, or out of context. Additionally, some panelists emphasized favorable findings while omitting context, creating a partial view of the evidence, particularly for combined estrogen plus progestin (CEE+MPA). To inform evidence-based health care decisions for the nation's women, and in the interests of public safety, the FDA needs to make recommendations for health care based on the best available data, for which the gold standard is the peer reviewed summaries of the randomized controlled clinical trials. The FDA should not make decisions based on anecdote or misinformation presented by persons with known bias or conflicts of interest. As representatives of WHI, we herewith provide a summary of the WHI peer reviewed trial design and results, together with a historical context and commentary where indicated.

Why were the WHI trials necessary?

Premarin (conjugated equine estrogens) started being used in the 1940's for the relief of menopausal symptoms. To counter a multifold increased risk of endometrial cancer in women who had not had a hysterectomy, a progestogen (medroxyprogesterone acetate) was added in the late 1970's. By the 1980's and 1990's MHT was increasingly being used for very different reasons: prevention of osteoporosis and cardiovascular disease. Though the potential risk for breast cancer was recognized, the benefit for prevention of coronary heart disease (heart attacks) was thought to outweigh the risks of MHT. Whereas earlier use of these hormones for treatment of menopausal symptoms was primarily in younger women (who were the most likely group to have vasomotor symptoms), the later use for prevention of osteoporosis and cardiovascular disease shifted the age spectrum towards older women (who were most likely to have these conditions). According to National Health and Nutrition Examination Survey (NHANES) data in 2001-2002 overall prevalence of hormone use was 29.5%, with 26.2% prevalence in women aged <52, 38.5% at age 52-<65, and 23.2% at age ≥65 years.[1] Use of hormones for prevention of heart attacks at all ages and including women with existing heart disease was encouraged by medical society guidelines.

The enthusiasm for hormones for heart attack prevention was driven by promising findings from non-randomized observational studies in women free of heart disease as well as in women with existing heart disease. These studies predominantly involved use

of conjugated estrogens alone but also studied use of CEE+MPA compared to non-users. Observational studies could be biased towards benefit for many reasons, including that women using MHT were generally younger, healthier and more likely to engage in favorable health behaviors than nonusers, leading to confounding by indication and lifestyle. However, that is not the entire explanation, since MHT also appeared to protect against second heart attacks in women with existing disease. Hence, there was a need for large randomized controlled trials to settle the issue of prevention of chronic disease in both primary prevention in healthy women, and secondary prevention in women with existing heart disease. The Heart and Estrogen/Progestin Replacement Study (HERS) of CEE+MPA tested whether promising observational studies in women with existing heart disease would hold up in a rigorous clinical trial,[2] and similarly the WHI trials tested whether observational studies suggesting benefit in generally healthy women would hold up. WHI tested conjugated equine estrogens (CEE-alone, in women with a hysterectomy) and CEE+MPA (in women with an intact uterus) (the trials are also known as E-alone and E+P trials).[3,4] Both placebo-controlled trials studied the drugs and doses that promised benefit based on observational data, and which were the drugs most prescribed at the time. The enrollment age range in the WHI trials was 50-79 years so that informative data could be generated for both younger and older women and to ensure statistical power for the primary outcome of coronary heart disease (heart attacks). The WHI trials were not designed to test the effects of hormones on vasomotor symptoms, a well-established benefit, but contrary to a common misconception, women with vasomotor symptoms were enrolled if they passed a 1-month placebo run-in period; women currently on hormones could be enrolled if in addition they passed a 3-month washout period. WHI randomized 8833 women aged 50-59 years in the MHT trials, and one quarter of them reported moderate-severe vasomotor symptoms at baseline, with smaller percentages at older ages.[5] The WHI was and still is the largest study of MHT in this age-group and hence, much of the high-quality data cited by the panel about health outcomes on MHT in younger women is derived from the WHI trials.

What did the trials show? HERS results were announced in 1998 followed by the results of the WHI trial of CEE+MPA stopped early in 2002 (after mean follow-up time of 5.2 years) following a recommendation from the trials' Data Safety and Monitoring Board (DSMB). Both trials showed no benefit for prevention of heart attacks and an increased risk of blood clots, with significantly higher risks for both heart attacks and blood clots in the first 2 years.[2,3] The WHI CEE+MPA trial also showed an increased risk of stroke and breast cancer, and a benefit for fractures and colorectal cancer. In 2004, the WHI trial of CEE-alone was also stopped early following a decision by the National Institutes of Health (NIH) and results published (after mean follow-up time of 6.8 years); these showed an increased risk of stroke, reduced risk of fractures, and non-significant trends towards reduced risk of heart attacks and breast cancer.[4] Thus, the trials achieved their primary aim of clarifying that menopausal hormone therapy did not significantly reduce risk of heart attack. Importantly, the risk-benefit profile of E-alone was better than that of E+P. Note that the primary results were based on incomplete follow-up at the time of early stopping, and that complete treatment period follow up of 5.6 years in the CEE+MPA trial showed some subtle but important changes, in that the increased risk for heart attacks was no longer statistically significant, but the increased

risk for breast cancer became significant. CEE-alone trial results after full follow up of 7.2 years did not differ from those of the primary papers.[6]

What was the impact of the trials? WHI investigators have recently published a comprehensive review of trial results and their clinical implications.[7] Following publication of the WHI CEE+MPA trial results, practice guidelines no longer recommended MHT for prevention of heart disease, and the FDA applied a black box warning to all MHT products. There was a marked reduction in the use of MHT for disease prevention in older women. But even though use of hormones for menopause symptom management was not part of the aims of WHI, the findings led to a marked reduction in use of both combined E+P and E-alone for relief of vasomotor symptoms in younger women and a reduction in training for menopause management at medical schools. According the NHANES data, in 2017-2020 prevalence of hormone use was down to 4.7% overall, with 9.4% prevalence in women aged <52, 4.5% in women aged 52-<65, and 4.3% in women aged ≥65 years.[1]

From the outset WHI investigators have recognized that use of MHT for treatment of vasomotor symptoms in younger women is a reasonable option despite the findings for major health outcomes. As early as during the 2002 announcement of the WHI trial results, the NIH included in the press release a statement from Dr. Jacques Rossouw, Acting Director of the WHI that "Women with a uterus who are currently taking estrogen plus progestin should have a serious talk with their doctor to see if they should continue it. If they are taking this hormone combination for short-term relief of symptoms, it may be reasonable to continue since the benefits are likely to outweigh the risks. Longer term use or use for disease prevention must be re-evaluated given the multiple adverse effects noted in WHI."
https://www.sciencedaily.com/releases/2002/07/020710081413.htm. Dr. Rossouw also stressed the small absolute risks in individual women, though noting that on a population basis the effects could be large. Since the WHI trials were stopped in 2002 and 2004, WHI investigators have published a series of papers to clarify risks and benefits by age group and by years since menopause. These analyses collected and adjudicated health events linked to the intervention for the full treatment period of 5.6 years in the CEE+MPA trial and 7.2 years in the CEE-alone trials, providing more outcomes and follow-up during the treatment period than the initial trials' reports. In addition, cumulative long-term (intervention plus post-intervention) follow-up results describing over 2 decades of information—particularly relevant for cancer outcomes—have been published. The papers confirm that although the relative risks of CEE+MPA for coronary heart disease (heart attacks) did not differ significantly by age, the absolute risks are small in women under age 60, while absolute risks are high in women over age 70, and especially so in older women with persistent vasomotor symptoms.[5-8] In addition, the influence of MHT on cardiovascular outcomes quickly diminished and was not evident during postintervention phase, while the influence on breast cancer persisted (breast cancer remained significantly increased in the CEE+MPA trial, and the previously non-significant reduction in the CEE-alone trial became significant).

What is the current status of hormone therapy? Over the years since release of the WHI findings *The Menopause Society* and others have continued to emphasize that hormone therapy is the mainstay of treatment for vasomotor symptoms, and that absolute risks of such therapy are low in younger women; however, NHANES data

indicate that as of 2020 the uptake of hormone therapy in younger women has not increased during the last 2 decades.[1] Oral estrogens are now prescribed less frequently than transdermal and intravaginal routes, and among oral products CEE and CEE+MPA are less frequently prescribed than estradiol and progesterone. Unlike the MHT pharmaceuticals tested in WHI, use of other MHT pharmaceuticals is not supported by the same high-quality data on health effects.

Issues raised by panel members:

Timing hypothesis for coronary heart disease and total mortality: Several speakers assumed that the timing hypothesis was valid, i.e., that hormones started at an early age would have lower risks and that the lower risk would carry over into subsequent decades. The first part is supported by WHI data from the 8,833 women aged 50-59 years enrolled in the trials, at least insofar that they have lower absolute risks than older women.[5-8] The second part, however, remains untested and cannot be proven from WHI clinical trial data or observational studies; it reflects hope rather than solid scientific evidence. The WHI trial data describe initiation of relatively short-term (5-7 years) MHT use; it is not feasible to obtain longer term trial data capturing initiation at younger ages and continued into older ages. Traditional observational studies of hormone users can do this, but such studies are not well suited to address long term effects because they are prone to several biases and confounders that skew results in a favorable direction; some of these biases can be overcome with newer methods of analysis, which then provide estimates similar to those of the trials.[9,10]

More specifically, in these newer analyses the trial and observational data align in showing an increased risk of heart attacks in the first 2 years, and then an attenuation or a reversal to benefit in later years. So, in addition to any differences by age or time since menopause at the time of initiation, the apparently more favorable overall results in the observational studies are due in large part to their longer duration, when the initially increased heart attack risks in susceptible women are countered by reduced risk in surviving women. Long term observational studies have other issues, since women who continue hormones for decades are very different from non-users in terms of general medical status and health behaviors. A very long term very large randomized controlled trial in younger women with perfect adherence would be needed to answer this question, but such a trial is not feasible. Thus, the question of whether initiation at a younger age and continued into older ages will result in benefit or harm as women and their arteries age remains open. What we do know is that risks increase when hormones are initiated at older ages, especially so in those with persistent vasomotor symptoms.[5,6]

The panel was shown data from the trials in the age group 50-59 years which show low absolute risks or benefits for a number of trial outcomes. The data shown are correct, but somewhat misleading. For most health outcomes there was no statistical evidence that the MHT relative risks differed by age groups. In addition, the materials presented large absolute reductions for all fractures and diabetes, but not the large absolute increases in gallbladder disease and urinary incontinence.[6, 11,12] We encourage the FDA to review Manson et al. (2013; 2017; 2024) for the influence of MHT across a comprehensive range of outcomes, for the full cohort, as well as stratified by age group, and to consider the formal statistical tests for age-related trends.[6-8]

The WHI trial data support short-term use of hormones at younger ages because of their low absolute risks, and that is sufficient reason to allow for short-term use for their traditional indication--relief of vasomotor symptoms. On the other hand, WHI does not provide information on long term use for heart disease or mortality prevention. Instead, WHI data reflect the effects of MHT taken during the 5-7 years of the intervention, with prolonged non-intervention follow-up, rather than prolonged use. Since initiation of hormones at older ages is associated with increased risks, they should not be used to prevent heart disease or mortality.

The panel was informed about a Finnish observational study showing that discontinuation of hormone therapy was associated with higher risks of cardiac and stroke deaths compared to population controls or to women who continued therapy.[13] It is unclear why this observational study was referenced when we have data from a randomized placebo-controlled trial where hormones and placebo were simultaneously stopped programmatically at the end of the treatment, as opposed to unknown reasons why women elected to start and stop in the Finnish study. In the WHI trials, the increased risk of cardiovascular events was seen during the intervention and rapidly diminished during the postintervention. In addition, the relative risks for cardiac and stroke mortality were neutral during 18 years of follow-up (including ~11 years of post-trial follow-up).[8] In the CEE+MPA trial the risk of heart attacks decreased after stopping, and in both the CEE-alone and CEE+MPA trials risks of strokes and blood clots decreased after stopping.[6,7] Thus, the trial findings are not only diametrically opposed to those of this particular observational study but also indirectly support the causal role of hormones during the trial. It would be ironic if observational data were now used to counter the very trial evidence designed to address the limitations of earlier observational studies. We encourage the FDA to review Manson et al. (2013; 2017) for the cumulative influence of MHT across a comprehensive range of outcomes, and Heiss et al. (2008) and LaCroix et al. (2011) for detailed analyses of shorter-term postintervention follow-up.[6,7,14,15]

The panel was told that 50,000 women died over 10 years because they were denied estrogen at age 50-59 after publication of the WHI findings.[16] Their estimate was based on the difference in absolute mortality rates for women aged 50-59 years[15] and declines in hormone use after the publication, but selectively ignores that the estimated reduction in mortality during the trial was not statistically significant, as well as results of women aged 60-79 y that were also randomized in the WHI trial.[15] We encourage the FDA to review the original results reported by LaCroix et al,[15] methods used by Sarrel et al,[16] and WHI's published reply.[17] Nonetheless, we agree that younger women have lower relative risks of mortality than older women,[7,8] and that the low absolute risks in younger women, particularly in the E-alone trial, do allow for the safe use of hormones to treat vasomotor symptoms.

Timing hypothesis for cognitive function and dementia: The panel was shown observational data to support that hormone therapy and longer duration of hormone therapy is associated with lower risk of neurodegenerative diseases including Alzheimer's, supported by rather elegant metabolic studies of brain glucose and ketone metabolism, inflammation, and loss of white matter across the menopause transition.

The hypothesis is that the effect of hormones on the brain is dependent on whether they are initiated at the peri-menopausal, immediately menopausal, or post-menopausal time with benefit at earlier periods and harm later. While attractive, the framework is partially informed by observational studies which we know to be biased due to predominant enrollment of generally healthier people (e.g., fewer people who smoke, more people who engage in recreational physical activity and have healthy weights). Short-term trials of MHT for cognition have given mixed results. We do not have long term trials of MHT for dementia prevention started in early menopause, but in the WHI trial of women aged 50-55 studied ~7 years after trial ended there was no residual benefit for MHT regarding cognition.[18]In women aged 65 and older, there was harm for probable dementia/mild cognitive impairment during the trials.[19,20] We encourage the FDA to review WHI's MHT trial results on cognitive function, mild cognitive impairment, and probable dementia. [18-20]

Breast and other cancers: The presentations and discussions were potentially misleading, particularly regarding breast cancer, and incorrect for other cancers.

Most importantly, it was repeatedly mentioned that the 2002 CEE+MPA paper only "suggested" an increase in breast cancer incidence and that there was no significant increase in breast cancer mortality. This statement distorts the appropriate statistical inference and ignores the totality of the evidence that has been presented over time.

The CEE+MPA trial was stopped early, on the advice of the independent DSMB, when the protocol-specified breast cancer statistic (weighted logrank Z=-3.19, 2-sided p=0.001) crossed the prespecified monitoring boundary for harm (Z=-2.32, 2-sided p=0.01) at mean follow-up time of 5.2 years. [3] This adverse effect emerged approximately 10 years earlier than the protocol projected time at which adequate power to detect breast cancer harm would be achieved.[3] Using trial data through the end of blinded intervention (5.6 years), the risk of incident invasive breast cancer increased progressively over time and was significantly increased (HR 1.24)[6,7,21] An increased risk in breast cancer was evident across all age groups, including younger participants randomized to CEE+MPA and no statistically significant variation by age group in breast cancer outcomes has been seen in any of the analyses. These increased risks have persisted throughout the post-intervention period; a recent published update reported a significant 28% increase at 20 years of cumulative follow-up, again with no variation by age group and in fact the age group younger than 60 years had a significantly increased cumulative risk (HR 1.36; 95%CI 1.09 - 1.69).[221]

Additional analyses support a causal interpretation. Analyses examining risk by time in study and adherence to study pills found that breast cancer risk increased for women in the CEE+MPA group with both of these measures of increasing exposure to study hormones.[23] In another analysis that considered duration of exposure, those with hormone exposure prior to the trial were at higher risk, whereas those without prior use showed no elevation during the active intervention period.[24] The distinction by prior hormone use was no longer significant in the 20-year update, as breast cancer incidence was significantly elevated with CEE+MPA in both those with prior MHT use (HR 1.52; 95%CI 1.16-1.98) and those without prior use (HR 1.21; 95%CI 1.05-1.40), directly refuting claims that the overall WHI conclusion rests on an "anomalous" placebo rate.[22]

The statement about no significance for mortality is similarly problematic. It is dismissive of real injury to women with breast cancer who must undergo arduous therapies including chemotherapy, radiation and surgery, with lasting physical and emotional consequences, as well as significantly increased all-cause mortality.[22] It also does not acknowledge the fact that tumors in the CEE+MPA group were larger, later stage, and more likely to involve lymph nodes than those in the placebo group--findings inconsistent with chance variation, but consistent with delayed detection due to increased breast density attributable to CEE+MPA.[21] Further, while no increase in breast cancer mortality was observed at the time the trial was stopped, likely because of few deaths observed at that point, longer term follow-up found a significant 96% increase in deaths attributed to breast cancer at 11 years mean follow-up.[25]

During the panel discussion, a speaker claimed that the decline in U.S. breast cancer incidence that followed the stopping of the WHI CEE+MPA trial was "a statistical change in how the data was being analyzed by the group from the CDC." The speaker's claim is unsubstantiated and not consistent with SEER coding. The report by Ravdin et al. (2007) attributed the sharp decline in U.S. breast cancer incidence after 2002 primarily to the abrupt reduction in postmenopausal hormone therapy use, particularly combined estrogen plus progestin, following the early termination of the WHI CEE+MPA trial.[26] The analysis was peer-reviewed and published in one of the most rigorous medical journals. There are no known technical flaws in the methodology, NEJM has never retracted, corrected, or revised these findings. We encourage the FDA to fully examine the U.S. breast cancer incidence following the stopping of the WHI trial, and temporal trends reported by Chlebowski et al.[21,23,27]

As accurately noted by one speaker, CEE-alone showed a nonsignificant reduction in risk for breast cancer during the trial (at 7.1 years).[27] This reduction persisted and became statistically significant in longer term follow-up.[7] Breast cancer mortality was also reduced after 20 years.[8,22]

We encourage the FDA to fully examine the influence of MHT and particularly CEE+MPA on breast cancer incidence, tumor characteristics, mammography rates, and breast density, as well as the long-term follow-up.[21,28.29]

Other Cancers: The speaker's statements regarding WHI portrayal of MHT's association with lung cancer and ovarian cancer are inaccurate, as evident in our trial reports.[30-32]

The panel was told that neither WHI trial showed an increased risk of lung cancer among 50–59-year-old women. While technically accurate, it is misleading to focus on a specific age-group without considering the larger picture. There was no statistically significant age trend in either trial so conclusions should be based on the entire dataset. CEE+MPA significantly increased risk of lung cancer deaths, but not incidence[30] whereas CEE-alone did not significantly increase either lung cancer incidence or death.[31] The evidence for WHI's MHT trials on lung cancer should be interpreted cautiously, however, as this outcome was not a designated endpoint.

CEE-alone significantly increased risk of ovarian cancer incidence by 104% and risk of dying from ovarian cancer by 179%, while CEE+MPA did not.[32] Again, the lack of

significant interactions by age indicates that the most reliable inference is based on the overall results.

Conclusions

The WHI trials were primarily designed to study whether MHT would reduce heart attacks across all ages spanning 50-79 years. Additional outcomes that might be affected by MHT were studied, including breast cancer as the primary safety endpoint. The trials achieved their primary objectives. Results showed that MHT did not reduce the risk of heart attacks but increased the risk of stroke and blood clots. Breast cancer risk was increased, and endometrial cancer decreased in the CEE+MPA trial. Fractures were reduced in both trials.

The WHI trials were not designed to study the effects of MHT specifically in younger menopausal women with vasomotor symptoms (the main current indication for MHT); nonetheless the 8,833 women aged 50-59 years represent the largest MHT trial in this age group. In this younger age group, the relative risks were like those of older age groups in the CEE+MPA trial, whereas in the CEE-alone trial women aged 50-59 years had significantly lower risks for heart attack, and all-cause mortality compared with older age groups. The important take-home messages from the results in the younger age groups are that CEE-alone has a more favorable risk profile, and that in both trials the absolute risks were low. The low absolute risk in younger women is a sufficient rationale to justify short term use of MHT for relief of vasomotor symptoms. Additionally, WHI has recently published data specifically addressing risk of cardiovascular diseases in women with vasomotor symptoms; the findings confirm that cardiovascular risks due to MHT are low in younger women with vasomotor symptoms, but on the other hand they are particularly high in older women with vasomotor symptoms.[33] This analysis does not consider the of the risk of breast cancer.

The panel discussion raised the issue of the black box warning on MHT products, particularly topical vaginal products. The WHI investigators do not take a position on whether the FDA should remove or modify the black box warning on MHT products. We recognize that the FDA's boxed warning for all estrogen products was rooted in the WHI systemic (oral) hormone trials conducted to test chronic disease prevention in women aged 50–79. However, those randomized trial results do not evaluate and may not apply to vaginal estrogen used locally for the genitourinary syndrome of menopause or to transdermal MHT for vasomotor symptom relief. We encourage the FDA to reevaluate whether extrapolating systemic WHI findings to local products is appropriate.

In summary, WHI has contributed enormously valuable knowledge to help women make health care decisions. It is unknown whether other systemic MHT products such as estradiol or progesterone will have similar effects to the conjugated equine estrogens and medroxyprogesterone used in the WHI trials, because of a lack of similarly large and rigorous trials in healthy women. The WHI data remain the best data available to inform health care recommendations with regard to systemic MHT.

Respectfully submitted by the Women's Health Initiative Steering Committee, with special acknowledgment to Jacques Rossouw, MD and Aaron K. Aragaki, MS.
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