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TRANSLATIONAL PERSPECTIVE

The oestrogen equation: What is the key to unlocking the cardiovascular benefits of oestrogen for postmenopausal women?

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Oestrogen has long been thought to promote cardiovascular health in women, and the loss of oestrogen with menopause has been considered a primary mechanism contributing to the increased cardiovascular disease (CVD) prevalence in menopausal women. As such, oestrogen replacement for postmenopausal women – or menopausal hormone therapy (MHT) – was the standard of care prior to the release of the Women's Health Initiative (WHI) study in 2002, which concluded that MHT increased the risk for heart attack and stroke. Although these findings have since been debunked, the controversy surrounding the safety and efficacy of MHT has persisted (Langer et al., 2021). Recent guidelines from The Menopause Society state that MHT is the gold standard for treating menopausal symptoms and can be used safely by women with appropriate consideration for their age, time since menopause and underlying risk factors (The North American Menopause Society Advisory Panel, 2022). However, MHT is not considered a primary prevention for CVD as the current data do not conclusively support significant cardiovascular benefits in postmenopausal women using MHT compared to placebo (The North American Menopause Society Advisory Panel, 2022).

In the current study by Dillon et al., the authors aimed to examine the vascular effects of exogenous oestradiol in pre- and postmenopausal women (Dillon et al., 2025). One of the primary study outcomes was endothelial function, a biomarker of cardiovascular health. Endothelium-dependent and -independent dilatation was assessed by measuring forearm blood flow via venous occlusion plethysmography during brachial artery infusions of acetylcholine and sodium nitroprusside in the presence and absence of concurrent acute 17β-oestradiol administration. In addition, β_2-adrenergic receptor-mediated dilatation was assessed by infusing terbutaline in the presence and absence of 17β-oestradiol to investigate specific mechanisms known to regulate vascular control of blood pressure in women. The primary study findings are that acute administration of 17β-estradiol enhanced endothelial and smooth muscle function in premenopausal women, but not in postmenopausal women. Further, 17β-oestradiol augmented vasodilatory responsiveness to terbutaline in premenopausal women, but had no impact in postmenopausal women, suggesting that the lack of a beneficial effect of oestradiol on the vasculature in postmenopausal women may be related, in part, to alterations in β-adrenergic signalling. In addition to new insight on vascular function in premenopausal women, the current study also highlights that mechanisms associated with oestradiol benefits appear to be altered in postmenopausal women, together providing novel data to improve our understanding of MHT.

The findings of this carefully designed study are very intriguing and challenge the dogma that exogenous oestradiol is protective or beneficial for the cardiovascular system in postmenopausal women, particularly with longer time elapsed post menopause. The postmenopausal women in the current study were 6–10 years post menopause, suggesting that older postmenopausal women may become insensitive to the vasodilatory effects of oestradiol. Consistent with the current findings, our group recently showed a lack of an effect of exogenous oestradiol (7 days, transdermal patch) to improve cutaneous microvascular endothelial function in postmenopausal women who were on average 5 years postmenopausal (Nuckols et al., 2025). While these findings collectively support the idea that time since menopause may be a key factor in determining whether or not oestradiol is beneficial to the vasculature (Vitale et al., 2008), neither of the studies by Dillon and Nuckols observed correlations between the change in vasodilatation with oestradiol and the time since menopause. Although these studies are acute and short term in duration, they both lend support to the current Menopause Society guidelines that MHT – particularly oestradiol – may not offer primary protection for vascular health in postmenopausal women. Importantly, these studies provide insight into mechanisms that are altered with menopause, such as β_2-adrenergic receptors or endothelin-B receptors, and provide avenues for future research into underlying mechanisms by which MHT may exert cardiovascular effects.

In the studies by Dillon and Nuckols, although the overall mean values indicate that exogenous oestradiol does not improve endothelial function in postmenopausal women, it is interesting to note the substantial inter-individual variability in vascular responsiveness to exogenous oestradiol observed in both studies. In the current study by Dillon, acute oestradiol infusions *did improve* endothelium-dependent dilatation in five of the nine postmenopausal women (Fig. 1D), whereas dilatation was reduced in three women and not affected in one. Similarly, we observed that 7 days of oestradiol administration via transdermal patch *improved* cutaneous microvascular function in 7 of the 10 postmenopausal women, whereas dramatic reductions were noted in three postmenopausal women. Thus, a beneficial effect of oestradiol is, in fact, apparent in some postmenopausal women, and may suggest that we should focus on individual responsiveness in conjunction to MHT timing initiation when determining those most likely to benefit from oestradiol and/or MHT. Together, the mechanisms behind this phenomenon remain unclear.

The findings from Dillon give rise to new questions related to exogenous hormone use and cardiovascular health for menopausal women. Given the individual variability in the vascular responses to

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oestradiol in postmenopausal women, what psychological factors and physiological mechanisms may account for this variability that yields a beneficial vascular effect of oestradiol for some women but not others? Alternatively, can we better understand and predict which postmenopausal women could be negatively impacted by oestradiol use and why? Answering these questions and others will be critical as the field moves toward personalized medicine approaches to improve health for menopausal women. It is crucial to continue and expand research on women's health to ensure treatments and preventative strategies are uniquely tailor to the physiological needs of women, ultimately enhancing quality of life and health outcomes.

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Additional information

Competing interests

None declared.

Author contributions

All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

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