

Women's heart health is not just about hormones

Heart-disease risk increases as women get older. Explanations that centre on changes after the menopause don't tell the full story, says Jumana Saleh.

The common view is that cardiovascular disease mainly affects men, but it is also the leading cause of death in women worldwide. And, as with men, morbidity and mortality in women increase drastically with age.

Despite its burden, cardiovascular disease is considered to be largely preventable. Reports from the World Health Organization, as well as heart-health agencies around the globe, conclude that the onset of cardiovascular disease can be avoided by controlling several risk factors, including cholesterol levels, blood pressure and tobacco use.

But the big question regarding women and heart disease pertains to the steep rise in incidence at menopause. And this is where conventional wisdom needs to be updated.

In 2020, the American College of Cardiology issued updated guidelines for preventing heart disease in women. This set of recommendations acknowledged sex-specific risk markers for cardiovascular disease. It highlighted pregnancy-related conditions (in particular, hypertension and gestational diabetes) as well as premature menopause, polycystic ovary syndrome and psychological stress.

Several lines of evidence support the idea that cardiovascular disease is linked to variations in female hormones. First, women develop cardiovascular disease on average ten years later than men, and incidence of the disease increases after the menopause. This delay is typically attributed to the protective effects of female hormones before the menopause. Second, people who go through early menopause as a result of surgery to remove the ovaries have a higher incidence of cardiovascular disease, an effect that is attributed to a reduction in the levels of female hormones. Moreover, reproductive-age women who do a lot of exercise sometimes experience a disruption to ovarian function leading to a deficiency of female hormones, which causes them to stop menstruating. Known as exercise-associated amenorrhea, this condition has been found to accelerate the progression of plaque build-up inside arteries (atherosclerosis).

The situation gets murkier when deciding whether this hormonal link also applies to postmenopausal women. Should disease in these women be diagnosed and treated with consideration of low female-hormone levels – an approach that could lead to recommending menopausal hormone therapy (MHT). Or should postmenopausal



“The role of hormones in women's heart health demands new research.”

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women be evaluated using similar criteria to those for men, in which hormone levels are not generally considered?

There is no clear answer to this question, and much uncertainty remains regarding how menopausal transition correlates with cardiovascular risk. Reports by the Heart and Estrogen/Progestin Replacement Study, Women's Health Initiative study and others have not proved that MHT offers protection against cardiovascular disease in older women. In fact, it might increase the risk of thrombosis. Moreover, results suggesting MHT can reduce cardiovascular disease risk if it is given soon after the onset of the menopause are still open to debate.

This uncertainty suggests that, when it comes to women's cardiovascular disease, hormones do not tell the whole story. After all, menopause transition is associated with more than just sex-hormone changes – major physiological, biochemical and behavioural alterations also take place (S. R. El Khoudary *et al. Circulation* **142**, e506–e532; 2020). In particular, menopause marks the end of menstruation, leading some to ask whether the monthly blood loss provides protection against cardiovascular disease. For example, iron builds up in blood after the menopause. The connection between altered iron levels and cardiovascular disease risk is under intense debate. Iron is linked to oxidative stress – a hallmark of atherosclerosis progression.

The detrimental effect of excess iron on heart health is not a new concept. Indeed, disorders linked to iron overload are known to be associated with cardiovascular risk. Perhaps other risk factors for cardiovascular disease start to build up in serum after the menopause, as well – a topic that deserves further research.

Women have long been at a disadvantage when it comes to prevention and management of cardiovascular disease. One reason is that medical practitioners tend to lend importance to symptoms that are common in men, such as chest pain. Women, however, sometimes present with a different constellation of symptoms, such as nausea, dizziness, jaw or neck pain, and a sore back, which often go unrecognized by conventional diagnostic procedures (L. S. Mehta *et al. Circulation* **133**, 916–947; 2016).

Moreover, there is a belief among physicians and the public that women are at lower risk. Although there is some truth to this, the relative difference tends to diminish as women age. The under-representation of women in clinical studies exacerbates both problems.

The role of hormones in women's heart health, and therefore the importance of the menopause, demands new research. Ideally, emerging cardiovascular disease risk factors associated with menopausal transition would be explored in randomized controlled cross-sectional and longitudinal studies that involve postmenopausal women. But designing controlled studies to compare pre and postmenopausal women is a major challenge, owing to the limitations of monthly hormonal variations and of menopausal changes.

Working out why women lose their protection as they go through the menopause – beyond the overly simple story of changes related to sex hormones – could yield insights into how to prioritize preventative strategies. Women, and men, all over the world would gain a heartfelt benefit from such research.