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EDITORIALS

Sex differences in the risk of cardiovascular disease

The accelerated risk at menopause may not be as clear as previously thought

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Long before the landmark Women's Health Initiative clinical trial studied the effects of hormone replacement therapy (HRT) on cardiovascular disease in postmenopausal women, several questions framed the debate about whether menopause truly represented a period of equalisation between women and men in the risk of cardiovascular disease.[1 2] Was menopause a pathophysiological turning point for women, or was the acceleration in risk due to natural ageing processes, independent of the hormonal effects of menopause? Recent studies have asked whether cardiovascular disease risk factors lead to menopause rather than the other way around.[3] Still, the overarching question remains: if a sex gap exists in the risk of cardiovascular disease, how can we use our understanding of what drives this difference to take better care of our patients and ultimately to close the divide?

The linked study by Vaidya and colleagues (doi:10.1136/bmj.d5170) substantially extends our understanding of the epidemiology of sex differences in death from ischaemic heart disease.[4] The authors used longitudinal data in men and women from the United States and from England and Wales to quantitatively test whether ischaemic heart disease mortality significantly changes (either accelerates or decelerates) around the estimated time of menopause (45-54 years of age). They found that, unlike deaths from breast cancer, rates of death from ischaemic heart disease did not rise around the estimated time of menopause in women. Interestingly, a deceleration in the rate of death from ischaemic heart disease was seen in men at age 45, which the authors argue might account for the perceived equalisation of risk in women at the time of menopause. The use of longitudinal data, two large geographically separate cohorts, and statistical methods to test for the ischaemic heart disease mortality rate changes strengthen the authors' observations.

While Vaiyda and colleagues' results seem to exonerate menopause as the sole driver of sex differences in death from ischaemic heart disease, the story may not be that simple. Current data from clinical trials do not support a protective effect of maintaining a pre-menopausal hormonal milieu; in fact, HRT in postmenopausal women was associated with modest increases in cardiovascular disease compared with placebo.[5] However, debate continues about whether HRT is efficacious in younger, recently postmenopausal women compared with older, remotely menopausal women.[6] With the so called "timing hypothesis" as yet unresolved, evidence based practice guidelines appropriately advise that HRT should not be used primarily for the prevention of cardiovascular disease in postmenopausal women.

Vaidya and colleagues' study confirms previous reports of a deceleration in the rate of ischaemic heart disease among men at age 45 years. The concept of a male climacteric or "andropause" has been popularised in the lay press[7] and has been referred to in the scientific literature as late onset hypogonadism or male testosterone deficiency. Testosterone levels fall steadily in men between their 30s and 90s.[8] However, testosterone deficiency has not been convincingly linked to incident cardiovascular disease in men and experts have called for more scientifically rigorous clinical trials of androgen replacement.[9] Biological processes aside from those related to sex hormones might account for the increased ischaemic heart disease risk among younger men, and this would be an interesting area for further study.

Vaidya and colleagues show that ischaemic heart disease in women is a life course disease that steadily marches forward, showing no midlife acceleration. However, this does not mean that cardiovascular disease risk factors in women are entirely "sex neutral." Increasing evidence shows that factors related to pregnancy—such as a history of pre-eclampsia,[10] gestational diabetes,[11] preterm delivery,[10] and having babies with low birth weight[10]—increase the risks of long term cardiovascular disease in women. Indeed, for the first time, guidelines on preventing cardiovascular disease in women from the American Heart Association advocate that doctors take a reproductive history when stratifying the risk of cardiovascular disease.[12] Knowledge of pregnancy related risk factors may help physicians identify women who are at risk earlier than midlife. Whether these factors confer an independent risk of cardiovascular disease above and beyond classic risk factors in women is still uncertain, but is an important area for further study.

Although use of epidemiological data to answer clinical questions is not without its faults, a major strength is that it generally offers a bird's eye view rather than a keyhole vantage point. To answer the challenging question of what drives

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differences in cardiovascular disease in men and women over their lifespan, a combination of science from both far and near perspectives will be needed.

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