Letter to the Editor

Sex hormones and risk of coronary artery disease in women

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We challenge the implication of the article on coronary artery disease in women,[1] based on the Zhao analyses of 2834 postmenopausal women,[2] that oestradiol is cardioprotective and explains women's lower rates of cardiovascular disease, compared with men, before menopause.

We undertook an analyses of the large-scale UK Biobank, involving 57,204 women with detectable oestradiol concentrations.[3] In both pre- and post-menopausal women, in unadjusted analyses, the hazard ratio (HR) (95% confidence interval) per unit higher in log-transformed oestradiol for myocardial infarction was 0.73 (0.58; 0.92), indicating that higher oestradiol was associated with a lower risk of myocardial infarction. However, after adjusting for age, this HR became 0.94 (0.75; 1.17) and the association was no longer apparent. After further adjusting for classical cardiovascular disease risk factors, the HR was 1.05 (0.83; 1.31). Furthermore, results were similar in subgroup analyses defined by age, menopausal status, socioeconomic status, contraceptive pill use and the use of hormone replacement therapy. Zhao and colleagues undertook their analyses in postmenopausal women alone, thus not allowing for the vital comparison between women pre and post menopause.

Indeed, we did observe the rates of myocardial infarction were higher with increased age, and that oestradiol concentrations were lower with increased age, although this was not necessarily a consequence of the menopause. The presumed cardioprotective effects of oestradiol seem to be largely confounded by age and further by other cardiovascular risk factors, and menopause itself does not seem to be a causal factor for coronary heart disease risk.[4]

The article also states that higher concentrations of androgens contribute to a higher risk of cardiovascular disease in women based on findings from Zhao et al.[2] However, there is conflicting evidence within this domain. Islam and colleagues, in an analysis of the SHOW (Sex Hormones in Older Women) sub-study of the ASPREE trial,[5] showed that higher quarters of testosterone (Q3 vs Q1 and Q4 vs Q1) were associated with a lower risk of major adverse cardiovascular events. Sievers and colleagues also demonstrated that low baseline testosterone in women 70 years and older was associated with increased cardiovascular disease events.[6] Studies have also demonstrated no associations with testosterone and cardiovascular disease events[7] or cardiovascular mortality[8] in women.

We therefore propose that the associations of oestrogen and testosterone with coronary artery disease in women are not so clear cut in light of the numerous conflicting findings.

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REFERENCES

1. Montarello N, Chan WPA. Coronary artery disease in women. Aust Prescr 2022;45:193-9. https://doi.org/10.18773/austprescr.2022.065
2. Zhao D, Guallar E, Ouyang P, Subramanya V, Vaidya D, Ndumele CE, et al. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J Am Coll Cardiol 2018;71:2555-66. https://doi.org/10.1016/j.jacc.2018.01.083
3. Peters SAE, Woodward M. Oestradiol and the risk of myocardial infarction in women: a cohort study of UK Biobank participants. Int J Epidemiol 2021;50:1241-9. https://doi.org/10.1093/ije/dyaa284
4. Dam V, Onland-Moret NC, Burgess S, Chirlaque MD, Peters SAE, Schuit E, et al. Genetically determined reproductive aging and coronary heart disease: a bidirectional 2-sample Mendelian randomization. J Clin Endocrinol Metab 2022;107:e2952-961. https://doi.org/10.1210/clinem/dgac171
5. Islam RM, Bell RJ, Handelsman DJ, McNeil JJ, Nelson MR, Reid CM, et al. Associations between blood sex steroid concentrations and risk of major adverse cardiovascular events in healthy older women in Australia: a prospective cohort substudy of the ASPREE trial. Lancet Healthy Longev 2022;3:e109-18. https://doi.org/10.1016/S2666-7568(22)00001-0

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6. Sievers C, Klotsche J, Pieper L, Schneider HJ, März W, Wittchen HU, et al. Low testosterone levels predict all-cause mortality and cardiovascular events in women: a prospective cohort study in German primary care patients. Eur J Endocrinol 2010;163:699-708. https://doi.org/10.1530/eje-10-0307
7. Meun C, Franco OH, Dhana K, Jaspers L, Muka T, Louwers Y, et al. High androgens in postmenopausal women and the risk for atherosclerosis and cardiovascular disease: the Rotterdam Study. J Clin Endocrinol Metab. 2018;103:1622-30. https://doi.org/10.1210/jc.2017-02421
8. Schederecker F, Cecil A, Prehn C, Nano J, Koenig W, Adamski J, et al. Sex hormone-binding globulin, androgens and mortality: the KORA-F4 cohort study. Endocr Connect 2020;9:326-36. https://doi.org/10.1530/ec-20-0080

Natalie Montarello and Wai Ping (Alicia) Chan, the authors of the article, comment:

We agree that menopause as a cause of cardiovascular disease is not clear-cut with multiple studies showing conflicting results. However, it has been shown consistently that women develop cardiovascular disease 7 to 10 years later than men,[1] and that early age at menopause is associated with increased risk of cardiovascular disease.[2] The increased risk here is clearly not solely attributed to oestrogen depletion, as you have pointed out in the UK Biobank Study on the effect of oestradiol on cardiovascular disease, but a combination of factors including age and the transition period into menopause.

Postmenopausal women have higher total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations and lower high-density lipoprotein cholesterol (HDL-C) concentrations. LDL-C and apolipoprotein B concentrations, the more 'atherogenic' components of the lipid profile, have been shown to be associated with menopause and not age alone.[3] Similarly, weight gain and loss of skeletal mass have been attributed to ovarian ageing, rather than chronological ageing alone.[4] Postmenopausal women are also more insulin-resistant, have higher blood pressure and central obesity,[5] contributing to the development of metabolic syndrome. It is therefore possible that oestrogen depletion worsens the cardiovascular risk-factor profile, which leads indirectly to increased cardiovascular disease during the menopause transition.

Finally, in relation to androgens and cardiovascular disease in women, high and low concentrations have both been associated with cardiovascular disease, and there are even some studies that show no association. The increased events of cardiovascular disease in women with polycystic ovarian syndrome have been attributed to the increased adiposity and, possibly, an interaction with hyperandrogenism,[6] although the mechanism has yet to be elucidated. The role of hyperandrogenism is likely to be due to the negative interaction with cardiovascular risk factors, as above.

We acknowledge and are aware of the complex interaction of sex hormones and cardiovascular disease in women. However, we chose not to discuss these as the paper was aimed at providing an overview of the approach and management of coronary artery disease in women.

REFERENCES

1. Maas AHEM, Appelman YE. Gender differences in coronary heart disease. Neth Heart J 2010;18:598-602. https://doi.org/10.1007/s12471-010-0841-y
2. Ossewaarde ME, Bots ML, Verbeek ALM, Peeters PHM, van der Graaf Y, van der Schouw YT. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology 2005;16:556-62. https://doi.org/10.1097/01.ede.0000165392.35273.d4
3. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366-73. https://doi.org/10.1016/j.jacc.2009.10.009
4. Sowers M, Zheng H, Tomey K, Karvonen-Gutierrez C, Jannausch M, Li X, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92:895-901. https://doi.org/10.1210/jc.2006-1393
5. El Khoudary SR, Thurston RC. Cardiovascular implications of the menopause transition: endogenous sex hormones and vasomotor symptoms. Obstet Gynecol Clin North Am 2018;45:641-61. https://doi.org/10.1016/j.ogc.2018.07.006
6. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010;95:2038-9. https://doi.org/10.1210/jc.2009-2724