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Commentary: Mendelian randomization and women's health

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Women and men are not biologically identical; differences in body shapes and compositions, hormone levels, enzymes, lifestyles and other factors lead to alterations in the presentation, diagnosis and natural history of disease, as well as drug efficacy and safety.[1–3] Yet, such differences have historically been disregarded and women's health conditions continue to be under-researched, under-diagnosed and under-treated.

Estimates suggest that up to 10% of women between 18 and 45 years are affected by polycystic ovarian syndrome (PCOS), making it the most common endocrinopathy among women of reproductive age.[4,5] Despite this, most PCOS studies have had small sample sizes,[6–10] and survey data suggest that over a third of PCOS patients have to wait more than 2 years for diagnosis.[11] At the same time, comorbidities are under-diagnosed and under-treated,[7–9] despite substantial effects on patient health and quality of life.[10,12]

Women are disproportionately affected by common diseases such as Alzheimer's and osteoarthritis, as compared with men, and experience more disease-related disability.[13] In addition to such disease that affects both women and men, it is estimated that 5% of disability-adjusted life years (DALYs) in women arises from diseases specific to women, with the corresponding value being almost 10-fold lower in men at 0.7% of DALYS.[13] Despite this, therapeutic options for women's health conditions remain limited. In the 5-year period between 2014 and 2018, the US Food and Drug Administration (FDA) approved 213 novel drugs.[14] Of these, only seven (3.3%) drugs were for female-specific indications, with a further five for breast cancer-related indications.[14] The corresponding value for male-specific indications was two (both related to prostate cancer), a value that is iniquitous to the proportion of DALYs arising from sex-specific disease.[14] Historically, the FDA also excluded women of childbearing potential

from participating in clinical trials, largely driven by concerns of teratogenicity and a perceived difficulty in accounting for female-specific hormonal fluctuations.[1,15] Although guidelines and policies established in the 1990s and 2000s[15,16] led to greater inclusion of women in clinical trials,[1] a recent study found that 72% of clinical trials did not provide sex-specific outcome data.[17] With pharmacokinetic and pharmacodynamic differences evident between men and women for many drugs,[18] and with most drugs withdrawn from the market having greater health risks in women,[18,19] a detailed analysis of sex-specific effects of drug efficacy and safety is essential.

Genetic epidemiology may potentially offer solutions here. Mendelian randomization (MR) presents an opportunity to explore causal relationships between risk factors (e.g. obesity), therapeutic targets (e.g. proteins, metabolites and hormones) and disease risk.[20] In MR, genetic variants associated with altered levels of an exposure are used as a proxy for the risk factor or therapeutic target.[20] Causal effects of the exposure on the outcome can be estimated by assessing how these variants affect the outcome.[20] Since genetic variants are randomly allocated at conception, estimates from MR should be less affected by confounding, and the non-modifiable nature of genotype abrogates reverse causation.[20] Most large genome-wide association studies (GWAS) include a large proportion of women (48–100%),[21] and sex-specific effect estimates are increasingly reported,[22,23] albeit still only for a minority of GWAS. By leveraging these sex-specific genetic data, MR could ameliorate the historical under-representation of women in research studies in a safe and cost-effective manner. With increasingly large GWAS and biobank datasets publicly available for risk factors, potential drug targets (e.g. protein concentrations) and disease outcomes, this represents an opportune moment to identify causal risk factors and novel drug targets in a sex-stratified manner.

In this MR-themed special issue of the journal, the three articles by Dimou *et al.*[24], Shu *et al.*[25] and Harris *et al.*[26] together advance our knowledge of how metabolic risk factors and sex hormones affect female health.

First, Dimou *et al.* show that sex hormone-binding globulin (SHBG) may have opposing effects on estrogen receptor-positive and- negative breast cancer risk. Their results provide evidence for higher SHBG levels decreasing risk of estrogen receptor-positive breast cancer and increasing risk of estrogen receptor-negative breast cancer, although they note that the latter needs to be confirmed in future studies. They included body mass index (BMI) in their multivariable analyses as it might be a confounder—and metabolic traits might have an impact on SHBG.[27,28] Other hormones such as insulin have also been linked to SHBG levels and breast cancer risk,[29,30] and further work is needed to tease apart the causal relationships between specific obesity traits (e.g. fat distribution), glycaemic traits (e.g. insulin levels), sex hormones and SHBG, and their respective roles in the development of different breast cancer subtypes.

BMI has been suggested as having opposing effects on breast cancer risk depending on menopausal status (higher BMI being associated with lower risk of breast cancer risk in premenopausal women and with higher risk of breast cancer in postmenopausal women).[31–33] Contradicting this, the study by Shu *et al.*, suggests that BMI is protective for both pre- and postmenopausal breast cancer, in keeping with a previous large MR study.[34] The explanation for this inconsistency is unclear, but it might be due to differences in whether the BMI measurement, or the genetic instrument for BMI, largely captures 'lifetime' adult BMI (including early life BMI), BMI after menopause or postmenopausal weight gain.[34] This discrepancy highlights the need for more precise measurements of risk factors to tease apart these relationships; e.g. the effects of weight gain and body fat composition and distribution, and the interplay of these at different ages and for various durations.

Next, Harris *et al.* corroborate previous evidence linking genetic liability to PCOS to lower risk of ovarian cancer, and show that the causal link between these two conditions may only be limited to certain histological subtypes (particularly endometrioid tumours). However, the associations are still relatively weak and it remains unclear whether this protective effect, if real, is mediated by oligo-anovulation, hyperandrogenism, or other PCOS-related mechanisms.

Collectively, these three contributions highlight the need for more precise and specific definitions of phenotypes, and equally important, larger sample sizes when assessing robust causal relationships. It is evident from these studies and the broader literature that metabolic traits play a major role in female health, though causality and directions of effects remain largely unexplored in the complex interplay between metabolic traits, hormones and female-specific diseases. With the rising obesity epidemic,[35] it is ever more important to elucidate the precise nature of these associations to reliably inform public health policies.

As we improve our understanding of the biology underlying women's health, we should advocate for improvements in women's health not only from a biological perspective but more holistically. For instance, recent legislation in several US states has restricted access to abortion, despite evidence that shows improving such access leads to better maternal health outcomes.[36] Thus, a broader approach to prioritize and advance women's health which

encompasses biological, political and social aspects should be embraced by all.

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