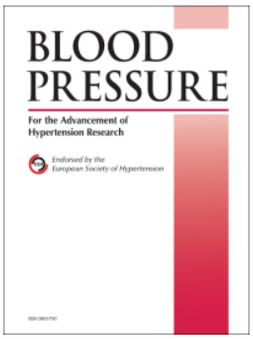

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REVIEW ARTICLE

Genetics of hypertension-related sex differences and hypertensive disorders of pregnancy

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ABSTRACT

Background: Hypertension and hypertensive disorders of pregnancy (HDP) cause a significant burden of disease on societies and individuals by increasing cardiovascular disease risk. Environmental risk factors alone do not explain the observed sexual dimorphism in lifetime blood pressure (BP) trajectories nor inter-individual variation in HDP risk.

Methods: In this short review, we focus on the genetics of hypertension-related sex differences and HDP and discuss the importance of genetics utilization for sex-specific hypertension risk prediction.

Results: Population and twin studies estimate that 28–66% of variation in BP levels and HDP is explained by genetic variation, while genomic wide association studies suggest that BP traits and HDP partly share a common genetic background. Moreover, environmental and epigenetic regulation of these genes differ by sex and oestrogen receptors in particular are shown to convey cardio- and vasculoprotective effects through epigenetic regulation of DNA. The majority of known genetic variation in hypertension and HDP is polygenic. Polygenic risk scores for BP display stronger associations with hypertension risk in women than in men and are associated with sex-specific age of hypertension onset. Monogenic forms of hypertension are rare and mostly present equally in both sexes.

Conclusion: Despite recent genetic discoveries providing new insights into HDP and sex differences in BP traits, further research is needed to elucidate the underlying biology. Emphasis should be placed on demonstrating the added clinical value of these genetic discoveries, which may eventually facilitate genomics-based personalized treatments for hypertension and HDP.

KEY POINTS

- Blood pressure trajectories and age-related prevalence of hypertension differ between men and women.
- Vasculoprotective qualities of oestrogen, mediated by oestrogen receptors, are lost at menopause.
- Certain genetic variants linked to hypertension are sex-specific, i.e. only observed in one sex.
- Hypertension and preeclampsia are polygenic diseases, i.e. several different genes influence the susceptibility for these conditions.
- Hypertension and hypertensive disorders of pregnancy have a partially shared genetic basis.
- The combined effect of several genetic variants can be evaluated using polygenic risk scores (PRSs). Individuals, and especially women, with a high blood pressure PRS develop hypertension a decade earlier compared to those with a low PRS.
- Environmental and lifestyle factors can modify genetic risk by altering gene expression. Sex differences in the association between gene expression and hypertension remain largely unknown.

PLAIN LANGUAGE SUMMARY

Hypertension (high blood pressure [BP]) and hypertensive disorders of pregnancy (HDP), such as preeclampsia, increase the risk of heart attacks, stroke and heart failure. Lifestyle factors alone do not explain the BP differences between men and women nor HDP risk in women.

Approximately half of the variation in BP levels and HDP is explained by genes, and these two conditions have been partly linked to the same genes. Moreover, the regulation of these genes differs by sex.

The majority of the known genetic variation in hypertension and HDP is caused by the additive effect of thousands of genes. Genetic risk scores for BP display stronger associations with hypertension

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risk in women than in men and are associated with sex-specific age of hypertension onset. Forms of hypertension caused by a single gene are rare and mostly present equally in both sexes.
In this short review, we focus on the genetics of hypertension-related sex differences and HDP and discuss the importance of genetics utilisation for sex-specific hypertension risk prediction.

Introduction

Blood pressure (BP) trajectories in men and women start to diverge during puberty with a more rapid increase in men, possibly due to the increase in testosterone production [1]. This sex difference in systolic BP (SBP) decreases during early adulthood as SBP begins to increase faster in women than in men [2]. In menopause, declining oestrogen levels further accelerate the rate of SBP increase, pushing SBP in women higher than in men in late adulthood [1,2]. Thus, differences in BP trajectories can be attributed in part to hormonal differences between sexes and, ultimately, sex chromosomes [3].

After menopause, lower levels of oestrogen lead to increased BP through arterial stiffening, loss of nitric oxide-mediated vasodilatation, worsening endothelial dysfunction, increase in oxidative stress and inflammation, increased renin levels, salt sensitivity, renin–angiotensin–aldosterone system (RAAS) activation and increased sympathetic tone [4]. Before menopause, all these factors are inhibited to some extent by the activation of oestrogen receptors (ER) located throughout the body [4]. Also, comorbidities and environmental factors, such as increased BMI, excessive alcohol intake, increased salt intake, physical inactivity, insulin resistance and diabetes all contribute to BP increases after menopause [4].

Hypertensive disorders of pregnancy (HDP) include chronic hypertension, gestational hypertension, preeclampsia, eclampsia and preeclampsia superimposed on hypertension. HDP complicates 5–8% of pregnancies and is associated with increased risk for future hypertension, stroke, coronary heart disease, heart failure and cardiac death [5–8]. Furthermore, early and recurrent preeclampsia both carries an even greater risk for these cardiovascular disease (CVD) complications, whereas gestational hypertension is a weaker predictor of future CVD [5–8]. Similarly, hypertension is a known risk factor for cardiovascular and renal complications, such as ischaemic heart disease, myocardial infarction, ischaemic and haemorrhagic stroke and chronic kidney disease [9,10]. However, major sex differences exist in hypertension outcomes as a 10 mmHg increment in SBP increases ischaemic heart disease risk by 10% and 25% in men and women, respectively.

The genetics of hypertension and HDP are strongly intertwined [11]. Hypertension before pregnancy and family history of preeclampsia are established clinical risk factors for preeclampsia [5]. Fittingly, genome-wide association studies (GWAS) on hypertension and preeclampsia have revealed shared genetic factors for these two conditions (Figure 1) [11]. Likewise, BP polygenic risk scores (PRSs) predict future preeclampsia and gestational hypertension, which suggests a partially shared genetic background between these traits [11,12]. This short review focuses on the genetics of hypertension-related sex differences and HDP. We review how genetics partly explains these traits and speculate how genetics could be utilised for sex-specific risk prediction in the future.

Heritability of hypertension and hypertensive disorders of pregnancy

Previous population and twin studies have estimated that the heritabilities of SBP, diastolic BP (DBP), and preeclampsia are 28–60%, 32–66% and 38–50%, respectively [13–15]. While the heritability of BP may depend on the sex of the parent or offspring, earlier studies have reported contradictory findings [16–18]. In one study of 220 healthy Americans, men with one or two hypertensive parents had higher ambulatory BP than women with hypertensive parents, whereas offspring of normotensive parents exhibited no sex differences in BP [19].

The heritability estimates for maternal preeclampsia, foetal preeclampsia and gestational hypertension are 35%, 20% and 24%, respectively [20,21]. A family history of preeclampsia in first-degree relatives is related to a two-fold risk of a preeclamptic pregnancy [22]. Furthermore, being born of a preeclamptic pregnancy confers an increased risk of having an elevated BP in childhood and antihypertensive medication in adulthood [23,24]. The lifelong risk for hypertension, ischaemic heart disease, and stroke is also elevated in offspring born of preeclamptic pregnancies [24]. However, it is unclear whether the heritability of these adverse traits is transferred to offspring through genetic inheritance, through epigenetic programming due to adverse circumstances in utero during hypertensive and preeclamptic pregnancies, or through the effects of the environment and shared lifestyles [24].

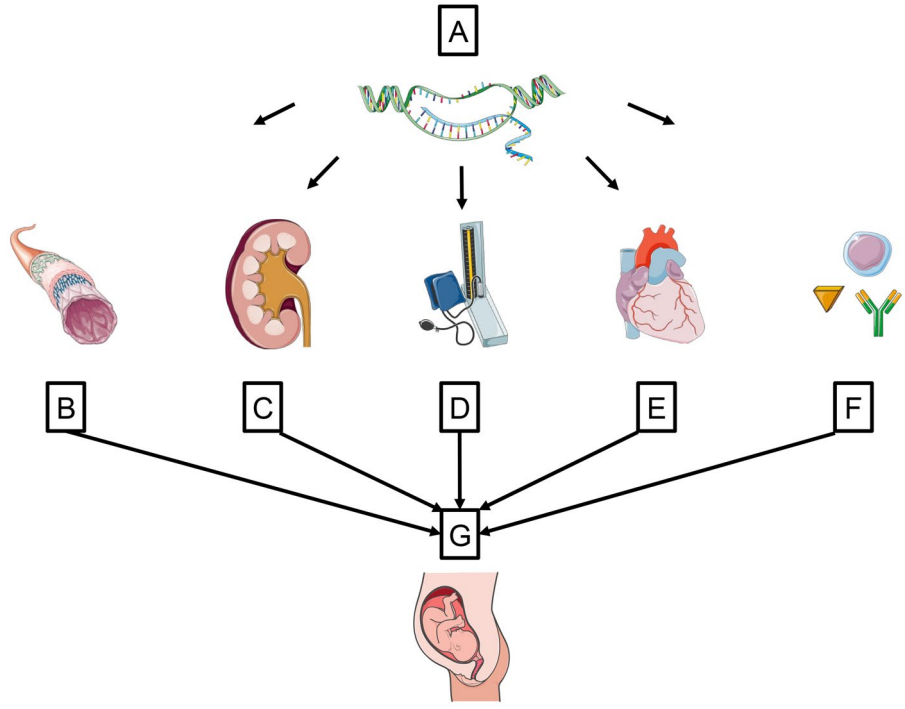

Figure 1. Preeclampsia (PE) and hypertension are both polygenic diseases and characterised by an increase in blood pressure and endothelial dysfunction. Other hallmarks of PE also include systemic inflammation, impaired vasodilatation, reduction in vascular integrity, and end-organ damage. Single nucleotide polymorphisms and genes (A) associated with preeclampsia are linked with angiogenesis and endothelial cells (FLT1/ZBTB46; (B), renal glomerular function (*ACTN4,* TRPC6, TNS2 and PLCE1; (C), blood pressure traits (*NPPA*, *NPR3*, *PLCE1*, *TNS2*, *FURIN*, *RGL3* and *PREX1*; (D), natriuretic peptide signalling (NPPA, NPR3 and FURIN; (E), immune dysregulation (MICA and SH2B3; (F), and foetal antiangiogenic and immunologic factors (FLT1, PZP and WNT3A), placenta development (*PGR*, *TRPC6*, *ACTN4* and *PZP),* and remodelling of uterine spiral arteries (*NPPA*, *NPPB*, *NPR3* and *ACTN4*; (G). Artwork shown in Figure 1 was adapted from material provided by Servier Medical Art (Servier; https://smart.servier.com/), licensed under CC BY 4.0.

The effect of sex chromosomes in cardiovascular disease

The presence or absence of a functional *SRY* gene on the Y chromosome determines the male sex, and the usual sex chromosome karyotypes are XY and XX for males and females, respectively. Despite the gene-rich X chromosome conveying some risk for complex traits and diseases, it does not explain most of the observed sex differences evident in complex traits such as hypertension [25]. The study of the role of the X chromosome is somewhat challenging as the second copy of the X chromosome is randomly silenced in different cells in females [26]. However, X chromosome aneuploidies in Klinefelter syndrome (XXY males) and Turner syndrome (X0 females) are associated with impaired cardiometabolic profiles, including hypertension, highlighting the role of the X chromosome in CVD [27,28].

In addition to sex chromosomes, autosomal chromosomes and environmental factors affecting gene expression, such as the effect of steroidal hormones to DNA, contribute to sex differences in complex diseases (Figure 2) [25]. Furthermore, while the Y chromosome is relatively poor in gene concentration, specific Y chromosome haplogroups are associated with an increased risk for coronary artery disease, an increase in femoral plaques, and changes in lipoprotein profiles [29–32].

Oestrogen receptor polymorphism and BP

Endogenous oestrogen has well-established cardioprotective effects mediated by ERs which are expressed throughout the body, including the cardiovascular system [3]. ERs are expressed in the cell nucleus and on the cell membrane and stimulated by oestrogen. Nuclear ERs regulate gene transcription *via* genomic mechanisms acting as a transcription factors, while membrane ERs produce rapid responses *via* various signalling cascades, including ion channel activation and enzymatic pathways [33,34]. In humans, ERs regulate many physiological processes relevant to BP, such as smooth muscle cell proliferation, energy metabolism, and calcium ion cycling. Oestrogen also affects BP through nitric oxide-mediated vasodilatation, prostacyclin production, hyperpolarization of endothelial cells, and by

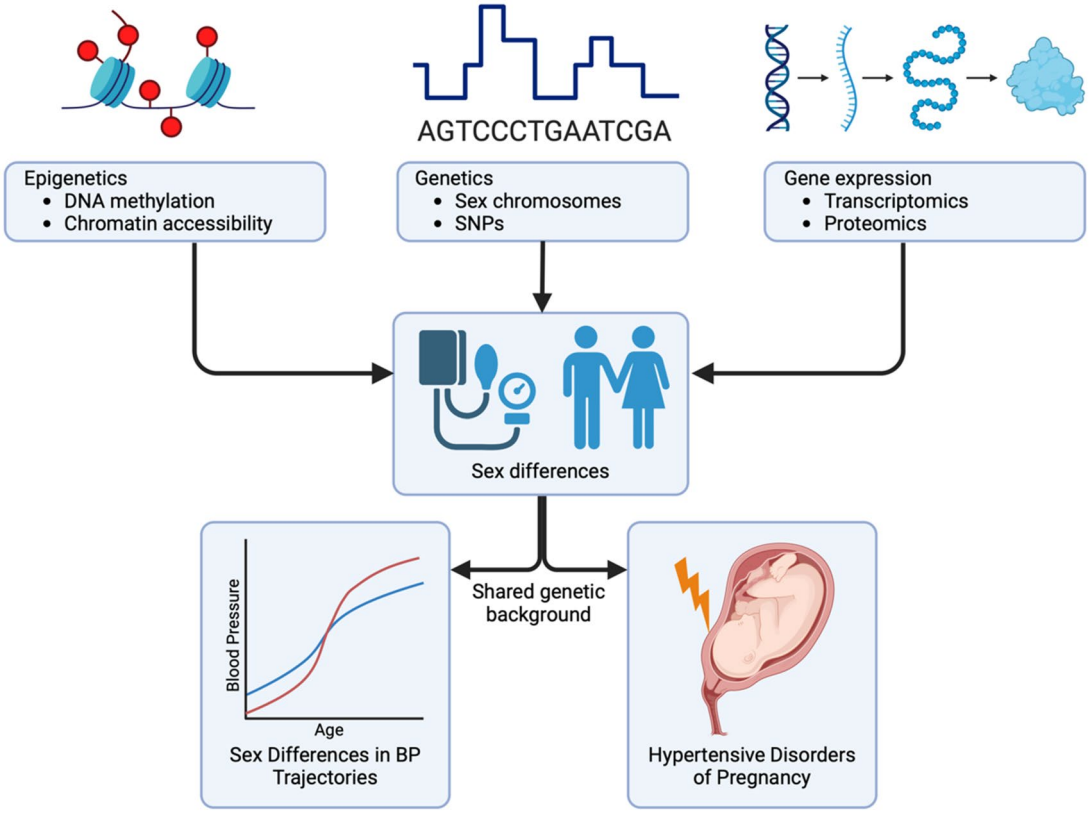

Figure 2. Genetic factors contributing to sex differences in hypertension. Hypertensive traits are shaped by the combined effects of an individual's genome, the environment and the interaction between the two. The most important genetic components that contribute to hypertension phenotypes include the sex chromosomes and genetic variation (single-nucleotide polymorphisms, SNPs). Sex differences can also exist in DNA accessibility and methylation status (epigenetic differences), as well as in levels and patterns of gene expression (transcriptomic differences), and all of these can be altered by environmental factors. Approximately half of variation in blood pressure levels and hypertensive disorders of pregnancy is explained by genetic variation, and the conditions partly share a common genetic background. Created in BioRender. Niiranen, T. (2024) BioRender.com/c39p426.

downregulation of the angiotensin converting enzyme and the angiotensin II receptor [35,36]. Polymorphisms, i.e. common DNA variation, in the ER coding areas alter ER structure which is associated with sex differences in hypertension-related traits, such as intima-media thickness and left ventricular mass [37–39].

In pre-clinical animal and human tissue models, epigenetic programming, i.e. activation or downregulation of DNA is in part mediated through oestrogens and ERs which is shown to activate several cardioprotective mechanisms in cardiomyocytes, endothelium and vascular smooth muscle cells [40]. Further, in animal models, ERs are responsible for protective effects against hypertension, pulmonary hypertension, atherosclerosis, ischaemia/reperfusion injury and heart failure with reduced ejection fraction [40].

However, in addition to gene regulation of oestrogen and ERs, there are other mechanisms through which genetics impacts the sex differences in hypertension and preeclampsia, as further discussed in the following sections.

Genetics of sex differences in hypertension

Primary hypertension is a polygenic trait, i.e. a trait that is influenced by more than one gene [41]. Most human genetic variation manifests as single nucleotide polymorphisms (SNPs), substitutions of single nucleotides at specific positions in the genome. SNPs can be detected and analysed from tissue or blood samples using DNA microarrays. These polymorphisms can be used to construct genetic risk prediction tools for different traits and diseases by calculating the weighed sum of the SNPs [42]. Over 90% of known SNPs are located in the non-protein coding area of the genome, and the association of a SNP with a trait or disease can be protective, neutral, or risk-enhancing [43]. However, the associations between SNPs and BP are usually small, <1 mmHg [44].

Monogenic forms of hypertension, i.e. mutation only in one gene leading to secondary hypertension, are rare. They often inhibit normal renal or adrenal BP regulation, highlighting the role of kidneys and the RAAS [45,46]. Most monogenic forms of hypertension

present similarly in both sexes [45,46]. As an exception, Geller syndrome is a rare autosomal dominant form of hypertension exacerbated by pregnancy [45].

Earlier candidate gene studies have detected sex-specific SNP associations with hypertension. For example, a mutation in the angiotensinogen coding gene *AGT* was associated with elevated plasma angiotensinogen in both sexes but elevated BP only in women [47]. Other mutations in the aldosterone and nitric oxide synthase genes were similarly associated with higher BP only in women [48]. Furthermore, the mutations in the G-protein coupled oestrogen receptor gene (*GPER*) were associated with elevated SBP and DBP in women, while a mutation in the oestrogen receptor 1 gene was associated with elevated SBP in men and DBP in women [49,50]. Similarly, oestrogen receptor 2 gene mutations were associated with salt sensitivity in premenopausal women [51]. Finally, mutations in adrenergic receptors beta-1 and alpha-2A were associated with increased DBP in women, whereas polymorphism in beta-2 receptors was associated with increased DBP in men [52].

Over the last decade, large-scale GWASs have become the golden standard for genetic discovery in complex traits, including BP and hypertension (Figure 2). In GWAS, a sample of individuals with a clinically confirmed trait of interest (cases), for example hypertension, is genotyped with a DNA array and then compared with a genotyped sample of people without the trait (controls) [53]. Historically, GWASs have been conducted without sex stratification. However, a recent sex-stratified GWAS (174,664 males, 174,664 females) for BP traits identified 412 female-specific and 142 male-specific loci associated with SBP, DBP, or pulse pressure [54]. Further, these sex-specific BP trait loci included oestrogen receptor 1 and androgen receptor highlighting the importance of hormone receptors in BP regulation. However, a key limitation of GWASs on preeclampsia and sex differences of hypertension is that they have been conducted mostly on populations of European ancestry. Additional GWASs with sex-specific analyses and more diverse study samples in this domain are therefore needed.

Polygenic risk scores

PRS can be used to quantify the total impact of a set of SNPs on a trait of interest [55]. The SNPs are usually identified from a GWAS, the quality and sample size of which largely determines the quality of the PRS. Modern PRS methods can incorporate information from hundreds of thousands of SNPs and also enable correction for possible genetic sources of error, such as linkage disequilibrium, resulting in improved predictive power compared to older methods [56]. Current approaches to PRS-based risk stratification can identify individuals with a disease risk comparable to those with monogenic disease [57].

PRSs for BP and hypertension show promise as risk stratification tools to categorise individuals based on their genetic hypertension risk [58,59]. For example, individuals who have a BP PRS in the highest 2.5% category have a 2.3-fold risk for hypertension and 11 years earlier hypertension onset compared to individuals who belong to a reference group of 20–80 percentile range of BP PRS [60]. Furthermore, a sex-specific BP PRS is more strongly associated with hypertension in women than in men, especially for early-onset hypertension [61,62]. These results suggest a greater genetic contribution to hypertension in women than in men (or alternatively, a greater environmental contribution in men than in women).

Genetics of hypertensive disorders of pregnancy

Most genetic studies on HPD have focused on preeclampsia. Although Mendelian patterns of disease inheritance have been reported for a small number of families, linkage analysis and twin studies point to a polygenic aetiology of preeclampsia, and no monogenic forms of preeclampsia have been discovered [13]. Some cases of preeclampsia are linked to aneuploidies, such as trisomy of chromosome 13, which increases preeclampsia risk, and trisomy 21, which may reduce preeclampsia risk [63,64]. Nevertheless, HPD can be considered complex diseases with environmental and polygenic aetiologies.

In 2023, a GWAS with 16,743 female cases identified 13 novel loci for preeclampsia, bringing the total number of known preeclampsia and HDP loci to 22 [11]. Known preeclampsia and HDP loci are associated with several salient phenotypes such as hypertension, endothelial and placental function, natriuretic peptide signalling, angiogenesis, renal glomerular function, trophoblast development and immune dysregulation [11]. Genetic correlations between SBP and gestational hypertension (r = 0.73) and preeclampsia (r = 0.52) point to an overlapping genetic basis between hypertension, preeclampsia and gestational hypertension [65].

In preeclampsia, defective spiral artery formation leads to hypoperfusion and ischaemic conditions in the placenta, which in turn manifests into maladaptive immunological reactions, systemic inflammation, systemic endothelial dysfunction and vasoconstriction, hypertension and end organ failure [66]. A hallmark study on preeclampsia genetics discovered a foetal genome SNP near *FLT1* [67]. *FLT1* encodes soluble fms-like tyrosine kinase 1 (sFlt-1), a placenta-derived

anti-angiogenic factor found at high concentrations in the maternal circulation in preeclampsia. SFlt-1 in conjunction with placental growth factor (PlGF) are already used as a biomarker in the clinical prediction of preeclampsia [68]. Also, the rising levels of sFlt-1 result in high levels of potent vasoconstrictor endothelin-1 which is responsible for the hypertensive state in preeclampsia [69]. Furthermore, endothelin receptor antagonists have been investigated in preclinical animal models of preeclampsia to reduce the hypertensive reaction [70]. However, the potential teratogenic properties of these medications limits their use in pregnancy, and further studies are needed to justify their wider use in preeclampsia [70].

Despite established screening programs, clinical models for incident preeclampsia have low predictive value [71]. While mean arterial pressure and biomarkers such as serum PlGFs and uterine artery pulsatile index improve model performance, the number needed to screen to prevent a single preeclampsia case is still 143 [72]. Previous evidence for the ability of preeclampsia PRSs to improve the c-statistic or area under the curve of clinical preeclampsia prediction models has been inconclusive [12,73]. A recent study by Honigberg et al. examined an established algorithm for allocating low-dose aspirin treatment to prevent preeclampsia and observed that incorporating BP GWAS based PRS and preeclampsia PRS substantially improved net reclassification [65]. In the same study, the odds ratios for preeclampsia and gestational hypertension between the top and bottom PRS deciles were 1.64 and 1.53 for preeclampsia PRS and BP PRS, even after adjusting for clinical risk factors.

Surprisingly, a register study observed that BP PRS was a better predictor of future gestational hypertension (N = 8488) and preeclampsia (N = 6643) than preeclampsia PRS, highlighting how genetic discoveries and advances in hypertension genetics can directly transfer into preeclampsia due to the shared genetic basis [12].

Compared to normotensive pregnancies, differences in DNA methylation patterns (i.e. modification of gene function by adding a methyl group to DNA), higher cell-free plasma DNA levels, and higher cell-free RNA expression are observed in preeclampsia [74–76]. In addition, in the subfamily of structural, non-protein coding RNAs, there are changes in circular RNA, long non-coding RNA and microRNA which all contribute to changes in placental trophoblast invasion, function, regulation, and angiogenesis [77]. Because DNA methylation changes can be detected during the first trimester with an 80% sensitivity and 78% specificity, they could potentially be used to improve preeclampsia screening [78]. Cell-free DNA produced by maternal and foetal cells has also been suggested as a potential new biomarker for preeclampsia [74–76]. Similarly, cell-free RNA expression is associated with neuromuscular, endothelial, and immune cell types observed in preeclampsia physiology which again offers possibilities for prediction and precision treatment of preeclampsia [79].

In addition to genetic susceptibility and the effect of sex hormones, several other environmental factors may modify genetic risk or act as independent risk factors for hypertension and HDP. Obesity is a significant risk factor for hypertension in both sexes, but its effect is stronger in women [80]. Obesity increases sympathetic muscle tone in men but not in premenopausal women [80]. However, after menopause, visceral fat deposition and increased leptin hormone levels increase sympathetic activity [80]. Finally, the vasculoprotective qualities of oestrogen are diminished in obese and diabetic women, highlighting the effect of obesity as a sex-specific risk factor for hypertension [80].

Other lifestyle factors such as sedentary lifestyle, alcohol and drug abuse, psychological stress, comorbidities (e.g. chronic kidney disease), obstructive sleep apnoea and environmental factors such as air pollution increase hypertension risk in both sexes. Whether these factors affect hypertension risk in a sex-specific manner is not well known [4,81]. However, salt-sensitive hypertension is more common in women than in men and salt sensitivity is further increased in women after menopause [82]. This finding may be explained by less intensive RAAS suppression and increased levels of aldosterone in women [82].

High and low BMI are also risk factors for HPD. Other clinical risk factors include advanced or young age, diabetes, chronic kidney disease and autoimmune diseases [71]. Peculiarly, in some studies, smoking has been associated with reduced risk of preeclampsia [83]. In high-risk patients, aspirin prophylaxis may be used to reduce the risk of preeclampsia [71].

In addition to genetic factors, environmental factors play crucial role in the development of hypertension and HPD. Whether they directly or indirectly modify DNA transcription and how environmental factors affect hypertension risk differently in men and women warrants further research. However, the genetic makeup of an individual is not determinist for a disease as positive lifestyle changes as well as environmental factors can modify gene expression thereby affecting genetic risk.

Knowledge gaps and future prospects

Hypertension and HDP are complex diseases with both environmental and polygenic components. Recent large-scale GWASs have enabled researchers to construct well-powered PRSs for these conditions and demonstrate an overlapping genetic basis *via* shared risk loci and genetic correlations. However, the biological mechanisms underlying these GWAS-derived associations remain poorly understood. Moreover, gene–gene and gene–environment interactions related to hypertension and HDP are understudied and warrant further research.

Men and women have different lifetime BP trajectories, which are partly driven by genetics: sex chromosomes, gene expression and common genetic variation, including ER polymorphisms. While several sex differences in the associations between SNPs and hypertensive traits have been observed, few have been replicated and their biological underpinnings remain largely unknown. Future research on sex differences in hypertensive traits should favour genome-wide approaches instead of candidate gene studies and sex-specific PRSs instead of traditional, aggregate PRSs.

Genetic discoveries harbour untapped potential for reproductive health. Clinical trials are needed to assess the potential of PRSs in prediction and prevention of preeclampsia, while genetic epidemiological studies on HDP should extend their focus from genetic discovery to assessing long-term cardiovascular consequences of HDP genetics.

In summary, despite recent genetic discoveries providing new insights into HDP and sex differences in BP traits [11,54], further research is needed to elucidate the underlying biology. Emphasis should be placed on demonstrating the added clinical value of these genetic discoveries, which may eventually facilitate genomics-based personalised treatments for hypertension and HDP.

Disclosure statement

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