

Maternal hypertensive traits and adverse outcome in pregnancy: a Mendelian randomization study

Maddalena Ardissono^{a,b,*}, Rohin K. Reddy^{a,*}, Eric A.W. Slob^{c,d,e}, Jack Griffiths^f, Joanna Girling^g, and Fu Siong Ng^{a,g}

Introduction: Hypertensive disorders of pregnancy are associated with adverse fetomaternal outcomes. Existing evidence is mostly limited to observational studies, which are liable to confounding and bias. This study investigated the causal relevance of component hypertensive indices on multiple adverse pregnancy outcomes using Mendelian randomization.

Methods: Uncorrelated ($r^2 < 0.001$) genome-wide significant ($P < 5 \times 10^{-8}$) single-nucleotide polymorphisms associated with SBP, DBP and pulse pressure (PP) were selected as instrumental variables. Genetic association estimates for outcomes of preeclampsia or eclampsia, preterm birth, placental abruption and hemorrhage in early pregnancy were extracted from summary statistics of genome-wide association studies in the FinnGen cohort. Two-sample, inverse-variance weighted Mendelian randomization formed the primary analysis method. Odds ratios (OR) are presented per-10 mmHg higher genetically predicted hypertensive index.

Results: Higher genetically predicted SBP were associated with higher odds of preeclampsia or eclampsia [OR 1.81, 95% confidence interval (CI) 1.68–1.96, $P = 5.45 \times 10^{-49}$], preterm birth (OR 1.09, 95% CI 1.03–1.16, $P = 0.005$) and placental abruption (OR 1.33, 95% CI 1.05–1.68, $P = 0.016$). Higher genetically predicted DBP was associated with preeclampsia or eclampsia (OR 2.54, 95% CI 2.21–2.92, $P = 5.35 \times 10^{-40}$). Higher genetically predicted PP was associated with preeclampsia or eclampsia (OR 1.68, 95% CI 1.47–1.92, $P = 1.9 \times 10^{-14}$) and preterm birth (OR 1.18, 95% CI 1.06–1.30, $P = 0.002$).

Conclusion: This study provides genetic evidence to support causal associations of SBP, DBP and PP on multiple adverse outcomes of pregnancy. SBP and PP were associated with the broadest range of adverse outcomes, suggesting that optimized management of blood pressure, particularly SBP, is a key priority to improve fetomaternal health.

Keywords: genetics, hemorrhage, hypertension, Mendelian randomization, placental abruption, preeclampsia, pregnancy, preterm birth

Abbreviations: GWAS, genome-wide association study; PP, pulse pressure; RCT, randomized controlled trial

INTRODUCTION

Hypertensive disorders of pregnancy are a major cause of maternal and fetal morbidity. The spectrum of hypertensive disorders of pregnancy encompasses chronic hypertension, gestational hypertension and preeclampsia [1]. Chronic hypertension either predates pregnancy or is diagnosed before 20 weeks' gestation, whilst gestational hypertension arises *de novo* post-20 weeks' gestation in the absence of proteinuria, biochemical or hematologic abnormalities [1]. Preeclampsia, at the more severe end of the spectrum, is characterized by hypertension occurring *de novo* after 20 weeks' gestation with evidence of proteinuria, intrauterine growth restriction or end-organ damage. Multiple observational studies have demonstrated associations between maternal blood pressure prior to pregnancy and adverse maternal and fetal outcomes [2–4]. However, observational studies are liable to confounding and reverse causality. Even with careful adjustment for measured confounders, it is nearly impossible to accurately mirror the complex panoply of biological, behavioral and psychosocial factors that factor into the interplay between obstetric and cardiovascular risk. This is especially true for outcomes such as preterm birth and preeclampsia, where the pathophysiology remains relatively poorly understood. Improving our understanding of determinants of adverse fetomaternal outcomes in pregnancy is a public health priority, which may help improve risk stratification and targeted care provision to ultimately improve obstetric outcome.

Journal of Hypertension 2023, 41:1438–1445

^aNational Heart and Lung Institute, Imperial College London, London, ^bRoyal Papworth Hospital, Cambridge Biomedical Campus, ^cMRC Biostatistics Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK, ^dDepartment of Applied Economics, Erasmus School of Economics, ^eErasmus University Rotterdam Institute for Behavior and Biology, Erasmus University Rotterdam, Rotterdam, The Netherlands, ^fRoyal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust and ^gWest Middlesex Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK

Correspondence to Dr Fu Siong Ng, 4th Floor, Imperial Centre for Translational and Experimental Medicine, National Heart and Lung Institute, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, UK. E-mail: f.ng@imperial.ac.uk

*M.A. and R.K.R. are co-first authors with equal contribution.

Received 10 February 2023 **Revised** 8 April 2023 **Accepted** 24 May 2023

J Hypertens 41:1438–1445 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI:10.1097/HJH.0000000000003486

Mendelian randomization leverages genetic variants as proxies for exposures in instrumental variable analysis to study exposure-outcome relationships. Given the independent and random distribution of genetic variants at meiosis, the Mendelian randomization paradigm is less vulnerable to limitations of phenotypic observational study, namely confounding and reverse causality. Our group previously applied the Mendelian randomization framework to provide genetic evidence for the causal effect of SBP, alongside other cardiometabolic traits, on preeclampsia or eclampsia risk [5]. We also demonstrated that SBP is associated with reduced birthweight independently of preeclampsia or eclampsia [5]. Further investigation of drug-target perturbation verified safety and efficacy profiles of genetically proxied beta-adrenergic antagonism and calcium channel blockade on risk of preeclampsia and low birthweight [6], echoing recent large randomized controlled trials (RCTs) [7,8]. However, the causal relevance of blood pressure on other important obstetric outcomes, such as preterm birth and placental abruption, remains unexplored. In addition, no genetic data exist exploring the role of blood pressure indices other than SBP. These data are relevant, as isolated diastolic hypertension is commonest in the age range overlapping with the majority of pregnancies. NHANES III highlighted that isolated diastolic hypertension was the commonest hypertensive subtype in participants aged less than 40 years [9], with the Framingham Heart study also showing that young age was a predictor for isolated diastolic hypertension [10].

In light of this evidence gap, we extended our prior Mendelian randomization work [5], to explore the additional causal relevance of genetically predicted DBP and pulse pressure (PP), on a broader range of maternal and fetal outcomes, including preterm birth, placental abruption and hemorrhage in early pregnancy. We thus utilized Mendelian randomization to explore the causal relevance of SBP, DBP and PP on adverse outcomes of pregnancy, including preeclampsia or eclampsia, preterm birth, placental abruption and hemorrhage in early pregnancy.

MATERIALS AND METHODS

Ethical approval, data availability and reporting

All data used in this study are openly available and appropriately cited. All original studies obtained relevant participant consent and ethical approval. This study is reported on the basis of recommendations by the STROBE-MR Guidelines [11]. A flowchart detailing the design of this study is provided in Fig. 1.

Data sources

Instrumental variants for the exposures of SBP, DBP and PP were extracted from a sex-adjusted genome-wide association study (GWAS) on 738 168 individuals [12]. Instrumental SNPs for each exposure were selected if they were associated with the exposure at genome-wide significance level ($P < 5 \times 10^{-8}$). Only uncorrelated variants were retained,

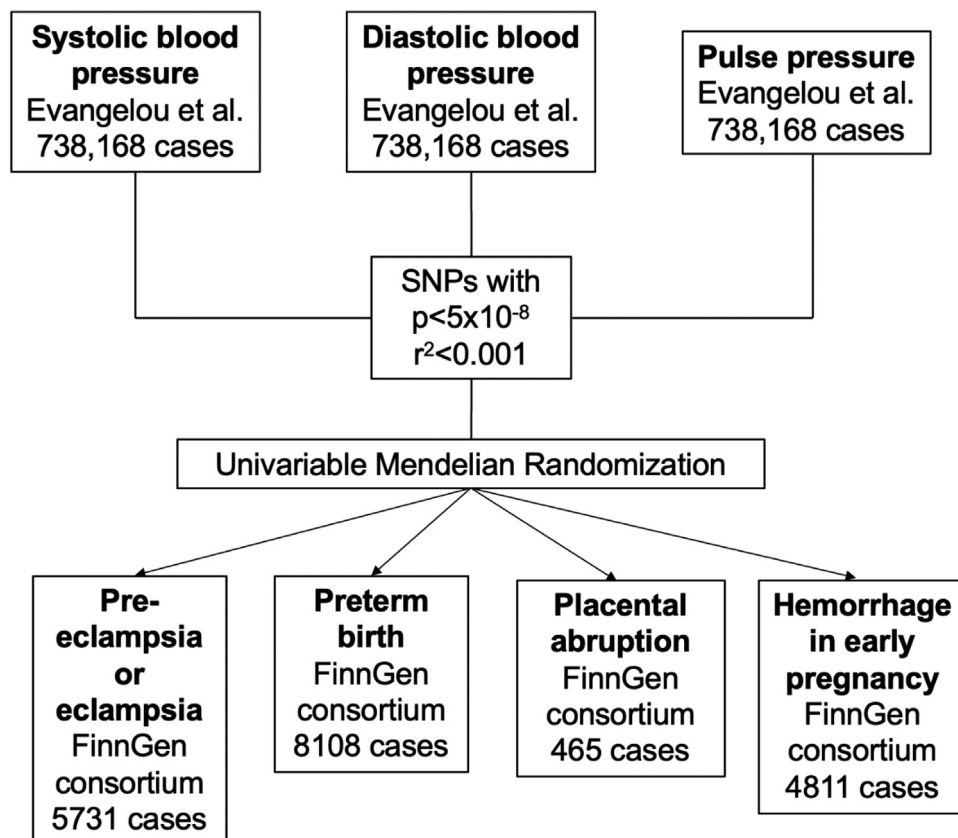


FIGURE 1 Data acquisition and analysis flowchart. SNPs, single nucleotide polymorphisms.

with pair-wise linkage disequilibrium with r^2 less than 0.001. Clumping was performed using the TwoSample MR package in R [13].

The genetic association estimates of the instrumental variants with outcomes were extracted from summary statistics of GWAS analyses in FinnGen Round 7 female participants ($n_{\text{total}} = 392\,423$, $n_{\text{women}} = 219\,462$) [14]. These included 5731 cases for preeclampsia or eclampsia, 8108 cases for preterm birth, 465 cases for placental abruption and 4811 cases for hemorrhage in early pregnancy. Analyses were restricted to women for all outcomes. Definitions for all obstetric endpoints are based on the WHO International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes. Details of relevant ICD-10 codes are provided in Table S1, <http://links.lww.com/HJH/C213>.

Detailed summaries of population characteristics for each of these cohorts are available in the original publications. A brief overview of the included studies is provided in Table S2, <http://links.lww.com/HJH/C213>. Only variants for which genetic association estimates were available for the exposure and outcome under investigation were considered in the analysis.

Statistical analysis

Inverse-variance weighted Mendelian randomization with multiplicative random effects formed the primary analysis method for all models, to estimate the effect of genetically predicted SBP, DBP and PP on risk of adverse outcome of pregnancy. Results are presented as odds ratios (ORs) and 95% confidence intervals (95% CIs) per 10 mmHg higher genetically predicted SBP, DBP or PP. Sensitivity analyses using weighted median Mendelian randomization [15] and the MR-Egger [16] intercept test were used to assess the consistency of results using methods more robust to directional pleiotropy.

To account for multiple comparisons across the three primary exposures increasing the risk of type I statistical errors, the Bonferroni correction was applied. α was set at 0.0167 (0.05/3), P values less than 0.0167 were considered statistically significant. All statistical analyses were performed using the MendelianRandomisation package [17] in R version 4.2.1.

RESULTS

Diastolic blood pressure

Higher genetically predicted SBP was associated with higher odds of preeclampsia or eclampsia (OR 1.81, 95% CI 1.68–1.96, $P = 5.45 \times 10^{-49}$), consistent with previously reported results. In addition, higher genetically predicted SBP was associated with higher odds of preterm birth (OR 1.09, 95% CI 1.03–1.16, $P = 0.005$) and placental abruption (OR 1.33, 95% CI 1.05–1.68, $P = 0.016$).

There was no association between genetically predicted SBP and hemorrhage in early pregnancy (OR 0.97, 95% CI 0.89–1.05, $P = 0.466$). All Mendelian randomization estimates for SBP and adverse outcomes of pregnancy are displayed in Fig. 2.

Systolic blood pressure

Higher genetically predicted DBP was associated with higher odds of preeclampsia or eclampsia (OR 2.54, 95% CI 2.21–2.92, $P = 5.35 \times 10^{-40}$).

There was no association between genetically-predicted DBP and preterm birth (OR 1.09, 95% CI 0.98–1.21, $P = 0.113$), placental abruption (OR 1.39, 95% CI 0.94–2.06, $P = 0.104$) or hemorrhage in early pregnancy (OR 1.002, 95% CI 0.88–1.14, $P = 0.976$). All Mendelian randomization estimates for DBP and adverse outcomes of pregnancy are displayed in Fig. 3.

Pulse pressure

Higher genetically predicted PP was associated with higher odds of preeclampsia or eclampsia (OR 1.68, 95% CI 1.47–1.92, $P = 1.90 \times 10^{-14}$) and preterm birth (OR 1.18, 95% CI 1.06–1.30, $P = 0.002$).

Higher genetically predicted PP was not associated with placental abruption (OR 1.35, 95% CI 0.94–1.96, $P = 0.109$), or hemorrhage in early pregnancy (OR 0.94, 95% CI 0.84–1.07, $P = 0.358$). All Mendelian randomization estimates for PP and adverse outcomes of pregnancy are displayed in Fig. 4.

Sensitivity analyses

The results were largely consistent following sensitivity analyses, as displayed in Table S3, <http://links.lww.com/HJH/C213>.

DISCUSSION

This study provides genetic evidence to support a causal role of higher genetically predicted SBP, DBP and PP on multiple adverse outcomes of pregnancy, including preeclampsia, preterm birth and placental abruption. The results have multiple important implications. First, they support recent clinical trial evidence that has shown improved outcomes of pregnancy with strict blood pressure control in women with gestational hypertension. Second, they identify key adverse outcomes associated with higher blood pressure that are of clinical relevance for risk stratification and surveillance in at-risk pregnancies. Finally, they support a causal relationship between all three blood pressure indices and adverse outcomes, highlighting the requirement for ongoing research aimed at carefully outlining blood pressure targets to aim for in different clinical situations in order to minimize risk of adverse outcomes.

Preeclampsia and eclampsia

We previously reported the association between genetically predicted SBP with preeclampsia and eclampsia [5]. In this study, through our extended analyses, we showed that genetically predicted DBP and PP are also associated with risk of preeclampsia and eclampsia. This is consistent with multiple prior observational studies [18–22] and an observational meta-analysis [23]. Elevated DBP has been shown to be an independent predictor of preeclampsia in a large, health primiparous cohort [20] and DBP increases of at least 15 mmHg have been shown to be 92% sensitive for a diagnosis of preeclampsia [24]. Likewise, PP at 7–15 weeks

Systolic blood pressure

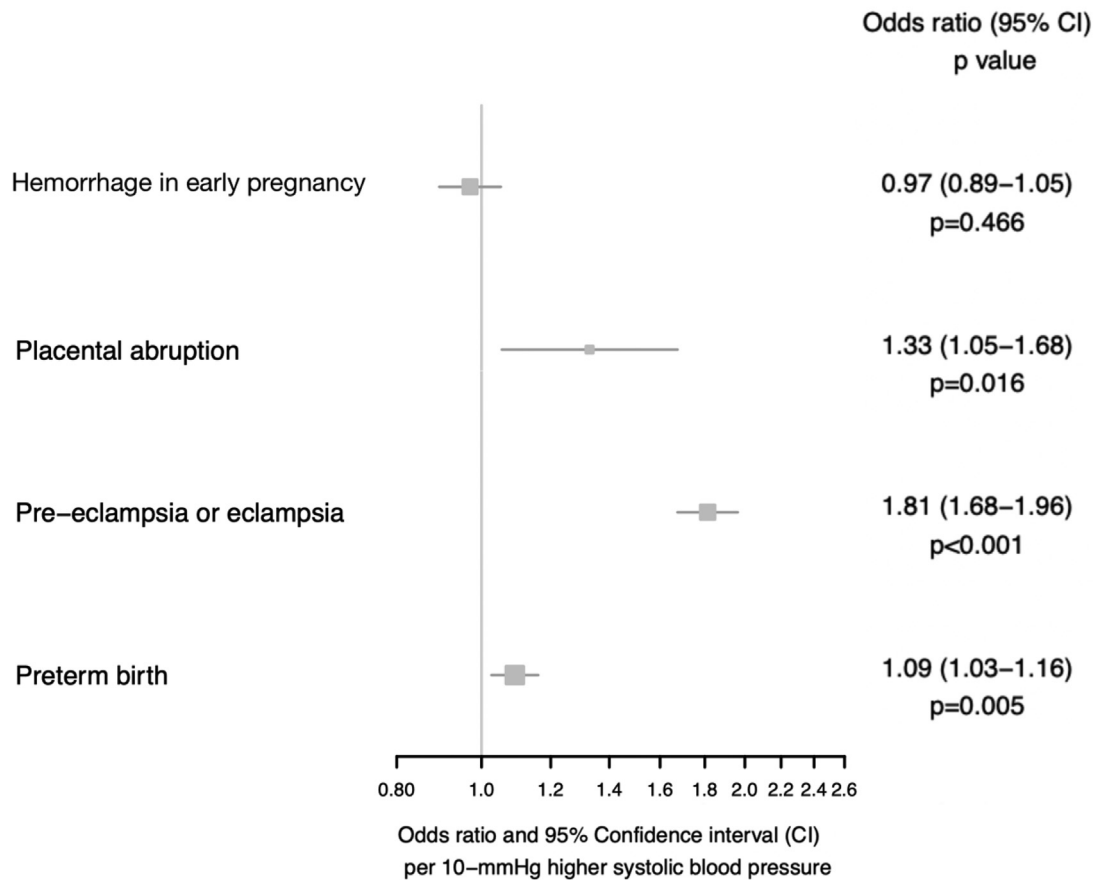


FIGURE 2 Mendelian randomization estimates displaying the effect of genetically predicted SBP on adverse outcomes of pregnancy.

has been shown to be significantly elevated in women who subsequently developed preeclampsia [21]. This study augments the previous literature by providing genetic evidence supporting a causal nature of this association. There are a number of potential mechanisms behind this. First, spiral artery formation might be impaired by a higher maternal blood pressure, purely through hemodynamic effects of the increased pressure and the severity of resultant vascular damage [25]. Alternatively, the alteration in the milieu of circulating vasoactive mediators known to occur secondary to hypertension might directly or indirectly impair spiral artery formation and effective placentation, leading to downstream risk of preeclampsia [26,27]. The subsequent failure of cytotrophoblasts to deeply invade the spiral arteries is thought to be related to failure to adopt an endothelial phenotype, with lack of expression of vascular adhesion molecules [28]. Instead of the physiological remodelling of decidual arteries into high-capacitance and low resistance vessels, hypertension contributes to development of constricted, high-resistance vessels that are inadequate for provision of oxygen and nutrients to the placenta and developing fetus [26]. Thus, the consequent histopathologic hallmark of defective placentation is decidual vasculopathy, which consists of features such as muscular hypertrophy,

endothelial thickening, vascular thromboses and ectasia, vascular wall fibrinoid necrosis and atherosclerosis [25]. Although this is often related to de-novo preeclampsia or that which is superimposed on chronic hypertension, there is evidence that features of decidual vasculopathy are also present in patients with gestational [29] and chronic hypertension [30].

Preterm birth

In this study, genetically predicted SBP and PP were associated with increased odds of preterm birth. This is in line with previous literature. High baseline PP at 12 to 19 weeks' gestation has been demonstrated to be a risk factor for early spontaneous preterm birth in normotensive nulliparous women, and rises in SBP and DBP between baseline and mid-third trimester values associated with an increased risk of early and late spontaneous preterm births in a dose-response manner [31] especially in women with obesity [32]. A plausible mechanism for this finding is that raised hypertensive indices increase preeclampsia risk: term preeclampsia in a first pregnancy is a major risk factor for subsequent preterm birth with or without recurrent preeclampsia [33]. Overall, elevated SBP and PP should alert clinicians to the possibility of pregnancies at a higher risk of preterm delivery and trigger appropriate peripartum care.

Diastolic blood pressure

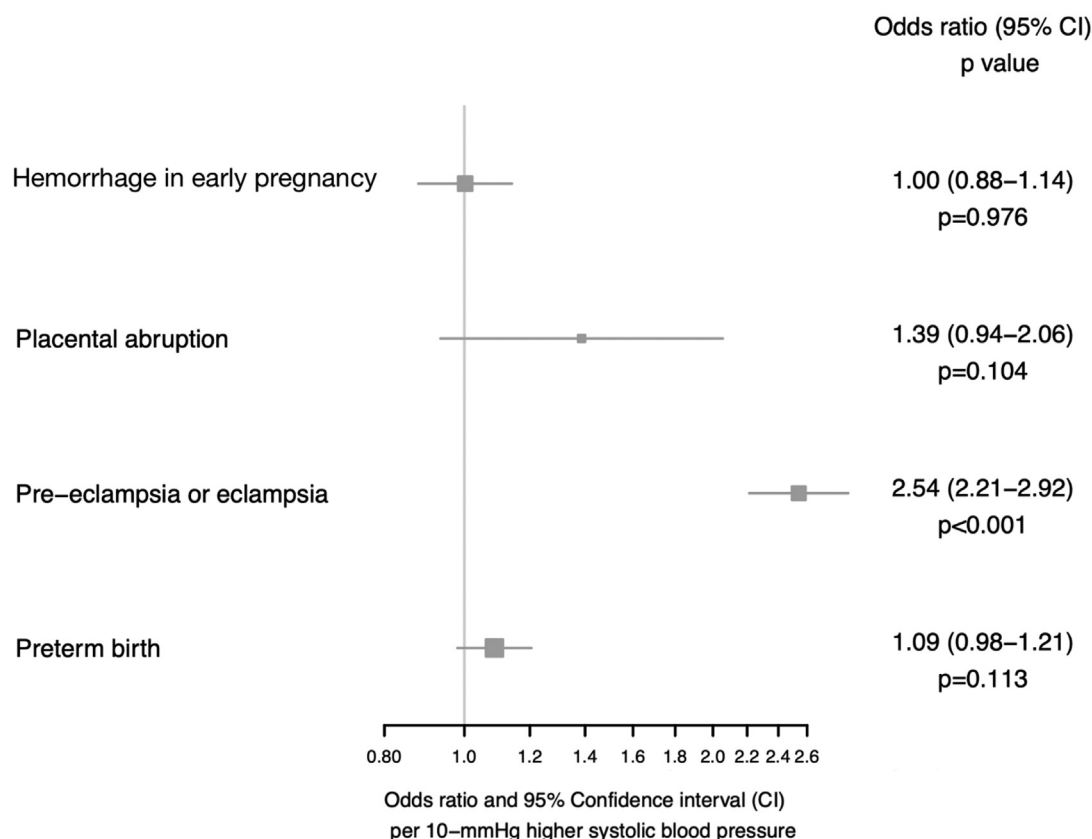


FIGURE 3 Mendelian randomization estimates displaying the effect of genetically predicted DBP on adverse outcomes of pregnancy.

Placental abruption

The association between higher genetically predicted SBP and placental abruption is supported by a prior observational meta-analysis of 54 studies [3] and a recent analysis linking U.S. natality and fetal death data in over 30 million pregnancies [34]. Together with the results of our study, these support the hypothesis that vascular and ischemic placental diseases, including abruption and preeclampsia, could be connected by a unifying cause [34]. From a mechanistic perspective, it is biologically plausible that higher blood pressure on the maternal side might encourage both the initiation and propagation of placental abruption, especially in the setting of increased resistance in the placental circulation. Given the life-threatening nature of this outcome, the results of this study suggest further work to assess the role of tight blood pressure control in women at risk for abruption.

Hemorrhage in early pregnancy

This study did not find evidence of a relationship between genetically predicted hypertensive indices and increased odds of hemorrhage in early pregnancy. Hemorrhage in early pregnancy is a significant source of maternal anxiety and estimates of bleeding prevalence in early pregnancy range from 7 to 24% [35], and is associated with a higher risk

of preterm delivery, antepartum hemorrhage, placenta previa and preterm premature rupture of membranes [36]. In the present study, we examined this outcome because it has been suggested that a mechanism behind it includes defective placentation, characterized by thinner and more fragmented trophoblast shells, and reduced cytotrophoblast invasion of spiral arterioles [36]. The lack of association in this study might reflect a lack of true underlying biological association with a blood pressure-related cause, given that other causes such as infection, inflammation, ectopic pregnancies and chorionic/cervical neoplasia may cause injury to the decidual vasculature or reproductive tract. An alternative explanation might relate to insufficient power in the instrumented SNPs. For this reason, the null result should not be interpreted as final evidence of lack of an association.

Strengths and limitations

For the first time, this Mendelian randomization study provides genetic evidence for the causal effects of hypertensive indices on a variety of adverse outcomes of pregnancy, including novel data on DBP and PP. Key to the present analysis is reduced liability to confounding. As gametes are independently and randomly distributed at conception, the Mendelian randomization paradigm is

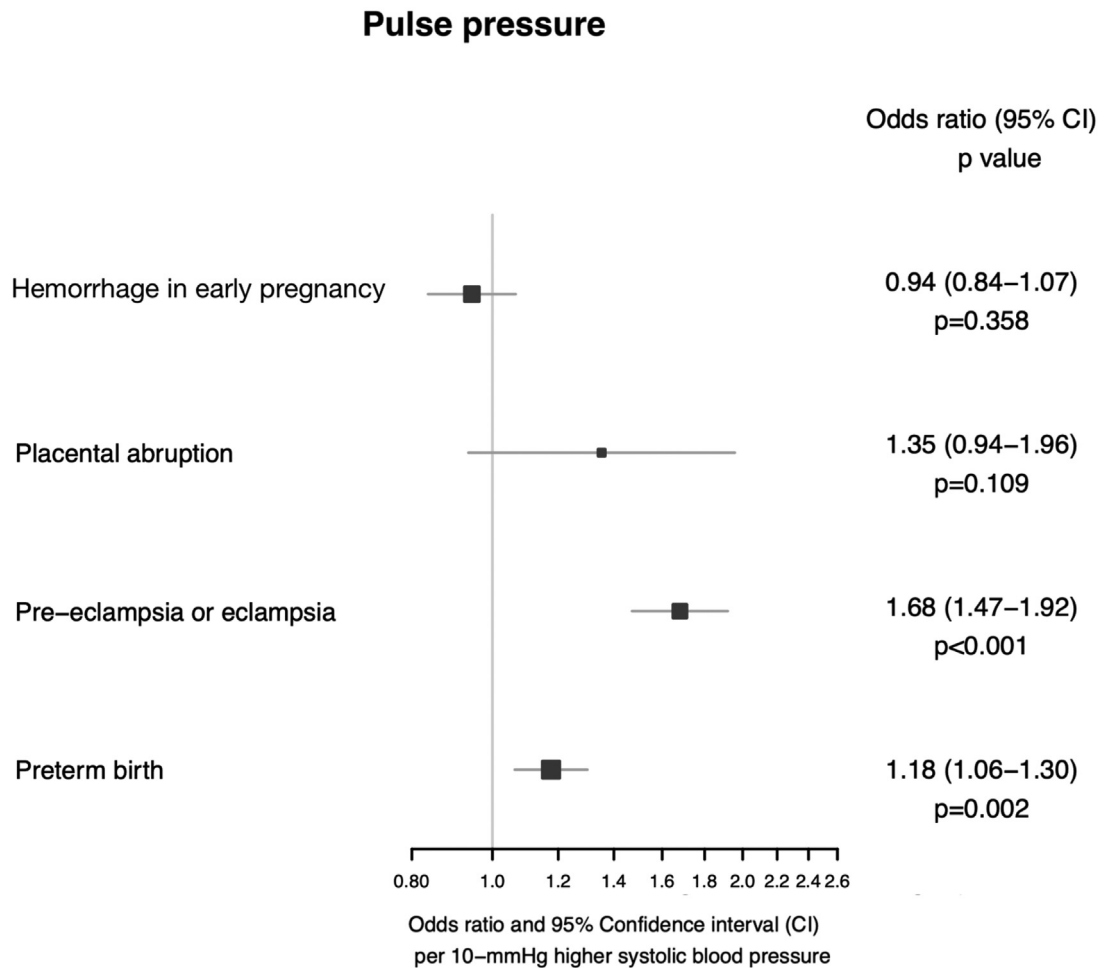


FIGURE 4 Mendelian randomization estimates displaying the effect of genetically predicted pulse pressure on adverse outcomes of pregnancy.

analogous to randomization to higher or lower blood pressure targets in an RCT. Furthermore, as with RCTs, reverse causality is minimized because inheritance of genetic variants temporally precedes outcomes.

Limitations of this study exist. First, we were unable to parse the role of genetically predicted hypertensive indices on the potentially important subtypes of early versus late-onset preeclampsia, or early versus late preterm birth as the requisite genetic association data did not exist. Second, the Bonferroni correction is a conservative approach to the multiple comparisons problem with a greater risk of failure to reject false null hypotheses, thereby increasing the risk of a type II statistical error. In the same vein however, the associations reported are likely to be robust and not the result of false positives, given the high level of statistical significance demonstrated. Third, the data sources for this study concentrated in European ancestry individuals. By including an ethnically homogenous population, we minimized the possibility of confounding by population stratification; however, the results may not be fully generalizable to all ethnicities. Replication on more ancestrally diverse cohorts when data become available is salient, given the high prevalence of chronic hypertension in many non-European ethnicities [37].

Clinical relevance

The results of our study stress the fact that optimal blood pressure management, for all three blood pressure indices, is likely to play a key role in optimization of maternal and fetal outcomes in pregnancy. Given the highlighted importance of blood pressure management, it is important to mention that considerable work remains to be done in outlining exact, evidence-based blood pressure targets in pregnancy across a spectrum of different clinical situations. Recently, the practice-changing Chronic Hypertension and Pregnancy (CHAP) randomized trial demonstrated that a lower threshold for treating chronic hypertension in pregnancy (140/90 mmHg) resulted in an 18% reduction in a primary composite outcome of preeclampsia, preterm birth, placental abruption or fetal/neonatal death, compared with a treatment threshold of 160/105 mmHg or greater [8]. The clinically important difference highlighted in this study emphasizes the clear unmet need for improved clarity in definition of blood pressure thresholds for treatment in pregnancy, and the results of our present study, causally linking blood pressure traits with adverse outcomes, further stress this. Optimization of blood pressure also bears relevance for future maternal health beyond the antenatal and peripartum periods. A systematic review and

meta-analysis of 73 observational studies demonstrated that women with preeclampsia had around two-fold increased risk of cardiovascular and cerebrovascular disease, in addition to over double the risk of cardiovascular death compared with those with previous normotensive pregnancy [38]. Similarly, in parous participants without prior cardiovascular disease enrolled within the Nurses' Health Study II, women with hypertensive disorders of pregnancy in their first pregnancy had a 63% higher hazard of later cardiovascular disease compared with normotensive pregnancies [39]. The increase in cardiovascular disease was consistent in women with gestational hypertension or preeclampsia, though preeclampsia conferred a larger hazard. We recently applied Mendelian randomization to corroborate these observational data and revealed that genetically predicted hypertensive disorders of pregnancy likely causally associate with risk of coronary artery disease and stroke [40]. Ongoing trials aimed at defining clear optimal antenatal blood pressure targets for different clinical situations (e.g. based on preexisting hypertension, preeclampsia, obstetric risk level) are a key priority for the improvement of both obstetric outcomes and the lifelong health of parous women.

In conclusion, this study illuminates the effects of genetically predicted hypertensive indices, namely SBP, DBP and PP, on various adverse outcomes of pregnancy. Higher hypertensive indices may be useful to identify women whose pregnancies might benefit from enhanced surveillance and eventually therapeutic intervention. The results stress the key importance of blood pressure management by highlighting the importance of all three blood pressure indices as major direct drivers of multiple adverse outcomes of pregnancy. Further research elucidating optimal blood pressure targets in different clinical situations is a key priority.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the participants and investigators of the FinnGen project, UK Biobank and the International Consortium of Blood Pressure Genome Wide Association Studies.

This study was supported by Imperial National Institute for Health Research (NIHR) Biomedical Research Centre for RKR, NIHR Academic Clinical Fellowship for M.A., NIHR Cambridge Biomedical Research Centre BRC-1215-20014 for S.B., Imperial NIHR Biomedical Research Centre funding for F.S.N.

British Heart Foundation (RG/F/22/110078 and RE/18/4/34215 for F.S.N.).

All other authors report no relevant funding.

This work has been accepted for presentation at the American College of Cardiology Annual Scientific Sessions 2023.

Conflicts of interest

The authors report no relevant disclosures or conflicts of interest.

REFERENCES

1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 2018; 72:24–43.
2. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *BMJ* 2014; 348:g2301.
3. Ananth CV, Savitz DA, Williams MA. Placental abruption and its association with hypertension and prolonged rupture of membranes: a methodologic review and meta-analysis. *Obstet Gynecol* 1996; 88:309–318.
4. Sheiner E, Sarid L, Levy A, Seidman DS, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. *J Matern Fetal Neonatal Med* 2005; 18:149–154.
5. Ardissino M, Slob EAW, Millar O, Reddy RK, Lazzari L, Patel KHK, et al. Maternal hypertension increases risk of preeclampsia and low fetal birthweight: genetic evidence from a Mendelian Randomization Study. *Hypertension* 2022; 79:588–598.
6. Ardissino M, Slob EAW, Rajasundaram S, Reddy RK, Woolf B, Girling J, et al. Safety of beta-blocker and calcium channel blocker antihypertensive drugs in pregnancy: a Mendelian randomization study. *BMC Med* 2022; 20:288.
7. Magee LA, von Döbeln P, Rey E, Ross S, Szatalos E, Murphy KE, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015; 372:407–417.
8. Tita AT, Szychowski JM, Boggess K, Dugoff L, Sibai B, Lawrence K, et al. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med* 2022; 386:1781–1792.
9. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension* 2001; 37:869–874.
10. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, et al. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. *Circulation* 2005; 111:1121–1127.
11. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR Statement. *JAMA* 2021; 326:1614–1621.
12. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, et al. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018; 50:1412–1425.
13. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; 7:e34408.
14. Kurki M, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner K, et al. FinnGen: unique genetic insights from combining isolated population and national health register data. *medRxiv* 2022. Available at: <https://www.medrxiv.org/content/10.1101/2022.03.03.22271360v1>.
15. Rees JMB, Wood AM, Dudbridge F, Burgess S. Robust methods in Mendelian randomization via penalization of heterogeneous causal estimates. *PLoS One* 2019; 14:e0222362.
16. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol* 2017; 32:377–389.
17. Yavorska OO, Burgess S. MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol* 2017; 46:1734–1739.
18. Gan B, Wu X, Lu L, Li X, Li J. The value of prenatal first systolic blood pressure can predict severe preeclampsia and birth weight in patients with preeclampsia. *Front Med (Lausanne)* 2021; 8:771738.
19. Ueda A, Hasegawa M, Matsumura N, Sato H, Kosaka K, Abiko K, et al. Lower systolic blood pressure levels in early pregnancy are associated with a decreased risk of early-onset superimposed preeclampsia in women with chronic hypertension: a multicenter retrospective study. *Hypertens Res* 2022; 45:135–145.
20. Gunnarsdottir J, Akhter T, Högberg U, Cnattingius S, Wikström AK. Elevated diastolic blood pressure until mid-gestation is associated with preeclampsia and small-for-gestational-age birth: a population-based register study. *BMC Pregnancy Childbirth* 2019; 19:186.
21. Thadhani R, Ecker JL, Kettyle E, Sandler L, Frigoletto FD. Pulse pressure and risk of preeclampsia: a prospective study. *Obstet Gynecol* 2001; 97:515–520.
22. Hale S, Choate M, Schonberg A, Shapiro R, Badger G, Bernstein IM. Pulse pressure and arterial compliance prior to pregnancy and the development of complicated hypertension during pregnancy. *Reprod Sci* 2010; 17:871–877.

23. Bartsch E, Medcalf KE, Park AL, Ray JG, Group HRoP-eI. Clinical risk factors for preeclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 2016; 353:i1753.
24. Bullarbo M, Rylander R. Diastolic blood pressure increase is a risk indicator for preeclampsia. *Arch Gynecol Obstet* 2015; 291:819–823.
25. Roberts DJ, Post MD. The placenta in preeclampsia and intrauterine growth restriction. *J Clin Pathol* 2008; 61:1254–1260.
26. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation* 2011; 123:2856–2869.
27. Hecht JL, Zsengeller ZK, Spiel M, Karumanchi SA, Rosen S. Revisiting decidual vasculopathy. *Placenta* 2016; 42:37–43.
28. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? *J Clin Invest* 1997; 99:2152–2164.
29. Kitzmiller JL, Watt N, Driscoll SG. Decidual arteriopathy in hypertension and diabetes in pregnancy: immunofluorescent studies. *Am J Obstet Gynecol* 1981; 141:773–779.
30. Frusca T, Morassi L, Pecorelli S, Grigolato P, Gastaldi A. Histological features of uteroplacental vessels in normal and hypertensive patients in relation to birthweight. *Br J Obstet Gynaecol* 1989; 96:835–839.
31. Zhang J, Villar J, Sun W, Merialdi M, Abdel-Aleem H, Mathai M, et al. Blood pressure dynamics during pregnancy and spontaneous preterm birth. *Am J Obstet Gynecol* 2007; 197:162.e1–6.
32. Madan J, Chen M, Goodman E, Davis J, Allan W, Dammann O. Maternal obesity, gestational hypertension, and preterm delivery. *J Matern Fetal Neonatal Med* 2010; 23:82–88.
33. Dunne J, Tessema GA, Pereira G. The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study. *BJOG* 2022; 129:890–899.
34. Ananth CV, Peltier MR, Kinzler WL, Smulian JC, Vintzileos AM. Chronic hypertension and risk of placental abruption: is the association modified by ischemic placental disease? *Am J Obstet Gynecol* 2007; 197:273.e1–7.
35. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. *Ann Epidemiol* 2010; 20:524–531.
36. Saraswat L, Bhattacharya S, Maheshwari A. Maternal and perinatal outcome in women with threatened miscarriage in the first trimester: a systematic review. *BJOG* 2010; 117:245–257.
37. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; 303:2043–2050.
38. Dall'Asta A, D'Antonio F, Saccone G, Buca D, Mastantuoni E, Liberati M, et al. Cardiovascular events following pregnancy complicated by preeclampsia with emphasis on comparison between early- and late-onset forms: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2021; 57:698–709.
39. Stuart JJ, Tanz LJ, Rimm EB, Spiegelman D, Missmer SA, Mukamal KJ, et al. Cardiovascular risk factors mediate the long-term maternal risk associated with hypertensive disorders of pregnancy. *J Am Coll Cardiol* 2022; 79:1901–1913.
40. Rayes B, Ardissino M, Slob EAW, Patel KHK, Girling J, Ng FS. Association of hypertensive disorders of pregnancy with future cardiovascular disease. *JAMA Netw Open* 2023; 6:e230034.