Hypertension

ORIGINAL ARTICLE

Maternal Hypertension Increases Risk of Preeclampsia and Low Fetal Birthweight: Genetic Evidence From a Mendelian Randomization Study

Maddalena Ardissino, Eric A.W. Slob, Ophelia Millar, Rohin K. Reddy, Laura Lazzari, Kiran Haresh Kumar Patel, David Ryan, Mark R. Johnson, Dipender Gill*, Fu Siong Ng*

BACKGROUND: Maternal cardiovascular risk factors have been associated with adverse maternal and fetal outcomes. Given the difficulty in establishing causal relationships using epidemiological data, we applied Mendelian randomization to explore the role of cardiovascular risk factors on risk of developing preeclampsia or eclampsia, and low fetal birthweight.

METHODS: Uncorrelated single-nucleotide polymorphisms associated systolic blood pressure (SBP), body mass index, type 2 diabetes, LDL (low-density lipoprotein) with cholesterol, smoking, urinary albumin-to-creatinine ratio, and estimated glomerular filtration rate at genome-wide significance in studies of 298 957 to 1 201 909 European ancestry participants were selected as instrumental variables. A 2-sample Mendelian randomization study was performed with primary outcome of preeclampsia or eclampsia (PET). Risk factors associated with PET were further investigated for their association with low birthweight.

RESULTS: Higher genetically predicted SBP was associated increased risk of PET (odds ratio [OR] per 1-SD SBP increase 1.90 [95% CI=1.45–2.49]; P=3.23×10^{-6}) and reduced birthweight (OR=0.83 [95% CI=0.79–0.86]; P=3.96×10^{-18}), and this was not mediated by PET. Body mass index and type 2 diabetes were also associated with PET (respectively, OR per 1-SD body mass index increase =1.67 [95% CI=1.44–1.94]; P=7.45×10^{-12}; and OR per logOR increase type 2 diabetes =1.11 [95% CI=1.04–1.19]; P=1.19×10^{-3}), but not with reduced birthweight.

CONCLUSIONS: Our results provide evidence for causal effects of SBP, body mass index, and type 2 diabetes on PET and identify that SBP is associated with reduced birthweight independently of PET. The results provide insight into the pathophysiological basis of PET and identify hypertension as a potentially modifiable risk factor amenable to therapeutic intervention. **(*Hypertension*. 2022;79:588–598. DOI: 10.1161/HYPERTENSIONAHA.121.18617.)** • **Supplemental Material**

Key Words: birth weight ■ blood pressure ■ body mass index ■ preeclampsia ■ risk factors

Cardiovascular risk factors, such as elevated blood pressure (BP), dyslipidemia, and type 2 diabetes (T2D), increase in prevalence with age. With the steady increase in maternal age in the past 4 decades, combined with the global rise in obesity, there has been an increase in pregnancies among women with preexisting cardiovascular risk factors.[1] For this reason, investigating the effect of maternal cardiovascular risk profiles on outcomes of pregnancy, both in terms of maternal and fetal outcomes, is becoming increasingly relevant.[1–3]

Hypertensive disorders of pregnancy are the leading cause of maternal and fetal morbidity globally. Among the hypertensive disorders of pregnancy, preeclampsia and eclampsia (PET) are especially harmful. Not only do they adversely affect maternal health leading to risk of death and long-term organ damage, they are also associated

Correspondence to: Fu Siong Ng, Imperial Centre for Translational and Experimental Medicine, National Heart and Lung Institute, Imperial College London, 4th Floor, Hammersmith Campus, Du Cane Rd, London W12 0NN, United Kingdom. Email f.ng@imperial.ac.uk
*D. Gill and F.S. Ng are joint senior authors.
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NOVELTY AND RELEVANCE

What Is New?

Past research has identified observational associations between body mass index, systolic blood pressure (SBP), LDL-C (low-density lipoprotein cholesterol), smoking, type 2 diabetes, urinary albumin-to-creatinine ratio and glomerular filtration rate and risk of preeclampsia or eclampsia (PET). This study uses Mendelian randomization to explore the causal pathways underlying these observational associations. We found evidence to support that genetically predicted body mass index, type 2 diabetes, and SBP were causally associated with a higher risk of developing PET. Genetically predicted SBP was also associated with lower birthweight, although multivariable MR did not identify PET as a mediator in this relationship.

What Is Relevant?

The results are of clinical significance, as they imply that women with high genetically predicted body mass index, type 2 diabetes risk, and SBP (as indicated by personal or family history) are at greater risk of PET. Furthermore, children of women with personal or family history of hypertension are at risk of low birthweight, regardless of whether the mother develops PET. This causal association may be explained by a common genetic predisposition to higher vascular reactivity and endothelial dysfunction that underlies both pathologies. Further study on the impact of BP lowering on PET and child birthweight is warranted.

Clinical/Pathophysiological Implications?

We explored the previously reported associations between cardiovascular risk factors with adverse maternal and fetal outcomes using MR. Our results show that higher genetically predicted body mass index, type 2 diabetes, and SBP were associated with higher risk of PET. SBP was also associated with lower birthweight of the first-born child, and this relationship was not mediated by PET.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
CARPREG	Cardiac Disease in Pregnancy
CHIPS	Control of Hypertension in Pregnancy Study
eGFR	estimated glomerular filtration rate
LDL-C	low density lipoprotein cholesterol
MR	Mendelian randomization
MR-Egger	Mendelian randomization Egger
MR-PRESSO	Mendelian Randomization Pleiotropy Residual Sum and Outlier
OR	odds ratio
PET	preeclampsia or eclampsia
SBP	systolic blood pressure
SNP	single-nucleotide polymorphism
T2D	type 2 diabetes
uACR	urinary albumin-to-creatinine ratio

with preterm birth and low birthweight, which in turn are negative predictors of the child's future health and cardiovascular risk.[4,5]

Cardiovascular risk factors, such as elevated body mass index (BMI),[6,7] BP,[6,7] LDL-C (low-density lipoprotein cholesterol),[7] T2D,[6,7] and renal dysfunction,[8,9] have all been observationally identified as risk factors for hypertensive disorders of pregnancy. Cardiovascular risk factors themselves are also associated with adverse fetal outcomes, including higher risk of preterm birth,[10,11] low birthweight, neonatal morbidity[12,13] and, in the long-term, worse cardiometabolic profiles.[14] However, despite the wealth of retrospective evidence, it is difficult to establish a causal relationship between these cardiovascular risk factors and adverse maternal and fetal outcomes. Conclusive causal relationships are difficult to establish on the basis of observational evidence alone, due to the potential for residual confounding, due to unmeasured or unmeasurable factors, in these study designs. Even with careful adjustment for measured confounders, several unmeasurable factors such as health education, engagement with health care and lifestyle behaviors may bias causal estimates.

The Mendelian randomization (MR) paradigm leverages genetic variants predicting variation in an exposure to explore causal effects of that exposure on an outcome. At a practical level, the approach explores associations of genetically predicted levels of an exposure with the outcome. Since alleles are randomly distributed during meiosis and conception, this helps eliminate confounding from environmental factors, similar to randomization in a clinical trial. We, therefore, performed MR to investigate the effect of traditional cardiovascular risk factors on the development of PET and its downstream effect child birthweight.

METHODS

Ethical Approval, Data Availability, and Reporting

All data used in this study are publicly available. All original studies obtained written, informed participant consent

for use of the presented data. The paper is reported on the basis of recommendations by the Strengthening the Reporting of Observational Studies in Epidemiology using MR guidelines.[15] All statistical analyses were performed using R version 4.0.4 (2021-02-15)[16] using the TwoSampleMR[17] and Mendelianrandomization packages.[18]

Data Sources

For the primary analyses, genetic association estimates for BMI were obtained from Pulit et al's[19] genome-wide association study including 806 834 patients of European ancestry. Genetic association estimates for systolic blood pressure (SBP) and LDL-C (low-density lipoprotein cholesterol) were obtained from the Neale lab second release analysis of UK Biobank data, respectively on 340 159 and 343 621 patients of European ancestry (http://www.nealelab.is/uk-biobank/). Genetic associations for T2D were obtained from Mahajan et al's[20] investigation on 289 957 individuals of European ancestry (48 286 cases and 250 671 controls). Smoking genetic association estimates were obtained from Wootton et al's[21] investigation of 462 690 European ancestry individuals on whom a smoking index was calculated to quantify lifetime exposure to smoking. Genetic association estimates for urinary albumin-to-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) estimated by creatinine were obtained respectively from Teumer et al's[22] study on 547 361 individuals and Stanzick et al's[23] genome-wide association study on 1 201 909 individuals, both of European ancestry. The genetic association estimates for the primary outcome of PET were extracted from the analysis of the FinnGen consortium data's third release (https://finngen.gitbook.io/documentation) using the phenotype of PET, which included 3903 cases and 114 735 controls of Finnish ancestry. The secondary outcome of birthweight was investigated using genetic association estimates for weight of the first-born child from the Neale lab second release analysis of UK Biobank data (http://www.nealelab.is/uk-biobank/) on 155 202 individuals from the UK Biobank. Details of population characteristics for each of these studies are available in the original publications and websites. Studies were chosen such that there is no sample overlap between the exposure and outcome data sets. A summary table for all the data used for the analyses is outlined in Table S1.

Instrumental Variable Selection

Instrumental variable single-nucleotide polymorphisms (SNPs) were selected if they were associated with the exposure of interest in the respective genome-wide association study at genome-wide significance ($P<5\times10^{-8}$) and if they were in pair-wise linkage disequilibrium at $r^2<0.001$. The SNPs explained 15.1% of the variance for SBP, 32.7% of the variance for BMI, 8.3% of the variance for LDL-C, 18.0% of the variance for T2D, 2% of the variance for smoking index, 4.3% of the variance for uACR, and 9.8% of the variance for eGFR. Estimates of variance explained were obtained from the respective original study publications for BMI, smoking, T2D, uACR, and eGFR and from the Neale lab heritability browser (https://nealelab.github.io/UKBB_ldsc/) for SBP and LDL-C. These heritability estimates were used in a power calculation using the mRnd online power calculator (https://shiny.cnsgenomics.com/mRnd/).[24] The analyses had a power of 80% to detect a true MR estimate for the outcome of PET, smaller and greater the following odds ratios (ORs), respectively: BMI 0.88 and 1.22, SBP 0.82 and 1.18, LDL-C 0.76 and 1.24, T2D 0.84 and 1.17, smoking 0.50 and 1.51, uACR 0.89 and 1.11, and eGFR 0.95 and 1.05.

Statistical Analysis

The flowchart for the statistical analysis plan is displayed in Figure 1. For the variants selected as genetic instruments, genetic association summary statistics were used to investigate the causal association between the exposure and the outcome, in a 2-sample MR design. Inverse-variance weighted MR with multiplicative random effects[25] was used as the primary analysis method for all models to estimate the association between the genetically predicted risk factors and PET risk.[26] Results are presented as ORs with respective 95% CIs.

The inverse-variance weighted MR approach assumes that instrumental variables are not associated with confounder traits of the association between the risk factor and the outcome and that the instrumental variables are only associated with the outcome through their association with the risk factor. In situations where genetic variants have effects multiple parallel biological pathways and subsequent phenotypes, these assumptions are violated. This is termed horizontal pleiotropy. Three sensitivity analyses, including MR-Egger regression,[27] the weighted median,[28] and Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO),[29] were performed to explore this. We opted for these 3 analyses as they operate in different ways and rely on different assumptions for valid inferences to assess the reliability of MR analyses.[30] MR-Egger regression produces an estimate of MR effects that accounts for directional pleiotropy by introducing an intercept in the weighted regression model. The intercept can detect pleiotropy by a *P* value. After correcting for pleiotropic effects under the Instrument Strength Independent of Direct Effects assumption, MR-Egger provides robust effect estimates at the cost of statistical power.[27] The weighted median method can provide consistent estimates assuming at least half the weight is derived from valid SNPs. While the 2 previous methods rely on different consistency assumptions, the MR-PRESSO analysis can detect outlying SNPs and is able to provide consistent casual estimates after removing the (possible) outliers assuming the remaining SNPs are valid.

For any cardiovascular risk factors that were significantly associated with PET risk in our MR analyses, we further performed analysis investigating birthweight of the first child as an outcome. If the risk factor was also associated with lower birthweight in MR, we investigated the proportion of this that is mediated by PET using a summary data multivariable MR.[31] In this analysis, the variant-birthweight genetic association estimates were regressed on the variant-exposure and variant-PET estimates weighted for the precision of the variant-birthweight association, with the intercept fixed to zero. If the effect estimate is attenuated after adjustment for PET, the proportion of this relationship mediated by PET can be calculated as the difference between the total unadjusted effect estimate of the risk factor on birthweight and the direct effect estimate of the risk factor on birthweight adjusted for PET, and dividing this by the total unadjusted effect estimate of the risk factor on birthweight.[32]

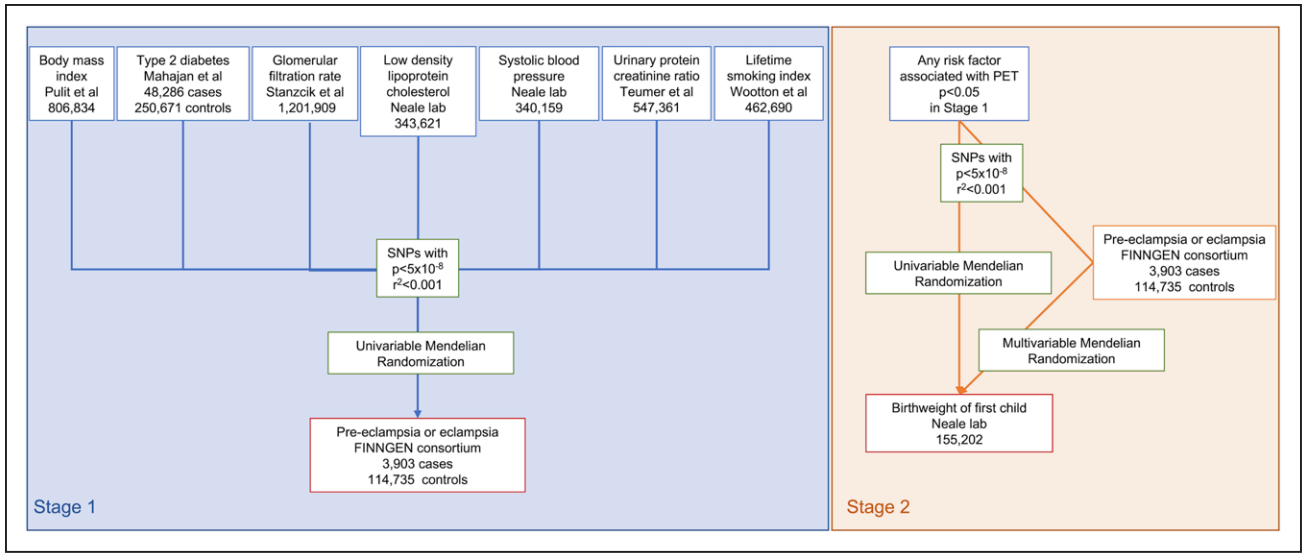

Figure 1. Data acquisition and analysis flowchart.
PET indicates preeclampsia or eclampsia; and SNP, single-nucleotide polymorphism.

RESULTS

Cardiovascular Risk Factors and PET

The risk of PET was greater in patients with higher genetically predicted BMI (OR per 1-SD increase in BMI: 1.67 [95% CI=1.44–1.94]; P=7.45×10^{-12}), higher genetically predicted T2D (OR per logOR increase in T2D risk 1.11 [95% CI=1.04–1.19]; P=1.19×10^{-3}) and higher genetically predicted SBP (OR per 1-SD increase in SBP 1.90 [95% CI=1.45–2.49]; P=3.23×10^{-6}) on the primary analysis, as shown in Figure 2.

Sensitivity analyses with weighted median MR, MR-Egger, and MR-PRESSO produced consistent results for all 3 exposures, identifying no evidence of significant pleiotropy or outliers: BMI (weighted median estimate OR=1.72 [95% CI=1.38–2.14]; MR-Egger

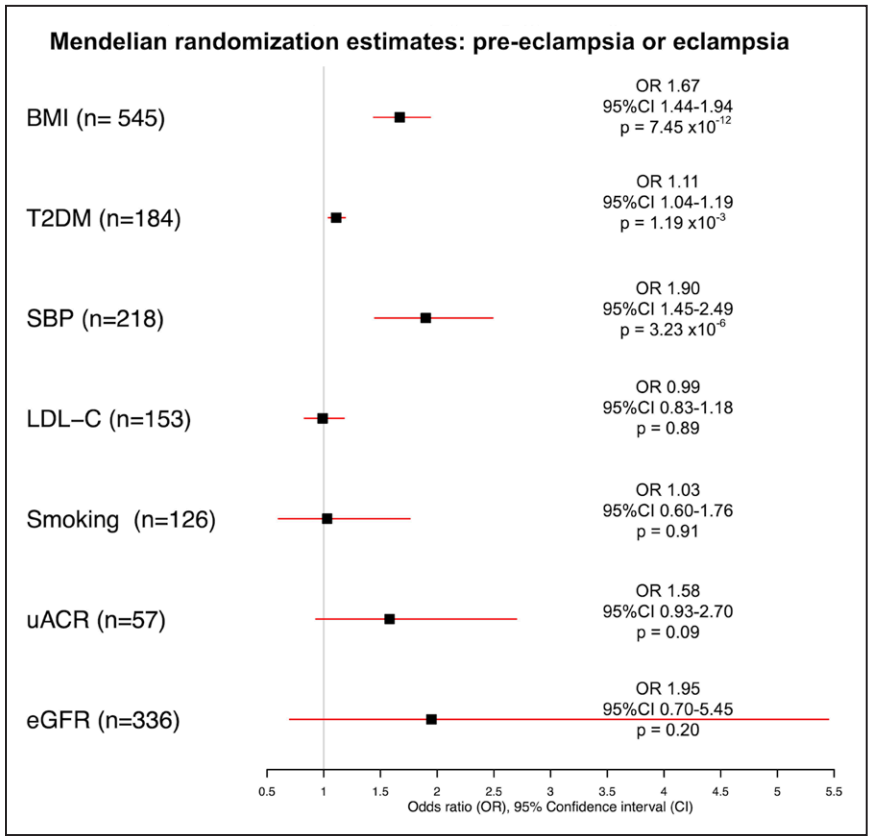

Figure 2. Mendelian randomization inverse-variance weighted estimates for effect of genetically predicted body mass index (BMI), type 2 diabetes (T2D), systolic blood pressure (SBP), LDL-C (low-density lipoprotein cholesterol), smoking, urinary albumin-to-creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR) on the outcome of preeclampsia or eclampsia.
OR indicates odds ratio.

intercept 0.00 [95% CI=−0.01 to 0.01]; *P*=0.96; MR-PRESSO outliers identified =0), T2D (weighted median estimate OR=1.13 [95% CI=1.02–1.25]; MR-Egger intercept −0.00 [95% CI=−0.01 to 0.01]; *P*=0.42; MR-PRESSO outliers identified=0) and SBP (weighted median estimate 2.27 [95% CI=1.62–3.16]; MR-Egger intercept −0.02 [95% CI=−0.03 to 0.00]; *P*=0.06; MR-PRESSO outliers identified=3, *P* distortion=0.50). The effect estimates from the sensitivity analyses are displayed in Figure 3.

As illustrated in Figure 2 and Table 1, genetically predicted LDL-C, smoking, uACR, or eGFR were not associated with PET: OR per 1-SD increase in LDL-C: 0.99 (95% CI=0.83–1.18), *P*=0.89; OR per 1-SD increase in lifetime smoking index: 1.03 (95% CI=0.60–1.76), *P*=0.91; OR per 1-SD increase in uACR: 1.58 (95% CI=0.93–2.70), *P*=0.09; and OR per 1-SD increase in eGFR 1.95 (95% CI=0.70–5.45), *P*=0.20. Sensitivity analyses for each risk factor are displayed in Figure 3.

Birthweight of the First Child

The relationship between genetically predicted BMI, T2D, and SBP and birthweight was investigated as these were the risk factors significant in the primary outcome analysis for PET. Genetically predicted BMI was not associated with birthweight of the first child (OR per 1-SD increase in BMI: 0.99 [95% CI=0.97–1.02]; *P*=0.52). Genetically predicted T2D was associated with higher birthweight of the first child (OR per increase in logOR

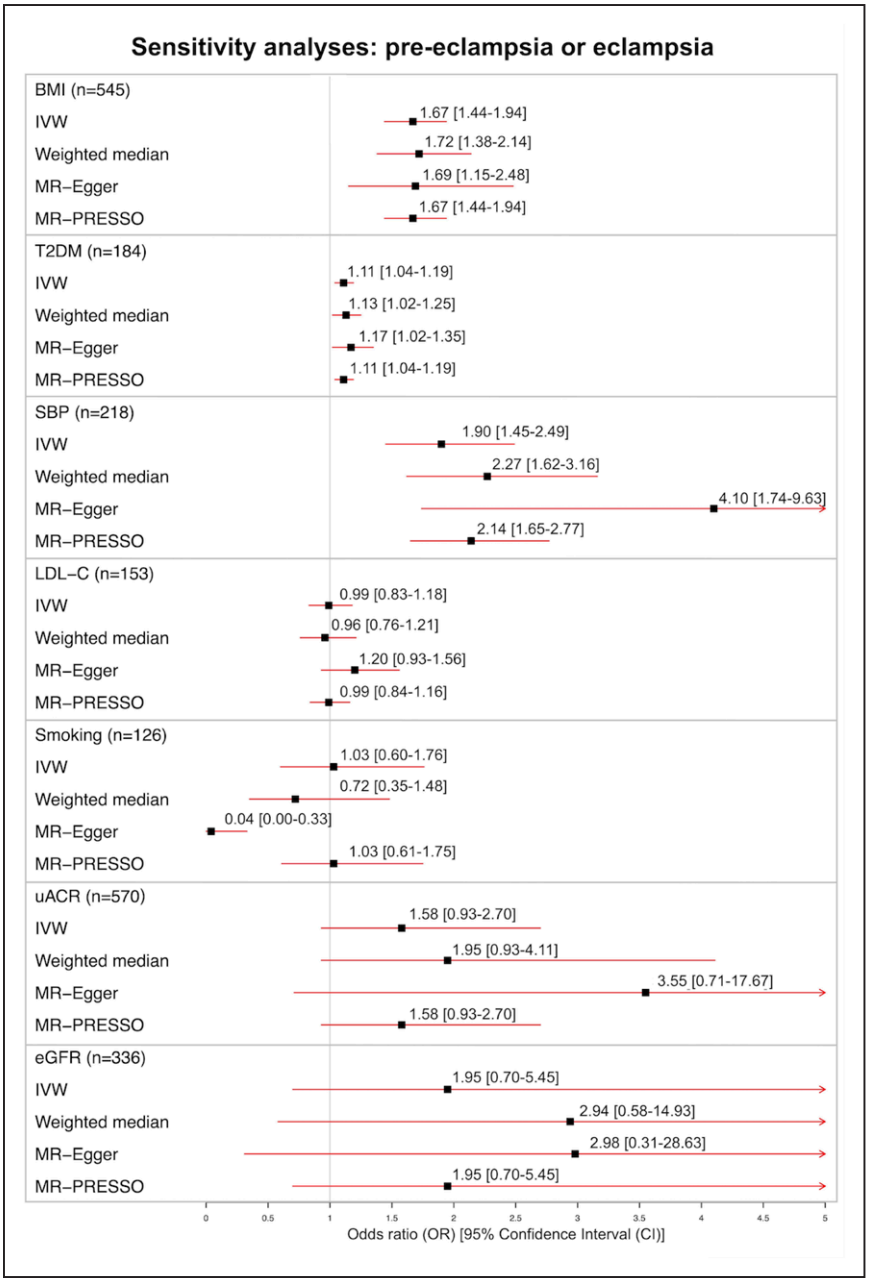

Figure 3. Sensitivity analyses for effect of genetically predicted body mass index (BMI), systolic blood pressure (SBP), LDL-C (low-density lipoprotein cholesterol), type 2 diabetes (T2D), smoking, urinary albumin-to-creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR) on the outcome of preeclampsia or eclampsia: Mendelian randomization Egger (MR-Egger), weighted median, and Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) estimates.
Odds ratios (OR) and 95% CI are presented for every 1-SD increase genetically predicted BMI, SBP, LDL-C, smoking index, uACR, and eGFR; and for every logOR increase in T2D liability. IVW indicates inverse-variance weighted.

Table 1. MR Estimates for Effect of BMI, T2D, SBP, LDL-C, Smoking Index, uACR, and eGFR Investigated on the Primary Outcome of Preeclampsia or Eclampsia

	Method	SNPs	OR	LCI 95%	UCI 95%	*P* value
BMI (1-SD kg/m^2 ↑)	IVW	545	1.67	1.44	1.94	7.45×10^{-12}
	Weighted median		1.72	1.38	2.14	1.94×10^{-6}
	MR-Egger		1.69	1.15	2.48	0.01
	MR-PRESSO		1.67	1.44	1.94	2.02×10^{-11}
T2D (log OR ↑)	IVW	184	1.11	1.04	1.19	1.19×10^{-3}
	Weighted median		1.13	1.02	1.25	0.03
	MR-Egger		1.17	1.02	1.35	0.03
	MR-PRESSO		1.11	1.04	1.19	1.42×10^{-3}
SBP (1-SD mm Hg ↑)	IVW	218	1.90	1.45	2.49	3.23×10^{-6}
	Weighted median		2.27	1.62	3.16	1.49×10^{-6}
	MR-Egger		4.10	1.74	9.63	1.21×10^{-3}
	MR-PRESSO		2.14	1.65	2.77	3.00×10^{-8}
LDL-C (1-SD mg/dL ↑)	IVW	153	0.99	0.83	1.18	0.89
	Weighted median		0.96	0.76	1.21	0.73
	MR-Egger		1.20	0.93	1.56	0.16
	MR-PRESSO		0.99	0.84	1.16	0.85
Smoking (1-SD lifetime smoking ↑)	IVW	126	1.03	0.60	1.76	0.91
	Weighted median		0.72	0.35	1.48	0.37
	MR-Egger		0.04	0.00	0.33	3.27×10^{-3}
	MR-PRESSO		1.03	0.61	1.75	0.91
uACR (1-SD mg/g ↑)	IVW	57	1.58	0.93	2.70	0.09
	Weighted median		1.95	0.93	4.11	0.08
	MR-Egger		3.55	0.71	17.67	0.12
	MR-PRESSO		1.58	0.93	2.70	0.10
eGFR (1-SD mL/min per 1.73 m^2 ↑)	IVW	336	1.95	0.70	5.45	0.20
	Weighted median		2.94	0.58	14.93	0.19
	MR-Egger		2.98	0.31	28.63	0.34
	MR-PRESSO		1.95	0.70	5.45	0.20

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; IVW, inverse-variance weighted with mixed random effects; LCI, lower CI; LDL-C, low-density lipoprotein cholesterol; MR-Egger, Mendelian randomization Egger; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; OR, odds ratio; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes; uACR, urinary albumin-to-creatinine ratio; and UCI, upper CI.

T2D: 1.02 [95% CI=1.00–1.03]; *P*=0.02). Genetically predicted SBP was inversely associated with birthweight of the first child (OR per 1-SD increase in SBP: 0.83 [95% CI=0.79–0.86]; $P=3.96\times10^{-18}$), as displayed in Table 2 and Figure 4.

The findings for SBP were consistent when using weighted median MR (OR=0.83 [95% CI=0.80–0.87]; $P=1.84\times10^{-18}$) and MR-Egger (OR=0.84 [95% CI=0.73–0.96]; *P*=0.01), where no significant pleiotropy was identified (MR-Egger intercept: 0.00 [95% CI=0.00–0.00]; *P*=0.84). Results using MR-PRESSO were also consistent (OR=0.85 [95% CI=0.82–0.88]; $P=1.23\times10^{-16}$) after elimination of 11 outlier SNPs (distortion test *P*=0.08). When adjusting for PET, the relationship between SBP and birthweight remained similar (OR=0.82 [95% CI=0.79–0.87]; $P=4.81\times10^{-14}$), indicating no mediation by PET.

DISCUSSION

In this study, we explored the relationship between cardiovascular risk factors and maternal and fetal outcomes of pregnancy (PET and first child's birthweight) using MR. Our results demonstrate that genetically predicted BMI, T2D, and SBP are associated with a higher risk of developing PET. Genetically predicted SBP demonstrated the strongest effect and was also associated with lower birthweight of the child. Multivariable MR did not identify PET as a mediator in this relationship, indicating that genetically predicted SBP reduces birthweight through pathways independent of PET.

The pathophysiology of PET continues to be debated. Current knowledge supports a disease process that is initiated by abnormal placentation[33] where failure of spiral artery transformation leads to high oxidative stress,

Table 2. MR Estimates for Effect of BMI, T2D, and SBP, Alone and With Adjustment for PET, on the Outcome of Birthweight of the First Child

	Method	SNP number	OR	LCI 95%	UCI 95%	*P* value
BMI (1-SD mm Hg ↑)	IVW	545	0.99	0.97	1.02	0.52
	Weighted median		0.99	0.96	1.03	0.66
	MR-Egger		1.00	0.95	1.06	0.89
	MR-PRESSO		0.99	0.97	1.01	0.43
T2D (logOR ↑)	IVW	195	1.02	1.00	1.03	0.02
	Weighted median		1.01	1.00	1.02	0.10
	MR-Egger		1.03	1.00	1.06	0.06
	MR-PRESSO		1.02	1.01	1.03	3.95×10^{-3}
SBP (1-SD mm Hg ↑)	IVW	219	0.83	0.79	0.86	3.96×10^{-18}
	Weighted median		0.83	0.80	0.87	1.84×10^{-18}
	MR-Egger		0.84	0.73	0.96	0.01
	MR-PRESSO		0.85	0.82	0.88	1.23×10^{-16}
	Multivariable MR adjusted for PET	217	0.82	0.79	0.87	4.81×10^{-14}

BMI indicates body mass index; IVW, inverse-variance weighted with mixed random effects; LCI, lower CI; MR-Egger, Mendelian randomization Egger; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; Multivariable MR, multivariable Mendelian randomization; PET, preeclampsia or eclampsia; SBP, systolic blood pressure; SNP, single-nucleotide polymorphism; T2D, type 2 diabetes; and UCI, upper CI.

hypoperfusion, and ischemia at the materno-fetal interface. In the second stage, an imbalance in circulating angiogenic factors and soluble fms-like tyrosine kinase 1, a ligand trap antagonising vascular endothelial growth factor,[34] results in widespread maternal endothelial lesions, glomerular endotheliosis and dysfunction,[35] leading to the characteristic pattern of progressive thrombomicroangiopathic organ damage. However, not all PET are the same and 2 phenotypes have been described: early (<34 weeks) and late onset (>34 weeks). Early onset PET is characterized by abnormal uterine artery Dopplers, fetal growth restriction, lower cardiac output,[36] and adverse maternal and neonatal outcomes.[37] By contrast, late-onset PET is usually associated with normal or mildly abnormal uterine artery Doppler, a lower risk of fetal involvement, and generally more favorable maternal and child outcomes.[37,38]

Impact of SBP on Maternal and Fetal Outcomes

The results of our study corroborate previous observational evidence on the association between maternal SBP and PET risk,[7] while providing evidence for a causal link using the MR paradigm. We also show an inverse association between genetically predicted SBP and birthweight of the first child. This finding is in line

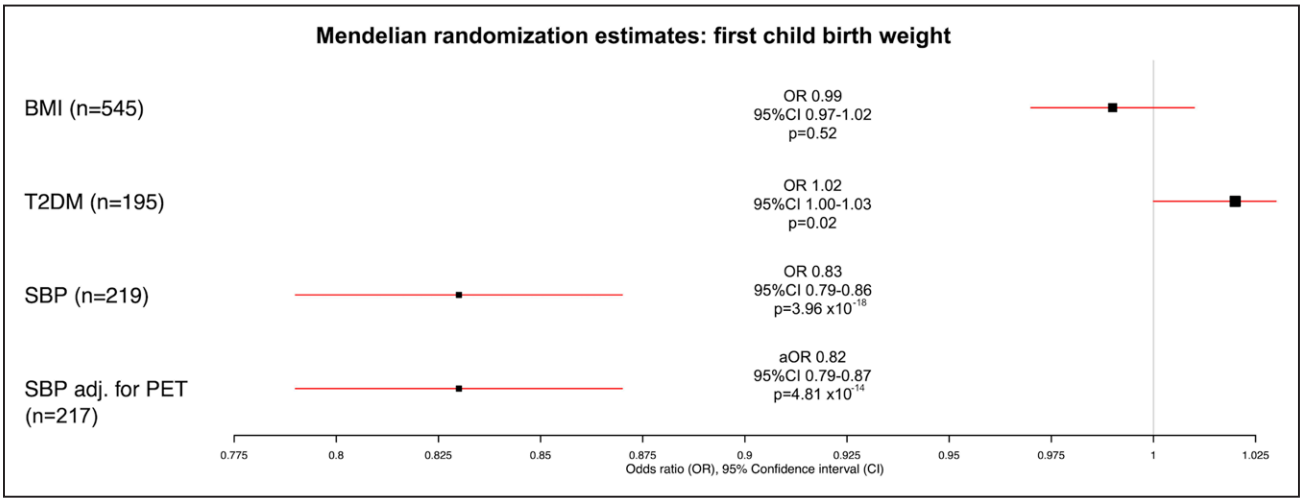

Figure 4. Univariable and multivariable Mendelian randomization estimates for effect of body mass index (BMI), type 2 diabetes (T2D), and systolic blood pressure (SBP), alone and with adjustment for preeclampsia or eclampsia (PET) on the outcome of birthweight of first child for mediation analysis.
Odds ratios (ORs) and 95% CI are presented for every 1-SD increase genetically predicted BMI and SBP and for every logOR increase in T2D liability. Adjusted OR (aOR) and 95% CI is presented for every 1-SD increase genetically predicted SBP adjusted for the effect of every logOR increase in PET risk on birthweight.

with the higher risk of PET we identified in this study. Previous studies have shown that PET, especially if early onset, is associated with higher rates of growth restriction and therefore lower birthweight.[39] However, in our study, we found that PET was not a major mediator in the relationship between SBP and low birthweight. This is of clinical significance, as it implies that women with high genetically predicted SBP (as indicated by personal or family history) are at risk of low birthweight regardless of whether they develop PET.

The causal association between higher SBP and risk of PET that was identified in this study may be explained by a common genetic predisposition to higher vascular reactivity, propensity for atherosclerosis and endothelial dysfunction that underlies both pathologies. Women who suffer from PET are known to develop hypertension at higher rates and younger ages (≈30–40 versus ≈50–60) than women who have a normal pregnancy,[40] and to be at higher risk of developing metabolic syndrome.[41] Concordant with this, multiple studies have identified higher rates of long-term major cardiovascular events in women who have a background of PET when compared with those with normal pregnancy.[42–44]

Maternal hypertension has been recognized as a risk factor for low birthweight in previous studies.[45] There are many possible mechanisms for this. First, higher maternal prepregnancy SBP has been associated with higher risk of preterm birth, which may explain a part of the association with low birthweight.[46] Second, for women with already manifest hypertension at the time of the pregnancy, high BP is known to increase endothelial dysfunction and decrease placental perfusion, and this may contribute to low birthweight due to poor placental blood flow in the early stages of pregnancy.[47] However, it is important to note that some studies have failed to identify an association between prepregnancy BP and birthweight.[48] This gives rise to an important possibility. In view of the naturally young age of the cohort at risk of PET, typically in the range of 20 to 45 years, many may not have manifest hypertension despite having a genetic risk for higher SBP. It is, therefore, possible that low birthweight of the child, even in women without diagnosed hypertension at the time of pregnancy, is an early manifestation of the endothelial and vascular dysfunction which underlies the pathophysiology of systemic arterial hypertension. This is an important possibility, especially in view of previous studies that have identified that delivery of an infant of low birthweight is associated with higher risk of maternal major cardiovascular events and cardiovascular death in later life.[49] This could imply that women who have child that is born with a low birthweight could be an important cohort to target for primary prevention of cardiovascular disease.

Tight BP control in hypertensive disorders of pregnancy has been shown to reduce the risk of maternal end-organ damage and adverse perinatal outcomes for the baby.[50,51] However, it remains unclear whether a tight approach to maternal BP control actually reduces PET risk,[52] and whether it benefits birthweight. Paradoxically, observational evidence has shown an association between tight pharmacological BP reduction in pregnancy and decreased birthweight of the baby,[53,54] even in the setting of gestational hypertension.[55] In the CHIPS trial (Control of Hypertension in Pregnancy Study), randomization of women with nonsevere gestational hypertension to the tighter BP control group (diastolic BP aim <85 mm Hg versus <100 mm Hg) did not reduce the risk of PET, and when randomized before 24 weeks of gestation led to increased risk of <10th centile birthweight of the baby. This does not refute the benefits of adequate BP control, but it identifies that there may be a U-shaped, and not linear, association between BP and birthweight. This is a conceivable hypothesis since excessive reductions in BP may reduce placental blood flow. Of further interest, in the study, this association was not present in women randomized after 24 weeks of gestation,[56] highlighting a possible time-dependent effect. Overall, the results of this trial are the only randomized evidence providing information on the targets and approach to BP control in pregnancy. Our results highlight the requirement for further research to characterize the optimal treatment, timing and targets for the management of hypertension both before, and during pregnancy.

Impact of BMI on Maternal and Fetal Outcomes

The association between BMI and PET that we found in this study is in line with past observational evidence from cohort studies and their meta-analyses.[10,57,58] For example, in the recent CARPREG cohort study (Cardiac Disease in Pregnancy), as many as 8% of women with obesity developed PET.[57] The pathophysiology behind this risk increase is likely multifactorial, with contributions from metabolic, inflammatory and placentation factors that differ with higher BMI.[59] In contrast, high BMI was not associated with birthweight of the first child in this study. The lack of association has multiple potential explanations. First, as well as causing PET, high BMI is associated with gestational diabetes, which is a major cause of increased birthweight. It is possible that this association, which is not accounted for in our study, compensates for any potential reduction in birthweight that may be mediated by the association between BMI and PET. Second, genetic predisposition to higher BMI is likely to contribute to higher birthweight if the weight is not standardized to the expected weight of the baby when considering parental BMI. Finally, high BMI is more commonly associated with late-onset PET, in which risk of fetal growth restriction is lower, perhaps explaining the lack of evidence in our analyses exploring the association between BMI and birthweight.

Impact of T2D on Maternal and Fetal Outcomes

We observed a positive association between genetically predicted T2D and PET, in line with past observational evidence.[6] We also observed a positive association between genetically predicted T2D and birthweight. This is biologically plausible, as maternal diabetes (both preexisting and gestational) is known to cause high birthweight.[60,61] It is important to consider that despite the overall association between higher T2D liability and increased birthweight, this represents an overall estimate that balances factors that may contribute to low birthweight as well as those that contribute to high birthweight in women with high T2D risk. For example, women with high genetic liability to T2D are both at risk of PET (which is associated with reduced birthweight) and gestational diabetes (which is associated with increased birthweight). The predisposition for gestational diabetes may outweigh the one for PET, tilting the overall balance towards high birthweight and masking potential opposite effects of PET. Due to the lack of individual-level data, this could not be further explored in this study. Overall, our results indicate that T2D was not associated with reduced birthweight, but this should not be interpreted to indicate that women with T2D who develop PET are not at risk of delivering a baby with low birthweight. Similar to BMI, the impact of T2D liability on birthweight specifically in women who develop PET should be further studied.

LDL-C, Smoking, uACR, and eGFR

Contrary to previous observational studies, we did not find significant associations between genetically predicted LDL-C, smoking, uACR, and eGFR with the risk of developing PET.[6,7,10,57,58] It is important to note, however, that the power for these analyses was limited. The results of this study, therefore, do not exclude an association between these risk factors and PET that are smaller than the specific thresholds that we had power to detect. Furthermore, it is important to note that the MR paradigm assumes a linear dose-response relationship, which may not be valid for variables such as eGFR and uACR as it may be that only below a certain threshold eGFR (or above a certain threshold uACR) clinical sequelae are observed.

Study Limitations

Unfortunately, we could not explore some clinically important questions due to limitations in data availability. First, due to lack of publicly available genome-wide association study summary data, we could not assess the association between the cardiovascular risk factors and preterm birth, which would be important to explain the mechanisms of low fetal birthweight. Second, our summary data MR study design does not allow for detailed clinical characterization of study participants, because it does not consider individual participant data. As a result, we were not able to perform stratified analyses that separately considered early- and late-onset PET. Similarly, we could not make a distinction between preeclampsia and eclampsia in our analyses. Finally, the sources of data for this study mainly concentrate on European cohorts, and this may impair the generalizability of the study results to women of other ethnicities.

Conclusions

We explored possible causal associations between cardiovascular risk factors with adverse maternal and fetal outcomes using MR. Higher genetically predicted BMI, T2D, and SBP were associated with higher risk of PET. SBP was also associated with lower birthweight of the first-born child, supporting a causal association between these factors. PET was not a major mediator of the association between genetically predicted SBP and lower birthweight of the first-born child.

Perspectives

The results of this study should be considered when assessing and managing women with a personal or family history of obesity, T2D, and hypertension who are planning a pregnancy. Targeted control of elevated BP has an especially important potential to reduce the risk of complications for both the mother and the child.[3,62]

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Affiliations

National Heart and Lung Institute (M.A., O.M., R.K.R., L.L., K.H.K.P., F.S.N.), Division of Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction (M.R.J.), and Department of Biostatistics and Epidemiology, School of Public Health (D.G.), Imperial College London, United Kingdom. Nuffield Department of Population Health, University of Oxford, United Kingdom (M.A.). MRC Biostatistics Unit, University of Cambridge, United Kingdom (E.A.W.S.). St George's University Hospitals NHS Foundation Trust, London, United Kingdom (D.R., D.G.).

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