Hypertension

ORIGINAL ARTICLE

Investigating a Potential Causal Relationship Between Maternal Blood Pressure During Pregnancy and Future Offspring Cardiometabolic Health

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ABSTRACT: Observational epidemiological studies have reported that higher maternal blood pressure (BP) during pregnancy is associated with increased future risk of offspring cardiometabolic disease. However, it is unclear whether this association represents a causal relationship through intrauterine mechanisms. We used a Mendelian randomization (MR) framework to examine the relationship between unweighted maternal genetic scores for systolic BP and diastolic BP and a range of cardiometabolic risk factors in the offspring of up to 29 708 genotyped mother-offspring pairs from the UKB study (UK Biobank) and the HUNT study (Trøndelag Health). We conducted similar analyses in up to 21 423 father-offspring pairs from the same cohorts. We confirmed that the BP-associated genetic variants from the general population sample also had similar effects on maternal BP during pregnancy in independent cohorts. We did not detect any association between maternal (or paternal) unweighted genetic scores and cardiometabolic offspring outcomes in the meta-analysis of UKB and HUNT after adjusting for offspring genotypes at the same loci. We find little evidence to support the notion that maternal BP is a major causal risk factor for adverse offspring cardiometabolic outcomes in later life. **(*Hypertension*. 2022;79:170–177. DOI: 10.1161/HYPERTENSIONAHA.121.17701.)** • **Supplemental Material**

Key Words: adult children ■ blood pressure ■ cardiometabolic risk factors ■ cohort studies ■ genotype ■ pregnancy ■ Mendelian randomization analysis

Observational epidemiological studies using multivariable regression have shown that gestational hypertensive disorders are associated with increased risk of offspring cardiometabolic diseases in later life, including cardiovascular diseases and type 2 diabetes.[1–5] These associations could be due to intrauterine effects (ie, developmental programming), in which case intervening to prevent gestational hypertensive disorders could also lower cardiometabolic risk in the offspring.[6] However, although maternal blood pressure (BP) during pregnancy is associated with offspring cardiometabolic risk factors, in particular offspring BP,[7] sibling studies have indicated that the associations could be explained by confounding due to postnatal environmental factors or inherited genetic variants instead of intrauterine programming.[8–10] Consequently, definitive evidence as to whether increased maternal BP during pregnancy has long-term impacts on offspring cardiometabolic health in human populations is lacking. Understanding this relationship will help determine whether intervening on maternal BP during pregnancy will combat the rising incidence of offspring cardiometabolic diseases in adulthood.

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Novelty and Significance

What Is New?

- Our investigation is the largest genetic study to date to have explored the impact of maternal blood pressure during pregnancy on long-term offspring cardiometabolic health.
- Our analyses used a Mendelian randomization framework to provide a more rigorous assessment of causality.

What Is Relevant?

- Maternal blood pressure during pregnancy is unlikely to cause large increases in the risk of offspring cardiometabolic diseases in later life, including hypertension.
- Understanding this relationship will help determine whether intervening on high maternal blood pressure during pregnancy will combat the rising incidence of offspring cardiometabolic diseases in adulthood.

Summary

Our study suggests that high maternal blood pressure, as proxied by maternal SNPs that influence blood pressure is unlikely to be a key determinant of adverse cardiometabolic outcomes in offspring.

Nonstandard Abbreviations and Acronyms

ALSPAC	Avon Longitudinal Study of Parents and Children
BP	blood pressure
CRP	C-reactive protein
HDL-C	high-density lipoprotein cholesterol
HUNT	Trøndelag Health
IGF-1	insulin-like growth factor 1
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein A
MR	Mendelian randomization
UKB	UK Biobank

Mendelian randomization (MR) is an epidemiological method used to estimate the causal relationship between a modifiable environmental exposure of interest and a medically relevant trait or disease.[11,12] Mendel's Laws of Inheritance (ie, segregation, independent assortment) mean that genetic variants are often less susceptible to confounding and reverse causality than the variables used in traditional observational epidemiological studies.[13] We have previously developed a MR framework to investigate the potential maternal exposures on offspring's health and disease in later life[14] (Figure S1A).

Most previous MR studies investigating the relationship between early life environmental exposures and later-life cardiometabolic traits and diseases have not distinguished between maternal and offspring genetic effects, which has complicated interpretation of the results of such investigations.[15–18] This has partly been due to the paucity of cohorts world-wide with genotyped mother-offspring pairs and offspring of advanced age, hindering the estimation of maternal genetic effects on offspring who have developed cardiometabolic disease. In the current study, we addressed these issues by performing a genetic association study in up to 29 708 genotyped mother-offspring pairs and up to 21 423 father-offspring pairs from the UKB study (UK Biobank)[19] and HUNT study (Trøndelag Health).[20] Specifically, we regressed offspring cardiometabolic risk factors on maternal genetic risk scores (GRSs) for BP while simultaneously conditioning on offspring genotypes at the same loci, thereby accounting for the potential contaminating influences of genetic pleiotropy through the offspring genome.[14] Associations between maternal GRSs and offspring outcomes would be consistent with a causal effect of maternal BP on the offspring outcomes.

METHODS

Data Availability

Human genotype and phenotype data from the UKB on which the results of this study were based were accessed with accession ID 12703 and 53641. The genotype and phenotype data are available upon application to the UKB (http://www.ukbiobank.ac.uk/). Phenotype and genotype data from the ALSPAC (Avon Longitudinal Study of Parents and Children) and HUNT studies are archived centrally with the corresponding cohort studies. Individual-level data can be made available to researchers upon application to the resources. Requirements for data access to the UKB, ALSPAC,[21–23] and the HUNT studies are described at https://www.ukbiobank.ac.uk/, http://www.bristol.ac.uk/alspac/, and www.ntnu.edu/hunt/, respectively.

UKB Study

The UKB study is a study of over 500 000 volunteers (with 5.45% response rate of those invited[24]), recruited from across the United Kingdom at age 40 to 69 years between 2006 and 2010, with a broad range of health-related information and genome-wide genetic data[25] (further details are provided in the Supplemental Material[26,27]). Only individuals of European ancestry were included in the present study (Supplemental Material).

Parent-offspring relationships were inferred by the KING software using genotyping data[28] (Supplemental Material).

After cleaning, there were 4119 mother-offspring pairs and 1829 father-offspring pairs available for analysis (not all offspring had phenotypic data available for each of the cardiometabolic risk factors of interest, so the numbers are smaller for each specific analysis; Table S1).

The HUNT Study

The HUNT is a large population-based study of ≈240 000 participants (with >50% response rate of those invited) with a broad range of health-related information and genome-wide genetic data[20,29] (Supplemental Material[30,31]). Similar to the UKB, parent-offspring pairs were identified using the KING software,[28] reported sex, and date of birth.[32] Only individuals of European ancestry were included in the study (Supplemental Material[33,34]). After cleaning, there were 26 057 mother-offspring pairs and 19 792 father-offspring pairs available for analysis (Table S1).

Offspring Cardiometabolic Risk Factors

The offspring cardiometabolic risk factors included in our analysis were systolic BP, diastolic BP, body mass index, lipid profile (ie, ApoA [Apolipoprotein A], ApoB [Apolipoprotein B], total cholesterol, LDL-C [low-density lipoprotein cholesterol], Lp(a) [lipoprotein A], HDL-C [high-density lipoprotein cholesterol], and triglycerides), glycemic biomarkers (ie, nonfasting glucose, glycated hemoglobin, and IGF-1 [insulin-like growth factor 1]), and other relevant cardiometabolic traits (ie, CRP [C-reactive protein] and urate). Further details of the collection and availability of UKB and HUNT variables are given in the Supplemental Material[35–41] and Table S1.

Selection of BP-Associated single nucleotide polymorphisms (SNPs)

The BP-associated SNPs were identified from external genome-wide association studies performed by the International Blood Pressure Consortium.[35,42–44] The genome-wide association studies of BP used for the selection of instruments did not include participants from the UKB or HUNT studies in the discovery stages, which avoids potential sample overlap with mothers/fathers that were included in the current analysis. Unweighted genetic scores were constructed by summing BP-raising alleles (Supplemental Material[45,46] and Table S2).

We conducted 3 analyses to confirm that the BP-associated SNPs from the general population sample also had similar effects on BP during pregnancy (further details are given in the Supplemental Material[22,47]).

Statistical Analysis

Maternal BP during pregnancy was not physically measured in the UKB or HUNT cohorts; instead, we instrumented this exposure using maternal GRSs for BP. Thus, we directly tested the association between maternal unweighted genetic scores and offspring outcomes in up to 29 708 mother-offspring pairs from UKB and HUNT, adjusting for the offspring's genetic score calculated from the same BP-associated SNPs (Figure S1B).[32] The details of the regression analyses and secondary analyses in mother-offspring pairs are given in the Supplemental Material[48,49] and Table S3.[32,48]

If the effect of maternal BP is operating on offspring via the intrauterine environment, then we would expect no causal relationship in father-offspring pairs. Therefore, we also conducted sensitivity analyses in up to 21 423 father-offspring pairs from the UKB and the HUNT studies to explore the possibility of postnatal effects (Supplemental Material[50]).

We meta-analyzed the results of the primary analyses from the UKB and HUNT studies for each offspring variable using Stouffer Z score which weights each study's contribution by the square root of the sample size; this facilitated meta-analysis of variables that were scaled differently in UKB versus HUNT.[51] Meta-analysis was conducted using R (version 3.5.3). In the case of all analyses, we present *P* values that have not been corrected for multiple testing.

Power Calculation

We calculated the statistical power to detect maternal genetic effects on offspring cardiometabolic risk factors conditional on offspring genotype using the Maternal and Offspring Genetic Effects Power Calculator (https://evansgroup.di.uq.edu.au/MGPC/)[52] (Supplemental Material).

RESULTS

SNPs Associated With BP in Pregnancy

We found strong evidence that our selected BP-associated SNPs from the general population sample have relatively consistent direction of effects on BP during pregnancy and gestational hypertensive disorders in independent cohorts (FinnGen and ALSPAC; Supplemental Material,[53,54] Figure S2 and Tables S4 and S5).

Association Between Maternal Genetic Scores and Later-Life Offspring Traits in UKB and HUNT

The results from the analyses assessing the association between unweighted maternal genetic scores for systolic BP- or diastolic BP-associated SNPs and offspring cardiometabolic traits, after adjusting for offspring genetic scores, in the UKB and HUNT studies are presented in the Table, along with the meta-analysis *P* values. We did not detect any association between maternal unweighted genetic scores and cardiometabolic offspring outcomes in the meta-analysis (Table). Similarly, we did not detect any association in the father-offspring pairs in the meta-analysis, consistent with the absence of a postnatal effect operating (Table S6). The results of the main analyses in individual cohorts (UKB and HUNT) are presented in the Table, and the results of sensitivity analyses are given in Tables S7 through S14.

Power Calculations

Power calculations indicated that we had ≥80% power to detect a maternal genetic effect that explained as little as 0.035% of the variance in the offspring cardiometabolic trait with 29 708 mother-offspring pairs (2-tailed

Table. Associations Between the Maternal Genetic Score for Blood Pressure and Offspring's Traits in UK Biobank and HUNT Studies

Exposure	Offspring's outcomes, units	UK Biobank			HUNT			P_{meta}
		β (SE)	*P* value	N pairs	β (SE)	*P* value	N pairs	
Maternal SBP genetic score*	SBP, mm Hg	0.0339 (0.0569)	0.5516	3756	0.0053 (0.0229)	0.8154	25 948	0.6686
	DBP, mm Hg	−0.0203 (0.0396)	0.6077	3756	0.0041 (0.0154)	0.7886	25 948	0.9472
	BMI, kg/m²	0.0366 (0.0193)	0.0580	3704	0.0001 (0.0002)	0.646	25 952	0.2552
	ApoA, g/L	0.0001 (0.001)	0.9375	3254	NA	NA	NA	NA
	ApoB, g/L	0.0026 (0.0009)	0.0029†	3568	NA	NA	NA	NA
	TC, mmol/L	0.0112 (0.0038)	0.0033†	3582	−0.0003 (0.0015)	0.822	25 589	0.3993
	LDL-C, mmol/L	0.0092 (0.003)	0.0021†	3577	−0.0006 (0.0014)	0.6526	25 536	0.4978
	Lp(a), nmol/L	−0.115 (0.2183)	0.5983	2875	NA	NA	NA	NA
	HDL-C, mmol/L	−0.0001 (0.0013)	0.9662	3263	0 (0.0005)	0.954	25 560	0.9886
	TG, mmol/L	0.0041 (0.002)	0.0419†	3586	−0.0001 (0.0008)	0.9451	25 923	0.5537
	Glucose, mmol/L	−0.0008 (0.0026)	0.7601	3222	0.0003 (0.0003)	0.2921	25 509	0.4009
	HbA1c, mmol/mol	0.0259 (0.0151)	0.0867	3566	−0.0001 (0.0085)	0.9894	16 770	0.4792
	IGF-1, nmol/L	0.0142 (0.0217)	0.5119	3535	NA	NA	NA	NA
	CRP, mg/L	0.0094 (0.0043)	0.0281†	3587	0.0016 (0.0018)	0.3724	22 088	0.1007
	Urate, μmol/L	0.1965 (0.2395)	0.4121	3586	NA	NA	NA	NA
Maternal DBP genetic score	DBP, mm Hg	−0.0249 (0.0378)	0.5102	3756	−0.0102 (0.0148)	0.49	25 948	0.3798
	SBP, mm Hg	0.0087 (0.0545)	0.8727	3756	−0.0285 (0.022)	0.1956	25 948	0.2486
	BMI, kg/m²	0.0392 (0.0185)	0.0339†	3704	−0.0002 (0.0002)	0.3864	25 952	0.8528
	ApoA, g/L	−0.0011 (0.0009)	0.2638	3254	NA	NA	NA	NA
	ApoB, g/L	0.0019 (0.0008)	0.0200†	3568	NA	NA	NA	NA
	TC, mmol/L	0.0068 (0.0036)	0.0614	3582	−0.0001 (0.0014)	0.9689	25 589	0.5560
	LDL-C, mmol/L	0.006 (0.0029)	0.0347†	3577	−0.0003 (0.0013)	0.8466	25 536	0.6000
	Lp(a), nmol/L	−0.1058 (0.2076)	0.6104	2875	NA	NA	NA	NA
	HDL-C, mmol/L	−0.0011 (0.0013)	0.3958	3263	0.0001 (0.0004)	0.8802	25 560	0.9598
	TG, mmol/L	0.0024 (0.0019)	0.2119	3586	0.0003 (0.0007)	0.7018	25 923	0.4026
	Glucose, mmol/L	−0.0013 (0.0025)	0.6113	3222	0.0001 (0.0002)	0.7099	25 509	0.7635
	HbA1c, mmol/mol	0.0237 (0.0144)	0.1011	3566	0.0007 (0.0082)	0.9311	16 770	0.4427
	IGF-1, nmol/L	−0.0037 (0.0207)	0.8565	3535	NA	NA	NA	NA
	CRP, mg/L	0.0073 (0.0041)	0.0735	3587	0.0008 (0.0017)	0.6544	22 088	0.2796
	Urate, μmol/L	0.0121 (0.2287)	0.9578	3586	NA	NA	NA	NA

β indicates beta coefficient; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HUNT, Trøndelag Health; IGF-1, insulin-like growth factor 1; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; N pairs, number of mother-offspring pairs; NA, not applicable; P_{meta}, *P* value of meta-analyses; SBP, systolic blood pressure; SE, standard error; TC, total cholesterol; and TG, triglycerides.

*Genetic scores were constructed by summing blood pressure-raising alleles.

†$P<0.05$.

α=0.05). For the traits that were available in the UKB only, with 3756 mother-offspring pairs, we were underpowered (19%) to detect an effect size as low as 0.04%; however, we had >80% power to detect a large effect size of 0.28% of the variance in the offspring cardiometabolic outcome (Figures S3 and S4, Table S15, and Supplemental Material).

DISCUSSION

Our investigation is the largest genetic study to date to have explored the impact of maternal BP during pregnancy on long-term offspring cardiometabolic health. Our study leverages the considerable number of genotyped mother-offspring (and father-offspring) pairs in the UKB and HUNT studies to examine a possible causal relationship between these variables using MR. Importantly, all offspring from the UKB and the majority of offspring from the HUNT study are middle-aged and elderly adults who are old enough to manifest elevated levels of risk factors for cardiometabolic disease. Our results in general, however, did not support a strong association between genetically predicted maternal BP and offspring cardiometabolic risk factors. The implication is that modest increases in maternal BP during pregnancy are unlikely to drive large increases in offspring cardiometabolic risk

in later life. This implication is consistent with a previous study of siblings in HUNT.[9] That study reported that offspring born to hypertensive pregnancies had similar cardiovascular risk factors in young adulthood as their siblings born after normotensive pregnancies, suggesting that the association observed in the unrelated sample was driven by shared genetic or environmental factors, instead of intrauterine effects.

We did not find any strong indications of effects of maternal BP on offspring outcomes, however, in the smaller and underpowered analysis of UKB alone, we did identify 2 nominal associations between maternal systolic BP risk score and ApoB. We were unable to meta-analyze/replicate this finding in the HUNT study as ApoB was not available for analysis. It is also likely given that the UKB analysis on its own is underpowered, that the finding may be due to type 1 error (false positives). Thus, the association needs to be replicated in a larger sample of mother-offspring pairs.

Asymptotic power calculations suggested that our study was well powered (≥80%) to detect an effect size as low as 0.035% of the variance explained in the offspring outcome by the unweighted maternal genetic score. However, given that an unweighted genetic score of BP variants explains about 0.8% in maternal BP, the above power calculation translates to a causal effect of maternal BP on offspring cardiometabolic risk which is quite large (ie, standardized $\beta = 0.2$). This implies that whilst our study is well powered to rule out strong effects of maternal BP on offspring cardiometabolic risk factors, it has less power to investigate small to moderate effects. The corollary is that the nominal associations found in the UKB are likely to reflect false positives (type 1 error) brought about by multiple testing.

Differences in results between UKB and HUNT may reflect differences in sample size between the studies, and potentially, contrasting selection biases. For example, over 50% of the inhabitants in the Nord-Trøndelag County participated in the HUNT study,[20] while the UKB study only had a participation rate of 5.45%, tending to enroll healthier people with higher socioeconomic status than the general population.[24,55]

Previous observational association studies in humans[1–4] have focused on the relationship between gestational hypertension and preeclampsia (ie, gestational hypertension accompanied by maternal organ dysfunction during the second half of pregnancy). We did not specifically investigate gestational hypertension or preeclampsia in the current study due to the lack of genetic variants associated specifically with these diagnoses. A recent genome-wide association study of preeclampsia identified 2 regions of the genome that reached genome-wide significance, both of which have been previously associated with BP in nonpregnant women and men.[56] Additionally, that study showed that a GRS for hypertension in a sample of nonpregnant women associated with preeclampsia,[56] providing further evidence for the genetic overlap between the 2 diagnoses. It is, therefore, likely that the GRSs used in our study not only increase maternal BP during pregnancy but also increase risk of preeclampsia.

Our analyses used genetic variants that were associated with BP as a quantitative trait in population-based samples of individuals. We, therefore, did not explicitly model the effect of gestational hypertensive disorders (or preterm births/adverse birth outcomes) in our analyses. However, as GRSs which increase maternal BP are also likely to increase the risk of gestational hypertensive disorders, we expect that the presence of mothers with gestational hypertensive disorders in our data set may also contribute to any association between maternal (BP associated) GRS and future cardiometabolic risk in offspring. Nevertheless, it is difficult to assess the relative contribution of each of these sources of variation to our results without detailed clinical information across pregnancy, with the caveat that our study is likely to be better powered to detect the causal effect of quantitative changes in maternal BP during pregnancy particularly within the normal range (systolic BP<140 mm Hg; diastolic BP<90 mm Hg).[57] That being said, we note that it is still possible that extreme exposures like gestational hypertension and preeclampsia may causally increase future offspring cardiometabolic risk, but it is difficult to examine these hypotheses via MR until the scientific community discovers genetic instruments that specifically instrument gestational hypertension/preeclampsia.

There are several limitations to the current study. First, our framework does not formally estimate the size of the causal effect of maternal BP on offspring cardiometabolic traits as is done in most MR analyses (ie, because the magnitude of SNP-BP associations may differ in pregnancy compared to in the general population), but it nevertheless uses MR principles to provide evidence for or against a causal relationship between these traits.[14] Second, we have assumed that genetic variants identified in large genome-wide association studies of BP in males and nonpregnant females are also associated with BP (in a similar direction) in pregnant women. Our analyses performed in pregnant mothers in ALSPAC and FinnGen support the assumption that many BP-associated loci operating in the general population also exert similar effects during pregnancy. Third, we assume a linear relationship between and within maternal BP-associated loci and later-life cardiometabolic traits in their offspring, which may not optimally capture the true relationship between the two. Fourth, the blood tests for lipid and glucose traits were performed using nonfasting samples in both UKB and the HUNT studies which may have influenced the estimates for triglycerides and glucose; however, other biomarkers such as glycated hemoglobin, cholesterol, and lipoprotein levels do not change or only

differ minimally in fasting versus nonfasting tests.[58] Fifth, our model did not completely control for possible pleiotropy through the maternal genome. Although the current model blocks pleiotropic paths through the offspring genome (and addresses the possibility of postnatal pleiotropic effects by performing the same analyses in father-offspring pairs), BP-associated SNPs in the mother could still exert prenatal pleiotropic effects and maternal-specific postnatal effects on offspring cardiometabolic risk through effects other than raising BP. However, this is perhaps less of a concern for the negative results in our study, as any pleiotropic effect would have to have an equal and opposite effect to obscure a true effect of maternal BP on offspring cardiometabolic risk, which is an unlikely scenario. Furthermore, our models do not account for assortative mating, but it seems unlikely that this would cause our observed negative results.[59] Sixth, we did not have enough power with the current sample size to conduct analyses stratified by offspring sex, to investigate sexual dimorphism in the maternal genetic effects under study. Seventh, because the analyses were conducted only in participants of European descent, the results need to be replicated in other populations. Finally, only a selection of cardiometabolic traits of interest was available in the HUNT study. Therefore, we could not replicate the association between genetically predicted maternal BP and offspring outcomes, such as ApoB and CRP. These associations will need to be replicated in larger cohorts.

PERSPECTIVES

In conclusion, our results suggest that perturbations in maternal BP during pregnancy are unlikely to cause large increases in the risk of offspring cardiometabolic disease in later life. Although previous conventional epidemiological studies have found some evidence for associations between maternal BP and offspring cardiometabolic risk factors, our analyses, which provide a more rigorous assessment of causality, suggest that offspring genetic effects and confounding by environmental factors may be the predominant explanation for such population-level associations. MR studies that specifically examine the long-term effects of extreme exposures like gestational hypertension and preeclampsia on future offspring cardiometabolic risk are needed.

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Disclosures

None.

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