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## Genetic Variation in Cardiometabolic Traits and Medication Targets and the Risk of Hypertensive Disorders of Pregnancy

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Hypertensive disorders of pregnancy (HDP, e.g., gestational hypertension, preeclampsia) are associated with significant maternal and fetal morbidity and mortality. Additionally, HDP are associated with heightened future risk of cardiometabolic risk factors (e.g., hypertension, type 2 diabetes [T2D]) and cardiovascular disease. Whether HDP reflect latent preceding cardiometabolic risk is unclear. Here, we tested whether genetic predisposition to cardiometabolic traits and variants related to antihypertensive medication targets are associated with HDP.

Analyses used individual-level genomic and phenotypic data from women in the UK Biobank who reported 1 live birth. Genetic instruments were constructed from genome-wide association studies (GWAS) external to the UK Biobank, using independent ( $r^2 < 0.2$ , European 1000Genomes) single nucleotide polymorphisms (SNPs). Instruments for systolic (SBP) and diastolic blood pressure (DBP) each included 75 SNPs (53 in common).<sup>1</sup> We created genetic instruments for BMI (141 SNPs),<sup>2</sup> resting heart rate (28 SNPs),<sup>3</sup> low-density lipoprotein cholesterol (LDL-C, 277 SNPs),<sup>4</sup> T2D (64 SNPs),<sup>5</sup> and ever-smoking (10 SNPs, TAG Consortium 2010), and genetic proxies for beta blockers (rs11196597, rs1801253, rs4359161), calcium channel blockers (rs7340705, rs2488136, rs1888693, rs16916914, rs10828399, rs10828452, rs12780039, rs11014170, rs7923191, rs12258967, rs1998822, rs4748474, rs2239046), and nitrates (rs13139571, rs3918226, rs891511). Individual-level polygenic risk scores (PRS) were associated with HDP using multivariable logistic regression, adjusted for enrollment age, the first 20 principal components of ancestry, and genotyping array. The Massachusetts General Hospital institutional review board approved these analyses.

Of 214,365 women (mean age 56.9 years), 2,772 (1.29%) had prior HDP. Women with prior HDP had higher adjusted SBP<sup>1</sup> by 10.53 mmHg ( $P < 0.001$ ), higher adjusted DBP<sup>1</sup> by 5.97 mmHg ( $P < 0.001$ ), higher heart rate (71.6 vs. 70.4 beats per minute,  $P < 0.001$ ), and higher BMI (28.1 vs 27.1 kg/m<sup>2</sup>,  $P < 0.001$ ); were less likely to have ever smoked tobacco (32.9% vs. 40.7%,  $P < 0.001$ ); and were more likely to have T2D (2.3% vs. 1.6%,  $P = 0.007$ ).

All genetic instruments had F-statistics  $> 10$  and were strongly associated with corresponding exposures among UK Biobank participants ( $P < 2 \times 10^{-16}$  for all), implying low risk of weak-instrument bias.

For both SBP and DBP, the OR for HDP per standard deviation (SD) of PRS was 1.22 ( $P < 0.001$ ) (Figure 1A). Associations with SBP PRS were similar in women with gestational hypertension (OR 1.24 per SD, 95% CI 1.13–1.35) or preeclampsia (OR 1.19 per SD, 95% CI 1.08–1.31). Genetic predisposition for increased BMI also increased HDP odds (OR 1.06 per SD;  $P = 0.004$ ). BP and BMI PRS were independent and additive. Genetic predisposition for increased heart rate, T2D, smoking, and LDL-C were not associated with HDP. Results were unchanged in analyses restricted to 180,846 women with white British ancestry. Two-sample Mendelian randomization using the inverse variance-weighted method yielded consistent findings ( $P = 1.7 \times 10^{-18}$  for SBP,  $P = 1.7 \times 10^{-4}$  for BMI) without evidence of

horizontal pleiotropy ( $P=0.91$  and  $P=0.70$  for SBP and BMI, respectively, with MR-Egger intercept).

We tested the effect of genetic predisposition for HDP on SBP using 205 SNPs at least nominally associated with HDP ( $P<5*10^{-4}$ ,  $r^2<0.01$ ) in the UK Biobank, with the outcome extracted from the 2011 International Consortium for Blood Pressure GWAS. HDP showed a nominally significant association with SBP using both the inverse variance weighted ( $\beta=+0.17$  mmHg,  $P=0.015$ ) and MR.RAPS ( $\beta=+0.16$  mmHg,  $P=0.04$  [Huber];  $\beta=+0.15$  mmHg,  $P=0.05$  [Tukey]) methods.

Genetic variants mimicking effects of beta blockers, calcium channel blockers, and nitrates all demonstrated reduction in HDP risk proportional to SBP effect (Figure 1B). Additionally, rs7692387-A (intron variant of *GUCY1A3*) was associated with HDP (OR 0.90, 95% CI 0.84–0.97,  $P=0.004$ ). The association of rs7692387-A with HDP appeared disproportionately large (OR 0.21 per 5-mmHg SBP lowering;  $P=0.004$ ;  $P_{\text{heterogeneity vs. SBP PRS}} = 0.037$ ).

In a large cohort of UK women, genetic predisposition to elevated SBP, DBP, and BMI were significantly associated with HDP, implying that these cardiometabolic risk pathways are causal for development of HDP. BP and BMI may therefore represent viable preventive targets for reducing HDP risk. In the Control of Hypertension in Pregnancy Study, tight BP control decreased rates of severe gestational hypertension but not preeclampsia. However, women enrolled <24 weeks gestation derived greater benefit from tight control, implying earlier BP lowering may be required to effectively prevent HDP. Further, the protective effect of *GUCY1A3* rs7692387 variation relative to BP-lowering suggests that NO signaling may be particularly protective against HDP via BP-independent pathways.

Our study has limitations. HDP prevalence in the UK Biobank is lower than population estimates, possibly due to healthy participant bias, underreporting of HDP history, or both, potentially biasing findings toward the null. Only 17 women had eclampsia. Reduced power may have hindered our ability to detect smaller associations for T2D and ever-smoking, although point estimates were entirely neutral. We lacked adequate power to perform dedicated subgroup analysis in black women, who are disproportionately affected by HDP. Genetic risk scores are not intended for the prediction of HDP and are used as tools of causal inference to gain mechanistic insights.

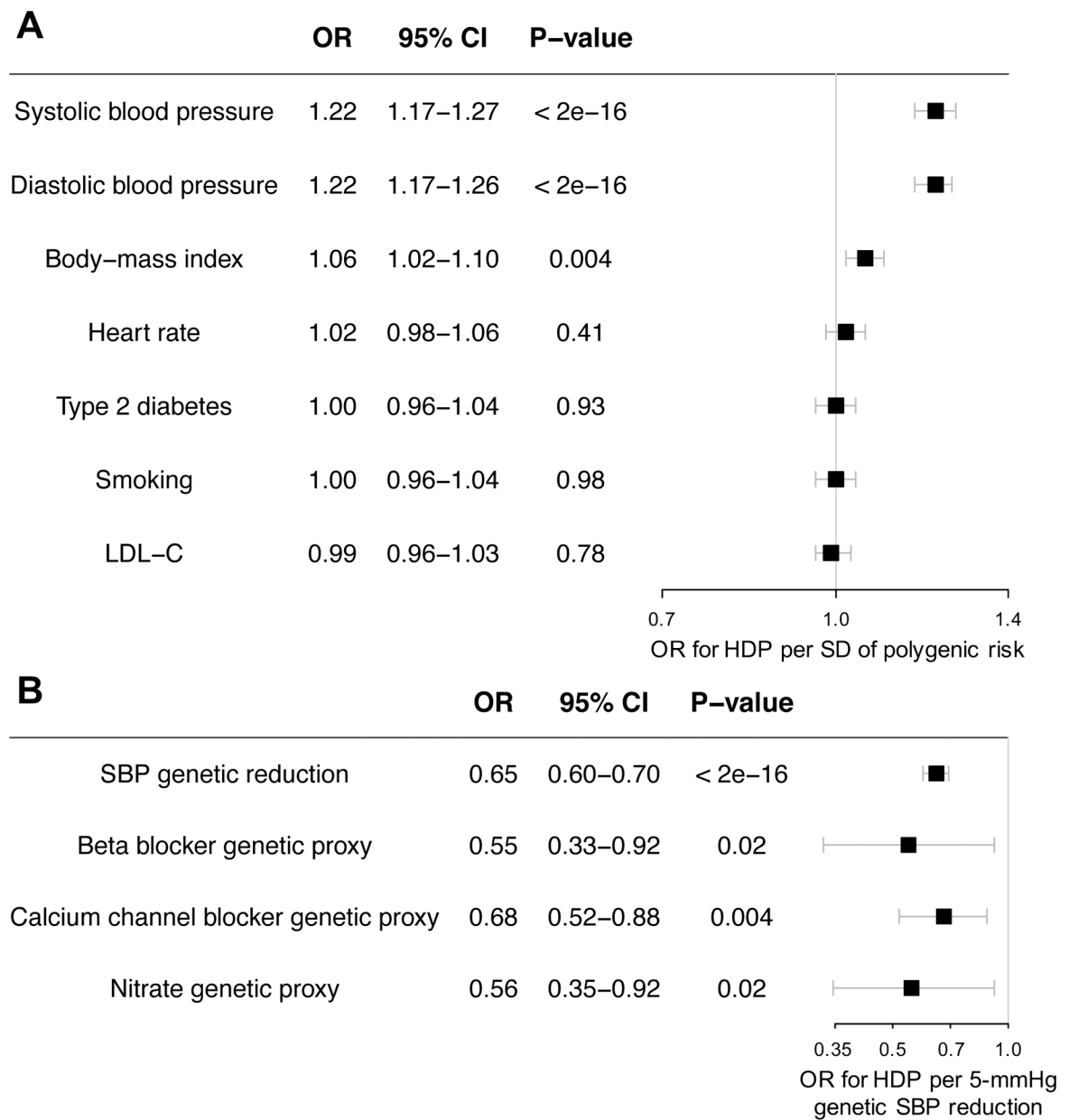
In conclusion, genetic predisposition to elevated BP and BMI are associated with HDP, implying causal pathways well-positioned for HDP prevention. Whether HDP risk may be reduced in at-risk women through antepartum BP-lowering and weight-loss strategies warrants prospective assessment in adequately powered randomized trials.

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**Figure 1.** (A) Risk of hypertensive disorders of pregnancy conferred by genetic predisposition to cardiometabolic risk factors and genetically determined resting heart rate. (B) Risk reduction associated with genetic proxies for multiple blood pressure-lowering drug classes.\* Odds ratios are adjusted for age, the first 20 principal components of ancestry, and genotype array. \*Risk reduction associated with antihypertensive medications is displayed per 5 mmHg of lower systolic blood pressure due to genetic variation in antihypertensive medication target pathways. OR = odds ratio; CI = confidence interval; HDP = hypertensive disorders of pregnancy; SD = standard deviation; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure