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Maternal hypertension-related genes affect the fetal growth via placenta

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(Introductory paragraph)

Low birth weight is associated with the development of cardio-metabolic diseases later in life¹⁻⁴. A recent Mendelian Randomization Study concluded that the susceptibility of low-birth-weight infants to develop hypertension during adulthood is due to the inheritance of hypertension genes from the mother, and not to an unfavorable intrauterine environment⁵. Therein, it has been assumed that low birth weight is caused by maternal hypertension^{5,6}, although there is no evidence to support such a linear relationship. In the present study, we have noted that most of blood pressure SNPs are related to vascular regulation⁷⁻⁹ and found that the relationship between maternal blood pressure-increasing polygenic score and reduction of offspring birth weight is mediated by a reduced growth of the placenta but not by the mother's high blood pressure. This suggests that the risk of hypertension of low-birth-weight infants may result from a poor placental environment.

38 Main

39 The increasing prevalence of cardio-metabolic diseases leading to premature death is a raising
40 concern¹⁰. Although major risk factors are lifestyle factors after birth, epidemiological studies have
41 associated low birth weight (LBW) and/or fetal growth restriction (FGR) with hypertension,
42 cardiovascular diseases, and type 2 diabetes, indicating the existence of prenatal risk factors^{1,3,4}.
43 However, the underlying mechanisms explaining the relationship between LBW/FGR and diseases in
44 adulthood are not fully understood. It is suggested that maternal undernutrition and/or poor placental
45 function could alter long-lasting body function and physiology, predisposing individuals to cardio-
46 metabolic diseases^{2,11}. Therefore, identifying risks of hindering the fetal growth process will help
47 prevent cardio-metabolic diseases.

48 FGR pathophysiology and etiology are complex but most cases are thought to arise from
49 placental dysfunction^{4,12}. Birth and placenta weight highly correlate^{13,14}, and placenta weight is an
50 important determinant of fetal growth in the third trimester¹⁴. FGR is classified into two categories
51 according to the gestational age of onset and nearly 80% are late-onset (≥ 32 weeks)¹⁵. The trajectory
52 of individual fetal growth velocity is a valid indicator for fetal growth assessment¹⁶. We previously
53 showed that heterogeneity of growth velocity trajectories is most pronounced after 30 weeks of
54 gestation¹⁶. In our cohort, $\geq 10\%$ of the fetuses showed a third-trimester growth acceleration or
55 deceleration. The latter could include late-onset FGR, and individual trajectories analysis highlighted
56 the continuity of the degree of growth restriction.

57 Although severe hypertension in preeclampsia is the only condition that presents association
58 between maternal blood pressure (BP) and fetal growth¹⁷, multiple studies^{5,6} have formalized that
59 maternal BP-increasing polygenic score (PGS) is related to a decreased birth weight, based on the
60 assumption of inverse linear association between birth weight and maternal BP. As for BP genetics,
61 recent genome-wide association study (GWAS) uncovered numerous BP-associated genes involved
62 in regulating the vascular system development and function⁷⁻⁹. The placenta being a vascular organ,

63 we hypothesized that BP-increasing maternal SNPs influence placenta weight, which in turn affects
64 birth weight.

65 To decipher the correlation between maternal BP-increasing PGS and fetal/placental parameters,
66 we tested the association between maternal PGS for four BP phenotypes (systolic BP [SBP],
67 diastolic BP [DBP], mean arterial pressure [MAP], pulse pressure [PP]) and various phenotypes
68 including fetal growth velocity, birth- and placenta- weight (Supplementary Tables 1-4). We found
69 that maternal PGS for all BP phenotypes, especially SBP-PGS associated with placenta weight
70 (Fig.1d). SBP-PGS became negatively associated with fetal growth velocity as the gestation proceed
71 towards 36 weeks (Fig.1e-i). While placenta weight correlated with birth weight ($r = 0.57$, $p <$
72 $2.2e^{-16}$), the degree of association of SBP-PGS with placenta weight was larger than with birth
73 weight (Fig.1c), suggesting that maternal BP gene effects on the placenta could mediate the effects
74 on birth weight. Fetal BP-increasing PGS also associated with placenta weight, but at a lower
75 significance than maternal PGS for all four BP phenotypes. In contrast, maternal SBP-PGS had a
76 small positive effect on observed SBP (Supplementary Table 1 and Fig.1b). Altogether, these
77 findings indicate that maternal SBP-PGS influences offspring birth weight through placental growth
78 rather than BP.

79 Mendelian Randomization analyses^{5,6} commonly associate observed BP linearly with birth
80 weight. To verify this assumption and clarify which of a linear or a quadratic model better fits, we re-
81 evaluated the relationship between measured maternal BP and birth weight (Supplementary Tables 5-
82 8). As maternal BP generally changes during pregnancy (decrease during the first 20 weeks and then
83 increase until parturition), analyses were performed separately in three gestational periods (see
84 Methods). For SBP, DBP, and MAP, the quadratic model better explained the relationship between
85 BP and birth weight in all three periods. For PP, however, the linear model was better fitted,
86 although offspring birth weight was positively correlated with maternal PP (Supplementary Figs1-2;
87 Fig.2). The adjusted R-squared was small for all (less than 0.017), implying that the effect of

maternal BP on birth weight is limited. These results suggest that maternal SBP-PGS influences birth weight through factors other than maternal SBP.

Given that BP-increasing SNPs appear to reduce birth weight through a BP independent mechanism, and that many BP-SNPs have been related to vascular regulation⁷⁻⁹, we speculated that SNPs could affect the placenta by vascular dysregulation. We aimed at clarifying that the polygenic effect of BP-increasing SNPs on placenta weight is maintained when SNPs are restricted to high relevance to the vasculature. Partitioned PGS was constructed using functionally-specified SNPs derived from 41 SNPs associated with SBP, DBP, MAP, and PP identified by Kanai *et al.*¹⁸ with genome-wide significance (Supplementary Table 9; Fig.3a). We used bioinformatics tools and literature review to clarify their relevance to the vasculature (see Methods). Of the 41 SNPs, 18 were in the “vasculature-related”, 12 in the “unlikely related,” and 11 in the “unknown” classification (Fig. 3a). We observed a significant negative association between maternal PGS and placenta for the “vasculature related” PGS, but not for the “unlikely related” PGS (Fig. 3b). To confirm that the association of “vasculature-related” PGS with placental weight was not due to the larger number of SNPs, we also performed a similar partitioned PGS analysis, using the top 67 SBP-SNPs (SBP association p -value $< 1 \times 10^{-6}$; Supplementary Table 10). Of these, 21 were in the “vasculature related”, 30 in the “unlikely related”, and 16 in the “unknown” classification. We repeatedly observed that the negative association between maternal PGS and placenta weight was maintained for the “vasculature related” PGS but not for the “unlikely related” PGS (Supplementary Table 11). Altogether, these findings suggest that “vasculature related” SNPs could be responsible for reducing placenta weight by affecting placental vasculature.

To determine the relative contributions of maternal and fetal genotypes to the relationship between BP-increasing allele and placenta weight, we estimated mother-offspring allele transmission based on local haplotype sharing¹⁹ for the 41 BP SNPs¹⁸ (Fig.3a). Both transmitted and non-transmitted maternal haplotype genetic scores were associated with placenta weight; however, we

113 found no association between paternally inherited haplotype genetic score and placenta weight (Fig.
114 3c). To further confirm that maternal genes affect the placenta by “vasculature-related” SNPs, we
115 generated the partitioned haplotype score of either “vasculature-related” or “unlikely-related” and
116 compared its association with placenta weight. The “vasculature-related” haplotype allele counts of
117 both transmitted and non-transmitted maternal alleles were inversely associated with the placenta
118 weight, while those of the paternal transmitted alleles were not (Supplementary Table 12). Taken
119 together, our results show that the effects of BP-increasing alleles on reducing placental weight
120 derive from maternal genetic origin.

121 This is the first study to show a notable association between maternal BP-related genes and
122 placenta weight. We also demonstrate that maternal SBP-increasing PGS is inversely associated with
123 fetal growth velocity near term (36 weeks). We have shown that BP-increasing SNPs lower birth
124 weight by reducing placenta weight but not by raising maternal BP. Usually, the placenta growth rate
125 decreases from about 30 weeks, and the fetus/placenta growth ratio increases gradually until 37-38
126 weeks²⁰. Considering the time sequence of events, the placental size determined by maternal BP-
127 related polygenic background may indirectly affect fetal growth velocity in late gestation and
128 subsequently birth weight. Analyses of partitioned PGS into “vasculature related” and “unlikely
129 related” revealed that “vasculature related” among SBP-increasing SNPs could be primarily
130 responsible for reducing placenta weight. The effect of BP-increasing alleles through vasculature on
131 placenta weight was predominantly driven by maternal genotype. Although fetal genes have been
132 focused on as involved in placental vascularization^{21,22}, our study sheds new light on the importance
133 of maternal genes.

134 The main strength of our study is the cohort of mother-offspring pairs containing genotype and
135 unique phenotype data of time-series fetal growth velocity and placenta weight. In addition, birth
136 weight and placenta weight were ideally adjusted for gestational age, fetal sex, and maternal parity to
137 eliminate well-known confounding factors. However, some limitations should be noted. First, the

sample size of the cohort with available genotype was small, around 100, which is the minimum target sample size for PGS analysis²³. The association between SBP-PGS and placenta was much stronger than the association between typical PGS and the corresponding traits; the variance of placenta trait explained by the PGS, represented by adjusted R-squared exceeded 0.18, therefore, we were able to perform a statistically reliable association analysis with this sample size. Nevertheless, results of this study will need to be replicated in another cohort possessing complete data of fetal growth velocity and placenta weight. Second, we classified PGSs based on literature and open-source data on gene activities and chromatin status in vascular tissues of genes affected by SNPs. Although these methods were commonly used in previous studies⁷⁻⁹, some information is not yet complete and will improve as more data accumulate.

Our finding is highly important for perinatal management of FGR. Given that many FGRs are late-onset and difficult to diagnose^{4,12,15}, maternal SBP-PGS will be useful to screening for late-onset FGR high-risk groups, regardless of the presence or absence of maternal hypertension during pregnancy. Suboptimal intrauterine environment due to reduced placenta growth could generate future hypertension in LBW offspring. This study reconciles the long-held debate on prenatal origin of diseases: between adverse intrauterine environment or genetic effects, and will contribute to the prevention of hypertension and cardiovascular diseases.

155

156 **Methods**

157 **Study cohorts**

The characteristics of the two cohorts analyzed in this study are presented in Supplementary Table 13. More details about the participants of these cohorts have been described previously^{16,24,25}. We excluded women with any hypertensive disorder of pregnancy (HDP) in this study. The study population was comparable with the general Japanese pregnant women on perinatal parameters such as birth weight, maternal age, height, weight, body mass index, and BP^{26,27}.

BC-GENIST. Clinical information and genotype data were obtained from the Birth Cohort Gene and Environment Interaction Study of Tokyo Medical and Dental University (TMDU) (BC-GENIST) project, which is a prospective mother-offspring cohort designed to evaluate the effects of prenatal environment and genotype on the epigenetic state of mothers and their offspring at TMDU Medical Hospital²⁴. Ninety-three mother-child pairs of Japanese ancestry were analyzed in this study. All of the participants provided written informed consent. The parents/guardians provided consent for their children to participate.

The *TMDU pregnant women cohort*. Clinical information including maternal BP and birth outcome were obtained from the retrospective cohort of women who gave birth at TMDU Hospital from 2013 to 2017^{16,25}. The eligible criteria for this study were as follows: Japanese singleton delivery with available placental weight and live birth, without malformation, completing more than >34 weeks of gestation at the time of delivery. Maternal age was above >20 years and existing maternal BP data in two gestational periods (before 20 weeks and from 20 to 34 weeks) were available. BC-GENIST participants were excluded. Total 993 women were eligible for this study. Informed consent was obtained in the form of opt-out on the website of TMDU Life Science and Bioethics Research Center.

This study was approved by the Institutional Review Board of TMDU and was conducted according to the Declaration of Helsinki.

Observational maternal BP and perinatal outcomes

The relationship between observational BP and birth weight was analyzed using the TMDU pregnant women cohort. BP is typically measured at prenatal check-ups scheduled every four 4 weeks until 24 weeks, every two 2 weeks between 24 and 36 weeks, and weekly beyond 36 weeks of gestation. Pulse pressure (PP) was calculated by subtracting the diastolic blood pressure (DBP) from

the systolic blood pressure (SBP). The PP was divided by three and added to the DBP to calculate the mean arterial pressure (MAP).

Hypertension of pregnancy is classified according to the time of onset, which is also thought to be different in its pathogenesis²⁸. Chronic hypertension is defined if hypertension occurs before 20 weeks, and early and late-onset HDP if HDP occurs between 20 and 34 weeks and after 34 weeks, respectively. Therefore, we divided the gestation period into three categories: (1) early, gestational age <20 weeks; (2) middle, $20 \leq$ gestational age < 34 weeks; (3) late, $34 \text{ weeks} \leq$ gestational age. For each pregnant woman, the mean value of SBP, DBP, MAP, and PP at each period was calculated and used for analysis. However, in this study, Chronic hypertension and HDP were excluded.

Birth weight and placental weight were adjusted for gestational age, fetal sex, and parity using a reference chart^{20,29}. Estimated fetal growth velocity was calculated as described previously¹⁶. To compare the genetic effect size across all the phenotypes using the BC-GENIST cohort, we scaled trait to have zero mean and unit variance by Z-score transformation.

Genotyping and imputation of target data for polygenic score (PGS) analysis

The DNA was extracted from maternal peripheral blood and cord blood of the BC-GENIST participants using a standard procedure²⁴. All samples were genotyped with the Illumina Infinium Asian Screening Array BeadChip by iScan, in accordance with the Illumina protocol, at the Center for Molecular Biology and Genetics/Core-Lab, Graduate School of Regional Innovation Studies, Mie University, Mie, Japan. Genotype calling was performed for all samples as a single project using the Genotyping Module (version 1.9) of the GenomeStudio data analysis software package. The quality control (QC) of participants and genotypes was performed using a standard procedure^{23,30-32}. Briefly, there were no individuals with incorrect sex assignment, excessive heterozygosity, or low call rate (< 98%). There were no incorrect mother-child relationship and cryptic relatedness, as assessed by identity-by-descent (IBD) estimation. Principal component analysis (PCA) anchored with HapMap

212 III reference samples confirmed that all samples taken were from individuals of East Asian descent.
213 At a marker level, SNPs with low call rate ($< 95\%$), low minor allele frequency (MAF) (< 0.01), or
214 significant deviation from Hardy-Weinberg equilibrium ($p < 1 \times 10^{-5}$) were excluded. We excluded
215 non-autosomal chromosomes from the analysis.

216 Following QC procedures, we conducted genome-wide imputation using the 1000 Genome
217 Phase 3 reference panel³³. SNP alleles were oriented to the forward strand of the GRCh37/hg19
218 reference sequence of the human genome. Haplotype phasing and imputation were performed in all
219 maternal and fetal samples using Beagle 5.1 software^{34,35}. After the imputation, we excluded variants
220 with the measurement Dosage R-squared ($DR2$) < 0.7 or those with low MAF (< 0.01). The sample
221 size was 93, which was equivalent to the minimum target sample size for PGS analysis²³.

222

223 **Construction of individual polygenic scores (PGSs)**

224 A classic clumping and thresholding method was used to derive individual polygenic scores
225 (PGSs) for the target BC-GENIST participants. As a base data, we used GWAS summary statistics
226 (the normalized effect sizes and P values) for BP phenotypes (SBP, DBP, MAP, and PP) from
227 Japanese individuals ($n > 136,000$) from the BioBank Japan (BBJ)¹⁸. We performed QC relevant to
228 base and target data for the PGS calculation²³. The reported heritability estimates of SBP, DBP,
229 MAP, and PP, were 0.0569, 0.04, 0.0496, and 0.0438, respectively³⁶. First, a set of independent
230 variants were extracted using linkage disequilibrium (LD) clumping³² using the following flags: --
231 clump-p1 1 --clump-p2 1 --clump-r2 0.1 --clump-kb 1000. Next, we selected variants meeting the
232 following p-value thresholds: 1×10^{-6} , 1×10^{-5} , 1×10^{-4} , and 1×10^{-3} . The trait variance
233 explained by the derived PGSs by calculating the adjusted R^2 attributable to the PGSs was mostly
234 increased as the threshold increased up to 1×10^{-4} , but not up to 1×10^{-3} . We derived PGSs by
235 multiplying the dosage of BP-increasing alleles for each variant by the normalized effect size in the
236 GWAS and summing the scores across all the selected variants unless otherwise indicated.

237 Partitioned PGS was constructed using the functionally specified SNPs derived from 41 SNPs
238 associated with SBP, DBP, MAP, and PP identified by Kanai *et al.*¹⁸ with genome-wide significance.
239 They were highly overlapping across multiple BP phenotypes and the reported directions of BP-
240 increasing effects were concordant for all BP phenotypes, except for seven PP-associated SNPs.
241 Because the effect size of each SNP varies among the four BP phenotypes, alleles with SBP-
242 increasing effect were counted in an unweighted manner. For the seven discordant SNPs mentioned
243 above, counting SBP-increasing alleles was rational because the direction was the same among PP,
244 SBP, and MAP.

245

246 **Parental origin determination and computation of individual haplotype allele counts**

247 For a series of genome-wide significant SNPs associated with any BP phenotypes ($P < 5.0 \times$
248 10^{-8}) reported by Kanai *et al.*¹⁸, we estimated mother-offspring allele transmission for each mother-
249 offspring pair after phasing and imputation using Beagle 5.1 software^{34,35}. When either or both
250 mother and fetus were homozygote, the allelic transmission could be unambiguously determined.
251 When both mother and fetus were heterozygote, allelic transmission from mother to child was
252 inferred based on local haplotype sharing, following the method described by Zhang, G *et al.*¹⁹. For
253 each SNP, we calculated three haplotype allele counts: (1) unweighted sum of the number of BP-
254 increasing alleles in maternal transmitted haplotypes, (2) unweighted sum of the number of BP-
255 increasing alleles in maternal non-transmitted haplotypes, and (3) unweighted sum of the number of
256 BP-increasing alleles in paternal transmitted haplotypes.

257

258 **Variant annotation and relevance to the vascular system**

259 Genome-wide significant SNPs associated with BP phenotypes¹⁸ were annotated with genes
260 using data obtained on 12/18/2020 from multiple bioinformatic tools such as Variant Effect Predictor
261 (VEP, Ensemble release 102)³⁷, SNPnexus³⁸, and post-GWAS³⁹. We evaluated all SNPs in LD ($r^2 \geq$

0.8) with each variant for evidence of mediation of expression quantitative trait loci (eQTLs) in all 54 tissues using the GTEx database Release V8, to identify affected genes and tissues. GeneHancer database⁴⁰ was also used to identify potentially affected genes by SNPs (Supplementary Tables 9-10).

For the relevance to the vascular system, we assessed all SNPs in LD ($r^2 \geq 0.8$) with each variant for evidence of the overlap with ENCODE DNase I regulatory regions and/or Candidate Cis-regulatory elements^{38,41} in blood vessels (umbilical vein endothelial cell [HUVEC]; brain microvascular endothelial cell [HBMEC]; lung microvascular epithelium blood [HMVEC-LBI]; brain vascular smooth muscle cell [HBVSMC]; pulmonary artery fibroblast [HPAF]; aorta fibroblast [AoAF]). We conducted a literature review of the annotated genes and investigated whether the genes were relevant to the vasculature (function of the vascular smooth muscle, the vascular endothelial cells, the vascular tone, the vascular assembly, placental vasculature, and HDP; Supplementary Tables 9-10). Among 42 BP-associated SNPs reported¹⁸, rs139293840 (located in RPTOR) was excluded for the analysis, as it is monomorphic in non-Asian population and there was no available GTEx data.

Statistical analyses

All tests were two-sided. Associations between genotype-based BP-increasing PGSs and various phenotypes were examined by regression analysis. The PGSs for each trait were scaled to have zero mean and unit variance by Z-score transformation to obtain and compare the effect sizes across the investigated phenotypes. To visualize the relationship between BP-increasing PGSs and quantitative phenotype levels, we stratified the participants according to the tertiles of normalized PGSs.

Association between haplotype-based BP-increasing allele counts and placenta weight was similarly examined by regression analysis using the polygenic allele counts of maternal transmitted, maternal non-transmitted, and paternal transmitted, respectively.

287 Global Validation of Linear Model Assumptions (GVLMA)⁴² and the Akaike information
288 criterion (AIC) were used to evaluate whether a simple linear or a quadratic model was appropriate
289 to explain the association between observed maternal BP and normalized birth weight for gestational
290 age.

291 A minimum required sample size of 47 for the linear regression was calculated with an alpha
292 value of 0.05, a power of 0.80, and an R^2 of 0.15 representing the moderate effect size, using the
293 `pwr.f2.test` function in the `pwr` package⁴³.

294

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Fig. 1 Maternal SBP-increasing PGS associates with placenta weight rather than measured SBP.

a. Distribution of normalized maternal systolic blood pressure (SBP)-increasing polygenic score (PGS) constituted of a set of SNPs exceeding a GWAS association p -value of 1.0×10^{-4} and the stratification according to the tertiles. **b–i.** Phenotype data across maternal PGS tertiles. Each subject ($n = 93$) is shown in the box-and-whisker plots, with the boxes indicating the median and interquartile range and the whiskers denoting the range. The observed SBP shown in **b** is the mean SBP during late gestation period, which was the most correlated with PGS among early, mid, and late periods. Birth weight and placenta weight are adjusted for gestational age, fetal sex, and parity. All phenotype data are scaled to have zero mean and unit variance by Z-score transformation. Regression coefficient (Est.), standing for the change per strata increase, and P -value are shown.

Fig. 2: The relationship between maternal BP in late gestation and offspring birth weight is not a negative linear association

Association between birth weight and mean late-gestational SBP (a), DBP (b), MAP (c), and PP (d), respectively. Each subject is included ($n = 993$) in the box-and-whisker plots, with the boxes indicating the median and interquartile range and the whiskers denoting the range. Birth weight is adjusted for gestational age, fetal sex, and parity and scaled to have zero mean and unit variance by Z-score transformation. Regression lines are shown in red.

a

b

c

Fig. 3: Maternal “vasculature related” alleles among BP-increasing SNPs are primarily responsible for reducing placenta weight

a. Venn diagram of 41 genome-wide significant single nucleotide polymorphisms (SNPs) for BP phenotypes. There is a considerable overlap of association across four BP phenotypes, with a consistent direction of the effect, except for seven loci that present opposite or unclear effect directions for DBP (indicated by †). SNPs are classified into “vasculature-related” (red), “unlikely related” (blue), and “unknown” (green) groups, respectively, as described in the results and Supplementary Table 9.

b. Relationship between total or partitioned genotypic allele counts and the placenta weight shown as scatter plots ($n = 93$). **c.** Relationship between the placenta weight and the haplotype allele counts for maternal transmitted, maternal non-transmitted, and paternal transmitted allele, respectively, shown as scatter plots ($n = 93$). Placenta weight is adjusted for gestational age, fetal sex, and parity and scaled to have zero mean and unit variance by Z-score transformation. Regression coefficient (Est.) and P -value are shown.

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Author Contributions

N.S., A.F, C.I, H.T, I.T, T.A, S.Y., M.O., and N.M. collected the BC-GENIST samples. N.M. collected TMDU pregnant women samples. N.S. contributed to data cleaning, statistical analysis, overall study design and writing of the manuscript. S.M. and N. M. supervised the study.

Ethics declarations

Our study was approved by the Institutional Review Board of the Medical Research Institute and Faculty of Medicine, TMDU (No. G2000-181, M2017-337), and was conducted according to the Declaration of Helsinki.

Competing interests

The authors declare no conflicts of interest.

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422 **Supplementary Information** is available for this paper.

423 Correspondence and requests for materials should be addressed to Noriko Sato.

424 **Supplementary Tables**

425 Supplementary Table 1. Association between maternal and fetal SBP-increasing PGS and various
426 phenotypes

427 Supplementary Table 2. Association between maternal or fetal DBP-increasing PGS and various
428 phenotypes

429 Supplementary Table 3. Association between maternal or fetal MAP-increasing PGS and various
430 phenotypes

431 Supplementary Table 4. Association between maternal or fetal PP-increasing PGS and various
432 phenotypes

433 Supplementary Table 5. Evaluation of the models for relationship between birth weight and maternal
434 observational SBP

435 Supplementary Table 6. Evaluation of the models for relationship between birth weight and maternal
436 observational DBP

437 Supplementary Table 7. Evaluation of the models for relationship between birth weight and maternal
438 observational MAP

439 Supplementary Table 8. Evaluation of the models for relationship between birth weight and maternal
440 observational PP

441 Supplementary Table 9. Genome-wide Significant loci for blood pressure phenotypes and
442 classification based on vasculature relevance

443 Supplementary Table 10. Variants constituting SBP-increasing PGS at p-value threshold of 1×10^{-6}
444 and classification based on vasculature relevance

445 Supplementary Table 11. Association between the partitioned maternal SBP-increasing PGS and
446 placenta weight

447 Supplementary Table 12. Association between the partitioned haplotype genetics scores and placenta
448 weight

449 Supplementary Table 13. Characteristics of participants included in this study

450

451 **Supplementary Figures**

452 Fig. S1: The relationship between maternal BP in early gestation and offspring birth weight is not a
453 negative linear association

454 Fig. S2: The relationship between maternal BP in mid gestation and offspring birth weight is not a
455 negative linear association

456

457

Figures

Figure 1

Maternal SBP-increasing PGS associates with placenta weight rather than measured SBP. a. Distribution of normalized maternal systolic blood pressure (SBP)-increasing polygenic score (PGS) constituted of a set of SNPs exceeding a GWAS association pvalue of 1.0×10^{-4} and the stratification according to the

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Offspring birth weight

Figure 2

The relationship between maternal BP in late gestation and offspring birth weight is not a negative linear association Association between birth weight and mean late-gestational SBP (a), DBP (b), MAP (c), and PP (d), respectively. Each subject is included (n = 993) in the boxand- whisker plots, with the boxes indicating the median and interquartile range and the whiskers denoting the range. Birth weight is adjusted for gestational age, fetal sex, and parity and scaled to have zero mean and unit variance by Z-score transformation. Regression lines are shown in red.

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b

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Figure 3

Maternal “vasculature related” alleles among BP-increasing SNPs are primarily responsible for reducing placenta weight a. Venn diagram of 41 genome-wide significant single nucleotide polymorphisms (SNPs) for BP phenotypes. There is a considerable overlap of association across four BP phenotypes, with a consistent direction of the effect, except for seven loci that present opposite or unclear effect directions for DBP (indicated by †). SNPs are classified into “vasculature-related” (red), “unlikely related” (blue), and “unknown” (green) groups, respectively, as described in the results and Supplementary Table 9. b. Relationship between total or partitioned genotypic allele counts and the placenta weight shown as scatter plots (n = 93). c, Relationship between the placenta weight and the haplotype allele counts for maternal transmitted, maternal non-transmitted, and paternal transmitted allele, respectively, shown as scatter plots (n = 93). Placenta weight is adjusted for gestational age, fetal sex, and parity and scaled to have zero mean and unit variance by Z-score transformation. Regression coefficient (Est.) and P-value are shown.

Supplementary Files

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