Supplementary material relating to Warrington et al. (2019), Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nature Genetics,* 51(5):804-814. Doi: 10.1038/s41588-019-0403-1. Epub 2019 May 1.

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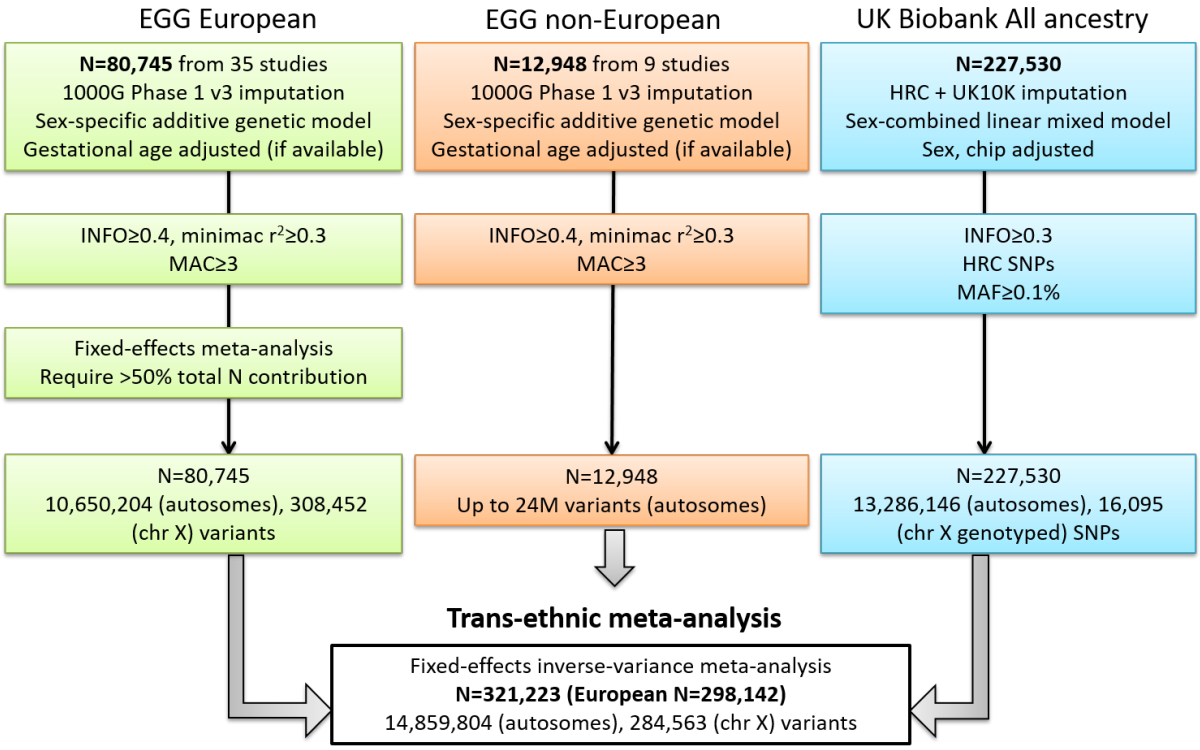
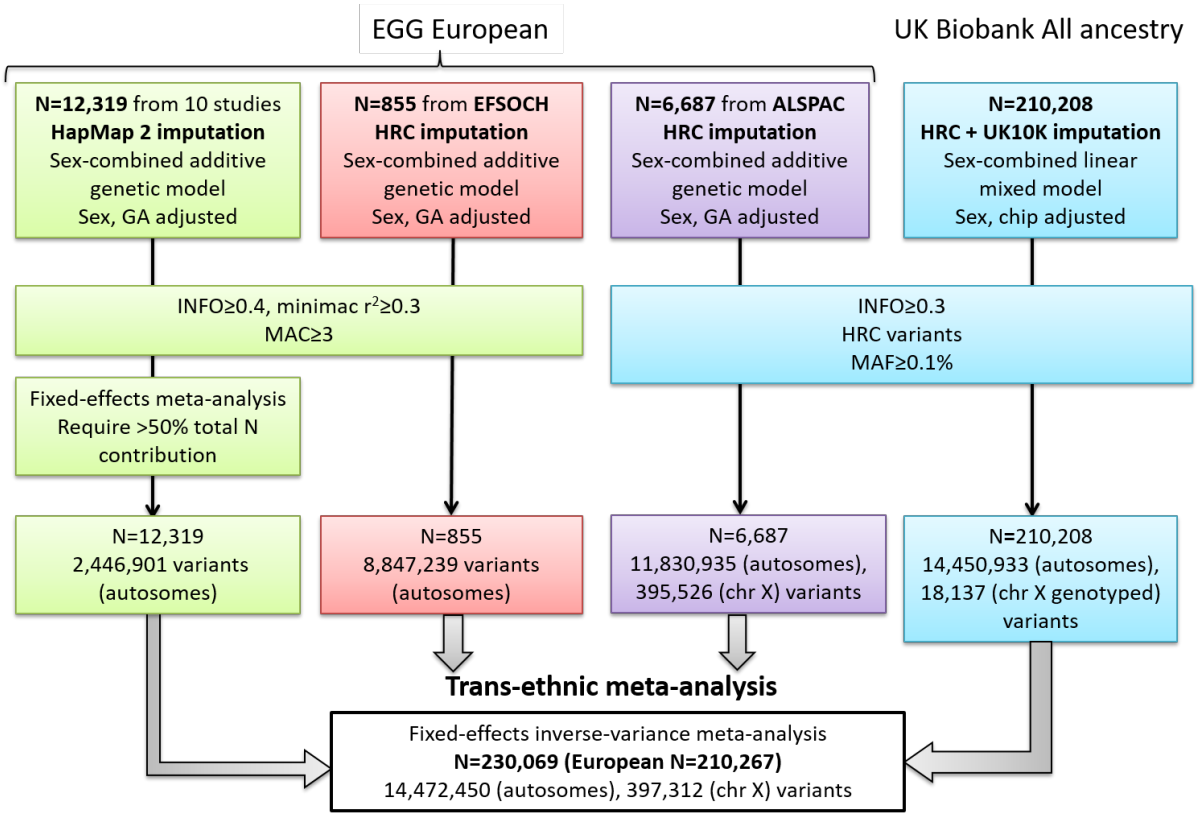


Supplementary Figure 1

Flow diagram of the study design for the genome-wide association analysis of own birth weight.

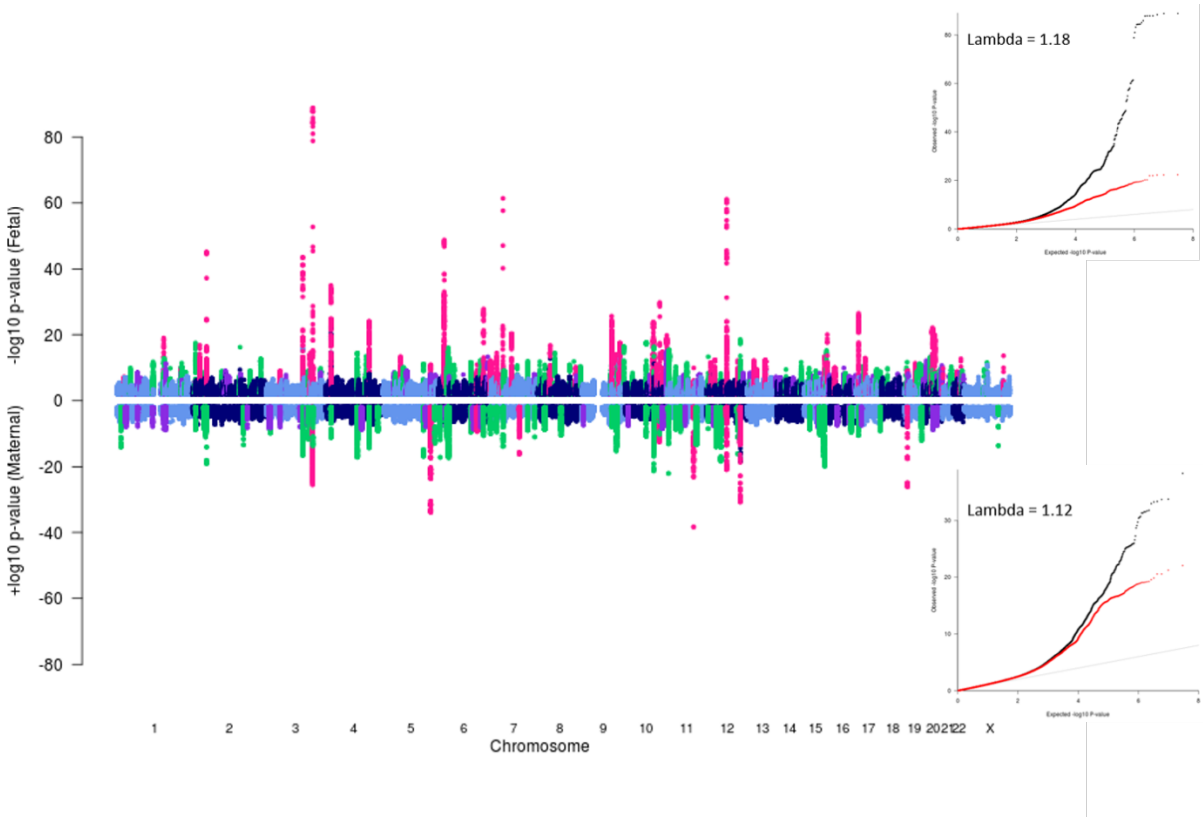
MAC, minor allele count; MAF, minor allele frequency; chr, chromosome.



Supplementary Figure 2

Flow diagram of the study design for the genome-wide association analysis of offspring birth weight.

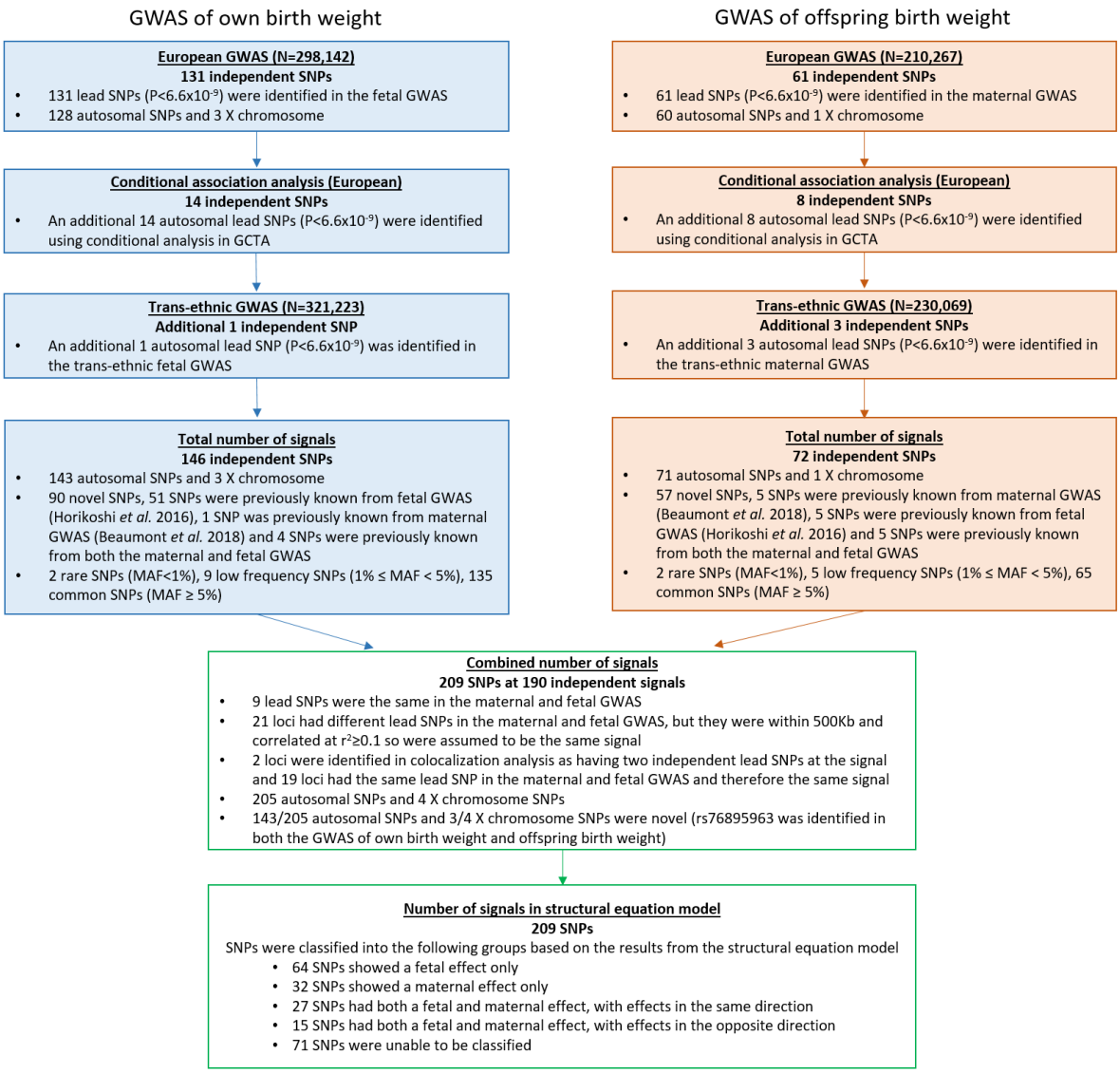
GA, gestational age; MAC, minor allele count; MAF, minor allele frequency; chr, chromosome.



Supplementary Figure 3

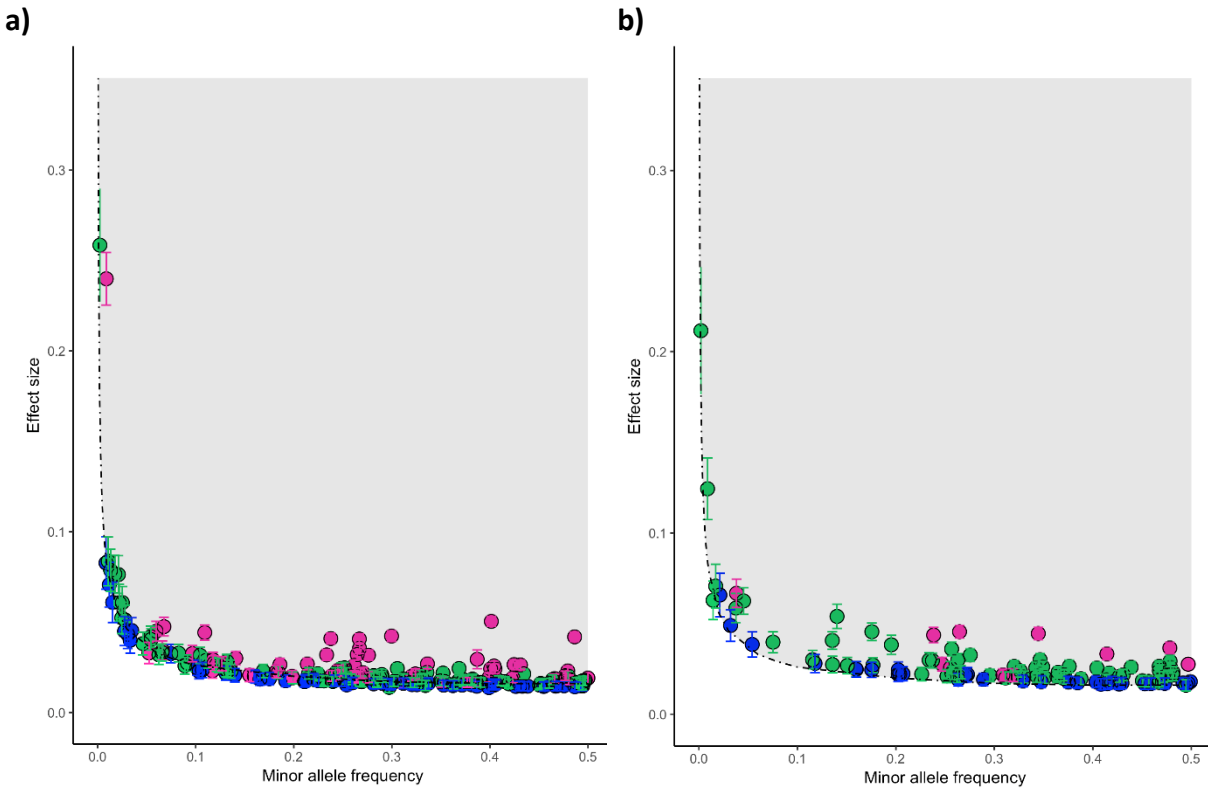
Miami plot and quantile-quantile (QQ) plots of the trans-ethnic meta-analysis of own birth weight (top panel; N=321,223) and offspring birth weight (bottom panel; N=230,069).

The two-sided association P-value (on the $-\log_{10}$ scale for the results of own birth weight and $\log_{10}$ scale for the results of offspring birth weight) obtained from the inverse-variance-weighted fixed-effects meta-analysis for each of the SNPs (y-axis) was plotted against the genomic position (NCBI Build 37; x-axis). Association signals that reached genome-wide significance ($P < 6.6 \times 10^{-9}$) are shown in green if they are novel and pink if they have been previously reported. Association signals with $6.6 \times 10^{-9} < P < 5 \times 10^{-8}$ are shown in purple. In the QQ plots, the black dots represent observed P-values and the grey line represents expected P-values under the null distribution. The red dots represent observed P-values after excluding the previously identified signals (Horikoshi et al. 2016, https://www.nature.com/articles/nature19806; Beaumont et al. 2018, https://academic.oup.com/hmg/article/27/4/742/4788598).



Supplementary Figure 4

Flow diagram describing the genome-wide significant SNPs and loci identified in both the GWAS of own and offspring birth weight.

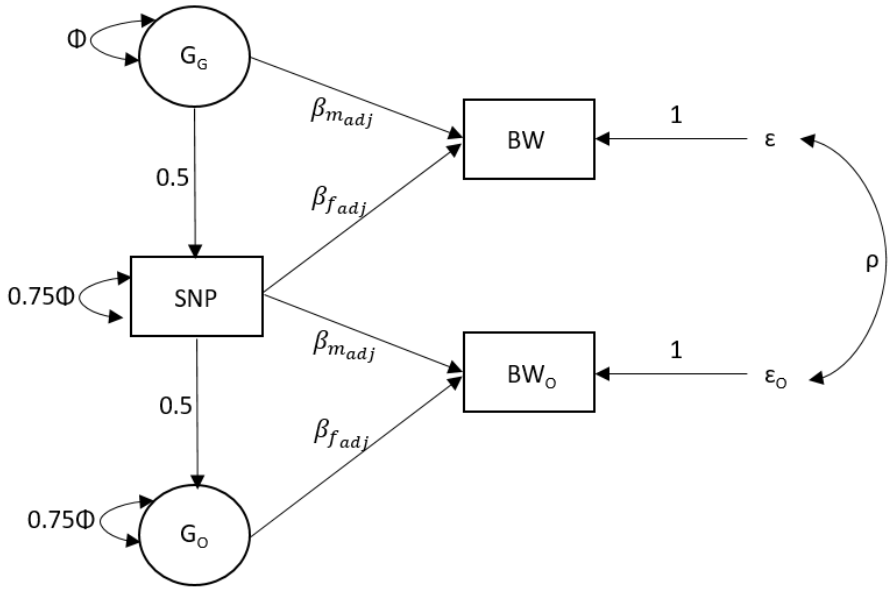


Supplementary Figure 5

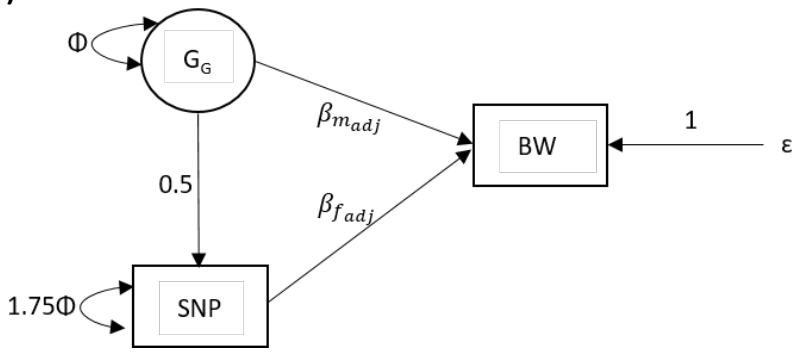
The effect of the 209 SNPs associated with birth weight ($P<6.6 \times 10^{-9}$) in the GWAS inverse-variance-weighted fixed-effects meta-analysis of own birth weight (a; N=321,223) or offspring birth weight (b; N=230,069) as a function of minor allele frequency.

The effect of the 146 independent SNPs from the GWAS of own birth weight **(a)** and 72 independent SNPs from the GWAS of offspring birth weight **(b)** (absolute value of β with 95% confidence interval, y-axis) is given as a function of the minor allele frequency (x-axis) for the known (pink) or novel (green) birth weight associated loci from the meta-analyses. The 96 SNPs with $6.6 \times 10^{-9} < P < 5 \times 10^{-8}$ are presented in blue. Error bars represent the standard error of the effect size. The dashed line indicates 80% power to detect association at genome-wide levels of significance for the sample size in the meta-analysis (assuming a linear regression model was used for the analysis).

a)



b)



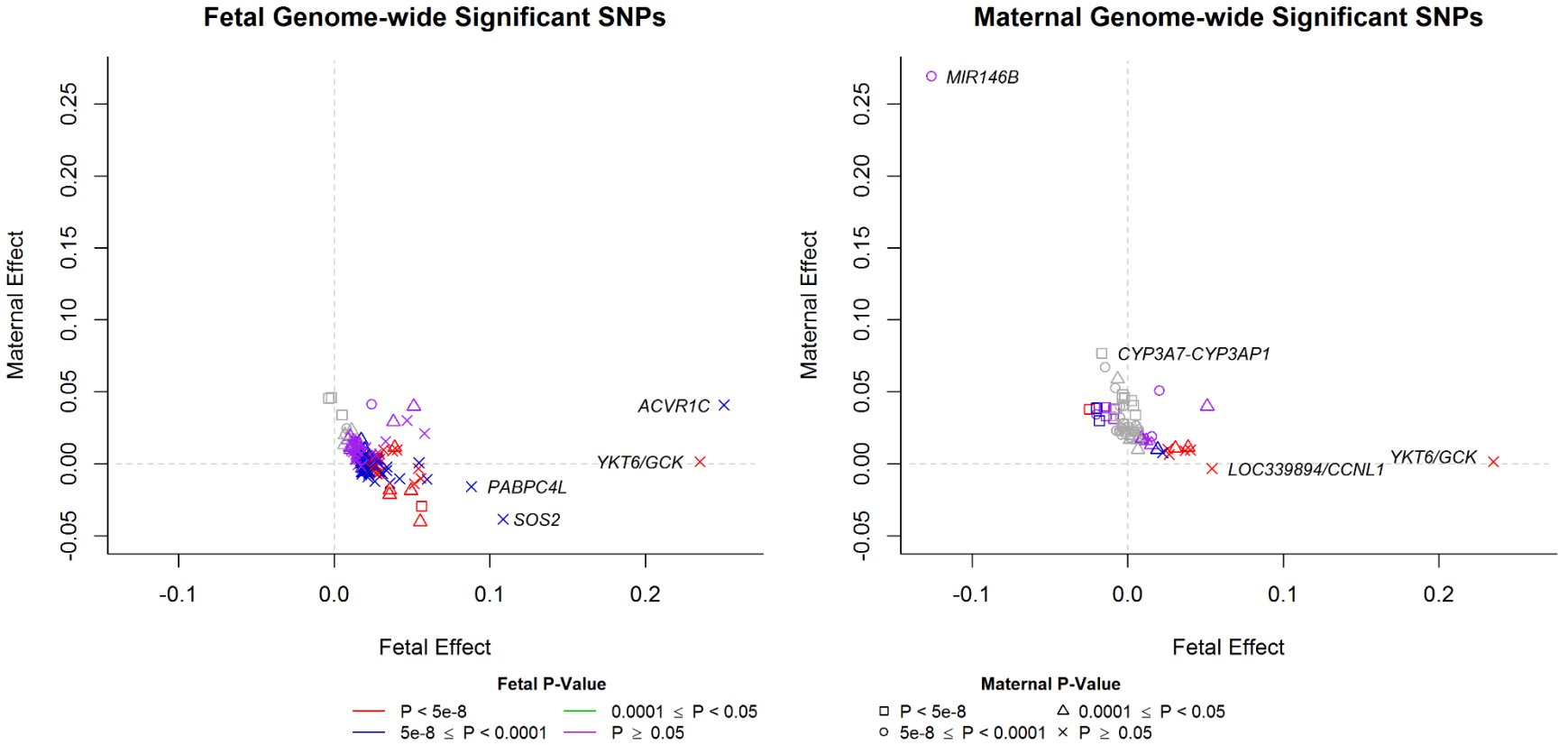
Supplementary Figure 6

Path diagram of the structural equation model (SEM) used to estimate the maternal and fetal effect on birth weight.

The observed variables, displayed in boxes in the path diagram, represent the birth weight of the individual (BW), the birth weight of their offspring (BW_O) and the genotype of the individual (SNP). The two variables in circles represent the unobserved latent genotypes of the individual's mother (G_G) and their offspring (G_O). The $\hat{\beta}_{f_{adj}}$ and $\hat{\beta}_{m_{adj}}$ path coefficients refer respectively to the SEM-adjusted fetal and maternal effects on birth weight. The residual error terms for the birth weight of the individual and their offspring are represented by ε and ε_O respectively.

a) for autosomal SNPs and the X chromosome in females: The total variance of the latent genotypes is set to Φ, the variance of the observed SNP (i.e. $var(G_G) = \Phi$; $var(SNP) = 0.5^2\Phi + 0.75\Phi$; $var(G_O) = 0.5^2\Phi + 0.75\Phi$). The covariance between residual genetic and environmental sources of variation is given by ρ.

b) for X chromosome SNPs in males: The total variance of the latent genotype is set to Φ, the variance of the observed SNP in females (i.e. $var(G_G) = \Phi$) , whereas the variance of the observed genotype in males is set to 2Φ (i.e. $var(SNP) = 0.5^2\Phi + 1.75\Phi = 2\Phi$). Note that male individuals in UKBB do not report the birth weight of their offspring.

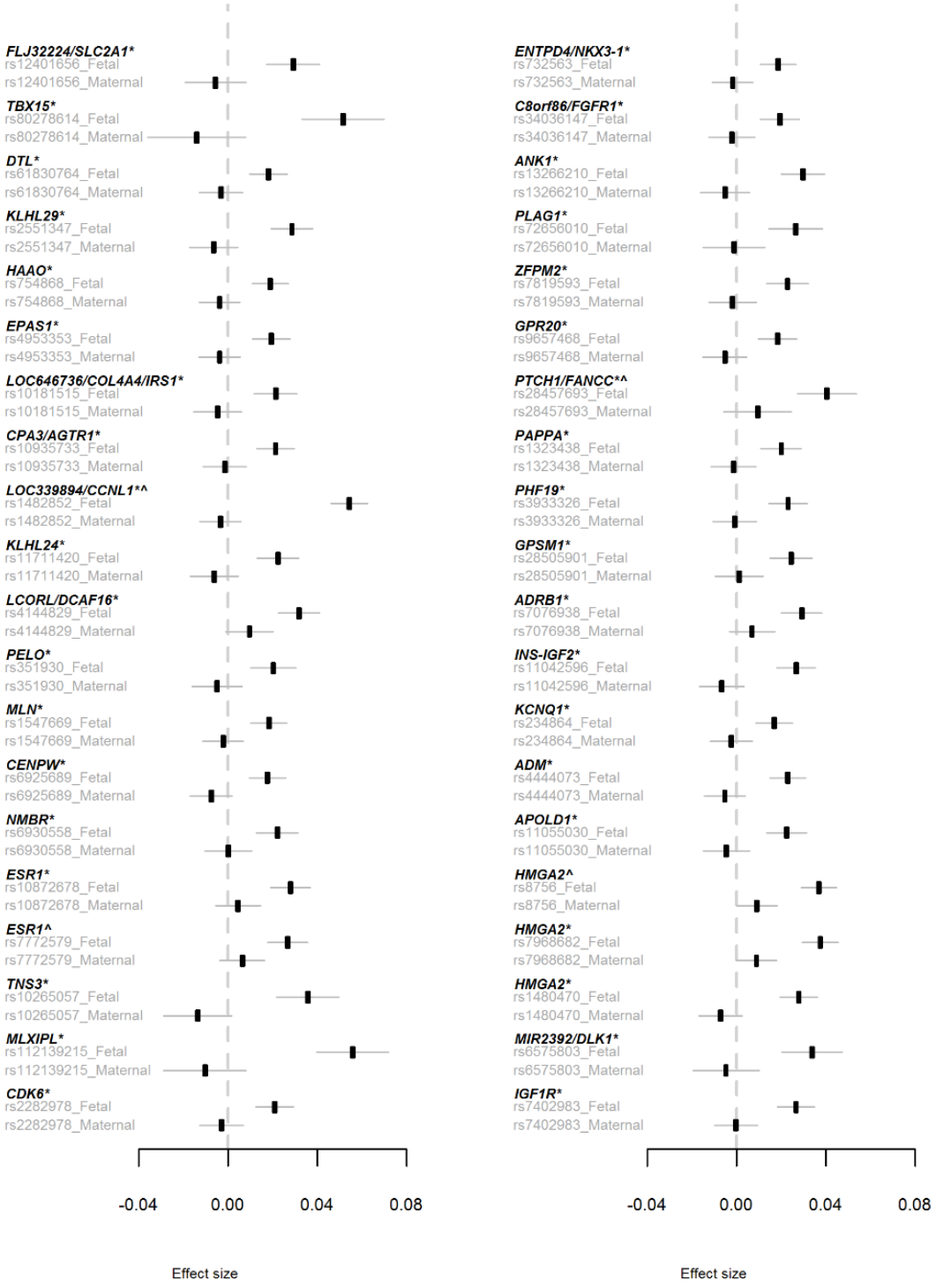


Supplementary Figure 7

Structural equation model (SEM)-adjusted fetal and maternal effects estimated from the SEM for the 209 genome-wide significant SNPs that were identified in either the GWAS meta-analysis of own birth weight (146 independent SNPs; left panel) or offspring birth weight (72 independent SNPs; right panel).

The SEM included 85,518 individuals from the UK Biobank with both their own and offspring's birth weight, 178,980 and 93,842 individuals from the UK Biobank and the EGG consortium with only their own birth weight or offspring's birth weight respectively. The colour of each point indicates the SEM-adjusted fetal effect on own birth weight association P-value and the shape of each point indicates the SEM-adjusted maternal effect on offspring birth weight association P-value. P-values for the fetal and maternal effect were calculated using a two-sided Wald test. SNPs are aligned to the birth weight increasing allele from the GWAS. SNPs with large estimated SEM-adjusted maternal or fetal effects are labelled with the name of the closest gene.

(a)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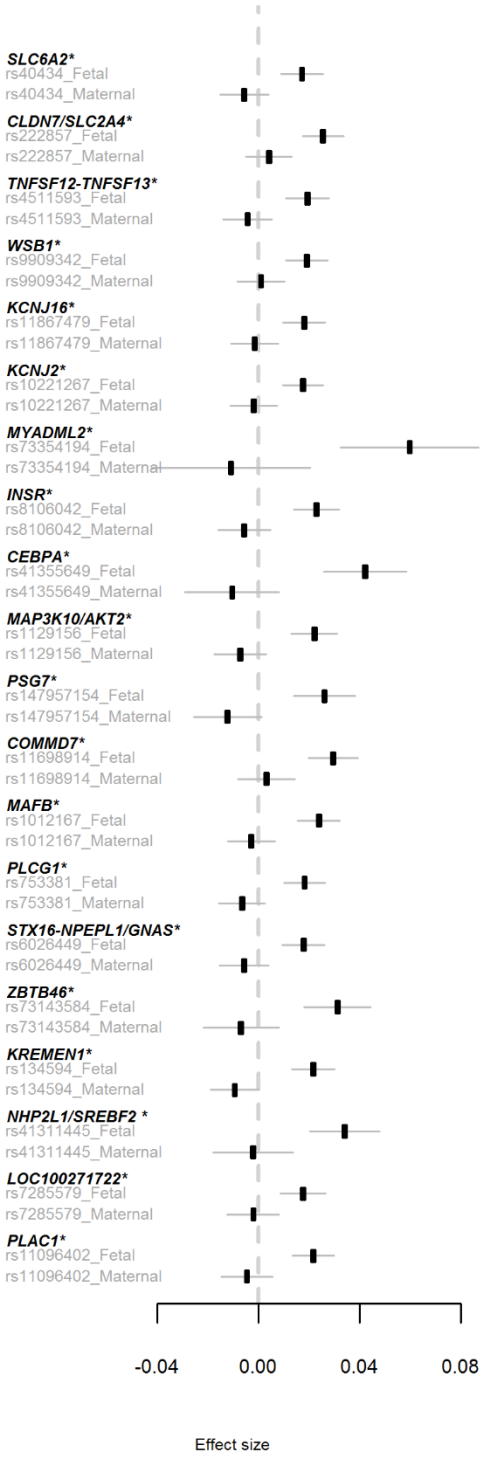
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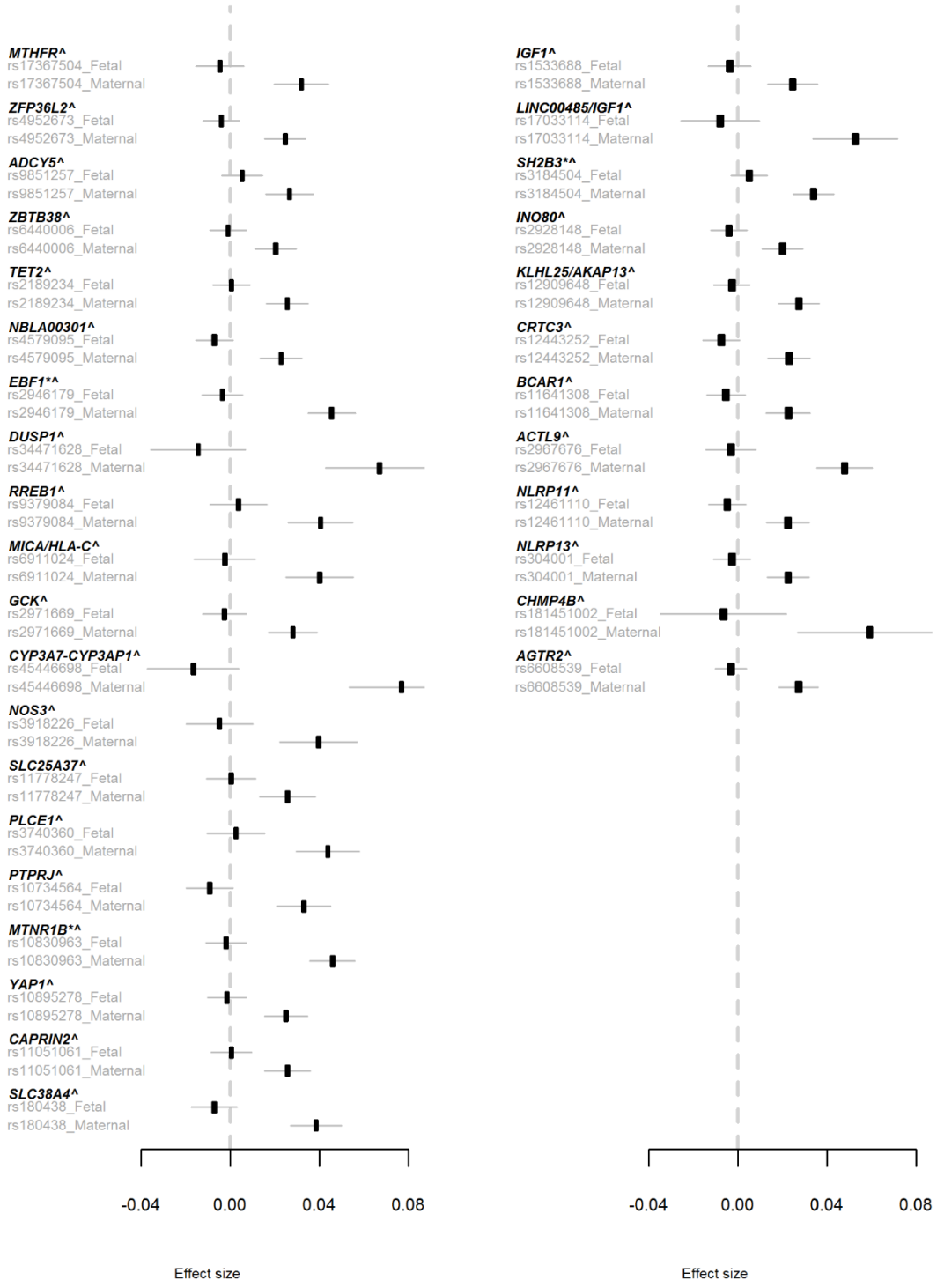
(b)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0.04
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Effect size

(c)


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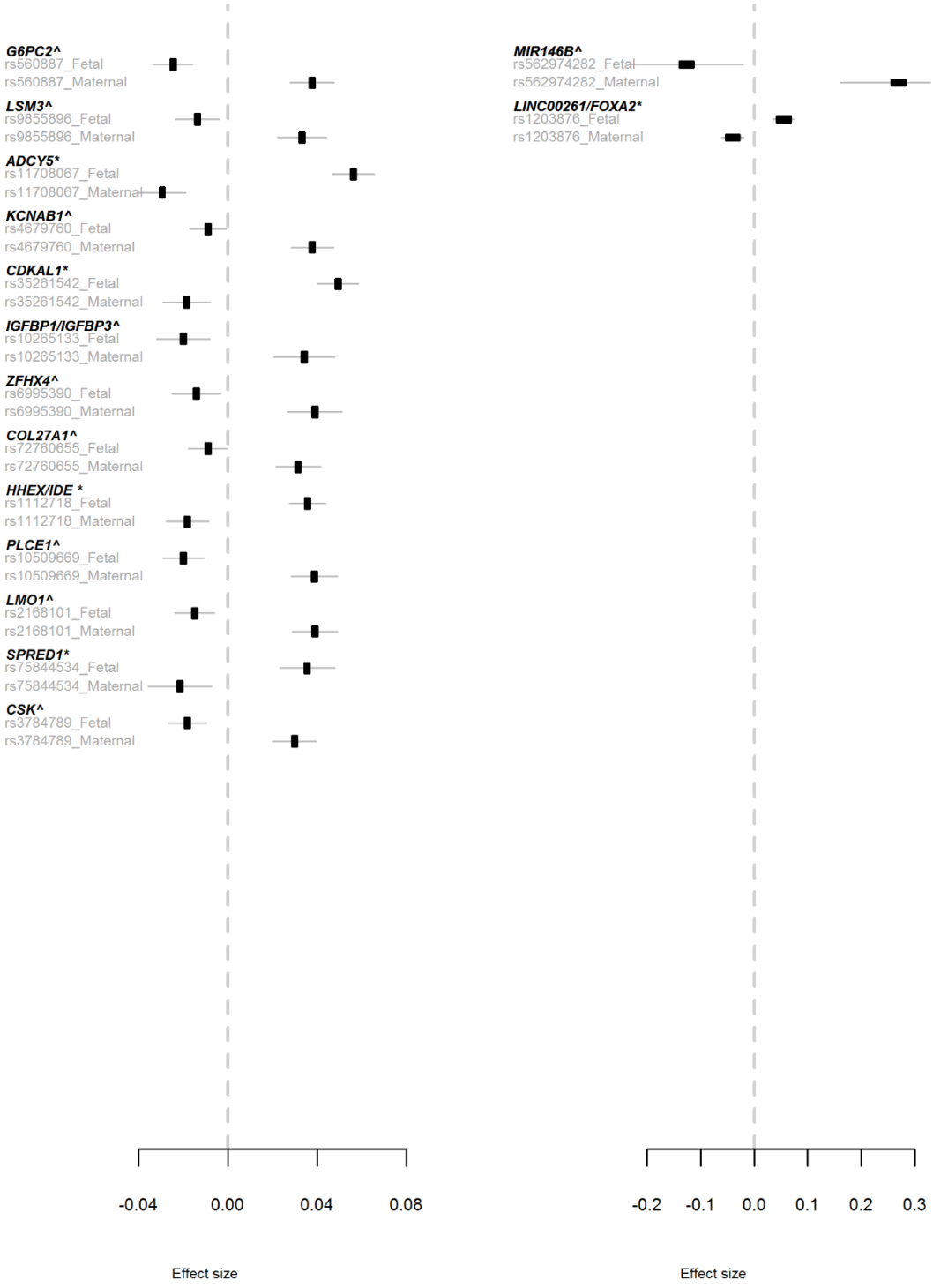
Effect size

(d)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0.2
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Effect size

(e)


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0.00
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Effect size
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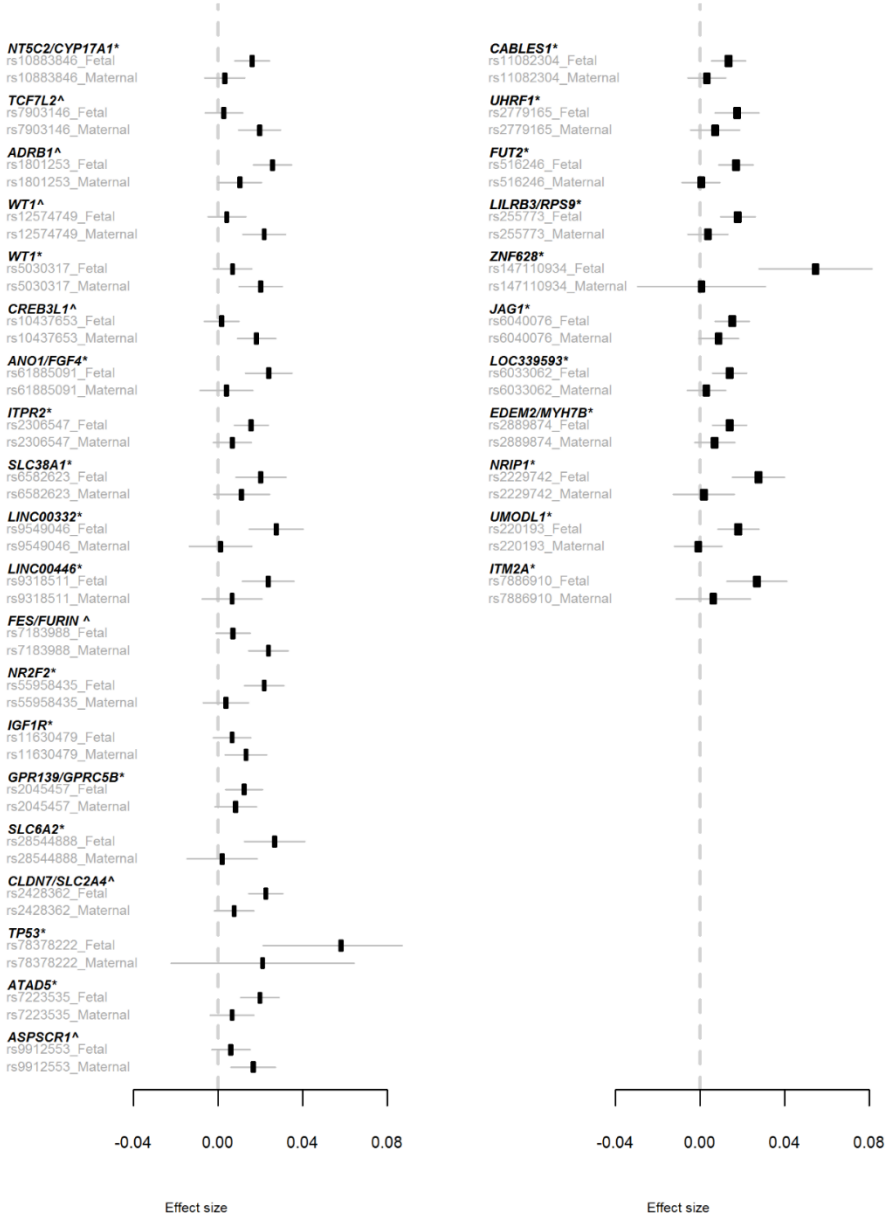
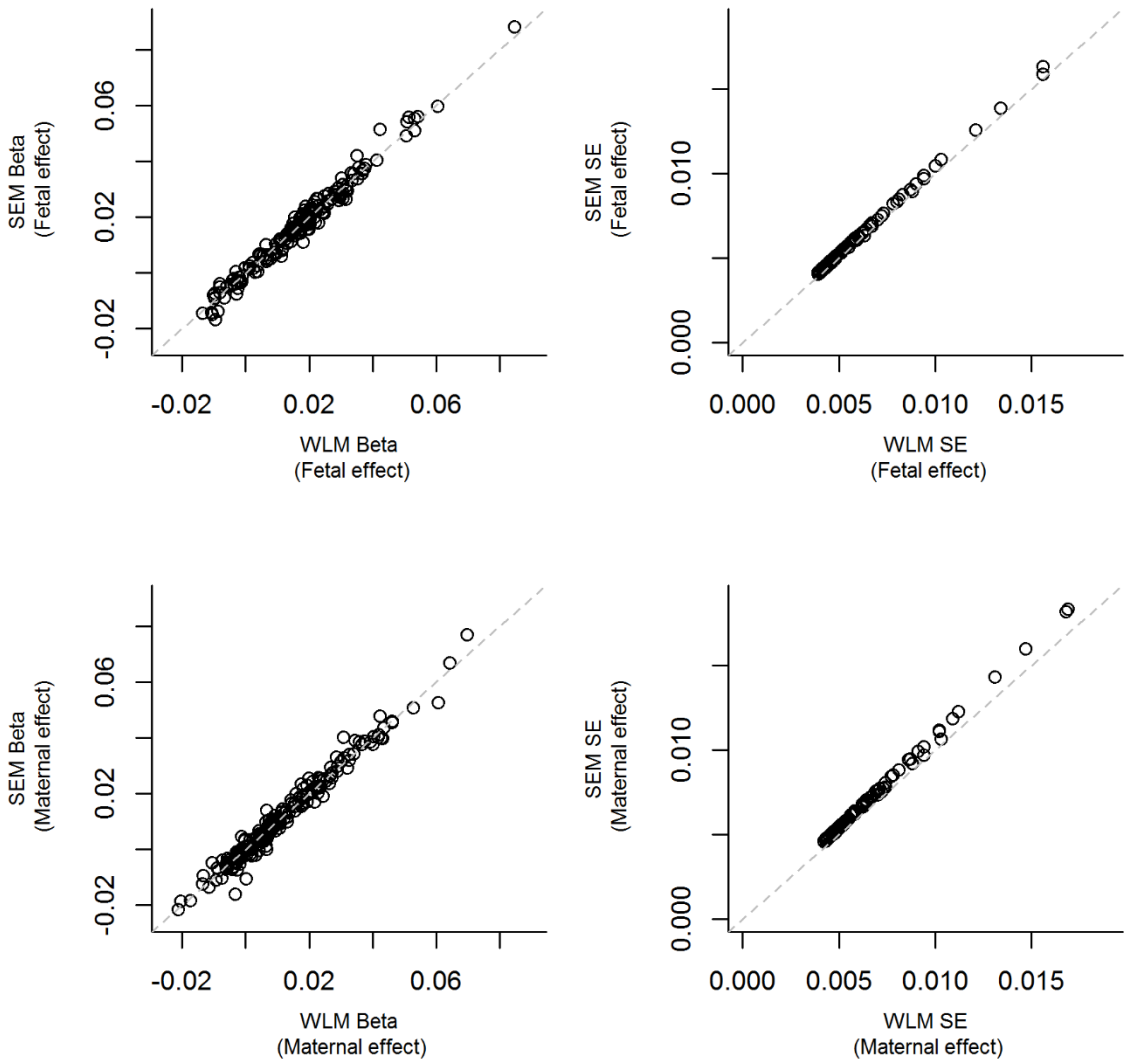
MYL7/GCK^
rs2908279_Fetal
rs2908279_Maternal
IGFBP3*
rs11983722_Fetal
rs11983722_Maternal
MCPH1*
rs62496903_Fetal
rs62496903_Maternal
ENPP2*
rs10283100_Fetal
rs10283100_Maternal
TRIB1*
rs13271368_Fetal
rs13271368_Maternal
SLC45A4*
rs13257363_Fetal
rs13257363_Maternal
PTPDC1*
rs7854962_Fetal
rs7854962_Maternal
RABGAP1/GPR21*
rs10985827_Fetal
rs10985827_Maternal
ARHGAP21*
rs4350272_Fetal
rs4350272_Maternal
PLCE1*
rs2274224_Fetal
rs2274224_Maternal
-0.04
0.00
0.04
0.08
Effect size



Supplementary Figure 8

Comparison of structural equation model (SEM)-adjusted fetal and maternal effect sizes for the 209 genome-wide significant SNPs that were identified in the meta-analysis of own or offspring birth weight.

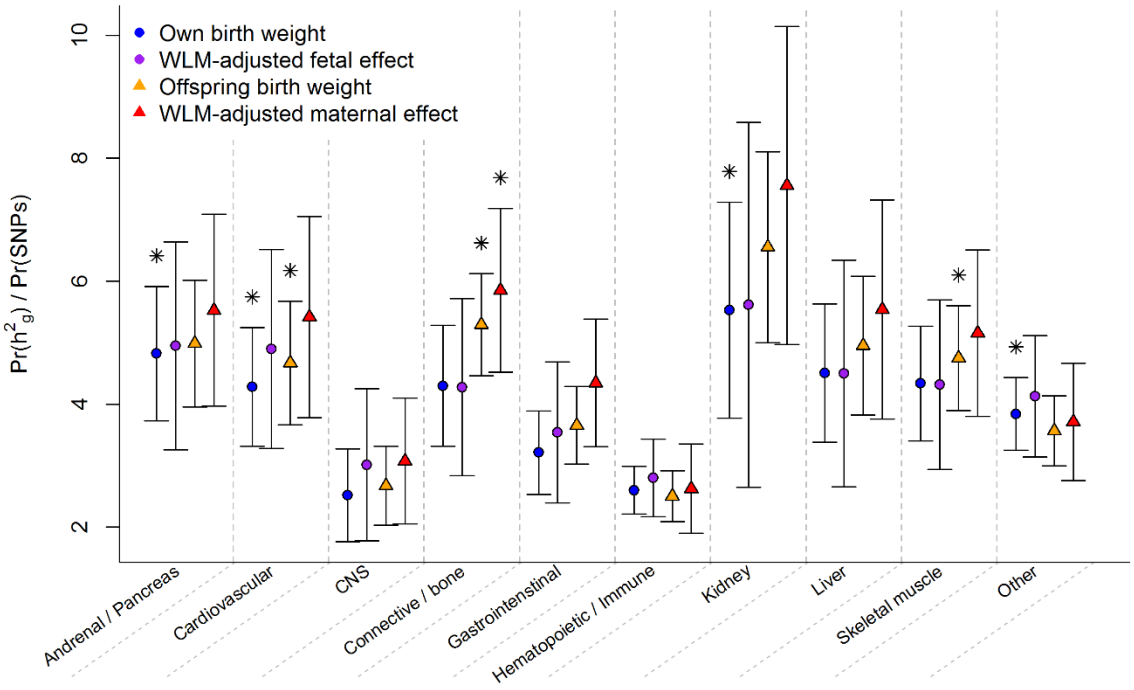
The SEM included 85,518 individuals from the UK Biobank with both their own and offspring's birth weight, 178,980 and 93,842 individuals from the UK Biobank and the EGG consortium with only their own birth weight or offspring's birth weight respectively. The SNPs in panel **(a)** were categorized, based on the SEM results, as having only a fetal effect (N=64 SNPs), panel **(b)** have only a maternal effect (N=32 SNPs), panel **(c)** have both a maternal and fetal effect which are in the same direction (N=27 SNPs), panel **(d)** have both a maternal and fetal effect in opposite directions (N=15 SNPs) and panel **(e)** were unclassified (N=71 SNPs). Within each panel, the SNPs were ordered by chromosome and position. Each SNP is aligned to the birth weight increasing allele from the meta-analysis that it was identified in (i.e SNPs from the GWAS of own birth weight are aligned to the allele that increases own birth weight). The effect sizes shown (with 95% CI) are: 'lead SNP rs number'_Fetal, SEM-adjusted allelic effect on own birth weight; 'lead SNP rs number'_Maternal, SEM-adjusted allelic effect on offspring birth weight. A * after the signal name indicates SNPs that were identified in the GWAS of own birth weight, ^ from the GWAS of offspring and *^ indicates it was identified in both GWAS.



Supplementary Figure 9

Comparison of the effect estimates (left panel) and standard errors (right panel) for the fetal effect (top panel) and maternal effect (bottom panel) from the full SEM (y-axis) and the weighted linear model (WLM; x-axis) for all 197 autosomal genome-wide significant SNPs that converged in the SEM.

The SEM included 85,518 individuals from the UK Biobank with both their own and offspring's birth weight, 178,980 and 93,842 individuals from the UK Biobank and the EGG consortium with only their own birth weight or offspring's birth weight respectively. The WLM included 101,541 individuals from the UK Biobank with both their own and offspring's birth weight, 195,815 and 108,707 individuals from the UK Biobank and the EGG consortium with only their own birth weight or offspring's birth weight respectively. All SNPs are aligned to the birth weight increasing allele from the meta-analysis.

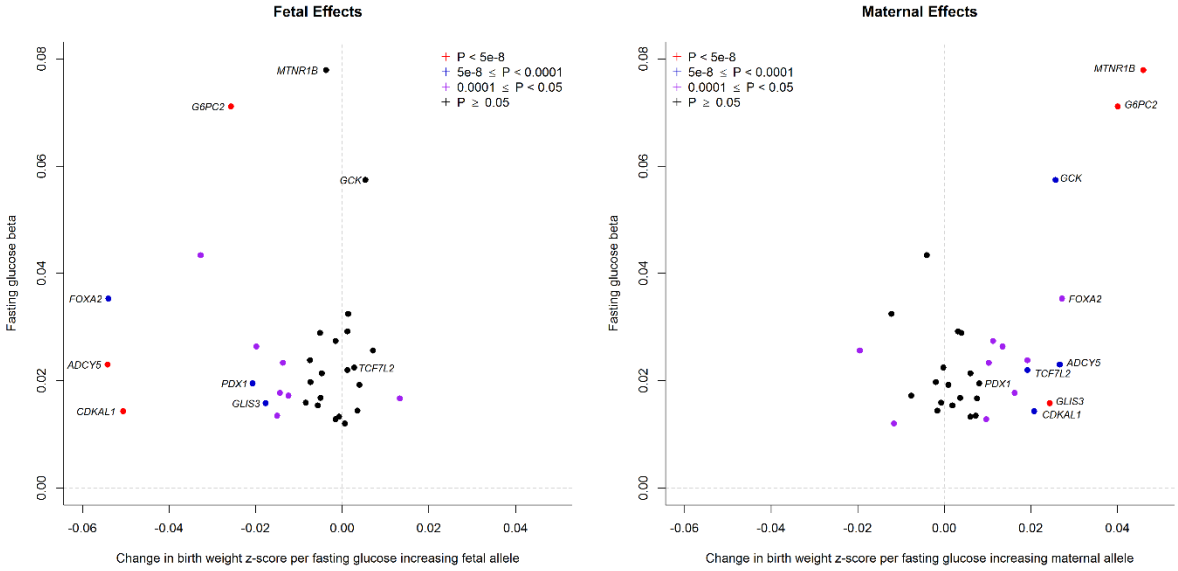


Supplementary Figure 10

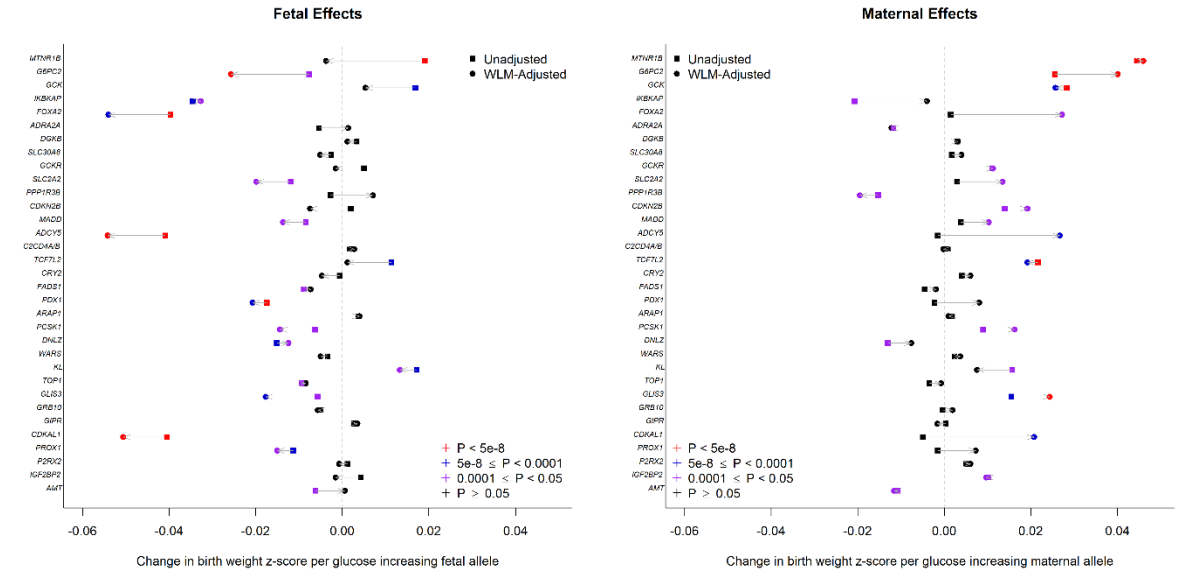
Global enrichment estimates across tissues sampled from the GTEx project.

The enrichment of each cell type group (x-axis) is defined to be the proportion of SNP heritability in the category divided by the proportion of SNPs in that category ($Pr(h^2_g)$ / Pr(SNP); y-axis), estimated using LD-SEG (Finucane et al. 2018, https://www.nature.com/articles/s41588-018-0081-4). Each point is the estimate of enrichment with corresponding 95% confidence interval (calculated using the jackknife standard errors). An asterisk indicates significance at P<0.05 after Bonferroni correction for the 40 hypotheses tested using the P-value for the coefficient corresponding to the annotation (P-values for those asterisks are: Adrenal/Pancreas, Own birth weight=$4.4x10^{-4;}$ Cardiovascular, Own birth weight=$1.9x10^{-4}$; Cardiovascular, Offspring birth weight=$1.7x10^{-4}$; Connective/Bone, Offspring birth weight=$5.4x10^{-8}$; Connective/Bone, WLM-adjusted maternal effect=$6.7x10^{-4}$; Kidney, Own birth weight=$1.1x10^{-3}$; Skeletal muscle, Offspring birth weight=$8.6x10^{-4}$; Other, Own birth weight=$5.9x10^{-6}$). The blue points were estimated using the summary statistics from the GWAS of own birth weight ("Own birth weight"; N=298,142), the purple points using the summary statistics from the GWAS using the weighted linear model (WLM) to estimate the fetal effect on own birth weight ("WLM-adjusted fetal effect"; N=406,063 with their own and/or their offspring's birth weight), the orange triangles using the GWAS of offspring birth weight ("Offspring birth weight"; N=210,267), and the red triangles the WLM for the maternal effect on offspring birth weight ("WLM-adjusted maternal effect"; N=406,063 with their own and/or their offspring's birth weight). CNS, central nervous system.

(a)



(b)

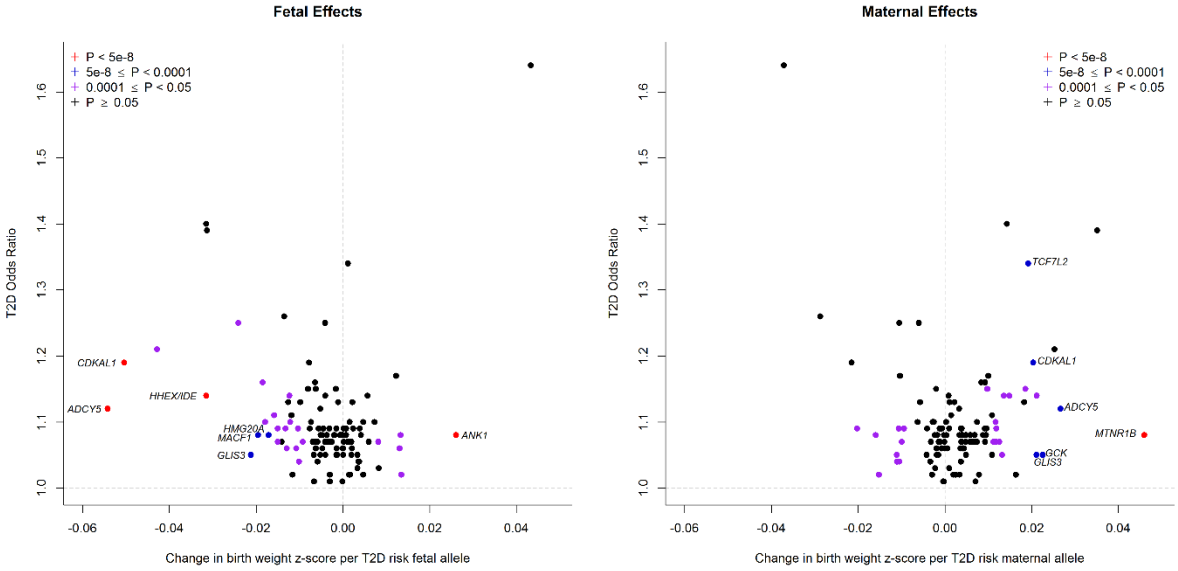


Supplementary Figure 11

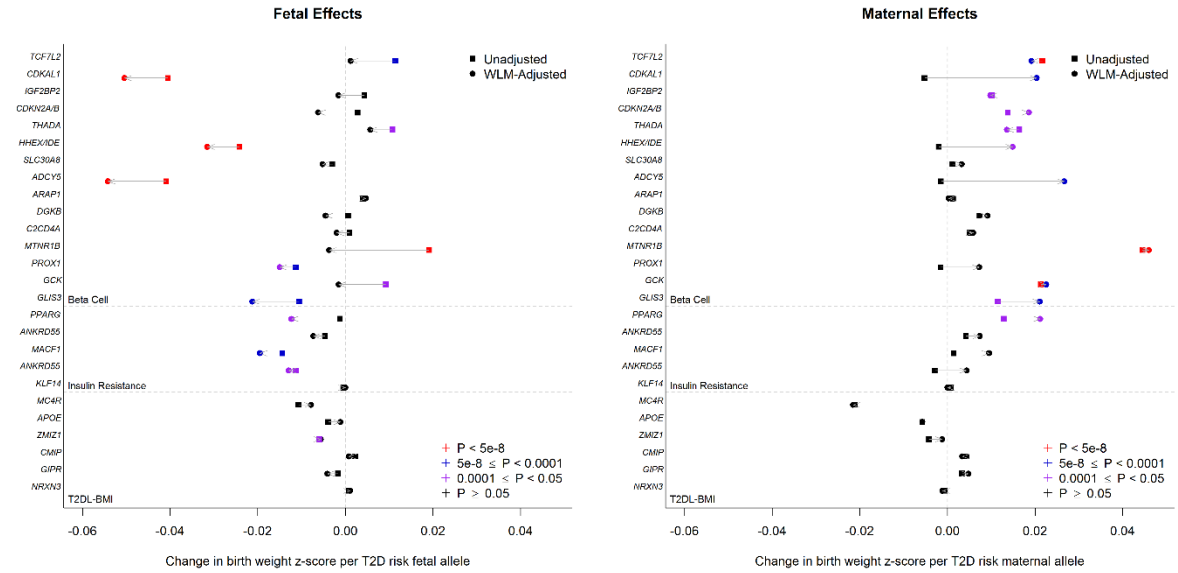
Summary of previously reported loci for fasting glucose and their effect on birth weight.

(a): Effect size (y axis) of the 33 previously reported SNPs for fasting glucose plotted against the effect on birth weight (x axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x-axis) for the 33 known fasting glucose SNPs (y-axis) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment. Details of the SNPs are provided in Supplementary Table 14.

(a)



(b)

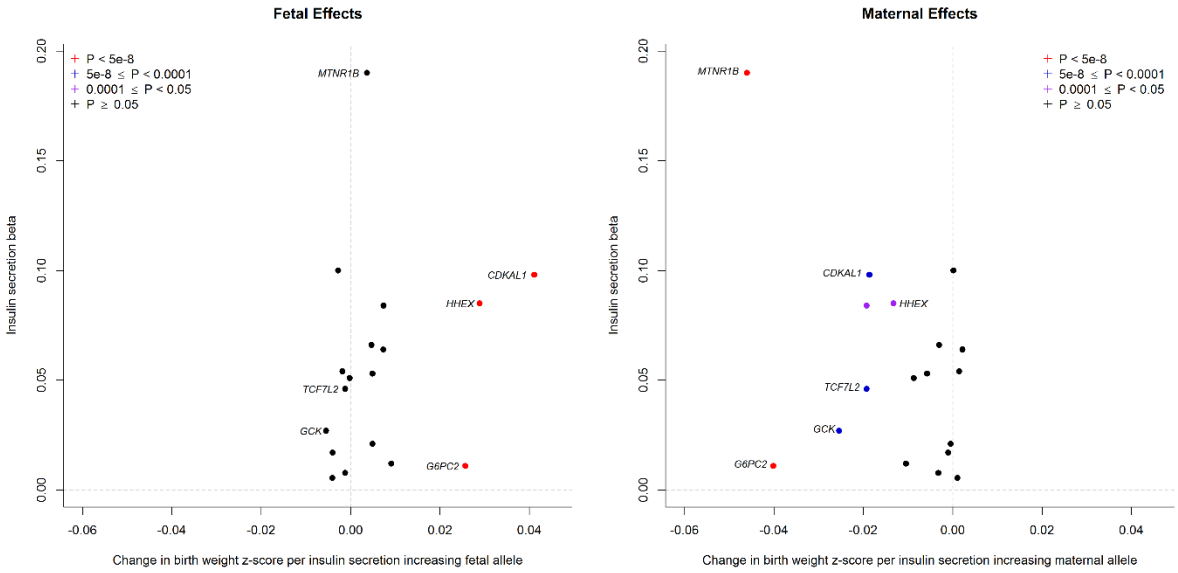


Supplementary Figure 12

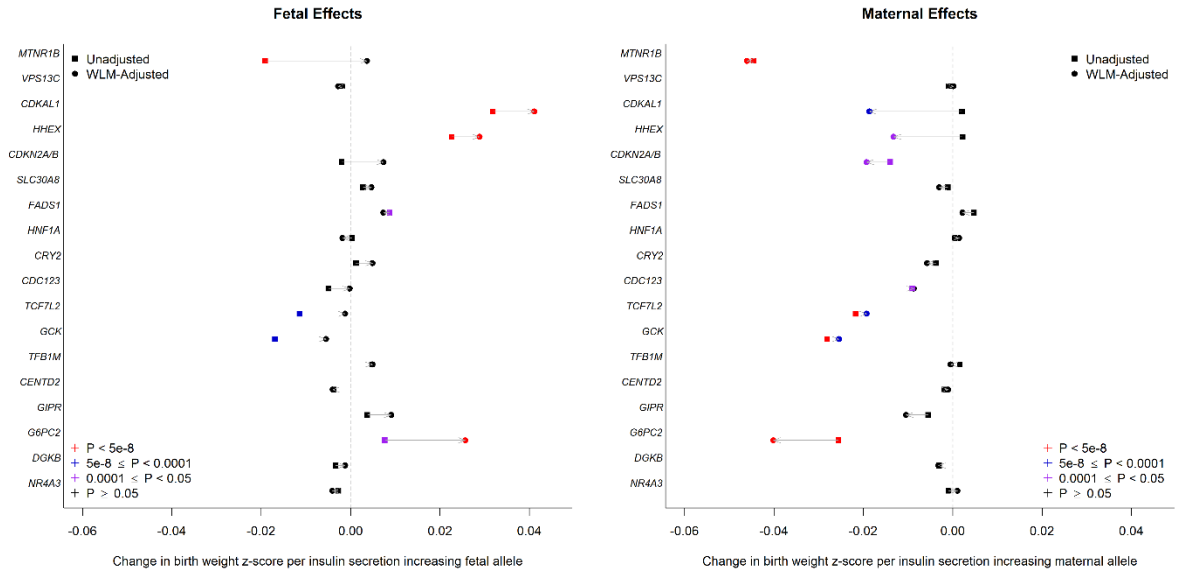
Summary of previously reported loci for type two diabetes (T2D) and their effect on birth weight.

(a): Effect size (y axis) of the 127 previously reported SNPs for T2D (Scott et al. 2017, http://diabetes.diabetesjournals.org/content/early/2017/05/25/db16-1253) plotted against the effect on birth weight (x axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x axis) for the subset of 26 known T2D SNPs which have been categorized by their function (y axis; Scott et al. 2017, http://diabetes.diabetesjournals.org/content/early/2017/05/25/db16-1253) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment.

(a)



(b)

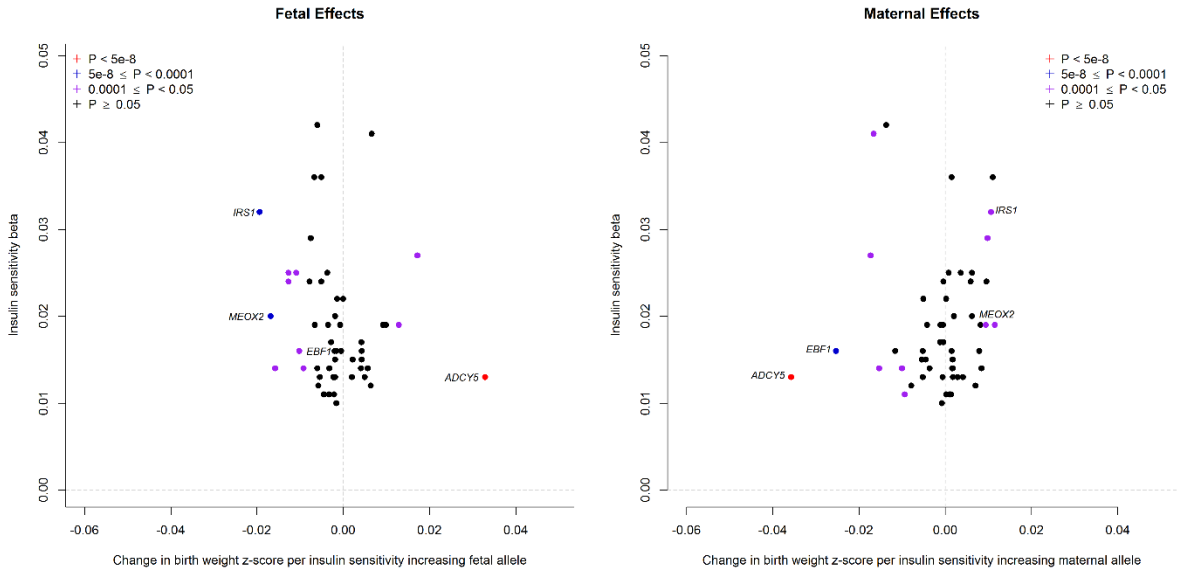


Supplementary Figure 13

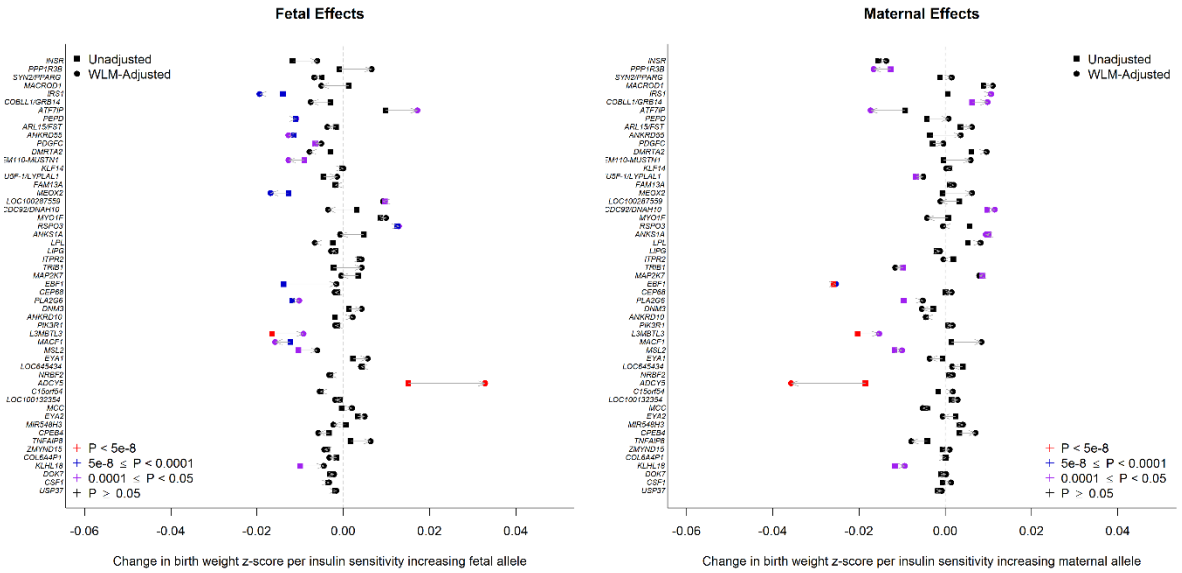
Summary of previously reported loci for insulin secretion and their effect on birth weight.

(a): Effect size (y-axis) of the 18 previously reported SNPs for insulin secretion plotted against the effect on birth weight (x-axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x-axis) for the 18 known insulin secretion SNPs (y-axis) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment. Details of the SNPs are provided in Supplementary Table 14.

(a)



(b)

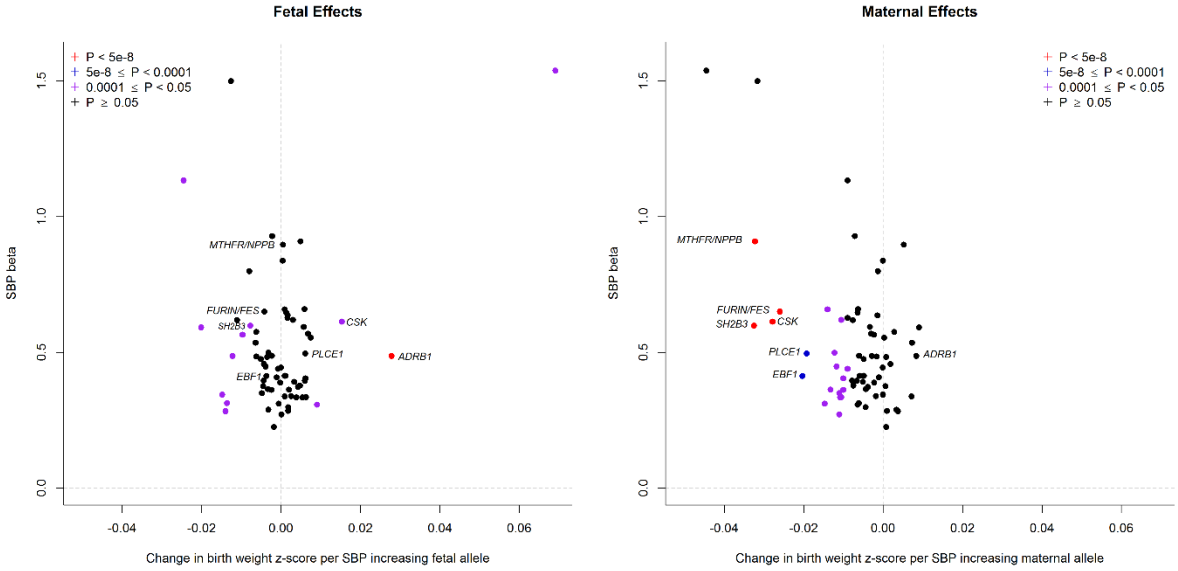


Supplementary Figure 14

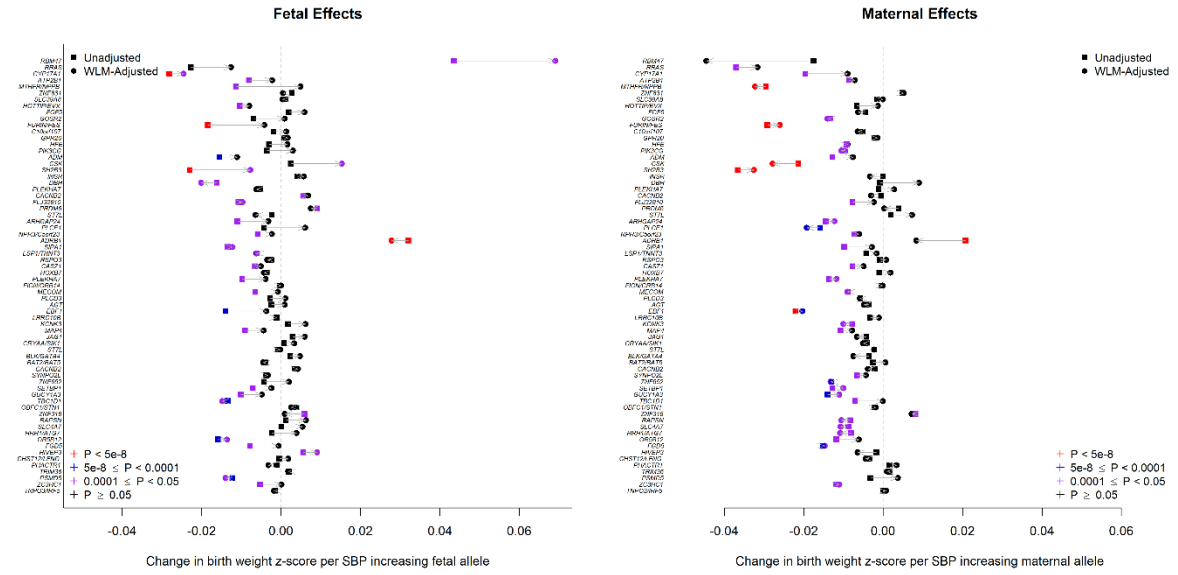
Summary of previously reported loci for insulin sensitivity and their effect on birth weight.

(a): Effect size (y-axis) of the 53 previously reported SNPs for insulin sensitivity plotted against the effect on birth weight (x-axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x-axis) for the 53 known insulin sensitivity SNPs (y-axis) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment. Details of the SNPs are provided in Supplementary Table 14.

(a)



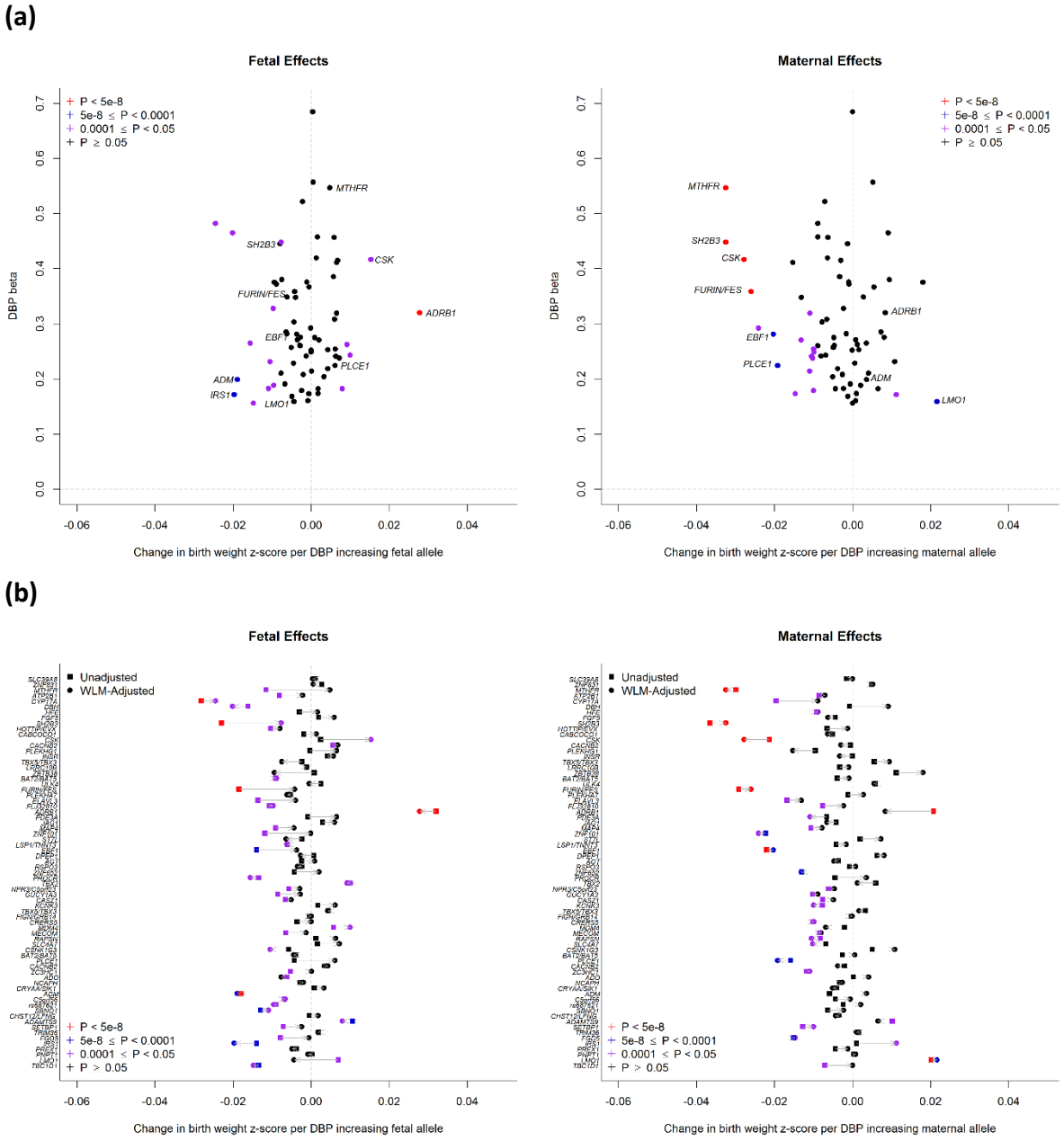
(b)



Supplementary Figure 15

Summary of previously reported loci for systolic blood pressure (SBP) and their effect on birth weight.

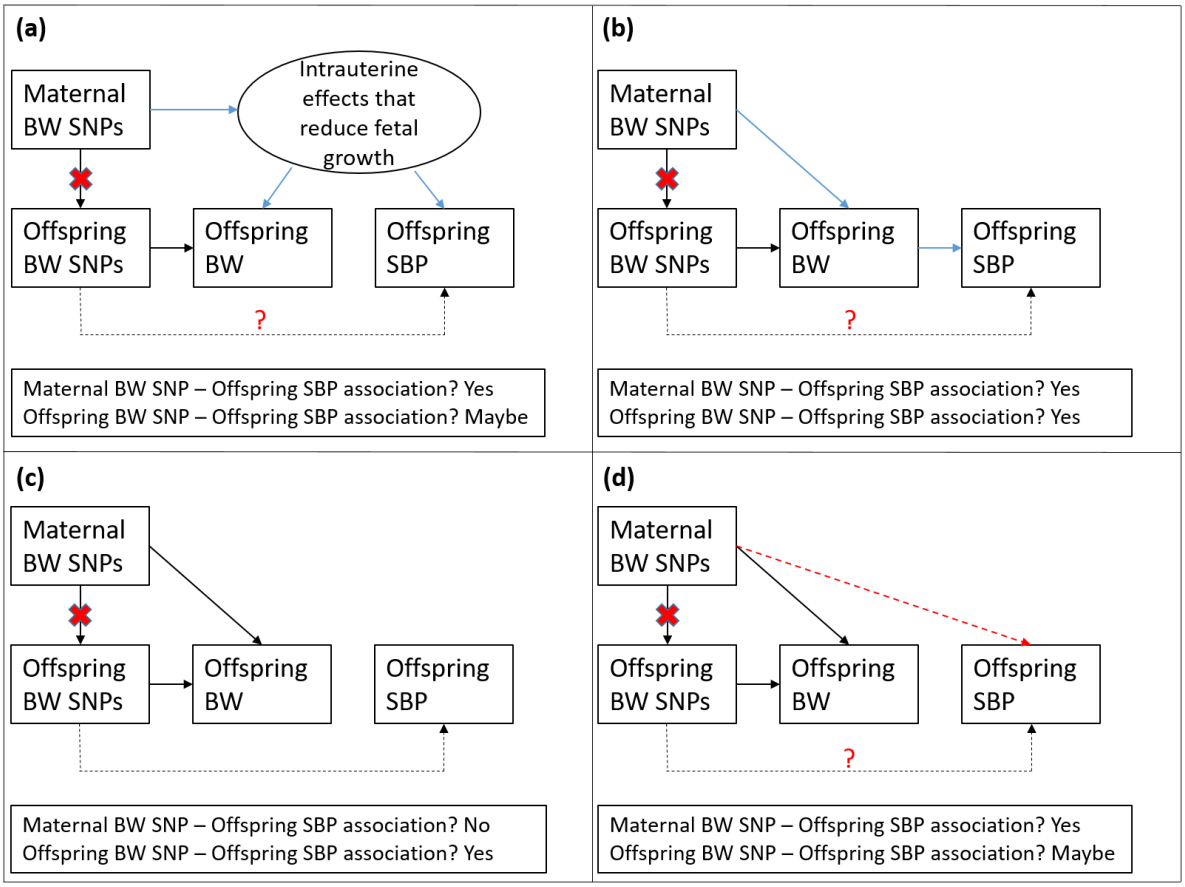
(a): Effect size (y-axis) of the 68 previously reported SNPs for SBP plotted against the effect on birth weight (x-axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x-axis) for the 68 known SBP SNPs (y-axis) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment. Details of the SNPs are provided in Supplementary Table 14.



Supplementary Figure 16

Summary of previously reported loci for diastolic blood pressure (DBP) and their effect on birth weight.

(a): Effect size (y-axis) of the 71 previously reported SNPs for DBP plotted against the effect on birth weight (x-axis) from the weighted linear model (WLM)-adjusted fetal effect on own birth weight in the left plot and the WLM-adjusted maternal effect on offspring birth weight in the right plot. The colour of each dot indicates the birth weight association P-value, which were calculated using a two-sided Wald test. (b): effect sizes on birth weight (x-axis) for the 71 known DBP SNPs (y-axis) in the GWAS meta-analysis (squares) for own birth weight (left plot) and offspring birth weight (right plot). The circles in the left plot represent the WLM-adjusted fetal effect on own birth weight, and in the right plot they represent the WLM-adjusted maternal effect on offspring birth weight. The colour of each point indicates the birth weight association P-value, which were calculated using a two-sided Wald test. The arrows indicate the change in the effect estimate after adjustment. Details of the SNPs are provided in Supplementary Table 14.



Supplementary Figure 17

Possible explanations for the negative genetic correlation between birth weight (BW) and later life systolic blood pressure (SBP).

SNPs may exert indirect maternal and/or direct fetal genetic effects on birth weight. The dashed black path represents the direct fetal effects of inherited birth weight -lowering alleles that also increase offspring SBP. The blue paths represent indirect (intrauterine) effects of maternal SNPs associated with both reduced offspring birth weight and higher offspring SBP. The dashed red path represents possible postnatal effects of maternal SNPs. A red cross indicates a blocked path due to conditioning on offspring/maternal genotype.The existence of SNPs in the mother that exert indirect maternal genetic effects on both offspring birth weight and SBP implies pathways consistent with the Developmental Origins of Health and Disease (DOHaD) hypothesis (blue paths in **panels a and b**). For example, in **panel (a)**, maternal SNPs associated with offspring birth weight produce an adverse intrauterine environment that leads to both reduced fetal growth (and hence birth weight) and to developmental compensations that cause higher offspring SBP in later-life. Under this scenario, SNPs with maternal effects on offspring birth weight will be inversely associated with offspring SBP, whereas SNPs that exert fetal effects on birth weight may not be inversely associated with SBP after conditioning on maternal genotype (depending on whether these fetal genotypes also exert pleiotropic effects on offspring SBP in later life, as indicated by the dashed path with the red question mark).

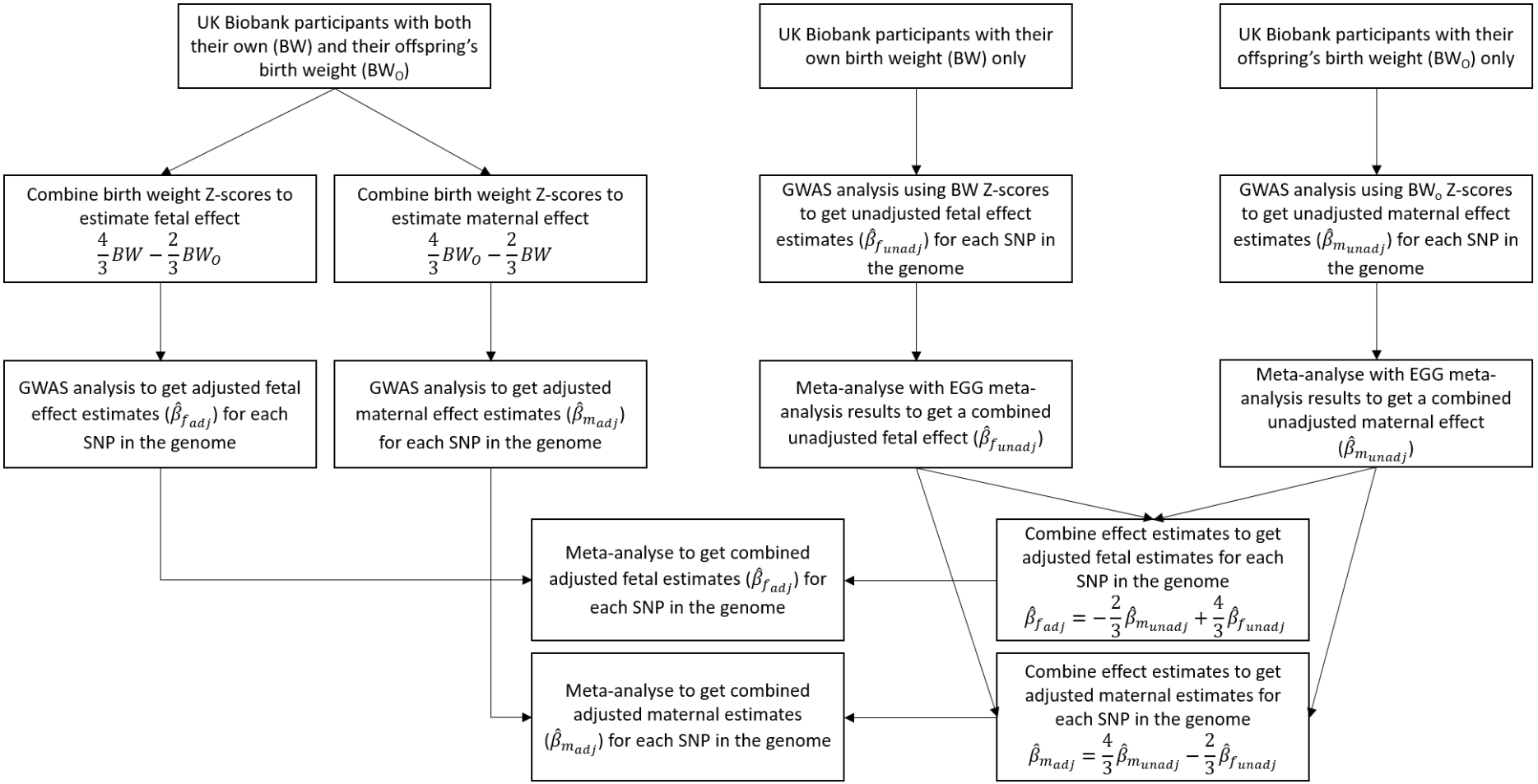
In **panel (b)**, lower offspring birth weight is causal for higher offspring SBP. Under this scenario, SNPs with maternal effects on offspring birth weight will be inversely associated with offspring SBP, as will SNPs with direct fetal effects on birth weight. We stress that although this model is broadly consistent with the DOHaD hypothesis, birth weight *itself* is generally not considered to be directly causal for future cardio-metabolic risk, but rather a marker of an adverse intrauterine environment, like in **panel (a)**. Nevertheless, it is important to consider this possibility, particularly as naïve analyses making similar assumptions have begun to appear[4-6]. Importantly, under **panels (a) and (b)**, the existence of an inverse association between maternal birth weight -associated SNPs and offspring SBP would provide strong support for the DOHaD hypothesis.

In **panel (c)**, the negative genetic correlation between offspring birth weight and offspring SBP is driven by pleiotropic effects of SNPs inherited by the offspring. This model encompasses the possibility of maternal SBP-associated SNPs directly affecting offspring birth weight. These SBP alleles are then transmitted to the offspring where they increase offspring SBP in later life. Under this scenario, offspring birth weight SNPs may be inversely associated with offspring SBP through genetic pleiotropy, whereas maternal SNPs will not be inversely

associated with offspring SBP after conditioning on offspring genotype. In other words, under this model (which is inconsistent with DOHaD), there is no inverse association between maternal birth weight -associated SNPs and offspring SBP.

Finally, in **panel (d)**, SNPs that exert indirect maternal effects on offspring birth weight also pleiotropically influence offspring SBP through the postnatal environment. Under this model, SNPs with maternal intrauterine effects on offspring birth weight will be associated with offspring SBP, whereas SNPs that exert fetal effects on birth weight may not be associated with offspring SBP after conditioning on maternal genotype (again depending on the existence of pleiotropy in the fetal genome). In general, however, we think this last model is less likely since the primary effect of these variants is likely to be on birth weight though the intrauterine environment. Any postnatal environmental effects of these variants, if they exist, on offspring SBP are likely to be small in comparison to their intrauterine effects. We note that the availability of mature genotyped father-offspring duos allows us to test this assumption, since we would expect that paternal genotypes not to be associated with offspring SBP (after conditioning on offspring genotype) in the absence of postnatal environmental effects.

The scenario in **panel (c)** is the most consistent scenario with the results of the current study. NB We have not included environmental factors in these diagrams because our focus is on explaining the genetic correlation between variables.



Supplementary Figure 18

Flow diagram outlining the analysis pipeline to estimate the weighted linear model (WLM)-adjusted fetal and maternal effects on birth weight for each SNP in the genome.

Supplementary Table 1. Description of studies contributing to trans-ancestry GWAS meta-analysis of own birth weight: ancestry group and country of origin, sample size, data collection methods, and birth weight summaries and exclusions.

(a) Component 1: European ancestry GWAS

Study	Ancestry group	Country of origin	Year(s) of birth	Sample size (M/F)	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)			Median (IQR) GA (week) at delivery
							Males	Females	Combined	
1958 British Birth Cohort	European	UK	1958	4,595 (2,320/2,275)	Measured by midwives; supplemented with obstetric records and interviews with mothers	Multiple births, GA <37 weeks	3439 (484)	3277 (468)	3359 (483)	40 (39-41)
ABCD	European	Netherlands	2003-2004	1,107 (536/571)	Youth Health Care Registration	Multiple births, GA <37 weeks	3616 (502)	3498 (449)	3555 (479)	40 (39-41)
ALSPAC[a,b]	European	UK	~1992	7,285 (3,722/3,563)	Identified from obstetric data, records from the ALSPAC measurers, and birth notification	Multiple births, GA <37 weeks, 5 SD winsorisation	3553 (491)	3423 (450)	3490 (476)	40 (40-41)
CHOP-Caucasian	European	USA	1988-present	9,405 (5,040/4,365)	Questionnaire and medical records	Multiple births, GA <37 weeks (when available)	3447 (582)	3343 (549)	3398 (569)	N/A
CoLaus	European	Switzerland	1928-1970	2,089 (892/1,197)	Self-reported as adults	N/A	3490 (668)	3250 (661)	3352 (675)	N/A
COPSAC-2000	European	Denmark	1998-2001	352 (173/179)	Medical records	Multiple births, GA <37 weeks	N/A	N/A	3555 (485)	40 (39-41)
COPSAC-2010	European	Denmark	2008-2011	589 (306/283)	Medical records	Multiple births, GA <37 weeks	3635 (483)	3536 (474)	3588 (481)	40 (39-41)
COPSAC-REGISTRY	European	Denmark	1987-1999	1,210 (804/406)	Medical Records	Multiple births, GA <37 weeks	3609 (498)	3443 (447)	3553 (488)	40 (39-41)
DNBC	European	Denmark	1996-2003	915 (475/440)	Danish Medical Birth Register	Multiple births, GA <37 weeks, congenital abnormalities	3767 (480)	3625 (443)	3699 (468)	40 (40-41)
ERF	European	Netherlands	Various	459 (187/272)	Interview	GA <37 weeks	3161 (680)	2955 (608)	3039 (644)	N/A
EPIC	European	UK	1993-1997	8,939 (3,448/5,491)	Self-reported	N/A	3505 (786)	3266 (750)	3358 (772)	N/A
Fenland (GA+)	European	UK	1950-1975	5,188 (2,088/3,100)	Self-reported as adults	GA described as "very pre-term" or "pre-term"	3433 (638)	3260 (594)	3394 (555)	N/A
Fenland (GA-)	European	UK	1950-1975	833 (509/324)	Self-reported as adults	None	3465 (593)	3154 (608)	3354 (624)	N/A
Generation R	European	Netherlands	2002-2006	2,701 (1,378/1,323)	Hospital records and community midwives	Multiple births, GA <37 weeks	3628 (494)	3518 (475)	3574 (488)	40 (39-41)

Study	Ancestry group	Country of origin	Year(s) of birth	Sample size (M/F)	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)			Median (IQR) GA (week) at delivery
							Males	Females	Combined	
GINIplus & LISA (GA+)	European	Germany	1996-1999	656 (360/296)	Parental report of medical records	Multiple births, GA <37 weeks, <2500g	3498 (406)	3376 (417)	3443 (415)	40 (39-41)
GINIplus & LISA (GA-)	European	Germany	1996-1999	790 (391/399)	Parental report of medical records	Multiple births, GA <37 weeks, <2500g	3499 (429)	3348 (423)	3423 (433)	N/A
GOYA	European	Denmark	1943-1952	149/0 (obese), 141/0 (control)	School health records	N/A	N/A	N/A	3553 (711)	N/A
GOYA offsprings	European	Denmark	1996-2002	907 (461/446)	Measured by midwives and obtained from the Danish National Birth Registry	Multiple births, GA <37 weeks	3808 (504)	3696 (482)	3753 (496)	40 (39-41)
HAPO-EUR	Caucasian	Canada, UK, Australia	2000-2006	1,333 (659/664)	Measured within 72 hours of birth using methods and equipment standardized across all centres	Multiple births, GA <37 weeks, abs(BW-z)>5	3500 (500)	3352 (485)	3425 (498)	40 (39-41)
HBCS	European	Finland	1934-1944	1,472 (639/833)	Birth records	Multiple births, GA <37 weeks	3536 (460)	3375 (439)	3444 (454)	40 (39-41)
HEALTH2006	European	Denmark	1927-1988	1,176 (442/734)	Self-reported as adults	None	3487 (614)	3257 (564)	3343 (593)	NA
INMA	European	Spain	1997-2006	1,021 (527/494)	Well-trained midwives and nurses	None	3362 (406)	3188 (422)	3278 (423)	40 (39-41)
INTER99	European	Denmark	1939-1969	4,243 (1,981/2,262)	Measured by midwives and obtained from obstetric record registry	Multiple births, GA <37 weeks	3505 (493)	3370 (469)	3433 (485)	N/A
Leipzig	European	Germany	1985 - 2010	597 (304/293)	Questionnaire to mothers, documentation of medical screening examination if available	GA <37 weeks	3573 (531)	3480 (538)	3527 (536)	40 (39-40)
NEO	European	Netherlands	1943-1963	504 (exact; 200/304), 3,215 (range; 1,450/1,765)	Questionnaire	N/A	3669 (1068)	3236 (973)	3514 (1271)	N/A
NFBC1966	European	Finland	1966	5,009 (2,393/2,616)	Measured in hospitals	Multiple births, GA <37 weeks or unknown	3607 (506)	3480 (466)	3541 (489)	40 (39-41)
NFBC1986	European	Finland	1986	4,680 (2,306/2,374)	Measured in hospitals	Multiple births, GA <37 weeks or unknown	3626 (543)	3519 (521)	3572 (535)	40 (39-40)
NTR	European	Netherlands	1926-1998	1,265 (447/818)	Parental report or self-reported	Multiple births, GA <37 weeks	3414 (619)	3544 (630)	3343 (601)	40 (40-40)
ORCADES	European	Scotland	1920-1991	960 (330/630)	Self-reported as adults	N/A	3401 (607)	3654 (685)	3488 (640)	N/A
PANIC	European	Finland	1999-2002	436 (231/205)	Medical records and parental questionnaire	Multiple births, GA <37 weeks	3646 (488)	3528 (444)	3588 (474)	40 (39-41)
RAINE	European	Australia	1989-1991	1,347 (693/654)	Recorded at delivery by study personnel or obtained from hospital reports	Multiple births, GA <37 weeks	3505 (471)	3390 (462)	3449 (470)	40 (39-41)

Study	Ancestry group	Country of origin	Year(s) of birth	Sample size (M/F)	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)			Median (IQR) GA (week) at delivery
							Males	Females	Combined	
SKOT	European	Denmark	2006-2007, 2011-2013	348 (173/175)	Measured by midwives and general practitioners; obtained from health records kept by the parents	Multiple births, GA <37 weeks	3706 (472)	3509 (475)	3607 (483)	40 (39-41)
SORBS	European	Germany	1925-1988	298 (113/185)	Interview at recruitment	N/A	N/A	N/A	3393 (673)	N/A
STRIP	European	Finland	1989-1991	599 (311/288)	Medical records	Multiple births, GA <37 weeks	3696 (471)	3535 (443)	3619 (465)	40 (39-40)
TEENAGE (GA+)	European	Greece	1993-1998	279 (126/153)	Measured by midwives or paediatricians; supplemented with data from mothers' interviews	GA <37 weeks	3403 (467)	3280 (421)	3336 (445)	40 (38-40)
TEENAGE (GA-)	European	Greece	1993-1998	551 (234/317)	Measured by midwives or paediatricians; supplemented with data from mothers' interviews	N/A	3398 (459)	3298 (438)	3341 (449)	N/A
TDCOB-cases	European	Denmark	1987-2007	669 (391/278)	Measured by midwives and registered in Danish Civil Registry	Multiple births	3682 (536)	3629 (545)	3660 (540)	40 (39-41)
TDCOB-controls	European	Denmark	1991-2006	560 (211/349)	Measured by midwives and registered in Danish Civil Registry	Multiple births	3627 (517)	3483 (485)	3540 (502)	40 (39-41)
YFS	European	Finland	1962-1977	1,915 (861/1,054)	Mothers' interview	Multiple births, GA >3 weeks pre-term	3648 (491)	3510 (451)	3572 (475)	N/A

(b) Component 2: UK Biobank (European only or All samples)

Study	Ancestry group	Country of origin	Year(s) of birth	Sample size (M/F)	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)			Median (IQR) GA (weeks) at delivery
							Males	Females	Combined	
UK Biobank	European	UK	2006-2010	217,397 (85,063/132,334)	Self-reported as adults	Multiple births, birth weight <2500g or >4500g	3455 (416)	3350 (415)	3391 (418)	N/A
UK Biobank	All	UK	2006-2010	227,530 (89,037/138,493)	Self-reported as adults	Multiple births, birth weight <2500g or >4500g	3452 (417)	3346 (415)	3387 (419)	N/A

(c) Component 3: Non-European ancestry GWAS

Study	Ancestry group	Country of origin	Year(s) of birth	Sample size (M/F)	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)			Median (IQR) GA (weeks) at delivery
							Males	Females	Combined	
CHOP-AA	African American	USA	1988-present	6,635 (3,343/3,292)	Questionnaire and medical records	Multiple births, GA <37 weeks (when available)	3276 (554)	3184 (535)	3231 (546)	N/A
CLHNS	Filipino	Philippines	1983-1984	1,449 (755/694)	Local birth attendants	Multiple births, GA <37 weeks	3067 (401)	3018 (403)	3043 (403)	40 (38-40)
Generation R Turkish	Turkish	Netherlands	2002-2006	420 (215/205)	Hospital records and community midwives	Multiple births, GA <37 weeks	3477 (500)	3369 (415)	3424 (463)	40 (39-41)
Generation R Moroccan	Moroccan	Netherlands	2002-2006	365 (188/177)	Hospital records and community midwives	Multiple births, GA <37 weeks	3642 (447)	3417 (344)	3533 (416)	41 (40-41)
Generation R Surinamese	Surinamese	Netherlands	2002-2006	395 (215/180)	Hospital records and community midwives	Multiple births, GA <37 weeks	3288 (556)	3130 (490)	3216 (532)	40 (39-41)
HAPO-AC	Afro-Caribbean	Barbados	2000-2006	1,052 (544/508)	Measured within 72 hours of birth using methods and equipment standardized across all centres	Multiple births, GA <37 weeks, abs(BW-z)>5	3288 (460)	3163 (410)	3228 (441)	40 (39-41)
HAPO-MA	Hispanic	USA	2000-2006	612 (303/309)	Measured within 72 hours of birth using methods and equipment standardized across all centres	Multiple births, GA <37 weeks, abs(BW-z)>5	3463 (438)	3408 (431)	3435 (435)	40 (39-41)
HAPO-TH	Thai	Thailand	2000-2006	1,180 (575/605)	Measured within 72 hours of birth using methods and equipment standardized across all centres	Multiple births, GA <37 weeks, abs(BW-z)>5	3163 (385)	3027 (368)	3093 (382)	40 (39-41)
SCORM	Chinese	Singapore	1992-1995	840 (420/420)	Documented medical record booklet	GA <37 weeks	3229 (422)	3182 (475)	3205 (450)	39 (38-40)

M, Males; F, Females; GA, gestational age; IQR, interquartile range; N/A, not applicable; SD, standard deviation.

[a]Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* 42, 111-127 (2013).

[b]The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Supplementary Table 2. Description of studies contributing to trans-ancestry GWAS meta-analysis of own birth weight: genotyping, quality control, pre-phasing, imputation, and association analysis.

(a) Component 1: European ancestry GWAS

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda (M/F)
		Call rate	Additional filters	Call rate	HWE *P*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
1958 British Birth Cohort	I550, I610	None	Relatedness, ancestry outliers, sex discrepancy, identity, channel contrast	95%	$1x10^{-4}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	ProbABEL	GA	1.01/1.00
ABCD	ICE	97%	Heterozygosity, relatedness, sex discrepancy, identity	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-4	0.95/0.95
ALSPAC	I550	97%	Heterozygosity, relatedness, ancestry outliers	95%	$5×10^{-7}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC7	1.02/1.01
CHOP-Caucasian	I550, I610	95%	Relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-3	0.96/0.96
CoLaus	A5	90%	Relatedness, ancestry outliers	90%	$1x10^{-7}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	In-house	None	0.99/1.00
COPSAC-2000	I550	97.5%	Heterozygosity, relatedness, ancestry outliers	98%	$1x10^{-6}$	MAF<0.1%	MaCH	Minimac	1000G Mar 2012	mach2qtl	GA	1.00/1.01
COPSAC-2010	IOEE	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	QuickTest	GA, PC1-5	1.01/1.00
COPSAC-REGISTRY	IOEE	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	97.5%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	QuickTest	GA, PC1-5	1.00/1.00
DNBC	I660	96%	Heterozygosity, ancestry outliers, sex discrepancy	98%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA	1.00/1.00
ERF	Various	98%	Relatedness, ancestry outliers, sex discrepancy	98%	$5x10^{-8}$	MAF<0.5%	MaCH	Minimac	1000G Mar 2012	ProbABEL	Kinship matrix	1.02/0.95
EPIC	AUKBB	97%	Heterozygosity, relatedness, sex discrepancy, singletons, channel contrast	95%	$1x10^{-6}$	MAC<1	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-10	1.00/1.01
Fenland (GA+)	AUKBB	95%	Sex discrepancy, identity	95%	$1x10^{-6}$	MAC<2	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-10	1.00/1.01
Fenland (GA-)	AUKBB	95%	Sex discrepancy, identity	95%	$1x10^{-6}$	MAC<2	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-10	0.99/1.00
Generation R	I610, I660	97.5%	Heterozygosity, ancestry outliers, sex discrepancy	98%	$1x10^{-6}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	mach2qtl	GA, PC1-4	1.03/1.01
GINIplus & LISA	A5, A6	95%	Heterozygosity, ancestry outliers, sex discrepancy	95%	$1x10^{-5}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA	0.99/1.00
GOYA	I610	95%	Heterozygosity, ancestry outliers, sex discrepancy	95%	$1x10^{-7}$	MAF<1%	MaCH	MaCH	1000G Mar 2012	QuickTest	None	1.00/0.99

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda (M/F)
		Call rate	Additional filters	Call rate	HWE *p*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
GOYA offsprings	ICE	95%	Heterozygosity, relatedness	95%	$1x10^{-6}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	GA	1.00/1.01
HAPO-EUR	I610	97%	Heterozygosity, relatedness, non-European ancestry, sex discrepancy, chromosomal anomalies	98%	$1x10^{-4}$	MAF<2%	IMPUTE2	IMPUTE2	1000G Mar 2012	R	GA, PC1-2, field centre	0.99/1.00
HBCS	I670	95%	Heterozygosity, relatedness, ancestry outliers	95%	$1x10^{-6}$	MAF<1%	MaCH	MaCH	1000G Mar 2012	mach2qtl	GA	1.02/1.02
HEALTH2006	ICM	95%	Relatedness, non-European ancestry, sex discrepancy	95%	$1x10^{-4}$	MAF<1%	IMPUTE2	IMPUTE2	1000G Mar 2012	SNPTEST	PC1	1.02/0.98
INMA	IOQ	98%	Heterozygosity, relatedness, ancestry outliers, duplicates	95%	$1.1x10^{-6}$	MAF<1%	IMPUTE2	IMPUTE2	1000G Mar 2012	SNPTEST	GA	1.00/0.99
INTER99	ICM	95%	Relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-4}$	MAF<1%	IMPUTE2	IMPUTE2	1000G Mar 2012	SNPTEST	PC1	0.97/1.02
Leipzig	ICM	95%	Duplicates, ancestry outliers, sex discrepancy	95% (99% if MAF<5%)	$1x10^{-4}$	MAF<1%	IMPUTE2	IMPUTE2	1000G Mar 2012	SNPTEST	GA	0.95/0.96
NEO	ICE	98%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	98%	$1x10^{-6}$	None	IMPUTE2	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-5	0.99/0.99
NFBC1966	I370	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy, duplicates, withdrawn consent	95% (99% if MAF<5%)	$5.7x10^{-7}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-3	1.00/0.99
NFBC1986	ICM	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy, duplicates, withdrawn consent	95% (99% if MAF<5%)	$5.7x10^{-7}$ ($1x10^{-4}$ if MAF<5%)	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-3	1.00/1.10
NTR	A6, I370, I660, IOQ	90%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-5}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	PLINK	GA, array, PC1-6 (global), PC1-3 (local)	1.08/1.04
ORCADES	I300, IOQ, IOE	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy, duplicates	95% (99% if MAF<5%)	$1x10^{-6}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	ProbABEL	array, PC1-3	1.00/0.99
PANIC	ICM, ICE	90 %	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-4	1.01/1.01
RAINE	I660	97%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy, chromosomal abnormalities	95%	$5.7x10^{-7}$	MAF<1%	MaCH	MaCH	1000G Mar 2012	ProbABEL	GA, PC1-2	1.01/0.99

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda (M/F)
		Call rate	Additional filters	Call rate	HWE *p*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
SKOT	ICE	95%	Heterozygosity, relatedness	95%	$1x10^{-6}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	GA	1.01/1.01
SORBS	I660	94%	Relatedness, ancestry outliers, sex discrepancy, duplicates	95%	$1x10^{-4}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	ProbABEL	Kinship matrix	1.01/1.01
STRIP	A5, A6	95%	Heterozygosity, ancestry outliers, twins	95%	$1x10^{-6}$	MAF<0.1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1-4	1.01/1.01
TEENAGE (GA+)	ICM	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	95% (99% if MAF<5%)	$1x10^{-4}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	GA	1.02/1.00
TEENAGE (GA-)	IOE	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy	95% (99% if MAF<5%)	$1x10^{-4}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	None	1.02/0.98
TDCOB-cases	IOE	95%	Heterozygosity, relatedness, ancestry outliers	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1	1.02/1.01
TDCOB-controls	ICE	95%	Heterozygosity, relatedness, ancestry outliers	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA, PC1	1.02/1.05
YFS	I670	95%	Heterozygosity, relatedness, sex discrepancy, duplicates	95%	$1x10^{-6}$	MAF<1%	SHAPEIT	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-4	0.99/1.01

(b) Component 2: UK Biobank

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda
		Call rate	Additional filters	Call rate	HWE *P*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
UK Biobank	AUKBB	98%	Heterozygosity, relatedness, ancestry outliers	95%	N/A	MAF<1%	SHAPEIT2	IMPUTE2	HRC	BOLT-LMMv2.3	Sex, genotype array	N/A

(c) Component 3: Non-European ancestry GWAS.

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda (M/F)
		Call rate	Additional filters	Call rate	HWE *P*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
CHOP-AA	I550, I610	95%	Relatedness, ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	PC1-3	0.98/0.98
CLHNS	ICM	98.6%	Relatedness, sex discrepancy	97%	$1×10^{-6}$	N/A	MaCH	MaCH	1000G Mar 2012	mach2qtl	GA	1.02/1.02
Generation R Turkish	I610, I660	97.5%	Heterozygosity, ancestry outliers, sex discrepancy	95%	$1x10^{-7}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	mach2qtl	GA, PC1-4	1.01/1.02
Generation R Moroccan	I610, I660	97.5%	Heterozygosity, ancestry outliers, sex discrepancy	90%	$1x10^{-7}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	mach2qtl	GA, PC1-4	1.01/0.98
Generation R Surinamese	I610, I660	97.5%	Heterozygosity, ancestry outliers, sex discrepancy	98%	$1x10^{-7}$	MAF<1%	MaCH	Minimac	1000G Mar 2012	mach2qtl	GA, PC1	0.99/0.95
HAPO-AC	IOQ	97%	Heterozygosity, relatedness, non-European ancestry, sex discrepancy, chromosomal anomalies	98%	$1x10^{-4}$	MAF<2%	IMPUTE2	IMPUTE2	1000G Mar 2012	R	GA, PC1-2, field centre	1.01/1.01
HAPO-MA	IOQ	97%	Heterozygosity, relatedness, non-European ancestry, sex discrepancy, chromosomal anomalies	98%	$1x10^{-4}$	MAF<2%	IMPUTE2	IMPUTE2	1000G Mar 2012	R	GA, PC1-2, field centre	0.99/0.98
HAPO-TH	IOQ	97%	Heterozygosity, relatedness, non-European ancestry, sex discrepancy, chromosomal anomalies	98%	$1x10^{-4}$	MAF<2%	IMPUTE2	IMPUTE2	1000G Mar 2012	R	GA, PC1-2, field centre	0.99/1.00
SCORM	I550	95%	Heterozygosity, relatedness, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	SHAPEIT2	IMPUTE2	1000G Mar 2012	SNPTEST	GA	0.98/0.99

HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; MAC, minor allele count; GA, gestational age; PC, principal component.

[a]Genotype array codes: Affymetrix 5.0 (A5); Affymetrix 6.0 (A6); Affymetrix Axiom UK BiLEVE (AUKBL); Affymetrix Axiom UK Biobank (AUKBB); Illumina Human370CNV (I370); Illumina HumanHap550 (I550); Illumina HumanHap610 (I610); Illumina HumanHap660 (I660); Illumina HumanHap670 (I670); Illumina CardioMetabochip (ICM); Illumina OmniQuad (IOQ); Illumina OmniExpress (IOE); Illumina CoreExome (ICE); Illumina OmniExpressExome (IOEE).

Supplementary Table 3. Description of studies contributing to trans-ancestry GWAS meta-analysis of offspring birth weight: ancestry group and country of origin, sample size, data collection methods, and birth weight summaries and exclusions.

(a) Component 1: European ancestry GWAS

Study	Ancestry group	Country of origin	Year(s) of birth of offspring	Mean (SD) maternal age at delivery (year)	Sample size	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)	Median (IQR) GA (week) at delivery
1958 British Birth Cohort (B58C-WTCCC)	European	UK	1972-2000	26.2 (5.2)	858	Maternal self-report	Multiple births, GA <37 weeks, still birth, congenital anomalies	3325 (483)	40 (40-41)
1958 British Birth Cohort (B58C-T1DGC)	European	UK	1972-2000	26.1 (5.4)	836	Maternal self-report	Multiple births, GA <37 weeks, still birth, congenital anomalies	3379 (469)	40 (40-41)
ALSPAC[a,b] Mothers	European	UK	1991-1992	28.0 (5.0)	6,686	Identified from obstetric data, records from the ALSPAC measurers, and birth notification	Multiple births, GA <37 weeks, still birth, congenital anomalies	3468 (478)	40 (40-41)
DNBC-GOYA Random set	European	Denmark	1996-2002	29.2 (4.2)	1,805	Danish Medical Birth Register	Multiple births, GA <37 weeks, still birth, congenital anomalies	3643 (495)	40 (39-41)
DNBC-PTB-CONTROL Mothers	European	Denmark	1987-2009	29.9 (4.2)	1,656	Danish Medical Birth Register	Multiple births, GA <37 weeks, still birth, congenital anomalies	3595 (497)	40 (39-40)
EFSOCH Mothers	European	UK	2000-2004	30.5 (5.2)	855	Measured within 12 hours of birth	Multiple births, GA <37 weeks, still birth, congenital anomalies	3506 (472)	40 (37-43)
HAPO Mothers	Caucasian	Canada, UK, Australia	2000-2006	31.5 (5.3)	1,280	Medical record abstraction	Multiple births, GA <37 weeks, still birth, congenital anomalies	3557 (517)	40 (SD 1.7)
MoBa-2008 Mothers	European	Norway	1999-2008	28.5 (3.3)	650	Medical Birth Register of Norway	Multiple births, GA <37 weeks, still birth, congenital anomalies	3679 (430)	40 (SD 0.86)
NFBC1966	European	Finland	1987-2001	26.5 (3.7)	2,035	Birth Register Data	Multiple births, GA <37 weeks or unknown, still birth, congenital anomalies	3525 (461)	40 (SD 2)
NTR	European	Netherlands	1946-2003	27.1 (3.7)	707	Parental report or self-reported	Multiple births, GA <37 weeks, still birth, congenital anomalies	3469 (529)	40 (38-42)
QIMR	European	Australia	1929-1990	24.5 (4.0)	892	Self-report through questionnaire	Multiple births, still birth, congenital anomalies	3344 (532)	N/A
TWINSUK	European	UK	N/A	N/A	1,603	Questionnaire	Multiple births, still birth, congenital anomalies	N/A	N/A

(b) Component 2: UK Biobank (European only or All samples)

Study	Ancestry group	Country of origin	Year(s) of birth	Mean (SD) maternal age at delivery (year)	Sample size	Data collection	Phenotype exclusions	Mean (SD) birth weight (grams)	Median (IQR) GA (weeks) at delivery
UK Biobank	European	UK	1936-1970	25.3 (4.5)	190,406	Maternal self-report	Multiple births, birth weight <2200g or >4600g	3227.1 (477)	N/A
UK Biobank	ALL	UK	1936-1970	25.3 (4.6)	210,208	Maternal self-report	Multiple births, birth weight <2200g or >4600g	3218.5 (478)	N/A

M, Males; F, Females; GA, gestational age; IQR, interquartile range; N/A, not applicable; SD, standard deviation.

Replication data for 18 SNPs collected from the following studies were used in the previous Maternal GWAS paper (Beaumont RB, Warrington NM et al. 2018): Berlin Berth Cohort Mothers (N=1,319), CHOP Mothers (N=312), COPSAC-2000 Mothers (N=282), FHS Mothers (N=1,118), GEN-3G Mothers (N=685), Generation R Mothers (N=3,187), HAPO Mothers (non-GWAS, N=3,701), INMA Mothers (N=1,525), NCCGP Mothers (N=1,113), RAINE Mothers (N=1,337), RHEA Mothers (N=970) and SWS Mothers (N=1,928). These data were not combined in the current meta-analysis, but meta-analysis results including these 12,129 individuals for the 2 signals (out of 18) that achieved $p<5x10^{-8}$ are included in the footnote of Supplementary Table 5

[a]Fraser A, Macdonald-Wallis C, Tilling K, Boyd A et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *Int J Epidemiol* 42, 97-110 (2013).
[b]The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

Supplementary Table 4. Description of studies contributing to trans-ancestry GWAS meta-analysis of offspring birth weight: genotyping, quality control, pre-phasing, imputation, and association analysis.

(a) Component 1: European ancestry GWAS

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Imputation		Association analysis		Lambda
		Call rate	Additional filters	Call rate	HWE *P*-value	Frequency	Software	Reference panel	Software	Covariates or adjustment	
1958 British Birth Cohort or NDCS (B58C-WTCCC)	A6	None	Relatedness, ancestry outliers, sex discrepancy, identity, channel contrast	98%	$1x10^{-20}$	MAF<1%	IMPUTE2	HapMap Phase II	SNPTEST	Sex, GA	0.984
1958 British Birth Cohort or NDCS (B58C-T1DGC)	I550	97%	Heterozygosity, ancestry outliers, sex discrepancy	95%	$1x10^{-7}$	MAF<1%	IMPUTE2	HapMap Phase II	SNPTEST	Sex, GA	1.007
ALSPAC Mothers	I660	95%	Heterozygosity, ancestry outliers, identity	95%	$1×10^{-7}$	MAF<1%	MaCH	HRC	SNPTEST	Sex, GA, PC	1.003
DNBC-GOYA Random set	I610	95%	Heterozygosity, ancestry outliers, sex discrepancy	95%	$1x10^{-7}$	MAF<1%	MaCH	HapMap Phase II	mach2qtl	Sex, GA	1.006
DNBC-PTB-CONTROL Mothers	I660	95%	Ancestry outliers, sex discrepancy, Mendelian inconsistency	98%	$1x10^{-3}$	MAF<1%	MaCH	HapMap Phase II	mach2qtl	Sex, GA	1.006
EFSOCH Mothers	ICE	98%	Ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<1%	MaCH	HRC	SNPTEST	Sex, GA, PC	1.003
HAPO Mothers	I610	95%	Heterozygosity, non-European ancestry, sex discrepancy	98%	$1x10^{-4}$	MAF<2%	Beagle	HapMap Phase III	SNPTEST	Sex, GA, PC, field centre	1.016
MoBa-2008 Mothers	I660	98%	Ancestry outliers, sex discrepancy	95%	$1x10^{-6}$	MAF<5%	PLINK v.1.07	HapMap Phase II	SNPTEST	Sex, GA	N/A
NFBC1966	I370	95%	Heterozygosity, relatedness, ancestry outliers, sex discrepancy, duplicates, withdrawn consent	95% (99% if MAF<5%)	$5.7x10^{-7}$	MAF<1%	IMPUTE2	HapMap Phase II	SNPTEST	Sex, GA, PC	1.02
NTR	A6, I370, I660, IOQ	90%	Heterozygosity	95%	$1x10^{-5}$	MAF<1%	IMPUTE1	HapMap Phase II	SNPTEST	Sex, GA, array, PC	1.002
QIMR	I370	95%	Relatedness, ancestry outliers, sex discrepancy, Mendelian inconsistency	95%	$1x10^{-6}$	MAF<1%	MaCH	HapMap Phase II	MERLIN	Sex	1.012
TWINSUK	I300, I1M, I1.2M	98%	Heterozygosity, ancestry outliers, identity	97% (99% if MAF<5%)	$1x10^{-6}$	MAF<1%	IMPUTE2	HapMap Phase II	SNPTEST	Sex	1.00

(b) Component 2: UK Biobank

Study	Genotyping array(s)[a]	Sample quality control		SNP scaffold quality control			Prephasing software	Imputation		Association analysis		Lambda
		Call rate	Additional filters	Call rate	HWE *P*-value	Frequency		Software	Reference panel	Software	Covariates or adjustment	
UK Biobank	AUKBB	98%	Heterozygosity, relatedness, ancestry outliers	95%	N/A	MAF<1%	SHAPEIT2	IMPUTE2	HRC	BOLT-LMMv2.3	Sex, genotype array	N/A

HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; MAC, minor allele count; GA, gestational age; PC, principal component.

[a]Genotype array codes: Affymetrix 5.0 (A5); Affymetrix 6.0 (A6); Affymetrix Axiom UK BiLEVE (AUKBL); Affymetrix Axiom UK Biobank (AUKBB); Illumina HumanHap300 (I300); Illumina Human370CNV (I370); Illumina HumanHap550 (I550); Illumina HumanHap610 (I610); Illumina HumanHap660 (I660); Illumina HumanHap670 (I670); Illumina Human1M-Duo (I1M); Illumina Human1.2MDuo 1M (I1.2MD); Illumina CardioMetabochip (ICM); Illumina OmniQuad (IOQ); Illumina OmniExpress (IOE); Illumina CoreExome (ICE); Illumina OmniExpressExome (IOEE).

Supplementary Table 16: Results from linear regression analyses assessing the association between offspring birth weight and maternal non-transmitted allele score, maternal transmitted (or shared) allele score or paternal transmitted allele score for adult height, glycaemic traits and blood pressure in 4,962 mother-child pairs from the ALSPAC study. The SNPs used to generate the weighted allele scores are shown in Supplementary Table 14.

Exposure	Outcome[a]	Score	Beta[b]	Standard Error	P-value
Height	Birth Weight	Maternal non-transmitted	0.043	0.029	0.139
		Maternal transmitted/Shared	0.263	0.030	2.58E-18
		Paternal transmitted	0.190	0.029	1.12E-10
Fasting Glucose	Birth Weight	Maternal non-transmitted	0.641	0.188	0.001
		Maternal transmitted/Shared	0.326	0.187	0.081
		Paternal transmitted	-0.103	0.185	0.576
Insulin Secretion[c]	Birth Weight	Maternal non-transmitted	-0.131	0.097	0.178
		Maternal transmitted/Shared	-0.193	0.100	0.054
		Paternal transmitted	-0.048	0.098	0.629
Insulin Sensitivity[d]	Birth Weight	Maternal non-transmitted	0.262	0.248	0.290
		Maternal transmitted/Shared	0.273	0.251	0.278
		Paternal transmitted	0.204	0.244	0.403
SBP	Birth Weight	Maternal non-transmitted	-0.016	0.008	0.041
		Maternal transmitted/Shared	-0.014	0.008	0.076
		Paternal transmitted	-0.014	0.008	0.080
DBP	Birth Weight	Maternal non-transmitted	-0.026	0.012	0.036
		Maternal transmitted/Shared	-0.038	0.013	0.003
		Paternal transmitted	-0.010	0.013	0.446

[a] Birth weight effect sizes were converted from SD units to grams using 484g to represent 1 SD in birth weight (Freathy *et al*. 2010; https://www.nature.com/articles/ng.567)

[b] Birth weight effect sizes are reported in grams per weighted allele

[c] Disposition index of insulin secretion calculated from oral glucose tolerance test (OGTT) results as Corrected Insulin Response x 10,000 / √ Fasting Plasma Glucose x Fasting Insulin x Mean Glucose during OGTT x Mean Insulin During OGTT. Full details are presented in http://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1004235

[d] Insulin sensitivity is calculated as fasting insulin adjusted for body mass index (BMI)

Supplementary Table 18: Results from linear regression analyses assessing the association between maternal, paternal or offspring allelic scores of birth weight (a) or systolic blood pressure (b) associated SNPs and offspring systolic blood pressure (SBP), without and with adjustment for offspring SNPs, in 3,886 mother-offspring pairs and 1,749 father-offspring pairs from the UK Biobank.

a) Birth weight associated SNPs

			205 autosomal SNPs			72 autosomal SNPs with maternal effect			31 autosomal SNPs with only maternal effect		
Outcome	**Analysis sample**	**Exposure**	**Beta**	**Standard Error**	**P-value**	**Beta**	**Standard Error**	**P-value**	**Beta**	**Standard Error**	**P-value**
Maternal SBP	Mother/offspring pairs (N=3,886)	Maternal allele score	-0.060	0.035	0.084	-0.061	0.059	0.300	-0.196	0.099	0.046
Paternal SBP	Father/offspring pairs (N=1,749)	Paternal allele score	-0.087	0.050	0.084	-0.150	0.087	0.085	-0.140	0.144	0.330
Offspring SBP	Mother/offspring pairs (N=3,886)	Maternal allele score	0.025	0.025	0.319	0.063	0.043	0.140	0.062	0.072	0.388
		Maternal allele score, adjusted for offspring SNPs	0.043	0.030	0.152	0.117	0.050	0.018	0.213	0.083	0.011
		Offspring allele score	-0.009	0.026	0.722	-0.056	0.044	0.200	-0.173	0.073	0.018
		Offspring allele score, adjusted for maternal SNPs	-0.025	0.030	0.411	-0.110	0.050	0.029	-0.283	0.085	8.13E-04
	Father/offspring pairs (N=1, 749)	Paternal allele score	0.022	0.037	0.545	0.000	0.064	0.998	-0.158	0.106	0.138
		Paternal allele score, adjusted for offspring SNPs	0.032	0.044	0.459	0.091	0.075	0.221	0.029	0.125	0.820
		Offspring allele score	-0.011	0.038	0.772	-0.106	0.063	0.094	-0.246	0.102	0.016
		Offspring allele score, adjusted for paternal SNPs	-0.011	0.045	0.802	-0.132	0.074	0.075	-0.259	0.120	0.031

Beta values are in mmHg per birth weight-raising allele

b) SBP associated SNPs

			68 SNPs		
Outcome	**Analysis sample**	**Exposure**	**Beta**	**Standard Error**	**P-value**
Maternal SBP	Mother/offspring pairs (N=3,886)	Maternal allele score	0.335	0.065	2.71E-07
Paternal SBP	Father/offspring pairs (N=1,749)	Paternal allele score	0.346	0.091	1.37E-04
Offspring SBP	Mother/offspring pairs (N=3,886)	Maternal allele score	0.135	0.048	0.005
		Maternal allele score, adjusted for offspring SNPs	0.007	0.055	0.903
		Offspring allele score	0.254	0.047	5.25E-08
		Offspring allele score, adjusted for maternal SNPs	0.245	0.054	4.97E-06
	Father/offspring pairs (N=1,749)	Paternal allele score	0.177	0.067	0.008
		Paternal allele score, adjusted for offspring SNPs	0.079	0.080	0.319
		Offspring allele score	0.250	0.067	1.74E-04
		Offspring allele score, adjusted for paternal SNPs	0.225	0.078	0.004

Beta values are in mmHg per birth weight-raising allele

Supplementary Note 1: Supplementary Methods

Genome-wide association analysis in the Early Growth Genetics (EGG) consortium

Own birth weight

Studies from the EGG Consortium conducted genome-wide association analysis of own birth weight that was Z-score transformed separately in males and females, and adjusted for study-specific covariates, including gestational duration, where available (**Supplementary Table 1**). This included 35 studies with 80,745 individuals of European ancestry and an additional nine studies with 12,948 individuals of diverse ancestry groups (**Supplementary Figure 1**). GWASs were imputed up to the 1000 Genomes[7] (1000G) reference panel. We combined the sex-specific birth weight association summary statistics across the EGG studies in a fixed-effects meta-analysis, implemented in GWAMA[8].

Offspring birth weight

Studies from the EGG Consortium conducted genome-wide association analysis on offspring birth weight that was Z-score transformed, and adjusted for sex, gestational duration and ancestry informative principal components where necessary (**Supplementary Table 3**). This included 10 studies with 12,319 individuals of European descent that were imputed up to the HapMap 2 reference panel and an additional two studies with 7,542 individuals of European descent imputed up to the HRC reference panel (**Supplementary Figure 2**). We combined the birth weight association summary statistics across the 10 HapMap 2 imputed EGG studies in a fixed-effects meta-analysis, implemented in GWAMA[8].

UK Biobank phenotype preparation for genome-wide association analyses

The UK Biobank is a study of 502,655 participants[9]. A total of 280,315 participants reported their own birth weight in kilograms at either the baseline visit or at least one of the follow-

up visits. Participants reporting being part of a multiple birth were excluded from our analyses (N=7,706). For participants reporting birth weight at more than one visit (N=11,214), the mean value of the reported birth weights was used, and if the mean difference between any 2 time points was >1kg, the participant was excluded (N=74). Data on gestational duration were not available; however, in order to exclude likely pre-term births, participants with birth weight values <2.5kg or >4.5kg were excluded (N=36,330). The remaining birth weight values were Z-score transformed separately in males and females for analysis.

Female participants were also asked to report the birth weight of their first child. A total of 216,839 women reported the birth weight of their first child on at least one assessment center visit. Values were recorded to the nearest whole pound, and were converted to kilograms for our analyses. Where women reported the birth weight of the first child at multiple time points (N=11,353) these were averaged and women were excluded if the mean difference between any two offspring birth weight measurements was >1kg (N=31). Women who reported the birth weight of their first child <2.2kg or >4.6kg were excluded (N=6,333). Birth weight of first child was regressed against age at first birth and assessment center location. Residuals from the regression model were converted to Z-scores for analysis (sex of the first child was not available, so we were unable to calculate sex-specific Z-scores).

UK Biobank ethnicity classification and genome-wide association analysis

We analysed data from the May 2017 release of imputed genetic data from the UK Biobank, a resource extensively described elsewhere[9]. Given the reported technical error with non-

HRC imputed variants, we focused exclusively on the set of ~40M imputed variants from the HRC reference panel.

In addition to the quality control metrics performed centrally by the UK Biobank, we defined a subset of "white European" ancestry samples. To do this, we generated ancestry informative principal components (PCs) in the 1000 genomes samples. The UK Biobank samples were then projected into this PC space using the SNP loadings obtained from the principal components analysis using the 1000 genomes samples. The UK Biobank participants' ancestry was classified using K-means clustering centred on the three main 1000 genomes populations (European, African, and South Asian). Those clustering with the European cluster were classified as having European ancestry. The UK Biobank participants were asked to report their ethnic background. Only those reporting as either "British", "Irish", "White" or "Any other white background" were included in the clustering analysis. In total, 217,397 participants with a valid measure of their own birth weight and 190,406 women with a valid measure of birth weight of first child were classified as European and included in analyses. For trans-ethnic analyses all participants with valid phenotypes were included regardless of ancestry (N=227,530 participants with a valid measure of their own birth weight and N=210,208 with a valid measure of the birth weight of their first child). Association analysis was conducted using a linear mixed model implemented in BOLT-LMM v2.3[10] to account for population structure and relatedness. Only autosomal genetic variants which were common (MAF>1%), passed QC in all 106 batches and were present on both genotyping arrays were included in the genetic relationship matrix (GRM). For the genome-wide association study (GWAS) of the participants' own birth weight, genotyping array and year of birth were included as covariates in all models. For the GWAS of the birth weight of the first child, genotyping array and genotyping release (interim vs. full) were included as

covariates in the regression model, and indels, regions of long range LD (as defined in [9]) and SNPs with Hardy-Weinberg equilibrium P-values<1x10-6 were excluded from the GRM.

Sensitivity analyses for genome-wide association meta-analyses

After conducing meta-analyses to combine the results from the EGG consortium and the UK Biobank, we conducted a series of sensitivity analyses to ensure that our results were accurate. Firstly, we were concerned that self-reported birth weight as adults in the UK Biobank would not be comparable with that obtained from more stringent collection methods used in the EGG studies. We conducted a heterogeneity test using Cochran's Q statistic[11], as implemented in GWAMA[8], to assess the difference in allelic effects between the EGG meta-analysis and the UK Biobank. We acknowledge that the power to detect evidence for heterogeneity using the Cochran's Q statistic when comparing two groups is low and we use it here to highlight any SNPs with large differences in allelic effects. For the European meta-analysis of own birth weight, we were unable to detect evidence of heterogeneity at lead SNPs after Bonferroni correction (all P>0.004; **Supplementary Table 5**); however, there was an enrichment for low P, with almost double the expected number of SNPs with P<0.05 (13/131; Supplementary Table 5). For the trans-ethnic meta-analysis of own birth weight, the one additional lead SNP did not show evidence of heterogeneity in birth weight allelic effects across the three components after Bonferroni correction (Cochran's Q P=0.714; **Supplementary Table 5**). For both the European and trans-ethnic meta-analyses of offspring birth weight, there was no evidence of heterogeneity in birth weight allelic effects at any of the lead SNPs, after Bonferroni correction (Cochran's Q P>0.05), between the UK Biobank and EGG studies and there was no enrichment for low P (**Supplementary Table 5**).

Secondly, the UK Biobank lacked information on gestational duration, which could impact the strength of association compared to the results obtained from the EGG studies that adjusted for gestational duration. Therefore, we conducted a further sensitivity analysis of the meta-analysis of own birth weight to specifically assess the impact of adjustment for gestational duration testing for heterogeneity in allelic effects at lead SNPs between EGG studies which adjusted for gestational duration (N=43,964) and the European subset of the UK Biobank. The only locus where the lead SNP showed significant heterogeneity, after Bonferroni correction, was rs1482852 at the LOC339894/CCNL1 signal (P_{het}=0.00015), which was a locus showing the strongest association with own birth weight and genome-wide significant in both EGG and the UK Biobank components independently.

Thirdly, there is potential for individuals to be in both the UK Biobank and EGG studies (i.e. the same individual in both the UK Biobank and a study within EGG) and this might lead to false positive association signals. We performed a bivariate linkage-disequilibrium (LD) score regression[12] analysis using the European UK Biobank GWAS and European EGG meta-analysis summary statistics of own birth weight, and observed a regression intercept of 0.0266 (0.0077), indicating that the equivalent of approximately 3,524 individuals were in both GWAS analyses. Bivariate LD score regression[12]using the European UK Biobank GWAS and European EGG meta-analysis summary statistics of offspring birth weight, we observed a regression intercept of 0.0165 (0.0063), indicating that the equivalent of approximately 1,015 individuals were in both the EGG and UK Biobank GWAS analyses of offspring birth weight.

Structural equation model for estimating adjusted maternal and fetal effects of the genome-wide significant variants

The structural equation modelling (SEM) approach used to estimate adjusted maternal and fetal effects has been described elsewhere[13]. Briefly, to estimate the parameters for the SEM-adjusted fetal and maternal effects on birth weight, we use three observed variables available in the UK Biobank; the participant's genotype, their own self-reported birth weight, and in the case of the UK Biobank women, the birth weight of their first child (**Supplementary Figure 6a**). Additionally, the model comprises two latent (unobserved) variables, one for the genotype of the UK Biobank participant's mother and one for the genotype of the participant's offspring. From biometrical genetics theory, these latent genetic variables are correlated 0.5 with the participant's own genotype, so we fix the path coefficients between the latent and observed genotypes to be 0.5. Participants who only report their own birth weight (including males), contribute directly to estimation of the fetal effect of genotype on birth weight and also indirectly to estimation of the maternal effect on birth weight since their observed genotype is correlated with their mother's unmeasured latent genotype at the same locus. Similarly, summary statistics from the EGG meta-analysis of the unadjusted fetal effect (i.e. the European GWAS meta-analysis of own birth weight) can be incorporated into the model in this manner. Participants who report only their offspring's birth weight (including mother's reporting birth weight of their male offspring), contribute directly to estimation of the maternal effect on birth weight and indirectly to the estimate of the fetal effect on birth weight, since their observed genotype is correlated with their offspring's latent genotype at the same locus. Again, summary statistics from the EGG meta-analysis of the unadjusted maternal effect (i.e. the European GWAS meta-analysis of offspring birth weight) can be incorporated into the model this way. These five components

are fit to the five subsets of data (i.e. the UK Biobank participants with complete data, the UK Biobank participants with their own birth weight and genotype data only, EGG summary statistics for the unadjusted fetal effect of genotype on birth weight, the UK Biobank participants with their offspring's birth weight and maternal genotype only and EGG summary statistics for the unadjusted maternal effect of genotype on birth weight) and then the likelihoods from each subset are combined. In addition to fitting the SEM to estimate the SEM-adjusted maternal and fetal effects, we fit a second model constraining the maternal and fetal effects to be zero and conducted a two degree of freedom Wald test to assess any effect of the SNP on birth weight. There is likely to be measurement error in the birth weight data in the UK Biobank, as well as some of the EGG studies, due to difficulty recalling birth weight. Additionally, the women in UK Biobank were asked to recall their offspring birth weight to the nearest pound. We have shown using simulations that both random measurement error (for example, due to difficulty in recall) and measurement error in offspring birth weight due to rounding to the nearest pound do not have a substantial influence on the estimation of either the maternal or fetal effects (see Warrington et al. [13]). We therefore do not think that the imprecision of the UK Biobank birth weight data will substantially influence the results of downstream analyses.

Structural equation model (SEM) for estimating adjusted maternal and fetal effects on genome-wide significant variants on the X chromosome: Supplementary Figure 6A displays the SEM that was fit to data on the genome-wide significant subset of SNPs from the autosomes to estimate the maternal and fetal effect on birth weight. The three observed variables displayed in boxes in the path diagram (**Supplementary Figure 6a**) represent the birth weight of the individual (BW), the birth weight of their offspring (BW_O) and the

genotype of the individual (SNP). The two variables in circles represent the unobserved latent genotypes of the individual's mother (G_G) and their offspring (G_O). The total variance of these latent genotypes are set to Φ, the variance of the observed SNP (i.e. var(G_G) = Φ; var(SNP) = 0.5^2Φ + 0.75Φ; var(G_O) = 0.5^2Φ + 0.75Φ). The $\hat{\beta}_{f_{adj}}$ and $\hat{\beta}_{m_{adj}}$ path coefficients refer respectively to the adjusted fetal and maternal effects of the genotypes on birth weight. The residual error terms for the birth weight of the individual and their offspring are represented by ε and ε_O respectively. The covariance between the residual error terms is given by ρ.

However, for the genome-wide significant SNPs on the X chromosome a slightly different model was fit to the data due to males having twice the expected genetic variance at X linked loci compared to females. For example, if SNP_f denotes the genotypic effect of the SNP in females (i.e. 0, 1 or 2) and SNP_m denotes the genotypic effect of the SNP in males (i.e. 0 or 2), and p represents the increaser allele frequency, then:

$$
\begin{aligned}
E(SNP_f) &= 2p(1-p) + 2p^2 \\
&= 2p(1-p+p) \\
&= 2p \\
E(SNP_f^2) &= 2p(1-p) + 4p^2 \\
&= 2p(1-p+2p) \\
&= 2p(1+p) \\
Var(SNP_f) &= E(SNP_f^2) - [E(SNP_f)]^2 \\
&= 2p(1+p) - [2p]^2 \\
&= 2p + 2p^2 - 4p^2 \\
&= 2p(1-p)
\end{aligned}
$$

$$E(SNP_m) = 2p$$

$$E(SNP_m^2) = 4p$$

$$Var(SNP_m) = E(SNP_m^2) - [E(SNP_m)]^2$$

$$= 4p - [2p]^2$$

$$= 4p(1-p)$$

Therefore, we fit the SEM displayed in **Supplementary Figure 6a** to the X chromosome SNPs in the UK Biobank females that reached genome-wide significance. For the males in the UK Biobank, we fit the SEM displayed in **Supplementary Figure 6b** to account for the increased SNP variance. Parameters were constrained equal across the models, and the likelihoods jointly maximized to get an overall estimate of the maternal and fetal effects on birth weight at these SNPs.

Although we do not know the sex of the UK Biobank women's offspring (since this information was not recorded in the UK Biobank), fitting the model using 0.75Φ or 1.75Φ for the variance of the offspring's latent genotype did not produce a change to estimates of the maternal and fetal effects (to four decimal places).

Derivation of the linear approximation of the SEM for genome-wide analyses: The SEM is computationally intensive to fit via maximum likelihood, making it difficult to run the model on all SNPs across the genome. Therefore, we developed an approximation of the SEM using a linear transformation and ordinary least squares linear regression. Using path tracing rules[14] for the full path diagram (**Supplementary Figure 6a**), we can show that:

$$var(SNP) = \phi$$

$$cov(BW, SNP) = \phi\left(\beta_{f_{adj}} + \frac{1}{2}\beta_{m_{adj}}\right)$$

$$cov(BW_O, SNP) = \phi\left(\beta_{m_{adj}} + \frac{1}{2}\beta_{f_{adj}}\right)$$

If we let $\hat{\beta}_{f_{unadj}}$and $\hat{\beta}_{m_{unadj}}$be the unadjusted fetal and maternal effect estimates respectively and $\hat{\beta}_{f_{adj}}$and $\hat{\beta}_{m_{adj}}$ be the adjusted fetal and maternal effect estimates respectively (as denoted in **Supplementary Figure 6a**), then we can derive the adjusted estimates from the unadjusted estimates using the following calculation:

$$\hat{\beta}_{f_{unadj}} = \frac{cov(BW, SNP)}{var(SNP)}$$

$$= \frac{\hat{\phi}\left(\hat{\beta}_{f_{adj}} + \frac{1}{2}\hat{\beta}_{m_{adj}}\right)}{\phi}$$

$$= \hat{\beta}_{f_{adj}} + \frac{1}{2}\hat{\beta}_{m_{adj}}$$

$$\hat{\beta}_{m_{unadj}} = \frac{cov(BW_O, SNP)}{var(SNP)}$$

$$= \frac{\hat{\phi}\left(\hat{\beta}_{m_{adj}} + \frac{1}{2}\hat{\beta}_{f_{adj}}\right)}{\phi}$$

$$= \hat{\beta}_{m_{adj}} + \frac{1}{2}\hat{\beta}_{f_{adj}}$$

$$Therefore: \hat{\beta}_{m_{adj}} = 2\left(\hat{\beta}_{f_{unadj}} - \hat{\beta}_{f_{adj}}\right) = \hat{\beta}_{m_{unadj}} - \frac{1}{2}\hat{\beta}_{f_{adj}}$$

$$-2\hat{\beta}_{f_{adj}} + \frac{1}{2}\hat{\beta}_{f_{adj}} = \hat{\beta}_{m_{unadj}} - 2\hat{\beta}_{f_{unadj}}$$

$$-\frac{3}{2}\hat{\beta}_{f_{adj}} = \hat{\beta}_{m_{uncadj}} - 2\hat{\beta}_{f_{unadj}}$$

$$\hat{\beta}_{f_{adj}} = -\frac{2}{3}\hat{\beta}_{m_{unadj}} + \frac{4}{3}\hat{\beta}_{f_{unadj}} \qquad (1)$$

$$And: \hat{\beta}_{m_{adj}} = \hat{\beta}_{m_{unadj}} - \frac{1}{2}\hat{\beta}_{f_{adj}}$$

$$= \hat{\beta}_{m_{unadj}} - \frac{1}{2}\left(-\frac{2}{3}\hat{\beta}_{m_{unadj}} + \frac{4}{3}\hat{\beta}_{f_{unadj}}\right)$$

$$= \hat{\beta}_{m_{unadj}} + \frac{1}{3}\hat{\beta}_{m_{unadj}} - \frac{2}{3}\hat{\beta}_{f_{unadj}}$$
$$= \frac{4}{3}\hat{\beta}_{m_{unadj}} - \frac{2}{3}\hat{\beta}_{f_{unadj}} \quad (2)$$

And the standard errors for the adjusted estimates are

$$var\left(\hat{\beta}_{f_{adj}}\right) = var\left(-\frac{2}{3}\hat{\beta}_{m_{unadj}} + \frac{4}{3}\hat{\beta}_{f_{unadj}}\right)$$
$$= var\left(-\frac{2}{3}\hat{\beta}_{m_{unadj}}\right) + var\left(\frac{4}{3}\hat{\beta}_{f_{unadj}}\right)$$
$$= \frac{4}{9}var\left(\hat{\beta}_{m_{unadj}}\right) + \frac{16}{9}\ var\left(\hat{\beta}_{f_{unadj}}\right)$$
$$SE\left(\hat{\beta}_{f_{adj}}\right) = \sqrt{\frac{4}{9}var\left(\hat{\beta}_{m_{unadj}}\right) + \frac{16}{9}\ var\left(\hat{\beta}_{f_{unadj}}\right)} \quad (3)$$

$$var\left(\hat{\beta}_{m_{adj}}\right) = var\left(\frac{4}{3}\hat{\beta}_{m_{unadj}} - \frac{2}{3}\hat{\beta}_{f_{unadj}}\right)$$
$$= \frac{16}{9}var\left(\hat{\beta}_{m_{unadj}}\right) + \frac{4}{9}\ var\left(\hat{\beta}_{f_{unadj}}\right)$$
$$SE\left(\hat{\beta}_{m_{adj}}\right) = \sqrt{\frac{16}{9}var\left(\hat{\beta}_{m_{unadj}}\right) + \frac{4}{9}\ var\left(\hat{\beta}_{f_{unadj}}\right)} \quad (4)$$

The independence of the unadjusted estimates for the fetal and maternal effect are guaranteed in our case because the regressions are performed on different subsets of individuals. If the model is truly linear, then the same estimates can be obtained by transforming the reported birth weights rather than the regression coefficients[15].

Supplementary Figure 18 outlines the analysis pipeline undertaken to estimate the adjusted maternal and fetal effects on birth weight, incorporating both the UK Biobank data and the summary statistics from the EGG meta-analysis. First, we grouped the European subset of the UK Biobank data into three subsets; 1) participants who reported both their own birth

weight and the birth weight of their offspring (N=101,541), 2) participants who only reported their own birth weight (N=115,070), and 3) participants who only reported their offspring's birth weight in the UK Biobank (N=88,846). The UK Biobank sample sizes used in this analysis are larger than those used in the SEM as the GWAS analyses are conducted in BOLT-LMM and can therefore account for the complex cryptic relationships between individuals and population structure. Similar to the SEM analyses, birth weight Z-scores in the UK Biobank participants were calculated from residuals of a regression model adjusting for sex (own birth weight only) and assessment centre, after the same exclusions were made as in the GWAS.

For the UK Biobank participants in the first subset with both birth weight measures, we could combine their own and their offspring's birth weight to create two new outcome variables that were used to directly estimate the adjusted fetal and maternal effects in a GWAS. Instead of using the raw birth weight measures to calculate the combined measures, we used the Z-scores that were used in the GWAS of own birth weight (which were adjusted for sex and assessment center) and offspring birth weight (which were adjusted for assessment center). We then conducted the GWAS analysis in BOLT-LMM[10], adjusting for genotyping chip, to estimate the adjusted fetal and maternal effects at each SNP.

For the UK Biobank participants in the second subset with only their own birth weight, we conducted a GWAS analysis in BOLT-LMM[10] adjusting for chip, of birth weight z-scores that were adjusted for sex and assessment center. We then meta-analysed these results with the results of the meta-analysis of the fetal effect from the EGG consortium using a fixed-effects, inverse-variance weighted meta-analysis in METAL[16] to get a combined estimate of

the unadjusted fetal effect ($\hat{\beta}_{f_{unadj}}$). We used the same procedure for the third subset of the UK Biobank participants with only their offspring's birth weight, and combined their results with the meta-analysis of the maternal effect from the EGG consortium to get a combined estimate of the unadjusted maternal effect ($\hat{\beta}_{m_{unadj}}$). To get the adjusted maternal and fetal effect estimates, we combined the meta-analysis results of the unadjusted maternal and fetal effects for each SNPs using equations (1) and (2) and their corresponding standard errors from equations (3) and (4). Finally, we conducted another fixed effects, inverse-variance weighted meta-analysis to combine the adjusted maternal and fetal effect estimates from the UK Biobank participants with both birth weight measures and the combined adjusted effect estimates from the UK Biobank and EGG meta-analysis.

To check whether this linear approximation gave similar results as the full SEM, we compared $\hat{\beta}_{f_{adj}}$ and $\hat{\beta}_{m_{adj}}$and their corresponding standard errors for the subset of genome-wide significant SNPs that we conducted the full SEM on. **Supplementary Figure 9** shows that there was very good concordance between the full SEM and this linear approximation for both the effect estimates and the standard errors. The standard errors are slightly larger for the full SEM due to the exclusion of related individuals from the analysis resulting in a smaller sample size.

The advantages of this linear transformation include its computational efficiency, especially when you only have individuals with both their own and their offspring's birth weights, and ability to use available GWAS software such as BOLT-LMM[10] that accounts for relatedness

between individuals. However, when using only summary statistics from previous GWAS analyses, where it is unknown how many individuals have contributed to both analyses (i.e. there is some sample overlap between the GWAS of own birth weight and the GWAS of offspring birth weight), the estimates from this linear approximation may be biased. Therefore, we recommend using the SEM for more complex data structures such as this as the degree of sample overlap can be estimated using LD score regression[12] and then the SEM likelihood can be weighted appropriately to take into account the overlap.

Phenotype preparation for the UK Biobank traits used in BOLT-LMM analysis estimating the covariance between birth weight and adult traits

Height: standing and sitting height were measured in cm. Participants were excluded if height was more than 4.56SD from the mean and sitting height-to-standing height ratio was greater than 0.75. **Body mass index (BMI):** BMI was calculated from weight (kg)/height^2 (m^2). **Obesity & Morbid Obesity:** normal weight was classified as 18.5≤BMI<25, obese 30≤BMI<35 and morbid obese 35≤BMI. Normal weight was used as the control group for obesity and morbid obesity phenotypes. **Waist Circumference, Hip Circumference and Waist-Hip Ratio (WHR)**: waist and hip circumference were measured at the UK Biobank assessment center visits. WHR was calculated from these measures and adjusted for BMI in analyses. **SBP & DBP:** two blood pressure readings were taken in the UK Biobank, approximately 5 minutes apart, and two valid readings were available for most participants. An average of these was calculated, excluding individuals where the two readings differed by more than 4.56SD. In participants where only one valid blood pressure was available, this was used. Blood pressure measurements more than 4.56D away from the mean were excluded. Blood pressure medication use was accounted for by adding 10 and 15 to diastolic

(DBP) and systolic (SBP) measures respectively. **Type 2 diabetes (T2D):** participants in the UK Biobank were asked about which cancer and non-cancer illnesses they suffered from. Individuals were classified as having T2D if they reported either T2D or generic diabetes to these questions. Participants were excluded if they reported using insulin within 1 year of diagnosis, or if they reported being diagnosed under the age of 35 or with no known age of diagnosis. Participants diagnosed within the preceding year were also excluded, as we were unable to determine whether they used insulin within this time frame. **Coronary artery disease (CAD):** CAD was defined from the non-cancer illnesses questions. Participants reporting angina and/or heart attack at the interview stage were excluded from CAD cases. Controls were participants without these conditions. **Incident T2D and CAD:** incident cases were defined using health episode statistics (HES) and self-report non-cancer illness questionnaire. HES was used to define incident cases as those with a first entry of CAD or T2D using primary or secondary ICD10 codes occurring after their first UK Biobank assessment center visit. Any participant reporting CAD or T2D at a follow-up questionnaire visit who had not reported it at the original visit was also classified as an incident case. **Asthma:** asthma cases were defined using non-cancer illness questions. **Cigarettes Per Day, Current Smoker, Ever Smoker, Former Smoker & Maternal Smoking**: smoking status, duration and frequency were attained for all UK Biobank participants. Participants were classified as former, current or never smoker. Ever smoker includes both former and current smokers. For ever smokers cigarettes per day was defined from the UK Biobank question about number of cigarettes smoked per day. Participants were also asked whether their mother regularly smoked around the time of their birth. **Menarche:** Female participants were asked at what age their periods started. Where participants had answered the

question at multiple assessment center visits the most recent valid value was taken. Values <9 years and >17 years were then excluded.

Systolic blood pressure (SBP) phenotype preparation for Mendelian randomization analysis of maternal birth weight allele scores on offspring SBP

SBP was measured at three time points in the UK Biobank. At each follow-up participants were either measured using an automated machine or manually. The protocol was for each participant to have their SBP measurement taken twice at each follow-up, however some participants have only one measurement recorded.

For each follow-up, the average of the two SBP measures was calculated if both were recorded, otherwise the one recorded measure was used. If the participant reported being on blood pressure medication at the time of their measurement, then 10mmHg was added to their SBP measurement. If participants had an SBP measurement from the automated machine at baseline, then this was used, otherwise their SBP from follow-up 1 or 2 or the manual measurements from baseline, follow-up 1 or follow-up 2 were used (in this order). Finally, measures greater or less than 4.56 standard deviations from the mean were set to missing. This resulted in 501,242 participants, out of 502,647, with cleaned SBP measurements for analysis.

Simulations to ensure Mendelian randomization causal estimates were unbiased in the presence of a negative correlation between the maternal and fetal genetic effects:

There is a negative correlation between the maternal and fetal genetic effects, estimated from either the SEM or a conditional linear regression model, due to two reasons:

1. For a subset of loci that influence pancreatic beta cell function (e.g. certain fasting glucose or T2D-susceptibility loci), we expect the same allele to have opposite effects on birth weight when present in the mother vs. when present in the fetus due to the underlying biology. Pancreatic beta cells secrete insulin, and maternal insulin influences fetal growth differently from fetal insulin: variants in the mother that reduce pancreatic beta cell function and hence insulin production would be expected to raise maternal glucose levels. Maternal glucose crosses the placenta, but maternal insulin does not. Instead, fetal insulin is secreted in response to maternal glucose, and acts as a growth hormone in utero. A rise in maternal glucose levels causes the fetus to secrete insulin, which promotes growth. Thus, a variant that reduces insulin secretion in the mother would indirectly lead to higher growth of the fetus, while the same variant in the fetus would lead to reduced growth due to reduced availability of fetal insulin. The paradigm is illustrated in a study of heterozygous glucokinase mutations in pregnancy (Hattersley et al 1998, Nat Genet), where a fetus with a paternally-inherited mutation was 500g lighter than average, while a fetus with no mutation, born to an affected mother was 600g heavier on average. Since then, a number of common type 2 diabetes variants have been shown to reduce birth weight when in the fetus, independently of maternal genotype (Freathy et al Diabetes 2009), and in our current study, we show opposite directions of maternal and fetal genetic correlation estimates genome-wide for T2D and fasting glucose loci using WLM-adjusted effects (NB, please note that we do not show this for SBP effects).
2. It is a consequence of there being a negative sampling covariance between the regression weights (β_m and β_f). A negative correlation like this always occurs when

you regress a variable on correlated predictors. Intuitively, given a fixed amount of variance explained, each predictor tries to explain as much variance as possible; when one explains more of the variance, the other explains less. The sampling variance-covariance matrix for an ordinary least squares regression is $\sigma_e^2(X'X)^{-1}$ where σ_e^2 is the residual variance and X is the matrix of predictor variables. The diagonal elements are the sampling variance of the regression coefficients, and the off diagonal terms are the sampling covariance's between them. Whenever the predictors are correlated (as they are in the case of the maternal and fetal genotype), these off diagonal terms are going to be greater than or less than zero.

Although this negative correlation was expected, we wanted ensure that it did not have an impact on our Mendelian randomization analyses. Therefore, we conducted a series of simulations to estimate any potential bias on the causal estimates due to the negative correlation between the maternal and fetal genetic effects used as the SNP-exposure estimates.

Simulations

For each replicate we generated grandparental (on the maternal side) and paternal genotypes at 100 SNPs. Assuming autosomal Mendelian inheritance, additivity and unit variance, the individual's own genotype and offspring's genotype were generated. The grand-maternal ($Exposure_{G_i}$), maternal ($Exposure_{M_i}$) and offspring's ($Exposure_{O_i}$) exposure variable for each family *i*, was generated using the following equations:

$$Exposure_{G_i} = \sum_{j=1}^{100} \left(\beta_{SNP_j} \times SNP_{G_i,j}\right) + \beta_U \times U_i + \varepsilon_{G_i}$$

$$Exposure_{M_i} = \sum_{j=1}^{100} \left(\beta_{SNP_j} \times SNP_{M_i,j}\right) + \beta_U \times U_i + \varepsilon_{M_i}$$

$$Exposure_{O_i} = \sum_{j=1}^{100} \left(\beta_{SNP_j} \times SNP_{O_i,j} \right) + \beta_U \times U_i + \varepsilon_{O_i}$$

where β_{SNP_j} denotes the effect size of SNP_j on the exposure, $SNP_{X_i,j}$ is the genotype of individual *X* (either the grandmother [G], mother [M] or offspring [O]) in family *i* at SNP *j*, *U* is a standard normal random variable representing all residual genetic and environmental sources of similarity between mother and offspring, β_U is the total effect of *U* on the exposure of the individual in family *i*, and ε_{X_i} is a random normal variable with mean zero and variance needed to ensure that the exposure has unit variance asymptotically. For each SNP, the effect size and minor allele frequencies were drawn from two uniform distributions.

Birth weight of the mother (BW_M) for each family *i*, was generated using the following equation:

$$BW_{M_i} = \beta_M \times Exposure_{G_i} + \beta_F \times Exposure_{M_i} + \beta_U \times U_{BW_i} + \varepsilon_{BW\_M_i}$$

where β_M is the causal effect of maternal exposure on offspring birth weight, β_F is the causal effect of an individual's own exposure on their own birth weight, β_U is the total effect of U_{BW_i} on birth weight, and $\varepsilon_{BW\_M_i}$ is a random normal variable with mean zero and variance needed to ensure that BW_M has unit variance asymptotically. Similarly, offspring birth weight for each family *i,* was generated using the following equation:

$$BW_{O_i} = \beta_M \times Exposure_{M_i} + \beta_F \times Exposure_{O_i} + \beta_U \times U_{BW_i} + \varepsilon_{BW\_O_i}$$

In all simulations, the regression of phenotype on residual shared genetic and environmental factors was set to 0.5 (i.e., $\beta_U = 0.5$). We considered the effects of: the strength of the causal effect of the maternal exposure on offspring birth weight ($\beta_M = -0.15, 0, 0.15$); the strength of the causal effect of the individuals own exposure on their own birth weight ($\beta_F = 0, 0.15$); and the strength of the genetic instruments on the exposure (β_{SNP_j}; weak instruments had an effect size between 0.01 and 0.04 and a minor allele frequency between 0.1 and 0.5; medium instruments had an effect size between 0.02 and 0.04 and a minor allele frequency between 0.15 and 0.5; strong instruments had an

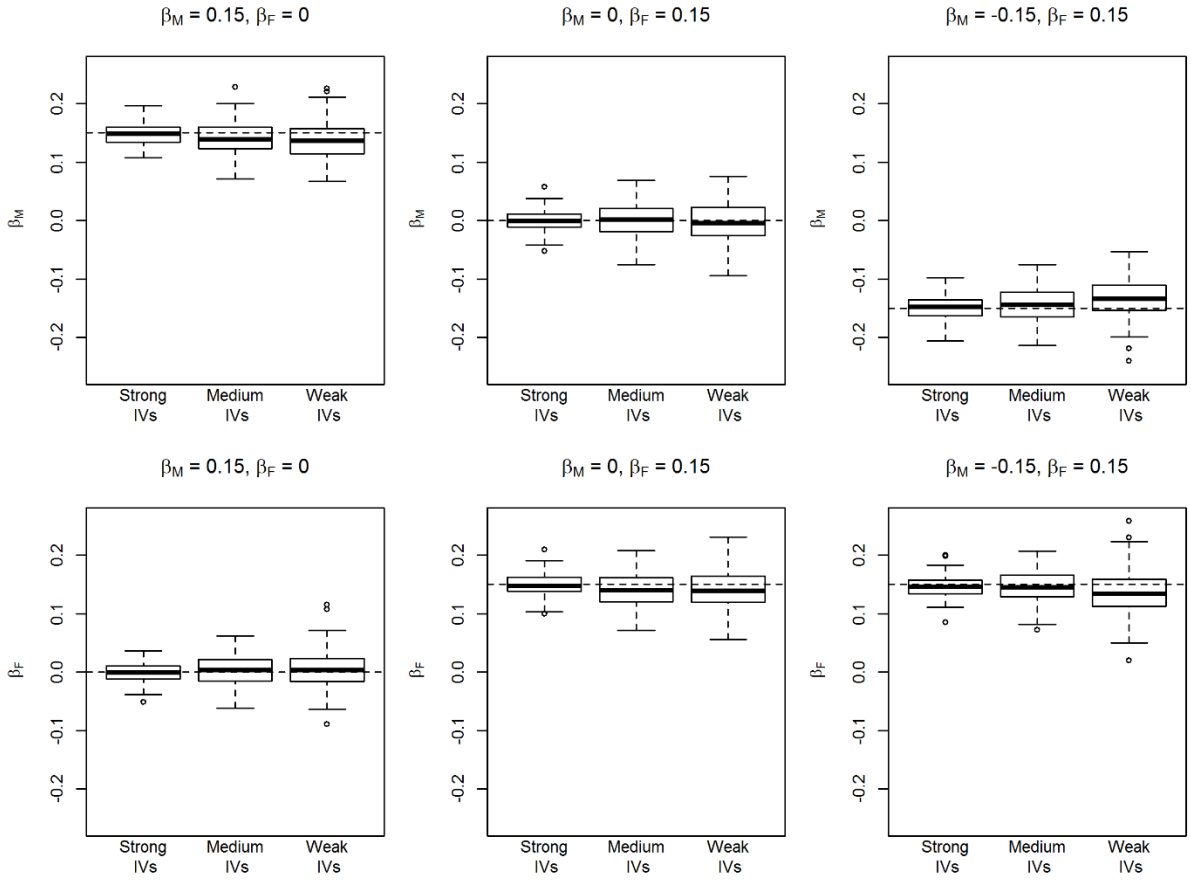
effect size of 0.05 and a minor allele frequency of 0.3). For each scenario, we generated 100 replicates of 40 000 families, the first 20 000 families were used to obtain the SNP-exposure estimates and the second 20 000 families were used to obtain the SNP-birth weight estimates.

Results of the simulations

On average across the 100 replicates, the 100 SNPs that were weak instruments explained approximately 7% of the variance in the exposure, the 100 SNPs that were medium instruments explained approximately 10% of the variance and the 100 SNPs that were strong instruments explained approximately 25% of the variance. The correlation between the maternal and fetal genetic effects on birth weight was approximately -0.7 across all scenarios.

Supplementary Figure 19 illustrates the results of the simulations, with the estimated causal effect of the maternal exposure on offspring birth weight (β_M) displayed in the top panel and the estimated causal effect of the individuals own exposure on their own birth weight (β_F) displayed in the bottom panel. The left panel show the results from simulations where there is only a causal effect of the maternal exposure on offspring birth weight (β_M=0.15, β_F=0); the middle panel displays simulations where there is a causal effect of the individual's own exposure on their own birth weight (β_M=0, β_F=0.15); and the right panel is where there is a causal effect of both the maternal and the individual's own exposure on birth weight and the effects are in opposite directions (β_M=-0.15, β_F=0.15). As can be seen in **Supplementary Figure 19**, there is a very small degree of weak instruments bias in the estimation of both the maternal and fetal causal effects when the instruments have a weak

or moderate effect on the exposure (with the median causal effect estimated from the simulations slightly biased towards zero). However, when we used strong instruments there was no appreciable bias for maternal or fetal causal effects, indicating that there is no bias introduced by the negative correlation between the maternal and fetal genetic effects on birth weight.



Supplementary Figure 19

Boxplots of the bias in the maternal (top panel) or fetal (bottom panel) causal effect estimates from simulations with a negative correlation between the maternal and fetal genetic effects on the outcome.

There were 100 replicates of the simulation with 100 SNPs in each replicate and 20,000 families for the SNP-exposure estimate and an additional 20,000 families for the SNP-birth weight estimate. Each boxplot includes the median (midline), the first and third quartiles (box), 1.5 times the interquartile range (whiskers) and any outliers (points outside the whiskers).

Supplementary Note 2: Study limitations

There are some limitations to this study. Although we were able to fit the full SEM at the 209 lead SNPs, we were unable to fit the SEM at all SNPs across the genome. We have shown previously how a two degree of freedom test based on this SEM (i.e. where maternal and fetal paths are constrained to zero) can have greater power to detect associated loci than the one degree of freedom test used in the GWAS meta-analyses, particularly when maternal and fetal genetic effects on the phenotype are similar in magnitude (including situations where the effects operate in opposite directions). However, we are currently unable to fit the SEM nor conduct an equivalent test in a computationally feasible manner across the genome. If such a test were developed, it would provide greater power than the current one degree of freedom tests used in the WLM-adjusted analyses, particularly for SNPs where maternal and fetal genetic effects operate in opposite directions, and could therefore be used for locus detection in future analyses. In addition, we have not considered paternal genotype and it is possible that this omission has biased the results of some of our analyses. Furthermore, there are a number of limitations relating to the MR analyses. First, the MR results concern BW variation within the normal range and do not necessarily reflect the effects of extreme environmental events (e.g. famine), which may exert qualitatively different effects and produce long-term developmental compensations in addition to low BW. Additionally, we have assumed a linear relationship between BW and later life traits, which is an oversimplification, particularly for T2D: higher BW is associated with later T2D risk, in addition to lower BW, particularly in populations with a high prevalence of T2D. MR is not well placed to examine the effects of extreme events, or non-linear relationships, and alternative methodology will be necessary to investigate life-course associations in this context. Second, BW is the end marker of a developmental process, with

critical periods during the process that may make the fetus particularly sensitive to environmental influences. The MR analyses could therefore be masking effects at certain critical periods. We would need to look at maternal exposures on intrauterine growth trajectories or the specific function of the genetic variants on BW to interrogate this further. Third, we have assumed that genetic variants identified in large GWAS of SBP and glycemic traits in males and non-pregnant females are similarly associated in pregnant women. This assumption is reasonable, given that genetic associations are generally similar in pregnant vs non-pregnant women, though there is some indication that genetic effects on SBP are weaker in pregnancy (see Table 2, eTable 5 and eTable 6f in Tyrrell et al. [17]). Fourth, we have not investigated the potential gender difference in the associations between BW and later life traits. There is evidence that the association between BW and both T2D[18] and SBP[19] is stronger in females than males. However, to perform the MR analyses, we would require male and female-specific effect sizes for each of the exposures, which are currently not available. Finally, we have assumed that the critical period of exposure to maternal indirect genetic effects is pregnancy, and that the estimates do not reflect pre-pregnancy effects on primordial oocytes or post-natal effects[20]. However, since we have used BW-associated SNPs, the maternal effects are most-likely mediated *in utero*. While we cannot rule out postnatal effects[21], our analysis of offspring SBP associations with BW-associated SNPs in father-child pairs showed different associations compared with mother-child pairs, implying postnatal effects were unlikely.

References

1 Horikoshi, M. *et al.* Genome-wide associations for birth weight and correlations with adult disease. *Nature* **538**, 248-252, doi:10.1038/nature19806 (2016).

2 Beaumont, R. N. *et al.* Genome-wide association study of offspring birth weight in 86 577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics. *Hum Mol Genet* **27**, 742-756, doi:10.1093/hmg/ddx429 (2018).

3 Finucane, H. K. *et al.* Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat Genet* **50**, 621-629, doi:10.1038/s41588-018-0081-4 (2018).

4 Zanetti, D. *et al.* Birthweight, Type 2 Diabetes and Cardiovascular Disease: Addressing the Barker Hypothesis with Mendelian randomization. *bioRxiv*, doi:10.1101/208629 (2017).

5 Wang, T. *et al.* Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study. *Diabetologia* **59**, 1920-1927, doi:10.1007/s00125-016-4019-z (2016).

6 Freathy, R. M. Can genetic evidence help us to understand the fetal origins of type 2 diabetes? *Diabetologia* **59**, 1850-1854, doi:10.1007/s00125-016-4057-6 (2016).

7 Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68-74, doi:10.1038/nature15393 (2015).

8 Magi, R. & Morris, A. P. GWAMA: software for genome-wide association meta-analysis. *BMC bioinformatics* **11**, 288, doi:10.1186/1471-2105-11-288 (2010).

9 Bycroft, C. *et al.* The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203-209, doi:10.1038/s41586-018-0579-z (2018).

10 Loh, P. R. *et al.* Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nat Genet* **47**, 284-290, doi:10.1038/ng.3190 (2015).

11 Ioannidis, J. P., Patsopoulos, N. A. & Evangelou, E. Heterogeneity in meta-analyses of genome-wide association investigations. *PloS one* **2**, e841, doi:10.1371/journal.pone.0000841 (2007).

12 Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-1241, doi:10.1038/ng.3406 (2015).

13 Warrington, N. M., Freathy, R. M., Neale, M. C. & Evans, D. M. Using structural equation modelling to jointly estimate maternal and fetal effects on birthweight in the UK Biobank. *International journal of epidemiology*, doi:10.1093/ije/dyy015 (2018).

14 Neale, M. & Cardon, L. *Methodology for Genetic Studies of Twins and Families*. (Springer Netherlands, 1992).

15 Mardia, K. V. *Multivariate analysis / K.V. Mardia, J.T. Kent, J.M. Bibby*. (Academic Press, 1979).

16 Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics (Oxford, England)* **26**, 2190-2191, doi:10.1093/bioinformatics/btq340 (2010).

17 Tyrrell, J. *et al.* Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight. *JAMA : the journal of the American Medical Association* **315**, 1129-1140, doi:10.1001/jama.2016.1975 (2016).

18 Zimmermann, E., Gamborg, M., Sorensen, T. I. & Baker, J. L. Sex Differences in the Association Between Birth Weight and Adult Type 2 Diabetes. *Diabetes* **64**, 4220-4225, doi:10.2337/db15-0494 (2015).

19 Gamborg, M. *et al.* Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *American journal of epidemiology* **166**, 634-645, doi:10.1093/aje/kwm042 (2007).

20 Lawlor, D. *et al.* Using Mendelian randomization to determine causal effects of maternal pregnancy (intrauterine) exposures on offspring outcomes: Sources of bias and methods for assessing them. *Wellcome open research* **2**, 11, doi:10.12688/wellcomeopenres.10567.1 (2017).

21 Kong, A. *et al.* The nature of nurture: Effects of parental genotypes. *Science (New York, N.Y.)* **359**, 424-428, doi:10.1126/science.aan6877 (2018).

Supplementary Note 3: EGG Membership

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