Prenatal famine exposure restricts genetic effects on birth weight with implications for metabolic disease risk – Supplementary Material.

M. Jazmin Taeubert, Karlijn van den Kieboom, Jiayi Zhou, Thomas B. Kuipers, Dalton C. Conley, Chihua Li, Shuang Wang, Tian Wang, Daniel W. Belsky, L. H. Lumey, Bastiaan T. Heijmans.

Index

Supplementary Table 1. Distribution of individuals classified as exposed in early and mid-to-late gestation across the 10-week exposure windows.

10-week categories	Early gestational exposure *(n =145)*	Mid-to-late gestational exposure *(n = 283)*
Conception to week 9	94	0
Weeks 1-10	73	0
Weeks 11-20	24	100
Weeks 21-30	0	144
Weeks 31 to delivery	0	133

Note: participants can belong to up to two of the 10-week gestational exposure windows. Therefore, the total of the 10-week categories add up to more than the total of the early and mid-to-late gestational exposure categories.

Supplementary Table 2. Population characteristics among those exposed to any famine.

	Controls *(n = 161)*	**Famine-exposed** *(n = 479)*	**p value**
Gestational age [days], mean ± SD	284 ± 9.4	282 ± 10.4	0.006
Sex [males], n (%)	72 (44.7)	226 (47.2)	0.653
Firstborn [yes], n (%)	77 (47.8)	204 (42.6)	0.283
Adult age [years], mean ± SD	59.2 ± 2.0	58.8 ± 0.5	0.006

Values are shown as the mean ± standard deviation or count (valid %) for famine-exposed and controls of the study population. Comparing the two categories by a two-sample t-test (two-sided) or chi-square test (two-sided), as appropriate.

Supplementary Table 3. Birth weight and birth weight polygenic index (PGI) distribution among controls, and famine-exposed in early and mid-to-late gestation.

	Controls *(n = 161)*	**Early gestational exposure** *(n = 145)*	**Mid-to-late gestational exposure** *(n = 283)*	**p value**
Birth weight [g], mean ± SD	3498 ± 486	3472 ± 580	3233 ± 459	9.7×10^{-9}
Birth weight PGI [SD], mean ± SD	0.086 ± 0.92	-0.085 ± 0.95	0.001 ± 1.01	0.31

Values are shown as the mean ± standard deviation for famine-exposed (split into exposure in early gestation and mid-to-late gestation) and controls of the study population. Comparing the three categories by ANOVA (two-sided).

Supplementary Table 4. Number of preterm births and low birth weight individuals across famine-exposed groups and controls.

	Controls *(n = 161)*	**Early gestational exposure** *(n = 145)*	**Mid-to-late gestational exposure** *(n = 283)*
Preterm births (<37 weeks) [yes], n (%)	0 (0%)	2 (1.4%)	9 (3.2%)
Low birth weight (<2500g) [yes], n (%)	3 (1.9%)	5 (3.4%)	14 (4.9%)

Values are shown as (valid %) for famine-exposed (split into early and mid-to-late gestational exposure) and controls of the study population.

Supplementary Table 5. Association between famine exposure in early and mid-to-late gestation and body mass index (BMI).

	$\mathbf{B_{early}}$**(95%CI)**	**p** $\mathbf{value_{early}}$	$\boldsymbol{\beta}_{\mathbf{mid\text{-}late}}$**(95%CI)**	**p** $\mathbf{value_{mid\text{-}late}}$
BMI	0.24 (0.01-0.47)	0.04	0.26 (0.07-0.46)	0.008

β_{early}: effect estimate for famine exposure in early gestation.

$B_{mid\text{-}late}$: effect estimate for famine exposure in mid-to-late gestation.

95%CI: 95% confidence interval.

The association between famine exposure and BMI was assessed using multivariable linear regression models adjusted for sex and adult age. Shown are the adjusted differences in BMI between famine-exposed (mid-to-late (n=283) and early (n=145) gestation) and control (n=161) groups. Effect estimates and 95% confidence intervals are provided for each model and are reported in standard-deviation (SD) scores of BMI. BMI was log-transformed prior to the calculation of the Z scores.

Supplementary Table 6: Association between birth weight and adult outcomes.

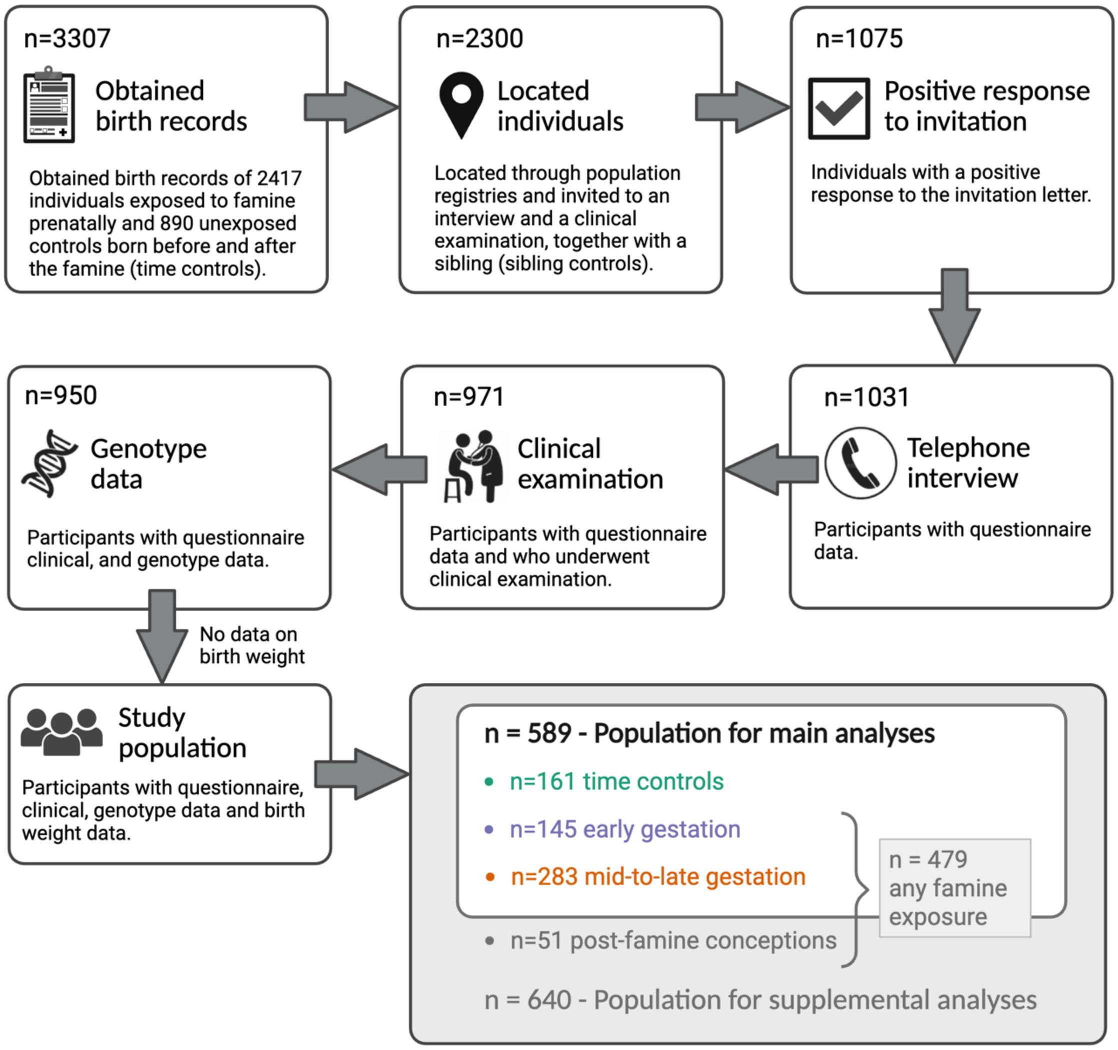
	Effect estimate (95% CI) [SD]*	**p value**
Fasting glucose		
Controls	-0.10 (-0.25, 0.06)	0.22
Early gestational exposure	0.02 (-0.17, 0.20)	0.85
Mid-to-late gestational exposure	-0.27 (-0.42, -0.12)	6.2×10^{-4}
Waist circumference		
Controls	0.12 (-0.05, 0.29)	0.16
Early gestational exposure	0.03 (-0.13, 0.18)	0.75
Mid-to-late gestational exposure	-0.01 (-0.16, 0.14)	0.88
BMI		
Controls	0.12 (-0.05, 0.29)	0.18
Early gestational exposure	0.05 (-0.12, 0.23)	0.54
Mid-to-late gestational exposure	-0.11 (-0.27, 0.04)	0.15

*Effect estimates and 95% confidence intervals (CI) for the multivariable linear regression analysis of birth weight and adult outcomes (fasting glucose, waist circumference, and BMI) are reported in standard-deviation (SD) scores of the adult outcomes. The linear regression analyses were adjusted for sex, first-born status, gestational age, and adult age, and are presented separately for individuals exposed in early (n=145) and mid-to-late (n=283) gestation and controls (n=161). Fasting glucose and BMI were log-transformed prior to the calculation of the Z scores.

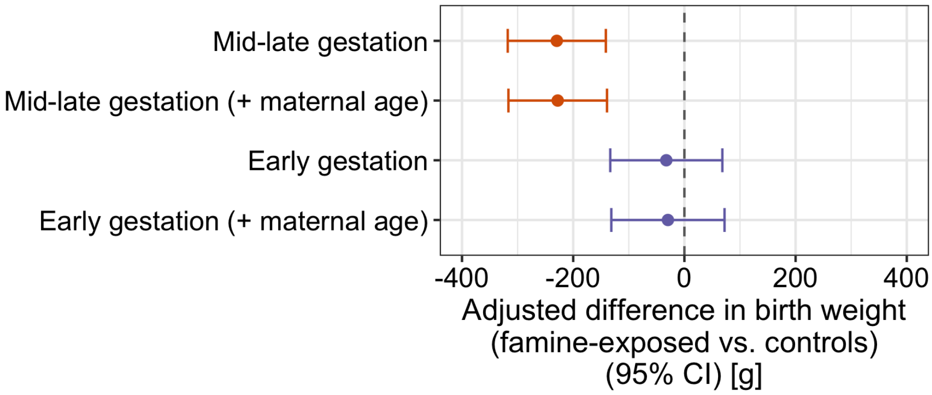
Supplementary Table 7: Association between birth weight polygenic index (PGI) and adult outcomes.

	Effect estimate (95% CI) [SD]*	**p value**
Fasting glucose		
Controls	-0.11(-0.26, 0.03)	0.11
Early gestational exposure	0.00 (-0.18, 0.19)	0.98
Mid-to-late gestational exposure	0.05 (-0.07, 0.18)	0.41
Waist circumference		
Controls	-0.06 (-0.22, 0.10)	0.48
Early gestational exposure	0.01 (-0.14, 0.14)	0.92
Mid-to-late gestational exposure	0.09 (-0.03, 0.21)	0.15
BMI		
Controls	-0.07 (-0.23, 0.09)	0.37
Early gestational exposure	-0.01 (-0.18, 0.16)	0.92
Mid-to-late gestational exposure	0.04 (-0.08, 0.17)	0.52

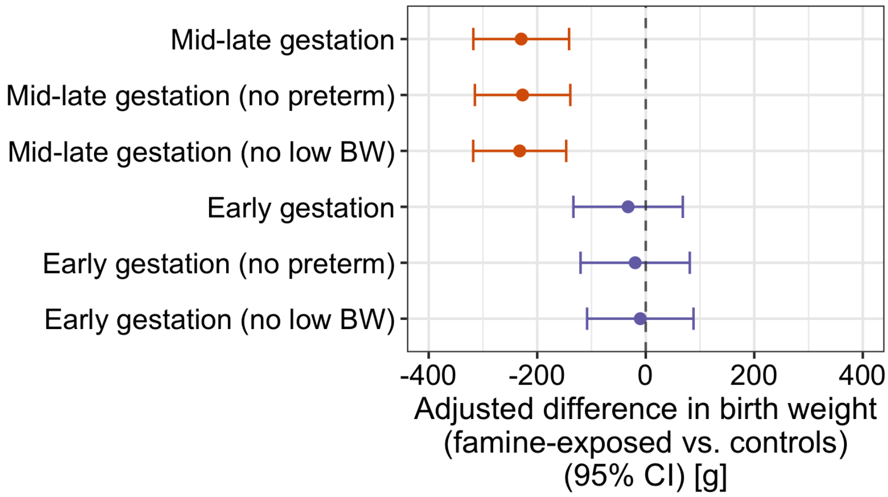
*Effect estimates and 95% confidence intervals (CI) for the multivariable linear regression analysis of the birth weight polygenic index (PGI) and adult outcomes (fasting glucose, waist circumference, and BMI) are reported in standard-deviation (SD) scores of the adult outcomes. The linear regression analyses were adjusted for sex, first-born status, gestational age, and adult age, and are presented separately for individuals exposed in early (n=145) and mid-to-late (n=283) gestation and controls (n=161). Fasting glucose and BMI were log-transformed prior to the calculation of the Z scores.



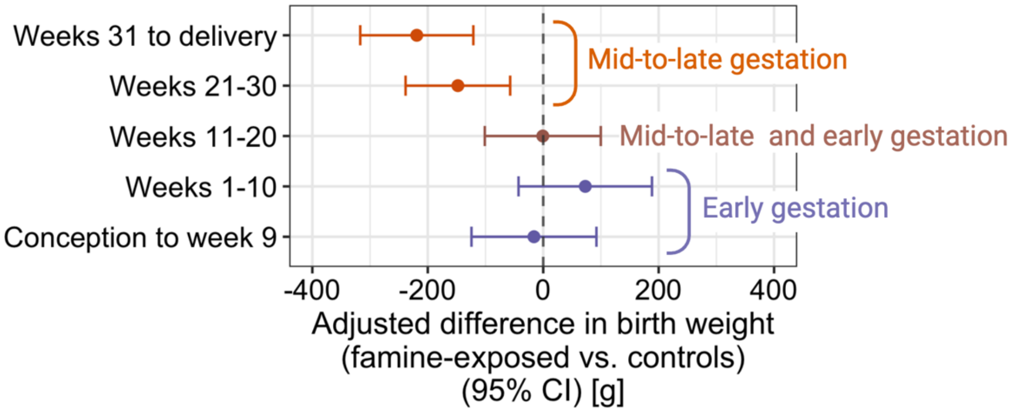
Supplementary Figure 1. Flow chart of the study population. Historical birth records were retrieved from three institutions in famine-exposed cities, including all singleton births between 1 February 1945 and 31 March 1946 and a systematic sample of births from 1943 and 1947. From these records, we identified 3,307 individuals: 2,417 whose mothers were exposed to famine during or immediately preceding pregnancy and 890 unexposed time controls born before or after the famine. Of these 3,307 individuals, 2,300 were traced through population registries and invited to participate in a telephone interview and a clinical examination, along with a same-sex sibling not exposed to famine (sibling controls). In total, 1,075 individuals responded positively to the invitation. Between 2003 and 2005, 1,031 interviews and 971 clinical examinations were conducted. DNA extracted from blood samples was available for 950 individuals. Birth weight data were unavailable for all sibling controls (n = 310) because they were not recruited through clinics that maintained obstetric records; these individuals were therefore excluded from the present analysis. The analysis sample comprised participants recruited via obstetric records with complete birth weight and genetic data. The main analysis population included 161 time controls, 145 individuals exposed to famine in early gestation, and 283 individuals exposed in mid-to-late gestation. The supplementary analysis additionally included 51 individuals conceived shortly after the end of the famine, incorporated into the broader "any famine exposure" group that combined all famine-exposed categories. This figure was created using BioRender (https://biorender.com)



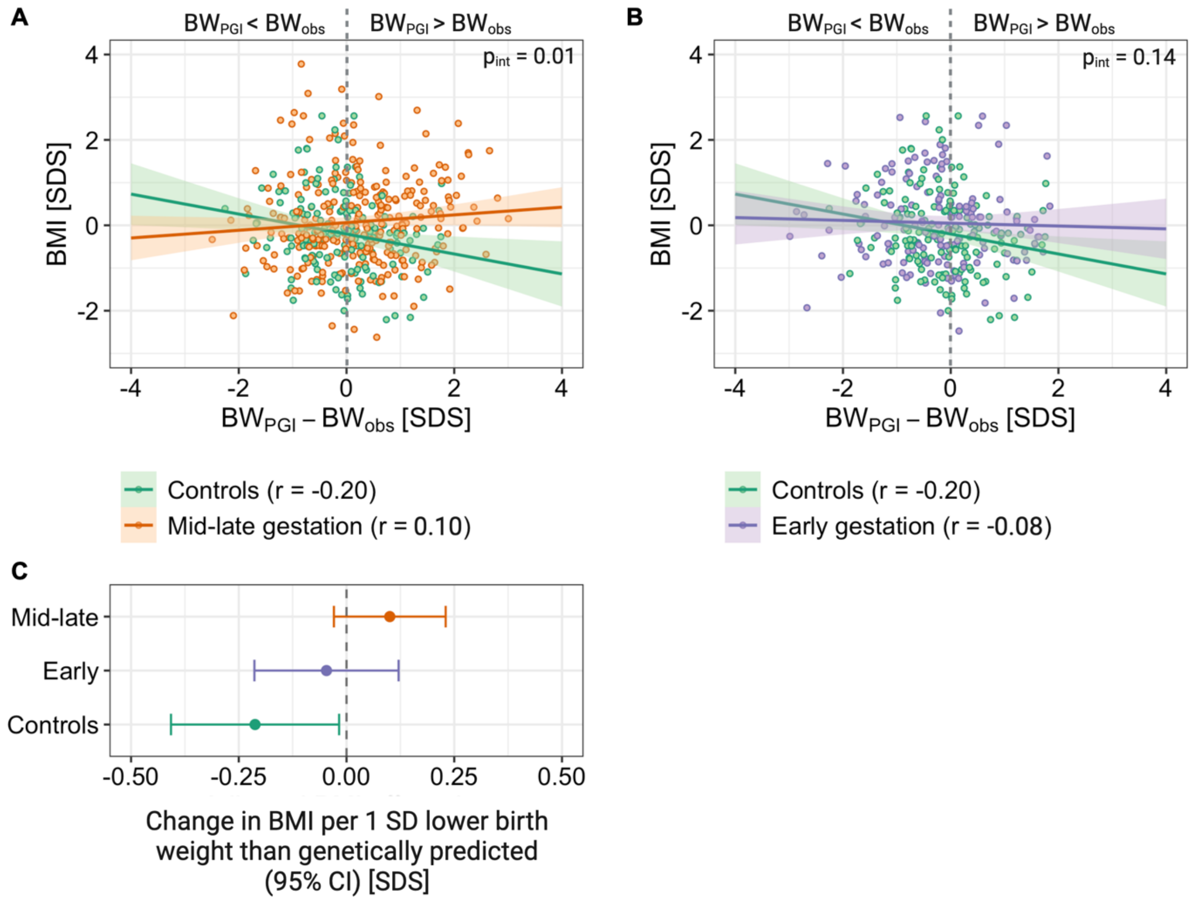
Supplementary Figure 2: Effect of additional adjustment for maternal age on the association between prenatal famine exposure and observed birth weight. Shown are the adjusted differences in birth weight between famine-exposed (mid-to-late (n=283) and early (n=145) gestation) and control (n=161) groups using multivariable linear regression models. The main models are adjusted for sex, firstborn status, and gestational age. As a sensitivity analysis, models were also run with additional adjustment for maternal age at time of birth (+ maternal age). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in grams.



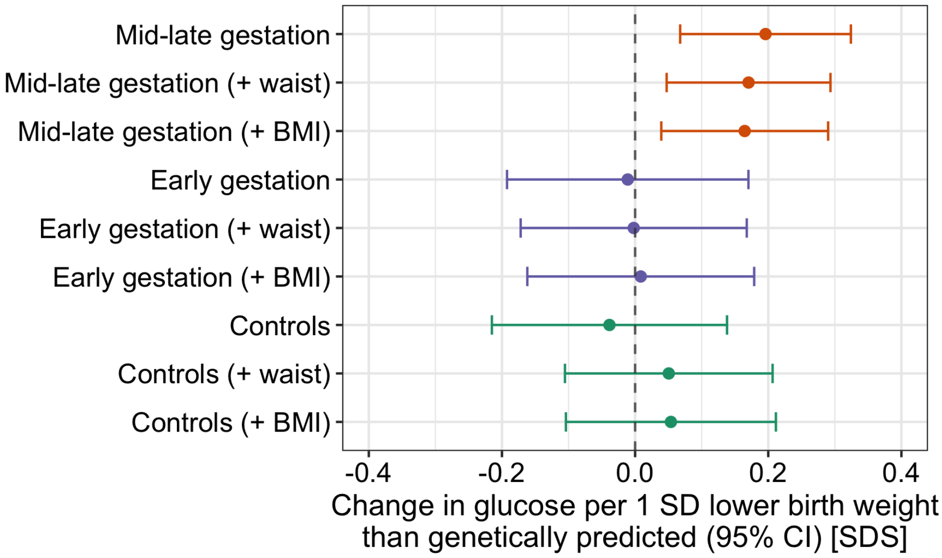
Supplementary Figure 3. Effect of excluding preterm and low birth weight births on the association between prenatal famine exposure and observed birth weight. Shown are the adjusted differences in birth weight between famine-exposed (mid-to-late (n=283) and early (n=145) gestation) and control (n=161) groups using multivariable linear regression models. The main models are adjusted for sex, firstborn status, and gestational age. For comparison purposes models were run excluding participants born preterm (n=11, <37 weeks) and those with a low birth weight (n=22, <2500g). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in grams.



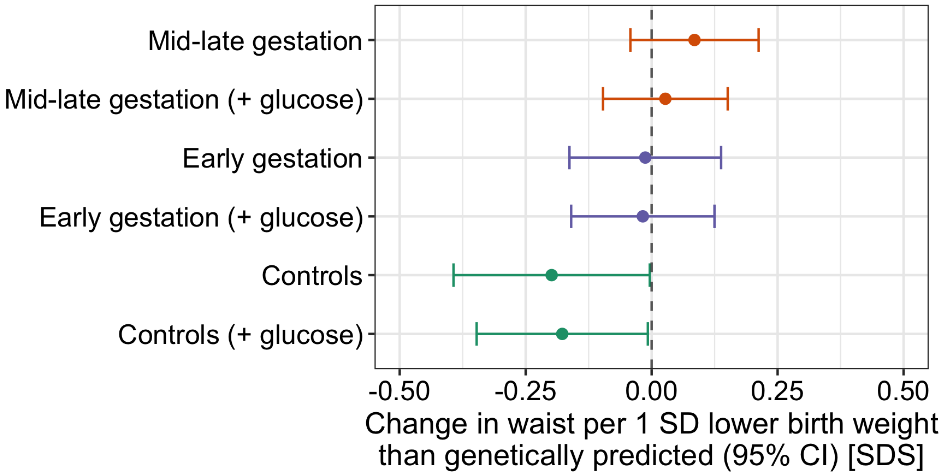
Supplementary Figure 4: Association between 10-week prenatal famine exposure groups and observed birth weight. The association between 10-week prenatal famine exposure groups and observed birth weight was assessed using multivariable linear regression models. Shown are the adjusted differences in birth weight between famine-exposed (exposed between conception to week 9 of gestation (n=94), as well as exposed in gestation weeks 1-10 (n=73), 11-20 (n=124), 21-30 (n=144), and 31 up until delivery (n=133)) and control (n=161) groups, accounting for sex, firstborn status and gestational age. Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in grams.



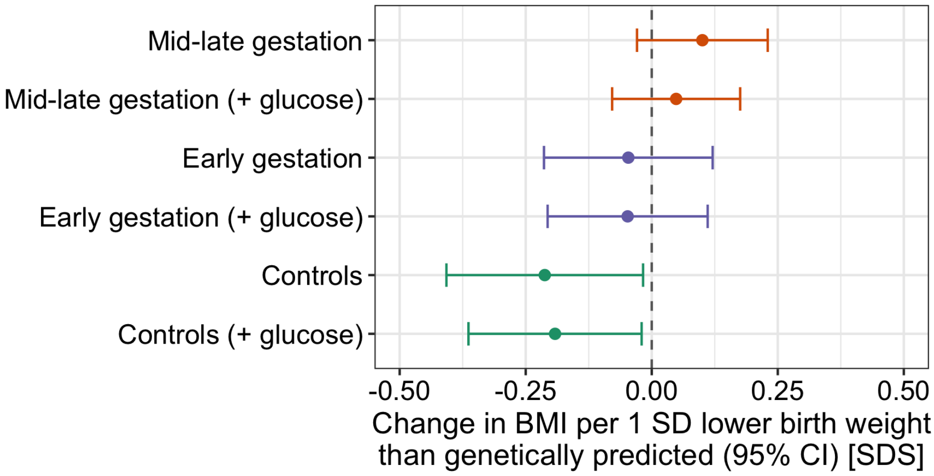
Supplementary Figure 5. Deviation from genetically predicted birth weight and BMI. A-B. Scatterplots of associations between the deviation from genetically predicted birth weight (polygenic index (PGI) minus observed birth weight) and BMI in adulthood, in famine-exposed participants in mid-to-late gestation (**A**) and early gestation (**B**), compared to controls. Solid lines show fitted linear regression models and shaded bands denote 95% confidence intervals around the estimated regression line. **C.** The association between the deviation from genetically predicted birth weight and BMI was assessed using multivariable linear regression models adjusted for sex, firstborn status, gestational age, and adult age, separately for individuals exposed in mid-to-late (n=283) and early (n=145) gestation and controls (n=283). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in standard-deviation (SD) units of BMI. BMI was log-transformed prior to the calculation of the Z scores.



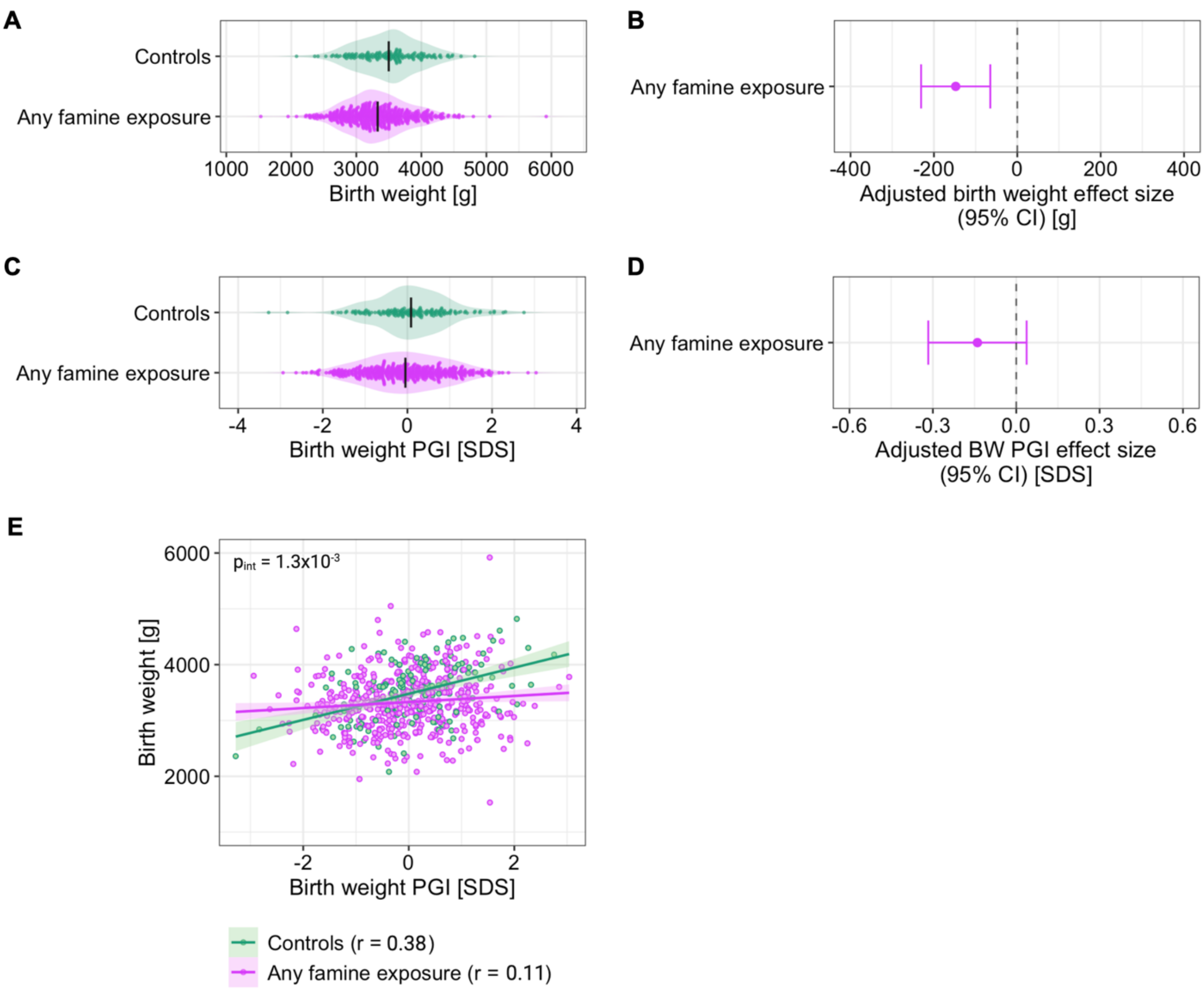
Supplementary Figure 6. Deviation from genetically predicted birth weight and adult fasting glucose – effect of adjusting for waist circumference and BMI. The association between the deviation from genetically predicted birth weight and fasting glucose was assessed using multivariable linear regression models. Shown are the changes in fasting glucose per 1 SD lower birth weight than genetically predicted, adjusted for sex, first-born status, gestational age, and adult age, and presented separately for individuals exposed in mid-to-late (n=283) and early (n=145) gestation and controls (n=161). These models were additionally adjusted for waist circumference (+ waist) and BMI (+ BMI). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in standard-deviation (SD) scores of fasting glucose. Fasting glucose was log-transformed prior to the calculation of the Z scores.



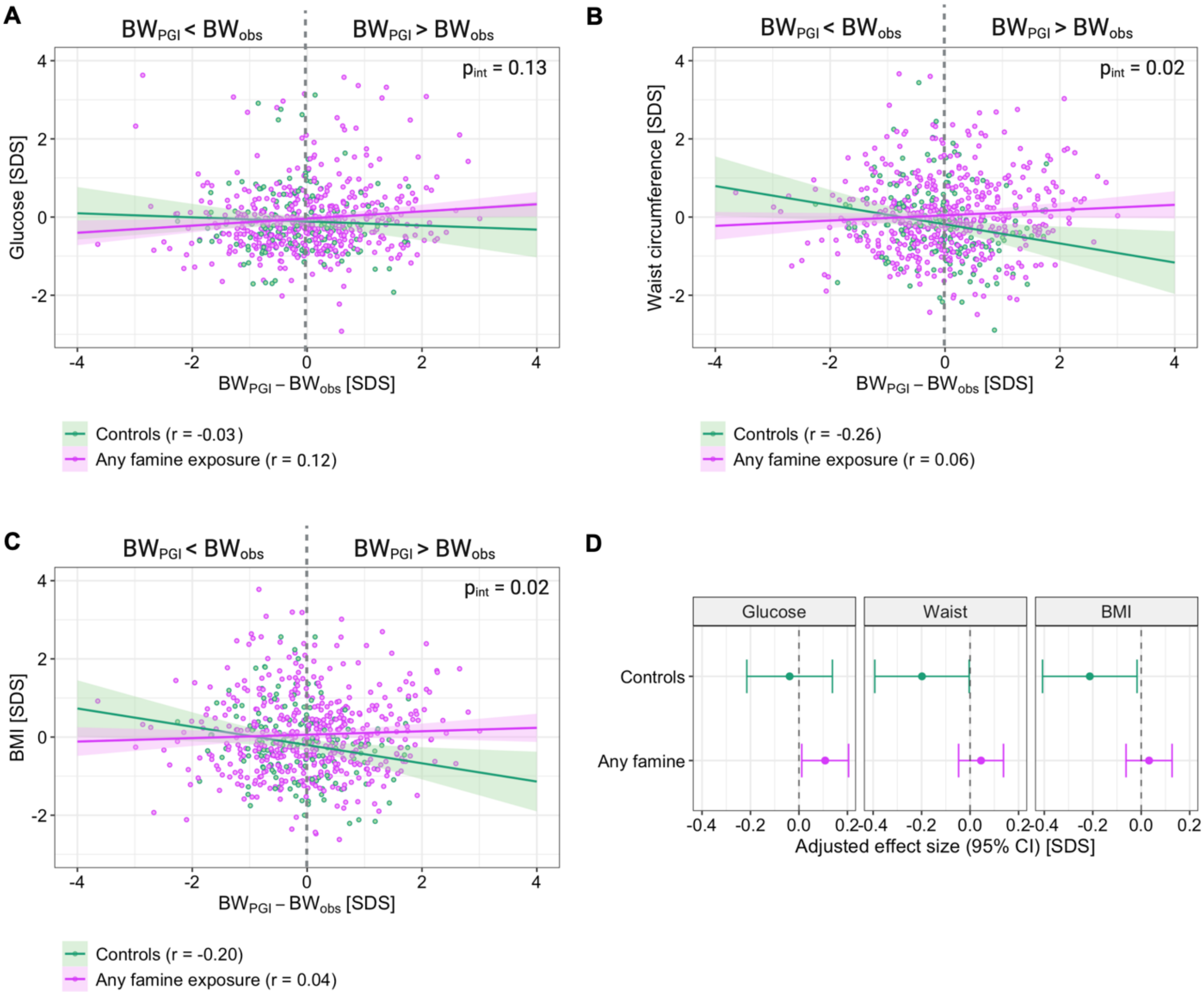
Supplementary Figure 7. Deviation from genetically predicted birth weight and waist circumference – effect of adjusting for fasting glucose. The association between the deviation from genetically predicted birth weight and waist circumference was assessed using multivariable linear regression models. Shown are the changes in waist circumference per 1 SD lower birth weight than genetically predicted, adjusted for sex, first-born status, gestational age, and adult age, and presented separately for individuals exposed in mid-to-late (n=283) and early (n=145) gestation and controls (n=161). These models were additionally adjusted for fasting glucose (+ glucose). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in standard-deviation (SD) scores of waist circumference.



Supplementary Figure 8. Deviation from genetically predicted birth weight and BMI – effect of adjusting for fasting glucose. The association between the deviation from genetically predicted birth weight and BMI was assessed using multivariable linear regression models. Shown are the changes in BMI per 1 SD lower birth weight than genetically predicted, adjusted for sex, first-born status, gestational age, and adult age, and presented separately for individuals exposed in mid-to-late (n=283) and early (n=145) gestation and controls (n=161). These models were additionally adjusted for fasting glucose (+ glucose). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in standard-deviation (SD) scores of BMI. BMI was log-transformed prior to the calculation of the Z scores.



Supplementary Figure 9. Associations of any famine exposure with observed birth weight and birth weight PGI. A) Birth weight distribution in controls and individuals exposed to famine at any point of gestation. The black line indicates the mean per group and the shaded area represents the density of the data points. **B)** The association between prenatal famine exposure and observed birth weight was assessed using multivariable linear regression models adjusted for sex, firstborn status and gestational age. Shown are the adjusted differences in birth weight between famine-exposed individuals (n=479) and controls (n=161). Effect estimates (point) and 95% confidence intervals (error bars) are depicted and are reported in grams. **C)** Birth weight PGI distribution in controls and individuals exposed to famine at any point of gestation. The black line indicates the mean per group and the shaded area represents the density of the data points. **D)** The association between prenatal famine exposure and birth weight PGI was assessed using multivariate linear regression models adjusted for sex, firstborn status and gestational age. Shown are the adjusted differences in birth weight PGI between famine-exposed individuals (n=479) and controls (n=161). Effect estimates (point) and 95% confidence intervals (error bars) are depicted and are reported in standard-deviation (SD) units. **E)** Gene-environment interaction between genetic predisposition for birth weight and prenatal famine exposure. The figure shows scatterplots of associations between the birth weight polygenic index (PGI) and observed birth weight in famine-exposed participants compared to controls. Solid line shows fitted linear regression model and the shaded band denotes 95% confidence intervals around the estimated regression line.



Supplementary Figure 10. Deviation from genetically predicted birth weight and metabolic health in individuals exposed to any famine. A-C. Scatterplots of associations between the deviation from genetically predicted birth weight (polygenic index (PGI) minus observed birth weight) and adult metabolic outcomes (fasting glucose (**A**) and waist circumference (**B**), and BMI (**C**)), participants exposed to famine at any point of gestation, compared to controls. Solid lines show fitted linear regression models and shaded bands denote 95% confidence intervals around the estimated regression line. **D.** The association between the deviation from genetically predicted birth weight and fasting glucose, waist circumference, and BMI was assessed using multivariable linear regression models adjusted for sex, firstborn status and gestational age, separately for individuals exposed to any famine (n=479) and controls (n=161). Effect estimates (point) and 95% confidence intervals (error bars) are depicted for each model and are reported in standard-deviation (SD) units of the deviation from genetically predicted birth weight. Fasting glucose and BMI were log-transformed prior to the calculation of the Z scores.