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communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-026-01495-9

Prenatal famine exposure restricts genetic effects on birth weight with implications for metabolic disease risk

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Abstract

Background Prenatal growth is shaped by genetic and environmental influences. Prenatal exposure to famine, particularly later in gestation, stunts growth and leads to lower birth weight. Here, we evaluated the effect of prenatal famine exposure on the expression of genetic influences on birth weight and how this relationship shapes associations between the early environment and metabolic disease risk in later life.

Methods We analysed data from the Dutch Hunger Winter Families Study, including 283 individuals conceived in the months before the 1944–45 Dutch Famine and therefore exposed during mid-to-late gestation, 145 conceived during the famine and thus exposed in early gestation, and 161 unexposed controls with available obstetric records and genetic data. Genetic influences on birth weight were assessed using a polygenic index (PGI). We tested for gene-environment interactions between the birth weight PGI and the timing of famine exposure, and examined whether deviations from genetically predicted birth weight were associated with fasting glucose and waist circumference in adulthood.

Results While the birth weight PGI explains 14% of the variation in birth weight in controls ($r = 0.38$, $p < 0.001$), genetics does not have a detectable influence on birth weight in famine-exposed individuals, particularly those exposed in mid-to-late gestation ($r = 0.10$, $p = 0.09$) ($p_{interaction}<0.001$). Six decades later, being born lighter than genetically predicted is associated with increased fasting glucose levels and waist circumference in those exposed to famine in mid-to-late gestation as compared to controls ($p_{interaction}<0.04$).

Conclusions Prenatal exposure to famine during mid-to-late gestation overrides genetic influences on birth weight and modifies the relationships that are observed between birth weight and metabolic risk factors in later life.

Plain language summary

Growth before birth is influenced by both genetic and environmental factors during pregnancy. In this study, we examined whether prenatal exposure to the Dutch Famine affected how strongly genes influenced birth weight, and whether this had long-term health consequences. We found that exposure to famine late in pregnancy, but not early, greatly reduced birth weight and markedly restricted the effect of genetic influences on birth weight. These prenatal effects played out later in life. Among individuals exposed later in pregnancy, failure to achieve a birth weight consistent with their genetic predisposition translated into higher blood sugar levels and larger waist circumference in adulthood as compared with unexposed controls. Our findings indicate that severe undernutrition during pregnancy can override genetic influences on early growth and shape long-term disease risk.

Gene-environment interactions are widely recognized as a critical mechanism linking nature and nurture. However, their empirical isolation in human populations remains challenging. On one hand, this difficulty may stem from limited statistical power, as the contributions of individual genetic and environmental factors to variation in common traits are often modest. On the other hand, some environmental exposures are partly shaped by an individual's genetic make-up (e.g., genetic influences on diet, socioeconomic status, or smoking behavior), complicating the identification of environmental exposures that are truly exogenous[1–4].

This study leverages a well-documented exogenous environmental exposure—the Dutch Famine. Also known as the Dutch Hunger Winter, this severe wartime famine at the end of World War II in the Netherlands provides a quasi-experimental setting to examine the effects of prenatal famine exposure on a range of human traits[5]. We, as well as others, have

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previously reported that this environmental exposure has a marked effect on birth weight, in particular when occurring later in gestation[6–9]. Likewise, genome-wide association studies have identified a series of genetic variants that, when combined into a polygenic index, explain a substantial proportion of the variance in birth weight[10–12]. Through the analysis of genome-wide genetics data, we recently ruled out substantial correlations between genetic variation, prenatal famine, and later-life outcomes[13]. Taken together, birth weight may be a trait that is especially well-suited to investigate gene-environment interactions in the context of prenatal famine exposure, as well as the potential influence of such interactions on long-term health outcomes[14–16].

Using data from the Dutch Hunger Winter Families Study (DHWFS), we first confirm the major impact of prenatal famine on birth weight in mid-to-late, but not early gestation. We also establish the influence of common genetic variation on birth weight in our cohort using a polygenic index (PGI) for birth weight. Next, we evaluate the interaction between prenatal famine exposure and genetic predisposition in their effects on birth weight, while ruling out any correlation between the two. Finally, we examine whether deviations from genetically predicted birth weight in famine-exposed individuals have implications for metabolic risk factors in later life, as expressed by fasting glucose and waist circumference.

Methods

Historical background: the Dutch Hunger Winter of 1944 to 1945

The Dutch famine occurred between 26 November 1944 and 12 May 1945 and began as a result of a food-supply embargo by German occupying forces in early October 1944, a consequence of wartime policies that severely restricted civilian access to food. The severity and widespread nature of the famine are well documented[5,17]. Prior to the famine, nutrition in the Netherlands had been generally adequate. Official rations fell below 900 kcal/day in late November 1944, and were as low as 500 kcal/day by April 1945. The famine ended a week after liberation 5 May 1945, after which available food supplies rapidly increased by Allied efforts.

Study population

The Dutch Hunger Winter Families study (DHWFS) is described in detail elsewhere[18,19]. Famine-exposed individuals and non-exposed individuals born 2 years before and after the famine (time controls) were identified from the review of archival obstetric records. Data collection was conducted from 2003 to 2005, approximately six decades after the famine. Participants were interviewed, participated in a clinic exam, and DNA was extracted from blood samples and sent for genotyping[13,18]. The analysis sample for this study was formed from participants for whom birth weight and genetic data were available, including 161 time controls, 145 individuals exposed to famine in early gestation, and 283 individuals exposed in mid-to-late gestation ($n = 589$). Additional details on the recruitment process and study population are found in Supplementary Fig. 1.

In line with the Declaration of Helsinki, we obtained ethical approval both from the Institutional Review Board of Columbia University Medical Center and from the Medical Ethical Committee of the Leiden University Medical Center (LUMC) (P02.082). The study participants provided written consent during clinical examinations.

Assessment of birth weight, gestational age, sex, firstborn status, and maternal age

Birth weight, gestational age, sex, information on whether the participant was the firstborn (firstborn status), and maternal age at delivery were obtained from the birth records of the famine-exposed individuals and the time controls. Birth weight was recorded in grams (g) and rounded to the nearest 10 g. Gestational age was measured in days and estimated from the last menstrual period of the mother and the date of birth of the child.

Assessment of adult health outcomes

Fasting glucose was measured from serum samples using ^{1}H-NMR (Nightingale Health Ltd., Helsinki, Finland; biomarker quantification version 2021)[20–22]. The measurement of waist circumference (at the level of iliac crests, intersection with midaxillary line) was carried out to the nearest 1 mm with the use of a non-extensible measuring tape (Hoechstmass). Height was measured to the nearest millimeter using a portable stadiometer (Seca), and body weight was measured to the nearest 100 g by a portable scale (Seca). BMI was subsequently calculated from these measures (weight (kg)/[height (m)]^2).

Famine exposure definitions

A participant was categorized as being exposed to any famine if their mother was exposed to <900 kcal/day for a minimum of 10 weeks during or immediately preceding pregnancy[13,19,22,23]. The gestational period was estimated from the last menstrual period of the mother recorded on the obstetric record and the date of birth of the child. Exposure to any famine included participants with a maternal last menstrual period date between 20 April 1944 and 30 July 1945. The effect of prenatal famine exposure on birth weight is largely confined to individuals exposed later in pregnancy, and those exposed periconceptionally show little to no effect[7]. We therefore defined exposure based on timing of conception: individuals conceived during the famine (maternal last menstrual period date between 26 November 1944 and 12 May 1945) were classified as exposed in early gestation, while those conceived before the famine (maternal last menstrual period date between 20 April and 25 November 1944) were classified as exposed in mid-to-late gestation (Fig. 1A). This approach allows us to distinguish exposure groups with well-established differences in birth weight outcomes, while maximizing the number of participants within each group. To note, any famine exposure group is composed of individuals exposed in early ($n = 145$) and in mid-to-late ($n = 283$) gestation, as well as those conceived shortly after the famine period ended ($n = 51$) (Supplementary Fig. 1).

10-week famine exposure group definitions. We considered the mother exposed in gestational weeks 1–10, 11–20, 21–30, or 31 to delivery if these gestational time windows were entirely contained within this period and had an average exposure of <900 kcal/day during an entire gestation period of 10 weeks. As the famine lasted 6 months, some participants were exposed to famine during two adjacent 10-week periods. In chronological order, pregnancies with LMP between 30 April 1944 and 24 August 1944 were considered exposed in weeks 31 to delivery; between 9 July 1944 and 15 October 1944 in pregnancy weeks 21–30; between 17 September 1944 and 24 December 1944 in pregnancy weeks 11–20, between 26 November 1944 and 4 March 1945 in pregnancy weeks 1–10. Individuals with an LMP between 4 February and 12 May 1945 were exposed to an average of <900 kcal/day for less than 10 weeks before conception and up to 8 weeks post-conception, and are denoted as the weeks 9–0 weeks group. The distribution of individuals classified as exposed in early and mid-to-late gestation across these 10-week exposure windows can be found in Supplementary Table 1.

Genotype data and birth weight polygenic index

The genetic database for DHWFS has been described previously[13]. Briefly, genotyping and quality controls were performed by the Human Genomics Facility at the Erasmus University Medical Center (Rotterdam, The Netherlands) using the Infinium Global Screening Array (version 24 v3.0 Bead Chip Arrays. Illumina Inc., San Diego, USA). The genotype data were imputed to the 1000G P3v5 reference panel[24].

We measured participants' genetic predisposition toward lower/higher birth weight using a polygenic index. Polygenic indices summarize genome-wide genetic influences on a trait as revealed from genome-wide association studies (GWAS). In their simplest form, polygenic indices are computed as the average weighted count of trait-associated alleles, where the weights are defined by GWAS regression coefficients[25]. To compute the birth weight PGI, following the practice of the Social Science Genetic Association Consortium[26], we analyzed results from the largest available GWAS on birth

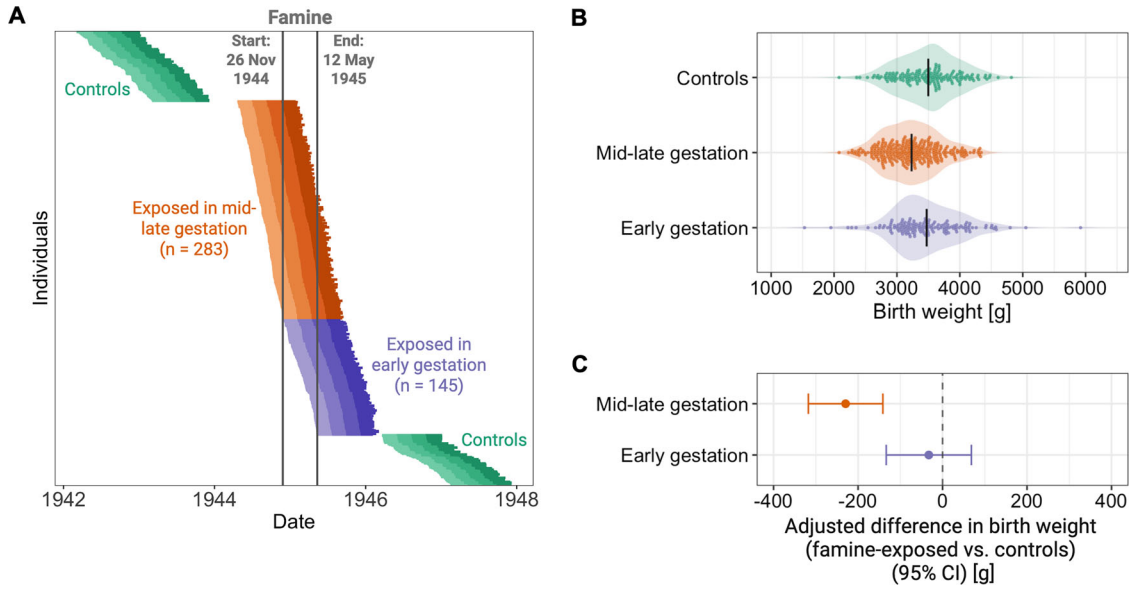

Fig. 1 | Associations of prenatal famine exposure with observed birth weight. **A** Gestational timing of exposure to famine in the Dutch Hunger Winter Families Study. The figure shows individual gestations of 283 individuals exposed to famine in mid-to-late gestation (orange lines), 145 individuals exposed in early gestation (purple lines), and 161 time controls (green lines). Each gestation is plotted as a single horizontal line. The start of the line is the date of the mother's last menstrual period. The end of the line is the participant's date of birth. Individual gestations are plotted from the top of the graph to the bottom, ordered by last menstrual period date. The shading of each line represents 10-week gestational windows; within exposure and control groups, lighter colors indicate earlier gestational windows and darker colors indicate later windows. The *x*-axis shows the date. The vertical lines show the start and end of the famine exposure period (November 26, 1944 to May 12, 1945). **B** Birth weight distribution in controls and individuals exposed to famine in early and mid-to-late gestation. The black line indicates the mean per group, and the shaded area represents the density of the data points. **C** The association between prenatal famine exposure and observed birth weight was assessed using multivariable linear regression models. Points indicate the adjusted mean differences in birth weight between famine-exposed (mid-to-late ($n = 283$) and early ($n = 145$) gestation) and control ($n = 161$) groups, accounting for sex, firstborn status, and gestational age, and error bars represent 95% confidence intervals. Estimates are reported in grams.

Table 1 | Population characteristics

	Controls ($n = 161$)	Early gestational exposure ($n = 145$)	Mid-to-late gestational exposure ($n = 283$)	*p* value
Gestational age [weeks], mean ± SD	40.6 ± 1.3	40.6 ± 1.5	40.0 ± 1.5	7.1×10^{-5}
Sex [males], *n* (%)	72 (44.7)	71 (49.0)	134 (47.3)	0.750
Firstborn [yes], *n* (%)	77 (47.8)	70 (48.3)	116 (41.5)	0.244
Adult age [years], mean ± SD	59.2 ± 2.0	58.5 ± 0.5	59.0 ± 0.5	3.5×10^{-7}

Values are shown as the mean ± standard deviation or count (valid %) 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) or chi-square test (two-sided), as appropriate.

weight[10] using the LDpred2 software, which takes into account patterns of linkage disequilibrium when defining SNP-specific weights from GWAS results[12]. To summarize the polygenic index computation process, SNPs in the selected GWAS results, DHWFS genotype data, and HapMap3+ variants reference were first matched and extracted by taking the intersection of the three variant datasets. Next, correlation matrices indicating the linkage disequilibrium (LD) between variants were created using the HapMap3 reference data. Finally, the 'auto' model within LDPred2 requires the tuning parameters of SNP heritability (h^2SNP) and the prior proportion of variants assumed to be causal (p). We estimated h^2SNP within the LDPred2 software from LD-score regression applied to the GWAS summary statistics for birth weight. We set the prior value of p as a sequence with a length of 30 evenly spaced on a logarithmic scale from 1×10^{-4} to 0.3.

To account for potential residual population stratification, the birth weight PGI was residualised for the first ten principal components (PCs) estimated from the genome-wide SNP data using the 'PC-AiR' method from the GENESIS R package, which accommodates data that includes genetic relatives[27]. For analysis, the residualised birth weight PGI were standardized to have a mean of 0 and a standard deviation of 1 in the sample population ($n = 640$).

Statistics and reproducibility

All analyses, as well as the generation of graphs, were performed with the R programming environment (version 4.3.1). Figures were created using BioRender (https://biorender.com/). Regression models included covariates for factors known to be associated with birth weight: gestational age, sex, and firstborn status[28–30]. It has been shown that the effect of famine exposure on birth weight is dependent on the timing of the exposure[6]. Therefore, we performed all analyses examining famine exposure in early and mid-to-late gestation. We additionally performed analyses with the full group of famine-exposed individuals.

Prenatal famine exposure and birth weight. Multivariable linear regression was used to test the associations of prenatal famine exposure with birth weight using the following model:

$$BW = \beta_0 + \beta_1 * \exp_{early} + \beta_2 * \exp_{mid-late} + \beta_3 * sex + \beta_4 * gestational\ age + \beta_5 * first\ born\ status + \varepsilon$$

where BW denotes birth weight, $\exp_{early}$ exposure to famine in early gestation, and $\exp_{mid\text{-}late}$ exposure to famine in mid-to-late gestation.

Sensitivity analyses of the effect of prenatal famine exposure on birth weight. As a sensitivity analysis, we first re-estimated the association between prenatal famine exposure and birth weight using the aforementioned model with additional adjustment for maternal age at delivery. To further test the robustness of the observed effects, analyses were repeated after excluding individuals born preterm (gestational age <37 weeks) or with a low birth weight (<2500 g). To obtain more fine-grained effects of exposure timing during gestation, the association between prenatal famine and birth weight was examined using 10-week gestational exposure windows that have previously been used in this cohort[13,19,22]. In the regression analysis, the two indicators of famine exposure were replaced with indicator variables identifying exposure within each of the gestational time windows.

Prenatal famine exposure and birth weight PGI. Univariable linear regression models were first used to test the association between the birth weight PGI and observed birth weight:

$$BW = \beta_0 + \beta_1 * BW\ PGI + \varepsilon$$

where BW denotes birth weight and BW PGI birth weight polygenic index.

To rule out potential gene-environment correlation between prenatal famine exposure and birth weight genetics, we compared birth weight PGIs of famine-exposed with control participants using multivariable linear regression[13]:

$$BW\ PGI = \beta_0 + \beta_1 * exp_{early} + \beta_2 * exp_{mid-late} + \beta_3 * sex + \beta_4 * gestational\ age + \beta_5 * first\ born\ status + \varepsilon$$

where BW PG*I* denotes birth weight polygenic index, exp_{early} exposure to famine in early gestation, and $exp_{mid\text{-}late}$ exposure to famine in mid-to-late gestation.

Gene-environment interaction. To investigate the modification of genetic association with birth weight by prenatal famine exposure, we first tested the association between the birth weight PGI and observed birth weight using Spearman correlation and multivariable linear regression stratified per exposure group:

$$BW = \beta_0 + \beta_1 * BW\ PGI + \beta_2 * sex + \beta_3 * gestational\ age + \beta_4 * first\ born\ status + \varepsilon$$

where BW denotes birth weight and BW PGI birth weight polygenic index.

We then fitted multivariable linear models in which the dependent variable was birth weight and famine exposure, birth weight PGI, and a product term modeling their interaction (famine exposure * birth weight PGI) were the predictor variables:

$$BW = \beta_0 + \beta_1 * (exp * BW\ PGI) + \beta_2 * exp + \beta_3 * BW\ PGI + \beta_4 * sex + \beta_5 * gestational\ age + \beta_6 * first\ born\ status + \varepsilon$$

where BW denotes birth weight, exp exposure to famine in either early or mid-to-late gestation, and BW PGI birth weight polygenic index.

Deviation from genetically predicted birth weight and adult outcomes

First, multivariable linear regression models were used to assess the association between famine exposure and adult fasting glucose, adjusted for age and sex:

$$adult\ outcome = \beta_0 + \beta_1 * exp + \beta_2 * sex + \beta_3 * adult\ age + \varepsilon$$

where *exp* denotes exposure to famine in either early or mid-to-late gestation.

Next, deviation from genetically predicted birth weight was calculated by subtracting observed birth weight from the birth weight PGI (birth weight PGI minus observed birth weight; both in standard deviation units). The association of this deviation with adult fasting glucose was then examined using Spearman correlation and multivariable linear regression stratified by exposure group:

$$adult\ outcome = \beta_0 + \beta_1 * gen.BW\ deviation + \beta_2 * sex + \beta_3 * adult\ age + \beta_4 * gestational\ age + \beta_5 * first\ born\ status + \varepsilon$$

where gen. BW deviation denotes the difference between the birth weight polygenic index and birth weight.

To formally test for an interaction, multivariable linear regression models were fitted in which the dependent variables were fasting glucose and famine exposure, genetically predicted birth weight deviation, and a product term modeling their interaction (famine exposure * genetically predicted birth weight deviation) were the predictor variables. These models were adjusted for age, in addition to the previously mentioned birth weight related factors:

$$adult\ outcome = \beta_0 + \beta_1 * (exp * gen.\ BW\ deviation) + \beta_2 * \exp + \beta_3 + gen.\ BW\ deviation + \beta_4 * sex + \beta_5 * adult\ age + \beta_6 * gestational\ age + \beta_7 * first\ born\ status + \varepsilon$$

where gen. BW deviation denotes the difference between the birth weight polygenic index and birth weight and exp exposure to famine in either early or mid-to-late gestation.

These analyses were repeated for waist circumference and BMI as additional metabolic risk factors.

Results

Population characteristics

Within the Dutch Hunger Winter Families Study, data on birth weight and genotypes were available for 283 individuals exposed to famine in mid-to-late gestation, 145 exposed to famine in early gestation, and 161 unexposed "time controls" born at the same institution as the exposed individuals either before or after the famine period (Fig. 1A). Famine-exposed individuals in mid-to-late gestation had on average a 4-day shorter gestational age compared to those exposed in early gestation and controls ($p = 7.1 \times 10^{-5}$). As expected, those exposed to famine in early gestation were on average slightly younger than those exposed in mid-to-late gestation and controls at the time of follow-up ($p = 3.5 \times 10^{-7}$). No differences were observed in sex or first-born status (Table 1). Characteristics for any famine exposure can be found in Supplementary Table 2.

Prenatal famine exposure and birth weight

We first reproduced previous observations that mid-to-late, but not early gestational famine exposure, is associated with a lower birth weight in our dataset (Fig. 1B, C and Supplementary Table 3)[6,7]. Famine exposure in mid-to-late gestation was associated with a 230 g decrease in birth weight compared to controls (95% CI: −318 to −141; $p = 4.7 \times 10^{-7}$). In contrast, individuals exposed in early gestation showed no difference in birth weight from controls ($\beta = -33$ g, 95% CI: −133–68; $p = 0.53$) (Fig. 1C). Additional adjustment for maternal age at delivery did not materially change these estimates (Supplementary Fig. 2). These findings were also unchanged after excluding preterm and low birth weight births, indicating that the observed effects are not driven by these extreme cases (Supplementary Table 4 and Supplementary Fig. 3). Finally, we repeated this analysis using more finely defined 10-week gestational exposure windows previously applied in this cohort[13,19,22], which confirmed the same overall pattern of associations (Supplementary Fig. 4).

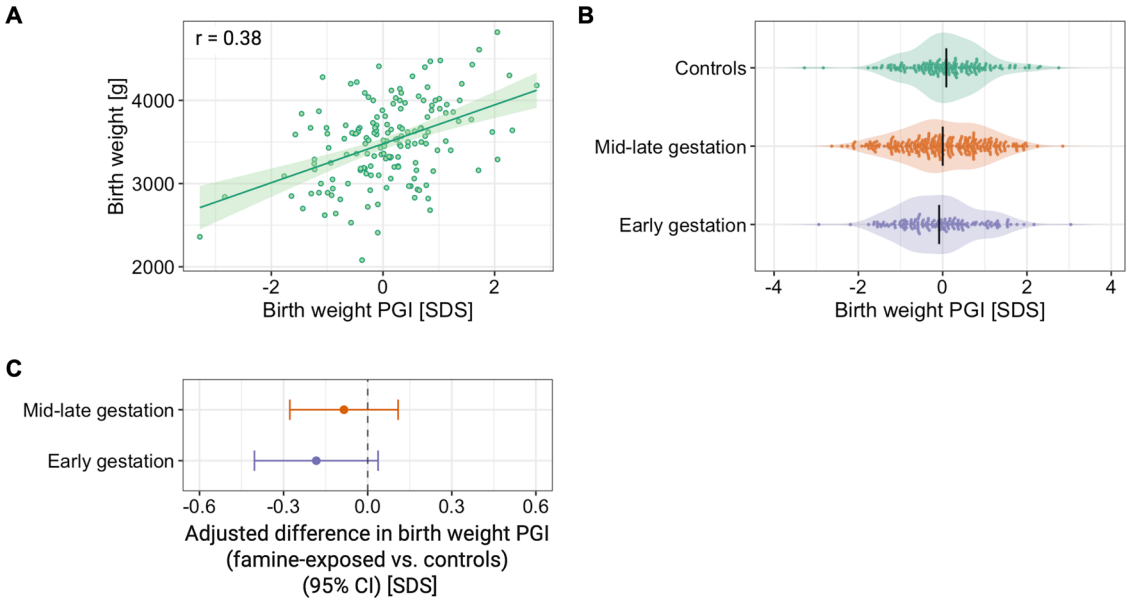

Fig. 2 | Associations of prenatal famine exposure with birth weight polygenic index. A Scatterplot of the association between the birth weight polygenic index (PGI) and observed birth weight in the control group only ($r = 0.38$, $R^2 = 0.14$, $p = 5.5 \times 10^{-7}$). Solid line shows the estimated mean regression line and the shaded band denotes 95% confidence intervals around this estimate. The Spearman correlation coefficient is shown. **B** Birth weight PGI distribution in controls and individuals exposed to famine in early and mid-to-late gestation. The black line indicates the mean per group and the shaded area represents the density of the data points. **C** The association between prenatal famine exposure and birth weight PGI was assessed using multivariable linear regression models. Points indicate the adjusted mean differences in birth weight PGI between famine-exposed (mid-to-late ($n = 283$) and early ($n = 145$) gestation) and control ($n = 161$) groups, accounting for sex, firstborn status and gestational age, and error bars represent 95% confidence intervals around these estimates. Estimates are reported in standard deviation (SD) units of the birth weight PGI.

Birth weight PGI and birth weight

We evaluated the performance of the polygenic index (PGI) of birth weight based on results from a large GWAS[10] in our population by testing its association with observed birth weight among control participants ($n = 161$). The PGI explained 14% of the variation in birth weight ($p = 5.5 \times 10^{-7}$), showing that the PGI captured a sizeable proportion of the genetic influences on variation in birth weight (Fig. 2A).

Prenatal famine exposure and birth weight PGI

To exclude a correlation between birth weight genetics and famine exposure (for example, due to selective survival according to genotype), which would violate the assumptions when testing gene-environment interactions, we compared the birth weight PGI between famine-exposed individuals and controls (Supplementary Table 3). The birth weight PGI did not differ between famine-exposed individuals and controls. The effect estimates, however, suggested a potential modest reduction among those exposed in early gestation, with a less pronounced difference among those exposed in mid-to-late gestation (for early gestation $\beta = -0.18$ SD, 95% CI: −0.40–0.04; $p = 0.10$; for mid-to-late gestation $\beta = -0.08$ SD, 95% CI: −0.28–0.11; $p = 0.39$) (Fig. 2B, C).

Interaction between prenatal famine exposure and birth weight PGI

We first compared effect sizes for associations of the birth weight PGI with birth weight among famine-exposed and unexposed individuals. While the birth weight PGI was moderately correlated with birth weight among controls ($r_{control} = 0.38$, $p = 5.5 \times 10^{-7}$), the correlation was strongly reduced in those exposed to famine in mid-to-late gestation ($r_{mid\text{-}to\text{-}late} = 0.10$, $p = 0.09$). In a multivariable analysis, the birth weight PGI was associated with an increase of 210 g in birth weight per SD increase in the PGI among control individuals (95% CI: 142–277; $p = 9.5 \times 10^{-9}$). In contrast, this increase was reduced to 54 g (95% CI: 6–102; $p = 0.03$) per SD increase in the PGI among those exposed in mid-to-late gestation. In those exposed to famine in early gestation, the correlation between PGI and birth weight ($r_{early} = 0.15$, $p_{early} = 0.07$) and the multivariable association ($\beta = 81$ g, 95% CI: −2–163; $p = 0.06$) was also reduced as compared to controls, although to a lesser extent (Fig. 3). An interaction test confirmed that the effect of birth weight PGI on birth weight was reduced in individuals exposed to famine compared to controls independent of the timing of exposure during gestation ($p_{interaction}$ for exposure in mid-to-late gestation $= 3.1 \times 10^{-4}$; $p_{interaction}$ for exposure in early gestation $= 3.2 \times 10^{-2}$).

Deviation from genetically predicted birth weight and risk factors for metabolic disease

In adulthood, exposure to prenatal famine was associated with risk factors for metabolic disease in the Dutch Hunger Winter Families Study[23,31]. Here, we focus on fasting glucose and waist circumference, and first confirmed their association with prenatal famine exposure in the subset of individuals with complete birth weight and genotype data analyzed here. Specifically, in our analysis sample, famine exposure in mid-to-late gestation was associated with a 0.21 SD increase in fasting glucose levels (95% CI: 0.01–0.40; $p = 0.04$) and a 0.26 SD increase in waist circumference (95% CI: 0.07–0.45; $p = 0.007$) as compared with controls. These effects were attenuated for those exposed in early gestation (fasting glucose: $\beta = 0.14$ SD, 95% CI: −0.09–0.37; $p = 0.23$; waist circumference: $\beta = 0.16$ SD, 95% CI: −0.06–0.39; $p = 0.15$).

Our earlier analysis implied that famine exposure, in particular in mid-to-late gestation, impeded individuals to attain a birth weight in line with their genetic potential. To explore whether this interaction had consequences on metabolic risk factors in later life, we examined whether deviations from genetically predicted birth weight (calculated as birth weight PGI minus observed birth weight) were associated with fasting glucose levels or waist circumference in adulthood. Among individuals exposed to famine during mid-to-late gestation, being born lighter than genetically predicted was associated with a higher adult fasting glucose level. Specifically, our stratified analyses revealed that being born 1 SD lighter than the genetically predicted birth weight was associated with a 0.20 SD increase in fasting glucose levels (95% CI: 0.07–0.32; $p = 0.003$). This association was

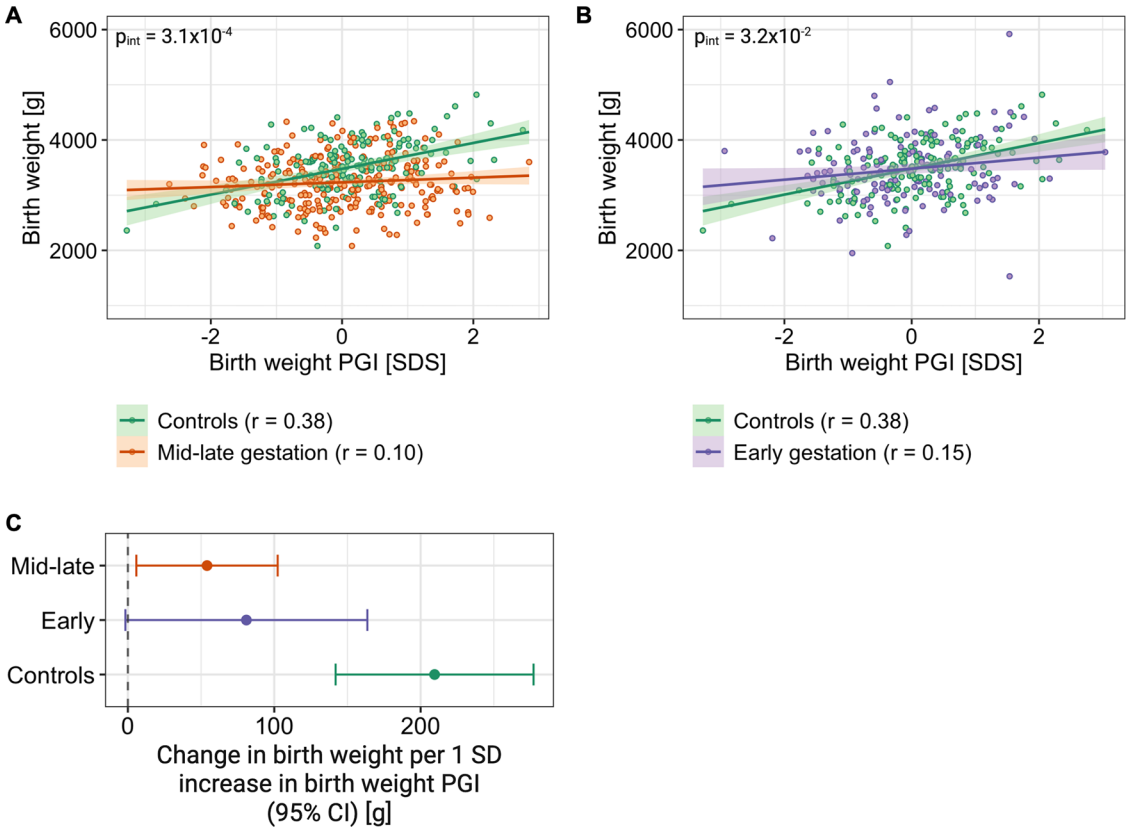

Fig. 3 | Gene-environment interaction between genetic predisposition for birth weight and prenatal famine exposure. The figure shows scatterplots of associations between the birth weight polygenic index (PGI) and observed birth weight in famine-exposed participants in mid-to-late gestation (**A**) and in early gestation (**B**), compared to controls. Solid lines show estimated mean regression lines, and shaded bands denote 95% confidence intervals around these estimates. Spearman correlation coefficients and p values for the interaction term are shown. **C** The association between the birth weight PGI and birth weight was assessed using multivariable linear regression models. Points indicate the mean change in birth weight per 1 SD increase in birth weight PGI adjusted for sex, first-born status, and gestational age, and presented separately for individuals exposed in mid-to-late (n = 283) and early (n = 145) gestation and controls (n = 161), and error bars represent 95% confidence intervals around these estimates. Estimates are reported in grams.

absent among controls and those exposed early in gestation. An interaction test confirmed that the effect was confined to mid-to-late exposure ($p_{interaction}$ = 0.04; Fig. 4).

Similarly, the effect of deviations from genetic birth weight on adult waist circumference was different for mid-to-late gestation exposure to famine as compared with controls ($p_{interaction}$ = 0.01), whereas no difference was observed for early gestation exposure compared to controls ($p_{interaction}$ = 0.10) (Fig. 5). Among controls, being born lighter than genetically predicted was associated with a lower waist circumference, with a 1 SD lower birth weight corresponding to a 0.20 SD decrease in waist circumference (95% CI: −0.39 to −0.004; p = 0.048). This effect was absent in famine-exposed individuals, and in those exposed during mid-to-late gestation, the effect size shifted in the opposite direction (p > 0.05). Findings for BMI were comparable to those for waist circumference (Supplementary Table 5 and Supplementary Fig. 5). As a sensitivity analysis, we assessed whether associations between deviations from genetically predicted birth weight and adult outcomes were independent of one another by mutually adjusting models for fasting glucose, BMI, and waist circumference. Although effect estimates differed slightly after mutual adjustment, the overall patterns remained consistent, indicating largely independent associations (Supplementary Figs. 6–8). Lastly, the individual associations between birth weight and the birth weight PGI and these adult outcomes are provided in the Supplementary Material (Supplementary Tables 6 and 7).

Results for the any famine exposure group, which combines the different exposure groups to increase sample size and assess timing-independent effects, can be found in the Supplementary Material (Supplementary Figs. 9 and 10).

Discussion

We investigated the interplay between genetic and environmental factors in shaping the relationship between famine exposure, birth weight, and metabolic risk factors in individuals who were exposed to the Dutch Hunger Winter of 1944–1945 in utero. First, we replicated previous findings that famine exposure during mid-to-late gestation, but not early gestation, is associated with lower birth weight[6,7]. We then extended prior research by demonstrating that this effect is not driven by genetic differences[13], such as those that could arise from selective fetal or infant survival and would introduce correlation. Crucially, we found that prenatal famine exposure largely overrides the effect of genetic influences on birth weight. Finally, we explored the implications of this interplay for metabolic disease risk in later life.

Our findings corroborated existing literature reporting that individuals exposed to prenatal famine in the later stages of gestation, but not in early gestation, have lower birth weights compared to controls[6]. Notably, this pattern is consistent with the fact that fetal weight gain accelerates rapidly toward the end of gestation, making birth weight particularly sensitive to nutritional constraints during this period[32]. When examining potential genetic selection related to fetal growth traits under famine conditions, we found no discernible differences in birth weight polygenic index between individuals exposed to famine and the control group. These results are in line with previous research from our cohort that similarly found no evidence of genetic selection based on BMI genetics or other health and behavioral traits, suggesting a low likelihood of selection bias due to genetic variation across these traits in our cohort[13].

Our study investigated how prenatal famine exposure may alter the impact of genetic predisposition on birth weight. We observed a strong

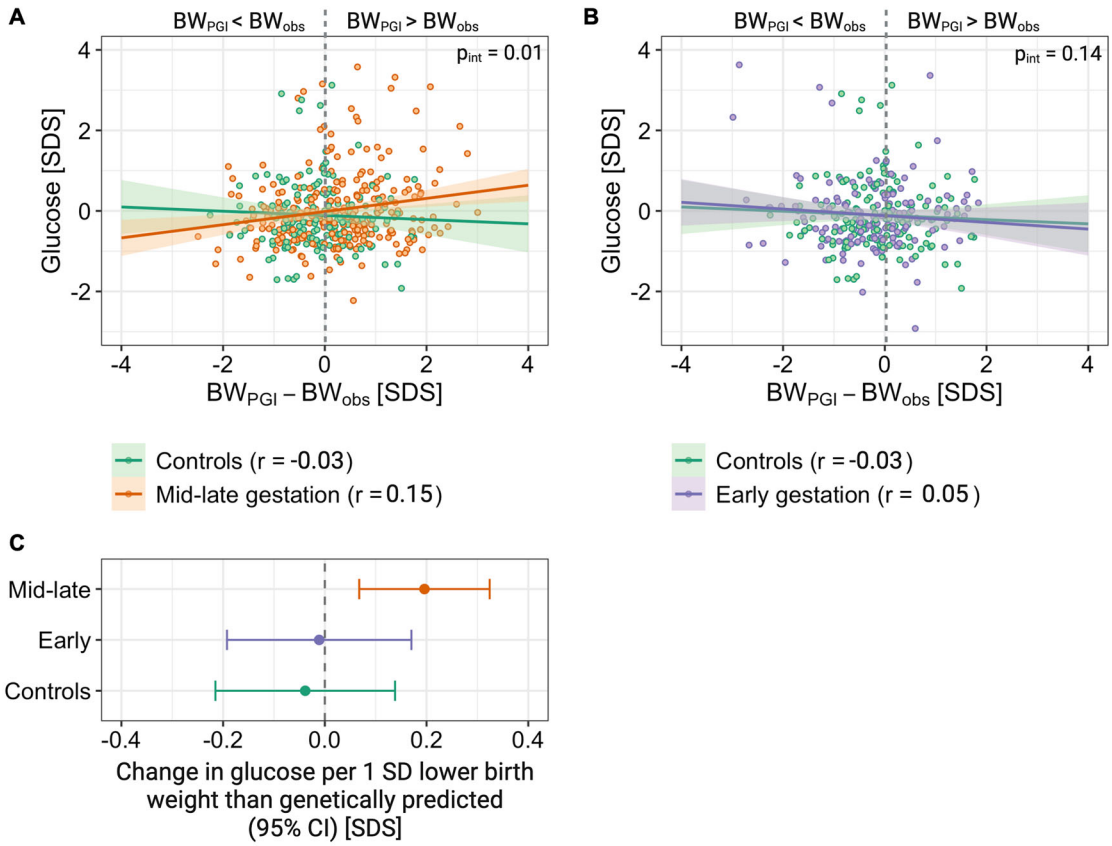

Fig. 4 | Deviation from genetically predicted birth weight and adult fasting glucose. Scatterplots of associations between the deviation from genetically predicted birth weight (polygenic index (PGI) minus observed birth weight) and fasting glucose, in famine-exposed participants in mid-to-late gestation (**A**) and in early gestation (**B**), compared to controls. Solid lines show estimated mean regression lines and shaded bands denote 95% confidence intervals around these estimates. Spearman correlation coefficients and p values for the interaction term are shown. **C** The association between the deviation from genetically predicted birth weight and fasting glucose was assessed using multivariable linear regression models. Points indicate the mean change 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 ($n = 161$), and error bars represent 95% confidence intervals around these estimates. Estimates are reported in standard deviation (SD) scores of fasting glucose. Fasting glucose was log-transformed prior to the calculation of the *Z* scores.

association between the birth weight PGI and birth weight among the control group. This effect was markedly reduced among individuals exposed to famine in mid-to-late gestation, the time-point at which we observed the strongest effects of famine exposure on birth weight. The effect of the PGI on birth weight was also notably attenuated for those exposed in early gestation, although to a lesser degree compared to those exposed in mid-to-late gestation. Few studies have investigated environmental factors that might modulate the link between genetics and fetal growth. One study found that maternal BMI during gestation modestly moderates the PGI-birth weight relationship in offspring[14], whereas another study found no evidence of effect modification by maternal smoking[33]. These findings highlight the challenge in detecting strong gene–environment interactions and the need for further research on factors that might modify the effect of genetic predisposition on birth weight. Our study provides a valuable example of how an environmental influence can override the effect of genetic make-up in humans.

Lastly, we explored whether the inability to attain a birth weight in line with one's genetic potential due to famine exposure is linked to metabolic risk factors in adulthood. Among those exposed to famine in mid-to-late gestation, a lower than genetically predicted birth weight was associated with higher fasting glucose levels—an association that was absent in early gestation and control groups. In contrast, among controls, a lower than genetically predicted birth weight was associated with a lower waist circumference, suggesting a potentially protective effect. This pattern was absent in individuals exposed to early gestation and reversed among those exposed in mid-to-late gestation. Together, these findings suggest that famine-related reductions in prenatal growth during mid-to-late gestation may be involved in the risk of metabolic disease later in life. They also underscore how prenatal environmental factors may modify the pathways linking birth weight to long-term health outcomes, including cardiovascular disease and type 2 diabetes[34,35].

To date, numerous studies assessing the effects of prenatal famine exposure on later health have identified early gestation as a critical period for long-term health outcomes, linking it to increased rates of chronic diseases and mortality[36–39]. Additionally, DNA methylation has been proposed as a potential mechanism linking prenatal adversity to later-life health outcomes, and differences in DNA methylation have also been predominantly observed in individuals exposed to famine during early gestation[40–42]. Here, our findings illustrate that famine exposure in mid-to-late gestation may also contribute to disease risk later in life, which could in part be through its association with lower birth weight and interaction with birth weight genetics. Further studies will be required to assess the broader relevance of the interplay between the prenatal environment, birth weight and genetic predisposition for birth weight in long-term health.

We acknowledge limitations. First, our study was limited to individuals who survived to at least age 58. For example, previous studies have reported a modest increase in infant mortality in famine-affected cities of the western Netherlands[43]. Therefore, any impact of famine exposure or lower birth

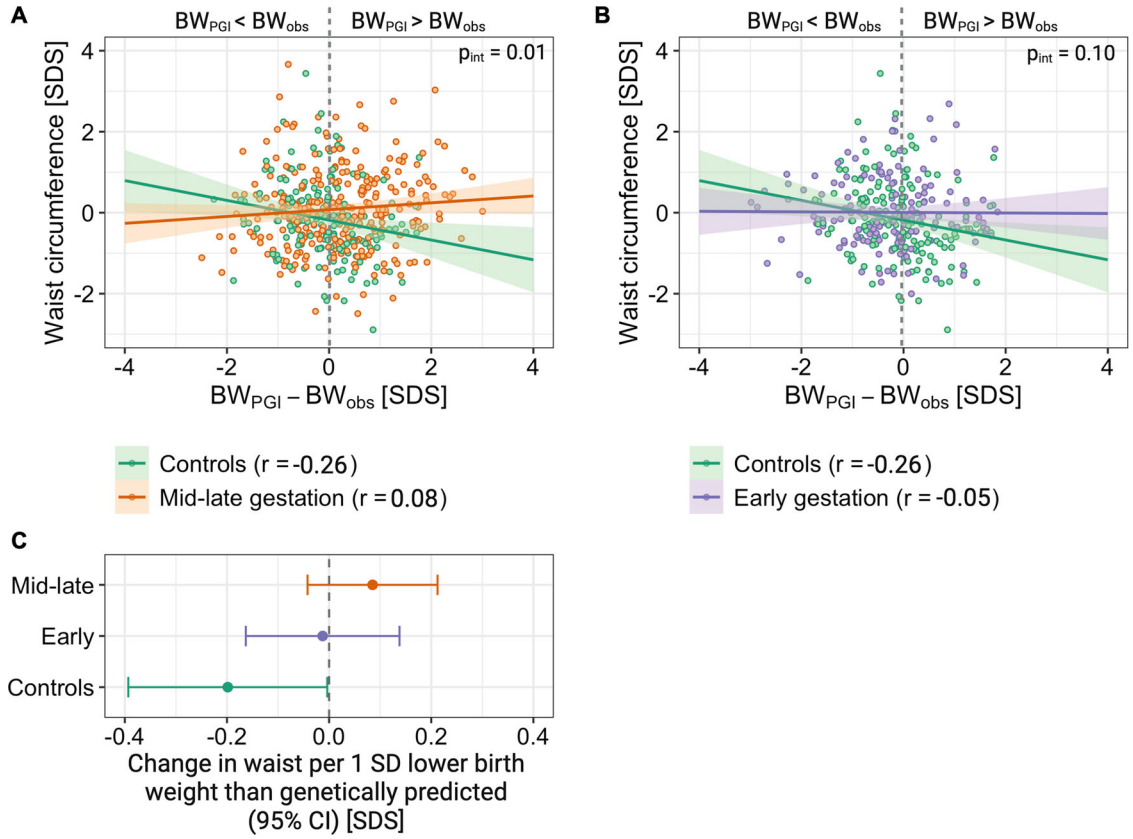

Fig. 5 | Deviation from genetically predicted birth weight and waist circumference. Scatterplots of associations between the deviation from genetically predicted birth weight (polygenic index (PGI) minus observed birth weight) and waist circumference in adulthood, in famine-exposed participants in mid-to-late gestation (**A**) and early gestation (**B**), compared to controls. Solid lines show estimated mean regression lines and shaded bands denote 95% confidence intervals around these estimates. Spearman correlation coefficients and p values for the interaction term are shown. **C** The association between the deviation from genetically predicted birth weight and waist circumference was assessed using multivariable linear regression models. Points indicate the mean change in waist circumference per 1 SD lower birth weight than genetically predicted, 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 ($n = 161$), and error bars represent 95% confidence intervals around these estimates. Estimates are reported in standard deviation (SD) units of waist circumference.

weight on severe health complications leading to early mortality would result in an underestimation of the full impact of prenatal famine exposure in our analyses. Second, while PGIs based on common genetic variation are valuable tools for estimating genetic predisposition, they are incomplete measurements of genetic influences on traits, which may reduce the statistical power of our analysis. Nevertheless, our PGI showed a strong association with birth weight in our control population, also in the context of other birth weight PGI studies[14,33,44]. Third, follow-up of the cohort extends only to the sixth decade of life, precluding analysis of lifespan and other long-term outcomes. Fourth, the cohort studied is relatively small, and our analysis could only include the subset of members for whom birth records were available; our relatively small sample size limits the precision with which effects can be detected. Finally, the generalizability of our findings warrants consideration. The Dutch Hunger Winter affected a previously well-nourished population of predominantly European ancestry, and the famine was characterized mainly by severe caloric restriction with relatively stable macronutrient composition[5,17]. As such, the observed effects are more likely driven by undernutrition rather than specific nutrient deficiencies. However, evidence from more recent analyses suggests that reductions in protein intake during the most extreme phases of the famine may have contributed to long-term health outcomes[45]. These historical and population-specific circumstances may limit direct extrapolation to other famine settings, particularly those involving prolonged malnutrition, different nutritional profiles, or populations with different genetic backgrounds. Nonetheless, our findings may still inform a broader understanding of how severe caloric restriction during pregnancy can influence fetal growth, its association with genetics, and later-life metabolic risk.

Conclusion

Famine exposure in mid-to-late gestation can override the effect of genetic influences on birth weight, and this interplay between nature and nurture can have long-term consequences for metabolic disease risk. Our findings highlight how genetic and environmental factors interact to influence health trajectories and may provide insights into the mechanisms linking prenatal adversity, birth weight, and adult disease susceptibility.

Data availability

Source data for the main figures in the manuscript with statistical analyses are provided in Supplementary Data file 1. The DHWFS data underlying this article are not publicly available due to privacy considerations. They can be requested through contact with B.T.H. (b.t.heijmans@lumc.nl) and shared for replication purposes if replication is conducted within the secure Leiden University Medical Center network environment. Timelines involved in securing access to data vary according to the complexity of the request.

Code availability

The code developed to perform the analyses described is available at https://git.lumc.nl/mjtaeubert/dhwfs-bw-pgi.

Received: 28 July 2025; Accepted: 23 February 2026;
Published online: 12 March 2026

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Acknowledgements

This research was supported by US National Institutes of Health Grant R01AG066887. Genetic data on birth weight have been contributed by the EGG Consortium using the UK Biobank Resource and have been downloaded from www.egg-consortium.org.

Author contributions

M.J.T., D.W.B., L.H.L., and B.T.H. designed the analysis. L.H.L. designed the cohort. D.C.C., L.H.L., D.W.B., and B.T.H. designed the genetic data collection. T.B.K., M.J.T., J.Z., S.W., T.W., D.C.C., L.H.L., D.W.B., and B.T.H. developed the genetic data resource. M.J.T., K.K., and J.Z. analyzed the data. M.J.T. and B.T.H. drafted the manuscript. M.J.T., K.K., J.Z., T.B.K., D.C.C., C.L., S.W., T.W., D.W.B., L.H.L., and B.T.H. contributed to critical revision of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-026-01495-9.

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Peer review information *Communications Medicine* thanks Thorkild Sorensen, Juho Kuula and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.