

Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life

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Objective Maternal undernutrition during gestation is associated with increased metabolic and cardiovascular disease in the offspring. We investigated whether these effects may persist in subsequent generations.

Design Historical cohort study.

Setting Interview during a clinic or home visit or by telephone.

Population Men and women born in the Wilhelmina Gasthuis in Amsterdam between November 1943 and February 1947.

Methods We interviewed cohort members (F1) born around the time of the 1944–45 Dutch famine, who were exposed or unexposed to famine *in utero*, about their offspring (F2).

Main outcome measures Birthweight, birth length, ponderal index and health in later life (as reported by F1) of the offspring (F2) of 855 participating cohort members, according to F1 famine exposure *in utero*.

Results F1 famine exposure *in utero* did not affect F2 ($n = 1496$) birthweight, but, among the offspring of famine-exposed F1

women, F2 birth length was decreased (-0.6 cm, P adjusted for F2 gender and birth order = 0.01) and F2 ponderal index was increased ($+1.2$ kg/m³, P adjusted for F2 gender and birth order = 0.001). The association remained unaltered after adjusting for possible confounders. The offspring of F1 women who were exposed to famine *in utero* also had poor health 1.8 (95% CI 1.1–2.7) times more frequently in later life (due to miscellaneous causes) than that of F1 unexposed women.

Conclusions We did not find transgenerational effects of prenatal exposure to famine on birthweight nor on cardiovascular and metabolic disease rates. F1 famine exposure *in utero* was, however, associated with increased F2 neonatal adiposity and poor health in later life. Our findings may imply that the increase in chronic disease after famine exposure *in utero* is not limited to the F1 generation but persists in the F2 generation.

Keywords Adiposity, fetal, health, intergenerational, nutrition.

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Introduction

Previously, we described that individuals exposed to famine *in utero* have increased prevalence of cardiovascular disease,^{1,2} diabetes,^{3,4} obesity⁵ and breast cancer.⁶ Experimental evidence indicates that health traits, which have been induced by environmental insults during early development in one generation, may be transmitted to future generations without alterations to the genome.^{7–9} Exposure to undernutrition or glucocorticoids *in utero* can cause impaired glucose tolerance^{8,10–14} as well as alterations in cardiovascular function¹⁵

and body composition,^{8,14} which persist in subsequent generations, in the absence of the continuation of the environmental cue that initially gave rise to the alterations.

There is indirect evidence indicating that in humans, an adverse prenatal environment leads to multigeneration repercussions for chronic disease in later life. Low birthweight, a summary measure of poor intrauterine environment, is associated with increased cardiovascular and metabolic morbidity and mortality in later life.^{16–18} Large studies have demonstrated an intergenerational cycle of low birthweight, even when socio-economic status (SES) and adult parental body

mass index (BMI) are taken into account.^{19,20} Taken together, this may imply that the adverse conditions during early development may lead to poor health in later life across generations. However, these studies have not been able to rule out a common genetic cause, responsible for slow fetal growth as well as poor health in adult life. Furthermore, the interpretation of such studies is hampered by the fact that low birthweight and chronic disease in later life often co-occur in people of low SES, in whom poor dietary habits, smoking and lack of physical exercise cluster.

The hypothesis that poor nutrition during early development leads to detrimental effects on cardiovascular and metabolic disease risk across generations is supported by a limited amount of direct evidence in human populations. A historical study of three generations in an isolated town in northern Sweden reported that in comparison with an abundant harvest, crop failure during the period between grandmaternal conception and grandmaternal age 3 was associated with four-fold ($P < 0.01$) increase in the granddaughters' mortality risk.²¹ This was, however, a serendipitous finding in a study that was focused on the effects of smoking or poor nutrition in pre-pubescent boys on grand offspring health.

The Dutch famine was a period of food shortage, which occurred in the Western Netherlands during the past year of World War II, after the German occupying force placed an embargo on food transports to the Western Netherlands. Adult food rations were cut to as low as 400 calories/day, less than one-quarter of the pre-famine ration. Although it was a humanitarian disaster, the Dutch famine offers the unique opportunity to study the effects of a brief period of severe undernutrition during gestation on the health of the offspring and grand-offspring.

We hypothesised that the increase in obesity, cardiovascular and metabolic disease previously described among the offspring of pregnant mothers exposed to famine during gestation is perpetuated in their grand-offspring.

Methods

Selection procedure

The Dutch Famine Birth Cohort consists of 2414 liveborn term singletons, of which 1174 were female infants, born in the Wilhelmina Gasthuis in Amsterdam, the Netherlands, between 1 November 1943 and 28 February 1947. Cohort members were traced at age 50 years. The selection and tracing procedures have been described in detail elsewhere.²² Cohort members were eligible for participation in this study at age 58 if they lived in the Netherlands on 1 September 2002 and their address was known to the Dutch famine birth cohort researchers. One thousand four hundred and twenty-three people fulfilled the eligibility criteria. All eligible cohort members were invited to visit the hospital. People who were not able to come to the hospital were visited at home. People

who did not wish to be paid a house call or come to the hospital were interviewed by telephone. Seven hundred and thirty-four people visited the hospital, 71 people were visited at home and 50 people were interviewed by telephone. Participants who came to the hospital or were paid a home visit gave written informed consent. Subjects who were interviewed by telephone gave verbal informed consent, in accordance with the Dutch legislation regarding medical research in humans. The local medical ethics committee had approved the study. People who agreed to participate had mean birthweights similar to those of eligible people who did not participate (3350 versus 3343 g) and similar to the mean birthweights of the original cohort of 2414 people (3346 g).

Exposure to famine

We defined famine exposure according to the daily official food rations for adults. In addition to the official rations, food from other sources, such as church organisations, central kitchens and the 'black market', was also available. People may have had access to up to double the rationed amount at the peak of the famine. The rations do, however, adequately reflect the fluctuation of food availability during the famine.²³

Adult women with normal activities need a daily nutrient intake of 2500 calories (Oxford Nutritional Survey Standards, 1940). Cohort members were considered prenatally exposed to famine if the average daily ration for adults during any 13-week period of gestation was less than 1000 calories. Using this definition, all cohort members born between 7 January 1945 and 8 December 1945 had been exposed prenatally. All cohort members born between 1 November 1943 and 6 January 1945 (born before the famine) and between 9 December 1945 and 28 February 1947 (conceived after the famine) were thus unexposed to famine and served as the control group.

We defined periods of 16 weeks each to differentiate between those who were exposed in late gestation (born between 7 January and 28 April 1945), in mid-gestation (born between 29 April and 18 August 1945) and in early gestation (born between 19 August and 8 December 1945), in accord with previous publications on this cohort.^{2,22}

Generations

We studied three generations. F0 were defined as the mothers of Dutch famine birth cohort members. F1 were men and women from the Dutch famine birth cohort, who were born before, during or after the Dutch famine to F0 mothers as described above. F2 were the offspring of F1 men and women.

Data collection

The medical birth records provided information about the mother (F0), the course of pregnancy, the birthweight and length of the baby (F1) and the placenta at birth.²²

During the clinic or home visit at age 58 years, we measured F1 height using a fixed or a portable stadiometer, weight with

Seca scales or Tefal portable scales. F1 BMI was calculated by dividing weight in kilograms by the square of height in metres. We defined F1 current SES according to the participant's or their partner's ISEI-92 score,²⁴ whichever was highest. The ISEI-92 score is based on current or most recent level of employment and level of professional training. Values ranged from 16 (low status) to 87.

Nondiabetic participants underwent standard 75 g oral glucose tolerance testing. Blood was drawn for analysis of low-density lipoprotein, high-density lipoprotein and triglyceride plasma concentrations.

Participants were interviewed to obtain information about their medical history, lifestyle and children (F2). Trained nurses carried out all interviews (between September 2002 and September 2004). We asked participants (F1) about the birthweight, birth length, gestational age at delivery (premature [28–37 weeks], term [37–42 weeks], post mature [>42 weeks]), birth order, sex and health status of all their biological children (F2). Participants were also asked whether the child was part of twin pregnancy.

We asked whether the F2 child was alive, and, if not, we asked what the cause of death was and what the age at death was. To determine F2 health status, we asked whether the child was currently healthy, and, if not, the reason why the child was not healthy. We combined causes of poor health and causes of death, which occurred after the neonatal period, and categorised the answers into three categories based on the hypothesis that F1 famine exposure *in utero* could affect F2 health in later life by affecting intrauterine development, cardiovascular/metabolic disease^{1–5,25–27} prevalence or psychiatric disease prevalence.^{28–33} The categories were: congenital (including asphyxia, developmental delay, Down syndrome and congenital heart disorders), cardiovascular and metabolic (including diabetes, acquired cardiovascular conditions, hypercholesterolaemia, hypertension and obesity), psychiatric (including schizophrenia, depression, suicide [attempt], drug/alcohol dependency) or other (including accidental, acquired neurological, autoimmune, infectious, respiratory, neoplastic and dermatological conditions).

Statistical methods

We used linear regression for continuous variables and logistic regression for dichotomous variables to compare the F0 maternal characteristics and F1 offspring characteristics at birth and in adulthood, including total number of offspring according to famine exposure during various stages of gestation. We used the Mann–Whitney test to study the number of F2 offspring according to F1 famine exposure to famine *in utero*.

To take the correlation of characteristics between multiple offspring of the same parent into account, we used mixed models to analyse the association between F1 famine exposure during various stages of gestation and F2 size at birth and health status, correcting for possible confounding factors, including

markers of F1 health and markers of F0 fertility. We used SPSS 12.0.2 (Chicago, IL, USA) linear mixed models, unstructured variance/covariance matrix, for continuous outcome measures and SAS 9.1 (Cary, NC, USA), PROC GENMOD, unstructured variance/covariance matrix, for binary outcome measures.

To take the previously described^{14,21} differential intergenerational effects of F1 *in utero* famine exposure in the F2 offspring of F1 men and women into account, we tested for interaction (F1 sex \times famine exposure). The F2 characteristics are reported stratified according to F1 sex.

We report BMI, adult SES and 2-hour plasma glucose concentrations as geometric means because of their skewed distribution.

Results

Of the 1423 eligible cohort members, 855 (60%) participated in the current study. The mean age at participation was 58 years (range 56–61 years). Participating F1 men had 640 and F1 women had 856 F2 offspring (mean age 32 years, range 1–43 years).

F1 prenatal famine exposure and F0 maternal, F1 birth and F1 adult characteristics

Table 1 shows that F0 mothers were lighter at the end of gestation and less often in their first pregnancy if they were exposed to famine during gestation. F1 participants, born after prenatal exposure to famine, were lighter and shorter at birth than F1 participants who were not exposed to prenatal famine. In comparison with those who were unexposed, F1 participants who had been exposed to famine *in utero* had higher 2-hour glucose concentrations and had more F2 offspring but were similar in terms of smoking, SES and BMI at age 58 years.

F1 prenatal famine exposure and F2 birth size

Table 2 shows that the F2 offspring of F1 women who were exposed to famine at any stage of their own fetal life had similar birthweight but were 0.6 cm shorter (*P* adjusted for F2 sex and birth order = 0.01) and had a 1.2 kg/m³ higher ponderal index at birth (*P* adjusted for F2 sex and birth order = 0.001) than the F2 offspring of F1 women who were not exposed to famine during their fetal life. The table shows that this effect was not present in the offspring of F1 men (*P* for interaction F1 sex \times exposure to famine *in utero*, adjusted for F2 sex = 0.02).

F1 prenatal famine exposure and F2 health characteristics

F1 famine exposure *in utero* was not associated with any differences in prematurity rates, F2 mortality or F2 poor health in general (as reported by the participating F1 parent), or poor health due to cardiovascular disease, diabetes, obesity and congenital or psychiatric conditions (Table 2). However, more F2 offspring of famine-exposed F1 women, but not

Table 1. F0 characteristics during pregnancy and F1 birth and F1 adult characteristics according to timing of exposure to famine*

	Unexposed born before	Prenatal exposure to famine	Unexposed conceived after	All (SD)
Number	264	350	241	855
Male F1 (%)	46	42	48	45
Maternal characteristics (F0)				
Weight at the end of pregnancy F0 (kg)	66	65**	69	66 (9)
First pregnancy F0 (%)	37	30**	39	35
Birth characteristics (F1)				
Birthweight F1 (g)	3389	3259**	3439	3350 (468)
Birth length F1 (cm)	50.5	49.9**	50.6	50.3 (2.1)
Ponderal index (kg/m ³)	26.2	26.1	26.5	26.2 (2.4)
Adult characteristics (F1)				
SES F1***,****	46	48	48	48 (14)
Current smoker F1 (%)	22	28	23	25
BMI F1 (kg/m ²)****	28.1	27.9	28.7	28.2 (4.9)
LDL/HDL cholesterol ratio F1****	2.3	2.4	2.4	2.4 (1.0)
2-hour glucose concentration F1 (mmol/l)****	5.8	6.2**	5.9	6.0 (2.4)
N offspring (F2)	1.99	2.09**	1.95	2.02 (0.77)

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Means and SD, except where given as percentages.

** $P < 0.05$ compared with unexposed (born before and conceived after).

***SES according to the ISEI-92 (range 16–87).

****Geometric mean.

men, had poor health in the category ‘other causes’, which included atopic disease (12 exposed and 9 unexposed), autoimmune (12 exposed and 1 unexposed), cancer (3 exposed and 2 unexposed) and acquired neurological conditions (0 exposed and 3 unexposed) (OR 1.8, 95% CI 1.1–2.7).

To investigate the hypothesis that the timing of F1 exposure to famine during fetal life differentially affects aspects of health in the F2, we considered the effects of famine exposure during late, mid and early gestation on F2 health in later life. F1 men and women (21%) who had been exposed to famine in early gestation more often considered their F2 offspring unhealthy (OR 1.9 95% CI 1.2–2.9, adjusted for F2 offspring health and birth order) than did F1 men and women (13%) who had not been exposed to famine *in utero*. Again, the category of disease causes most often quoted was ‘other’ (15% among F2 of F1 men exposed in early gestation, 7% F2 offspring of unexposed F1 men and women; OR 2.3, 95% CI 1.4–4.0).

F1 prenatal famine exposure and increased F2 neonatal adiposity, multivariable model

F2 higher birth order was associated with increased neonatal adiposity (e.g. in offspring of F1 women, third born compared with first born ponderal index + 1.5 kg/m³, $P = 0.03$). F2 girls had higher mean ponderal indices at birth than F2 boys (+0.7 kg/m³, $P = 0.04$).

F1 BMI at age 58 years (0.1 kg/m³ per unit increase F1 BMI, $P < 0.001$) and F1 birthweight (0.7 kg/m³ per kg increase F1 birthweight, $P = 0.03$) were positively associated with F2 ponderal index. Higher F1 SES was associated with diminished F2 ponderal index (−0.02 per SES unit). F1 smoking and 2-hour glucose were not associated with F2 neonatal adiposity.

When we adjusted for F2 birth order and sex, F1 birthweight, smoking, SES, BMI and 2-hour glucose, the association in the offspring of F1 women between F1 famine exposure *in utero* and increased F2 ponderal index remained unaltered (fully adjusted estimate 1.4 kg/m³, $P = 0.002$).

F1 prenatal famine exposure and poor F2 health in later life, multivariable model

F1 women reported their children to have poor health 1.6 times more frequently than did F1 men ($P = 0.003$). F1 smoking, SES, BMI or 2-hour glucose showed any association with poor F2 health status. However, F1 and F2 smallness or thinness at birth were associated with poor health in F2. F1 birthweight was inversely associated with F2 poor health due to ‘other’ causes (OR 1.6 per kg decrease in birthweight, 95% CI 1.0–2.3). F2 ponderal index was inversely associated with poor F2 health due to cardiovascular and metabolic causes (OR 1.1 for every unit decrease in F2 ponderal index, 95% CI 1.0–1.2).

After we adjusted for F1 birthweight, BMI, 2-hour plasma glucose concentrations, smoking, SES, F2 sex and F2 birth order and ponderal index, the association in F1 women

Table 2. Birth and health characteristics of the F2 offspring of F1 participating women and men according to timing of prenatal exposure to the Dutch famine

	Unexposed born before	Prenatal exposure to famine	Unexposed conceived after
Characteristics of F2 offspring of F1 women			
Number	243	401	212
Age (years)	34	33	32
Birthweight F2 (g)	3476	3484	3468
Birth length F2 (cm)	50.5	49.6*	50.1
Ponderal index F2 (kg/m ³)	26.6	27.8*	26.5
Prematurity F2 (%)	7	11	7
Died after birth F2 (%)	3	4	2
F2 poor health (%)	16	18	14
Congenital (%)**	1	1	2
Cardiovascular/metabolic (%)**	3	2	2
Psychiatric (%)**	4	2	2
Other (%)**	7	12*	9
Characteristics of F2 offspring of F1 men			
Number	197	256	187
Age (years)	31	30	29
Birthweight F2 (g)	3304	3298	3313
Birth length F2 (cm)	50.3	50.5	50.3
Ponderal index F2 (kg/m ³)	25.9	25.9	26.3
Prematurity F2 (%)	7	4	4
Died after birth F2 (%)	3	1	1
F2 poor health (%)	12	12	8
Congenital (%)**	4	4	1
Cardiovascular/metabolic (%)**	1	0	1
Psychiatric (%)**	1	1	1
Other (%)**	7	7	6

* $P < 0.05$ compared with unexposed, adjusted for F1 sex and F1 birth order.

**Congenital: asphyxia, developmental delay, Down syndrome, congenital heart disorders; cardiovascular and metabolic: diabetes, acquired cardiovascular conditions, obesity; psychiatric: schizophrenia, depression, suicide (attempt), drug/alcohol dependency; other: accidental, acquired neurological, autoimmune, respiratory, infectious, neoplastic, dermatological conditions.

between prenatal famine exposure and F2 poor health due to 'other' causes remained unaltered (fully adjusted OR 1.8, 95% CI 1.0–3.2).

Discussion

We found that grandmaternal exposure to famine for a brief period during gestation did not affect birthweight nor rates of cardiovascular or metabolic disease. It was, however, associated with increased neonatal adiposity and poorer health among offspring of women who themselves had been exposed to famine *in utero*. These findings constitute the first direct evidence in humans that the detrimental effects of poor maternal nutrition during gestation on health in later life pass down to subsequent generations.

Asking parents about size at birth and current health of their children is not ideal. Many studies, however, have shown that parental recall of birthweight is reasonable,^{34–38} fewer

studies have assessed the validity of parental reports of their children's health,³⁹ but although it is suboptimal, using parental recall will only have introduced bias if recall differed according to exposure to famine, which seems highly unlikely.

We had hypothesised that among the F2 of famine-exposed F1 individuals, we would find evidence for the perpetuation of chronic disease in later life previously described in the F1. Famine exposure *in utero* has been linked to subsequent F1 obesity,^{5,40,41} cardiovascular disease,^{1,2} type II diabetes,^{3,4} hypertension,⁴² dyslipidemia,²⁶ respiratory disease,⁴³ breast cancer⁶ and a number of psychiatric diagnoses.^{28–31,33,44,45} Due to the relatively young age of the F2 (mean 32 years), our study had limited power in detecting an excess of outright cardiovascular disease associated with F1 famine exposure *in utero*. However, we also failed to find an association between F1 famine exposure *in utero* and F2 poor health related to any cardiovascular or metabolic risk factor, including obesity, hypertension, hypercholesterolaemia and

diabetes. The fact that we found increased neonatal adiposity among the offspring of women who had been famine exposed *in utero* might be the first evidence of increased obesity and diabetes risk because neonatal adiposity is linked to increased subsequent fat mass in later life.³⁴

The fact that we phrased the question in the interview with the F1 as 'Is your child healthy?' may have led to underreporting of cardiovascular risk factors, including hypercholesterolaemia and obesity. Although our finding of increased rates of 'other' causes of ill-health may be spurious and due to multiple testing, it may also be an indication that health domains such as (auto)immune function may be affected in F2 after F1 maternal famine exposure. Currently, we investigate cardiovascular and metabolic risk factors among the F2 offspring of F1 Dutch famine birth cohort parents to objectify effects in other health domains.

Our findings are broadly supported by evidence from animal studies, which have found transgenerational effects of maternal undernutrition during gestation in F0, on increased adiposity in later life,¹⁴ impaired glucose tolerance^{10,11,14} and altered cardiovascular function¹⁵ in the F1 and F2 generations. Interestingly, the only one of these studies to report on the F3 generation¹⁰ found evidence for persistence of glucose intolerance induced after F0 undernutrition during gestation.

The issue of generation-spanning effects of poor conditions during gestation is particularly relevant to populations in transition between traditional and western lifestyles because it may shed light on the epidemic of diabetes, obesity and cardiovascular disease, which is currently rapidly expanding in such countries. In India, currently transitioning to food abundance after generations of poor nutrition, babies are light and small at birth but have increased neonatal adiposity⁴¹ compared with European babies. Our findings may indicate that increased neonatal adiposity, and possibly increased diabetes risk, is the direct result of poor maternal nutrition, which occurred generations ago. Public health strategies that focus on improved maternal nutrition during gestation may provide a means of promoting cardiovascular and metabolic health, which will benefit generations to come.

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Details of ethics approval

This study was carried out in accordance with the Declaration of Helsinki. The local medical ethics committee had approved the study.

Contribution to authorship

T.J.R. set up the study. R.C.P. executed the study and analysed the data and also drafted the paper. All took part in revisions of the paper and T.J.R. wrote the final version.

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