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Increased reproductive success of women after prenatal undernutrition

Rebecca C. Painter[1], Rudi G.J. Westendorp[2], Susanne R. de Rooij[1], Clive Osmond[3], David J.P. Barker[3,4] and Tessa J. Roseboom[1,5]

[1]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center at the University of Amsterdam, PO Box 22660, 1100 DD, Amsterdam, The Netherlands; [2]Department of Geriatrics and Gerontology, Leiden University Medical Center, Leiden, The Netherlands; [3]MRC Epidemiology Resource Centre, University of Southampton, Southampton, UK; [4]Heart Research Center, Oregon Health and Science University, OR, USA

[5]Correspondence address. E-mail: t.j.roseboom@amc.uva.nl

BACKGROUND: Prenatal exposure to the Dutch famine is associated with an increased risk of chronic degenerative disease. We now investigate whether prenatal famine exposure affected reproductive success. METHODS: We assessed reproductive success (number of children, number of twins, age at delivery, childlessness) of men and women born around the time of the Dutch famine of 1944–1945 in the Wilhelmina Gasthuis, Amsterdam, whose birth records have been kept. RESULTS: Women who were exposed to the Dutch famine of 1944–1945 *in utero* are more reproductively successful than women who were not exposed to famine during their fetal development; they have more offspring, have more twins, are less likely to remain childless and start reproducing at a younger age. The increased reproductive success of these women is unlikely to be explained by genes which favor fertility and are passed from mothers to their daughters. *In utero* exposure to famine did not affect the reproductive success of males. CONCLUSIONS: These findings suggest that poor nutrition during fetal development, followed by improved nutrition after birth can give rise to a female phenotype characterized by greater reproductive success.

Keywords: environmental effects; epidemiology; pregnancy

Introduction

The growth, survival and reproductive success of wild mammals is influenced by the climatic and nutritional conditions that they experience during their early development (Lindstrom, 1999; Metcalfe and Monaghan, 2001). Early conditions also have consequences for the reproductive performance of humans. Environmental conditions which affect early development influence a range of measures of reproductive performance (Lummaa and Tremblay, 2003; Jasienska *et al*., 2006). This is one manifestation of developmental plasticity, the process by which one genotype can produce a range of different phenotypes (Bateson *et al*., 2004). Here, we describe the outcome of an experiment of human history, which provides evidence for increased reproductive success of women who were undernourished during gestation.

The Dutch famine was a 5-month period of severe food shortage, which ensued after the German occupying forces placed an embargo on all food transports to the western Netherlands in the winter of 1944–1945. Adult food rations dropped to as low as 400 calories/day. The famine was a humanitarian disaster, but it has provided us with the unique opportunity to study the effects of a circumscribed period of severe maternal undernutrition on the offspring's reproductive success.

Materials and Methods

Selection procedure

The Dutch Famine Birth Cohort consists of 2414 live-born term singletons born in the Wilhelmina Gasthuis in Amsterdam, the Netherlands, between 1 November 1943 and 28 February 1947. Cohort members were traced at age 50 and 58 years. The selection and tracing procedures have been described in detail elsewhere (Ravelli *et al*., 1998).

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. At the start of the study, there were 1423 men and women eligible for the study. A total of 855 persons participated 55% of whom were women. The birthweight of cohort members who participated in the study was similar to that of persons who did not participate (3350 versus 3344 g, $P = 0.8$).

The local Medical Ethics Committee had approved the study.

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 organizations, 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 (Trienekens, 1985).

A person was considered to be prenatally exposed to famine if the average daily ration for adults during any 13-week period of gestation was <1000 calories. Using this definition, all born between 7 January 1945 and 8 December 1945 were considered to be exposed *in utero*. 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 *in utero* and served as the control group.

We defined periods of 16 weeks each to differentiate between those who were exposed *in utero* in late gestation (born between 7 January and 28 April 1945), mid gestation (born between 29 April and 18 August 1945) and in early gestation (born between 19 August and 8 December 1945), which corresponds with previous publications on this cohort (Ravelli *et al*., 1998; Roseboom *et al*., 2000).

Data collection

The medical birth records provided information about the mother, the course of the pregnancy and the size of the baby and the placenta at birth. Socio-economic status (SES) of the mothers was based on the occupation of the head of the family at the time of delivery and classified as either manual or non-manual, using the information provided by the birth records.

Trained nurses carried out all interviews. All eligible cohort members were invited to visit the hospital. Those who were unable to come to the hospital were visited at home. People who did not wish to be paid a house call or visit 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.

Height was assessed using a fixed or a portable stadiometer, weight with Seca scales or Tefal portable scales. Body mass index was calculated by dividing weight in kilograms by the square of height in meters. Current SES was determined according to the participant's or their partner's ISEI-92 score (Bakker and Sieben, 1997), whichever was highest. The ISEI-92 score is based on current or most recent level of employment and level of professional training.

Participants were asked whether they had children, and if so, how many. We also asked whether they ever had twins or higher order multiple pregnancies, or whether any of their pregnancies had ended in an abortion (spontaneous or induced) before the gestational age of 28 weeks. Additionally, we recorded age at delivery of their first child. The delay until first pregnancy was defined as the time from active pregnancy attempt until the couple achieved the first pregnancy, or, alternatively, gave up trying.

Among women, age of menarche, menopause, and parity were also recorded. Spontaneous menopause was defined as the cessation of menstrual periods, not due to surgery of the ovaries or uterus, for a period of longer than 12 months.

Statistical methods

We used linear regression for continuous variables and logistic regression for dichotomous variables to compare the maternal characteristics, and offspring characteristics at birth and in adulthood as well as reproductive characteristics, including proportion of childlessness and twinning rates depending on famine exposure *in utero*. The total number of offspring among exposed and unexposed participants was compared with a Mann–Whitney *U*-test.

We used the Cox proportional hazards model (Cox, 1972) to compare duration of delay until first pregnancy was achieved and age at delivery of first child among people who were exposed to famine *in utero* in early, mid or late gestation with that in unexposed people (born before or conceived after). In women we additionally calculated Hazard Ratios (HRs) for age at menarche and age at menopause.

Age at delivery of the first child is reported in medians and interquartile ranges because of its skewed distribution. We also report body mass index and adult SES as geometric means, because of the skewed distributions. Maternal weight at the end of pregnancy was not available in 58 subjects. We imputed the mean value (67 kg for maternal weight) when actual information was missing and included an indicator of missingness, when using this variable as a covariate in the regression models. Subjects for whom SES at birth was missing were coded as a separate category when using as a covariate in regression models.

For clarity, we refer to women who were pregnant around the time of the famine as F0, their children as F1 and their grandchildren as F2.

Results

Reproductive success is increased among women who were exposed to famine in utero

Table I shows that F1 women who had been exposed to famine *in utero* had more children (mean number of children, 2.0) compared with F1 women unexposed to famine *in utero* (1.7, $P = 0.002$) were younger when they had their first child (23.2 compared with 23.7 years, $P = 0.05$), more frequently had twins (OR 2.7 [95% CI 1.1 to 7.0]), and were less frequently childless (OR 0.80 [95% CI 0.66–0.98]). Table II shows that, in F1 men, exposure to famine *in utero* was not associated with any alterations in reproductive success.

Fig. 1 displays the proportion of F1 women who delivered at least one baby, according to age and famine exposure. The figure shows that F1 women who were exposed to famine *in utero* were younger at the age of delivery of their first baby ($P = 0.03$).

Fig. 2 shows the same curve for F1 men who were exposed *in utero*: in F1 men, prenatal famine exposure was not associated with any changes in the age of delivery of their first child ($P = 0.2$).

Selective fertility

We investigated whether the association between prenatal famine exposure and increased reproductive success in F1 women could be due to fertility characteristics of their mothers (F0). In our cohort, women (F1) whose mothers (F0) were young tended to have their children (F2) at a younger age (HR 0.8 per 10 years increase in maternal age, $P = 0.01$). Women (F1) whose mothers (F0) were primiparous also tended to have their children (F2) at a younger age (HR 0.8 compared with multiparous mothers (F0), $P = 0.04$). However, when we adjusted for F0 maternal age and parity in a multivariable model, the reduction in age of first delivery that was associated with prenatal famine exposure was not attenuated (unadjusted HR 0.8, adjusted HR 0.8 [95% CI 0.6–1.0]). Additional adjustment for F0

Table I. Maternal, birth, adult and reproductive characteristics in women who were born around the time of the Dutch famine in the Wilhelmina Gasthuis.

	Born before famine	Exposed to famine	Conceived after famine	All (SD)
Number	144	204	125	473
Maternal characteristics(F0)				
Maternal age at delivery (years)	29	29	29	29 (6)
Maternal primiparity (%)	31	34	37	34
SES at birth manual (%)	86	66*	68	72
Birth characteristics(F1)				
Birthweight (g)	3356	3211*	3353	3293 (460)
Birth length (cm)	50.2	49.7*	50.4	50.0 (2.2)
Adult characteristics				
Body mass index (kg/m^2)[1]	27.9	27.8	29.1	28.2 (5.2)
SES[2]	44	47	49	47 (15)
Reproductive characteristics				
Age at menarche (years)	13.2	12.8	12.7	12.9 (1.7)
Age at spontaneous menopause (years)	50.7	50.2	49.3	50.1 (5.0)
Number of children	1.7	2.0*	1.7	1.8 (1)
Age at delivery first child (years)[3]	23.1	23.2*	24.2	23.5
Twins/triplets (%)	2	8*	3	4
Duration delay to first pregnancy (months)[4]	9	8	5	8
Childless (%)	16	8*	12	12

Means and standard deviations (SD), except where given as percentages or medians. *$P \leq 0.05$ exposed compared to unexposed (born before and conceived after).[1]Geometric mean. [2]SES according to the ISEI-92 (range 16–87). [3]Median age. [4]includes couples that gave up attempting pregnancy without having achieved pregnancy.

Table II. Maternal, birth, adult and reproductive characteristics in men who were born around the time of the Dutch famine in the Wilhelmina Gasthuis.

	Born before famine	Exposed to famine	Conceived after famine	All (SD)
Number	120	146	116	382
Maternal characteristics (F0)				
Maternal age at delivery (years)	28	29	28	29 (6)
Maternal primiparity (%)	44	25*	41	36
Socio-economic status at birth manual (%)	76	70	70	72
Birth characteristics (F1)				
Birthweight (g)	3429	3326*	3531	3420 (468)
Birth length (cm)	51.0	50.2*	50.9	50.7 (2.0)
Adult characteristics				
Body mass index (kg/m^2)[1]	28.4	27.9	28.3	28.2 (4.3)
Socio-economic status[2]	49	50	48	49 (13)
Reproductive characteristics				
Number of children	1.6	1.8	1.6	1.7 (1.0)
Age at birth first child (years)[3]	26.1	25.7	25.6	25.8 (5.3)
Twins/triplets (%)	2	1	0	1
Duration delay to first pregnancy (months)[4]	11	7	8	8 (26)
Childless (%)	18	13	18	16

Means and standard deviations (SD), except where given as percentages or medians. *$P \leq 0.05$ exposed compared to unexposed (born before and conceived after). [1]Geometric mean. [2]Socio-economic status according to the ISEI-92 (range 16–87). [3]Median age. [4]Includes couples that gave up attempting pregnancy without having achieved pregnancy.

maternal weight at the end of pregnancy, and SES of the F0 mothers did not lead to an attenuation of the effect on age at first delivery (adjusted HR 0.8 [95% CI 0.6–1.0]) or on any of the other measures of reproductive success.

Twinning rates and the median number of children were increased, regardless of whether F1 women had been exposed to famine in early (9%, median = 2.0), mid (8%, median $n = 2.0$) or late gestation (7% twins, median = 1.9 children). The percentage of F1 women who remained childless was lowest among those exposed in mid (5%) and early (4%) gestation (this percentage was 13 among those exposed in late gestation).

Selective survival

We examined whether the association between prenatal famine exposure and increased reproductive success could be explained by selective survival during the famine. We compared the reproductive outcomes of F1 women who were born before the famine, who had the highest infant mortality, to F1 women who were conceived after the famine, who had the lowest infant mortality. There were no differences in age at first delivery, twinning rate, or any of the other markers of reproductive success, between F1 women who were born before and those who were conceived after the famine.

Adjusting for F1 birthweight, a marker of early survival had no effect on the associations between prenatal exposure to famine and various markers of reproductive success.

Discussion

Women who were exposed to famine *in utero* had more offspring, more twins, were less likely to remain childless and

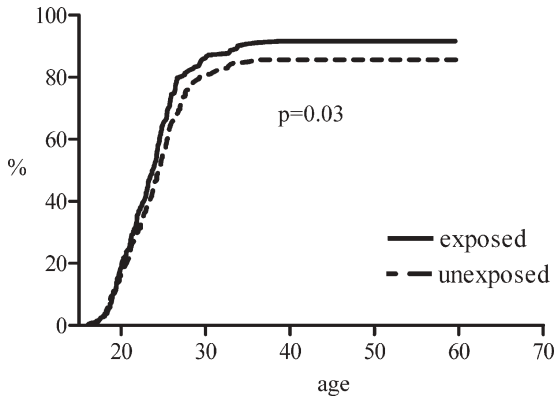

Figure 1: Cumulative incidence curve of delivery first offspring as a function of age at delivery in women who were exposed or unexposed (born before or conceived after the famine) to the Dutch famine *in utero*.

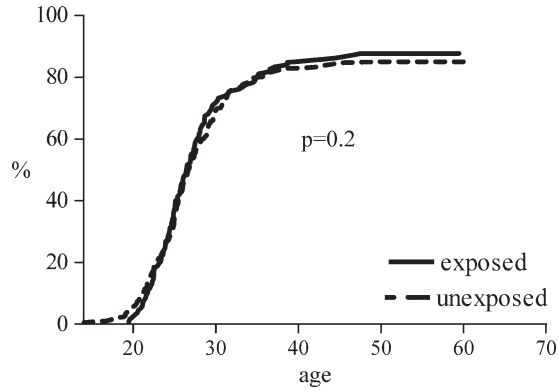

Figure 2: Cumulative incidence curve of birth of first offspring as a function of age at delivery in men who were exposed or unexposed (born before or conceived after the famine) to the Dutch famine *in utero*.

started reproducing at a younger age when compared with other women. We investigated whether these characteristics of reproductive success were likely to be due to selection for specific genotypic variation or, alternatively, developmental plasticity. There was a sharp decline in maternal fertility during the Dutch famine, and birth rates nine months after the famine began were decreased by as much as 50% (Stein and Susser, 1975). Mothers (F0) who were able to conceive despite the food shortage may themselves have had genetically enhanced fertility and could have passed this genetic trait down to their daughters (F1). However, our data show that the fertile phenotype was not only found in those conceived during the famine (and thus exposed in early gestation) but extended to women (F1) who were conceived prior to the start of the famine, and were exposed to it in mid or late gestation only. These findings suggest that any *in utero* exposure to famine is sufficient for the fertile phenotype to occur and makes selection of variants encoding fertility under adverse conditions less likely. When we adjusted for other variables linked to fertility including mother's (F0) parity, age, weight, and SES, the effect of prenatal famine exposure on reproductive success was not attenuated.

Infant mortality was high during the famine (Roseboom *et al*., 2001). Infants who were fit enough to survive the famine may also have been characterized by later reproductive fitness. This would lead to higher fertility among women (F1) who were born before the famine in comparison to those who were conceived after the famine. However, we found no differences in reproductive success between F1 women born before or conceived after the famine, who show the largest contrast in infant mortality. We were unable to investigate whether fetal survival under harsh conditions as a result of the genetic constitution could have played a role. The fact that stillbirth rates were not increased during the Dutch famine (Smith, 1947) makes it less likely that selective fetal survival plays a role in our findings.

The constellation of reproductive and metabolic adaptations during fetal development in response to undernutrition *in utero* may be part of a thrifty phenotype which is associated with enhanced reproduction. Post-war Holland provided a postnatal environment of food abundance, which was unlike the conditions anticipated by the environment *in utero*. This disadaptation of a thrifty phenotype may be important in the later occurrence of chronic disease. We and others have shown that people exposed to famine during gestation have increased risk of cardiovascular disease (Roseboom *et al*., 2000; Painter *et al*., 2006a,b), metabolic disease (Ravelli *et al*., 1998; de Rooij *et al*., 2006), breast cancer (Painter *et al*., 2006a,b) and higher obesity rates (Ravelli *et al*., 1976,1999). In conclusion, our findings are consistent with the theory of life history regulation, which proposes that the two traits fertility and body maintenance are mutually balanced, and that increased investments in one, are traded off by reduction in investment in the other (Stearns, 1992). Our findings show that the balance in phenotypic traits underpinning life history regulation may be set by the environmental conditions during fetal development.

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Author's roles

C.O., D.J.P.B. and T.J.R. designed the study. R.C.P. and S.dR carried out the study. T.J.R. supervised the study. R.C.P. and C.O. analyzed the results. R.C.P. wrote the paper. All authors provided intellectual input. T.J.R. wrote the final version of the paper.

All authors saw and approved of the final version of the paper.

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