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Abstract

Objective—To assess the effect of prenatal exposure to maternal malnutrition on coronary heart disease in people born around the time of the Dutch famine, 1944–45.

Design—Historical cohort study.

Setting—Community study.

Patients—Singletons born alive between November 1943 and February 1947 for whom detailed birth records were available.

Design—The prevalence of coronary heart disease was compared between those exposed to famine in late gestation (n = 120), in mid-gestation (n = 108), or in early gestation (n = 68), and those born in the year before the famine or those conceived in the year after the famine (non-exposed subjects, n = 440).

Main outcome measures—Prevalence of coronary heart disease, defined as the presence of angina pectoris according to the Rose questionnaire, Q waves on the ECG, or a history of coronary revascularisation.

Results—The prevalence of coronary heart disease was higher in those exposed in early gestation than in non-exposed people (8.8% *v* 3.2%; odds ratio adjusted for sex 3.0, 95% confidence interval (CI) 1.1 to 8.1). The prevalence was not increased in those exposed in mid gestation (0.9%) or late gestation (2.5%). People with coronary heart disease tended to have lower birth weights (3215 g *v* 3352 g, p = 0.13), and smaller head circumferences at birth (32.2 cm *v* 32.8 cm, p = 0.05), but the effect of exposure to famine in early gestation was independent of birth weight (adjusted odds ratio 3.2, 95% CI 1.2 to 8.8).

Conclusions—Although the numbers are very small, this is the first evidence suggesting that maternal malnutrition during early gestation contributes to the occurrence of coronary heart disease in the offspring.

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Keywords: coronary heart disease; fetal origins hypothesis; maternal malnutrition

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Small size at birth is linked to an increased risk of coronary heart disease and its major biological risk factors.[1] This has led to the hypothesis that coronary heart disease originates in utero through the persistence of adaptations made by the fetus in response to undernutrition during specific stages of gestation.[1]

The Dutch famine of 1944–45 offers a unique opportunity to test this hypothesis in humans. Food became scarce in the west of the Netherlands after the northward movement of the Allied forces came to a halt in September 1944, when attempts to take hold of the bridge across the river Rhine at Arnhem failed (operation "Market Garden"). The official daily rations for an adult in Amsterdam—which had gradually decreased from about 1800 kcal in December 1943 to 1400 kcal in October 1944—fell abruptly to below 1000 kcal in late November 1944. During the peak of the famine from December 1944 to April 1945, the rations varied between 400 and 800 kcal. After the liberation in early May, the rations improved rapidly to over 2000 kcal in June 1945.

We examined 50 year old people who were born around the time of the Dutch famine in a university hospital in Amsterdam. We have already shown that exposure to famine, especially in late gestation, is linked to impaired glucose tolerance,[2] while exposure in early gestation is linked to more atherogenic lipid profiles[3] and, at least in women, to higher levels of obesity.[4] In the same cohort, however, we did not find an effect of prenatal exposure to famine on overall or cardiovascular mortality between the ages of 18 and 50 years (TJ Roseboom, unpublished data, 1999). We now present data on the effects of prenatal exposure to famine on the prevalence of coronary heart disease in adult life.

Methods

The selection procedures of this study have been described in detail elsewhere.[2] We retrieved the medical records of 2414 full term babies born alive between 1 November 1943 and 28 February 1947 in the Wilhelmina Gasthuis. The population registry of Amsterdam traced 2155 of these (89.2%): 265 had died (21 of cardiovascular disease, International Classification of Diseases (ICD) code 410–414), 199 had emigrated from the Netherlands, and 164 did not allow the population registry to give us their address; of the remaining 1527, we asked 912 to participate, starting with those who lived in or close to Amsterdam, and 736 of these had a successful ECG recording. Birth weights of this group of 736 subjects (mean 3348 g) were not different from those of the 1678 who were not included (mean 3345 g, p adjusted for exposure = 0.3).

We defined the famine period according to the daily official food rations for the general population older than 21 years. The official rations rather accurately reflected the variation over time in the total amount of food available.[5] In addition to the official rations, food also came from other sources (for example, church organisations, central kitchens, and the black market), and the amount of food actually available to individuals was roughly twice as much as the official rations. The rations should therefore only be taken as a relative measure of nutritional intake for the population as a whole.

The official rations were about 1800 kcal/day in December 1943. This figure gradually decreased to about 1400 kcal/day in October 1944, and fell below 1000 kcal on 26 November 1944. The rations varied between 400 and 800 kcal from December 1944 to April 1945, and rose above 1000 kcal on 12 May 1945, one week after the liberation by the Allied forces. In June 1945, rations were over 2000 kcal/day. Children younger than one year were relatively protected during the famine, because their official daily rations never fell below 1000 kcal, and the specific nutrient components were always above the standards used by the Oxford nutritional survey.[6]

We considered fetuses to have been exposed to famine if the average official daily rations for adults during any 13 week period of gestation were less than 1000 kcal. Therefore, babies born between 7 January and 8 December 1945 were considered to be exposed to famine in utero. We differentiated between those who were mainly exposed to famine in late gestation (those born between 7 January and 28 April 1945), in mid-gestation (those born between 29 April and 18 August 1945), or in early gestation (those born between 19 August and 8 December 1945). Those born before the famine (born between 1 November 1943 and 6 January 1945) and those conceived after the famine (born between 9 December 1945 and February 1947) were considered not to have been exposed to famine in utero.

The medical birth records provided information about the mother, the course of pregnancy, and the size of the baby at birth. We calculated the gestational age at birth from the date of the last menstrual period or by the obstetrician's estimation at the first prenatal visit and at the physical examination of the child at birth. The socioeconomic status at birth was dichotomised into manual and non-manual labour according to the occupation of the head of the family.[7] We took maternal weight at the last prenatal visit, which was always within two weeks of delivery. Maternal height was not available.

The presence of coronary heart disease at age 50 was defined as the presence of one or more of the following: angina pectoris according to the Rose/World Health Organization questionnaire; Q waves on the ECG (Minnesota codes 1-1 or 1-2); or a history of coronary revascularisation (angioplasty or surgery).[8] We also performed a standard oral glucose tolerance test, took fasting blood samples to measure plasma concentrations of low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, measured weight and height, and measured blood pressures, twice before and twice after the glucose tolerance test, in the non-dominant arm after five minutes of rest while the participants were seated.

The participants were interviewed to obtain information about their medical history and lifestyle. Current socioeconomic status was determined from the subject's or partner's occupation, whichever was highest, according to the socioeconomic index (ISEI-92), with a scale ranging from 16 for the lowest to 87 for the highest status.[9]

We used linear and logistic regression analysis to compare one by one the characteristics of people with and without coronary heart disease, while always adjusting for sex. We log transformed body mass index, two hour glucose, and the LDL:HDL cholesterol ratio before analysis, because of the skewed distributions, and results are therefore given as geometric means and standard deviations. We calculated odds ratios (OR) using logistic regression to compare the prevalence of coronary heart disease in people exposed in early, mid-, or late gestation with that in non-exposed people (born before or conceived after). We considered differences to be significant if probability values were $p < 0.05$, and we therefore also report the 95% confidence intervals (CI).

Results

Of the 736 people included in the study, 24 (3.3%, 13 men and 11 women) had coronary heart disease. Five had symptoms of angina, eight had Q waves on the ECG, and 11 had a history of coronary revascularisation. People with coronary heart disease tended to have lower birth weights and smaller head circumferences, and were born to lighter mothers than those without (table 1). Socioeconomic status at birth or in adulthood did not differ between people with or without coronary heart disease, nor did smoking or drinking habits in adult life. People with coronary heart disease also had a raised adult body mass index, raised systolic blood pressure, reduced glucose tolerance, and a more atherogenic lipid profile (high LDL :HDL cholesterol ratio).

The prevalence of coronary heart disease was significantly greater in people exposed in early gestation than in those who were not exposed prenatally (8.8% *v* 3.2%; OR 3.0, 95% CI 1.1 to 8.1) (table 2). The prevalence of coronary heart disease was not increased in those exposed in mid-gestation (0.9%; OR 0.3, 0.0 to 2.2) or late gestation (2.5%; OR 0.8, 0.2 to 2.8).

The effect of exposure to famine in early gestation was independent of gestational age (adjusted OR 2.9, 95% CI 1.0 to 8.9), weight of the baby at birth (adjusted OR 3.2, 95% CI 1.2 to 8.8), and weight of the mother (adjusted OR 2.4, 95% CI 0.8 to 6.9). It was also independent of socioeconomic status at birth (adjusted OR 3.6, 95% CI 1.3 to 10.1) and at adult age (adjusted OR 3.0, 95% CI 1.1 to 8.0), current smoking (adjusted OR 3.0, 95% CI 1.1 to 8.2), and alcohol consumption

Table 1 Maternal, birth, and adult characteristics for people with and without coronary heart disease

	Coronary heart disease	*No coronary heart disease*	*p Value (adjusted for sex)*
Numbers	24	712	
Men/women	13/11	342/370	
Maternal characteristics			
Weight at end of pregnancy (kg)	62.1 (6.4)	66.3 (8.7)	0.02
Manual occupation	70%	72%	0.70
Birth characteristics			
Birth weight (g)	3215 (478)	3352 (470)	0.13
Birth length (cm)	50.2 (2.1)	50.3 (2.1)	0.62
Head circumference (cm)	32.2 (1.5)	32.8 (1.7)	0.05
Ponderal index (kg/m^3)	25.6 (2.9)	26.2 (2.3)	0.19
Gestational age (days)	284 (12)	285 (12)	0.63
Adult characteristics			
Body mass index* (kg/m^2)	29.7 (1.2)	26.9 (1.2)	< 0.01
Systolic blood pressure (mm Hg)	130.5 (15.5)	125.3 (15.7)	0.12
Glucose 120 min* (mmol/l)	6.8 (1.5)	5.9 (1.4)	0.04
LDL:HDL cholesterol*	3.6 (1.5)	2.9 (1.5)	0.01
SES (ISEI)	47 (15)	48 (14)	0.80
Smoking	36%	34%	0.81
Alcohol (units/week)	8 (9)	9 (12)	0.33

Values are mean (SD), except where given as percentages; p value of difference adjusted for sex calculated using linear or logistic regression.
*Geometric mean (SD).
Glucose 120 min, blood glucose 120 minutes after standard loading dose; HDL, high density lipoprotein; LDL, low density lipoprotein; SES (ISEI), socioeconomic status index.

(adjusted OR 3.0, 95% CI 1.1 to 8.1). Adjustment for adult risk factors—body mass index (adjusted OR 2.5, 95% CI 0.9 to 7.1), blood pressure (adjusted OR 3.2, 95% CI 1.2 to 8.6), two hour plasma glucose concentration (adjusted OR 2.5, 95% CI 0.8 to 7.2), and fasting plasma LDL:HDL cholesterol ratio (adjusted OR 2.6, 95% CI 1.0 to 7.2)—attenuated the effect of exposure to famine in early gestation to some extent.

Discussion

We found that people exposed to famine in early gestation—those who were conceived during the famine—had a higher prevalence of coronary heart disease than people who had not been exposed to famine in utero. Although the numbers are small, this is the first direct evidence suggesting that maternal starvation during gestation is linked to coronary heart disease in the offspring. People with coronary heart disease were born to lighter mothers, and tended to have lower body weights and head circumferences at birth, but the effect of maternal starvation in early gestation was independent of maternal weight and size of the baby at birth.

A study of people who were born at the time of the Leningrad siege, 1941 to 1944, did not find any effects of prenatal exposure to maternal malnutrition on the prevalence of coronary heart disease.[10] However, the essentially different circumstances before, during, and after the famine period in Leningrad and in the western part of the Netherlands hamper a direct comparison between those results and ours. The famine period in Leningrad lasted much longer than the Dutch famine (> 2 years *v* 5–6 months). Furthermore, it was preceded and followed by periods of relative shortage of food. Also, the standard of living in Russia remained rather poor after the second world war, whereas it rapidly improved in the Netherlands.[11]

Although not significant, people with coronary heart disease had been smaller at birth than people without coronary heart disease, which is in agreement with results from other studies.[1 8 12] The link between small size at birth and increased rates of coronary heart disease in later life is thought to reflect the long term consequences of undernutrition during gestation.[1] Previously, we have also found that people exposed to famine in late gestation had a reduced glucose tolerance at age 50,[2] whereas exposure to famine in early gestation was linked to higher levels of obesity in women[4] and

Table 2 Maternal characteristics, birth outcomes, and adult characteristics according to timing of prenatal exposure to famine

		Exposed to famine in:					
	Born before famine	*Late gestation*	*Mid-gestation*	*Early gestation*	*Conceived after famine*	*All (SD)*	*Number*
Date of birth	1/11/43 to 6/1/45	7/1/45 to 28/4/45	29/4/45 to 18/8/45	19/8/45 to 8/12/45	9/12/45 to 28/2/47		
Number	208	120	108	68	232	736	736
Men	50%	47%	40%	44%	51%	48%	
Women	50%	53%	60%	56%	49%	52%	
Coronary heart disease							
Prevalence (n)	3.8% (8)	2.5% (3)	0.9% (1)	8.8% (6)	2.6% (6)	3.3% (24)	736
Maternal characteristics							
Weight at end of pregnancy (kg)	66.4	62.9	63.4	67.5	68.6	66.2 (8.6)	643
Manual occupation	81%	73%	74%	65%	66%	73%	635
Birth characteristics							
Birth weight (g)	3380	3166	3216	3450	3442	3347 (470)	736
Birth length (cm)	50.5	49.5	49.8	51.0	50.5	50.3 (2.1)	729
Head circumference (cm)	32.9	32.4	32.2	33.0	33.1	32.8 (1.5)	728
Ponderal index (kg/m^3)	26.1	26.0	25.9	26.0	26.6	26.2 (2.3)	729
Gestational age (d)	284	284	286	289	286	285 (12)	640
Adult characteristics							
Body mass index* (kg/m^2)	26.7	26.7	26.6	28.1	27.2	27.0 (1.2)	736
Systolic BP (mm Hg)	126	127	125	123	125	126 (16)	734
Glucose 120 min* (mmol/l)	5.7	6.3	6.1	6.1	5.9	6.0 (1.4)	697
LDL:HDL cholesterol*	2.9	2.8	2.7	3.3	2.9	2.9 (1.5)	697
SES (ISEI)	46	50	49	48	48	48 (13)	736
Smoking	37%	32%	31%	41%	33%	34%	736
Alcohol (units/week)	10	10	7	8	9	9 (11)	736

Values are mean (SD), except where given as percentages.
*Geometric mean (SD).
BP, blood pressure; see table 1 for key to other abbreviations.

more atherogenic lipid profiles in both men and women.[3] Blood pressure was not affected by exposure to famine, although it was strongly negatively associated with size at birth.[13] These distinct relations between prenatal exposure to famine and fetal growth on the one hand and coronary heart disease and its risk factors on the other suggest that an adverse fetal environment contributes to several aspects of cardiovascular risk in adult life, but that the effects depend on its timing during gestation.

Because the famine ended abruptly, the women who conceived during the famine (and were thus exposed in early pregnancy) were well nourished in later pregnancy, which is reflected in the above average birth weight of their babies. It is in these babies that we found a higher prevalence of coronary heart disease in adult life. This may suggest that the transition from nutritional deprivation in early gestation to nutritional adequacy later on has led to metabolic conflicts, which in turn resulted in an increased risk of coronary heart disease. This explanation is broadly consistent with observations in Finland that have shown that coronary heart disease was related to reduced fetal growth followed by accelerated postnatal weight gain.[12] Furthermore, it matches results from rat experiments which showed that the combination of prenatal undernutrition with retarded fetal growth and good postnatal nutrition led to striking reductions in lifespan.[14]

During the embryonic period (the first eight weeks after conception in humans) there is no transfer of nutrients from the mother to the fetus through the placenta.[15] Nevertheless, our findings suggest that maternal malnutrition during this period may have permanent effects on the fetus. Studies in rats have also shown that maternal malnutrition during the first four days after conception increased body weight at birth as well as the relative weights of the heart, kidneys, and lungs.[16] It is not the shortage of food itself but endocrine changes in response to alterations in nutrient availability that seem to be responsible for the programming effects of maternal malnutrition during early gestation. It has also been suggested that programming of the hypothalamic-pituitary-adrenal axis because of maternal stress might explain the link between an adverse environment in utero and disease in later life.[17] This is, however, not a very likely explanation as we only observed an increase in the prevalence of coronary heart disease in the offspring of women exposed to famine in early gestation. One would expect at least the same or higher levels of stress in pregnant women exposed to famine in late or mid-gestation, and the prevalence of coronary heart disease in the offspring of these women was not increased.

People born around the time of the Dutch famine in 1944–45 are relatively young, which might explain why we have not been able to demonstrate any effect of prenatal exposure to famine on cardiovascular mortality (TJ Roseboom, unpublished data, 1999). We will follow these people to examine whether the observed trend towards increased prevalence of coronary heart disease among individuals whose mothers conceived during the famine will continue and result in premature mortality.

Although our findings are based on small numbers, if confirmed in future studies they may have important public health implications. First, a sudden improvement in the nutritional intake of women during pregnancy—for example, as a result of nutritional supplementation in the second half of pregnancy—may have far reaching consequences for the health of their children. Second, the known associations between the size of the babies at birth and adult disease underestimate the long term impact of nutrition of women before and during pregnancy on the rate of coronary heart disease in the offspring. We are only beginning to understand the effects of maternal malnutrition on fetal development and adult health. Further research is needed before we are able to formulate dietary recommendations to women both before and during pregnancy in order to prevent coronary heart disease in future generations.

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