Prenatal exposure to the Dutch famine and health in later life

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Plasma lipid profile in adults after prenatal exposure to famine

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Maternal malnutrition during gestation may have lasting effects on health without affecting the size of the baby at birth.

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Summary

Objective: We studied the effects of maternal malnutrition during specific periods of gestation on plasma lipid profile in people aged about 50.

Methods: We assessed the plasma lipid profile of 704 men and women born at term as singletons in a university hospital in Amsterdam, the Netherlands, between 1 November 1943, and 28 February 1947, around the time of a severe famine.

Results: People exposed to famine in early gestation had a more atherogenic lipid profile than those who were not exposed to famine *in utero*. Their LDL/HDL cholesterol ratios were significantly higher (13.9%, 95% confidence interval 2.6 to 26.4). Also, their plasma HDL cholesterol and apolipoprotein A concentrations tended to be lower, and their plasma total cholesterol, LDL cholesterol, and apolipoprotein B concentrations tended to be increased, although these differences were not statistically significant. The effect of famine was independent of size at birth and adult obesity.

Conclusion: An atherogenic lipid profile might be linked to a transition from poor maternal nutrition in early gestation to adequate nutrition later on. This suggests that maternal malnutrition during early gestation may program lipid metabolism without affecting size at birth.

Introduction

Small body size at birth has been reported to be associated with an atherogenic lipid profile (high plasma LDL cholesterol and low plasma HDL cholesterol concentrations). Some investigators found associations between low birth weight and reduced HDL cholesterol or high plasma triglyceride concentrations [1-3], others between short body length at birth or reduced abdominal circumference and raised total cholesterol, LDL cholesterol and apolipoprotein B. [4,5]

Observations in guinea pigs and rats suggest that manipulations of maternal dietary intake during gestation permanently alter cholesterol synthesis and plasma cholesterol concentrations. [6-9] So far, the only study in humans on the effect of maternal nutrition during gestation on later cholesterol concentrations was performed in people prenatally exposed to famine at the time of the 900 day Leningrad siege (1941 – 1944), and this study did not show any significant effects. [10]

We now present the effect of prenatal undernutrition during specific periods in pregnancy on lipid profile in adults born around the time of famine in the Netherlands during 1944 – 45. The Dutch famine was a 5-month period of extreme malnutrition in the western part of the Netherlands which was clearly delineated in time. We have already shown that the glucose tolerance of these people was reduced after prenatal exposure to famine especially in late or mid gestation [11], and that women exposed to famine in early gestation had an increased body mass index. [12] We assessed lipid profiles of people exposed to famine during late, mid or early gestation (exposed subjects) and people born in the year before or those conceived in the year after the famine (non-exposed subjects).

Methods

Selection procedures

All 5425 babies born in the Wilhelmina Gasthuis in Amsterdam between November 1, 1943 and February 28, 1947 were candidates to be included. Most patients in this hospital came from lower to middle social classes, but

little is known about the actual referral pattern during the period of our study. Firstly, we excluded 349 babies who were stillborn or part of a multiple pregnancy. Secondly, we retrieved the medical records of all 1380 babies born between November 1, 1944 and February 28, 1946, who were potentially exposed to famine during gestation. Thirdly, we retrieved the records of a random sample of 650 out of the 1305 babies born in the year before that period (born between November 1, 1943 and October 31, 1944) and a random sample of 650 out of the 2391 babies conceived in the year after that period (born between March 1, 1946 and February 28, 1947). Of these 2680 babies, 27 (1.0%) were excluded because their birth record was missing and 239 (8.9%) were excluded because they were born prematurely (gestational age at birth below 259 days, either as computed from the date of the last menstrual period, or as estimated by the obstetrician at the first prenatal visit and at the physical examination of the baby just after birth). In all, 2414 liveborn singletons were included.

The 'Bevolkingsregister' of Amsterdam (population registry) traced 2155 (89%) of the 2414 included babies. Of these, 265 had died, 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 people who lived in or close to Amsterdam to participate. 741 attended the clinic, and fasting blood samples could be successfully analyzed for plasma lipid and lipoprotein measurements in 704. Birth weights in this group of 704 subjects (mean birth weight 3348 g) were not different from the 1710 who were not included (mean birth weight 3332 g, p adjusted for exposure = 0.3).

Exposure to famine

We defined the famine period according to the daily official food-rations for the general population older than 21 years. The amount of protein, carbohydrate and fat decreased more or less proportionately. The official rations reflected rather accurately the variation over time in the total amount of food available in the west of the Netherlands. [13] In addition to the official rations, food came also from other sources (e.g. church organizations, central kitchens, and the 'black market'), and the amount of food actually available to individuals was roughly twice as high as the official rations. Pregnant and lactating women were entitled to an extra amount of 600 calories (2520 kJ) a day, but at the peak of the famine these extra supplies could not always be

provided. It is also likely that most women shared these extra supplies with their families. 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 calories (7560 kJ) per day in December 1943. This figure gradually decreased to about 1400 calories (5880 kJ) in October 1944, and fell below 1000 calories (4200 kJ) on 26 November 1944. The rations varied between 400 calories (1680 kJ) and 800 calories (3360 kJ) from December 1944 to April 1945, and rose above 1000 calories (4200 kJ) on 12 May 1945, one week after liberation by the Allied forces. In June 1945, rations were over 2000 calories (8400 kJ). Children younger than 1 year were relatively protected during the famine, because their official daily rations were always higher than 1000 calories (4200 kJ).[14]

We considered fetuses to have been exposed to famine if the average daily rations for people older than 21 during any thirteen-week period of gestation were less than 1000 calories (4200 kJ). Therefore, babies born between January 7, 1945 and December 8, 1945 were exposed *in utero*. We used three periods of 16 weeks to differentiate between people who were exposed in late gestation (born between January 7, 1945 and April 28, 1945), in mid gestation (born between April 29, 1945 and August 18, 1945), and in early gestation (born between August 19, 1945 and December 8, 1945).

Study parameters

The medical birth records provided information about the mother, the course of the pregnancy and the size of the baby at birth (for detailed information see reference 11). We also recorded the method of infant feeding at discharge, which took place about 10 days after delivery, and classified it as exclusive breast feeding, partial bottle feeding and exclusive bottle feeding.[18] Maternal weight gain in the third trimester was calculated from the difference in weight at the beginning and end of the third trimester divided by the duration of the time interval between the 2 measurements and multiplied by the duration of the trimester (13 weeks) The socio-economic status at birth was dichotomized into manual and non-manual labor according to the occupation of the head of the family. [15]

Total plasma cholesterol, HDL and LDL cholesterol, triglycerides, apolipoprotein A and apolipoprotein B concentrations were measured by standard enzymatic methods. [16,17] We measured height (with a fixed

stadiometer) and weight (Seca scale, Hamburg, Germany). All subjects were interviewed about their medical history, lifestyle and use of medication. Current socio-economic status was coded using ISEI-92 according to the occupation of the participants or their partners; whichever was highest. [19] Values ranged from 16 (low status) to 87.

Statistical methods

We calculated the differences between the lipid profiles of unexposed subjects and those exposed in late, mid or early gestation. The variables HDL cholesterol, LDL/HDL ratio, serum triglycerides and BMI had a skewed distribution, and were log transformed before analysis. The results for these variables are given as the geometric means and standard deviations and the differences are given as relative differences expressed as percentages of the means of non-exposed people. Firstly, we used multiple linear regression analysis to adjust for sex. Secondly, we also adjusted for adult BMI, and after that also for adult characteristics (current socio-economic status, smoking, and use of lipid lowering medication), and for maternal characteristics (age, parity, weight at last prenatal visit, socio-economic status at birth). We computed 95% confidence intervals.

For a relatively large number of participants, information on maternal weight at the end of pregnancy, weight gain or socio-economic status at birth was missing. Therefore, when adjusting for maternal weight or weight gain, we set the value for that variable with missing values to the mean of the non-missing values and entered an extra variable into the regression model with a value of 1 for those with missing values for that variable and a value of 0 for the rest. When adjusting for categorical variables (parity, socio-economic status at birth, smoking, use of lipid-lowering medication), we added an extra category for those participants with missing values.

Results

Of the 704 people included in the study, 283 (40.2%) had been exposed to famine *in utero* (table 1). Because it was more difficult to contact men, they were underrepresented in the groups that were exposed to famine *in utero*. Weight at the last prenatal visit was lower in mothers exposed to famine

during late and mid pregnancy than in non-exposed mothers. Weight gain during the last trimester of pregnancy was lower in mothers exposed to famine during late pregnancy (those who gave birth during the famine), and higher in those exposed in mid (those who conceived before the famine and gave birth after the famine) and those exposed in early pregnancy (those who conceived during the famine). Babies exposed to famine during late or mid gestation were lighter and shorter, and had smaller heads than babies who were not exposed. The percentage of babies who were exclusively breastfed in the first weeks after birth tended to be higher in babies exposed during mid or early gestation. Adult body mass index tended to be higher in those exposed to famine in early gestation, especially so in women.

People exposed to famine in late or mid gestation tended to have lower total cholesterol concentrations (table 2) but none of the lipid or lipoprotein concentrations were significantly different from the non-exposed participants (born before or conceived after the famine). People exposed to famine in early gestation, however, had a more atherogenic lipid profile than those who were not exposed. After adjustment for sex, their LDL/HDL cholesterol ratio was significantly higher than in non-exposed participants (table 2). Plasma HDL cholesterol and apolipoprotein A (the structural apolipoprotein linked to HDL cholesterol) concentrations tended to be lower and the total cholesterol, LDL cholesterol and apolipoprotein B (the structural apolipoprotein linked to LDL cholesterol) concentrations tended to be higher than in those who were not exposed. Triglyceride concentrations were not affected.

The slightly higher percentage of exclusive breastfeeding in people exposed to famine in mid and early gestation did not explain the observed effects of prenatal exposure to famine. We found for example after adjustment for the method of infant feeding that the LDL/HDL cholesterol ratio differed by −6.4% (95% confidence interval −15.6% to 2.8%) in those exposed to famine in mid gestation, and by 13.1% (95% confidence interval 2.4% to 23.8%) in those exposed to famine in early gestation. As women exposed to famine in early gestation tended to have a higher body mass index, their more atherogenic lipid profile might also be explained by their higher level of obesity. However, adjustment for body mass index reduced the magnitude of the effect only minimally. When adjusting for BMI, we found that the LDL/HDL cholesterol ratio differed, although not significantly, by 7.6% (95% confidence interval −7.0% to 24.5%) in men and by 12.4%

Table 1. Maternal characteristics, birth outcomes, and adult characteristics according to prenatal exposure to famine. Given as means and standard deviation (SD), except where given as percentages.

	exposure to famine						
	born before	in late gestation	in mid gestation	in early gestation	conceived after	all (SD)	n
General							
number	199	118	101	64	222	704	
proportion of men	50%	47%	42%	44%	52%	48%	704
Maternal characteristics							
age (years)	29	31	29	27	29	29 (6.4)	704
primiparous	35%	25%	30%	36%	35%	33%	704
manual labour	71%	66%	70%	60%	52%	63%	589
weight last prenatal visit (kg)	66.2	63.0	63.8	67.6	68.5	66.2 (8.5)	616
weight gain (kg)	2.92	0.10	4.74	4.64	3.60	3.06 (2.92)	499
breast feeding	76%	68%	84%	85%	61%	72%	604
Birth outcomes							
gestational age (days)	284	283	286	288	286	285 (12)	612
birth weight (g)	3384	3163	3231	3461	3442	3350 (467)	704
birth length (cm)	50.5	49.5	49.8	51.0	50.5	50.3 (2.1)	697
head circumference (cm)	32.9	32.4	32.2	33.0	33.1	32.8 (1.5)	696
ponderal index (kg/m^3)	26.2	26.0	26.0	26.1	26.6	26.3 (2.3)	697
Adult characteristics							
BMI (kg/m^2) *	26.6	26.7	26.5	27.9	27.2	26.9 (1.17)	704
SES (ISEI)	47.0	50.0	48.3	48.2	47.7	48.0 (13.4)	704
current smokers	36%	34%	32%	42%	34%	35%	704
cholesterol lowering medication	2.0%	3.4%	3.0%	3.1%	3.2%	2.8%	704
Lipids and lipoproteins							
total cholesterol (mmol/L)	6.06	5.83	5.80	6.13	6.00	5.97 (1.06)	704
HDL cholesterol * (mmol/L)	1.35	1.32	1.37	1.26	1.32	1.33 (1.33)	704
LDL cholesterol (mmol/L)	4.05	3.87	3.81	4.26	4.02	3.99 (1.01)	704
triglycerides * (g/L)	1.15	1.08	1.10	1.10	1.16	1.13 (1.71)	704
apolipoprotein A1 (g/L)	1.56	1.52	1.56	1.49	1.54	1.54 (0.29)	700
apolipoprotein B (g/L)	1.23	1.20	1.18	1.26	1.23	1.22 (0.29)	700
LDL/HDL *	2.91	2.82	2.69	3.26	2.94	2.90 (1.53)	704

* geometric means and standard deviation

(95% confidence interval −2.2% to 29.3%) in women exposed to famine in early gestation compared to non-exposed men or women, respectively. Further adjustments for adult characteristics (socio-economic status, smoking, and use of lipid lowering medication) did not alter the results. The effects of prenatal exposure to famine on plasma total, LDL or HDL cholesterol, the LDL/HDL cholesterol ratio and apolipoprotein A and B were not different for men and women (p for interaction always larger than 0.2).

Maternal weight at last prenatal visit or maternal weight gain were not associated with any of the plasma lipid or lipoprotein concentrations (p for trend adjusted for sex always larger than 0.5), and adjustment for these maternal characteristics did therefore not alter the results appreciably. We also found that adjusting for other maternal characteristics (maternal age, parity, socio-economic status) as well as gestational age at birth were not associated with any of the plasma lipid or lipoprotein concentrations and adjusting for them hardly affected our results.

Birth weight was positively associated with apolipoprotein A (table 3). Ponderal index was positively associated with HDL cholesterol and apolipoprotein A, but also with total cholesterol. Additional adjustment for adult BMI did not alter these associations. Other measures at birth were not significantly associated with plasma lipid or lipoprotein concentrations. The effects of exposure to famine *in utero* on the plasma lipid profile were hardly changed however by adjustment for any body measure at birth.

Discussion

In this study we were able to assess the effect of maternal malnutrition during specific periods in gestation on lipid profile among 50-year-old people. We found that men and women exposed to famine in early gestation had a more atherogenic plasma lipid profile than those who were not exposed to famine *in utero*. Women in this group also tended to have the highest BMI, but adjustment for body mass altered the size of this effect only slightly. People exposed to famine in late or mid gestation tended to have lower total cholesterol concentrations, but these reductions were not paralleled by differences in other lipid or lipoprotein concentrations. The effect of exposure to famine in early gestation on adult lipid profiles could not be explained by

Table 2. Differences with 95% confidence intervals, adjusted for sex, between participants prenatally exposed to famine (in late, mid, or early gestation) and non-exposed participants (those born before or conceived after the famine).

	exposure to famine		
	in late gestation	in mid gestation	in early gestation
total cholesterol (mmol/L)	-0.20 (-0.41 to 0.02)	-0.23 (-0.46 to 0.00)	0.10 (-0.18 to 0.38)
HDL cholesterol * (mmol/L)	-2.0% (-6.9% to 3.1%)	0.0% (-5.4% to 5.6%)	-7.0% (-13.0% to -0.6%)
LDL cholesterol (mmol/L)	-0.15 (-0.36 to 0.05)	-0.21 (-0.42 to 0.01)	0.24 (-0.02 to 0.51)
triglycerides * (g/L)	-5.5% (-15.1% to 5.3%)	-2.7% (-13.4% to 9.2 %)	-3.7% (-16.2% to 10.7%)
apolipoprotein A (g/L)	-0.04 (-0.09 to 0.01)	-0.02 (-0.08 to 0.04)	-0.07 (-0.14 to -0.01)
apolipoprotein B (g/L)	-0.03 (-0.09 to 0.03)	-0.05 (-0.11 to 0.02)	0.03 (-0.04 to 0.11)
LDL/HDL *	-2.5% (-10.1% to 5.6%)	-5.3% (-13.1% to 3.3%)	13.9% (2.6% to 26.3%)

* relative differences, expressed as percentages of the means in non-exposed people.

Table 3. Means of plasma lipid and lipoprotein concentrations by size at birth.

Birth weight (g)	<2750	-3250	-3750	>3750	p value adjusted for sex	p value adjusted for sex and BMI
number	62	232	266	144		
total cholesterol (mmol/L)	5.88	5.92	6.06	5.94	0.98	0.91
HDL cholesterol * (mmol/L)	1.25	1.32	1.36	1.33	0.25	0.09
LDL cholesterol (mmol/L)	3.97	3.93	4.07	3.97	0.88	0.77
triglycerides * (g/L)	1.20	1.16	1.12	1.07	0.13	0.04
apolipoprotein A (g/L)	1.47	1.54	1.55	1.56	0.04	0.01
apolipoprotein B (g/L)	1.19	1.22	1.23	1.22	0.97	0.77
LDL/HDL *	3.05	2.88	2.90	2.87	0.34	0.17
Head circumference (cm)	**<32**	**-33**	**-34**	**>34**	**p value adjusted for sex**	**p value adjusted for sex and BMI**
number	186	228	145	137		
total cholesterol (mmol/L)	5.96	5.96	5.97	6.00	0.73	0.87
HDL cholesterol* (mmol/L)	1.30	1.33	1.30	1.39	0.07	0.01
LDL cholesterol (mmol/L)	4.00	4.01	3.93	3.99	0.93	0.78
triglycerides * (g/L)	1.15	1.03	1.24	1.03	0.28	0.07
apolipoprotein A (g/L)	1.51	1.55	1.53	1.58	0.03	0.01
apolipoprotein B (g/L)	1.23	1.21	1.23	1.21	0.59	0.31
LDL/HDL *	2.98	2.91	2.93	2.76	0.18	0.05
Ponderal index (kg/m^3)	**<25**	**-26**	**-27**	**>27**	**p value adjusted for sex**	**p value adjusted for sex and BMI**
number	200	121	128	248		
total cholesterol (mmol/L)	5.83	5.94	6.05	6.07	0.02	0.01
HDL cholesterol * (mmol/L)	1.30	1.31	1.32	1.36	0.03	0.03
LDL cholesterol (mmol/L)	3.90	3.96	4.06	4.05	0.09	0.08
triglycerides * (g/L)	1.11	1.16	1.16	1.12	0.64	0.76
apolipoprotein A (g/L)	1.52	1.53	1.54	1.56	0.04	0.04
apolipoprotein B (g/L)	1.19	1.22	1.23	1.24	0.16	0.12
LDL/HDL *	2.89	2.92	2.98	2.87	0.65	0.78

* geometric mean

differences in maternal weight or weight gain, body size at birth, gestational age at birth, or method of infant feeding among the exposure groups.

The Dutch famine can be considered as a unique 'experiment of history' to study the effects of maternal malnutrition during different stages of gestation in humans. The famine, however, had a profound effect on the birth rate and early mortality. The number of births corresponding to conceptions at the peak of the famine – and consequently also to exposure during early gestation – was about 50% lower than its pre-famine level. [15] Perinatal mortality as well as mortality in the first year after birth were highest in those who were born during the famine period. [15] We can not exclude potential selection effects of increased abortion rates in babies who were conceived during the famine, but we consider it unlikely that the differences in birth rate or early mortality can fully explain our results. First, maternal characteristics that might relate to the biological or behavioural determinants of fertility (maternal age, parity, maternal weight, and socio-economic status) were not associated with plasma lipid concentrations in the adult offspring. Second, early mortality rates were highest in those born during the famine [15], whereas we found strongest effects on plasma lipid concentrations among people conceived during the famine and born after it (those exposed in early gestation).

A study in people who were born in or around Leningrad at the time of the siege (1941 – 1944) showed that lipid and lipoprotein concentrations were not affected by prenatal undernutrition. [10] The essentially different circumstances during the famines however do not allow a direct comparison between our findings and the Leningrad study. Firstly, the Dutch famine did not only have a shorter duration but also it was preceded and followed by adequate nutrition, whereas people in Leningrad were also undernourished before the siege. Secondly, the rations for infants under 1 year of age were found to be adequate throughout the famine [14], which indicates that babies born before or during the famine were not exposed in their first year of life. Finally, the Dutch people grew up in a period of increasing affluence whereas the Russian standard of living remained relatively poor. [20]

Our finding that people exposed to famine in early gestation had a more atherogenic lipid profile seems to be in agreement with results from animal experiments. Observations in animals show that maternal undernutrition just before and throughout pregnancy permanently alters cholesterol metabolism,

although the plasma total cholesterol concentrations were found to be increased in guinea pigs [8] and decreased in rats. [9] This suggests that the effects of maternal diet during gestation are complex and may be different from one species to another. [21] It was also found in rats that the composition of the maternal diet during pregnancy influences the activity of hepatic enzymes crucially involved in cholesterol metabolism in the offspring. [6,22] These results in animals suggest that the transition from nutritional deprivation in early gestation to nutritional adequacy later on has led to metabolic conflicts resulting in an altered cholesterol metabolism in people conceived during the Dutch famine.

Our study shows for the first time in humans that maternal nutrition during early gestation can permanently influence the lipid profile in later life. Exposure to famine in early gestation did not affect body size at birth but led to a higher LDL/HDL cholesterol ratio in adult life. It confirms findings from other studies in humans that maternal nutritional intake during pregnancy can have permanent effects on health in later life without affecting size at birth.[11,23] It is therefore difficult to predict the long-term effects of maternal starvation during gestation based on its effects on size at birth. Experiments in sheep have furthermore shown that different patterns of fetal growth can result in the same size at birth.[24] This might explain that several studies in humans have reported that small size at birth is linked with a more atherogenic lipid profile in adult life [1-4], whereas we found that a high ponderal index at birth was associated with increased plasma total cholesterol concentrations in adult life.

Our findings may have important implications for public health. The nutritional experience of babies who were exposed to famine in early gestation may resemble that of babies in developing countries whose mothers are undernourished in early pregnancy and receive supplementation in the second half of pregnancy, but also of babies in developed countries whose mothers suffer from hyperemesis gravidarum or keep a strict diet just before conception or in early pregnancy. Our findings suggest furthermore that the long-term impact that these imbalances in women's nutritional intake during pregnancy have on the health of their children may be underestimated by the known associations between small size at birth and adult disease.

We have previously shown in the same group of people that those exposed to famine in late or mid gestation have a reduced glucose tolerance [11], and that women exposed to famine in early gestation are more obese. [12] We

now found that cholesterol metabolism was most affected in those exposed to famine in early gestation, and that this link appeared to be largely independent from the effect of famine on obesity. This suggests that there are distinct sensitive periods during gestation for the programming of glucose and cholesterol metabolism. Animal experiments and prospective studies of mothers and their offspring are needed to unravel the mechanisms involved in nutritional programming.

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