Plasma lipid profiles in adults after prenatal exposure to the Dutch famine[1–3]

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ABSTRACT

Background: Small body size at birth has been reported to be associated with an atherogenic lipid profile in humans, and animal experiments have shown that undernutrition during pregnancy permanently alters cholesterol metabolism in the offspring. There is no direct evidence in humans that maternal malnutrition during pregnancy affects the lipid profiles of the offspring.

Objectives: We assessed the effects of maternal malnutrition during specific periods of gestation on plasma lipid profiles in persons aged ≈50 y.

Design: This was a follow-up study of men and women born at term as singletons in a university hospital in Amsterdam between 1 November 1943 and 28 February 1947 around the time of a severe famine.

Results: Persons exposed to famine in early gestation had a more atherogenic lipid profile than did those who were not exposed to famine in utero. Their LDL-HDL cholesterol ratios were significantly higher (by 13.9%; 95%CI: 2.6–26.4%). Additionally, 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 higher, although these differences were not statistically significant. The effect of famine was independent of size at birth and adult obesity.

Conclusions: 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. *Am J Clin Nutr* 2000;72:1101–6.

KEY WORDS Cholesterol, lipid profile, famine, undernutrition, fetal growth, fetal origins, the Netherlands

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 low HDL-cholesterol or high plasma triacylglycerol concentrations (1–3); others found an association between short body length at birth or reduced abdominal circumference and elevated total cholesterol, LDL-cholesterol, and apolipoprotein B concentrations (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 (6–8; JA Owens, A Sohlstrom, A Katsman, et al, unpublished observations, 1991). So far, the only study in humans on the effect of maternal nutrition during gestation on later cholesterol concentrations was performed in persons prenatally exposed to famine at the time of the 900-d Leningrad siege (1941–1944), and this study showed no significant effects (9).

We present the effects of prenatal undernutrition during specific periods in pregnancy on lipid profiles in adults born around the time of famine in the Netherlands (1944–1945). The Dutch famine was a 5-mo period of extreme malnutrition in the western part of the Netherlands that was clearly delineated in time. We showed previously that glucose tolerance in this group decreased after prenatal exposure to famine, especially in late or mid gestation (10), and that women exposed to famine in early gestation had a higher body mass index (BMI; in kg/m^2) than did those not exposed to famine (11). We assessed the lipid profiles of adults exposed to the famine in utero during late, mid, or early gestation (exposed subjects); of those born in the year before the famine began; and of those conceived in the year after the famine (nonexposed subjects).

SUBJECTS AND METHODS

Selection procedures

All 5425 babies born in the Wilhelmina Gasthuis in Amsterdam between 1 November 1 1943 and 28 February 1947 were

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possible candidates for study. Most patients in this hospital were of lower-to-middle social classes, but little is known about the actual referral pattern during the period of our study. First, we excluded 349 babies who were stillborn or part of a multiple pregnancy. Second, we retrieved the medical records of all 1380 babies born between 1 November 1944 and 28 February 1946 who were potentially exposed to famine during gestation. Third, we retrieved the records of a random sample of 650 of the 1305 babies born in the year before that period (born between 1 November 1943 and 31 October 1944) and a random sample of 650 of the 2391 babies conceived in the year after that period (born between 1 March 1946 and 28 February 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 <259 d, 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 live-born singletons were included in the study.

The Bevolkingsregister of Amsterdam (population registry) traced 2155 (89%) of the 2414 infants included. 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 infants, we asked 912 persons who lived in or close to Amsterdam to participate: 741 attended the clinic, and plasma lipid and lipoprotein concentrations were measured in fasting blood samples from 704 of them. Birth weights in this group of 704 subjects (mean birth weight: 3348 g) were not significantly different from those of the 1710 infants 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 aged >21 y. 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 (12). In addition to the official rations, food came from other sources (eg, church organizations, central kitchens, and the black market), and the amount of food actually available to individuals was roughly twice as much as the official rations. Pregnant and lactating women were entitled to an extra 600 kcal (2520 kJ)/d, but at the peak of the famine, this additional energy could not always be provided. It is also likely that most women shared these extra supplies with their families. Therefore, the rations should be considered only a relative measure of nutritional intake for the population as a whole.

The official rations provided ≈1800 kcal (7560 kJ)/d in December 1943. This figure gradually decreased to ≈1400 kcal (5880 kJ)/d by October 1944, and to <1000 kcal (4200 kJ) by 26 November 1944. The energy content of the rations varied between 400 kcal (1680 kJ)/d and 800 kcal (3360 kJ)/d from December 1944 to April 1945 and rose to >1000 kcal (4200 kJ)/d by 12 May 1945, 1 wk after liberation by the Allied forces. In June 1945, rations provided >2000 kcal (8400 kJ)/d. Children younger than 1 y were relatively protected during the famine because their official daily rations always provided >1000 kcal (4200 kJ)/d (13).

We considered fetuses to have been exposed to famine if the average energy content of the daily rations for persons older than 21 y during any 13-wk period of gestation was <1000 kcal (4200 kJ)/d. Therefore, babies born between 7 January 1945 and 8 December 1945 were exposed in utero. We used 3 periods of 16 wk to differentiate between persons who were exposed in late gestation (born between 7 January 1945 and 28 April 1945), in mid gestation (born between 29 April 1945 and 18 August 1945), and in early gestation (born between 19 August 1945 and 8 December 1945).

Procedures

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 10). We also recorded the method of infant feeding at discharge, which took place ≈10 d after delivery, and classified it as exclusive breastfeeding, partial bottle-feeding, or exclusive bottle-feeding (14). Maternal weight gain in the third trimester was calculated as 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, multiplied by the duration of the trimester (13 wk). The socioeconomic status at birth was dichotomized into manual and nonmanual labor according to the occupation of the head of the family (15).

Total plasma cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerol, apolipoprotein A, and apolipoprotein B concentrations were measured by standard enzymatic methods (16, 17). We measured height with a fixed stadiometer and weight with a Seca scale (Hamburg, Germany). All subjects were interviewed about their medical history, lifestyle, and use of medication. Current socioeconomic status was coded by using the International Socio-economic Index of occupational status according to the occupation of the participants or their partners, whichever was highest (18). 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 triacylglycerol, and BMI had a skewed distribution and were log transformed before analysis. The results for these variables are given as geometric means ± SDs and the differences are given as relative differences expressed as percentages of the means of nonexposed participants. First, we used multiple linear regression analysis to adjust for sex. Second, we also adjusted for adult BMI, then for adult (current socioeconomic status, smoking status, and use of lipid-lowering medication) and maternal (age, parity, weight at last prenatal visit, and socioeconomic status at birth) characteristics. We computed 95% CIs. When we compared separately the 3 prenatally exposed groups with the nonexposed group, the *P* values were Bonferroni adjusted for multiple comparisons.

For a relatively large number of participants, information on maternal weight at the end of pregnancy, weight gain, or socioeconomic 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 nonmissing 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, socioeconomic status at birth, smoking status, and use of lipid-lowering medication), we added an extra category for those participants with missing values. SPSS (version 9.0.0; SPSS Inc, Chicago) was used for the analyses.

TABLE 1
Maternal characteristics, birth outcomes, and adult characteristics according to time of prenatal exposure to famine

	Time of exposure to famine					
	Born before famine (n = 199)	Late gestation (n = 118)	Mid gestation (n = 101)	Early gestation (n = 64)	Conceived after famine (n = 222)	All
Proportion of men (%)	50	47	42	44	52	48 [704]
Maternal characteristics						
Age (y)	29	31	29	27	29	29 ± 6.4[1] [704]
Primiparous (%)	35	25	30	36	35	33 [704]
Manual labor (%)	71	66	70	60	52	63 [589]
Weight at last antenatal visit (kg)	66.2	63.0[2]	63.8[2]	67.6	68.5	66.2 ± 8.5[1] [616]
Weight gain (kg)	2.92	0.10[2]	4.74[2]	4.64[2]	3.60	3.06 ± 2.92[1] [499]
Breast-feeding	76	68	84	85	61	72 [604]
Birth outcomes						
Gestational age (d)	284	283	286	288	286	285 ± 12[1] [612]
Birth weight (g)	3384	3163[2]	3231[2]	3461	3442	3350 ± 467[1] [704]
Birth length (cm)	50.5	49.5[2]	49.8[2]	51.0	50.5	50.3 ± 2.1[1] [697]
Head circumference (cm)	32.9	32.4[2]	32.2[2]	33.0	33.1	32.8 ± 1.5[1] [696]
Ponderal index (kg/m^3)	26.2	26.0	26.0	26.1	26.6	26.3 ± 2.3[1] [697]
Adult characteristics						
BMI (kg/m^2)	26.6	26.7	26.5	27.9	27.2	26.9 ± 1.17[3] [704]
SES (ISEI)[4]	47.0	50.0	48.3	48.2	47.7	48.0 ± 13.4[1] [704]
Current smokers (%)	36	34	32	42	34	35 [704]
Antihypercholesterolemic 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[1] [704]
HDL cholesterol (mmol/L)	1.35	1.32	1.37	1.26	1.32	1.33 ± 1.33[3] [704]
LDL cholesterol (mmol/L)	4.05	3.87	3.81	4.26	4.02	3.99 ± 1.01[1] [704]
Triacylglycerol (g/L)	1.15	1.08	1.10	1.10	1.16	1.13 ± 1.71[3] [704]
Apolipoprotein A-I (g/L)	1.56	1.52	1.56	1.49	1.54	1.54 ± 0.29[1] [700]
Apolipoprotein B (g/L)	1.23	1.20	1.18	1.26	1.23	1.22 ± 0.29[1] [700]
LDL:HDL cholesterol	2.91	2.82	2.69	3.26	2.94	2.90 ± 1.53[3] [704]

[1] $\bar{x}$ ± SD.
[2] Significantly different from participants born before and conceived after the famine, $P < 0.05$ (Bonferroni adjusted).
[3] Geometric $\bar{x}$ ± SD.
[4] Socioeconomic status score according to the International Socio-economic Index (18).

RESULTS

Of the 704 participants 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 nonexposed 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 pregnancy (those who conceived before the famine and gave birth after the famine) and 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 did babies who were not exposed. The percentage of babies who were exclusively breast-fed in the first weeks after birth tended to be higher for those babies exposed during mid or early gestation. Adult BMI tended to be higher in those exposed to famine in early gestation, especially in women.

Participants exposed to famine in late or mid gestation tended to have lower total cholesterol concentrations but none of the lipid or lipoprotein concentrations were significantly different from those of the nonexposed participants (born before or conceived after the famine) (**Table 2**). Participants exposed to famine in early gestation, however, had a more atherogenic lipid profile than did those who were not exposed. After adjustment for sex, the subjects' LDL-HDL cholesterol ratios were significantly higher than those of nonexposed participants. Plasma HDL-cholesterol and apolipoprotein A (the structural apolipoprotein linked to HDL cholesterol) concentrations tended to be lower and total cholesterol, LDL-cholesterol, and apolipoprotein B (the structural apolipoprotein linked to LDL cholesterol) concentrations tended to be higher than in nonexposed participants. Triacylglycerol concentrations were not affected significantly.

The slightly higher percentage of exclusive breast-feeding in persons 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 was 6.4% (15.6–2.8%) lower in those exposed to famine in mid gestation and 13.1% (2.4–23.8%; P = 0.017) lower in those exposed to famine in early gestation than in those not exposed. Because women exposed to famine in early gestation tended to have a higher BMI than did those exposed to famine in mid or late gestation, their more atherogenic lipid profile might also be explained by their higher incidence of obesity. However, adjustment for BMI reduced the magnitude of the effect only minimally. After adjusting for BMI, we found that the LDL-HDL

TABLE 2
Differences (and 95% CIs), adjusted for sex, between participants prenatally exposed to famine (in late, mid, or early gestation) and nonexposed participants (those born before or conceived after the famine)

	Time of exposure to famine		
	Late gestation	Mid gestation	Early gestation
Total cholesterol (mmol/L)	−0.20 (−0.41, 0.02)	−0.23 (−0.46, 0.00)	0.10 (−0.18, 0.38)
HDL cholesterol (%)	−2.0 (−6.9, 3.1)	0.0 (−5.4, 5.6)	−7.0 (−13.0, −0.6)
LDL cholesterol (mmol/L)	−0.15 (−0.36, 0.05)	−0.21 (−0.42, 0.01)	0.24 (−0.02, 0.51)
Triacylglycerol (%)[1]	−5.5 (−15.1, 5.3)	−2.7 (−13.4, 9.2)	−3.7 (−16.2, 10.7)
Apolipoprotein A (g/L)	−0.04 (−0.09, 0.01)	−0.02 (−0.08, 0.04)	−0.07 (−0.14, −0.01)
Apolipoprotein B (g/L)	−0.03 (−0.09, 0.03)	−0.05 (−0.11, 0.02)	0.03 (−0.04, 0.11)
LDL:HDL cholesterol (%)[1]	−2.5 (−10.1, 5.6)	−5.3 (−13.1, 3.3)	13.9 (2.6, 26.3)[2]

[1] Log transformed; expressed as a percentage of means for participants not exposed to famine.
[2] Significantly different from participants not exposed to famine, $P < 0.05$ (Bonferroni adjusted).

cholesterol ratio differed, although not significantly, by 7.6% (7.0–24.5%) in men and by 12.4% (2.2–29.3%) in women exposed to famine in early gestation from that in nonexposed men or women, respectively. Further adjustment for adult characteristics (socioeconomic status, smoking status, and use of lipid-lowering medication) did not alter the results. The effects of prenatal exposure to famine on plasma total, LDL-, and HDL-cholesterol concentrations; the LDL-HDL cholesterol ratio; and apolipoprotein A and B concentrations were not significantly different for men and women.

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

Birth weight was positively associated with apolipoprotein A concentration (**Table 3**). The ponderal index (in kg/m^3) was positively associated with HDL cholesterol, apolipoprotein A, and 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 affected, however, after adjustment for any body measure at birth.

DISCUSSION

In this study we assessed the effect of maternal malnutrition during specific periods in gestation on the lipid profiles of 50-y-old persons. We found that men and women exposed to famine in early gestation had a more atherogenic plasma lipid profile than did those who were not exposed to famine in utero. Women in this group also tended to have the highest BMI, but adjustment for BMI altered the size of this effect only slightly. Persons exposed to famine in late or mid gestation tended to have lower total cholesterol concentrations, but this difference was 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 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 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 ≈50% lower than the number prefamine (15). Perinatal mortality and mortality in the first year after birth were highest in those who were born during the famine period (15). We cannot 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 fully explained our results. First, maternal characteristics that might relate to the biological or behavioral determinants of fertility (maternal age, parity, maternal weight, and socioeconomic 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 the greatest effects on plasma lipid concentrations among those who were conceived during the famine and born after it (those exposed in early gestation).

A study in persons 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 (9). The essentially different circumstances during the famines, however, did not allow a direct comparison between our findings and those of the Leningrad study. First, the Dutch famine was not only shorter but it was also preceded and followed by adequate nutrition; persons in Leningrad were also undernourished before the siege. Second, the rations for infants aged <1 y were found to be adequate throughout the famine (13), 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 (19).

Our finding that persons exposed to famine in early gestation had a more atherogenic lipid profile seems to agree with the results from animal experiments. Observations in animals show that maternal undernutrition just before and throughout pregnancy permanently alters cholesterol metabolism, although plasma total cholesterol concentrations increased in guinea pigs (JA Owens, A Sohlstrom, A Katsman, et al, unpublished observations, 1991) and decreased in rats (8). This suggests that the effects of maternal diet during gestation are complex and may be different between species (20). It was also shown in rats that the

TABLE 3

Means of plasma lipid and lipoprotein concentrations by size at birth[1]

	Cholesterol				Apolipoprotein		
	Total	HDL[2]	LDL	Triacylglycerol[2]	A	B	LDL:HDL cholesterol[2]
		mmol/L		*mmol/L*		*g/L*	
Birth weight (g)							
<2750 g (*n* = 62)	5.88	1.25	3.97	1.20	1.47	1.19	3.05
2750–3250 (*n* = 232)	5.92	1.32	3.93	1.16	1.54	1.22	2.88
3251–3750 (*n* = 266)	6.06	1.36	4.07	1.12	1.55	1.23	2.90
>3750 (*n* = 144)	5.94	1.33	3.97	1.07	1.56	1.22	2.87
P (adjusted for sex)	0.98	0.25	0.88	0.13	0.04	0.97	0.34
P for trend (adjusted for sex and BMI)	0.91	0.09	0.77	0.04	0.01	0.77	0.17
Head circumference (cm)							
<32 (*n* = 186)	5.96	1.30	4.00	1.15	1.51	1.23	2.98
32–33 (*n* = 228)	5.96	1.33	4.01	1.03	1.55	1.21	2.91
33–34 (*n* = 145)	5.97	1.30	3.93	1.24	1.53	1.23	2.93
>34 (*n* = 137)	6.00	1.39	3.99	1.03	1.58	1.21	2.76
P (adjusted for sex)	0.73	0.07	0.93	0.28	0.03	0.59	0.18
P for trend (adjusted for sex and BMI)	0.87	0.01	0.78	0.07	0.01	0.31	0.05
Ponderal index (kg/m^3)							
<25 (*n* = 200)	5.83	1.30	3.90	1.11	1.52	1.19	2.89
25–26 (*n* = 121)	5.94	1.31	3.96	1.16	1.53	1.22	2.92
26–27 (*n* = 128)	6.05	1.32	4.06	1.16	1.54	1.23	2.98
>27 (*n* = 248)	6.07	1.36	4.05	1.12	1.56	1.24	2.87
P (adjusted for sex)	0.02	0.03	0.09	0.64	0.04	0.16	0.65
P for trend (adjusted for sex and BMI)	0.01	0.03	0.08	0.76	0.04	0.12	0.78

[1] All values, except where indicated, are means.

[2] Geometric means.

composition of the maternal diet during pregnancy influences the activity of hepatic enzymes crucially involved in cholesterol metabolism in the offspring (6, 21). 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 persons conceived during the Dutch famine.

Our study showed 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 confirmed 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 (10, 22). It is therefore difficult to predict the long-term effects of maternal starvation during gestation on the basis of its effects on size at birth. Furthermore, experiments in sheep have shown that different patterns of fetal growth can result in the same size at birth (23). This might explain how 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 suffered from hyperemesis gravidarum or followed a strict diet just before conception or early in pregnancy. Furthermore, our findings suggest that the long-term effect that these imbalances in women's nutritional intakes 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 showed previously in the same group of persons that those exposed to famine in late or mid gestation have a lower glucose tolerance than do those not exposed to famine (10), and that women exposed to famine in early gestation are more obese (11). We found that cholesterol metabolism was most affected in those exposed to famine in early gestation, and was largely independent of the effect of famine on obesity. This finding 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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