The metabolic syndrome in adults prenatally exposed to the Dutch famine[1–3]

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ABSTRACT

Background: Epidemiologic studies have shown that the metabolic syndrome may originate in utero.

Objective: We aimed to determine whether exposure to prenatal famine is associated with a greater prevalence of the metabolic syndrome.

Design: We assessed the prevalence of the metabolic syndrome according to the National Cholesterol Education Program definition in 783 members of the Dutch Famine Birth Cohort. Participants were born as term singletons around the time of the 1944–1945 Dutch famine.

Results: Exposure to famine during gestation was not significantly associated with the metabolic syndrome (odds ratio: 1.2; 95% CI: 0.9, 1.7). Birth weight also was not significantly associated with the metabolic syndrome (odds ratio: 1.3/1-kg decrease in birth weight; 95% CI: 0.9, 1.8/1-kg decrease in birth weight). Exposure to famine during gestation was associated with significantly higher triacylglycerol concentrations (0.1 g/L; 0.0, 0.2 g/L). Men exposed to famine in early gestation had significantly lower HDL-cholesterol concentrations (−0.08 mmol/L; −0.14, 0.00 mmol/L) than did unexposed men.

Conclusions: Prenatal exposure to famine or reduced birth weight is not associated with a significantly greater prevalence of the metabolic syndrome. Our findings suggest that, although elements of the metabolic syndrome may be programmed by fetal undernutrition, the origin of the syndrome as a whole is not likely to be found in poor nutrition during gestation. *Am J Clin Nutr* 2007;86:1219–24.

KEY WORDS Metabolic syndrome, fetal origins hypothesis, prenatal famine, birth weight

INTRODUCTION

The metabolic syndrome is known by several names: syndrome X, the deadly quartet, and the insulin resistance syndrome (1–3). It is a constellation of interrelated metabolic risk factors that predisposes a person to develop type 2 diabetes and cardiovascular disease (4, 5). Clinical manifestations of the syndrome include glucose intolerance, insulin resistance, central obesity, dyslipidemia, and hypertension. Several different definitions are currently used to diagnose the metabolic syndrome (6–9).

Several studies have shown that small size at birth is associated with a greater risk of the metabolic syndrome. It has even been suggested that the syndrome should be renamed the small baby syndrome (10–17). This association is hypothesized to result from permanent structural and physiologic adaptations made by the fetus in response to a poor environment in utero (18). Results of the studies of the association between low birth weight and the metabolic syndrome should, however, be interpreted with caution. Half of these studies found associations between low birth weight and the metabolic syndrome only if low birth weight was combined with high adult BMI (14), catch-up growth (15, 16), or lifestyle factors such as smoking and low physical activity (17). In addition, the use of birth weight as a marker of the fetal environment has limitations, because birth weight is the result of a wide range of maternal, placental, and fetal factors.

The Dutch famine birth cohort is a unique group within which to evaluate a possible association between poor prenatal nutrition and the development of the metabolic syndrome in later life. Cohort members were born around the time of the Dutch famine that occurred near the end of World War II—ie, between November 1944 and May 1945. The mean caloric rations during the famine were as low as 400–800 cal/d. Previous findings in this cohort study showed that exposure to famine during any stage of gestation was associated with impaired glucose tolerance (19, 20), exposure to famine during midgestation was related to a greater prevalence of microalbuminuria (21), and exposure to famine during early gestation was related to dyslipidemia (22), obesity in women (23), altered blood clotting (24), and a greater prevalence of coronary heart disease (25, 26). The effects were independent of size at birth and of adult risk factors. On the basis of all of these associations, one could expect that there is an association between exposure to the Dutch famine in utero and the prevalence of the metabolic syndrome at a mean age of 58 y. In the present study, we aimed to test this possible association.

SUBJECTS AND METHODS

Population

All participants were members of the Dutch Famine Birth Cohort. This cohort consists of 2414 men and women who were

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born between 1 November 1943 and 28 February 1947 as term singletons in the Wilhelmina Gasthuis, a hospital in Amsterdam, Netherlands. The selection procedure (19) and subsequent loss to follow-up (27) have been described in detail elsewhere. Cohort members who were still living in the Netherlands and whose address was known to the investigators were invited to participate in the study. Of the group of 1423 eligible people, 810 agreed to participate.

All participants gave written informed consent. The study was approved by the local Medical Ethics Committee and carried out in accordance with the Declaration of Helsinki.

Exposure to famine

The official daily food rations for the general population aged ≥21 y were used to define exposure to famine (28). A person was considered to be prenatally exposed to famine if the average daily food ration of the mother during any 13-wk period of gestation contained <1000 calories. On the basis of this definition, infants born between 7 January 1945 and 8 December 1945 had been exposed in utero. We delineated periods of 16 wk each within those 11 mo to differentiate between those infants exposed in late gestation (born between 7 January and 28 April 1945), those exposed in midgestation (born between 29 April and 18 August 1945), and those exposed in early gestation (born between 19 August and 8 December 1945). Persons born before 7 January 1945 and conceived after 8 December 1945 were considered not to have been exposed to famine in utero, and they acted as control subjects.

Study variables

Information about the mother, the course of the pregnancy, and infant's size at birth was extracted from medical birth records (19). We measured height by using a fixed or portable stadiometer and measured weight with SECA (Hamburg, Germany) and Tefal portable (Groupe SEB Nederland BV, Veenendaal, Netherlands) scales. We measured waist circumference with a flexible tape measure placed midway between the costal margin and the iliac crest. Blood pressure was measured 2 times on 2 occasions (morning and afternoon) by using an automated device (Omron 705 CP/IT; Omron Healthcare UK, Milton Keynes, United Kingdom) and appropriate cuff sizes. Mean systolic and diastolic blood pressures were calculated by using all available measurements.

Blood was drawn for analysis of plasma glucose concentrations, which were measured by using a standardized enzymatic photometric assay on a Modular P analyzer (Roche, Basel, Switzerland), and HDL-cholesterol and triacylglycerol concentrations, which were measured by using an enzymatic colorimetric reagent on a P-800 Modular analyzer (both: Roche). Information on socioeconomic status, medical history, lifestyle (eg, smoking status and sports participation), and use of medication was obtained in a standardized interview. We defined current socioeconomic status according to the International Socioeconomic Index of Occupational Status (29), which is based on the participant's or the partner's occupation, whichever status is higher. Values in this index range from 16 (low status) to 87.

Definition of the metabolic syndrome

We used the widely applied National Cholesterol Education Program (NCEP) definition of the metabolic syndrome (8), which is a clustering of ≥3 of the following characteristics: waist circumference ≥ 102 cm in men and ≥ 88 cm in women, triacylglycerol ≥ 1.7 mmol/L, blood pressure ≥ 130/85 mm Hg or the use of antihypertensive medication, HDL cholesterol < 1.03 mmol/L in men and < 1.3 mmol/L in women, and fasting glucose ≥ 6.1 mmol/L or the use of antidiabetic medication. In addition, we applied the recently developed definition of the International Diabetes Federation (IDF) (9), which has lower thresholds for 2 components of the syndrome: waist circumference ≥ 94 cm in men and ≥ 80 cm in women and fasting glucose ≥ 5.6 mmol/L.

Statistical analysis

Logarithmic transformations were applied to variables with skewed distributions. We used linear and logistic regression analysis to compare maternal, birth, and adult characteristics between famine-exposed and -unexposed groups. In all analyses, we first compared participants who were prenatally exposed to famine with those who were not so exposed, and then we compared those exposed in late, mid-, and early gestation with those not exposed in gestation. We also used linear and logistic regression analyses to explore associations between birth weight and adult characteristics. For these analyses, we divided the study group into 3 birth-weight groups by using the cutoffs of <3000, 3000–3500, and >3500 g. We did not use the conventional cutoff of 2500 g for the low-birth-weight group, because that would have resulted in a group containing only 18 participants. We also studied birth weight as a continuous variable. We adjusted for sex and BMI in all analyses except those of the prevalence of components of the metabolic syndrome and of the syndrome itself, in which we adjusted for sex only.

Additional adjustment was done for maternal and birth characteristics, smoking status, participation in sports, and current socioeconomic status. We considered differences to be statistically significant if P values were <0.05. All data were analyzed with SPSS for WINDOWS software (version 12; SPSS Inc, Chicago, IL).

RESULTS

Population characteristics

A total of 810 men and women participated, of whom 27 had to be excluded from the analysis because of missing data due to failure of venipuncture or nonadherence to fasting instructions. Of the group of 783 participants for whom we had complete data for all components of the syndrome, 359 (46%) were men, and 424 (54%) were women; they had a mean ± SD age of 58 ± 1 y. A total of 452 participants (58%) were not exposed to famine during gestation, and 331 participants (42%) were exposed during gestation.

Infants exposed to famine during late gestation and midgestation had lower birth weights than did infants not exposed, and their mothers weighed less at the end of pregnancy than did the mothers of unexposed infants (**Table 1**). At age 58 y, there were no significant differences between famine-exposed and -unexposed subjects in smoking pattern, sports participation and socioeconomic status.

In **Table 2**, the various components included in the metabolic syndrome at age 58 y are shown by exposure group. Men who

TABLE 1
Maternal, birth, and adult characteristics according to timing of prenatal exposure to the Dutch famine[1]

	Exposure to famine						
	Born before the famine (n = 238)	In late gestation (n = 141)	In midgestation (n = 116)	In early gestation (n = 74)	Conceived after the famine (n = 214)	All (n = 783)	P
Age (y)	59.2 ± 0.7[2]	58.5 ± 0.5	58.2 ± 0.6	58.0 ± 0.5	57.4 ± 0.6	58.3 ± 1.0	0.36
Men (%)	48	43	39	43	51	46	0.05
Maternal and birth characteristics							
Weight gain in 3rd trimester (kg)[3]	2.8 ± 2.3	0.0 ± 2.0[4]	4.5 ± 3.6[4]	5.0 ± 2.0[4]	3.5 ± 2.7	2.9 ± 3.0	0.03[5]
Weight at last antenatal visit (kg)[6]	66.6 ± 8.4	62.5 ± 7.2[4]	63.7 ± 8.1[4]	69.8 ± 9.2	69.3 ± 824	66.5 ± 8.7	0.01[5]
Gestational age (d)[7]	284 ± 10	283 ± 10	286 ± 12	289 ± 11	285 ± 12	285 ± 11	0.49[5]
Birth weight (g)	3392 ± 462	3195 ± 472[4]	3201 ± 424[4]	3503 ± 434	3467 ± 471	3359 ± 472	0.01[5]
Adult characteristics							
Current smoker (%)[8]	22	27	26	31	23	25	0.11
Persons who practice sports (%)[8]	55	61	58	61	51	56	0.06
Current socioeconomic status[9,10]	48 ± 14	52 ± 15	51 ± 14	47 ± 13	50 ± 14	50 ± 14	0.22
BMI (kg/m^2)[11]	28.0 ± 1.2	28.0 ± 1.2	27.8 ± 1.2	27.5 ± 1.2	28.7 ± 1.2	28.1 ± 1.2	0.11

[1] n = 783 unless indicated otherwise.
[2] $\bar{x}$ ± SD (all such values).
[3] n = 549.
[4] Significantly different from participants unexposed to famine during gestation $P < 0.05$ (linear regression analysis, adjusted for sex).
[5] P values for differences between the groups exposed and unexposed to famine during gestation, based on linear regression analysis, were adjusted for sex.
[6] n = 691.
[7] n = 671.
[8] n = 781.
[9] n = 773.
[10] According to the International Socioeconomic Index of Occupational Status (29).
[11] Geometric $\bar{x}$ ± SD (all values).

were exposed to famine in utero had HDL-cholesterol concentrations 0.08 mmol/L (95% CI: 0.14, 0.00 mmol/L) lower than those of unexposed men, and the difference was greater (−0.13 mmol/L; −0.24, −0.01 mmol/L) when the exposure occurred in early gestation. In women, there was a trend toward significantly lower HDL-cholesterol concentrations in those exposed to famine in utero (−0.07 mmol/L; −0.14, −0.00 mmol/L) than in those so unexposed. Exposure to famine in utero was also associated with higher concentrations of triacylglycerol (0.1 g/L; 0.0, 0.2 g/L).

TABLE 2
Components of the metabolic syndrome according to timing of prenatal exposure to the Dutch famine[1]

	Exposure to famine						
	Born before the famine (n = 238)	In late gestation (n = 141)	In mid-gestation (n = 116)	In early gestation (n = 74)	Conceived after the famine (n = 214)	All (n = 783)	P
Waist circumference (cm)							
Men	101.5 ± 12.7[2]	100.9 ± 9.3	99.0 ± 11.2	102.5 ± 12.9	101.0 ± 11.0	101.0 ± 11.5	0.64
Women	92.6 ± 14.2	92.6 ± 13.9	92.0 ± 12.9	89.6 ± 11.4	94.1 ± 12.4	92.6 ± 13.2	0.23
Fasting glucose (mmol/L)[3]	5.6 ± 1.1	5.5 ± 1.1	5.5 ± 1.1	5.7 ± 1.1	5.5 ± 1.1	5.6 ± 1.1	0.48
HDL cholesterol (mmol/L)[3]							
Men	1.3 ± 1.3	1.2 ± 1.3	1.3 ± 1.3	1.2 ± 1.3[4]	1.3 ± 1.4	1.3 ± 1.3	0.05
Women	1.7 ± 1.3	1.6 ± 1.3	1.6 ± 1.4	1.7 ± 1.3	1.7 ± 1.3	1.7 ± 1.3	0.07
Triacylglycerol (g/L)[3]	1.2 ± 1.8	1.3 ± 1.8	1.3 ± 1.8	1.3 ± 1.9	1.3 ± 1.8	1.3 ± 1.8	0.04
Systolic blood pressure (mm Hg)[3]	137 ± 1.2	135 ± 1.2	136 ± 1.1	135 ± 1.1	135 ± 1.1	136 ± 1.1	0.99
Diastolic blood pressure (mm Hg)	81 ± 10	81 ± 10	80 ± 11	82 ± 10	82 ± 10	81 ± 10	0.67

[1] P values for differences between the groups exposed and unexposed to famine during gestation, based on linear regression analysis, were adjusted for BMI (HDL cholesterol) or for sex and BMI (fasting glucose, triacylglycerol, and blood pressure).
[2] $\bar{x}$ ± SD (all such values).
[3] Geometric $\bar{x}$ ± SD (all values).
[4] Significantly different from participants unexposed to famine during gestation, $P < 0.05$ (linear regression analysis, with adjustment for BMI).

TABLE 3
The prevalence of components of the metabolic syndrome and of the metabolic syndrome itself (as defined by the NCEP) according to the timing of prenatal exposure to the Dutch famine[1]

	Exposure to famine						
	Born before the famine (n = 238)	In late gestation (n = 141)	In mid-gestation (n = 116)	In early gestation (n = 74)	Conceived after the famine (n = 214)	All (n = 783)	P^2
Components							
Waist circumference ≥102 cm in men, ≥88 cm in women	0.50	0.48	0.53	0.51	0.54	0.52	0.51
Fasting glucose ≥6.1 mmol/L or treatment	0.29	0.28	0.22	0.31	0.24	0.27	0.68
Triacylglycerol ≥1.7 g/L	0.27	0.31	0.32	0.37	0.32	0.31	0.24
HDL cholesterol <1.03 mmol/L in men, <1.3 mmol/L in women	0.11	0.23[3]	0.18	0.24[3]	0.15	0.17	0.01
Blood pressure ≥130/85 mm Hg or treatment	0.69	0.67	0.69	0.62	0.67	0.67	0.78
Metabolic syndrome	0.30	0.38	0.29	0.38	0.30	0.32	0.16
Metabolic syndrome as defined by the IDF	0.48	0.51	0.47	0.51	0.47	0.49	0.50

[1] IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.
[2] P values for differences between the groups exposed and unexposed to famine during gestation, based on logistical regression analysis, after adjustment for sex.
[3] Significantly different from participants unexposed to famine during gestation, $P < 0.05$ (logistic regression analysis, adjusted for sex).

The metabolic syndrome and famine exposure

The prevalence of components of the metabolic syndrome and of the syndrome itself according to definitions of NCEP by exposure group is shown in **Table 3**. Exposure to famine during gestation was not significantly associated with the metabolic syndrome (OR: 1.2; 95% CI: 0.9, 1.7). Compared with those unexposed to famine, those exposed in late gestation had an OR of 1.4 (0.9, 2.1), and those exposed in early gestation had an OR of 1.4 (0.6, 1.5).

Participants prenatally exposed to famine more often had an HDL-cholesterol concentration below the metabolic syndrome threshold of 1.03 mmol/L for men and 1.3 mmol/L for women than did unexposed participants (1.8; 1.2, 2.6). The difference was most pronounced in those exposed in late (2.0; 1.2, 3.2) and early (2.1; 1.2, 3.8) gestation. Additional adjustment for maternal age, maternal weight gain during the third trimester, maternal weight at the end of pregnancy, gestational age, birth weight, smoking status, and sports participation did not change the results.

International Diabetes Foundation definition of the metabolic syndrome

When we used the definition of the IDF for the metabolic syndrome (Table 3), the mean prevalence was higher than when we used the NCEP definition. However, the difference in prevalence between those exposed to famine during late (1.2; 0.8, 1.7) and early (1.2; 0.7, 1.9) gestation and those unexposed to famine was much smaller with the IDF definition.

The metabolic syndrome and birth weight

The prevalence of the metabolic syndrome (NCEP definition) did not become significantly higher with decreasing birth weight (1.3; 0.9, 1.8/1-kg decrease in birth weight), as shown in **Table 4**. Men and women who were small at birth had a waist circumference above the metabolic syndrome threshold of 102 cm for men and 88 cm for women less often than did those who were normal-weight at birth (0.7; 0.5, 1.0/1-kg decrease in birth weight). Participants who were small at birth had a blood pressure above the metabolic syndrome threshold of 130/85 more

TABLE 4
The prevalence of components of the metabolic syndrome and of the metabolic syndrome itself (as defined by the NCEP) according to birth-weight groups[1]

	Birth weight (g)			
	<3000 (n = 179)	3000–3500 (n = 325)	>3500 (n = 279)	P^2
Components				
Waist circumference ≥102 cm in men, ≥88 cm in women	0.48	0.51	0.55	0.04
Fasting glucose ≥6.1 mmol/L or treatment	0.30	0.25	0.26	0.21
Triacylglycerol ≥1.7 g/L	0.35	0.30	0.30	0.15
HDL cholesterol <1.03 mmol/L in men, <1.3 mmol/L in women	0.20	0.15	0.18	0.74
Blood pressure ≥130/85 mm Hg or treatment	0.77	0.64	0.65	0.01
Metabolic syndrome	0.37	0.30	0.32	0.31
Metabolic syndrome as defined by the IDF	0.55	0.45	0.48	0.13

[1] IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program.
[2] P values for differences between birth weight groups were based on logistic regression analysis and adjusted for sex.

often than did those with greater birth weight (1.7; 1.2, 2.4/1-kg decrease in birth weight).

DISCUSSION

On the basis of previously reported associations between prenatal exposure to the Dutch famine and various metabolic outcomes, we hypothesized that the metabolic syndrome may be related to undernutrition in utero. However, we could not show an association between prenatal famine exposure and the metabolic syndrome, nor did we find an association between birth weight and the syndrome.

Several methodologic issues must be raised. The prevalence of the metabolic syndrome is highly dependent on the definition used to diagnose the syndrome. The mean prevalence in our cohort was 32% according to the widely applied NCEP definition (8), which resembles the prevalence found in a European population with a mean age of 56 y—ie, 32% in men and 29% in women (30). However, the prevalence of the metabolic syndrome was 49% according to the recently developed IDF definition (9). This discrepancy is due to the fact that the NCEP definition applies higher cutoffs for waist circumference and fasting glucose concentrations than does the IDF definition.

Differences between famine-exposed groups became much smaller with the use of the IDF definition than with that of the NCEP definition. The use of different definitions of the metabolic syndrome may explain why we could not confirm associations between the metabolic syndrome and birth weight. A wide range of definitions were used by the studies that reported such an association (10–17). The metabolic syndrome has been criticized with respect to its value as a marker for cardiovascular disease risk (31). The criticism centers around the notion that risk is a progressive function of such factors as hyperglycemia and hypertension and, thus, cannot simply be regarded as present or absent, depending on whether thresholds are exceeded or not.

As a consequence of selective participation, we may have underestimated the prevalence of the metabolic syndrome in participants who were exposed to famine during gestation. We found an increase in the occurrence of type 2 diabetes (19) and coronary heart disease (25) at age 50 y among those exposed to famine in utero. These increases may have led to greater mortality and disability among those exposed to prenatal famine, resulting in selective participation of persons who were fit enough to attend the clinic at age 58 y. In a recent follow-up study of adult survival, however, we found no evidence of greater mortality among subjects exposed to famine in utero (27). Nonetheless, selective participation may have had an influence on our findings.

Ever since the introduction of the concept of the metabolic syndrome, doubts have been raised about the integrity of the syndrome as a constellation of metabolic risk factors caused by a unifying underlying pathologic condition [*see* Kahn et al (31) for a review of the literature]. We previously showed in the present cohort that prenatal famine exposure was associated with several metabolic outcomes: participants exposed to famine during gestation had higher 2-h glucose and 2-h insulin concentrations than did those not so exposed (19, 20), and participants exposed during early gestation were more likely to have dyslipidemia (22), obesity in women (23), and altered blood clotting (24). We could not, however, show any effects on blood pressure or waist circumference. Our data suggest that the metabolic syndrome as a clustering of risk factors does not have a single underlying origin in poor fetal nutrition. However, individual features of the syndrome may originate from adverse conditions during gestation and may depend on the timing and nature of the insult in utero. Organs and tissues are more vulnerable during periods of rapid growth and development, the so-called "critical periods." Thus, exposure to famine during a specific period of gestation may lead to problems associated with the organs or physiologic systems that are undergoing development at that particular phase of gestation, whereas exposure during another period of gestation may lead to problems associated with other organs and systems. We previously showed this connection with respect to microalbuminuria, which is related to exposure in midgestation (21), and with respect to dyslipidemia (22), obesity in women (23), the concentration of fibrinogen (24), and coronary heart disease (25, 26), all of which are associated with exposure in early gestation.

In conclusion, neither prenatal exposure to famine nor reduced birth weight is associated with a greater prevalence of the metabolic syndrome. We suggest that, although elements of the metabolic syndrome are programmed during fetal life, the origin of the syndrome as a whole is not likely to be found in poor nutrition during gestation.

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The authors' responsibilities were as follows—TJR: conceived of and planned the study; SRdR, RCP, and TJR: carried out the study; SRdR, FH, and PMMB: performed the statistical analyses; SRdR: wrote the draft of the manuscript; and all authors: contributed to revision of the manuscript. None of the authors had a personal or financial conflict of interest.

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