Obesity at the age of 50 y in men and women exposed to famine prenatally[1–3]

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ABSTRACT

Background: It was shown that men who were conceived during the Dutch famine of 1944–1945 had higher rates of obesity at age 19 y than those conceived before or after it.

Objective: Our objective was to study the effects of prenatal exposure to the Dutch famine on obesity in women and men at age 50 y.

Design: We measured the body size of 741 people born at term between November 1943 and February 1947 in Amsterdam. We compared people exposed to famine in late, mid, or early gestation (exposed participants) with those born before or conceived after the famine period (nonexposed participants).

Results: The body mass index (BMI; in kg/m^2) of 50-y-old women exposed to famine in early gestation was significantly higher by 7.4% (95% CI: 0.7%, 14.5%) than that of nonexposed women. BMI did not differ significantly in women exposed in mid gestation (−2.1%; −7.0%, 3.1%) or in late gestation (−1.3%; −6.3%, 3.9%). In 50-y-old men, BMI was not significantly affected by exposure to famine during any stage of gestation: BMI differed by 0.4% (−3.5%, 4.5%) in men exposed to famine in late gestation, by −1.2% (−5.5%, 3.3%) in those exposed in mid gestation, and by 0.5% (−4.6%, 6.0%) in those exposed in early gestation compared with nonexposed men.

Conclusions: Maternal malnutrition during early gestation was associated with higher BMI and waist circumference in 50-y-old women but not in men. These findings suggest that pertubations of central endocrine regulatory systems established in early gestation may contribute to the development of abdominal obesity in later life. *Am J Clin Nutr* 1999;70:811–16.

KEY WORDS Obesity, critical period, reduced fetal growth, programming, maternal nutrition, metabolic syndrome

INTRODUCTION

Fetal life seems to be a critical period for the development of obesity (1). A study of ≈300 000 19-y-old conscripts who were exposed in utero to the Dutch famine of 1944–1945 showed that the effect of prenatal exposure to famine depended on its timing. The rate of obesity (body weight for height ≥120% according to an external standard) was higher in men exposed in the first half of gestation (2.8%) and lower in men exposed in the last trimester of gestation or the immediate postnatal period (0.8%) than in nonexposed men (1.8%) (2, 3).

However, the relation between fetal growth and obesity in later life is a complicated one. The extent to which the prenatal environment contributes to this is unclear (4, 5). First, several studies showed that people who were heavy at birth or at 1 y of age tended to be slightly more obese as adults, as measured by body mass index (BMI; weight divided by the square of height) (6–9). Second, there are also indications that those who were light as babies tended to have a more truncal or abdominal fat distribution as adults, which was independent of overall fatness (10–13). This central deposition of body fat in particular is known to be associated with the so-called metabolic syndrome, a clustering of dyslipidemia, hypertension, insulin resistance, and cardiovascular disease (14). Last, a study of monozygotic twins suggested that variations in birth weight within twin pairs, unquestionably due to environmental influences acting in utero, had a permanent effect on adult height rather than on obesity (15).

In general, the major increase in body fatness occurs after adolescence, more rapidly in women than in men, to a lifetime maximum at middle age (16). The effect of reduced fetal growth on body fatness may be most easily detected in middle-aged people. Therefore, we studied again the effect of prenatal exposure to the Dutch famine on obesity, but this time in women as well as in men who are now ≈50 y of age. The Dutch famine occurred at the end of World War II in the western part of the Netherlands and lasted ≈5 mo. At its peak in the first months of 1945, the official daily rations for the general population varied between 400 and 800 kcal (1680 and 3360 kJ). All participants were born in a university hospital in Amsterdam; we provided detailed information previously about the course of the pregnancies and the body measures of the subjects at birth (17).

SUBJECTS AND METHODS

Selection of participants

Between 1 November 1943 and 28 February 1947, 5425 children were born in the Wilhelmina Gasthuis, a university hospital in Amsterdam. Most patients of this hospital came from the lower and middle social classes, but little is known about the referral pattern for obstetric care during this period. We sought the birth records of the 1380 live-born singletons who were born between 1 November 1944 and 28 February 1946. We also sought the records of random samples of 650 live-born singletons born in the year before this period (ie, born between 1 November 1943 and 31 October 1944) and of 650 live-born singletons born in the year thereafter (ie, born between 1 March 1946 and 28 February 1947). Of these 2680 babies, 27 (1%) were excluded because their birth record was missing and 239 (9%) were excluded because their gestational age at birth was <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.

The Bevolkingsregister (population registry) of Amsterdam traced 2155 (89%) of these 2414 babies. We found that 265 (12%) had died, 199 (9%) had emigrated from Netherlands, and 164 (8%) did not allow the population registry to give us their address. Of the remaining 1527, we invited 912 people who lived in or close to Amsterdam to participate. Of those invited, 741 (81%) attended the clinic and underwent detailed anthropometry. Mean birth weight according to prenatal exposure to famine in this group of 741 participants was only slightly higher than that in the rest of the 2414 babies who were not included (difference in birth weight adjusted for prenatal exposure to famine: 22 g; *P* = 0.28). The research procedures were approved by the Medical-ethical Committee of the Academic Medical Centre of the University of Amsterdam.

Study measures

We took the maternal characteristics and birth data from the medical birth records. We took weight at the start of the third trimester of pregnancy and at the last prenatal visit, which was always within 2 wk of birth. Maternal weight gain in the third trimester of gestation was estimated as the difference between these weights multiplied by the ratio of trimester duration (13 wk) to the time interval between the weight measurements. Maternal height was not available. As a substitute measure of skeletal size, we used the mother's interspinous distance, which is the distance between the anterior superior iliac spines. Socioeconomic status at birth was derived from the occupation of the head of the family, which was dichotomized into manual and nonmanual labor classes.

Between March 1995 and August 1996, trained research nurses performed all measurements during the clinic visits, which took place in the morning after subjects fasted overnight. They measured height with a fixed stadiometer, weight of subjects in light clothes with a SECA scale (SECA, Hamburg, Germany), waist circumference with a flexible tape measure midway between the costal margin and the iliac crest, and hip circumference at the widest part of the hips, generally at the level of the greater trochanters. We calculated adult BMI as body weight divided by the square of height.

The participants were interviewed to obtain information about their medical histories and smoking habits. The participants were also asked to recall their body weight at the age of 20 y. We also recorded the reproductive history of women. Current socioeconomic status was determined from the subject's or their 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 (18). This measure of socioeconomic status was originally derived from the education needed for an occupation and the income generated by it. People with schooling up to and including lower general secondary education were considered to have a low level of education.

Exposure to famine

The famine period was defined solely according to official daily rations for the general population aged ≥21 y. The rations provided ≈1800 kcal (7560 kJ)/d in December 1943. This figure gradually decreased to ≈1400 kcal (5880 kJ)/d in October 1944, and fell below 1000 kcal (4200 kJ)/d on 26 November 1944. The energy intakes from protein, carbohydrate, and fat were proportionately reduced. The rations varied between 400 and 800 kcal (1680 and 3360 kJ)/d from December 1944 to April 1945 and rose above 1000 kcal (4200 kJ)/d after 12 May 1945—1 wk after liberation by the Allied forces. In June 1945 rations provided >2000 kcal (8400 kJ)/d. Children <1 y were relatively protected during the Dutch famine because their official daily rations never provided <1000 kcal (4200 kJ) and the specific nutrient components were always above the standards used by the Oxford Nutritional Survey (19). We considered a baby to be exposed to famine in utero if the average maternal daily ration during any 13-wk period of gestation provided <1000 kcal (4200 kJ). Babies born between 7 January 1945 and 8 December 1945 were thus exposed. We used 3 periods of 16 wk to distinguish between babies who were exposed during late gestation (born 7 January to 28 April), mid gestation (29 April to 18 August), and early gestation (19 August to 8 December).

Statistical analysis

We calculated the differences in the anthropometric measures between nonexposed people and those exposed in late, mid, or early gestation. We log-transformed BMI before analysis because of its skewed distribution; geometric means and SDs are given. Also, the differences in BMI between nonexposed people and those exposed in late, mid, and early gestation are expressed as percentages of the means of nonexposed people. We first used *t* tests to analyze these differences, and later, multiple linear regression when adjusting for potential confounders. When analyzing the effects of prenatal exposure to famine, we did not adjust for measures of body size at birth because we consider them to be intermediary variables. We indicated differences to be statistically significant if *P* values were <0.05. The statistical analysis program SPSS (SPSS Inc, Chicago) was used for the analyses.

For a relatively large number of participants, we did not have data on maternal weight gain in the third trimester of pregnancy, maternal weight at the end of pregnancy, or socioeconomic status at birth. When adjusting maternal weight gain and weight, 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 socioeconomic status at birth (categorized as manual or nonmanual labor), we added an extra category for those participants with missing values.

RESULTS

Of the 741 people included, 298 (40%) were exposed to famine at some time during gestation (**Table 1**). In our sample, there were fewer men among those exposed to famine during gestation. Mothers exposed in late pregnancy gained less weight in the third trimester than unexposed mothers did, whereas those who were exposed to famine in mid or early pregnancy and had an adequate diet during the rest of the pregnancy gained more. Mothers exposed in late or mid pregnancy weighed less at the end of pregnancy. Babies born after famine exposure during late or mid gestation had lower birth weights and lengths. Characteristics at adult age (socioeconomic status, level of education, frequency of current smoking, and alcohol intake) were similar across exposure groups. Women born after exposure to famine in early gestation had more frequently been pregnant at least once.

At age 50 y, body weight, BMI, and waist circumference were higher in participants exposed to famine in early gestation (Table 1). These effects of prenatal exposure to famine in early gestation were different between men and women. In women, body weight, BMI, and waist circumference were all higher in those exposed, whereas in men these measures were hardly affected (**Table 2**). Waist-to-hip ratio was not significantly higher after exposure to famine in early gestation in both men and women. If we allowed for BMI in our analyses, we still found a significantly higher waist circumference in women exposed in early gestation [by 2.2 (95% CI: 0.0, 4.5) cm] and no significant effects on waist-to-hip ratio in either sex.

Adjustment for potentially confounding variables (maternal age, parity, weight at end of pregnancy, weight gain in third trimester, interspinous distance, socioeconomic status at birth, and present level of education, smoking, and alcohol intake) hardly changed the results. Compared with nonexposed participants, BMI differed by 8.8% (95% CI: 2.0%, 16.0%) and waist circumference by 6.3 (1.7, 10.9) cm in women exposed to famine in early gestation when all these variables were adjusted for. Corresponding differences in men exposed in early gestation were 0.2% (−5.0%, 5.7%) for BMI and 1.9 (−2.4, 6.2) cm for waist circumference. When we adjusted waist circumference for BMI as well as for these confounders, we found that waist circumference was 2.0 (−0.3, 4.3) cm higher in women ($P = 0.09$) and 1.4 (−0.4, 3.2) cm higher in men ($P = 0.13$).

BMI derived from recalled weight at age 20 y was higher after exposure to famine in early gestation and lower after exposure to famine in late gestation (Table 2). The effect of exposure in early gestation was greater in men and that of exposure in late gestation greater in women.

Body weight and height increased significantly with birth weight in both men and women, but we did not find that BMI,

TABLE 1
Maternal characteristics, birth outcomes, adult characteristics, and body size according to prenatal exposure to famine[1]

| | Born before famine (n = 210) | Time of gestational exposure to famine | | | Conceived after famine (n = 233) | All (n = 741) | Missing observations |
		Late (n = 120)	Mid (n = 110)	Early (n = 68)			
Percentage male (%)	50	48	40	44	52	48	0
Maternal characteristics							
Age (y)	29	31[2]	29	27[2]	29	29.0 ± 6.4[3]	0
Percentage primiparous (%)	35	24[2]	32	38	35	33	0
Weight gain, third trimester (kg)	3.2	0.1[2]	5.1[2]	5.6[2]	4.3	3.5 ± 3.3	216
Weight, end of pregnancy (kg)	66.4	62.9[2]	63.5[2]	67.5	68.6	66.2 ± 8.6	93
Interspinous distance (cm)	26.1	26.0	25.7[2]	26.0	26.3	26.1 ± 1.8	8
Percentage in manual class (%)	79	70	72	64	62	70	184
Birth outcomes							
Weight (g)	3383	3166[2]	3212[2]	3450	3443	3348 ± 470	0
Body length (cm)	50.6	49.5[2]	49.8[2]	51.0	50.5	50.3 ± 2.1	7
Ponderal index (kg/m³)	26.1	26.0	26.0	26.0	26.6	26.2 ± 2.3	7
Characteristics at age 50 y							
Current socioeconomic status	46	50[2]	48	48	48	48 ± 13	5
Percentage with low education level (%)	64	58	67	68	71	66	0
Percentage currently smoking (%)	35	34	32	41	34	35	0
Alcohol intake (units/wk)	6	5	4	4	4	5 (0–112)[4]	0
Percentage nulligravidous, women (%)	11.3	9.5	7.6	5.3	12.5	10.1	0
Body size at age 50 y							
Weight (kg)	79.0	79.0	76.8	84.2[2]	80.6	79.7 ± 15.5	0
Height (cm)	171.0	170.9	168.6[2]	171.0	170.9	170.6 ± 8.9	0
Head circumference (cm)	56.9	57.0	56.6	56.8	57.0	56.9 ± 2.1	7
BMI (kg/m²)	26.7	26.7	26.6	28.1	27.2	27.0 ± 1.2	0
BMI ≥ 25 kg/m² (%)	65	63	64	75	67	66	0
Waist circumference (cm)	91.8	92.4	91.0	95.6	92.5	92.3 ± 13.0	6
Waist-to-hip ratio (×100)	87.2	88.0	86.5	88.4	87.5	87.4 ± 8.8	6
Weight recalled for age 20 y							
Weight (kg)	65.0	62.9	62.5[2]	67.2	65.4	64.6 ± 11.0	62
BMI (kg/m²)	22.2	21.3[2]	21.9	22.7	22.2	22.0 ± 1.1	62

[1] $\bar{x}$, except for BMI values, which are geometric means, and alcohol intake values, which are medians, or values given as %.
[2] Significantly different from nonexposed participants, $P < 0.05$.
[3] $\bar{x}$ ± SD.
[4] Range.

TABLE 2
Effect of prenatal exposure to famine on adult body size expressed as differences between participants prenatally exposed to famine (in late, mid, or early gestation) and nonexposed people (those born before or conceived after the famine pooled together)[1]

Sex and body characteristic	Time of gestational exposure to famine		
	Late	Mid	Early
Men			
Body size at age 50 y			
Weight (kg)	0.8 (−3.1, 4.7)	−2.3 (−6.6, 1.9)	1.5 (−3.5, 6.6)
Height (cm)	0.5 (−1.4, 2.5)	−1.5 (−3.7, 0.6)	0.9 (−1.7, 3.4)
Head circumference (cm)	0.2 (−0.3, 0.7)	−0.3 (−0.8, 0.2)	−0.1 (−0.7, 0.6)
BMI (% of nonexposed mean)	0.4 (−3.5, 4.5)	−1.2 (−5.5, 3.3)	0.5 (−4.6, 6.0)
Waist circumference (cm)	1.8 (−1.4, 4.9)	−1.0 (−4.5, 2.5)	1.8 (−2.4, 6.0)
Waist-to-hip ratio (×100)	1.3 (−0.5, 3.1)	−0.4 (−2.4, 1.6)	1.5 (−0.9, 3.9)
Weight recalled for age 20 y			
Weight (kg)	−1.0 (−3.8, 1.7)	−1.5 (−4.6, 1.6)	3.6 (0.0, 7.2)
BMI (% of nonexposed mean)	−1.9 (−5.2, 1.6)	−0.2 (−4.0, 3.9)	3.8 (−0.8, 8.5)
Women			
Body size at age 50 y			
Weight (kg)	−1.8 (−6.1, 2.5)	−1.5 (−5.7, 2.8)	7.9 (2.5, 13.2)
Height (cm)	0.1 (−1.6, 1.8)	−0.6 (−2.3, 1.0)	0.9 (−1.2, 2.9)
Head circumference (cm)	0.2 (−0.3, 0.6)	0.0 (−0.4, 0.5)	0.2 (−0.3, 0.7)
BMI (% of nonexposed mean)	−2.1 (−7.0, 3.1)	−1.3 (−6.3, 3.9)	7.4 (0.7, 14.5)
Waist circumference (cm)	−0.7 (−4.4, 3.0)	0.4 (−3.2, 4.1)	5.7 (1.1, 10.3)
Waist-to-hip ratio (×100)	0.8 (−1.2, 2.8)	0.9 (−1.1, 2.9)	2.2 (−0.3, 4.7)
Weight recalled for age 20 y			
Weight (kg)	−3.1 (−6.0, −0.1)	−1.3 (−4.2, 1.5)	1.8 (−1.7, 5.4)
BMI (% of nonexposed mean)	−5.0 (−9.1, −0.8)	−0.9 (−5.0, 3.4)	2.2 (−3.1, 7.8)

[1] $\bar{x}$; 95% CI in parentheses.

waist circumference, or waist-to-hip ratio were associated significantly with birth weight (**Table 3**). In women, however, BMI and waist circumference tended to increase with birth weight. The results for waist circumference and waist-to-hip ratio did not change when we adjusted for BMI.

DISCUSSION

We found that exposure to the Dutch famine in early gestation resulted in higher body weight, BMI, and waist circumference in women but not in men at 50 y of age. A poor maternal diet in early gestation that was followed by adequate nutrition during the remaining course of gestation was linked to increased obesity in middle-aged women. Results based on recalled body weight at age 20 y agreed with those of the study in 19-y-old Dutch male conscripts that indicated that rates of obesity were elevated after exposure to the famine in the first half of gestation and reduced after exposure in late gestation or in the immediate postnatal period (2).

The number of births corresponding to conceptions during the famine period decreased by ≈50% compared with the prefamine value (20). Therefore, women who conceived during this period might be a select group. In contrast with the study of Dutch conscripts (2), we had detailed information about the mothers and the pregnancies, and we found that the associations between famine exposure in early gestation and obesity at age 50 y were affected little if we adjusted for maternal characteristics that might be determinants of fertility. It is therefore unlikely that selective fertility fully explains the observed associations.

The Dutch famine was a unique nutritional challenge. It started and ended abruptly, lasted only 5 mo, and was preceded and fol-

lowed by more or less adequate nutrition. Moreover, the rations for infants were relatively spared, which confines the exposure principally to the prenatal period. The Dutch famine is therefore hardly comparable with other famine periods of which the long-term effects have been studied. For example, a study of people born in Leningrad around the time of the German siege of 1941–1944 did not find an association between prenatal exposure to famine and obesity, but the famine in Leningrad lasted for 28 mo and, evidently, most people were exposed during the whole period of gestation as well as during infancy (21). Moreover, people born in Amsterdam around the time of the Dutch famine grew up in a time of increasing affluence, whereas the living conditions remained relatively poor for those born in Leningrad.

The body size at birth of babies who were exposed to famine in early gestation was little affected and the observed associations between exposure to famine in early gestation and obesity in women at age 50 y were obviously independent of body size at birth. People born after exposure to famine in late and mid gestation were lighter, shorter, and somewhat thinner at birth, and it was in these people that we found low glucose tolerance, which was more severe than could be explained by the famine-related reductions in birth size (17). We did not find an effect of prenatal exposure to famine on adult blood pressure, although blood pressure was strongly inversely associated with body size at birth (22). These diverse links between prenatal exposure to famine and fetal growth on the one hand, and obesity, glucose tolerance, and blood pressure in adult life on the other indicate once again that undernutrition in utero has a variety of long-term effects that depend on its timing. These findings suggest that an adverse fetal environment contributes to all of these components of the metabolic syndrome, but also that these effects are medi-

TABLE 3
Adult body size at age 50 y according to birth weight[1]

	Birth weight				
Sex and body characteristic	≤2750 g (n = 26 M, 46 W)	2751–3250 g (n = 99 M, 150 W)	3251−3750 g (n = 146 M, 128 W)	>3750 g (n = 85 M, 61 W)	P for trend[2]
Men					
Weight (kg)	80.9	84.5	85.8	87.2	0.01
Height (cm)	172.9	176.1	177.3	179.6	<0.0005
BMI (kg/m²)	26.9	26.9	26.8	26.9	0.9
Waist circumference (cm)	95.8	97.6	97.3	97.3	0.9
Waist-to-hip ratio (×100)	93.1	93.9	93.2	93.3	0.4
Women					
Weight (kg)	69.9	72.9	75.2	79.5	0.002
Height (cm)	161.3	163.5	165.5	167.5	<0.0005
BMI (kg/m²)	26.5	26.7	27.0	27.9	0.3
Waist circumference (cm)	86.5	87.1	88.2	89.7	0.2
Waist-to-hip ratio (×100)	82.3	82.0	81.9	81.5	0.7

[1] $\bar{x}$, except for BMI values, which are geometric means.
[2] Adjusted for prenatal exposure to famine.

ated through different mechanisms operating at different times during gestation.

Exposure to famine during early gestation affected the degree of obesity and the distribution of body fat differently for men and women. BMI and waist circumference at age 50 y were higher in exposed women, but not in exposed men, than in unexposed participants. This suggests that these women store fat intraabdominally because it has been shown that waist circumference represents intraabdominal fat mass at least as accurately as does waist-to-hip ratio (23, 24). Intraabdominal obesity is linked to hyperandrogenicity in women and to low testosterone concentrations in men (25). The proposed mechanisms underlying obesity are sometimes divided into 2 categories (26). The first refers to hypothalamic dysfunction and the second to abnormalities at the level of the fat cell. Following this approach, we think that our findings indicating different effects in men and women support the idea that the increased levels of obesity after exposure to famine in early gestation are due to altered function of central endocrine regulatory mechanisms rather than to abnormalities of adipocytes.

In response to the study of prenatal exposure to famine in Dutch conscripts (2), a series of studies was performed in rats to examine the effects of famine exposure in early gestation in more detail. One group of investigators found that the effects of early gestational undernutrition on food intake, body weight, and obesity were dependent on the animals' sex and their diet after birth (27). Male and female offspring of mothers who were undernourished in the first 2 wk of pregnancy had a higher food intake and gained more weight when fed a standard laboratory diet than did control offspring. But when the diet was changed at 140 d after birth to a high-fat diet, only male offspring gained weight at a greater rate than control animals, which was not accompanied by hyperphagia. Maternal overeating after the food restriction during the first 2 wk of pregnancy contributed to these effects. In a second study, it was shown by the same investigators that body weight increased and hyperphagia ensued in male rats but not in female rats exposed to undernutrition in early gestation when they were fed a high-fat diet from the time of weaning (28). Another group of investigators found, using a different diet and another lineage of rats, that, compared with normal rats, undernutrition in the first 2 wk of gestation resulted in a lower

weight at 53 d after birth in male rats, whereas female rats had normal body weights but larger retroperitoneal and parametrial fat pads (29). Both groups of investigators concluded that increases in food intake in later life alone cannot account for the increased rate of obesity in these animals. Instead, they suggested several mechanisms that all relate to permanently altered regulatory mechanisms of energy intake and expenditure.

In conclusion, our findings imply that permanent adaptations of central regulatory mechanisms occurred as a result of changes in the mother's body brought about by poor nutrition in early pregnancy followed by rapid improvement later in pregnancy. These adaptations did not restrict linear growth but seemed to have resulted in a disturbed central regulation of the accumulation of body fat in later life.

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