Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine[1–4]

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ABSTRACT

Background: Few studies in humans have related maternal undernutrition to the size of the adult offspring.

Objective: The objective was to assess whether reductions in food intake by pregnant women during the Dutch famine of 1944–1945 were related to offspring length, weight, and indexes of adiposity in middle age.

Design: We recruited *1*) exposed persons born in western Netherlands between January 1945 and March 1946 whose mothers experienced famine during or immediately preceding pregnancy, *2*) unexposed persons born in the same 3 institutions during 1943 or 1947 whose mothers did not experience famine during this pregnancy, and *3*) unexposed same-sex siblings of persons in series 1 or 2. Anthropometric measurements (n = 427 males and 529 females) were obtained between 2003 and 2005. We defined 4 windows of gestational exposure (by ordinal weeks 1–10, 11–20, 21–30, and 31 through delivery) on the basis of exposure to a ration of <900 kcal/d during the whole 10-wk interval.

Results: Exposure to reduced rations was associated with increased weight and greater indexes of fat deposition at several tissue sites in women but not in men (P for interaction <0.01). Measures of length and linear proportion were not associated with exposure to famine.

Conclusion: Reduced food availability may lead to increased adiposity later in life in female offspring. *Am J Clin Nutr* 2007;85:869–76.

KEY WORDS Anthropometric measures, body composition, body mass index, body size, famine, maternal and infant health, Netherlands, nutrition, obesity

INTRODUCTION

Adult body mass is a function of height, girth, and tissue mass and distribution. Each of these measures has independent associations with risk of disease and may have specific associations with early development. Attained height, which is inversely associated with risk of cardiovascular disease (1), is strongly associated with birth length (2). Variations in body proportions, such as the ratio of the leg to trunk lengths, may have their origin in childhood (3) and are independent predictors of the risk of later morbidity and mortality (4). Little is known about the role, if any, of prenatal nutrition in the ontogeny of body proportions.

Birth weight, especially when adjusted for birth length, is positively associated with measures of body size in later life (2). Even so, and despite the consistent association between adult overweight and type 2 diabetes or cardiovascular disease (5), an increased birth weight is also associated with a decreased risk of major chronic diseases (6). An explanation for this apparent paradox might come from information on the sources of variation in size at birth (7), but few studies of humans can document the complex relations extending from maternal nutrition through fetal development and risk of adult disease.

The Dutch famine of 1944–1945 provides a rare opportunity to study the long-term consequences of maternal undernutrition in defined stages of gestation (8, 9). The Dutch famine affected the western Netherlands (10–12). Official rations, which by the end of the famine consisted almost exclusively of bread and potatoes, fell below 900 kcal/d by 26 November 1944 and were as low as 500 kcal/d by April 1945. The famine ceased immediately after liberation. This extraordinary period of deprivation affected fertility, weight gain during pregnancy, maternal blood pressure, and infant size at birth (13–15). The reduction in fertility was greater among manual than among nonmanual occupational classes (8). The decline in mean birth weight of 300 g was restricted to exposure to maternal undernutrition during the third trimester (16, 17).

An earlier investigation of Dutch men aged 19 y found a doubling of the prevalence of overweight with maternal exposure to famine in midgestation (18). A second study, with data collected when the famine-exposed birth cohort was aged 50 y, reported increased body mass index (BMI; in kg/m^2) in women (but not in men) who were exposed to famine in early gestation (19). To date, no studies have reported on other anthropometric indexes of adiposity after gestation during the Dutch famine. The present study was conducted to replicate the earlier findings, extend follow-up through age 59 y, and analyze a wider array of measures of tissue distribution. We also accounted statistically

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for familial determinants of growth and tissue distribution by including same-sex siblings as control subjects.

SUBJECTS AND METHODS

Population source and tracing

We identified 3307 live singleton births (probands) at 3 institutions in famine-exposed cities (midwifery training schools in Amsterdam and Rotterdam and the university hospital in Leiden) in 1945 and early 1946 (100% sample) and in 1943 and 1947 (the first 30 births/mo across the 3 institutions). At the time of the famine, a large majority of deliveries (≥70%) in the Netherlands were scheduled to occur at home. The client mix at the 2 midwifery training schools consisted of low-risk pregnancies of women of lower socioeconomic status whose home environment was unsuitable for delivery. The client mix in Leiden included such deliveries as well as women with higher-risk pregnancies identified during prenatal care and emergency admissions after complications of home labor. We extracted personal identifiers, including name and maternal address, birth weight, and other information from the admission logs and delivery progress charts.

To trace the adult offspring, we provided the names and addresses at birth of all 3307 persons to the population register in the municipality of birth. Of these named persons, 308 (9.3%) were reported to have died and 275 (8.3%) to have migrated. For 294 persons (8.9%) a current address could not be located, and the population registry in Rotterdam declined to trace 130 persons born out of wedlock. Thus, a current address was obtained for 2300 persons (70% of the institutional birth cohort).

Recruitment and examination

Traced persons were mailed a letter of invitation signed by the current director of the institution in which they were born, a brochure describing the study, and a response card. We mailed one reminder letter to nonresponders. Initially, our study design called for the recruitment of same-sex sibling pairs; hence, the lack of an available sibling was a reason for ineligibility. We received some reply from 1767 persons, of whom 347 (19.6%) expressed willingness to participate together with a sibling. Of those who declined, 67% reported not having a same-sex sibling available for study. To increase the overall number of participants, therefore, we attempted to enroll persons who had indicated ineligibility because of the lack of an available sibling.

We conducted a telephone interview, which was followed by a clinical examination at the Leiden University Medical Center. Most of the clinical examinations were conducted within 6 wk of the telephone interview. All study protocols were approved by the human subjects committees of the participating institutions, and participants provided verbal consent at the start of the telephone interview and written informed consent at the start of the clinical examination. We obtained anthropometric measurements from 971 subjects (437 men and 534 women): 311 proband-sibling pairs, 2 siblings whose matching proband did not complete the clinical examination, and 347 additional probands.

Anthropometric measures

All anthropometric measures were obtained by experienced research nurses, who were provided specific training in the methods by one of us (HSK); only trivial differences in means or in the variability of measures across nurses were observed. Weight was obtained to the nearest 100 g with the participant standing on a portable digital scale (SECA, Hamburg, Germany). Standing height was measured to the nearest 1 mm with a portable stadiometer (SECA), and seated height was obtained to the nearest 1 mm with the participant seated on a hard stool of known height with the use of the same stadiometer. Right arm length (tip of acromion to the distal tip of the third metacarpal bone) and waist (at level of iliac crests, intersection with midaxillary line), hip (buttocks at the point of maximum extension), and right midthigh (supine with hip flexed at 45 °, between lateral inguinal crease and proximal patella) circumferences were obtained to the nearest 1 mm with the use of a nonextensible measuring tape (Hoechstmass, Sulzbach, Germany). The supine sagittal abdominal diameter (SAD) at the level of the iliac crests was obtained to the nearest 1 mm with a sliding-beam caliper (Holtain, Dyfed, Wales, United Kingdom). Tricipital, subscapular, and anterior midthigh skinfold thicknesses were obtained to the nearest 0.2 mm with calipers with a maximal spread of 40 mm (Holtain). These calipers were calibrated daily. A single measurement was taken for height and weight. Two measurements were taken for other anthropometric outcomes, and the mean was used for the analysis. To ensure independence of the replicate measures, all markings of measurement points were erased before the second measure was obtained. If the first 2 measurements were not sufficiently close (arm length, waist circumference, midthigh circumference 1.0 cm; sagittal abdominal diameter 0.5 cm; subscapular or triceps skinfold thickness 2.0 mm) a third and fourth measure were taken and the 3 measures closest together from the 4 available measures were averaged.

Derived measures

Trunk length was calculated by subtracting the height of the stool from seated height, and leg length was obtained by subtracting trunk length from standing height. As indexes of body proportion, we computed the ratios of the right arm to leg lengths and the leg to trunk lengths. We computed the BMI. As additional indexes of mass distribution, we computed the ratios of waist-to-hip circumference, waist-to-midthigh circumference, and SAD-to-midthigh circumference. We excluded from the analysis individuals for whom any of the above anthropometric measures were missing ($n = 12$), for whom the ratio of trunk to leg length exceeded 1.10 ($n = 2$), and one man with polio-related atrophy of a lower limb; the analytic sample consisted of 956 subjects.

Because several of the participants had one or more skinfold thicknesses that exceeded the capacity of the calipers, we categorized the skinfold thicknesses into empirical quartiles. We then developed a 3-level indicator of the relative distribution of subcutaneous fat between the triceps and subscapular regions by cross-tabulating the quartile distributions for these 2 regions. We coded this indicator as −1 if the triceps value was in a higher quartile of the distribution than was the subscapular value, as +1 if the reverse was true, and 0 if both were in the same quartile.

Categorizing exposure to famine

We defined the start of each gestation by the date of the mother's last menstrual period (LMP), as noted in the original prenatal record, unless it was missing or the resulting gestational age was implausible (12.4%). In these cases, we approximated the date of LMP from the unambiguous date of birth and estimates of gestational age recorded on the birth record or from a gestational age estimate based on sex- and parity-specific birth weights of singleton live births at the Amsterdam midwives school and the University of Amsterdam Department of Obstetrics between 1931 and 1965 at each gestation between 24 and 46 wk (20).

We characterized exposure to famine during gestation by determining the weeks after the LMP during which the mother was exposed to an official ration of <900 kcal/d (the 24 wk included the period from 26 November 1944 to 12 May 1945). We defined the mother as exposed in specific periods if gestational weeks 1–10, 11–20, 21–30, or 31 to delivery were entirely included in this time window. Thus, pregnancies with an LMP between 26 November 1944 and 4 March 1945 (n = 74) were considered exposed in weeks 1–10, between 18 September 1944 and 24 December 1944 (n = 124) exposed in weeks 11–20, between 10 July 1944 and 15 October 1944 (n = 140) exposed between weeks 21–30, and between 2 May 1944 and 24 August 1944 (n = 128) exposed between week 31 and delivery. Because these time windows overlap, the participants could be considered exposed during one or (at most) two 10-wk periods; those exposed in at least one 10-week period (n = 350) were considered to have some exposure to famine. In this formulation, the estimate for the variable "any exposure to famine" is not necessarily an average of the estimates for the four 10-wk periods, because these may have independent and additive or counteractive associations with adult size.

Statistical methods

We computed means and SDs or categorical distributions, as appropriate. We developed independent linear regression models for all models that did not include skinfold thicknesses. Skinfold thicknesses and their ratios were analyzed by using logistic regression, with the highest category compared against all others. Because humans are sexually dimorphic and previous research has identified associations of famine with body composition in one or the other sex (18, 19), we tested for heterogeneity of associations by sex using F tests. We considered a P value <0.10 to indicate an interaction and conducted sex-stratified analyses where indicated.

We considered a set of models and regressed each outcome variable separately on exposure to famine. Exposure to famine was characterized by using an indicator for any gestational exposure, with the reference category being no exposure, and by using the four 10-wk intervals described, which we entered as a set of 4 indicator variables. We used the combined population of control subjects (unexposed births in the 3 hospitals: n = 296; siblings of the birth series: n = 310) as the reference, and we adjusted for age at examination. We used the *xtreg* and *xtlogit* commands in STATA 8 (Stata Corp, College Station, TX) to control for clustering within families. We assessed whether associations with exposure to famine were mediated through birth weight or length by entering these terms and comparing the changes in coefficients. These analyses were run on the institutional birth series alone (birth weight: n = 297 men and 348 women; birth length: n = 278 men and 325 women; we lacked information on size at birth for the sibling control subjects). Estimates of the effect of exposure to famine were similar in models that included the birth series and those that included the birth series and the siblings.

We examined whether measurement error in seated height because of excess adiposity in the buttocks might affect relations by adding hip circumference to the relevant models. In practice, this adjustment had no effect on any observed associations (data not shown), and models without this adjustment are presented. Models for circumferences, the SAD, and their resulting ratio measures included a term for standing height to account for allometric scaling; we also tested whether these associations were affected by body proportion by including a term for the leg-to-trunk ratio. Although the outcome measures were generally associated with both height and the leg-to-trunk ratio, addition of these terms did not alter the observed associations between the measures and exposure to famine (data not shown), and we present results without this adjustment. Models for indexes of mass distribution included adjustment terms describing adult measures that might be causally related to adiposity, including smoking status, intake of alcohol, intake of energy as estimated from a food-frequency questionnaire, physical activity level in the year before the examination as assessed by the SQUASH questionnaire (21), and, for women, parity. In practice, control for these factors did not affect the estimates (data not shown). We did not consider these variables relevant for analyses of lengths and body proportion because these outcomes are established by early adulthood.

RESULTS

Differences between traced and untraced persons

The proportion of participants identified as deceased was highest among probands born in 1943 (10.4%) and lowest among probands born in 1947 (6.0%). Status as an emigrant or other reasons why a current address was not found did not differ by year of birth or period of exposure to famine. When we compared the birth records of participants traced to a current address with those who had either died, emigrated, or had not been located we found no clinically significant differences in mean birth weight (3350 compared with 3314 g) or length (50.4 compared with 50.2 cm), placental weight (601 compared with 592 g), maternal age at delivery (28.2 compared with 27.4 y), or birth order (2.3 compared with 2.3).

Differences between interviewed and noninterviewed persons

Of the 2300 persons who were invited to join the study, we found no significant differences between those interviewed to those who were not interviewed in mean birth weight (3374 compared with 3339 g) or length (50.5 compared with 50.3 cm), placental weight (600 compared with 601 g), maternal age at delivery (28.6 compared with 28.1 y), or birth order (2.4 compared with 2.2). The response to our invitation, however, was lower for those born in 1947 (25%) than in all others (35%). Eleven percent of those who were interviewed lived within 5 km of the examination site compared with 10% of those who were not interviewed, and 34% of those interviewed lived >45 km from the examination site compared with 29% of those who were not interviewed.

Final sample for analysis

We analyzed anthropometric data (except for skinfold thicknesses) from 956 persons. On the basis of their behavior and anthropometric measures, these persons appeared unremarkable for Dutch populations of this age (**Table 1** and **Table 2**).

TABLE 1
Selected characteristics of Dutch men and women examined between 2003 and 2005

	Exposed to famine during gestation (n = 350)	Time control subjects[1] (n = 296)	Sibling control subjects (n = 310)	P[2]
Sex (% male)	45.7	46.3	41.9	NS
Age (y)	58.9 ± 0.49[3]	58.8 ± 1.57	57.3 ± 6.30	<0.01
Birth weight (kg)[4]	3.30 ± 0.51	3.45 ± 0.49	—	<0.01
Birth length (cm)[4]	50.3 ± 2.3	50.8 ± 2.2	—	<0.05
Energy intake (kcal/d)	2247 ± 625	2209 ± 649	2163 ± 630	NS
Physical activity score[5]	7230 ± 4268	7871 ± 4936	7182 ± 3720	NS
Current smoker (%)	25.5	24.0	22.3	NS
Alcohol consumption (%)				NS
<1 drink/wk	20.1	25.0	26.5	
1–7 drinks/wk	37.9	33.5	31.3	
8–14 drinks/wk	16.9	22.0	19.3	
15–21 drinks/wk	15.5	12.2	12.9	
>21 drinks/wk	9.5	7.4	10.0	
Number of children (%)				NS
0	10.3	13.9	14.2	
1	16.9	14.5	11.6	
2	56.6	53.7	52.3	
≥3	16.3	18.0	22.0	

[1] Born in the same institution and not exposed to famine during gestation.
[2] ANOVA or chi-square test as appropriate for comparison between categories.
[3] $\bar{x}$ ± SD (all such values).
[4] Birth series only; siblings excluded.
[5] Calculated from intensity of activity by reported average duration and frequency.

Exposure to famine and measures of length and body proportions

There was no evidence of a statistical interaction by sex in the association of maternal exposure to famine with measures of offspring length or their ratios (data not shown). There was no overall association between exposure to famine and these measures when famine was considered as a whole (**Table 3**); when considered as 4 periods of gestation, the ratio of the arm to leg lengths showed gestation-period—specific associations, which increased ($P < 0.10$) after exposure in weeks 21–30 and decreased ($P < 0.05$) after exposure in weeks 31 through delivery.

Exposure to famine and indexes of mass and mass distribution

Strong statistical evidence for interaction by sex in the association of any famine exposure was found for all indexes of mass distribution (P for heterogeneity < 0.001) except waist-to-hip ratio. For men, no association between any exposure to famine and any index was found, whether considered individually or when the 4 periods were considered as a group (**Table 4**; $P > 0.10$ for all). In contrast, all the indexes were elevated in women exposed to famine ($P < 0.05$ for all, except the waist-to-hip ratio, for which $P < 0.10$) (**Table 5**); when the 4 periods of exposure were considered as a group, the associations were significant ($P < 0.01$) for all measures, except the ratios of the waist-to-hip circumferences and waist to midthigh circumferences ($P > 0.05$ for both). Inspection of the period-specific estimates suggested similarities between men and women for the estimates for exposure in gestational weeks 1–10 and substantial divergence between men and women in the estimates for exposures in later 10-wk periods.

Skinfold thicknesses

In sex-pooled analyses (**Table 6**), the odds of being in the highest quartile of the subscapular skinfold thickness and the ratio of the subscapular to tricipital skinfold thickness were modestly elevated with any exposure to famine ($P < 0.10$). The test for interaction by sex was not significant ($P > 0.10$ in age-adjusted models) for any skinfold thickness. There was no strong indication of association with specific periods of exposure to famine.

Analyses on birth series alone

We repeated all analyses using the 645 participants with measures of birth weight and the 603 participants with measures of birth length. Results were very consistent with those reported for the whole sample (data not shown). In these groups, the results did not change when birth weight or birth length were included in the model (data not shown).

DISCUSSION

In a follow-up study of persons exposed during gestation to the Dutch famine of 1944–1945, we observed that maternal exposure to acute famine is associated with increases in several indexes of body mass and mass distribution among female offspring at age 59 y. We did not observe any strong independent association of prenatal exposure to famine with adult lengths or body proportions.

The circumstances of the Dutch famine provide a model to test for isolated effects of undernutrition at defined stages of development and do not speak to the situation in which inadequate prenatal nutrition is followed by continued undernutrition, as

TABLE 2
Selected body measurements and ratios for Dutch men and women examined between 2003 and 2005, by famine exposure and sex

	Men			Women		
	Exposed to famine during gestation (n = 160)	Time control subjects[1] (n = 137)	Sibling control subjects (n = 130)	Exposed to famine during gestation (n = 190)	Time control subjects[1] (n = 159)	Sibling control subjects (n = 180)
Height (cm)	177.4 ± 6.2[2]	178.3 ± 6.3	178.9 ± 5.7	165.4 ± 6.6	165.4 ± 6.3	166.5 ± 6.9
Trunk length (cm)	92.6 ± 3.2	93.0 ± 3.2	93.5 ± 3.2	87.0 ± 3.3	86.8 ± 3.1	87.4 ± 3.4
Leg length (cm)	84.7 ± 4.3	85.3 ± 4.2	85.5 ± 4.1	78.4 ± 4.2	78.6 ± 4.5	79.1 ± 4.6
Arm length (cm)	66.8 ± 3.3	67.0 ± 3.7	67.1 ± 2.9	61.6 ± 3.3	61.8 ± 3.4	62.3 ± 3.7
Ratio of arm to leg lengths (× 100)	78.9 ± 3.1	78.6 ± 3.0	78.6 ± 3.0	78.6 ± 2.9	78.6 ± 2.5	78.8 ± 3.3
Ratio of leg to trunk lengths (× 100)	91.5 ± 4.5	91.7 ± 4.2	91.5 ± 4.7	90.1 ± 4.2	90.7 ± 5.2	90.6 ± 4.8
Weight (kg)	87.6 ± 12.1	88.8 ± 13.4	86.0 ± 11.6	78.7 ± 14.9	73.6 ± 13.4	75.3 ± 14.1
Waist circumference (cm)	100.5 ± 10.1	101.4 ± 10.5	98.4 ± 9.1	99.0 ± 11.9	93.9 ± 11.1	94.7 ± 12.0
Hip circumference (cm)	102.7 ± 6.6	103.1 ± 6.9	101.0 ± 5.7	108.9 ± 12.4	104.3 ± 9.7	105.1 ± 10.0
Supine sagittal abdominal diameter (cm)	23.8 ± 3.0	23.9 ± 3.3	23.1 ± 2.8	23.2 ± 3.7	21.6 ± 3.4	21.7 ± 3.5
BMI (kg/m^2)	27.8 ± 3.6	27.9 ± 4.0	26.8 ± 3.3	28.8 ± 5.7	26.9 ± 4.5	27.1 ± 4.8
Midthigh circumference (cm)	52.1 ± 3.8	52.5 ± 4.1	51.8 ± 4.0	53.4 ± 6.5	51.4 ± 5.3	52.5 ± 5.3
Ratio of waist to hip circumferences (× 100)	97.7 ± 5.5	98.3 ± 5.5	97.3 ± 5.7	91.0 ± 5.4	89.9 ± 5.8	90.0 ± 6.0
Ratio of supine sagittal abdominal diameter to midthigh circumference (× 100)	45.6 ± 4.8	45.5 ± 4.7	44.6 ± 5.0	43.4 ± 4.8	42.1 ± 4.8	41.4 ± 5.5
Ratio of waist to midthigh circumferences (× 10)	19.3 ± 1.5	19.3 ± 1.5	19.0 ± 1.7	18.6 ± 1.7	18.3 ± 1.6	18.1 ± 1.9
Subscapular skinfold thickness (mm)[3,4]	21.0 ± 8.3 [151]	19.0 ± 10.3 [136]	18.7 ± 9.6	23.1 ± 12.0 [189]	20.6 ± 10.7 [151]	21.4 ± 12.0 [172]
Triceps skinfold thickness (mm)[4]	12.9 ± 4.3	13.0 ± 6.6	13.8 ± 7.1	23.2 ± 10.5 [185]	22.2 ± 8.6 [151]	22.9 ± 9.1 [172]
Anterior midthigh skinfold thickness (mm)[4]	14.2 ± 7.5 [145]	15.4 ± 12.1 [127]	15.4 ± 7.5 [118]	31.7 ± >16.1 [130][5]	27.4 ± 15.9 [105]	30.0 ± 14.1 [135]

[1] Born in the same institution and not exposed to famine during gestation.
[2] $\bar{x}$ ± SD (all such values).
[3] Sample sizes for skinfold thicknesses include subjects in whom skinfold thicknesses were measured but for whom the skinfold thickness exceeded the caliper capacity.
[4] All values are medians and interquartile intervals; n in brackets.
[5] The 75th percentile for this group exceeded the maximum caliper capacity of 40 mm. The 25th percentile was 23.9 mm.

was until recently common in many developing countries. Exposure to famine, as we defined it in relation to official rations, is an ecologic measure of undernutrition; we lacked individual dietary intake data. However, evidence of the severity of the famine was abundant, including evidence that during the height of the famine pregnant women actually lost weight over the second half of their pregnancy (15). Thus, our data support the notion that maternal undernutrition in gestation, if postnatal nutrition and infections are not limiting, neither programs a person for an altered trajectory of linear growth if it occurs in early pregnancy nor results in unrecoverable deficits in attained length if it occurs later in gestation. In women, however, the prenatal deprivation appears to have been associated with increased weight in middle age, with more of the increased mass deposited centrally.

Two earlier studies of persons exposed to the Dutch famine in utero have yielded mixed results. Among men examined at age 18 y, the absolute risk of obesity (defined as >120% of the ideal weight for height according to the Metropolitan Life Insurance Company tables) was elevated from 1.5% to 2.8% with exposure in midgestation (18). Our study lacked the power to detect an effect of that small a magnitude. A study similar in design to ours found an elevated BMI in women aged 50 y whose mothers were exposed to the famine early in gestation, but there was no association with other periods of exposure to famine or among men (19). Our results are broadly consistent with that study insofar as we also observed a marked difference in associations between men and women, but we did not identify early gestation as being the critical window for effects in adulthood. A third study of the consequences of exposure to famine, conducted among survivors of the siege of Leningrad, did not suggest any difference in BMI between those born before the siege commenced, born during the siege, or born in an area not subject to the siege (22). That study was unable to assess the timing of exposure to maternal undernutrition because the Leningrad siege lasted >2 y. All of the earlier studies considered only weight and height; we examined a wider range of anthropometric dimensions and indexes. We observed some suggestion that the heterogeneity of associations between famine exposure and adult body mass and mass distribution between men and women is established only after the first 10-wk period of gestation. This may reflect the increasing importance of sex-specific growth factors in fetal development (23).

There is ongoing debate about the relative utility of the available indexes of body mass distribution in predicting risk for chronic disease (24-26). Although BMI is widely used, it does

TABLE 3
Association of exposure to the Dutch famine overall or in the specified period of gestation with adult measures of length and with indexes of proportion for 956 persons examined between 2003 and 2005[1]

	Period of gestational exposure										
	Overall (n = 350)		Weeks 1–10 (n = 74)		Weeks 11–20 (n = 124)		Weeks 21–30 (n = 140)		Week 31 to delivery (n = 128)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	P[2]
Length											
Height (cm)	−0.39	−1.11, 0.33	−0.30	−1.72, 1.13	−0.35	−1.51, 0.82	−1.01	−2.13, 0.11	0.51	−0.62, 1.63	NS
Trunk (cm)	−0.03	−0.41, 0.35	0.11	−0.62, 0.85	−0.12	−0.73, 0.49	−0.28	−0.87, 0.30	0.17	−0.41, 0.76	NS
Leg (cm)	−0.40	−0.90, 0.10	−0.47	−1.45, 0.52	−0.26	−1.07, 0.55	−0.72	−1.50, 0.06	0.29	−0.49, 1.07	NS
Arm (cm)	−0.23	−0.65, 0.19	−0.41	−1.21, 0.40	−0.13	−0.80, 0.54	−0.07	−0.71, 0.57	−0.13	−0.77, 0.51	NS
Indexes of proportion											
Ratio of arm to leg lengths (× 100)	0.10	−0.28, 0.49	0.07	−0.65, 0.79	0.26	−0.34, 0.87	0.58	0.00, 1.16	−0.65	−1.22, −0.08	<0.05
Ratio of leg to trunk lengths (× 100)	−0.44	−1.00, 0.12	−0.75	−1.83, 0.34	−0.26	−1.16, 0.64	−0.53	−1.39, 0.34	0.30	−0.56, 1.17	NS

[1] Values represent differences from control group (n = 606). Estimates were obtained by linear regression and were adjusted for sex, age, and clustering of siblings. Models for each specific 10-wk period of gestational exposure were also adjusted for exposure in overlapping 10-wk periods. Estimates for any exposure may reflect additive effects of exposure in specific periods. Tests for interaction by sex were not significant ($P > 0.25$ for each outcome).

[2] Values reflect the overall test of association of all 4 periods of exposure considered as a group (Wald test, 4 df).

not differentiate between lean and fat tissue. The ratio of the subscapular and tricipital skinfold thicknesses, a widely used index of the distribution of subcutaneous fat, rather than of increased visceral fat, was only weakly associated in the present study with exposure to famine. Similarly, the waist-to-hip ratio, a presumed correlate of ischemic heart disease (27), was modestly associated with exposure in our study. We found, however, that exposure to the famine was associated among women with an increased ratio of SAD to the midthigh circumference—an alternative anthropometric correlate of ischemic heart disease (28). To date, there have been suggestions that exposure to famine in specific periods of gestation is associated with impaired glucose tolerance (29) and with prevalent coronary heart disease (30), inconsistently associated with blood pressure (31, 32), and

TABLE 4
Association of exposure to the Dutch famine overall or in the specified period of gestation with weight, circumferences, and indicators of body composition in adulthood for 427 men measured between 2003 and 2005[1]

	Period of gestational exposure										
	Overall (n = 160)		Weeks 1–10 (n = 35)		Weeks 11–20 (n = 59)		Weeks 21–30 (n = 69)		Week 31 to delivery (n = 59)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	P[2]
Weight and circumferences											
Weight (kg)	0.98	−1.22, 3.18	3.37	−0.73, 7.46	−1.63	−5.19, 1.93	2.08	−1.31, 5.47	−1.17	−4.49, 2.16	NS
Waist circumference (cm)	0.51	−1.40, 2.42	1.82	−1.73, 5.37	−1.28	−4.37, 1.81	1.88	−1.06, 4.82	−0.37	−3.25, 2.51	NS
Hip circumference (cm)	0.73	−0.43, 1.90	1.94	−0.27, 4.15	−0.48	−2.38, 1.43	0.93	−0.89, 2.76	−0.43	−2.21, 1.36	NS
Supine sagittal abdominal diameter (cm)	0.20	−0.38, 0.79	0.84	−0.26, 1.93	−0.42	−1.37, 0.54	0.37	−0.54, 1.28	0.01	−0.88, 0.90	NS
Midthigh circumference (cm)	0.11	−0.64, 0.87	1.04	−0.34, 2.42	0.22	−0.99, 1.43	−0.07	−1.22, 1.07	−0.73	−1.85, 0.40	NS
Indexes of mass distribution											
BMI (kg/m^2)	0.32	−0.37, 1.01	1.06	−0.23, 2.34	−0.49	−1.61, 0.63	0.66	−0.41, 1.72	−0.35	−1.40, 0.69	NS
Ratio of waist to hip circumferences (× 100)	−0.27	−1.34, 0.80	0.01	−1.97, 1.98	−0.86	−2.59, 0.86	0.82	−0.82, 2.46	0.11	−1.50, 1.72	NS
Ratio of supine sagittal abdominal diameter to midthigh circumference (× 100)	0.31	−0.61, 1.23	0.70	−1.00, 2.40	−0.86	−2.34, 0.62	0.66	−0.75, 2.06	0.76	−0.62, 2.14	NS
Ratio of waist to midthigh circumferences (× 100)	0.50	−2.47, 3.47	−0.17	−5.63, 5.29	−2.91	−7.68, 1.86	3.43	−1.10, 7.96	2.20	−2.25, 6.64	NS

[1] Values represent differences from control group (n = 267). Estimates were obtained by linear regression and were adjusted for age, height, and clustering of siblings. Estimates for specific 10-wk periods of gestational exposure were also adjusted for exposure in overlapping 10-wk periods. Estimates for any exposure may reflect the additive effects of exposure in specific periods.

[2] Values reflect the overall test of association of all 4 periods of exposure considered as a group (Wald test, 4 df).

TABLE 5
Association of exposure to the Dutch famine overall or in the specified period of gestation with weight, circumferences, and indexes of adiposity in adulthood for 529 women measured between 2003 and 2005[1]

	Period of gestational exposure										
	Overall (n = 190)		Weeks 1–10 (n = 39)		Weeks 11–20 (n = 65)		Weeks 21–30 (n = 71)		Week 31 to delivery (n = 69)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	P[2]
Weight and circumferences											
Weight (kg)	4.83[3]	2.51, 7.14	3.98	−0.53, 8.48	3.71	0.04, 7.39	3.53	0.02, 7.05	2.75	−0.77, 6.26	<0.01
Waist circumference (cm)	4.69[3]	2.66, 6.72	1.96	−1.93, 5.85	2.83	0.64, 7.02	3.88	0.83, 6.93	2.50	−0.53, 5.53	<0.01
Hip circumference (cm)	4.37[3]	2.58, 6.15	2.86	−0.66, 6.38	3.81	0.96, 6.66	3.27	0.54, 6.00	2.56	−0.18, 5.30	<0.01
Supine sagittal abdominal diameter (cm)	1.52[3]	0.91, 2.13	1.00	−0.18, 2.18	1.13	0.17, 2.10	0.84	−0.08, 1.77	1.34	0.42, 2.26	<0.01
Midthigh circumference (cm)	1.61[3]	0.65, 2.57	1.01	−0.86, 2.88	1.40	−0.12, 2.92	1.64	0.18, 3.09	0.56	−0.90, 2.01	<0.01
Indexes of mass distribution											
BMI (kg/m^2)	1.85[3]	1.01, 2.69	1.44	−0.21, 3.09	1.45	0.11, 2.80	1.34	0.06, 2.62	1.08	−0.20, 2.37	<0.01
Ratio of waist to hip circumferences (× 100)	0.89[4]	−0.15, 1.83	0.09	−1.80, 1.99	0.33	−1.22, 1.88	1.09	−0.04, 2.57	0.17	−1.31, 1.64	NS
Ratio of supine sagittal abdominal diameter to midthigh circumference (×100)	1.54[3]	0.69, 2.39	1.28	−0.35, 2.91	0.90	−0.44, 2.23	0.33	−0.94, 1.61	2.09	0.82, 3.36	<0.01
Ratio of waist to midthigh circumferences (× 100)	3.34[5]	0.38, 6.29	1.84	−3.82, 7.50	1.79	−2.85, 6.44	2.28	−2.16, 6.72	2.71	−1.70, 7.13	NS

[1] Values represent differences from control group (n = 339). Estimates were obtained by linear regression and were adjusted for age, height, and clustering of siblings. Estimates for specific 10-wk periods of gestational exposure were also adjusted for exposure in overlapping 10-wk periods. Estimates for any exposure may reflect the additive effects of exposure in specific periods.
[2] Values reflect the overall test of association of all 4 periods of exposure considered as a group (Wald test, 4 df).
[3] $P < 0.01$.
[4] $P < 0.10$.
[5] $P < 0.05$.

not associated with overall mortality (33); all these conditions have shown associations with adiposity. Thus, future research needs to consider how differences in adiposity consequent to exposure to famine during gestation, including differences in the distribution of lean and adipose tissue throughout the body, might mediate any effect of the famine on risk of disease.

It is possible that participation bias may have led to our findings if heavy women with famine exposure were more likely to

TABLE 6
Association of exposure to the Dutch famine overall or in the specified period of gestation with selected skinfold thicknesses in adulthood for persons measured between 2003 and 2005[1]

	Period of gestational exposure										
	Overall		Weeks 1–10		Weeks 11–20		Weeks 21–30		Week 31 to delivery		
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	P[2]
Subscapular (n = 929)[3]	1.38[4]	0.95, 1.99	0.87	0.43, 1.76	1.35	0.77, 2.37	1.09	0.64, 1.88	1.42	0.82, 2.44	NS
Tricipital (n = 935)[3]	1.30	0.89, 1.89	1.50	0.75, 3.00	1.16	0.64, 2.07	1.09	0.63, 1.91	1.37	0.79, 2.38	NS
Anterior midthigh (n = 760)[3]	1.21	0.80, 1.81	1.18	0.57, 2.47	1.10	0.59, 2.06	1.35	0.73, 2.52	0.84	0.45, 1.58	NS
Ratio of subscapular to tricipital (n = 916)[5]	1.55[6]	1.08, 2.22	1.07	0.55, 2.08	1.67	0.96, 2.92	1.46	0.86, 2.49	1.09	0.63, 1.87	<0.10

[1] Estimates were obtained by logistic regression and were adjusted for sex, age, height, and clustering of siblings. Tests for interaction by sex were not significant ($P > 0.10$). Estimates for specific 10-wk periods of gestational exposure were also adjusted for exposure in overlapping 10-wk periods.
[2] Values reflect the overall test of association of all 4 periods of exposure considered as a group (Wald test, 4 df).
[3] Odds ratios are for the highest quartile compared with all others.
[4] $P < 0.10$.
[5] Odds ratios are for the group in which the subscapular skinfold is in a higher quartile than is the tricipital skinfold compared with all others.
[6] $P < 0.05$.

participate in our study than were heavy women with no famine exposure. We have no method to test for this potential bias, however. We note that participation rates did not differ by sex or by distance from the examination site. It is also possible that parental characteristics associated with offspring adiposity differed by period of maternal exposure to famine. The effect of such bias was minimized in our study because we selected control subjects from among siblings born outside of the famine period (thus controlling for genetic sources of variation in adult adiposity) and among births in the same institutions (thus minimizing social class differences between exposed and unexposed persons). Adjustment for several variables that are themselves predictors of adiposity, including measures of energy balance and, in women, parity, did not affect our measures of association between famine exposure and body mass distribution of the offspring.

In conclusion, exposure to the Dutch famine was strongly associated with a wide range of indexes of body mass distribution in middle-age women, and it was not associated with these indexes in men or with measures of length or body proportions in either men or women. These data suggest sex-specific, long-lasting effects of maternal undernutrition during pregnancy.

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LHL, ADS, and HSK developed the study hypothesis and study protocols, designed the study, and developed and coordinated all data collection activities. LHL obtained the major funding. ADS conducted the data analysis and wrote the initial drafts of the manuscript. LHL and HSK participated in the data interpretation. KvdP participated in the development of the data collection protocols and initial data management and in data interpretation. PAZ managed the files and data cleaning and participated in the data interpretation. AR participated in the data analysis and interpretation. All authors reviewed and approved the final version of the manuscript. None of the authors declared any financial conflict of interest.

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