Offspring birth weights after maternal intrauterine undernutrition: a comparison within sibships
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Published in:
American Journal of Epidemiology

Citation for published version (APA):
Offspring Birth Weights after Maternal Intrauterine Undernutrition: A Comparison within Sibships

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The authors examined the effects of maternal intrauterine undernutrition on offspring birth weights in a cohort of women born between August 1944 and April 1946 in Amsterdam, The Netherlands. This period included the Dutch Hunger Winter, a war-induced famine. Undernutrition was defined separately for each trimester of pregnancy as an average supply of less than 1,000 calories per day from government food rations. For maximum control of potential maternal confounding factors related to offspring birth weight, the authors performed a within-family analysis, including 437 families with two siblings and 107 families with three siblings born between 1960 and 1985. As in other studies of the famine, maternal birth weight itself was decreased after third trimester intrauterine exposure but not after first trimester exposure. The expected increase in offspring birth weights with increasing birth order was not seen after maternal intrauterine exposure in the first trimester of pregnancy. In this group, secondborn infants weighed, on average, 252 g less at birth than their firstborn siblings (95% confidence interval (CI) -419 to -85), and thirdborn infants weighed 419 g less (95% CI -926 to 87), even after adjustment for trimester of maternal intrauterine exposure, maternal birth weight, smoking during pregnancy, and sex of infants in the sibling pairs. Additional adjustment for the birth weight of the elder sibling did not materially change this abnormal pattern. There were no abnormal patterns in offspring birth weights after maternal intrauterine exposure in the second or third trimester of pregnancy. The study outcomes could not be explained by other selected determinants of birth weight, by lack of control for socioeconomic status, or by loss to follow-up of the 1944-1946 birth cohort. This study suggests that there may be long-term biologic effects, even into the next generation, of maternal intrauterine undernutrition which do not correspond to the effects on the mothers’ own birth weights. Am J Epidemiol 1997;146:810-19.

Editor’s note: An invited commentary on this article and the preceding article by Coutinho et al. appears on page 820.

There is accumulating evidence in humans that the effects of the amount and quality of intrauterine nutrition may extend to adult life, perhaps even to the subsequent generation, and that the stage of gestation at exposure is crucial. Work by others in this area, such as that by Barker et al. (1), has focused on the association between birth weight (as a proxy for fetal nutrition) and the onset of adult chronic conditions in normal populations. The circumstances of the World War II Dutch famine provide an opportunity to examine the relations between fetal nutrition, birth weight, and adult health in considerable detail and across a range of intrauterine exposures not normally observed in human populations.

We have examined several measures of reproductive performance among women exposed in utero to this famine. In this paper, we refer to two generations of these women and their children as follows: Women exposed to the famine as adults are referred to as grandmothers; those born between 1944 and 1946 (potentially exposed in utero) are referred to as mothers; and the mothers’ children (those born between 1960 and 1985) are referred to as offspring.

The decrease in the mothers’ birth weights was associated with famine exposure during the third trimester of pregnancy (2–5). Among survivors, fetal undernutrition was not associated with measures of subsequent fertility, including age at first pregnancy, completed family size, and interpregnancy interval.
However, there was an increase in the risk of stillbirth and perinatal death among offspring of mothers exposed to famine in utero, particularly for mothers exposed during the third trimester of pregnancy (6).

The mothers' birth weights and those of their first-born offspring were strongly associated, regardless of the mothers' own intrauterine nutrition (7). In addition, we observed parity-specific effects of maternal undernutrition on offspring birth weight—namely, an increase in the birth weight of firstborn offspring of mothers exposed during the first trimester, followed by a reduction in the birth weights of their subsequent offspring (8, 9). The findings are intriguing and point to a relation between intrauterine nutrition and adult reproductive health.

In order to further examine some of these issues, we performed an analysis of within-family birth weight patterns. Birth weights in secondborn infants normally exceed birth weights in firstborn infants, and there is little if any increase for additional pregnancies (10). In addition, birth weights within sibships are highly correlated (11). Because of these established correlations, it is important to confirm that our previous findings based on an analysis of birth weights that ignored sibships (8, 9) also hold when sibship is the unit of analysis. Confounding by unmeasured maternal determinants of offspring birth weight, of either genetic, physical, or behavioral origin, is also less likely to occur when differences in birth weights within a sibship are the outcome of interest.

MATERIALS AND METHODS

Historical background

A severe famine affected the western Netherlands in the winter of 1944–1945, and it occurred in a society with a well-developed administrative structure where food supplies had been generally adequate (12–14). The famine was the result of an embargo on the transport of food supplies imposed by the German occupying forces in reprisal for a wave of partisan activity. During the famine, per capita food availability was progressively reduced, from prefamine levels of approximately 1,600 kcal per day to 1,400 kcal per day by January 1945, and to <1,300 kcal per day by April 1945. Official rations, which by the end of the famine consisted almost exclusively of bread and potatoes, declined much more rapidly, and were below 1,000 kcal per day between January and April of 1945. Pregnant women were allotted some additional food rations over and above those available to nonpregnant women, but the extent to which redistribution of these additional rations occurred within families is not known. The famine ceased immediately upon Libera-

tion in May 1945, when Allied food supplies became abundant. Dramatic effects of the famine on mortality and morbidity (12, 13, 15) and on pregnancy weight gain and infant birth size (3–5) have been documented.

Study population

The Dutch Famine Birth Cohort Study is a historical birth cohort study of the long-term reproductive effects of starvation in utero among a cohort of women born in Amsterdam before, during, and after the Dutch Hunger Winter. Details on the recruitment process have been published elsewhere (16). The obstetric records of all 1,116 females born between August 1, 1944, and April 15, 1946, at the Department of Obstetrics and Gynecology, Wilhelmina Gasthuis Hospital (Amsterdam, The Netherlands), were identified. Information about these births was collected from hospital administrative records that provided, among other information, personal identifiers, date of birth, and birth weight.

Women were traced through the national population registers, and those still alive and residing in the Netherlands were invited to participate in the study. In the course of home interviews conducted between 1987 and 1991, relevant information about a woman's medical and social history was collected. For each woman, this included self-reported height and weight at age 18, education, smoking habits, and the place of birth, estimated and actual date of birth, sex, and birth weight of each of her offspring. All interviews were performed by a single trained research nurse and lasted 1–1.5 hours. The study was approved by the Medical Ethics Committee of the Academic Medical Center (Amsterdam, The Netherlands) and by the Institutional Review Board of Columbia-Presbyterian Medical Center (New York, New York).

Inclusion criteria

We reported previously that, among singleton offspring, estimates of birth weight obtained by maternal Recall in this population are unbiased, except among stillborn and nonsurviving infants (17). Therefore, from the 626 interviewed women who delivered one child or more, we included in this analysis mother-child sets for whom both mother and child(ren) were singletons, the child was alive at the time of the interview, and the mother was able to recall her child's birth weight. We then excluded secondborn and third-born infants for whom birth weight data on any older sibling was missing, to allow for pairwise comparisons of parity-specific birth weights within sibships. The analysis was limited to first-, second-, and third-born offspring because of the limited number of offspring.
Famine exposure

On the basis of records of official food rations, the degree and timing of intrauterine exposure to famine during each trimester of pregnancy have been documented for all monthly cohorts born in Amsterdam between August 1944 and April 1946 (4). For all subjects, the date of conception was estimated by assuming that the duration of pregnancy was 9 calendar months. Since length of gestation during the famine was reduced by only 4 days, on average (4), this estimate is likely to have been sufficiently accurate for our purpose. The calendar month of birth was numbered 10, the preceding month 9, and so on, through month 1, the month of the last menstrual period. Intrauterine famine exposure was defined separately for trimesters 1, 2, and 3 as an average official ration of less than 1,000 calories (4,200 J) daily during that trimester. The mean ration in the first trimester was the average daily ration during months 1, 2, and 3; for the second trimester, the mean ration was the average during months 4, 5, and 6; and for the third trimester, the mean ration was the average during months 7, 8, and 9. By this definition, the cohorts severely exposed in utero to famine during the first trimester were born between August and December of 1945; cohorts exposed in the second trimester were born from May to September 1945, and cohorts exposed in the third trimester were born from February to June 1945. All other monthly birth cohorts were defined as unexposed in those trimesters. Subjects born in May–June 1945 were severely exposed in both the second and the third trimesters, and subjects born in August–September 1945 were exposed in both the first and the second trimesters.

Outcome measures

The outcome of interest was the difference in birth weights between siblings of different birth orders. We also examined the correlations between the birth weights of sibling pairs.

Statistical analysis

Offspring birth weights were tabulated according to the maternal trimester of possible intrauterine exposure to famine, as well as birth order and sibship size. Between-sibling birth weight correlations for sibling pairs of different birth orders were calculated within maternal intrauterine exposure categories. The associations between trimester of maternal intrauterine exposure and the paired within-sibship birth weight differences between offspring of different birth orders (secondborn-firstborn, thirdborn-secondborn, and thirdborn-firstborn) were evaluated in multiple linear regression models. We adjusted all models for intrauterine famine exposure in more than one trimester. Additional adjustments were carried out for sex of infants in the sibling pairs, maternal smoking during the first pregnancy, maternal birth weight (in eight strata), the birth weight of the older sibling (eight strata), maternal weight at age 18 years, and maternal education. These analyses were conducted separately for each birth order combination to avoid within-sibship correlations due to the multiple representation of study subjects.

In all analyses, each trimester of exposure was considered to have a potentially independent effect; separate trimesters were therefore examined collectively. Because some women were exposed during the first and second trimesters of pregnancy and some were exposed during the second and third trimesters, statistical comparisons of the effect of first versus second trimester exposure and of second versus third trimester exposure should be made with caution. Specifically, an (upward) adjustment of the standard errors of the group-specific outcomes is required to account for nonindependent observations. Analyses were performed using SPSS/PC+ (SPSS, Inc., Chicago, Illinois).

RESULTS

Study population

Between August 1, 1944, and April 15, 1946, 1,116 female infants were born in the Wilhelmina Gasthuis Hospital. All of their mothers were white, and nearly all had been born in the Netherlands. Follow-up status in 1987 (died, emigrated, or currently residing in the Netherlands) was confirmed for all subjects. Of the enumerated cohort, 191 (17 percent) had been stillborn or had subsequently died, and a further 91 (8 percent) had emigrated from the Netherlands. Home interviews were completed for 84 percent (700/834) of all surviving subjects residing in the country.

Of the 700 women interviewed, 626 (89 percent) had delivered one or more children. The total number of offspring was 1,334. Among firstborn children, 575 of 626 births (92 percent) met the inclusion criteria for this analysis; among secondborn children, 454 of 499 births (91 percent) met the criteria; and among thirdborn children, 119 of 149 met them (80 percent).
There were 107 sibships of size three or greater with complete data on first-, second-, and thirdborn infants, and there were an additional 330 sibships of size two with complete data on first- and secondborn infants (table 1).

Table 2 presents maternal and offspring birth weights according to the timing of the mothers' intrauterine exposure, offspring birth order, and sibship size. Mothers exposed in utero during the third trimester of pregnancy showed a 263-g decrease in their own birth weight relative to unexposed women (3,001 g vs. 3,264 g; 95 percent confidence interval (CI) –380 to –146). In comparisons of available matched pairs within each category of interest, secondborn offspring of women without intrauterine famine exposure were 101 g heavier at birth (95 percent CI 20–181) than their firstborn siblings (229 matched pairs), and thirdborn offspring were 67 g heavier (95 percent CI –157 to 290) than their firstborn siblings (57 matched pairs). The same pattern was seen among the offspring of mothers exposed in the second or third trimester of pregnancy. By contrast, secondborn offspring of mothers who were exposed in utero during the first trimester had a 25-g decrease in their birth weight relative to unexposed women (3,001 g vs. 3,026 g; 95 percent CI –363 to –61). The pattern was also seen among the offspring of mothers exposed in the second trimester of pregnancy. The same pattern was seen among the offspring of mothers exposed in the third trimester of pregnancy, but the differences were not statistically significant.

### Table 1: Study eligibility among offspring of 626 parous women born in Amsterdam, The Netherlands, between August 1944 and April 1945 and interviewed in 1987–1990: Dutch Famine Birth Cohort Study

<table>
<thead>
<tr>
<th>Birth Order</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firstborn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no.</td>
<td>626</td>
<td></td>
</tr>
<tr>
<td>No. eligible*</td>
<td>575</td>
<td>92</td>
</tr>
<tr>
<td>No younger siblings</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>One younger sibling</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>Two or more younger siblings</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Secondborn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no.</td>
<td>499</td>
<td></td>
</tr>
<tr>
<td>No. eligible*</td>
<td>454</td>
<td>91</td>
</tr>
<tr>
<td>No younger sibling</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>One or more younger siblings</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Missing data on older sibling</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Thirdborn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no.</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>No. eligible*</td>
<td>119</td>
<td>80</td>
</tr>
<tr>
<td>Missing data on older sibling(s)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Matched pairs (completed sibship size)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firstborn–secondborn (2)</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>Firstborn–secondborn (≥3)</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Firstborn–thirdborn (≥3)</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Secondborn–thirdborn (≥3)</td>
<td>107</td>
<td></td>
</tr>
</tbody>
</table>

* Eligible women: singleton women who delivered singleton offspring who were alive at the time of interview and for whom maternal recall of birth weight was available. Fourth- and later-born offspring (n = 60) were excluded.

### Table 2: Maternal and offspring birth weights (g) by timing of the mother's intrauterine exposure to famine, offspring birth order, and sibship size: Dutch Famine Birth Cohort Study

<table>
<thead>
<tr>
<th>Cohort Study</th>
<th>Mean</th>
<th>SD</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firstborn</td>
<td>3,499</td>
<td>85</td>
<td>459</td>
<td>3,490</td>
<td>82</td>
<td>499</td>
<td>3,393</td>
<td>612</td>
<td>149</td>
<td>3,342</td>
<td>668</td>
<td>12</td>
</tr>
<tr>
<td>Secondborn</td>
<td>3,342</td>
<td>62</td>
<td>499</td>
<td>3,444</td>
<td>27</td>
<td>459</td>
<td>3,393</td>
<td>19</td>
<td>149</td>
<td>3,437</td>
<td>625</td>
<td>23</td>
</tr>
<tr>
<td>Thirdborn</td>
<td>3,300</td>
<td>71</td>
<td>459</td>
<td>3,342</td>
<td>17</td>
<td>499</td>
<td>3,393</td>
<td>19</td>
<td>149</td>
<td>3,438</td>
<td>625</td>
<td>23</td>
</tr>
<tr>
<td>Offspring birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>3,342</td>
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<td>149</td>
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<td>17</td>
<td>499</td>
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<td>62</td>
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<td>3,342</td>
<td>62</td>
<td>149</td>
<td>3,300</td>
<td>71</td>
<td>149</td>
</tr>
</tbody>
</table>

* Maternal birth weight was calculated as the mean of the birth weights of the first, second, and third siblings (if present) for each mother. Offspring birth weight was calculated as the mean of the birth weights of all siblings for each mother. Mothers were included if they had at least one offspring, and offspring were included if they were alive at the time of interview and for whom maternal recall of birth weight was available. Fourth- and later-born offspring (n = 60) were excluded.

**Table 2 Notes:**
- Mean: arithmetic mean
- SD: standard deviation
- No.: sample size
FIGURE 1. Difference in birth weights (g) between offspring of different birth orders, paired within sibships, by timing of the mother's intrauterine exposure to famine: Dutch Famine Birth Cohort Study. *Order 2–1* refers to the birth weight of the secondborn sibling minus the birth weight of the firstborn sibling \( (n = 330 \text{ pairs}) \); likewise, *Order 3–1* \( (n = 107 \text{ pairs}) \) and *Order 3–2* \( (n = 107 \text{ pairs}) \) refer to the birth weight of the thirdborn sibling minus the birth weights of the firstborn and secondborn siblings, respectively. Controls include offspring of women with no intrauterine famine exposure; the categories *First,* *Second,* and *Third* include offspring of women prenatally exposed to the Dutch famine during the first, second, or third trimester of pregnancy, respectively. Some mothers had both first and second trimester exposure, and some had both second and third trimester exposure. Other exposure categories do not overlap.

TABLE 3. Between-sibling birth weight correlations,* by birth order and mother's intrauterine exposure status, among mothers born in Amsterdam in 1944–1946: Dutch Famine Birth Cohort Study

<table>
<thead>
<tr>
<th>Mother's Intrauterine Exposure Status†</th>
<th>Birth Order</th>
<th>Secondborn-firstborn ( (n = 437) )‡</th>
<th>Thirdborn-firstborn ( (n = 107) )</th>
<th>Thirdborn-secondborn ( (n = 107) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester (births from August–December 1945)</td>
<td>0.36 ( (0.22 \text{ to } 0.49) )§</td>
<td>0.14 ( (-0.21 \text{ to } 0.46) )</td>
<td>0.05 ( (-0.29 \text{ to } 0.38) )</td>
<td></td>
</tr>
<tr>
<td>Second trimester (births from May–September 1945)</td>
<td>0.51 ( (0.40 \text{ to } 0.61) )</td>
<td>0.17 ( (-0.11 \text{ to } 0.43) )</td>
<td>0.57 ( (0.35 \text{ to } 0.73) )</td>
<td></td>
</tr>
<tr>
<td>Third trimester (births from February–June 1945)</td>
<td>0.43 ( (0.31 \text{ to } 0.54) )</td>
<td>0.60 ( (0.38 \text{ to } 0.76) )</td>
<td>0.73 ( (0.56 \text{ to } 0.84) )</td>
<td></td>
</tr>
<tr>
<td>No intrauterine exposure</td>
<td>0.49 ( (0.42 \text{ to } 0.56) )</td>
<td>0.26 ( (0.08 \text{ to } 0.43) )</td>
<td>0.58 ( (0.44 \text{ to } 0.69) )</td>
<td></td>
</tr>
</tbody>
</table>

* Pearson correlation coefficients, partialled for sex of infants in the sibship pairs and maternal smoking in the first pregnancy.
† Some mothers had both first and second trimester exposure, and some had both second and third trimester exposure. Other categories do not overlap.
‡ Number of pairs.
§ Numbers in parentheses, 95% confidence interval.
to undernutrition, the correlation between the birth weights of the firstborn and secondborn children was 0.49 (95 percent CI 0.42–0.56), and the correlation between the birth weights of the secondborn and thirdborn children was 0.58 (95 percent CI 0.44–0.69) (table 3). These correlations were reduced among offspring of mothers exposed in utero during the first trimester of pregnancy, where the correlation coefficient comparing firstborn and secondborn siblings was 0.36 (95 percent CI 0.22–0.49) and that comparing secondborn and thirdborn siblings was 0.05 (95 percent CI −0.29 to 0.38). All correlation coefficients were adjusted for the sex of infants in the sibling pairs and maternal smoking during pregnancy.

Tables 4 and 5 show the differences between offspring birth weights among sibling pairs of different birth orders, by maternal intrauterine exposure status, with adjustment for various covariates. Within each birth order combination, the offspring birth weight difference is given for infants of mothers exposed in utero during the first, second, or third trimester relative to infants of control mothers without intrauterine famine exposure. With adjustment of the differences only for simultaneous exposure in another trimester (table 4), later-born offspring of women exposed in utero during the first trimester showed a decrease in birth weight compared with their elder siblings within all sibship combinations. The decrease was 279 g (95 percent CI −445 to −113) when comparing secondborn and firstborn, 378 g (95 percent CI −859 to 104) comparing thirdborn and firstborn, and 280 g (95 percent CI −649 to 88) comparing thirdborn and secondborn.

This pattern did not change materially after additional adjustment for sex of infants in the sibling pairs, maternal smoking during the first pregnancy, and maternal birth weight (table 5). After these adjustments, the decrease was 252 g (95 percent CI −419 to −85) comparing secondborn and firstborn, 419 g (95 percent CI −926 to 87) comparing thirdborn and firstborn, and 273 g (95 percent CI −642 to 96) comparing thirdborn and secondborn. Additional adjustment for the birth weight of the older sibling diminished the relative decrease in offspring birth weight with increasing birth order among women exposed in utero during the first trimester, but it did not affect the overall pattern (table 5). The effects of additional adjustment for maternal weight or education (data not shown) were negligible. Among offspring of women exposed in utero during any of the other trimesters of pregnancy, and among offspring of control women without intrauterine exposure, a higher birth order in the offspring was associated with no difference in birth weight or with an increase in birth weight (tables 4 and 5).

Adjustment for infant’s gestational age (preterm vs. non-preterm, with a cutoff point of 36 completed weeks) had only a marginal effect on the results. There were 18 preterm births among firstborn children and 16 among secondborn children in the comparison of these 437 sibling pairs. For an additional six first- and secondborn infants, gestational age was not known. The number of preterm infants was five or less for each birth order in the comparison of the 107 sibling pairs involving thirdborn infants (data not shown).

**DISCUSSION**

The normal increase in birth weight with increasing birth order documented by various cross-sectional (18,
TABLE 5. Adjusted* difference in birth weights (g) between offspring of different birth orders paired within sibships, by mother's intrauterine exposure status: Dutch Famine Birth Cohort Study

<table>
<thead>
<tr>
<th>Birth order</th>
<th>Mother's intrauterine exposure status†</th>
<th>Secondborn-firstborn</th>
<th>Additional adjustment for birth weight of older sibling (n = 437)‡</th>
<th>Thirdborn-firstborn</th>
<th>Additional adjustment for birth weight of older sibling (n = 107)</th>
<th>Thirdborn-secondborn</th>
<th>Additional adjustment for birth weight of older sibling (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester (births from August-December 1945)</td>
<td>No additional adjustment (n = 437)†</td>
<td>-252 (-419 to -85)§</td>
<td>-170 (-320 to 20)</td>
<td>-419 (-926 to 87)</td>
<td>-279 (-746 to 189)</td>
<td>-273 (-642 to 96)</td>
<td>-165 (-554 to 224)</td>
</tr>
<tr>
<td>Second trimester (births from May-September 1945)</td>
<td>152 (3 to 302)</td>
<td>115 (-19 to 249)</td>
<td>197 (-259 to 653)</td>
<td>159 (-256 to 573)</td>
<td>17 (-311 to 344)</td>
<td>-7 (-350 to 335)</td>
<td></td>
</tr>
<tr>
<td>Third trimester (births from February-June 1945)</td>
<td>42 (-108 to 191)</td>
<td>41 (-93 to 175)</td>
<td>32 (-409 to 472)</td>
<td>196 (-210 to 610)</td>
<td>220 (-103 to 542)</td>
<td>269 (-69 to 608)</td>
<td></td>
</tr>
</tbody>
</table>

p value (for trimesters of birth as a set) 0.007 0.05 0.34 0.25 0.11 0.18

* Adjusted for all trimesters of mother's intrauterine exposure, sex of infants in the sibship pairs, maternal smoking during the first pregnancy, and maternal birth weight in eight strata (52,500, 2,501-2,750, 2,751-3,000, 3,001-3,250, 3,251-3,500, 3,501-3,750, 3,751-4,000, and >4,001 g) in multiple logistic regression analysis. In all models, additional adjustment for offspring birth weight of the older sibling in eight strata (as above) was carried out. Each trimester was compared with no intrauterine exposure in that trimester.
† Some mothers had both first and second and some had both second and third trimester exposure. Other exposure categories do not overlap.
‡ Number of pairs.
§ Numbers in parentheses, 95% confidence interval.

19) and longitudinal (10, 20) studies was not seen within the families of mothers exposed in utero to undernutrition during the first trimester of pregnancy. Instead, this pattern was reversed, and our analysis showed a within-sibship birth weight decrease with increasing birth order among offspring of these mothers. In absolute terms, the decrease was considerable, amounting to 279 g (95 percent CI -445 to -113) for secondborn versus firstborn offspring and 378 g (95 percent CI -859 to 104) for thirdborn versus firstborn offspring. Adjustment for potential confounders did not affect this relation. These results confirm and extend our earlier findings of a parity-specific effect of maternal undernutrition early in pregnancy on offspring birth weight in analyses carried out without regard for sibships (8, 9).

Maternal intrauterine exposure status was a highly significant predictor of between-sibling birth weight differences in all models comparing the difference between firstborn and secondborn siblings. There were 437 such sets. For sets including higher birth orders (n = 107 pairs), the birth weight decrease associated with increasing birth order was of similar magnitude, but statistical power was reduced because of the relatively small sample size. The decrease resulted from the combined effects of a birth weight increase among the firstborn infant and a birth weight decrease among its later-born sibling(s). Since gestational age per se was not affected, decreased efficiency of a woman’s uterine circulation with successive pregnancies would provide an explanation for the effect. There were no differences in maternal pregnancy blood pressure or in the clinical prevalence of preeclampsia among these mothers, but the number of (pre)eclamptic women in the study was small. Information on other parameters relevant to the quality of maternofetal circulation was not collected for this study.

A further suggestion of an effect of maternal intrauterine exposure early in pregnancy on the birth weights of offspring is provided by the decrease in the correlation between the sibling birth weights among children of these mothers. In comparison with the offspring of controls without intrauterine exposure, the correlation coefficient (adjusted for sex of infants in the sibling pairs and maternal smoking during pregnancy) between first- and secondborn siblings decreased from 0.49 to 0.36, and that between second- and thirdborn siblings decreased from 0.58 to 0.05. Therefore, the birth weights of the later-born siblings were no longer associated in children of these mothers. Our findings among the nonexposed are in agreement with those of previous studies (20–22), wherein the highest correlation between birth weights in siblings was seen among siblings in which neither member of the pair was firstborn.
There is considerable evidence from animal studies that changes in nutrition in early life can permanently affect the growth and form of the body—its structures and functions (23). An example of first-generation effects was provided by Lister and McCance (24). Guinea pigs experimentally undernourished in utero through a reduction in the food supplies of their mothers were born small and became smaller adults than the young of well-fed mothers (24). A congenital deficiency in uterine blood supply produced similar effects (25). In many instances, such long-term effects are associated with undernutrition early in pregnancy, because of the increased sensitivity of the cell to undernutrition during periods of cell division compared with periods of cell growth (26, 27). In this context, it is of interest to note that the twofold increase in the risk of schizophrenia and schizoid personality disorder among males and females who were prenatally exposed to the Dutch famine is associated with intrauterine exposure in early pregnancy and not in late pregnancy (28, 29). In humans, no decrease in birth weights is seen when intrauterine undernutrition is limited to early pregnancy (3-5).

With regard to second-generation effects, this study did not show any long-term consequences for offspring birth weight patterns after maternal intrauterine undernutrition late in gestation where there was a profound decrease in maternal birth weight. Our findings are in agreement with other human studies that show no long-term effects of impaired fetal nutrition in late gestation on the birth weights of the next generation. Magnus et al. (30) showed that monozygotic female twins who are discordant (>300 g) for birth weight have offspring of similar birth weights. Emanuel et al. (31), studying singleton and twin mothers discordant for birth weight, reported similar findings. Therefore, the prenatal timing of a nutritional insult rather than its effect on maternal birth weight itself seems to be what is critical for any health effects on the next generation. Specifically, it points toward a predominant role of first trimester versus third trimester pregnancy nutrition for long-term health outcomes. In studies of rats, a decrease in offspring birth weights was seen after multigenerational chronic maternal undernutrition throughout pregnancy and after birth (32, 33). Because of the exposure throughout pregnancy, a distinction between the effects of early pregnancy versus late pregnancy insults could not be made in these studies.

The present analysis emerged from our previous reports in which within-sibship patterns were not taken into account (8, 9), and it is based on the belief that sibships are characterized by birth weights which, to a large extent, are determined by maternal characteristics. From that perspective, the comparison of paired birth weight differences within families is a logical approach, because it naturally adjusts for several genetic, social, and behavioral attributes which may be hard to measure. Many of these attributes, such as socioeconomic status or education, differ between women but remain constant over time for each individual. Some (measurable) physical characteristics such as maternal height and weight would also be effectively controlled. As it turns out, additional control for maternal weight and education at age 18 years (data not shown) had no effect on any of the results. In addition, follow-up of this cohort was virtually complete after 45 years, and there were no differences in the birth characteristics of the women with completed home interviews (~85 percent) and those without completed home interviews. For these reasons, concerns about the possibility of confounding by a lack of control for socioeconomic status and the potential for selection bias due to incomplete follow-up (34, 35) do not apply to this cohort.

Maternal weight change in successive pregnancies might differ by maternal intrauterine exposure status, but these data were not available for analysis. Age at first delivery and the interpregnancy interval between the first delivery and successive deliveries did not differ by maternal intrauterine exposure (6). Some might argue that the long-term effects of intrauterine undernutrition should be assessed without adjustment for a woman’s birth weight, which may be on the causal pathway between the exposure and the outcomes of interest. Our empirical findings, however, show no difference after control for maternal birth weight, since undernutrition early in pregnancy is not associated with a decrease in birth weight.

Some might also argue that the paired birth weight difference should be adjusted for the birth weight of a previous sibling, because this effectively reduces the variance of the birth weight of the later-born more than any maternal characteristic (36). A further supporting argument is that the paired birth weight difference is highly correlated with the component birth weights (37). Our position is that this depends on the question of interest. If the birth weights of all siblings taken together are the outcome of interest, there is clearly no need for further adjustment. In the present study, in which the difference itself is also of interest, adjustment for all maternal differences up to (and including) the outcome of the first pregnancy would probably amount to overcontrolling. For readers’ convenience, we have presented the data in table 5 with and without adjustment for birth weight in the first pregnancy. Such adjustment does not materially affect the conclusions of our analysis.
Reliable data on gestational age of the offspring were not available, and therefore gestational age in the offspring could only be categorized as preterm versus full term. Because the paired within-sibship differences in birth weight are more likely to result from differences in fetal growth rate than from differences in gestation, the tendency to repeat gestational age in successive pregnancies apparently being a maternal characteristic (11), the lack of accurate information on the length of gestation of the offspring does not seem to be of practical importance.

In summary, our within-family analysis of the birth weights of infants of women undernourished in utero confirms and extends our earlier reports of a deviant pattern after maternal intrauterine undernutrition in early pregnancy. We were not able to attribute these findings to well-established determinants of infant birth weight. The importance of the timing of the insult is illustrated by the absence of any long-term effects on offspring birth weights after maternal undernutrition in late pregnancy. Our study therefore provides additional evidence that the fetal environment experienced by a woman early in pregnancy is a determinant of the fetal environment provided by a woman to her offspring. However, it also suggests that the fetal origins hypothesis (38) needs to be modified: Long-term health effects after fetal undernutrition may occur in the absence of a birth weight effect, and may not be apparent even in its presence.

ACKNOWLEDGMENTS

This study was partially supported by grant 1RO1-HD-26492-02 from the National Institutes of Health, and by a grant from the Milupa Aktiengesellschaft, Friedrichsdorf, Germany.

This paper was presented in part at the Chaire Quetelet 1994 Symposium, Santé et Mortalité des Enfants en Europe, Louvain-la-Neuve, Belgium, September 1994.

Drs. P. E. Treffers and J. G. Koppe of the Academic Medical Center, University of Amsterdam, provided access to the hospital records from 1944–1946. The hospital’s medical archives department, the Gemeentearchief and Bevolkingsregister of Amsterdam, and other cities in the Netherlands assisted in patient location and follow-up. Drs. Z. A. Stein and M. W. Susser stimulated a follow-up study by securing graduate student support for one of the authors (L. H. L.) at Columbia University. The authors thank A. C. J. Ravelli for her contributions to this study.

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