How did the study come about?

Historical setting

The winter of 1944–45 is known as the ‘Hunger Winter’ in The Netherlands, which was occupied by the Germans in May 1940. Beginning in September 1944, Allied troops had liberated most of the South of the country, but their advance towards the North came to a stop at the Waal and Rhine rivers and the battle of Arnhem. In support of the Allied war effort, the Dutch government in exile in London called for a national railway strike to hinder German military initiatives. In retaliation, in October 1944, the German authorities blocked all food supplies to the occupied West of the country.

Despite the war, nutrition in The Netherlands had generally been adequate up to October 1944.1 Thereafter, food supplies became increasingly scarce. By November 26, 1944, official rations, which eventually consisted of little more than bread and potatoes, had fallen below 1000 kcal per day, and by April 1945, they were as low as 500 kcal per day. Widespread starvation was seen especially in the cities of the western Netherlands.1–5 Food supplies were restored immediately after liberation on May 5, 1945. On the basis of these historical data it is possible to accurately define the beginning and the end of the famine period. The famine affected fertility, weight gain during pregnancy, maternal blood pressure, infant size at birth and central nervous system development.6–11 The reduction in fertility was greater among manual workers than among those in other occupations.2 A decline in mean birth weight of 300 g was seen among those exposed to maternal undernutrition during the third trimester.2,6,7,9,12 After liberation and the restoration of food supplies, birth weights and other measures of infant size rapidly rebounded to pre-famine levels.12 Because the Dutch population was typically well fed before and after the Hunger Winter, the circumstances of the famine created what can be regarded as a ‘natural experiment’ in which exposure to famine is assigned based on an individual’s time and place of birth. This design was used to examine how maternal undernutrition during specific gestational time windows may affect the subsequent life course of offspring who experienced the famine in-utero.

Previous follow-up studies of people with prenatal famine exposure

The first investigators to study a possible association between prenatal exposure to famine and health outcomes at age 18 analysed records from over 400,000 men examined at conscription for military service.2,13 These studies, conducted in the 1970s, used the Dutch Famine to analyse adult health outcomes in relation to specific periods of gestation. Exposure to the famine was defined by place and date of birth in relation to distributed food rations. Exposure during gestation was not associated with altered performance on the Raven’s Progressive Matrices test of intelligence,13 but exposure to famine in early and mid-gestation was associated with a doubling of the then low prevalence of obesity.14 While benefiting from the large sample provided by a national birth cohort, these studies were limited to men, as women were never conscripted in The Netherlands, and the available data do not include birth records.

These investigators also adopted a number of complementary approaches. For subgroups in the population, data on births were analysed in relation to birth weight, length, placental weight and the post-partum body weight of the mother.15,16 In the general population, periconceptional and early gestational exposures were related to fertility and fecundity,8 and to births with congenital neural defects (mainly neural tube defects).17 Available data on vital statistics provided information on mortality rates by age of death up to early adulthood for those exposed in utero.18
A second approach used the information in the national Dutch psychiatric registries to examine adult psychiatric outcomes among persons exposed to famine at specific times during gestation. The best known finding from these studies is the increased risk of schizophrenia among the birth cohort conceived at the height of the famine,19–21 a finding subsequently replicated in a study based on the Chinese famine of 1959–61.22 There was also some evidence of an increased risk of affective disorders after prenatal exposure.23 These findings prompted investigators to also return to the data on military conscripts, in which the results of psychiatric examinations were recorded, to examine the relation of prenatal famine to schizophrenia spectrum and to antisocial personality disorders.24–26

A third approach was developed through a series of studies based on infants identified at birth from hospital records, who were sampled according to exposure to prenatal famine and traced to their current address through the Dutch population registration system and examined as adults. The first such study included 1067 singleton girls born between August 1, 1944 and April 13, 1946 in the former Wilhelmina Gasthuis hospital in Amsterdam. This study, conducted in the early 1990s when the famine-exposed cohort was aged 43 years, established that it was possible to identify, trace and interview a large group of famine-born infants after a long follow-up period. Excluding deaths (16% of cohort) and emigrations from The Netherlands (8%), losses to follow-up were minimal and participation in face-to-face interviews was high. In all, >700 women were interviewed.10 This study confirmed the clear decline in birth weight after third-trimester exposure, and showed an increase in birth weight following exposure in the first-trimester.

The availability of prenatal and birth records also provided the opportunity to study the course of pregnancy itself. Maternal weight gain up to 0.5 kg/week was strongly associated with infant size at birth.9 There was a 2–5% increase in the ratio of placental weight to infant birth weight among births with first trimester famine exposure, suggesting that placental growth may be related to the nutritional status of women at the beginning of pregnancy.27 At least four indicators of reproductive performance, including age at first birth, completed family size, birth spacing and probability of not having any children by age 40, were not related to exposure.28 The normal increase in birth weights of offspring with increasing birth order was not seen, however, among women who themselves were exposed to famine in the first trimester of pregnancy.29 An overview of this series of studies is given elsewhere.30

In a fourth series of studies, male births from the same institution were added, resulting in a birth series of 2414 singleton men and women. From this group, ~740 men and women were successfully examined at age 50 years. Selected outcomes include the glucose and insulin profile,31 blood pressure32 and body mass index (wt/ht 2).33 An overview of this fourth series of studies is given elsewhere.34 The series has subsequently been resurveyed at age 58 years.35

The Dutch Hunger Winter Families study thus represents the fifth in the series of Dutch famine birth cohort studies and includes 3307 singleton births in three clinics in cities affected by the famine.12 Endpoints are similar to those selected for the third and fourth series, with some measures of cardiovascular disease risk and hand morphology added. To avoid potential biases related to the clustering of health outcomes across the generations, we examined whenever possible an unexposed same-sex sibling of each clinic birth as a family control. The survivors in this study were interviewed and examined at the age of 59 years.

Additional studies have focused on the health outcomes of persons who experienced the famine as young adults36–39 but these will not be further discussed here.

Who set it up, and how is it funded?

The study was set up by L.H. Lumey, in collaboration with Ana Diez-Roux at Columbia University, New York, NY (current affiliation: University of Michigan), Ezra Susser at Columbia University, New York, NY, Aryeh D. Stein at Emory University, Atlanta, GA, Henry S. Kahn at the Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, GA, and executed with S.P. Verloove-Vanhorick, A.L. den Ouden, M. van de Bor and K. van der Pal-de Bruin at the Institute for Preventive Health (TN0-PG), Leiden, The Netherlands and G.J. Blauw at the Study Center for Gerontology and Geriatrics, Leiden University Medical Center (LUMC). Study funding was provided by the National Heart Lung and Blood Institute, US National Institutes of Health (RO-1 HL87914; Principal Investigator: LHL).

What does the study cover?

The primary aims of the study are (i) to examine whether changes in maternal nutrition in pregnancy affect the risk among offspring for metabolic and cardiovascular disease in adulthood; (ii) to identify critical time windows of pregnancy at which fetal programming might occur; (iii) to document to what extent the time windows of prenatal programming might differ with respect to the adult risk of Type 2 diabetes mellitus, blood pressure and obesity and (iv) to validate the performance of selected morphological measures of the hand (e.g. fingertip ridge-count differences and digit-length ratios) as specific markers of disturbances in early gestation. The study also included measures of other outcomes of interest such as cognitive status and depressive symptoms.

Who is in the sample?

We identified 3307 live-born singleton births at three institutions in famine-exposed cities (the midwifery training schools in Amsterdam and Rotterdam and the university hospital in Leiden). We selected (i) all 2417 births between February 1, 1945 and March 31, 1946 (infants whose mothers were exposed to the famine during or immediately preceding that pregnancy) and (ii) a sample of 890 births from 1943 and 1947 as time controls (infants whose mothers did not experience famine during this pregnancy). The sample of controls included an equal number of births for each month, allocated across the three institutions according to their size. At the time the large
majority of deliveries (70% or more) were scheduled to occur at home. The client mix at the two midwifery schools consisted of low-risk pregnancies to women of lower socioeconomic status whose home environment was unsuitable for delivery. The client mix in Leiden also included higher-risk pregnancies identified during prenatal care and emergency admissions following complications of labour or delivery.

Whenever possible, we also enrolled a same-sex sibling of each member of the birth series as controls. For participants recruited as siblings, no information from prenatal or delivery records is available, as they were not members of the primary birth cohort and were generally delivered at home or in other institutions.

How often have they been followed up?

Members of the study population were traced to their current address in 2003. A telephone interview and medical examination were conducted in 2003–05.

What has been measured?

Birth records

We extracted the following information from the pregnancy and delivery medical records: mother’s and infant’s names; address; age at delivery; occupation; religion; last menstrual period (LMP); gravidity and parity; lifetime number of spontaneous abortions; date of first prenatal visit; weight, height and blood pressure at prenatal visits; date and time of delivery; maternal postpartum weight (two clinics only); obstetrical presentation; mode of delivery; sex; birth weight; crown-to-heel length; head circumference; placental weight (two clinics only) and vital status at discharge. Abstraction of records of the 3307 birth records was completed in May 2003.

We submitted the names and addresses at birth to the local population registers with a request to provide a current address. We then invited by mail all traced members of the birth cohort to participate in the study. Initially, we enrolled only traced people along with a same-sex sibling; later we revisited the selection criteria and enrolled all available members of the birth cohort, regardless of the availability of a sibling.

We conducted a telephone interview, followed by a clinical examination at the Leiden University Medical Center. All study protocols and materials for data collection were approved by the human subjects committees of all the participating institutions. Participants provided oral consent at the start of the interview and written informed consent at the start of the clinical examination for all study procedures.

Telephone Interview

The telephone interview included questions on sociodemographic characteristics and socioeconomic status. In addition, we collected information on health and reproductive history, on current health status, on prevalent medical conditions such as stroke and cardiac problems (including the Rose angina questionnaire), on high blood pressure and on diabetes. We also collected information on smoking and drinking habits. For selected conditions, participants were asked for information on their parents and siblings. After the telephone interview, an appointment was made with participants for a medical examination in the study clinic at Leiden University Medical Center. This examination was usually completed within 6 weeks of the telephone interview. In all, 1031 telephone interviews were completed, including 718 participants from the hospital series and 313 same-sex siblings.

Clinical examinations

Participants were asked to fast overnight before a morning appointment; over 95% complied with this request. On their arrival at the clinic, we first obtained written informed consents for study examinations and blood collection and storage, including consent for later study of DNA. We then measured blood pressure with an automated blood pressure monitor with digital readout, recorded three successive electrocardiogram (ECG) readings and drew a blood sample to obtain fasting measures of lipids, glucose and insulin. We administered a standard oral glucose tolerance test with blood samples obtained at 30 and 120 min after a 75 gm glucose load.

Measures of adult weight, height (standing and seated), lengths (leg and arm), circumferences (waist, hip and right midthigh), skinfold thicknesses (right subcapular, right triceps and right anterior midthigh) and the supine sagittal abdominal diameter (SAD) were collected. Participants were asked to recall their body weight at ages 20 and 30 years. Current hand preference (right vs left) was assessed and rolled fingerprints were obtained from all 10 digits using conventional ink-and-paper methods. In addition, the lengths of the second and fourth fingers on each hand were measured using a sliding caliper with digital readout.

During the clinical examination, several questionnaires were completed by the participants: a standardized food frequency questionnaire; a physical activity questionnaire; a neuropsychological test battery for cognitive function [Mini-Mental State Examination (MMSE)], visual verbal learning, colour scale performance (Stroop), letter digit coding, and verbal fluency; a quality-of-life assessment [Short Form 36 (SF-36)]; a sleep questionnaire; and an assessment of depressive symptomatology (Centers for Epidemiologic Studies Depression Scale [CES-D]) and perceived anger (Spielberger State-Trait Anger Scale) with versions adapted for use in The Netherlands. Whenever possible, we used validated questionnaires for which normative data are available from large study samples from The Netherlands.

Upon completion, all questionnaires were checked by study staff and participants were asked to provide missing information where necessary.

All collected study information was entered twice into a database (double entry keypunching) and any discrepancies were resolved by re-checking against the original coding sheets. In all, we completed the clinical examination in 94% of the people interviewed by telephone. Full details of causes of attrition for eligible participants to interview and clinical examinations, together with comparisons of perinatal characteristics between those who were included in these follow-up data collections and those who could not be are provided below.
Defining exposure to the famine

To define exposure to the famine for all selected participants, we have used an ecological measure to classify stage of gestation in relation to the available food rations. Several approaches have been developed in the past. Here, for the first time, we provide an overview of all definitions of exposure that have been used in studies of the Dutch famine and compare the degree to which these overlap.

Although maternal nutrition in pregnancy cannot be ascertained at the individual level, evidence for the impact of the famine on morbidity and mortality at the population level is abundant. With regard to nutrition in pregnancy, we have shown that many women actually lost weight in pregnancy.

Exposure by date of last menstrual period

We used the date of last menstrual period (LMP) listed on the birth record to define the start of gestation unless it was missing or implausible (12%). In those cases we inferred the LMP date from the date of birth, annotations of estimated gestation age from birth weight and date of birth, using cutoffs from published tables of sex-, parity- and gestation-specific birth weights from the combined birth records of the Amsterdam midwives school (1948–57) and the University of Amsterdam obstetrics department (1931–65). For each infant the most consistent and plausible estimate of gestation was selected and used together with date of birth to infer the LMP.

We have characterized exposure to famine during gestation by determining the gestational ages (in weeks after the LMP) during which the mother was exposed to an official ration of <900 kcal/day between November 26, 1944, and May 12, 1945. We considered the mother exposed in gestational weeks 1–10, 11–20, 21–30 or 31–delivery if these gestational time windows were entirely included in this period. Thus, pregnancies with LMP’s between November 26, 1944, and March 4, 1945, were exposed in weeks 1–10; between September 18, 1944, and December 24, 1944, in weeks 11–20; between July 10, 1944, and October 15, 1944, in weeks 21–30; and between May 2, 1944, and August 24, 1944, in weeks 31 through delivery.

By these definitions, participants could have been exposed to famine during at most two 10-week periods. A limitation of this approach is that persons conceived towards the end of the famine when it was most severe—can only be included among the exposed if they had 10 weeks of exposure before delivery.

We also quantified exposure to famine in the 6 months preceding conception by assigning a weight of one to any week during which the ration was 900–1500 kcal/day (October 1–November 25, 1944, and May 13–May 20, 1945; 9 weeks), and a weight of two to any week in which the ration was <900 kcal/day (November 26, 1944–May 12, 1945; 24 weeks). The score ranges from zero for births without any reduction in rations before conception to 57 for conceptions at the end of the famine period.

Exposure by date of birth

In contrast to this prospective approach, in most studies of the Dutch famine to date, prenatal exposure to famine has been defined relative to date of birth and an assumed gestation of 40 weeks for each pregnancy. For convenience and ease of comparison of current and future studies, these studies are summarized subsequently.

Stein et al. in their report on mental performance at age 18 in relation to prenatal exposure to famine and in a subsequent monograph on the Dutch famine arrayed the study population by week of birth and defined groupings based on ‘the criterion of stage of gestation in relation to famine exposure’. This approach was modified slightly with a smaller mid-pregnancy exposure group by Ravelli et al. for the analysis of anthropometric data from military records.

It was formalized by Lumey et al. and by Susser et al. as an average ration of <1000 kcal/day during a trimester. Lumey et al. used this approach for the analyses of reproductive outcomes among women born in the Wilhelmina Gasthuis hospital in Amsterdam. The approach results in partially overlapping windows of 5 months’ duration. In subsequent studies of schizophrenia related outcomes, E. Susser and colleagues defined exposure in early gestation at the height of the famine by combining the following criteria; (i) low food rations of <1000 kcal/day during the first trimester of gestation; (ii) conception at the height of the famine as indicated by adverse health effects in the general population and (iii) a detectable excess of congenital neural defects.

In the studies carried out by Ravelli et al. of men and women born in the Wilhelmina Gasthuis in Amsterdam, ‘babies were considered to be exposed to famine in utero if the average maternal ration during any 13-week period of gestation provided <1000 kcal. Babies born between 7 January, 1945, and 8 December, 1945, were thus exposed. Subsequently, three non-overlapping periods of 16 weeks were used to distinguish between babies who were exposed primarily during late-, mid- and early-gestation.

As shown in Table 1 and Figure 1, the approaches based on date of birth show a substantial overlap in the assignment of broad categories of exposure and no gross misclassification comparing exposures in early and late pregnancy. Moderate misclassification remains a concern however, particularly for those exposed in mid-gestation by most definitions.

Comparison of a recent date of birth based approach with the LMP based approach for the 3307 births in our hospital series (Table 2) shows that the LMP approach appears to be more accurate in categorizing participants with early exposure. As noted earlier, our definition will exclude participants with exposure of less than 10 weeks during early gestation and like other approaches it therefore has its advantages and disadvantages. We feel that on balance the LMP approach is well tailored, however, to the particular sample and questions of this study.

What is attrition like?

Here we provide information on (i) the tracing from birth to current address; (ii) the response to letters of invitation sent to current address; (iii) participants enrolled for interview and medical examination; (iv) characteristics of traced and untraced persons; (v) characteristics of responders and non-responders to the letter of invitation and (vi) characteristics of infants
enrolled for study and non-enrolled infants from the eligible birth cohort.

**Tracing from birth to current address**

The name and address for 3307 births were provided to the population register in the municipality of birth with a request for tracing to their current address. Of them, 308 (9%) were reported to have died in The Netherlands (10% of men and 8% of women) and 275 (8%) to have migrated (7% of men and 10% of women). The population registry in Rotterdam declined to trace 130 persons born out of wedlock (4%) and for 294 subjects (9%) a current address could not be located. Address information was therefore obtained for 2300 offspring (70% of the birth cohort).

**Response to the letter of invitation**

A letter of invitation signed by the current director of the institution in which they were born was sent to the 2300 traced persons, together with a brochure describing the study and a response card. We mailed one reminder letter to non-responders. Initially, our study design called for the recruitment of same-sex sibling pairs, and the lack of an available sibling was a reason for ineligibility. We received some reply to 58% of the initial letters and to 44% of the reminder letters; 347 persons (20% of 1767 respondents) expressed willingness to participate together with a sibling. Among the 1415 who responded, 751 births from the hospital series and 324 of their siblings. The higher positive response was consistent across all exposure categories. Individuals who indicated they were not able to travel to the site of the clinical examination were enrolled for a telephone interview where possible.

**Study subjects enrolled for interview and medical examination**

We completed the study telephone interview in 96% (1031/1075) of those with an initial positive response and a clinical examination for 971 among this group (437 men, 534 women). This latter group includes 359 offspring with

---

<table>
<thead>
<tr>
<th>Reference</th>
<th>Birth date corresponding to start of period</th>
<th>Birth date corresponding to end of period</th>
<th>Author's designation of pregnancy period</th>
<th>Outcome studied and study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al. and other reports from this group</td>
<td>November 1, 1944</td>
<td>January 31, 1945</td>
<td>B1: 3rd trimester only</td>
<td>Mental performance at age 18 in Dutch recruits</td>
</tr>
<tr>
<td></td>
<td>February 1, 1945</td>
<td>April 31, 1945</td>
<td>B2: 2nd and 3rd trimester</td>
<td>Pregnancy outcomes and survival between age 0–18 years in men and women born in The Netherlands</td>
</tr>
<tr>
<td></td>
<td>May 1, 1945</td>
<td>June 30, 1945</td>
<td>C: Exposed in middle 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>July 1, 1945</td>
<td>September 30, 1945</td>
<td>D1: 1st and 2nd trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>October 1, 1945</td>
<td>January 31, 1946</td>
<td>D2: 1st trimester only</td>
<td></td>
</tr>
<tr>
<td>G.P. Ravelli et al.</td>
<td>November 1, 1944</td>
<td>January 31, 1945</td>
<td>B1: 3rd trimester only</td>
<td>Body size at age 18 in Dutch recruits</td>
</tr>
<tr>
<td></td>
<td>February 1, 1945</td>
<td>May 31, 1945</td>
<td>B2: 2nd and 3rd trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>June 1, 1945</td>
<td>September 30, 1945</td>
<td>D1: 1st and 2nd trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>October 1, 1945</td>
<td>January 31, 1946</td>
<td>D2: 1st trimester only</td>
<td></td>
</tr>
<tr>
<td>Lumey et al. and other reports from this group</td>
<td>February 1, 1945</td>
<td>June 30, 1945</td>
<td>T3: 3rd trimester</td>
<td>Health and reproductive outcomes at age 43 in women born in the Wilhelmina Gasthuis hospital, Amsterdam</td>
</tr>
<tr>
<td></td>
<td>May 1, 1945</td>
<td>September 30, 1945</td>
<td>T2: 2nd trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>August 1, 1945</td>
<td>December 31, 1945</td>
<td>T1: 1st trimester</td>
<td></td>
</tr>
<tr>
<td></td>
<td>November 1, 1945</td>
<td>March 30, 1946</td>
<td>T0: Peri-conception</td>
<td></td>
</tr>
<tr>
<td>Susser et al. 21,23,26</td>
<td></td>
<td></td>
<td>As above, but focus on early pregnancy exposure; peri-conception exposure period not defined</td>
<td>Schizophrenia, affective disorders, and anti-social personality disorders (ASPD) from inpatient psychiatric admissions to Dutch hospitals or from military records 26</td>
</tr>
<tr>
<td>Susser et al. 21,23,26 and other reports from this group</td>
<td>October 15, 1945</td>
<td>December 31, 1945</td>
<td>EX2: severe exposure in early gestation</td>
<td>Schizophrenia hospital admissions 19; schizoid personality disorders from military records 14; schizophrenia spectrum outcomes from hospital admissions or from military records 25 deaths from spina bifida and anencephaly from men and women births 25</td>
</tr>
<tr>
<td>A.C. Ravelli et al. and other reports from this group</td>
<td>January 7, 1945</td>
<td>April 28, 1945</td>
<td>Late-gestation</td>
<td>Health outcomes at age 50 and 58 in men and women born in the Wilhelmina Gasthuis hospital, Amsterdam</td>
</tr>
<tr>
<td></td>
<td>April 29, 1945</td>
<td>August 18, 1945</td>
<td>Mid-gestation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>August 19, 1945</td>
<td>December 8, 1945</td>
<td>Early-gestation</td>
<td></td>
</tr>
</tbody>
</table>
prenatal exposure to famine and 299 offspring without prenatal famine exposure born in the study hospitals as well as 313 siblings. We examined two siblings whose matching proband did not attend the clinical examination. The resulting sample size by (overlapping) periods of exposure was 74, 127, 145 and 133 for gestational weeks 1–10, 11–20, 21–30 and 31–delivery, respectively. There were no differences across periods of exposure in the proportion of probands who had siblings available for study.

Selected characteristics of traced and untraced offspring
We found no clinically significant differences in mean birth weight (3350 vs 3315 g), length (50.4 vs 50.2 cm), placental weight (601 vs 593 g), maternal age at delivery (28.2 vs 27.4 years) or birth order (2.3 vs 2.3) comparing the 2300 study subjects from the birth series who had been traced to their current address to the 1007 subjects who had died, emigrated or could not be located. The proportion of deceased offspring was somewhat higher among probands born in 1943 (10%) than in 1947 (6%) and was higher in men than in women (10 vs 8%). Emigration status or other reasons why a current address was not found did not differ by year of birth. Emigration was more common in women than in men (10 vs 7%).

Selected characteristics of respondents and non-respondents to letter
We found no clinically significant differences in mean birth weight (3372 vs 3339 g) or length (50.5 vs 50.3 cm), placental weight (600 vs 601 g), maternal age at delivery (28.6 vs 28.1 years) or birth order (2.4 vs 2.2) when we compared the 751 positive responders from the birth series to the 1549 who did not respond to our letter. The response was somewhat lower for the 646 persons born in 1943 or 1947 (30%) compared with the other birth years (34%). With respect to distance between current address and the examination centre, 11% of those who were interviewed lived within 5 km (3 miles) of Leiden, as compared with 10% of those who were not interviewed, and 34% of the interviewed lived >45 km (28 miles) from Leiden as compared with 29% of those not interviewed. The median 1998 post-tax incomes were somewhat higher for postal district catchments of the interviewed (Euro 23 116) than for those not interviewed (Euro 22 919).

Selected characteristics at birth of study participants and non-participants from the eligible birth cohort
We found only marginal increases in birth weight [43 gram; 95% confidence interval (CI): −0.3–85], crown to heel length (0.25 cm; CI: 0.04–0.45), placental weight (2 gram; CI: −10–14), maternal age at delivery (0.9 years; CI: 0.4–1.4), or infant birth order 0.13 (0.03–0.30) when we compared the birth characteristics of the 751 study participants of the hospital series with those of the remaining 2556 infants of the eligible birth cohort. These differences did not change with statistical adjustment for

Table 2 Cross-classification of famine exposure based on LMP date and partially overlapping exposure windows by exposure based on date of birth and non-overlapping exposure windows. Study cohort births in three institutions (Amsterdam, Rotterdam and Leiden) in the western Netherlands, 1943–47

| Exposure categories based on date of birth in the studies of Stein et al.,1 G.P. Ravelli et al.,13 Lumey et al.,14 Susser et al.,19 and A.C. Ravelli et al.11 | Exposure categories based on date of birth with non-overlapping exposure periods12 |
|---|---|---|---|---|---|
| Exposure period in pregnancy | No exposure | Early | Mid | Late | All |
| No exposure in pregnancy | 1639 | 8 | 35 | 1682 |
| Exposure period in pregnancy weeks 1–10 | 21 | 347 | 2 | 370 |
| weeks 11–20 | 225 | 343 | 568 |
| weeks 21–30 | 520 | 92 | 612 |
| weeks 31–delivery | 101 | 496 | 597 |
| Exposure at any time in pregnancy | 21 | 445 | 663 | 496 | 1625 |
| All | 1660 | 453 | 663 | 531 | 3307 |

*Count for categories weeks 1–10 to weeks 31–delivery combined may exceed count for exposure at any time in pregnancy because of partial overlap of exposure categories.
date of birth and follow-up status (died, emigrated, current address found and no current address available).

What has it found so far?

Based on birth records, we have shown to date that except for birth weight following exposure in late pregnancy, measures of newborn weight, length and head circumference, taken alone or as any of their ratios, are poor indicators of maternal nutrition in pregnancy, even under the extreme conditions of the Dutch famine. This makes their use as indicators of prenatal nutrition in studies of adult disease problematic. We also established that exposure to the famine was not associated with the proportion of boys and girls at birth (sex-ratio).

With respect to outcomes measured at age 59, we found significant changes in anthropometric measures indicative of the deposition of fat at several tissue sites in exposed women compared across exposure categories. Somewhat less of an issue for continuous outcomes such as vascular disease incidence or deaths. Statistical power may be especially for discrete outcomes such as incidence of cardiovascular disease or deaths. Although both approaches have their strengths and weaknesses, we believe that the use of LMP rather than date of birth is preferable for the long-term follow-up of exposures in specific periods of pregnancy.

Strengths and weaknesses

Exposure

The circumstances of the Dutch famine provide a natural experiment to directly examine the long-term health effects of profound nutritional changes at different stages in pregnancy. With archived records of the weekly food rations distributed in the affected areas, there is no need to use birth weight as a proxy measure of maternal nutrition in pregnancy.

In this study, we assigned exposure based on the date of mothers’ LMP from the birth record, adjudicated where necessary. In contrast, previous studies of birth cohorts from the Dutch famine have used date of birth, assuming a gestation of 40 weeks for all participants across all exposure categories. Although both approaches have their strengths and weaknesses, we believe that the use of LMP rather than date of birth is preferable for the long-term follow-up of exposures in specific periods of pregnancy.

Study population

We have traced and examined a new birth cohort series from three institutions in the western Netherlands for which this information was previously not available. This allows for an independent assessment of birth cohort observations from other institutions. Our study group also adds to the number of persons in birth cohorts drawn from the famine. This is important because individual studies have limited study power for the detection of the long-term effect of the exposure, especially for discrete outcomes such as incidence of cardiovascular disease incidence or deaths. Statistical power may be somewhat less of an issue for continuous outcomes such as weight, blood pressure or metabolic measures when they are compared across exposure categories.

We and others have shown that normally the loss to follow-up is low (11% or less) when infants are traced from their famine birth records to their current address in The Netherlands some 50 years later. In this study the loss to follow-up was 9% when we exclude the 130 infants (4% of the cohort) who were not traced by the Rotterdam registry as they had been born out of wedlock. Other local registries did not object to tracing for this reason. Subsequent study enrolment of the majority of traced people can be more of a problem, however, depending on study protocol.

The proportion of eligible participants among those alive and resident in The Netherlands who were enrolled for study was 84% in 1992 when only home interviews were conducted, 36% in 1998, when clinical examinations were carried out in men and women of the Amsterdam birth cohort, and 28% for the present study with a clinical examination between 2003 and 2005. Although we wished to enrol a larger proportion of those eligible for clinical examinations, we found that this was not possible with the current study protocol that included a clinical examination in a central study hospital. There is no evidence for follow-up bias in the current study, however, when we compare selected birth characteristics of the study participants with those of other eligible cohort members who did not participate because of death, emigration, loss to follow-up or refusal.

To maximize participation in future studies of the cohort, it will be important to consider the use of telephone or home interviews whenever possible and to simplify and shorten clinical study protocols. This will also be helpful in future studies of subsets of the current study population. An optimal enrolment strategy will depend on the study question and on available funds.

Sibling controls

Our use of sibling controls in this area of research is novel. These controls were chosen to reduce the potential for bias related to family-level factors with an effect on health outcomes that is independent of the exposure of interest. This is important in light of the strong associations between socioeconomic status of the family and fertility during the famine, with stronger declines in fertility among manual vs non-manual occupations.

We will analyse the effects of having such controls in a future publication.

Intermediary variables over the life course

Although extensive recorded information is available from the time of birth and from the time of examination at age 59 years, there is no source for intermediary data points except for the individual interview, in which we ascertained recalled weight at age 20 and 30 and collected a medical history.

Within The Netherlands health care system, well baby clinic records were collected for all study participants and reports from annual school health examinations were collected through adolescence that included height, weight and selected medical problems. Both these sets of data are no longer available for study, however, as they have been discarded by the local health authorities. Military examination records are not routinely available for analysis in The Netherlands. For the studies of mental performance and body size among Dutch recruits mentioned earlier, an anonymized computer data file was prepared by the military authorities with information on these research questions.
Study outcomes

Although the primary study focus is on risk factors for offspring cardiovascular and metabolic disease among offspring in relation to prenatal nutrition, we also collected measures of hand morphology (fingerprint ridge-count differences and digit-length ratios) as potential markers of early pregnancy circumstances as they are formed in early pregnancy and are unlikely to change thereafter. Our first analyses suggest that these measures may indeed be useful in epidemiological studies of fetal programming where specific prenatal exposures may not be well defined. In addition, we collected some measures in other domains (e.g. cognition and mental health) to provide a basis for further studies in these areas. Future analyses of biological specimens collected from the participants (including DNA) may point to other metabolic or to epigenetic effects of changes in the prenatal environment.

Can I get hold of the data? Where can I find out more about the study?

Specific proposals for collaborations are welcome. Further information about the study can be obtained from the Principal Investigator (LHL) who can be contacted through e-mail at lumey@columbia.edu.

Acknowledgements

We thank our study consultants H.A. Delemarre-van de Waal, Department of Paediatric Endocrinology, Free University, Amsterdam; J.A. Romijn, Department of Medicine, Leiden University Medical Center and J. van Roosmalen, Department of Obstetrics, Leiden University Medical Center; for their advice on study design and logistics.

We thank R.J. Prineas, Wake Forest University School of Medicine, Winston Salem North Carolina, USA for his training of the local study staff in ECG acquisition and transmission methods; R.A. Bausch-Goldbohm of the TNO Quality of Life Institute in Zeist for the design of the food frequency questionnaire; J. Jolles of the University of Maastricht for the design of the neuropsychological test battery and B.J.M. Delemarre, Department of Cardiology, Leyenburg Hospital, the Hague, for the clinical review of all ECG results.

The study External Advisory Board included George Davey Smith, University of Bristol, England; Leiv S. Bakketegh, University of Southern Denmark, Odense, Denmark and Mervyn W. Susser, Columbia University, New York, NY, USA. Finally, we thank Z.A. Stein for reviewing the manuscript and all participants for their involvement in the study.

The funding of the study was supported by grant RO1 HL067914 (Principal Investigator: LHL), National Institutes of Health, USA.

References


