Dutch Famine Birth Cohort

How a historical disaster has contributed to the field of maternal and child nutrition

A brief history of the war-induced famine

The Dutch famine lasted from November 1944 to May 1945. During this period, referred to as “hunger winter," food rations were less than 1,000 calories per person per day. Germany had occupied the Netherlands since May 1940, and by September 1944, ally troops had liberated most of the country except for a German occupied area, which had a population of 4.3 million people. The Dutch government called for a national railway strike to hinder German military advances. In retaliation, German authorities blocked off all food shipments to the remaining occupied area, which included Amsterdam. The blockade, in combination with an unusually harsh winter that stalled food and fuel shipments, culminated in famine. The strike was not called off until the German surrender at the end of WWII in May 1945.¹

The Dutch famine birth cohort consists of individuals who were born during the famine times and their matched controls. Clement Smith from Harvard Medical School was the first to realize the unique opportunity this historical disaster presented. He published the first paper, *the effect of famine on pregnancy and its product* ³ in 1947 and reported that babies born during the famine were 200 g lighter at birth.⁴

The Background
The original goals of the birth cohort, methods of recruitment and measurement, baseline data collected and more!

The Results
What they discovered, the challenges, strengths and limitations of the study

The Legacy
A brief overview of how the Dutch famine has contributed to our understanding of maternal nutrition
The Background

The original goal of the cohort: To study how changes in maternal nutrition during pregnancy affect the offspring’s risk for metabolic and cardiovascular disease in adulthood. They also searched for critical time windows when fetal programming might occur and examined outcomes such as cognitive status, depression, and type 2 diabetes.

Methods for recruitment:
Eligibility for recruitment includes single born offspring born in the Netherlands between November 1943 and February 1947. The babies were born in Midwifery training schools in Amsterdam, Rotterdam or the University Hospital in Leiden. They lived in the Netherlands at time of entry into the study. The cohort is split into smaller subgroups, which were exposed to famine at different stages of pregnancy.

Methods for Measurement:
From birth records, information such as address, names, last menstrual period, religion, occupation, number of previous births, spontaneous abortions and other vitals were recorded. Telephone interviews were conducted for socio-demographic characteristics including lifestyle and health status. In a clinical setting, participants fasted before giving blood samples for vital health checks.

Baseline data for mother:
Age at delivery, occupation, religion, last menstrual period, number of previous pregnancies, spontaneous abortion history, first prenatal visit, weight, height, blood pressure, date, time of delivery, postpartum weight (at 2 of 3 clinics), mode of delivery.

Baseline data for infant:
Birthdate, birth weight, sex, crown to heel length, head circumference, placental weight, vital status at discharge, address.

Baseline characteristics of the enrolled participants:
They experienced war-induced famine while they were in utero from November 1944 – May 1945. The control group did not experience famine.

How cohort was tracked and followed:
The original cohort had 1116 women, of which 16% died, 8% had emigrated from the Netherlands by 1993. Of the remaining women, 683 of 813 agreed to be interviewed in their homes. They tracked people down by name and address at birth to the local population registrars with a request to provide a current address. With their consent, they conducted telephone interviews on sociodemographic characteristics. When possible, same sex siblings of each member were recruited as a control, however there was missing information about prenatal and delivery care for these controls.

Earlier investigators who studied the same famine exposure:
1. Smith (1947): The first to investigate the cohort
2. Stein (1970’s): Studied Dutch Famine and health outcomes at 18 years old, analyzed from men conscripted at military service.
3. Gorman (Mid 1990’s): Use information in the national Dutch psychiatric registries to examine psychiatric outcomes among persons exposed to gestation. Found an increased risk of schizophrenia.
4. Lumey (Mid 1990’s - Present): Analyzed the famine-exposed cohort when aged 43 years. Found and interviewed 700 women after a long follow up period. Has an NIH Grant to continue studying famine.
5. Bleker (Early 2000’s): Added in male births, resulting in 2414 singleton men and women. Examined over 740 men and women’s health outcomes at 50 years.
### The Results

**Key Discoveries and more!**

**Exposure**

The main exposure is famine, for which the severity and duration is estimated by date and place of birth. Conception is estimated by the last menstrual cycle, or a 40-week gestational period was assumed. In general, this exposure is inadequate nutrition for pregnant women.

**Maternal and Child Health Outcomes associated with famine at individual and community levels:**

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Citation</th>
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<tbody>
<tr>
<td>Decreased fertility</td>
<td>2</td>
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<tr>
<td>Obesity</td>
<td>2</td>
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<tr>
<td>Glucose metabolism, diabetes</td>
<td>2</td>
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<tr>
<td>Congenital abnormalities if famine was during early gestation: neural tube defects, anencephaly, spina bifida</td>
<td>2</td>
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<tr>
<td>Schizophrenia</td>
<td>2</td>
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<tr>
<td>Low birth weight for 3rd trimester exposure and high birth weight for 1st trimester exposure</td>
<td>2</td>
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<tr>
<td>Fingerprint alteration</td>
<td>2</td>
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<tr>
<td>Irreversible damage to the brain</td>
<td>4</td>
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<tr>
<td>Anti-social personality disorder</td>
<td>4</td>
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<tr>
<td>Depression and psychoses (not all studies replicated this finding)</td>
<td>4</td>
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<tr>
<td>Less methylation of IGF2 gene compared to unexposed same sex siblings</td>
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**Research challenges**

- Impossible to verify the accuracy of historical data and self-reported data
- Went through population registries to identify 3307 singletons born during the Dutch Famine; time consuming and expensive
- Many well baby clinic records and adolescence medical records were discarded by local health authorities
- Loss of follow-up due to deaths, emigrations and noncompliance of protocols

**Strengths**

- Archived records of weekly food ration distributions in affected areas allows for detailed maternal nutrition log
- Large population size allows for more statistical power
- Have data on sibling controls, which allows for future research on sibling pairs to reduce possible confounders such as socioeconomic status and family environment
- Relatively low loss to follow-up, <9%

**Weaknesses**

- Have population data, not individual. They are at risk of ecological fallacy
- Missing important data such as socioeconomic status. At that time, only lower SES women gave birth at hospitals, risk of sampling bias

**Future Research Directions**

- Analyze using Dutch military records, which have detailed historical health records for 18 and 19 year olds.
- Epigenetics trends
**Study 1. Survival effects of prenatal famine exposure**

**Question studied.** Past studies have shown how prenatal famine exposure increases the incidence of cardiovascular and metabolic diseases in adulthood. Is prenatal famine exposure linked to shorter lifespan?

**Brief study description.** Roseboom et al. studied adult mortality among 1991 singletons. They compared overall and cause-specific mortality among people exposed to famine in early, mid, late gestational periods to unexposed controls using Cox proportional hazard models.

**Results.** 206 (10%) had died by the end of follow-up. Compared to controls, women exposed to famine in early gestation had a higher risk of adult mortality HR= 1.9, (1.1-3.4), cardiovascular mortality HR= 2.3 (1.1, 4.7) and breast cancer mortality HR= 8.3 (1.1, 63). In men there were no such significant observations.

**Strengths.** Relatively low rate of misclassification because they restricted this study to people born in Amsterdam, which was very severely affected by the famine. They also used detailed information about the type of nutritional deprivation.

**Weaknesses.** There is no individual data on famine exposure. Only lower/middle class women delivered at hospitals at the time, missing socioeconomic status information, a confounder.

**Why it is Important.** Undernutrition remains an issue in various parts of the world today. This shows that inadequate nutrition in utero is linked to higher mortality, heart disease & breast cancer.

**Study 2. Persistent epigenetic differences associated with prenatal famine exposure in humans**

**Question studied.** Are there epigenetic markers associated with prenatal famine exposure?

**Brief study description.** The mechanisms behind adult disease risk and prenatal famine are unknown and epigenetic deregulation is one hypothesis. Lumey et al. examined IGF2 (insulin-like growth factor II), which is a key gene for human growth and is maternally imprinted. They studied 60 individuals who experienced famine during early stages of development, and measured five CpG dinucleotides within IGF2.

**Results.** Four CpG sites were significantly less methylated among famine exposed individuals compared to their matched sibling controls (1.5 < E-4 < 8.1 E-3). The average methylation for all five sites was 0.488 among famine exposed and 0.515 for unexposed siblings. Thus, early prenatal famine exposure is associated with 5.2% lower methylation (P= 5.9 E-5). For late famine exposure, no difference was detected.

**Strengths.** Accurate technology, quantitative accuracy R2=0.98 for mass spectrometry.

**Weaknesses.** Small sample size, needs replication.

**Why it is Important.** Epigenetic markers affect future generations by altering gene expression. The famine is associated with adverse outcomes in future generations as well.

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**The Legacy: contributions to maternal/child nutrition:**

- Supports the **fetal origin hypothesis** that many chronic diseases originate in the womb due to adaptations made by the fetus in response to undernutrition.

- The effects of undernutrition depend on the **timing during gestation** and the organs and systems developing during that critical time window.

- The identification of **Celiac disease** can be partly attributed to the Dutch famine. Doctors realized that children gained weight and were healthier when precious bread supplies were no longer given to them. Post famine, the children started eating bread again, and got sick. Gluten was later identified as the culprit.