Neurodevelopmental Disorders after Prenatal Famine

The Story of the Dutch Famine Study

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The Dutch Famine Study (1) was one of the classic epidemiologic investigations that emerged from the Columbia University School of Public Health in the 1960s. In accord with its initial aim, the study has produced precious clues as to the role of prenatal nutrition in the etiology of neurodevelopmental disorders; yet the findings and their implications have emerged piecemeal, over decades. To our knowledge, the various branches of this neurodevelopmental research have never been tied together in a single thread. This commentary is intended to fill the gap and to tell the story of the Dutch Famine Study as an early model for epidemiologic research on prenatal exposures.

THE ORIGINAL DESIGN

The Dutch Famine Study was a “natural experiment” based on an extraordinary historical event known as the Dutch Hunger Winter. In 1940, the Netherlands were invaded by the German army, and by 1941 virtually all foods were being rationed. For several years, the rationing successfully ensured basic nutrition for the population, with a well-balanced average daily ration in the range of 1,500–2,000 kcal for most of the period. Toward the end of 1944, however, that situation changed. After the Allied defeat at Arnhem in September of 1944, the Nazi occupation force imposed an embargo on transport in the region still under occupation, which included the Netherlands’ six largest cities: Amsterdam, Rotterdam, The Hague, Utrecht, Leiden, and Haarlem. The embargo almost immediately produced a food shortage in these cities, which over the ensuing cold winter of 1944–1945 evolved into a severe famine. By February 1945, the daily ration comprised mainly bread, potatoes, and sugar beets and yielded less than 1,000 kcal (2, 3). The famine reached its peak during the 4 weeks before the Liberation of early May 1945, when the advance of Allied forces had completely separated the western region from the rest of the country (1–4; parents of H. W. H., personal communication, 1996). During the height of the famine, malnutrition was the leading cause of death in the six famine-stricken cities; more than 20,000 persons died of famine-related causes (1–3).

Unlike other famines, the Dutch Hunger Winter struck at a precisely circumscribed time and place, and in a society able to document the timing and severity of the nutritional deprivation as well as its effects on fertility and health. As a result, it was possible to define sequential birth cohorts that were exposed to the famine at specific times during gestation, as well as to define birth cohorts that were not exposed. Moreover, because the Dutch maintained comprehensive health records over a long period after the famine, the incidence of neurodevelopmental disorders could be compared in the exposed and unexposed cohorts during infancy, childhood, and adulthood.

The design of the Dutch Famine Study may be considered ecologic, since the central comparison was between exposed and unexposed monthly birth cohorts of 1944–1946 in the six famine-stricken cities (1, 5). This study had a number of strengths, however, that are rarely present in an ecologic design. Individual exposure was unlikely to be misclassified on the basis of birth cohort membership, because the famine was clearly demarcated in time and place, and was pervasive in the population of the six cities. The potential for confounding was minimized because the exposed and unexposed birth cohorts of the famine-stricken cities were highly similar, their members having been born only a few months apart in the same cities. Secular trends were controlled because of the inclusion of unexposed birth cohorts born before as well as after the exposed, and, in addition, by a further comparison with unexposed birth cohorts born at the same
time as the exposed in nonfamine cities. Thus, the study is perhaps better described as a natural experiment (6).

EARLY FINDINGS

The first investigations of the effects of prenatal famine on neurodevelopment were focused on cognitive development and mental retardation. The authors relied upon data obtained from the military induction of Dutch males aged 18 years (1, 5). In the Dutch military draft system at the time, the names of all men reaching the age of 18 were forwarded to the military authorities from population registers kept by each community. These men were called up for a thorough and standardized medical and psychological examination. Those institutionalized for mental disorders or other handicaps did not have to appear in person, but their clinical histories were reviewed and diagnoses were entered into the military record. The military authorities made available the complete results of these examinations for all Dutch men born during the years 1944-1946.

The findings were unambiguous—and negative. Despite the fact that birth cohorts exposed to acute famine at certain times in gestation showed an excess of low birth weight and infant mortality, there were at age 18 years no detectable adverse effects on cognitive ability, including intelligence quotient, nor was there an increased prevalence of mental retardation (1). This result was controversial, as it was widely believed that prenatal nutritional deficiency should lead to retarded cognitive development. Among the leading critics was Benjamin Pasamanick, a major figure of the time whose work on prenatal brain insult and neurodevelopment is still widely cited. Nonetheless, the result stood the test of time, and ultimately forced more precise formulation as well as more rigorous testing of the nutritional hypothesis.

A CLUE

For other neurodevelopmental outcomes, there was a single but salient finding. The birth cohort conceived during the peak of the famine exhibited an increased prevalence of congenital anomalies of the nervous system. Among military inductees, an increased prevalence of spina bifida, hydrocephalus, and cerebral palsy was detected (1). A complementary analysis of mortality data from birth to age 17 years hinted at an increase in deaths from a similar grouping of congenital neural defects (1).

This was possibly the first epidemiologic study of prenatal nutrition and neural tube defects. It helped to motivate a line of research which ultimately produced one of the most important contributions of post-World War II epidemiology. As is now well known, this work culminated in a series of randomized controlled clinical trials which demonstrated that folic supplementation to pregnant mothers during the periconceptional period has a substantial preventative effect against neural tube defects (7, 8).

Moreover, the original data of the Dutch Famine Study continue to yield potentially valuable clues as to the causes of neural tube defects. Twenty-five years later, the original mortality data were revisited (9).

Applying narrower definitions now available for both the famine exposure and the outcomes (10-12), the data were analyzed specifically for spina bifida, in males and females. The effect of early prenatal famine was seen only in males, suggesting sex-specific effects of prenatal nutrition on the incidence of spina bifida. These mortality data also suggested an opposite sex difference—an effect in females but not in males—for a group of other neurodevelopmental conditions that included epilepsy, cerebral palsy, and spastic diplegia.

A TWIST OF FATE

Decades later, the investigation was extended to neurodevelopmental disorders that are diagnosed in adulthood. The guiding hypothesis was that prenatal famine could have latent effects which manifest in midlife or even late stages of the life cycle. This work was carried out by us (10-13), and was initiated by the son (E. S.) of two of the original authors.

In general, this new research conformed closely to the design of the original study. Building on the previous work, however, the hypothesis was more specific with regard to the prenatal exposure. The original study set out with a broad focus on prenatal nutrition, examining the effects of famine at all stages of gestation. By contrast, the new studies began with a specific focus on the birth cohorts conceived at the height of the famine—cohorts which had shown an excess of congenital neural defects and therefore might be expected to also show an excess of neurodevelopmental disorders later in life.

We began with the outcome of schizophrenia, motivated by growing evidence that despite its onset in adulthood, schizophrenia may be a neurodevelopmental disorder. Similar to the investigators in the original study, we sought national data sets that would enable us to determine the incidence of schizophrenia in exposed and unexposed birth cohorts without resorting to a costly and probably infeasible follow-up of all of the individuals in these cohorts. The Dutch national psychiatric registry proved appropriate for this purpose; the registry ascertained cases of psychiatric disorder resulting in hospitalization, and included infor-
information on diagnosis as well as on date and place of birth, data required to identify cases as belonging to the exposed or unexposed birth cohorts.

As hypothesized, the risk of schizophrenia was significantly increased in the birth cohort conceived at the height of the famine. (The finding was seen mainly in women in an early, limited study (10) but in both men and women in a later, more complete study (11).) The increased risk was specific to schizophrenia; the incidence of other psychiatric disorders was not increased in this cohort (13). In a twist of fate, the originator of the prenatal nutritional hypothesis for schizophrenia was Benjamin Pasamanick (14), who led the criticism of the early results on intelligence quotient; this time the data proved him right.

Following the result obtained for schizophrenia, we once more found occasion to revisit the data of the original Dutch Famine Study, this time the military induction data (12). Although schizophrenia was rarely diagnosed among the inductees because of their young age, it was possible to examine the International Classification of Diseases (15) diagnosis of schizoid personality, a "schizophrenia spectrum" disorder likely to be etiologically related to schizophrenia. The prevalence of schizoid personality was significantly increased in the exposed birth cohort (12), complementing and extending the result for schizophrenia.

**FROM ECOLOGIC RESEARCH TO MOLECULAR RESEARCH**

The findings described thus far suggest an intriguing constellation of disorders thought to be related to neurodevelopment—central nervous system anomalies including neural tube defects, schizophrenia, and schizophrenia spectrum personality disorder—in the birth cohort conceived at the height of the Dutch famine (figure 1). Are these disorders etiologically related, and if so, in what way?

To answer this question, the Dutch Famine Study is now making the transition from ecologic findings to molecular epidemiology. Using the remarkable Dutch data registries that were vital to the original study, the exposed schizophrenia patients and two control groups—unexposed cases and exposed noncases—are being traced. Once these persons are located, they are studied in depth, using neuroimaging, serologic analysis, and genetic as well as psychosocial assessments (16). This study is spurred by the hope that, having suffered the same prenatal insult, the schizophrenia patients within the exposed cohort will be distinctive, and thereby demonstrate a "neurodevelopmental" subtype of schizophrenia. At the same time, because of the relative homogeneity of their prenatal exposure, studies of these patients represent a powerful design for the detection of genetic factors that confer a vul-

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** Neurodevelopmental disorders in the 1944-1946 Dutch birth cohorts: comparison of unexposed cohorts with those exposed to severe famine early in gestation. Case definitions were provided previously (12, 13, 15). Briefly, central nervous system (CNS) anomalies represent males only, and were computed as deaths of children aged 0–17 years (spina bifida, anencephaly, other CNS anomalies) plus cases (spina bifida, anencephaly, hydrocephalus) found among military inductees at age 18 years, per 2,000 live births. "Schizophrenia" includes both men and women, and was computed as International Classification of Diseases, Ninth Revision (ICD-9) cases of schizophrenia (paranoid, hebephrenic, residual, and catatonic) from the Dutch psychiatric registry occurring at age 24–48 years, per 1,000 survivors to age 18. "Schizoid personality" comprises males only, computed as number of ICD-6 cases of schizoid personality per 1,500 military inductees.
nerability to developing schizophrenia after prenatal insult.

CONCLUSION

The Dutch Famine Study provides a classic example of a well-designed epidemiologic study which made a lasting scientific contribution, albeit in some unexpected ways. At the same time, the story of this study calls to attention aspects of epidemiologic research that do not often draw comment. Science and history were interwoven, with this natural experiment being based on a tragic wartime experience. The elucidation of the findings required the continuation of the study over a long period of time—something which depended upon the strength of familial and personal ties, as the study was literally passed on from the original investigators to their children and other students.

This review of the Dutch Famine Study focuses on the results pertaining to neurodevelopment. The study was later extended to examine a broad range of outcomes, including obesity, cardiovascular disease, reproductive performance, and breast and ovarian cancer, and it has produced many important findings in these areas (17–20). For example, a separate branch of the study was begun in the mid-1980s by a Dutch student of the original investigators (18–20). Women born in Amsterdam during the famine were followed up to examine the reproductive outcomes of the next generation. Early prenatal exposure to the famine was related to adverse reproductive outcomes in the next generation. Thus, investigators are now tracing the health effects of prenatal famine into the late stages of the life cycle of the exposed, and, further, the transmission of health effects to the children of the exposed. As these branches grow from the tree of the Dutch Famine Study, the story yet unfolds, and this unfortunate wartime event continues to yield vital information.

REFERENCES