ORIGINAL ARTICLE

Schizophrenia After Prenatal Famine

Further Evidence

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Background: Suggestive findings of an earlier study that prenatal nutritional deficiency was a determinant of schizophrenia prompted us to undertake a second test of the hypothesis using more precise data on both exposure and outcome.

Methods: Among persons born in the cities of western Netherlands during 1944 through 1946, we compared the risk for schizophrenia in those exposed and unexposed during early gestation to the Dutch Hunger Winter of 1944/1945. The frequency of hospitalized patients with schizophrenia at age 24 to 48 years in the exposed and unexposed birth cohorts was ascertained from a national psychiatric registry.

Results: The most exposed birth cohort, conceived at the height of the famine, showed a twofold and statistically significant increase in the risk for schizophrenia (relative risk [RR] = 2.0; 95% confidence interval [CI] = 1.2 to 3.4; $P<.01$) in both men (RR = 1.9; 95% CI = 1.0 to 3.7; $P=.05$) and women (RR = 2.2; 95% CI = 1.0 to 4.7; $P= .04$). Among all birth cohorts of 1944 through 1946, the risk for schizophrenia clearly peaked in this exposed cohort.

Conclusion: Prenatal nutritional deficiency may play a role in the origin of some cases of schizophrenia.

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WE TESTED the hypothesis that early prenatal nutritional deficiency is associated with an increased risk for schizophrenia.[1-3] The evidence grows that schizophrenia is, in some cases, a neurodevelopmental disorder.[4-9] For instance, numerous studies have now demonstrated that schizophrenia can be associated with abnormalities in brain structure[9,10] and in cognitive and behavioral development.[11-13] Prenatal nutritional deficiencies are important causes of other neurodevelopmental defects.[14-16] Therefore, their possible contribution to schizophrenic illness warrants investigation.

Birth cohorts exposed to early prenatal nutritional deficiency during the Dutch Hunger Winter of 1944/1945[17-20] were compared with those unexposed, with regard to the risk of hospitalization for schizophrenia in adulthood. In an earlier, more limited study,[1-3] we found a significant increase in schizophrenia in exposed women but not in men. Because this association could have important implications for the origin of schizophrenia, these suggestive findings prompted us to undertake a larger and more systematic investigation using new data on exposure and outcome. The present study was not an independent replication, but it was designed to extend and refine our earlier work.

See also pages 11, 19, and 32

Toward the end of World War II, a Nazi blockade precipitated a severe famine in western Netherlands. The Dutch Hunger Winter began in October 1944, gradually increased in intensity over the ensuing months, and ended abruptly on liberation in early May 1945.[17-19] The cities of western Netherlands were affected more than rural areas. At the height of the famine from February to April 1945, the population of these cities suffered severe adverse effects including high mortality from malnutrition.[17-19] The Dutch Hunger Winter was unique in that a famine of brief and clearly defined duration afflicted a population that

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METHODS

We report on birth cohorts of 1944 through 1946 in the six cities in the famine region of the Netherlands with populations larger than 40 000 (Amsterdam, The Hague, Haarlem, Leiden, Rotterdam, and Utrecht). Obviously, the exact date of conception of the birth cohorts was not known. In a full-term pregnancy, conception would be 8 to 9 months prior to birth. For instance, full-term births in November 1945 would have been conceived in February and March 1945; full-term births in December 1945, in March and April 1945.

The cities of other regions of the Netherlands were not included in this analysis. These regions did experience periods of moderately low rations and were included in our earlier study.[1-3] However, because they were not exposed to severe famine and did not show a significant increase in congenital neural defects, a comparable refinement in the analysis was infeasible.

EXPOSURE

As stated above, three criteria were used to define the exposed birth cohorts: (1) low food rations during the first trimester, (2) conception at the height of the famine, and (3) increased congenital neural defects. To establish the first criterion, we used the average food ration during each trimester of gestation, previously documented for all monthly birth cohorts of 1944 through 1946.[17] For the birth cohorts of August through December 1945, average food rations during the first trimester were below 1000 kcal daily (4200 kJ).[1] These cohorts were defined as *exposed to low rations*. All other birth cohorts of 1944 through 1946 (born in 1944, in January through July 1945, and in 1946) were defined as *unexposed*.

For the second criterion, we relied on the documented health outcomes of the famine period. These data indicate that the height of the famine was toward the end of the Hunger Winter (during February through April 1945). The population was nutritionally depleted, and the effects on morbidity and mortality were most severe.[17-19] The early months of the Hunger Winter were not as harsh.

Among the cohorts of August through December 1945, only the later born (born October 15 through December 31, 1945) were conceived during the height of the famine and, therefore, met our second criterion for exposure. We shall refer to these later born as the EX2 cohort. Owing to the timing of their conception, the EX2 cohort was marked by fertility below 50% of previous levels.[17-19] The earlier born (born August 1 through October 14, 1945) were conceived in the early months of the Hunger Winter and did not meet our second criterion for exposure. We refer to these earlier born as the EX1 cohort. In accord with the lesser exposure, the EX1 cohort suffered a smaller decline in fertility.[17]

With regard to the third exposure criterion, increased risk for congenital neural defects, we examined the *International Classification of Diseases (ICD)* categories with established or strongly suspected links with early prenatal nutritional deficiency, including neural tube defects (*ICD-5*[22] spina bifida 731 and anencephaly 733; *ICD-6*[23] spina bifida 751 and other central nervous system anomalies including microcephaly 753.4). We reanalyzed the data of Stein et al[17] that were available only for male subjects. Data on deaths caused by these defects from birth to age 17 years were obtained from national mortality data of the Netherlands Central Bureau of Statistics.[17] Data on those surviving to age 18 years were obtained from military records.[17] Military induction was compulsory for all male individuals of these birth cohorts, and inductees were administered standardized medical examinations. The risk for congenital neural defects in the EX2, EX1, and unexposed

maintained excellent records on food rations during the famine and on health outcomes during the famine and in subsequent decades.[17-20]

With regard to exposure, our a priori hypothesis[1(p 983)] was that an increased risk for schizophrenia would be found among the birth cohorts conceived at the height of the famine and exhibiting an excess of congenital neural defects. Accordingly, in the present study, three criteria were used to define the exposed birth cohorts: (1) low food rations during the first trimester of gestation, (2) conception at the height of the famine as indicated by adverse health effects in the general population, and (3) a detectable excess of congenital neural defects. Whereas our prior study[1] relied on the first criterion alone, this current study obtained data that enabled us to differentiate between exposed birth cohorts satisfying only this first criterion and those satisfying all three criteria.

With regard to outcome, the data of the Dutch national psychiatric registry afforded comprehensive ascertainment of hospitalized patients with schizophrenia at 24 years of age and older in the exposed and unexposed birth cohorts. The registry data of our earlier study were restricted to schizophrenic patients hospitalized at age 32 years and older. This expansion of the outcome data was crucial because the first hospitalization for schizophrenia is most often before age 30 years, especially in men.[21] Taken together, the new data yielded, on the one hand, a considerably more precise definition of the exposed birth cohorts and, on the other, a larger number of cases that are more representative in terms of age at onset and course of illness. The sample size now ensured adequate statistical power to detect a meaningful association between a precisely defined prenatal famine exposure and the risk for narrowly defined schizophrenia.

RESULTS

Our a priori data analysis used the narrow definition of schizophrenia and the most recent discharge diagnosis. The risk for schizophrenia was significantly higher in the EX2 cohort than in the unexposed cohort (**Table 2**) (RR=2.0; 95% CI = 1.2 to 3.4; $P<.01$). The RR did not vary by gender; among men, the RR=1.9 (95% CI = 1.0 to 3.7; $P=.05$), and among women, the RR = 2.2 (95% CI = 1.0 to 4.7; $P=.04$). The risk for schizophrenia was not increased in the EX1 cohort.

Figure 2 shows the risk for schizophrenia in 17 successive birth cohorts of 1944 through 1946. The risk for schizophrenia peaked in the EX2 cohort and was otherwise stable.

We reanalyzed the finding for the EX2 cohort under a broad definition of schizophrenia and using other

cohorts was computed as the total number of cases (deaths plus survivors to age 18 years) divided by the number of births (stillbirths were not included because causes of mortality were not available for stillbirths). The EX2 cohort had a detectable excess of congenital neural defects (relative risk [RR] = 2.5; 95% confidence interval [CI] = 1.3 to 4.9; $P<.01$), while the EX1 cohort did not (RR = 1.1, not significant) (**Table 1**).

For further confirmation, we examined secular trends in congenital neural defects. The birth cohorts of the years 1944 through 1946 were divided into 2-month periods. However, to maintain the integrity of the EX1 and EX2 cohorts, the period of May through December 1945 was divided into May through July, August 1 through October 14 (EX1), and October 15 through December 31 (EX2). For each of the 17 successive birth cohorts so defined, the risk for congenital neural defects (in male subjects) was computed as the number of cases divided by the number of births. The risk clearly peaked in the EX2 cohort (**Figure 1**).

Thus, the exposed birth cohorts comprised two distinct groups. The EX2 cohort met all three exposure criteria. The EX1 cohort met only one of the three criteria.

OUTCOME

Cases of schizophrenia were ascertained from the Dutch national psychiatric registry. Registry data were available for 1970 through 1992, comprising persons 24 to 48 years of age for the birth cohorts of 1944 through 1946. Data on cases were derived from psychiatric and university hospitals, which account for more than 90% of psychiatric admissions in the Netherlands. Data on each case included *ICD-8–ICD-9*[24] diagnosis, place of birth, and week of birth.

We used *narrow* and *broad* definitions of schizophrenia as in our previous study. Narrowly defined schizophrenia included only those cases in which the *ICD-8–ICD-9* diagnosis was that of paranoid, hebephrenic, residual, or catatonic schizophrenia,[1] in accordance with the modern criteria for schizophrenia.[25] While severely restricting the number of cases, this definition also minimized the risk of misclassification of affective psychoses as schizophrenia. Broadly defined schizophrenia included all cases with an *ICD-9* diagnosis of schizophrenia, irrespective of the subtype.

DATA ANALYSIS

We analyzed the data under the a priori narrow definition of schizophrenia, using the most recent discharge diagnosis. The risks for schizophrenia in the EX2 cohort, the EX1 cohort, and the unexposed cohort were computed by dividing the number of cases by the number of births minus deaths up to age 18 years. Risk was multiplied by 1000 to derive the risk (ie, cumulative incidence) per 1000 persons. The RRs in the exposed compared with the unexposed were calculated, and 95% CIs for these RRs were derived using the Taylor series.[26]

The χ^2 statistic was used to test the null hypothesis of no association between exposure and disease.[26] Owing to the large numbers of births in both the unexposed (136 691) and the exposed (EX1 = 5466; EX2 = 4190) cohorts, statistical power was sufficient even with the smaller number of cases under a narrow definition of schizophrenia and a refined definition of exposure. For example, for a "true" RR of 2.2, the probability that the null hypothesis would be rejected at $\alpha=.05$ was greater than 80%.

Seasonal and other fluctuations in the rate of schizophrenia were examined by dividing the birth cohorts of 1944 through 1946 into 17 successive cohorts, as described above for congenital neural defects in male subjects.

procedures for selecting the diagnosis. The association between early prenatal exposure to famine and schizophrenia was consistent under six approaches (**Table 3**).

COMMENT

This study offers evidence of a relation between early prenatal nutritional deficiency and the risk for hospitalized schizophrenia in adulthood. The EX2 birth cohort, conceived at the height of the Dutch Hunger Winter, had a significant, twofold increase in the risk for schizophrenia. The increased risk for schizophrenia in the EX2 cohort was evident in men as well as in women and occurred in the context of an otherwise stable incidence of schizophrenia. The EX1 cohort exhibited no increased risk for schizophrenia.

The exposure of the EX2 cohort to early prenatal nutritional deficiency is well established. This birth cohort (although born after the famine) was conceived in the worst months of the Hunger Winter when supplementary food supplies were virtually exhausted. Extensive evidence documents the nutritionally depleted state of the population.[17-19] Women conceiving during this period were nutritionally depleted prior to conception and, in addition, were poorly nourished after conception.

On several counts, the findings possess a high degree of specificity regarding both the prenatal famine exposure and the psychiatric outcomes. First, the EX2 cohort, conceived in the last months of the famine, were exposed only during early gestation because food was plentiful immediately on liberation. Second, the EX1 cohort showed no increased risk for schizophrenia after a lesser exposure during early gestation. Third, birth cohorts exposed to the famine in later stages of gestation exhibited no increased risk for schizophrenia. Fourth, the increased risk for schizophrenia in the EX2 cohort did not extend to other neuropsychiatric disorders. Affective disorders may have been increased in cohorts exposed to the famine later in gestation but were not increased in the EX2 cohort.[17,18,27] Fifth, while the increased risk was evident under all definitions of schizophrenia, it was most marked under a narrow definition consistent with modern criteria. Taken together, the notable specificity in these domains enhances the credibility of these findings as a whole and of the proposed nutritional explanation in particular.

Nonetheless, it is also important to consider alternative explanations that may be consistent with our findings. Selection processes could have led to an artifactual association between prenatal famine exposure and schizophrenia. In addition, other factors may have mediated or confounded the effects of prenatal famine exposure.

Table 1. Congenital Neural Defects* in Males of Birth Cohorts Exposed† and Unexposed† to Early Prenatal Nutritional Deficiency During the Dutch Hunger Winter of 1944 Through 1945: Prevalence Data

	Cohort		
	Exposed		
Prevalence Data	EX2 (n=2327)	EX1 (n=2993)	Unexposed (n=74 245)
Prevalence, per 1000 live births (No. of cases)	3.9 (9‡)	1.7 (5‡)	1.5 (115)
Relative risk (95% confidence interval)	2.5 (1.3-4.9)	1.1 (0.4-2.6)	...
P	<.01	.7	...

**Deaths from birth to age 17 years plus survivors at age 18 years (*ICD [International Classification of Diseases]-5 *731, 733;* ICD-6 *751, 753.4).*

†EX2 indicates exposed birth cohort of October 15 through December 31, 1945; EX1, exposed birth cohort of August 1 through October 14, 1945; and unexposed, all other births of 1944 through 1946 in the famine cities.

‡One case of October 1945 excluded because day of birth was missing.

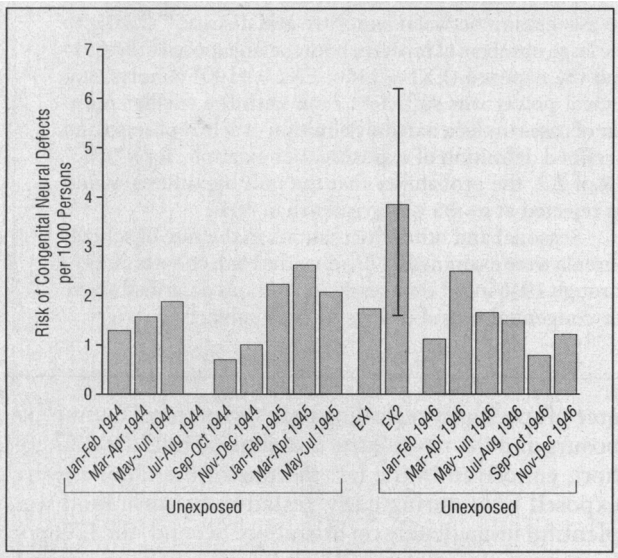

Figure 1. *Congenital neural defects in male individuals (death plus surviving subjects to age 18 years) in Dutch birth cohorts of 1944 through 1946. EX1 and EX2 indicate cohorts born August 1 through October 14, 1995, and October 15 through December 31, 1945, respectively; bar, 95% confidence limits.*

SELECTION BIAS

One possibility is selective conception. Persons conceiving during the famine, when fertility was low, may have had unusual characteristics. Hypothetically, women genetically predisposed to schizophrenia might be more inclined than others to attempt conception at such times. However, poor nutrition was probably the most critical factor in conception;[17] hence, the decline in fertility was more marked in the lower compared with the upper classes.[17,18] In this light, one might expect women predisposed to schizophrenia to have had especially *low* rates of conception during the famine period, as they may have been less successful than others in competing for black market and other extra ration food.

A second possibility is selective survival. The live births of the EX2 cohort represent conceptions that survived difficult circumstances. It has been suggested that the persistence of schizophrenia, despite reduced fertility and survival among cases, may be explained if genes that increase the risk for schizophrenia also confer a selective advantage in some other area.[28] Possibly EX2 births were selected for some genetic factor that is associated with better survival from conception to birth but that is also associated with an increased risk for schizophrenia.

OTHER FACTORS

Prenatal nutritional deficiency may have exerted an effect on the risk for schizophrenia only indirectly, via some other factor. Owing in part to their prenatal exposure to the famine, the EX2 cohort suffered a high perinatal mortality. Perinatal complications have been associated with an increased risk for schizophrenia.[7] However, some of the unexposed birth cohorts of 1944 through 1946 were also afflicted by high perinatal mortality, albeit for different reasons. The unexposed cohorts with high perinatal mortality did not experience increased rates of schizophrenia.

Prenatal nutritional deficiency could lead to maternal ingestion of food substitutes such as tulip bulbs,[1,17] could be a severe stressor that affects prenatal maternal hormones,[29] or could be followed by a rapid nutritional repletion.[20] These exposures could, in turn, have a toxic effect on fetal brain development. However, while there is extensive evidence that prenatal nutritional deficiency can directly affect brain development, there is no strong evidence to support these other exposures.

Finally, a thorough search was conducted for evidence of nonnutritional exposures that were specifically coincident with the height of the famine in the Netherlands and that could account for our findings.[17] None were identified. Moreover, there was no increased risk for schizophrenia among contemporaneous birth cohorts in the cities of other regions of the Netherlands unaffected by the famine (**Table 4**). Therefore, the increased risk cannot be caused by an exposure such as a viral epidemic coinciding in time with the famine, unless this exposure was also confined to the famine cities.

RELATION TO OUR PREVIOUS STUDY

Our earlier study of schizophrenia after prenatal exposure to the Dutch Hunger Winter[1] found an association in women but not in men. Three factors, the number of available patients, the age distribution of the patients, and the definition of the exposed cohort, probably all contributed to the difference in the present results. First, the smaller number of patients, 195 vs 284 in this study, allowed for more random fluctuation.[2,3] Second, in the previous study, patients hospitalized under the age of 32 years but not hospitalized after that age were omitted; therefore, we could not detect patients having an early onset of disease unless they were rehospitalized after age 32 years. The loss of early-onset cases may have weakened the results disproportionately in men because the average age at onset of schizophrenia is younger in men than

Table 2. Schizophrenia* in Birth Cohorts Exposed† and Unexposed† to Early Prenatal Nutritional Deficiency During the Dutch Hunger Winter of 1944 Through 1945: Cumulative Incidence Data

	All			Men‡			Women‡		
	Exposed			Exposed			Exposed		
Incidence Data	EX2 (n=4190)	EX1 (n=5466)	Unexposed (n=136 691)	EX2 (n=2184)	EX1 (n=2800)	Unexposed (n=69 943)	EX2 (n=2006)	EX1 (n=2666)	Unexposed (n=66 748)
Cumulative incidence per 1000 persons‡ (n cases)	3.8 (16)	2.0 (11)	1.9 (257)	4.1 (9)	2.5 (7)	2.2 (151)	3.5 (7)	1.5 (4)	1.6 (106)
Relative risk at age 24-48 y (95% confidence interval)	2.0 (1.2-3.4)	1.1 (0.6-2.0)	...	1.9 (1.0-3.7)	1.2 (0.5-2.5)	...	2.2 (1.0-4.7)	0.9 (0.4-2.6)	...
P	<.01	.82	...	.05	.70	...	.04	.91	...

Schizophrenia narrowly defined, ie, ICD-9 (International Classification of Diseases, Ninth Revision) *295.1,2,3,6.*

†*EX2 indicates exposed birth cohort of October 15 through December 31, 1945; EX1, exposed birth cohort of August 1 through October 14, 1945; and unexposed, all other births of 1944 through 1946 in the famine cities.*

‡*Denominators are live births minus deaths up to age 18 years. (Note that in men, denominators differ between Tables 1 and 2, being only live births in Table 1.)*

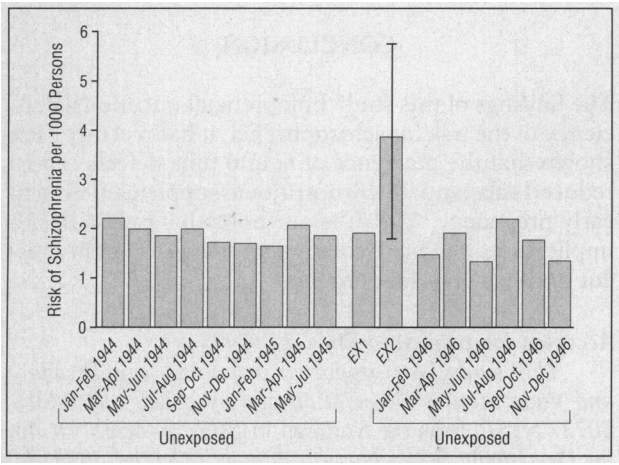

Figure 2. *Schizophrenia in adulthood (hospitalized subjects of 24 to 48 years of age) in Dutch birth cohorts of 1944 through 1946. EX1 and EX2 indicate cohorts born August 1 through October 14, 1995, and October 15 through December 31, 1945, respectively; bar, 95% confidence limits.*

Table 3. Schizophrenia in Birth Cohorts Exposed* and Unexposed to Early Prenatal Nutritional Deficiency During the Dutch Hunger Winter of 1944 Through 1945: Incidence Data Under Narrow and Broad Definitions of Schizophrenia

	Cumulative Incidence per 1000 Persons (No. of Cases)			
Approach	Exposed, EX2	Unexposed	Relative Risk (95% Confidence Interval)	*P*
Under Narrow Definition of Schizophrenia (*ICD-9* 295.1,2,3,6)				
Most recent discharge	3.8 (16)	1.9 (257)	2.0 (1.2-3.4)	<.01
Any discharge	4.5 (19)	2.4 (333)	1.9 (1.2-3.0)	<.01
Any discharge or admission	4.8 (20)	2.8 (385)	1.7 (1.1-2.7)	.02
Under Broad Definition of Schizophrenia (*ICD-9* 295, Any Subtype)				
Most recent discharge	5.3 (22)	3.6 (486)	1.5 (1.0-2.3)	.07
Any discharge	6.0 (25)	3.7 (510)	1.6 (1.1-2.4)	.02
Any discharge or admission	6.4 (27)	4.3 (584)	1.5 (1.0-2.2)	.04

**EX2 indicates exposed birth cohort of October 15 through December 31, 1945; unexposed, see Tables 1 and 2; and* ICD-9, International Classification of Diseases, Ninth Revision.

in women.[2,3] Third, the definition of the exposed birth cohort, based on official food rations alone, was relatively imprecise and did not take into account nutritional depletion over time, the precise timing of the exposure in gestation, and extra ration foods that could affect neurodevelopmental outcomes.

The RR under the broader classification of exposure (EX1+EX2) used in our previous study can be calculated from the data in Table 2. The overall RR was 1.5 (95% CI = 1.0 to 2.2; P =.048) and did not differ between men (RR=1.5) and women (RR=1.5). Thus, the effect of the new data was to remove the suggestion that the results varied by gender, as well as to reveal that the association is confined solely to the EX2 cohort.

IMPLICATIONS

Early prenatal nutritional deficiency, the most likely causative factor in the increased rate of schizophrenia among the EX2 cohort, could produce effects because of either general malnutrition or a specific micronutrient deficiency. Severe prenatal protein-calorie malnutrition is a rare exposure that occurs mainly in developing countries and, in developed countries, could account only for a small number of cases in special circumstances. A specific prenatal micronutrient deficiency, on the other hand, might play an important role in developed as well as in developing countries.[14,30,31]

The findings for neural tube defects such as spina bifida and anencephaly exemplify this point. Early prenatal folate deficiency has remained an important causative factor for neural tube defects in wealthy societies.[14,30,31] The incidence appears to depend on the specific micronutrient composition of the diet, and on the genetic background of the population, rather than on overall food intake, and it follows no simple gradient across rich and poor societies.

Table 4. Schizophrenia in Birth Cohorts of Nonfamine Cities of the Netherlands*: Incidence Among EX2 vs All Other Born in 1944 Through 1946

Diagnosis	Cumulative Incidence per 1000 Persons (No. of Cases) EX2 (n=3841)	All Other Births (n=57 138)	Relative Risk (95% Confidence Interval)	P
Schizophrenia under narrow definition	1.6 (6)	1.4 (81)	1.1 (.5-2.5)	.82

**Includes all nonfamine cities of population >40 000: Groningen, Leeuwarden, Zwolle, Enschede, Hengelo, Breda, Tilburgh, Eindhoven, Heerlen, and Maastricht. EX2 indicates exposed birth cohort of October 15 through December 15, 1945.*

Prenatal nutritional deficiency could act in conjunction with either genetic factors or other prenatal exposures.[1,5-7,32-34] In this regard too, neural tube defects may serve as a useful paradigm. These defects are influenced by genetic factors, as well as by prenatal nutrition, and comprise several types that may be genetically distinct.[31] Recent findings suggest that in the presence of an impairment in homocysteine metabolism, which may be genetically determined, a higher than average periconceptional intake of vitamin B_{12} or of folate may compensate by overcoming the metabolic defect and, thereby, reduce the risk for neural tube defects in offspring.[35]

LIMITATIONS

First, this study used group data to define individuals as exposed. In contrast with most ecologic studies, however, the exposure was documented in detail and known to be pervasive in the population.[36]

Second, unconfounded estimates of deficiencies of particular nutrients cannot be determined from the available data. Caloric deficiency, protein deficiency, and deficiencies of specific micronutrients occurred simultaneously in the Dutch Hunger Winter, and each of these has been shown to be capable of affecting brain development in animal experiments.[37,38] To obtain individual exposure data and specify the relevant exposure, we are presently conducting a study of a large birth cohort in the United States; stored prenatal maternal serum samples are available to measure prenatal nutritional exposures in schizophrenic patients and matched controls.

Third, the time of birth was known, but the time of conception had to be inferred. The time of conception was estimated on the assumption of a full-term pregnancy. The great majority of births, including schizophrenic births and births after prenatal famine exposure, occur at full term.[17,39] However, if short gestations were more frequent among schizophrenic births compared with other births, the effect of this misclassification would be to deflate the estimates of the true RR for the EX2 cohort.

Fourth, complete data on congenital neural defects were available only for male patients. The morbidity data from military induction examinations, the basis for our a priori specification regarding timing of exposure, were lacking for female patients.

Fifth, data on social class of origin were not available in the psychiatric registry. No relation has been found in the Netherlands between schizophrenia and low social class of origin.[40] Moreover, since the exposed birth cohort was weighted toward the upper classes, any such association would tend to reduce the estimated RR in this study.

Other limitations of this study included the use of registry diagnoses, the absence of patients younger than 24 years of age, and the loss to emigration of a small number of the members of these birth cohorts. Because each of these factors would affect the exposed and unexposed cohorts in the same way, they cannot account for the association between prenatal nutritional deficiency and schizophrenia in this study.[1] Rather, they would tend to diminish the observed association owing to nondifferential misclassification.

CONCLUSION

The findings of this study link prenatal nutritional deficiency to the risk for schizophrenia. It has recently been shown that the incidence of neural tube defects can be reduced substantially by nutritional supplementation in early pregnancy.[14,30,31] It is our hope that public health implications might eventually also emerge from the present findings on schizophrenia.

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