Prenatal Exposure to Wartime Famine and Development of Antisocial Personality Disorder in Early Adulthood

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MARKED REGIONAL AND temporal variations in rates of violent crime in the United States highlight the contribution of social, political, and economic forces to antisocial behavior. However, the possible role of prenatal and early developmental factors in risk for antisocial behavior remains of considerable scientific, public health, and policy interest, especially because such factors may be amenable to intervention. Several observational epidemiological investigations of this question, albeit not all, report an association of pregnancy or obstetric complications with conduct problems in childhood and with antisocial personality disorder (ASPD) or frank criminality in adulthood.

Despite the design and analytic strengths of these studies, research to date has several general limitations. First, many studies measure perinatal risk with a single numerical index that combines maternal, pregnancy, obstetric, and neonatal complications. Some of these conditions pertain to the mother's health and are often present before and throughout the pregnancy (eg, maternal chronic illness). Other difficulties arise only late in gestation, at the time of labor or delivery (eg, breech presentation). Yet others pertain to the neonate (eg, prolonged respiratory distress). Collapsing these diverse complications into a single index creates difficulties for identifying critical periods or factors in embryonic life crucial to the development of behavioral disturbance. It also obscures clues to

Context Several observational epidemiological studies report an association of pregnancy and obstetric complications with development of antisocial personality disorder (ASPD) in offspring. However, the precise nature and timing of the hypothesized biological insults are not known.

Objective To test whether severe maternal nutritional deficiency early in gestation is associated with risk for ASPD in offspring.

Design and Setting Retrospective cohort study. From October 1944 to May 1945, the German army blockaded food supplies to the Netherlands, subjecting the western Netherlands first to moderate (official food rations, 4200-6300 kJ/d) then to severe (<4200 kJ/d) nutritional deficiency. The north and south were subjected to moderate nutritional deficiency only.

Participants Dutch men born in large urban areas in 1944-1946 who were given psychiatric examinations for military induction at age 18 years (N = 100,543) were classified by the degree and timing of their prenatal exposure to nutritional deficiency based on their birthdate and birthplace.

Main Outcome Measure Diagnosis of ASPD by psychiatric interview at time of medical examination for military induction, using the International Classification of Diseases, Sixth Revision (ICD-6).

Results Men exposed prenatally to severe maternal nutritional deficiency during the first and/or second trimesters of pregnancy exhibited increased risk for ASPD (adjusted odds ratio [OR], 2.5; 95% confidence interval [CI], 1.5-4.2). Third-trimester exposure to severe nutritional deficiency and prenatal exposure to moderate nutritional deficiency were not associated with risk for ASPD.

Conclusions Our data suggest that severe nutritional insults to the developing brain in utero may be capable of increasing the risk for antisocial behaviors in offspring. The possible implications of these findings for both developed countries and developing countries, where severe nutritional deficiency is widespread and often exacerbated by war, natural disaster, and forced migration, warrant study.

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For editorial comment see p 479.
neuropathological mechanisms and intervention strategies.

Second, alternative explanations for the observed associations are not easily excluded. Several risk factors for adverse reproductive outcomes (eg, socioeconomic status) may also independently increase risk for antisocial behavior. Third, many of the studies focus on criminal offending, not ASPD. Antisocial individuals who are arrested and successfully prosecuted may not be typical of antisocial individuals or criminals in general.

The present investigation examines whether prenatal exposure to maternal nutritional deficiency is associated with an increased risk for ASPD in offspring at age 18 years. This association was tested using the quasi-experimental conditions created by the Dutch Hunger Winter of 1944-1945. In October 1944, the German army blockaded food supplies to the Netherlands to punish the Dutch for assisting the Allied invasion of Europe. Before the blockade, the food supply had been adequate, and in May 1945, following the German retreat, food became plentiful again. In the intervening months, the Dutch population, particularly in the western cities, received increasingly meager nutrition. At the start of the blockade, a number of Dutch women were pregnant; others conceived in the following months. This wartime catastrophe created a strategic epidemiological opportunity to examine the effect of prenatal nutritional deficiency of varying intensity imposed at different points in gestation on prenatal development and subsequent health and cognitive outcomes.13-15

The direct impact of starvation on mortality and morbidity both in developed and developing societies is well documented.16-18 A number of recent studies have investigated the effects on offspring of prenatal exposure to maternal starvation. Research on the Dutch famine has linked prenatal nutritional deprivation to perinatal mortality, obesity in young adulthood, decreased glucose tolerance in middle age, and altered patterns of birth weight distribution in second-generation offspring.19-22 Among psychiatric and neurodevelopmental disorders, previous studies offer evidence of an association of severe prenatal nutritional deficiency with schizophrenia, schizoid personality disorder, affective psychosis, and central nervous system anomalies.14,23-27

In the 1960s, when the surviving Dutch male children born during the period 1944-1946 reached their 18th birthday, they were summoned for military service and received physical, psychiatric, and psychological examinations at induction centers.14 Linkage of the psychiatric diagnostic information with the men’s date and place of birth permits a test of the association between prenatal exposure to maternal nutritional deficiency and the development of ASPD by age 18 years. This study affords an opportunity, therefore, to examine the effect of a relatively specific prenatal insult, introduced at varying points in gestation for different women, with ASPD measured for virtually the entire male population at a single chronological age.

We hypothesized a priori that prenatal exposure to maternal nutritional deficiency increases offspring’s risk for ASPD. Prenatal insults and toxic exposures in the first and second trimesters have been implicated in risk for central nervous system anomalies and neurodevelopmental disorders.14,19 In addition, minor physical anomalies originating early in gestation are reported in excess in persons with conduct disorder and aggression in childhood and violent offending in adulthood.26-32 Accordingly, we planned corollary analyses to examine whether any identified risk for ASPD in individuals with severe nutritional deficiency was concentrated in the first or second trimesters of embryonic life.

METHODS
Geographic Regions and Cities
For purposes of wartime food rationing, the Dutch government divided the country into 3 regions. The first, western Holland, where the German blockade exerted its greatest force, included the major cities of Amsterdam, Haarlem, Leiden, Rotterdam, Utrecht, and the Hague, hereafter referred to as the famine region. The remaining areas were split into north and south, which, for parsimony, we combine into a single nonfamine region. Consistent with prior investigations, we studied men born only in cities with populations exceeding 40,000 (throughout the Netherlands) since the blockade was felt most strongly in larger urban areas.15 Military records used in the current study were obtained in the 1960s from the Dutch government. The issue of informed consent from individual study subjects did not arise in the context of this investigation.

Nutritional Intake
Estimates of maternal nutritional intake are based on the caloric content of the weekly government wartime food rations. Moderate nutritional deficiency is defined as mean daily rations of 4200 to 6300 kJ (1000-1500 kcal; estimated ranges of 37-42 g of protein, 212-247 g of carbohydrates, and 24-41 g of fat). Severe nutritional deficiency is defined as mean daily rations of less than 4200 kJ (estimated ranges of 14-22 g of protein, 114-144 g of carbohydrates, and 12-28 g of fat).14,21 Precise information on micronutrient content of rations is not estimable.34 The biological validity of the 4200-kJ cut point is supported by a previous finding that risk for perinatal mortality increased only at or less than this level.34 In the famine region, the rations declined to less than 4200 kJ/d from February 1943 through early May 1945. Special supplements to pregnant women, available previously, were discontinued. Special supplements to infants were maintained through the first year of life. In the nonfamine region, daily rations declined to less than 6300 kJ but not less than 4200 kJ.14,23

Specification of Exposures by Trimester
Dutch men born in 1944-1946 are divided into 36 monthly birth cohorts. The degree and timing of their prenatal exposure to maternal nutritional deficiency is based on their dates of conception, as estimated backward from date and place of birth. Dates of con-
ception are calculated by subtracting average length of gestation from their dates of birth. Maternal caloric intake during a given trimester of pregnancy is estimated based on the mean daily ration size of the calendar weeks composing that trimester. Data on ration size and precise computational methods are described elsewhere.14,23

Famine Region. Using these methods, men born from February 1945 through December 1945 in the famine region (corresponding to conceptions from May 1944 through March 1945) were classified as prenatally exposed to severe nutritional deficiency. Among these individuals, men born in February, March, and April were exposed to severe nutritional deficiency in the third trimester only; born in May, June, and July, in the second trimester only; born in August and September, in the first and second trimesters only; born in October through December, in the first trimester only. Men born from September 1944 through January 1945 and in January 1946 (corresponding to conceptions from December 1943 through April 1944 and conceptions in April 1945) were classified as moderately exposed during 1 or more trimesters and otherwise adequately nourished. The remaining men—those born before the calendar period of moderate or severe nutritional deficiency and those conceived after these periods—were combined to form a single unexposed comparison group. The mean daily maternal intake per trimester for these months always exceeded 6300 kJ. These caloric classifications of exposure adhere to the exposure categories used in our previous research on psychiatric risk of offspring.23 Analyses specific to schizophrenia—spectrum disorder led to further refinement in these exposure categories, with severe exposure being divided into 2 subgroups.23 The use of these later refinements, crafted in accord with a specific hypothesis about schizophrenia, did not alter our findings.

Nonfamine Region. In the nonfamine region, men born during certain calendar periods (in the northern region, from September 1944 to November 1945; in the southern region, from September 1944 to August 1945) are classified as prenatally exposed to moderate nutritional deficiency. The remaining monthly birth cohorts, during which maternal mean daily intake per trimester always exceeded 6300 kJ, constitute the unexposed comparison group. Again, rates of ASPD did not differ between men born before the start of the period of moderate nutritional deficiency and those conceived afterward.

Diagnostic Criteria

Examining physicians performed psychiatric evaluations using the Dutch version29 of the International Classification of Diseases, Sixth Edition (ICD-6),30 with the final diagnostic decision rendered by the chief medical officer in charge. These examinations, performed in the 1960s, were conducted blind to the current study hypothesis. The diagnoses of institutionalized individuals (eg, persons with severe mental retardation) were made based on requested medical records. Each individual could receive up to 2 diagnoses. Clergy, police, long-term prisoners, emigrants, and men with 3 older brothers who had been in the service were exempt from examination. These persons comprised roughly 3% of potentially eligible individuals.34

While formal diagnostic criteria are not delineated in the early ICDs, Dutch psychiatric texts from the late 1940s to the 1960s37,38 evidence the strong similarity of this entity, ASPD, with that in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.39 Antisocial personality disorder was characterized as involving aggression, failure to conform to social norms with respect to lawful behavior (eg, thievery and other frank criminal acts), and disregard for the truth (eg, swindling, conning). In addition, behavioral instability and unreliability, outbursts of anger, and other interpersonal problems marked the person’s childhood.38

The Dutch version of ICD-6 comprised 2 subcategories of ASPD: onger- emden (unbridled) behavior (code 320.40), representing aggressive antisocial behavior, and moral insanity (code 320.41), representing nonaggressive antisocial behaviors.35 In the current study, persons with a primary or secondary diagnosis of ASPD (ICD-6 code 320.40 or 320.41) constitute the cases.

Other Variables

In addition to birth date and place, the records also contain information on social class (indexed by father’s occupation, trichotomized into nonmanual labor, manual labor, or farmer),34 IQ (the Ravens Progressive Matrices, a nonverbal test that is less dependent than other measures on verbal and numerical learning), sibship size, birth order, height, and weight.

Statistical Analysis

The association of nutritional deficiency with ASPD was estimated using odds ratios (ORs), 95% confidence intervals (CIs), and, in multivariate analyses, maximum likelihood logistic regression.40 First, in the famine region, the odds of having ASPD among men exposed prenatally to severe nutritional deficiency and moderate nutritional deficiency are compared with the reference odds of having ASPD among unexposed men. Second, the association of moderate nutritional deficiency with ASPD is examined in the nonfamine region. Third, the odds of having ASPD following severe prenatal nutritional deficiency in the famine region is refined further by specifying trimester(s) of exposure. Under the conditions prevailing in the current study, the ORs constitute a valid approximation to a risk ratio.

Candidate confounders and other potential correlates of conduct disorder and ASPD identified from previous literature included social class, sibship size, IQ, birth order, height, weight, and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters).41,42 Each variable associated with the exposure or with ASPD in univariate analyses was considered for inclusion in the final logistic regression equation. We decided a priori to retain in the model only
those covariates whose inclusion altered the value of the OR by more than 10%. Both unadjusted and adjusted ORs are presented in the tables. Only adjusted ORs are reported in the text, unless stated otherwise.

In the famine region, an increased odds of having ASPD in severely exposed cohorts compared with unexposed cohorts might reflect a coincidental countrywide excess for the calendar period corresponding to famine exposure. We tested this issue with a fourth analysis based on the entire sample of 100,543 Dutch men entering terms for the main effect of region, social class, and famine exposure months, and an interaction term for region by exposure months. In all analyses, statistical significance was set at $P<.05$.

Sample
Military examinations were conducted for 100,543 Dutch men born in Holland’s larger cities from January 1944 to December 1946 and residing in Holland at age 18 years. Among the 68,932 men born in the famine region, 14,310 were exposed prenatally to severe nutritional deficiency during 1 or more trimesters and 9,615 to moderate nutritional deficiency only. Among the 31,611 individuals born in the nonfamine region, 10,517 were exposed prenatally to moderate nutritional deficiency (Table 1).

In western Holland, 1 or both of the exposed cohorts were significantly different from the unexposed cohort with regard to each of the covariates under consideration, albeit the absolute magnitude of the differences are small (Table 2). In the northern and southern regions, the exposed and unexposed cohorts differed significantly by weight, sibship size, and IQ. Among variables associated with exposure status in either geographic region, only social class, IQ score, and BMI were significantly associated with rates of ASPD. Rates of ASPD were significantly higher among men with lower social class, higher BMI, and poorer IQ performance. Social class was retained as the only covariate because inclusion of other terms in the logistic regression model did not appreciably alter the OR.

RESULTS
Famine Region
In the famine region, the odds of ASPD were elevated among men with severe but not with moderate prenatal nutritional deficiency (Table 3).

Subjects were subgrouped further by trimester of severe nutritional deficiency (Table 4). Odds ratios for first- and second-trimester exposure and/or second-trimester exposure ranged from 2.1 to 3.0 and did not differ significantly from each other. Third-trimester nutritional deficiency was not associated with increased odds of ASPD. (The difference in odds between first- and/or second-trimester exposure and third-trimester exposure was significant at $P<.10$.) Parallel results with similar effect sizes were found in analyses stratified by social class.

No cases with prenatal exposure to severe nutritional deficiency had additional psychiatric diagnoses. Adjustment for presence of any comorbid medical conditions (eg, myopia, inguinal hernia, or organic brain disorders) did not change the ORs. No cases of ASPD were the product of a multiple birth with other male siblings.

Nonfamine Region
In the nonfamine region, the odds of having ASPD was not associated with moderate nutritional deficiency (adjusted OR, 1.0; 95% CI, 0.6-1.7).

Nationwide Analysis
Next, we tested whether the increased odds of having ASPD pertained only to the cities in the western Netherlands during the calendar months corresponding to the period of first and second trimesters of severe nutritional deficiency. Using the entire sample ($N=100,543$), we entered terms into the logistic model representing the calendar period of the famine in the West, region (famine or nonfamine), and social class as main effects.
followed by an interaction term for region by calendar period. The interaction term was statistically significant ($P = .04$). Thus, the elevated odds of having ASPD was restricted to men born in the famine region who were exposed to severe nutritional deficiency during their first and/or second trimester. It did not, thereby, reflect some countrywide excess extending beyond the geographic limits of the famine.

**Diagnostic Subtypes**

Among the 86 cases of ASPD in the famine region, 69 were diagnosed as violent ASPD (ICD-6 code 320.40) and 17 as nonviolent ASPD (ICD-6 code 320.41). Exposure to severe nutritional deficiency in the first and/or second trimesters was associated with significantly increased odds of having violent ASPD (OR, 2.6; 95% CI, 1.4–4.5) compared with the odds among men unexposed to moderate or severe deficiency.

Table 2. Sociodemographic and Physical Characteristics and IQ Scores for Men Born in Major Dutch Cities From 1944 to 1946 Residing in the Netherlands at Age 18 Years, Overall and by Region and Level of Exposure to Maternal Nutritional Deficiency*

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>Total</th>
<th>Subtotal</th>
<th>Unexposed</th>
<th>Moderate Exposed</th>
<th>Severe Exposed</th>
<th>North and South Holland</th>
<th>Total</th>
<th>Subtotal</th>
<th>Unexposed</th>
<th>Moderate Exposed</th>
<th>Severe Exposed</th>
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<tr>
<td>No. of subjects</td>
<td>100,543</td>
<td>68,932</td>
<td>45,007</td>
<td>9615</td>
<td>14,310</td>
<td>31,611</td>
<td>21,094</td>
<td>10,517</td>
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<td>Height, mean (SD), cm</td>
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<td>177.6 (6.5)</td>
<td>177.7 (6.6)</td>
<td>177.4 (6.5)§</td>
<td>177.5 (6.5)§</td>
<td>176.8 (6.6)</td>
<td>176.8 (6.6)</td>
<td>176.8 (6.7)</td>
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<tr>
<td>Weight, mean (SD), kg</td>
<td>67.9 (8.6)</td>
<td>68.2 (8.3)</td>
<td>68.2 (8.4)</td>
<td>67.8 (8.1)§</td>
<td>68.3 (8.3)</td>
<td>67.1 (8.3)</td>
<td>67.2 (8.4)</td>
<td>67.0 (8.1)</td>
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<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>21.5 (2.3)</td>
<td>21.6 (2.2)</td>
<td>21.6 (2.3)</td>
<td>21.5 (2.1)‡</td>
<td>21.7 (2.3)§</td>
<td>21.5 (2.2)</td>
<td>21.5 (2.3)</td>
<td>21.4 (2.2)</td>
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<td>Sibship size, %</td>
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<tr>
<td>1</td>
<td>7.3</td>
<td>8.1</td>
<td>8.3</td>
<td>7.9‡</td>
<td>7.7§</td>
<td>5.5</td>
<td>5.6</td>
<td>5.6</td>
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<td>24.2</td>
<td>25.0</td>
<td>23.4</td>
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<td>18.0</td>
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<td>3</td>
<td>22.3</td>
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<td>≥4</td>
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<td>47.3</td>
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<td>3</td>
<td>17.4</td>
<td>16.9</td>
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<td>≥4</td>
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<td>Nonmanual laborer</td>
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<td>49.8</td>
<td>49.8</td>
<td>48.2</td>
<td>51.0‡</td>
<td>42.6</td>
<td>42.8</td>
<td>42.2</td>
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<td>Manual laborer</td>
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<td>48.4</td>
<td>48.5</td>
<td>50.1</td>
<td>47.1</td>
<td>53.4</td>
<td>53.2</td>
<td>53.8</td>
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<td>Farmer</td>
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<td>1.7</td>
<td>1.8</td>
<td>1.9</td>
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<td>IQ score, %¶</td>
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<td>Category 1</td>
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<td>24.9</td>
<td>24.6</td>
<td>25.1‡</td>
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<td>36.0</td>
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<td>33.5</td>
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<td>19.7</td>
<td>20.8</td>
<td>20.4</td>
<td>21.7</td>
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<tr>
<td>Category ≥4</td>
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<td>20.1</td>
<td>20.8</td>
<td>19.1</td>
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<td>23.0</td>
<td>23.0</td>
<td>23.1</td>
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</tbody>
</table>
*Major Dutch cities comprise cities with populations exceeding 40,000 people. In this table, P values pertain to statistical tests of differences between a given exposed cohort (moderate or severe) and the corresponding unexposed cohort in the geographic region. The symbols for the P values are shown in the columns of the relevant exposed cohorts.
†Height data are missing for 1.9% of men; weight, 2.4%; body mass index, 2.4%; sibship size, 2.1%; birth order, 2.1%; social class, 7.8%; and IQ scores, 4.4%.
‡P < .01.
§P < .001.
¶IQ was measured using the Ravens Progressive Matrices test. Raw scores on the Ravens test were grouped into 6 categories, with lower scores corresponding to better performance. For ease of tabular display, the categories have been truncated at ≥4.

Table 3. Association Between Antisocial Personality Disorder in Dutch Men at Age 18 Years and Moderate or Severe Prenatal Nutritional Deficiency: Western Holland (Famine Region), 1944–1946

<table>
<thead>
<tr>
<th>Level of Nutritional Deficiency*</th>
<th>Population, No.</th>
<th>Cases of Antisocial Personality Disorder, No.</th>
<th>Prevalence of Antisocial Personality Disorder per 10000</th>
<th>OR (95% CI), Observed/Adjusted†</th>
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</thead>
<tbody>
<tr>
<td>Severe (&lt;4200 kJ/d)</td>
<td>14,310</td>
<td>26</td>
<td>18.2</td>
<td>1.6 (1.02–2.6)/2.0 (1.2–3.3)</td>
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<tr>
<td>Moderate (4200–6300 kJ/d)</td>
<td>9615</td>
<td>10</td>
<td>10.4</td>
<td>0.9 (0.6–1.9)/0.7 (0.3–1.6)</td>
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<tr>
<td>Unexposed (&gt;6300 kJ/d)</td>
<td>45,007</td>
<td>50</td>
<td>11.1</td>
<td>Reference</td>
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</table>
*Values pertain to average daily rations during 1 or more trimesters of pregnancy. For calendar birth dates corresponding to exposure categories, see "Methods" section of text.
†OR indicates odds ratio; CI, confidence interval. ORs to the right of the virgules are adjusted for social class (manual laborers including farmers and nonmanual laborers). The comparison between the odds of antisocial personality disorder associated with moderate vs severe exposure is statistically significant; the comparison between the moderately exposed and unexposed is not.
nutritional deficiency. The OR for nonviolent ASPD was 2.2 (95% CI, 0.7-7.1). Exposure in the third trimester was not associated with increased odds of having either subtype of ASPD.

COMMENT

These findings suggest that severe nutritional deficiency in the first or second trimester of intrauterine life is associated with risk for development of ASPD. The origins of the famine in large-scale extrinsic historical conflict confer several methodological strengths on these findings. First, in the Dutch Hunger Winter, we can examine the effect of 1 type of relatively specific antenatal insult—nutritional deprivation. Second, the timing of the exposure in prenatal development can be specified with unique precision. Third, the communitywide nature of the exposure and its imposition by military force creates a quasi-experimental condition likely to reduce the effect of potentially confounding factors. Under normal peace-time conditions, a range of socioeconomic factors and maternal health habits during pregnancy are associated with pregnancy complications. Some of the same socioeconomic factors are also associated with increased rates of antisocial behaviors in offspring. During the blockade, the antenatal insult (ie, severe nutritional deficiency) was introduced by external forces, not by socially patterned maternal behaviors. This fact probably reduces, although it cannot preclude the possibility of voluntary sources of confounding. Fourth, the absence of severe nutritional deficiency in the nonfamine region permitted a test of whether the increased odds of having ASPD reflected some countrywide increase unrelated to the nutritional crisis. Finally, the restriction of the sample to 18-year-old men eliminated an extraneous source of variance in the dependent measure, thereby affording a more precise estimate of effect.

Ecological Exposure Measurement

The study’s primary limitation is the ecological measurement of nutritional status. The nutritional status of pregnant women was not directly measured but was based on official government food rations. Redistribution of food rations within households, supplementation from the black market, or foraging in the countryside could introduce error into our estimates. Nonetheless, macrolevel historical data document the near ubiquity of the famine for urban populations. (Although the famine’s force varied somewhat by social class,13 this differential is adjusted for in our analyses.) Also, other studies of these same cohorts report associations between famine exposure, measured ecologically, and reproductive health and intergenerational health outcomes, thereby supporting the construct validity of this method of measuring exposure.14,15,20-27 Since date of conception is also not directly measured and preterm birth may be a risk factor for ASPD, error may exist in the assignment to exposure category. However, random misclassification of nutritional status would likely produce an underestimate, not an overestimate, of the risk.43

Table 4. Association Between Antisocial Personality Disorder and Severe Prenatal Nutritional Deficiency in Dutch Men at Age 18 Years Overall and by Trimester of Exposure: Western Holland (Famine Region), 1944-1946

<table>
<thead>
<tr>
<th>Trimester of Exposure*</th>
<th>Population, No.</th>
<th>Cases of Antisocial Personality Disorder, No.</th>
<th>Prevalence of Antisocial Personality Disorder per 10,000</th>
<th>OR (95% CI), Observed/Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2, or 3</td>
<td>14310</td>
<td>26</td>
<td>18.2</td>
<td>1.6 (1.02-2.6)/2.0 (1.2-3.3)</td>
</tr>
<tr>
<td>1 and/or 2</td>
<td>9252</td>
<td>20</td>
<td>21.6</td>
<td>2.0 (1.2-3.9)/2.5 (1.5-4.2)</td>
</tr>
<tr>
<td>1 only</td>
<td>2443</td>
<td>6</td>
<td>24.6</td>
<td>2.2 (0.95-5.0)/2.9 (1.2-6.7)</td>
</tr>
<tr>
<td>1 and 2 only</td>
<td>2223</td>
<td>6</td>
<td>27.0</td>
<td>2.4 (1.04-5.7)/3.0 (1.3-7.0)</td>
</tr>
<tr>
<td>2 only</td>
<td>4586</td>
<td>9</td>
<td>19.6</td>
<td>1.8 (0.9-3.6)/2.1 (1.03-4.4)</td>
</tr>
<tr>
<td>3 only</td>
<td>5056</td>
<td>5</td>
<td>9.9</td>
<td>0.9 (0.4-2.2)/1.1 (0.4-2.7)</td>
</tr>
<tr>
<td>Unexposed</td>
<td>45 007</td>
<td>50</td>
<td>11.1</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*Values pertain to average daily rations during 1 or more trimesters of pregnancy. For calendar birth dates corresponding to exposure categories, see “Methods” section of text. OR indicates odds ratio; CI, confidence interval. Offs to the right of the vigules are adjusted for social class (manual laborers [including farmers] and nonmanual laborers).

Diagnostic Validity and Case Ascertainment

Contemporaneous clinical descriptions of ASPD in the 1960s readily concur with current views of this entity.39 Additionally, the associations of ASPD with social class, IQ, and BMI are consistent with the published literature,41 thereby evidencing construct validity. The point prevalence rate of ASPD, albeit low, falls within the range of reported rates.44 However, it is reasonable to conclude both that ASPD was underdiagnosed at induction centers and that diagnosed individuals comprised only the more severe early-onset cases.

Long-term prisoners, of whom some would meet criteria for ASPD,45 were exempt from military induction. The number of 18-year-old Dutch men in this category is not known but is unlikely to be substantial. Moreover, any unascertained cases of ASPD threaten the validity of our positive findings only if young criminals who were unexposed to severe nutritional deficiency were at greater risk of long-term incarceration than young criminals with first- and/or second-trimester exposure. Unbiased case underascertainment per se will not affect the OR.43

Alternative Explanations

In the final months of the blockade, people ate tulip bulbs and other possibly toxic food substitutes. Furthermore, a nationwide rise in infant infections, including tuberculosis, typhoid, and dysentery, occurred in the months afterward.14 Arguably, 1 of these fac-
tors could play an etiologic role in the increase in ASPD, not nutritional deficiency. However, none of these factors follow a temporal or geographic pattern that could account for effects restricted to the famine region and to the first 2 trimesters of pregnancy. Consequently, they are unsatisfactory as competing explanatory factors.

These results are superficially compatible with superior fertility or infant survival under famine conditions among couples with characteristics associated with ASPD in offspring. For example, sociopathic parents might circumvent equitable official food rationing, thereby securing a reproductive advantage over principled couples. However, fertility was most affected by nutritional deficiency at time of conception; mortality in the first year of life was most affected by nutritional deficiency in the third trimester. Thus, such differential fertility, even if present, cannot explain the increased risk of ASPD associated with second-trimester famine exposure. Also noteworthy is that social class did not moderate the effect of famine on risk for ASPD, a possibility raised by prior research.40

Potential Mediators

Pregnancy complications may increase maternal or offspring risk for physical illness or compromise maternal-child interactions in other ways, thereby increasing offspring’s risk for behavioral problems.47-50 However, the similarity in rates of physical morbidity between exposed cases and noncases, together with the absence of a third-trimester effect of severe nutritional deficiency, renders these proposed intervening mechanisms implausible. Finally, the observed excess of ASPD among exposed cohorts is not explained by an independent effect of nutritional deficiency on detectable physical illness, depressed IQ, sibship size, or BMI.

Collateral Research

Earlier studies found associations of obstetric complications and brain damage with a range of neuropsychiatric problems and disorders, underscoring the plausibility that 1 type of insult may have multiple pathologic sequelae. For example, prenatal exposure to rubella is associated with increased risk for mental retardation, congenital deafness, cerebral palsy, and cardiac malformations.32 These findings of diverse sequelae from complex brain injury parallel recent reports linking severe prenatal malnutrition at different points in gestation with risk for schizophrenia and affective disorder.33-35 Similarly, our finding of a threshold effect for severe maternal nutritional deficiency agrees with research on child brain damage showing increased psychiatric risk only for substantial injury.33,34

Possible Mechanisms

Prenatal nutritional deficiency could influence risk for ASPD through mechanisms linked to general nutritional deficiency or through deficiency of a specific micronutrient. In developed countries, where severe prenatal protein-calorie deficiency is rare, the former mechanism would account for only a few cases. By contrast, a specific micronutrient deficiency could play a more sizable role, in a developed society as demonstrated by the central role of periconceptional folate intake in neural tube defects.35 These findings pertaining to first- and/or second-trimester nutritional deficiency are compatible with separate genetic and pregnancy or postnatal environmental contributions to risk. For example, in the folate model, periconceptional nutritional deficiency increases risk for neural tube defects but possibly only or primarily among genetically at-risk individuals.35 On the other hand, nutritional deficiency early in pregnancy may enhance fetal susceptibility to obstetric insults. Furthermore, these findings do not preclude a substantial contribution of poverty, social disadvantage, and early family environment to the development of antisocial behaviors, especially because maternal nutritional deficiency reflects in part the prenatal operation of social and economic forces. Finally, intrauterine factors can mimic genetic patterns of disease transmission. Therefore, identification of intrauterine factors in offspring’s risk for antisocial behavior may improve estimation and specification of possible genetic contributions, an issue whose place in history and current politics is highly charged.36

The strength of the reported associations, the security of the temporal order, specificity of first- and/or second-trimester effect, and the coherence with findings in collateral research support the view that early biological insults to the developing brain are implicated in antisocial behavior. However, these results apply strictly only to men and to ASPD diagnosed at the start of adulthood. Prenatal nutritional deficiency may not play the same role with women. Whether these results apply equally to persons with prepubertal and postpubertal onset of antisocial behavior1,37 is also not known. Furthermore, estimations of the magnitude of the contribution of prenatal factors to antisocial behavior are necessarily relativistic. In certain social environments (eg, in communities characterized by high concentrations of economic disadvantage, political disenfranchisement, and limited “collective efficacy”) postnatal risk factors may dwarf the independent role of prenatal ones. We emphasize, too, that the rate of antisocial behavior was extremely low (18 cases per 10 000 population) even among Dutch men prenatally exposed to severe nutritional deficiency.

The Dutch Hunger Winter imposed conditions of severe nutritional deficiency on a population that was reasonably well nourished prior to the blockade and in its immediate aftermath. The implications of these findings for developing countries, where episodes of maternal starvation, often associated with civil war, natural disaster, forced migration, and refugee status58,59 are superimposed on conditions of endemic undernutrition, await clarification. Future efforts at replication and extension of these results to more heterogeneous samples, including samples in developing countries, are needed.

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REFERENCES


