Pregnancy-associated Hypertensive Disorders and Adult Cognitive Function Among Danish Conscripts

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Initially submitted March 9, 2009; accepted for publication June 30, 2009.

The authors examined the association of gestational hypertensive disorders (hypertension, preeclampsia, eclampsia) with adult cognitive function among men born in 1978–1983 in a well-defined geographic area of northern Denmark. Data from the Danish Medical Birth Registry, the Danish National Registry of Patients, and draft board records were linked. Cognitive function was measured at conscription by using the Boerge Prien group intelligence test. Test scores were converted to the conventional IQ scale (mean = 100 (standard deviation, 15)). Low cognitive function was defined as IQ <85. Of the 17,457 men who underwent intelligence testing, 891 (5.1%) were born after a pregnancy involving hospitalization for a gestational hypertensive disorder. Compared with conscripts born after normotensive pregnancy, conscripts exposed to maternal gestational hypertension had an adjusted prevalence ratio for low cognitive function of 1.34 (95% confidence interval (CI): 1.01, 1.77). For those exposed to mild preeclampsia and severe preeclampsia/eclampsia, adjusted prevalence ratios were 1.34 (95% CI: 1.09, 1.65) and 1.10 (95% CI: 0.48, 2.51), respectively. The corresponding adjusted mean differences in IQ scores were −2.0 (95% CI: −4.0, 0.0), −3.2 (95% CI: −4.7, −1.8), and −2.0 (95% CI: −7.2, 3.2). In this study, prenatal exposure to gestational hypertensive disorders was associated with slightly reduced adult cognitive performance among male conscripts.

Abbreviations: BPP, Børge Prien Prøve; CI, confidence interval; ICD-8, International Classification of Diseases, Eighth Revision; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; PR, prevalence ratio; sFlt-1, soluble fms-like tyrosine kinase-1.

Pregnancy-associated hypertensive disorders affect about 8% of gestations (1). Preeclampsia, affecting 3%–5% of pregnancies (2), accounts for the majority of these disorders. Compared with offspring of normotensive pregnancies, offspring of preeclamptic pregnancies have a 1.5- to 2-fold increased risk of perinatal or infant mortality (3). About one-third of babies born after a preeclamptic pregnancy are growth restricted (1), and preeclampsia is responsible for 15% of all preterm births (1).

Little information exists about the neurodevelopmental outcome of offspring of hypertensive gestations. A recent large, population-based cohort study reported a 1.2- to 2.5-fold increase in the risk of epilepsy for children born at term after a preeclamptic gestation (4). A few studies have examined the association of gestational hypertensive disorders with offspring’s cognitive function (5–8), but each of these studies had few subjects, focused on childhood outcomes of infants born preterm or small for gestational age, and produced conflicting results (5–7). In the only known study to date of adult cognitive function, Seidman et al. (8) reported the IQ of sons of preeclamptic mothers to be on average 1.2 points lower than that of sons of nonpreeclamptic mothers; the result was interpreted as absence of an association. That study did not examine cognitive outcome after gestational hypertension and did not address effects of preeclampsia severity. We aimed to examine an association of gestational...
hypertension, preeclampsia, and eclampsia in the mother with offspring adult cognitive function using registry data and conscription records in Denmark.

MATERIALS AND METHODS

Study population and data sources

We studied Danish men born as singletons between 1978 and 1983 who presented for their mandatory army fitness evaluation at Denmark’s fifth conscription district. This district has jurisdiction primarily over the counties of North Jutland and Viborg. We linked records of these evaluations with the conscripts’ records in the Danish Medical Birth Registry (9) and with their mothers’ records in the Danish National Registry of Patients, which has tracked all somatic hospitalizations and associated diagnoses since 1977 (10). The unambiguous linkage of individual records is possible thanks to the unique identifier assigned at birth and is used in all Danish registries. The mother’s identifier is an entry in the newborn’s birth record.

Maternal hypertensive disorders and perinatal data

From the Danish National Registry of Patients, we ascertained maternal hypertensive disorders recorded during the relevant pregnancy. According to the 1972 diagnostic recommendations of the American College of Obstetricians and Gynecologists (11), used at the time, gestational hypertension was defined as new onset of hypertension (>140/90 mm Hg blood pressure) in the second half of pregnancy; a diagnosis of preeclampsia additionally required de novo proteinuria (>0.3 g over 24 hours) or edema. Severe preeclampsia was diagnosed in the presence of severe hypertension (>180/110 mm Hg) and/or severe proteinuria (>5.0 g over 24 hours) combined with subjective symptoms relating to one or more major organ systems.

Danish National Registry of Patients diagnoses were coded by using the *International Classification of Diseases, Eighth Revision* (ICD-8 (12)). We ascertained the following diagnoses: gestational hypertension (code 637.00), mild preeclampsia (code 637.03), unspecified preeclampsia (code 637.09), severe preeclampsia (code 637.04), toxemia (code 637.99), and eclampsia (code 637.19). We classified the recorded disorders into 3 groups in order of increasing severity: 1) gestational hypertension; 2) mild preeclampsia, unspecified preeclampsia, or toxemia; and 3) severe preeclampsia or eclampsia. Whenever more than one diagnosis was recorded during the relevant pregnancy, the most severe recorded diagnosis determined the category. Conscripts whose mothers had none of these diagnoses during the relevant pregnancy served as the reference group. From the Danish National Registry of Patients we also extracted data on history of maternal hospitalization because of diabetes mellitus (ICD-8 code 250 (13)) before the subject’s birth (recorded since 1977) because it is a risk factor for gestational hypertensive disorders.

From the Medical Birth Registry, we extracted data on maternal age, marital status, parity, conscripts’ birth weight, gestational age, 5-minute Apgar score, mode of delivery, year, and county of birth.

Cognitive function

All Danish men must register with the draft board at the age of approximately 18 years. At registration, men receive a questionnaire in which they report diseases that could preclude military service. These reports are verified by draft board physicians through medical records or in consultations with specialists (14). Men with verified disqualifying diseases are not drafted and are exempt from the standard evaluation. The standard evaluation of the remaining men includes a medical examination and an assessment of their cognitive function using the Boerge Prien group intelligence test (Danish: Børge Prien Prøve (BPP)). This test, developed for the Danish draft board in the 1950s, is a 45-minute, 78-item instrument, with the score calculated as the total of correct responses. The BPP has been shown to correlate closely with the Wechsler Adult Intelligence Scale (correlation = 0.82) and therefore is considered a valid measure of general intelligence (15, 16). We converted the BPP scores to the conventional IQ scale (mean = 100 (standard deviation, 15) (17), hereafter termed “converted BPP”) to facilitate comparability with other studies. Using this scale, we defined an outcome of “low cognitive function” as a score of <85 (or >1 standard deviation below the mean).

All diagnoses ascertained by the draft board before or during the standard evaluation are recorded by using *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) (18). Severe neurologic and psychiatric conditions, some of which may affect cognitive function (19), are grounds for exemption from the standard evaluation. To assess the potential for selection bias stemming from lack of cognitive data on the exempt men, we compared men with and without cognitive function measurements with respect to the distribution of gestational hypertensive disorders in the mother and with respect to the prevalence of neurologic or psychiatric conditions recorded in the conscription file (ICD-10 codes F, G).

Statistical analysis

We examined cognitive function according to the categories of pregnancy-associated hypertensive disorders. We then stratified the data by gestational age and by small-for-gestational-age status, defined as birth weight below the 10th percentile of liveborn male birth weights in a given gestational week. We estimated mean differences in converted BPP scores by linear regression and prevalence ratios for low cognitive function by log-binomial regression (20) while using generalized estimating equations to model correlated outcomes between sons of the same mothers (21). After obtaining crude estimates, we restricted the analysis sample to those not born small for gestational age (to control for the potential effects of growth restriction on neurodevelopment) while controlling for maternal age (in categories ≤20, 21–35, >35 years), parity (0, 1, 2, >2 previous births), marital status (married/unmarried), and history of diabetes
RESULTS

There were 19,843 men born as singletons in 1978–1983 and registered with the fifth conscription district. Of these men, 17,469 underwent the standard evaluation involving cognitive function measurement. We excluded 12 records with missing (n = 8) or invalid (n = 4) BPP scores, leaving 17,457 (88%) men in the analysis sample. Median age at testing was 19 years.

Overall, 891/17,457 (5.1%) men were born after a pregnancy affected by any pregnancy-associated hypertensive disorder. This total comprised 604 (3.5%) men born after a preeclamptic pregnancy, including 522 (3.0%) with a diagnosis of mild preeclampsia, 33 (0.2%) with a diagnosis of unspecified preeclampsia or toxemia, and 49 (0.3%) after severe preeclampsia or eclampsia.

Compared with the entire sample, mothers with gestational hypertension were more likely to be older at the conscript’s birth, while mothers with preeclampsia were more likely to be younger. Preeclampsia was, as expected, associated with nulliparity and preterm birth, whereas both gestational hypertension and preeclampsia were associated with an increased prevalence of maternal diabetes, instrument-assisted or surgical delivery, and being small for gestational age (Table 1). The median duration of gestation for those with a normotensive pregnancy was 40.0 weeks, with upper and lower quartiles of 39.0 and 41.0 weeks, respectively, and was similar for men whose gestation involved gestational hypertension or mild preeclampsia. For men whose mothers experienced severe preeclampsia or eclampsia, the median duration of gestation was 38.0 weeks, with quartiles of 35.0 and 40.0 weeks.

Cognitive function

The mean converted BPP scores were 100.3 after normotensive gestation, 98.7 after exposure to gestational hypertension, and 97.7 after exposure to preeclampsia of any severity. The overall prevalence of low cognitive function was 15.2% (2,662/17,457), as expected in the population given the distribution of IQ scores. Low cognitive function was slightly more prevalent among those exposed to any preeclampsia or eclampsia (15.4%) and for conscripts’ year of birth (indicators), county of birth (North Jutland, Viborg, other), birth weight in grams, and being large for gestational age (defined as birth weight in the 90th percentile for a given gestational week; for postterm births, the 90th percentile value of week 42 was used). The latter was used to control for potential residual confounding by maternal diabetes and to account for possible U-shaped effects of birth weight. We used SAS software, release 9.1.3 (SAS Institute, Inc., Cary, North Carolina). This study was approved by Danish Data Protection Agency.

The crude mean difference in IQ score associated with any maternal pregnancy-associated hypertensive disorder was −2.2 (95% confidence interval (CI): −3.2, −1.1), while controlling for correlation between sons of the same mothers. When analyzed by type of disorder, the crude mean differences in IQ score were −1.6 (95% CI: −3.5, 0.2) for gestational hypertension and −2.4 (95% CI: −3.7, −1.2) for preeclampsia of any severity. The mean differences were −2.4 (95% CI: −3.7, −1.1) for mild or unspecified preeclampsia and −3.1 (95% CI: −7.4, 1.2) for severe preeclampsia or eclampsia (Table 3). The crude prevalence ratio associated with any type of hypertensive disorder was 1.24 (95% CI: 1.08, 1.42). The crude prevalence ratios were 1.28 (95% CI: 1.01, 1.62), 1.20 (95% CI: 1.00, 1.43), and 1.44 (95% CI: 0.83, 2.47) for prenatal exposure to gestational hypertension, mild preeclampsia, and severe preeclampsia, respectively; however, the latter estimate is based on few observations. These estimates changed little after restricting the analysis to conscripts born not small for gestational age while adjusting for the potential confounders (N = 12,976, Table 3). The effect associated with preeclampsia of any severity seemed to be driven by mild or unspecified preeclampsia, and there was no evidence of a severity-associated dose-response pattern of association (Table 3).

According to our data set, 1,284 mothers had given birth to 2 or more conscripts (2,579 siblings and half-siblings). Of those, 1,021 mothers had more than one son with an IQ measurement (7 mothers with 3 sons and 1,014 mothers with 2 sons, a total of 2,049 men). Among them were 67 sibling pairs (134 conscripts) discordant on maternal diagnosis of prenatal gestational hypertensive disorders. In that small group, exposure to any gestational hypertensive disorder was associated with a mean difference in IQ of −2.6 points (95% CI: −5.9, 0.8) after controlling for birth order within each sibling pair.

Neurologic outcomes among exempt men

Twelve percent of the initially draft-liable men (n = 2,374) received a health-related exemption from the standard evaluation involving intelligence testing. Among 504 men exempt before IQ testing because of a neurologic or psychiatric diagnosis, the most frequent diagnostic group was disorders of speech and language (24.8%; ICD-10 codes F80–89), followed by episodic and paroxysmal disorders (20.8%; ICD-10 codes G40–47). Of 31 exempt men with a diagnosis of mental retardation (ICD-10 codes F70–F79), none had been born after a gestational hypertensive disorder. The exempt and nonexempt men were similar with respect to the prevalence of maternal gestational hypertensive disorders (5.2% and 5.3%, respectively). Overall, 1,829 (9.2%) of all men (exempt and nonexempt) had a record of neurologic or mental disorder in the draft file; the prevalence of these diagnoses among the exempt men (21.2%) was considerably greater than among the nonexempt men (7.6%). Overall, men born after a pregnancy affected by a gestational hypertensive disorder were slightly more likely than other men to have a prevalent diagnosis of neurologic or psychiatric disorder (10.8% vs. 9.1%; crude
prevalence ratio (PR) = 1.18, 95% CI: 0.99, 1.42). This association was limited to exempt men (crude PR = 1.57, 95% CI: 1.20, 2.05) and was not seen among nonexempt men (crude PR = 1.04, 95% CI: 0.83, 1.31). The crude prevalence ratio for having a neurologic or psychiatric diagnosis was 1.19 (95% CI: 0.88, 1.62) for gestational hypertension; the association was present among exempt men (PR = 1.88, 95% CI: 1.32, 2.67) and absent among nonexempt men (PR = 0.78, 95% CI: 0.49, 1.24). The crude prevalence ratio for neurologic or psychiatric diagnosis associated with preeclampsia of any severity was 1.18 (95% CI: 0.95, 1.48), with prevalence ratios of 1.35 (95% CI: 0.92, 1.98) among the exempt men and 1.16 (95% CI: 0.89, 1.51) among the nonexempt men.

**DISCUSSION**

We found a modest association between prenatal exposure to pregnancy-associated hypertensive disorders and worse cognitive performance among Danish conscripts. All data used for this analysis had been accumulated prospectively and independently during routine record keeping; registration of maternal hypertensive disorders preceded by many years the measurements of cognitive function, and draft board officials conducting intelligence testing were unlikely to be aware of maternal medical history. Our study adds to the existing evidence by providing estimates from a large unselected sample, enabling separate analysis of gestational hypertension and preeclampsia. We did not
observe a clear dose-response, severity-related pattern of association, but our estimates for the severe preeclampsia/eclampsia category were imprecise and, unlike other estimates, appeared to be confounded away from the null.

Because we examined outcomes among men who survived to conscription age rather than enumerating and following a birth cohort, we were able to measure only prevalence, as opposed to risk, of cognitive impairment. Therefore, our results should be interpreted as describing cognitive function among men conditional on surviving to conscription age. Because preeclampsia is a risk factor for fetal or neonatal death (3), prevalence of preeclampsia in this cohort of survivors probably differs somewhat from prevalence at birth. Among the men without an IQ measurement, the association between maternal hypertensive disorders and neurologic or psychiatric conditions tended to be greater than the associations observed for measured cognitive function in the nonexempt men. Thus, the lack of IQ data likely led to an underestimate of the associations.

Although there was negligible confounding by measured characteristics, residual or unmeasured confounding cannot be ruled out as a potential explanation for the modest associations we found. While accounting for correlated observations between sons of the same mothers may have removed some of the potential confounding by maternal weight, IQ, or education within sibling pairs, unmeasured confounding by paternal variables cannot be ruled out. We had no measurements of maternal IQ, weight, or education. Furthermore, we had no data on treatments that could affect the outcome of preeclamptic pregnancy, such as antihypertensive medications.

Table 2. Prevalence of Low Cognitive Functiona According to Pregnancy-associated Hypertensive Disorders Among Danish Conscripts Born as Singletons in 1978–1983, by Gestational Age and SGA Status

<table>
<thead>
<tr>
<th>Hypertensive Disorder</th>
<th>Gestation ≥37 Weeks</th>
<th>Gestation &lt;37 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-SGA</td>
<td>SGA</td>
</tr>
<tr>
<td></td>
<td>Low Cognitive</td>
<td>Low Cognitive</td>
</tr>
<tr>
<td></td>
<td>Function</td>
<td>Function</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>11,812</td>
<td>1,661</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>207</td>
<td>39</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>417</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td>12,436</td>
<td>1,779</td>
</tr>
</tbody>
</table>

Abbreviation: SGA, small for gestational age.

a Defined as a converted Boerge Prien Test score of <.85.

Table 3. Mean Differences in Converted BPP Scoresa and Prevalence Ratios for Low Cognitive Function Among 17,457 Danish Conscripts Born as Singletons in 1978–1983

<table>
<thead>
<tr>
<th>Gestational Hypertensive Disorder</th>
<th>Type of Analysis</th>
<th>Converted BPP Difference</th>
<th>Low Cognitive Function</th>
<th>Restricted to Conscripts Born Non-SGA (n = 12,976)</th>
<th>Converted BPP Difference</th>
<th>Low Cognitive Function</th>
<th>Restricted to Conscripts Born Non-SGA and Adjusted for Potential Confoundersb (n = 12,976)</th>
<th>Converted BPP Difference</th>
<th>Low Cognitive Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td></td>
<td>-1.6</td>
<td>-3.5, 0.2</td>
<td>1.28</td>
<td>1.01, 1.62</td>
<td>-1.7</td>
<td>-3.8, 0.4</td>
<td>1.33</td>
<td>1.01, 1.76</td>
</tr>
<tr>
<td>Any preeclampsia</td>
<td></td>
<td>-2.7</td>
<td>-3.7, -1.2</td>
<td>1.22</td>
<td>1.02, 1.44</td>
<td>-2.9</td>
<td>-4.4, -1.5</td>
<td>1.26</td>
<td>1.02, 1.54</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td>-2.4</td>
<td>-3.7, -1.1</td>
<td>1.20</td>
<td>1.00, 1.43</td>
<td>-3.0</td>
<td>-4.5, -1.4</td>
<td>1.26</td>
<td>1.02, 1.56</td>
</tr>
<tr>
<td>Severe, including eclampsia</td>
<td></td>
<td>-3.1</td>
<td>-7.4, 1.2</td>
<td>1.44</td>
<td>0.83, 2.47</td>
<td>-2.7</td>
<td>-8.1, 2.7</td>
<td>1.18</td>
<td>0.54, 2.62</td>
</tr>
</tbody>
</table>

Abbreviations: BPP, Boerge Prien test score (Danish: Børge Prien Prøve); CI, confidence interval; PR, prevalence ratio; SGA, small for gestational age.

a BPP scores were converted to the conventional IQ scale (mean = 100 (standard deviation, 15)).

b Adjusted for maternal age (in categories ≤20, 21–35, >35 years), parity (0, 1, 2, ≥2 previous births as indicator variables), marital status (married/unmarried), and history of diabetes (yes/no); and for conscripts’ year of birth (indicators for 1978, 1979, …, 1983), county of birth (North Jutland, Viborg, other), birth weight in grams, and being large for gestational age (defined as birth weight in the 90th percentile for a given gestational week; for postterm births, the 90th percentile value of week 42 was used).
antihypertensive or anticonvulsive medications received by mothers.

Incomplete or incorrect ascertainment of medical diagnoses is a limitation of studies based on registry data (22). Clinical diagnosis of preeclampsia can be difficult, and there is documented variability in diagnostic practices, indicating that even valid diagnoses may reflect heterogeneous conditions (23). According to the validation study of gestational hypertensive disorders recorded in the Danish National Registry of Patients in 1998–2002, sensitivity of the registry record was 49% for any gestational hypertensive disorder, 10% for gestational hypertension, 69% for all types of preeclampsia, and 44% for severe preeclampsia; specificity was >99% for all the diagnoses (24). We have no data on the validity of relevant hospitalization diagnoses for the period of conscripts’ birth, 1978–1983. Therefore, we do not know whether the later estimates are applicable to the diagnoses made during the study period. Edema, a criterion for preeclampsia diagnosis in 1978–1983, was later dropped as a nonspecific symptom of pregnancy. Therefore, some mothers identified as preeclamptic in our study based on hypertension and edema (without proteinuria) would be diagnosed with gestational hypertension according to current guidelines. This may explain the similarity of the estimates of association observed for hypertension and preeclampsia in this study. Sons of women who were diagnosed as outpatients represent an unknown proportion of false-negative observations. At the same time, inclusion of relatively severe cases, requiring hospitalization, serves to enhance specificity. The rates of underascertainment of these maternal conditions are not expected to differ systematically according to conscripts’ IQ measurements nearly 2 decades later; therefore, the comparisons we report are presumably biased toward the null value.

Most published studies of cognitive outcomes after exposure to pregnancy-associated hypertensive disorders report on childhood IQ in selected obstetric groups (5–7). Oumset et al. (5), in a study of 242 British children born to hypertensive mothers, found that, at age 7.5 years, offspring of mothers with superimposed preeclampsia had better intellectual performance than offspring of mothers with hypertension alone. In Australia, Gray et al. (6) reported no association between maternal hypertension and cognitive impairment at age 2 years in a sample of 214 preterm infants. In Israel, Many et al. (7) followed 75 growth-restricted infants until age 3 years and found a 10-point lower mean IQ among those born after a preeclamptic pregnancy (n = 12). These results may not be directly comparable with ours since we examined adult cognitive outcome. In the only known previous study of adult IQ among offspring of preeclamptic mothers (428 men and women exposed to preeclampsia in an underlying cohort of >30,000 Israeli conscripts), Seidman et al. (8) found preeclampsia to be associated with a 1.2-point mean decrease in IQ among men and a 1.6-point mean decrease in IQ among women. Our findings indicate a slightly greater mean difference (e.g., a crude mean difference of −2.4 (95% CI: −3.7, −1.1) associated with mild preeclampsia). This difference between studies could be due to chance, differences in diagnostic procedures, or true population variability.

Our data cannot be used to prove causality of the observed associations. If, however, our results were to reflect a true causal relation between pregnancy hypertensive disorders and cognitive impairment, obvious possible pathways involve fetal growth restriction and prematurity. Abnormal placentation, which may result in growth restriction and hypoxic damage, frequently accompanies preeclamptic pregnancies (25, 26). Evidence suggests that a hypoxic placenta releases into maternal circulation excessive amounts of soluble fms-like tyrosine kinase-1 (sFlt-1), a potent antiangiogenic molecule found in nonpreeclamptic mothers at lower concentrations (25, 26). Serum concentration of sFlt-1 in preeclamptic women is elevated before the onset of symptoms and decreases after delivery; in laboratory animals, sFlt-1 was shown to induce a preeclampsia-like state (26). Clinical manifestations of preeclampsia in the mother may thus be markers of preexisting growth restriction or hypoxic damage, which in turn may adversely affect neurodevelopment. Because restriction to non–small for gestational age births in our analysis did not explain all of the observed association, other mechanisms may likewise be at work.

An inflammatory state may be involved in several potential causal mechanisms connecting gestational hypertensive disorders with neurologic impairment in the offspring (25). The mild systemic inflammatory state typical of a normal pregnancy is intensified in a preeclamptic pregnancy. Maternal diseases associated with systemic inflammation, such as obesity or chronic hypertension, may contribute to susceptibility to preeclampsia (25). Mothers with increased susceptibility due to poor health may develop preeclampsia in the absence of abnormal placentation (the so-called maternal versus placental version of the disease (25)). In this case, neurologic damage may be caused by a severe systemic inflammatory response—and accompanying oxidative stress (25).

Both gestational hypertension and preeclampsia, if severe, may necessitate preterm delivery of the fetus. In this pathway, the association between hypertensive disorders and neurologic impairment may be mediated by prematurity. Among term infants, preeclampsia was shown to be associated with both maternal fever and neonatal encephalopathy (27), suggesting that some pathways between preeclampsia and impaired neurodevelopment may involve infection-related brain damage. Immunologic, epigenetic, and evolutionary aspects of mother-fetus interaction could also play a role (28).

ACKNOWLEDGMENTS

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This study was funded by the Danish Clinical Epidemiological Research Foundation.
Conflict of interest: none declared.

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