Original Contribution

Gestational Age, Birth Weight, Intrauterine Growth, and the Risk of Epilepsy

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The authors evaluated the association between gestational age, birth weight, intrauterine growth, and epilepsy in a population-based cohort of 1.4 million singletons born in Denmark (1979–2002). A total of 14,334 inpatients (1979–2002) and outpatients (1995–2002) with epilepsy were registered in the Danish National Hospital Register. Children who were potentially growth restricted were identified through two methods: 1) sex-, birth-order-, and gestational-age-specific z score of birth weight; and 2) deviation from the expected birth weight estimated based on the birth weight of an older sibling. The incidence rates of epilepsy increased consistently with decreasing gestational age and birth weight. The incidence rate ratios of epilepsy in the first year of life were more than fivefold among children born at 22–32 weeks compared with 39–41 weeks and among children whose birth weight was <2,000 g compared with 3,000–3,999 g. The association was modified by age but remained into early adulthood. Incidence rate ratios of epilepsy were increased among children identified as growth restricted according to either of the two methods. In conclusion, short gestational age, low birth weight, and intrauterine growth restriction are associated with an increased risk of epilepsy.

birth weight; Denmark; epilepsy; follow-up studies; infant, small for gestational age; premature birth; siblings

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (1). It affects 1 percent of the population before the age of 20 years (2, 3), but about 55–75 percent of childhood epilepsy is of unknown cause (4). More genes have been identified for human epilepsy, but they account for only a minority of all cases of epilepsy (5). Most common human epilepsies are multifactorial disorders in which more than one gene and environmental risk factors contribute to the seizure phenotype (6). The intrauterine environment has been shown to play an important role in the development of neurologic disorders such as cerebral palsy (7, 8). Preterm delivery and low birth weight have been associated with an increased risk of cerebral palsy (9), mental retardation (10), and behavioral disorders (11). Low birth weight and short gestational age are also risk factors for seizure
disorders, such as neonatal seizures and febrile seizures (12, 13).

Studies on the association between gestational age, birth weight, and epilepsy have, however, yielded conflicting findings. One earlier study found a higher frequency of low birth weight in children with epilepsy born to White mothers (14). Rocca et al. (15, 16) reported that individuals with complex partial seizures and absence seizures were more often small for gestational age or of low birth weight. Some studies (17–19), but not all (20, 21), reported an association between gestational age or birth weight and generalized tonic-clonic seizures or first unprovoked afebrile seizure. A recent, population-based cohort study showed that small-for-gestational-age children, compared with children considered to be of normal growth, had an increased risk of epilepsy (22).

We explored the risk of epilepsy as a function of gestational age, birth weight, and fetal growth in a large, population-based cohort of children followed up to 24 years of age.

MATERIALS AND METHODS

Study population

From the Danish Civil Registration System (23) we identified all singletons born in Denmark between January 1, 1979, and December 2, 2002, and alive on the 29th day of life (N = 1,470,182). The registry includes the unique identification number assigned to all residents of Denmark and has continuously updated information on vital status. The identification number enables accurate linkage between all national registers. Children were followed up from the 29th day of life (to exclude neonatal seizure) until the first diagnosis of epilepsy, death, emigration from Denmark, or December 31, 2002, whichever occurred first. The study was approved by the Danish Data Protection Agency.

Epilepsy

Diagnosis of epilepsy was derived from the Danish National Hospital Register (24), which contains information on discharge diagnoses for all inpatients from Danish hospitals since 1977, while discharge diagnoses for outpatients have been recorded since 1995. Diagnostic information is based on the Danish version of the International Classification of Diseases, Eighth Revision from 1977 to 1993 and the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision from 1994 onward. Cohort members were classified as having epilepsy if they had been hospitalized or had been in outpatient care because of a diagnosis of epilepsy (International Classification of Diseases, Eighth Revision, code 345; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, codes G40–G41). A modification code was given in the International Classification of Diseases, Eighth Revision system to describe on what basis the diagnosis was made. We omitted all diagnoses that bore the modification code “suspected” and “not found.” Time of onset of epilepsy was defined as the first day of contact with the hospital when patients were hospitalized or were in outpatient care with the first diagnosis of epilepsy according to the hospital register.

Gestational age, birth weight, Apgar score, congenital malformation, and cerebral palsy

Information on gestational age, birth weight, Apgar score at 5 minutes, and congenital malformations was obtained from the Danish Medical Birth Registry (25), which includes records for all births of Danish residents since 1973. Gestational age recorded in the Medical Birth Registry was based mainly on the date of the last menstrual period, but, in the last 15 years, ultrasound measurements have been increasingly used. Information on cerebral palsy was obtained from the Danish National Hospital Register (24) by using International Classification of Diseases, Eighth Revision codes 343.99 and 344.99 and, later, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision code G80.

We excluded 50,688 (3.4 percent) births because of missing information on birth weight or gestational age and 56 births registered with a gestational age of less than 22 weeks. Using a method described by Tentoni et al. (26), we excluded children whose records indicated both a short gestational age (22–33 weeks) and an improbably large birth weight. In brief, we considered the data inconsistent if the observed birth weight at a given gestational age was more than three times the standard deviation of the major Gaussian component of the distribution of birth weight. Among the 20,656 births registered with a gestational age of 22–33 weeks, we excluded 567 (2.7 percent) babies based on the above criterion.

Calculation of z score and birth-weight ratio

We calculated the sex-, birth-order-, and gestational-agespecific z score of birth weight for all babies based on the data in our study. Birth order was divided into three categories (1, 2, ≥3). The lowest 15th percentile of the z score was used to define “small for gestation” for all babies. For the subset of second-born children whose gestational age was greater than 27 completed weeks, we also used the birth-weight ratio to identify potentially growth-restricted babies. The birth-weight ratio is the observed birth weight divided by the expected birth weight multiplied by 100. The expected birth weight of the second-born child was estimated by using the birth weight of the first-born child based on a method described in detail elsewhere (27). Briefly, the method modified a model proposed by Skjærven et al. (28) by additionally taking into account gestational age and sex of the first-born child. Children in the lowest 15th percentile of the birth-weight ratio were considered potentially growth restricted.

Statistical analysis

We estimated the incidence rate ratio (IRR) of epilepsy by using log-linear Poisson regression in SAS version 8.1 software (29, 30). All IRRs were adjusted for calendar year,
age, and the interaction between age and sex. Age, calendar year, cerebral palsy, and a history of epilepsy in parents or siblings were treated as time-dependent variables (31), whereas all other variables were considered time independent. Age was categorized in 3-month intervals in the first year of life and in 1-year intervals between the first and the 19th birthdays, and ages 20–21 and 22–24 years represented the last two categories. *p* values were based on likelihood ratio tests, and 95 percent confidence intervals were calculated by using Wald’s test (31).

**RESULTS**

Of 1,418,871 children followed up to 24 years of age (15.5 million person-years at risk), 14,334 were hospitalized with epilepsy, corresponding to a crude incidence rate of 92.6 per 100,000 person-years.

The incidence rate of epilepsy increased consistently with decreasing gestational age and birth weight, but the association became weaker as age at diagnosis of epilepsy increased (figures 1 and 2). For example, compared with children whose gestational age at birth was 39–41 weeks, those whose gestational age was 22–32 weeks had a fivefold (IRR = 5.41, 95 percent confidence interval (CI): 4.44, 6.59) higher incidence rate of epilepsy in the first year of life but a twofold higher incidence rate between the ages of 15 and 24 years (IRR = 2.05, 95 percent CI: 1.32, 3.19). Compared with children born at 39–41 gestational weeks, children born postterm (42 gestational weeks or later) had a slightly increased risk of epilepsy up to 8 years of age, with IRRs of 1.00 (95 percent CI: 0.86, 1.17), 1.07 (95 percent CI: 0.88, 1.30), 1.09 (95 percent CI: 0.87, 1.35), 1.16 (95 percent CI: 0.94, 1.43), 1.21 (95 percent CI: 0.97, 1.51), 1.25 (95 percent CI: 1.00, 1.56), and 1.08 (95 percent CI: 0.91, 1.28) for each year of age from the first to the fifth years and for the sixth to seventh years. However, several of the confidence intervals included one (not shown in figure 1). Compared with children whose birth weight was 3,000–3,999 g, those whose birth weight was <2,000 g had an IRR of epilepsy of 5.09 (95 percent CI: 4.34, 5.96) in the first year of life and 1.73 (95 percent CI: 1.24, 2.41) between the ages of 15 and 24 years. Children whose birth weight was more than 4,000 g had an incidence of epilepsy similar to that for children whose birth weight was 3,000–3,999 g (data not shown in figure 2).

Because of the change in IRRs with age at first diagnosis of epilepsy, we restricted the following analyses to children up to 5 years of age. The incidence of epilepsy increased with decreasing gestational age and birth weight (table 1). Children born at term and whose *z* score was in the three lowest categories (<5 percent, 5–9 percent, 10–14 percent) of the distribution had a higher IRR of epilepsy than children whose *z* score was above the 15th percentile. Among children born preterm, those whose birth weight was below the lowest 5 percent of the *z* score distribution, compared with children whose *z* score was above the 15th percentile, had a significantly higher IRR of epilepsy. Among second-born children, the birth-weight ratio identified more children at high risk.
of epilepsy than the z score did, especially born at term (table 1).

Compared with those for children who achieved their expected birth weight (i.e., the observed birth weight was between 90 percent and 109 percent of their expected birth weight), the IRRs of epilepsy tended to increase for those with increasing deviations from the expected birth weight, although the findings were statistically significant for only

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**FIGURE 2.** Incidence rate ratio of epilepsy according to birth weight and age at first diagnosis of epilepsy, Denmark, 1979–2002. Birth weight of 3,000–3,999 g was the reference, and analyses were adjusted for calendar year, age, and the interaction between age and sex.

**FIGURE 3.** Incidence rate ratio of epilepsy according to gestational age and age at first diagnosis of epilepsy for children without cerebral palsy, congenital malformations, low Apgar score, and family history of epilepsy, Denmark, 1979–2002. Gestational age of 39–41 weeks was the reference, and analyses were adjusted for calendar year, age, and the interaction between age and sex.
those children born at term (table 2). Even children in the “normal range” of birth weights (3,500–3,999 g) had a higher IRR of epilepsy if they had not reached their expected birth weight (IRR = 1.48, 95 percent CI: 1.03, 2.14) (results not shown in tables). Among children who achieved their expected birth weight, the incidence rate of epilepsy increased with decreasing gestational age and birth weight (table 3).

Among children born in 1995–2002, when discharge diagnoses of epilepsy for outpatients were also recorded, 633 (25.2 percent of 2,512 cases) children were treated as outpatients only. The age-specific associations between gestational age and the risk of epilepsy were similar for total cases identified (inpatients and outpatients) and for inpatients only during this period. However, the estimates of the IRRs of epilepsy in the first 5 years for children born preterm in the period 1995–2002 were slightly lower than those for the whole population (1979–2002, figure 1). Similarly, we found no difference in the age-specific associations between birth weight and the risk of epilepsy for total cases identified and for inpatients only in the period 1995–2002.

DISCUSSION

The incidence of hospitalization for epilepsy increased consistently with decreasing gestational age and birth weight. The association was modified by age at diagnosis of epilepsy; the IRR of epilepsy decreased with age at diagnosis but remained elevated into early adulthood. Children with likely impairment of fetal growth had an increased IRR of epilepsy, even if their birth weight was within the “normal” range.

In general, children of a low birth weight include those who are constitutionally small, have a short gestational age at birth, or are growth restricted (32). In an attempt to disentangle these factors, we calculated the expected birth weight based on the birth weight of an older sibling to provide a better estimate of the biologic growth potential (33) and reduce the risk of misclassifying children who are constitutionally small as growth restricted (34). We estimated the risk of epilepsy as a function of the ratio between the observed birth weight and this expected birth weight. For children who achieved their expected birth weight, the risk of epilepsy increased consistently with decreasing gestational age, indicating that preterm birth is an independent risk factor for epilepsy.

Total brain-tissue volume increases linearly in the third trimester of fetal life, with a fourfold increase in cortical grey matter between 29 weeks and 41 weeks and a fivefold increase in myelinated white matter between 35 weeks and 41 weeks (35). Premature birth itself may lead to subtle neuropathologies, including cerebral white matter gliosis, hippocampal sclerosis, and subarachnoid hemorrhage, as shown in nonhuman primates (36). Furthermore, premature delivery is often associated with other risk factors during pregnancy, such as infections and preeclampsia (37, 38). The association between gestational age and the risk of epilepsy may therefore reflect the effect of both immaturity and that of a suboptimal intrauterine environment.

Cerebral palsy and congenital malformations, especially in the central nervous system, are associated with an
increased risk of epilepsy (39). We and others have shown that children whose Apgar scores are low have an increased risk of epilepsy and that the risk of epilepsy increases with decreasing Apgar scores (40, 41). In this analysis, we found that the risk of epilepsy related to low birth weight or short gestational age was not mediated by cerebral palsy, congenital malformations, or low Apgar scores. An early study showed that low birth weight, preterm birth, and smallness for gestational age were not related to the risk of afebrile seizures in children free of cerebral palsy (9). However, the highest risk of afebrile seizures was for children born at 37 or more gestational weeks and with a low birth weight of 1,501–2,500 g (9).

In our analysis, the association of low birth weight and short gestational age with the risk of epilepsy was particularly strong within the first 5 years of life, perhaps because the immature brain is more susceptible to seizures when exposed to risk factors operating during prenatal life than the mature brain is (42). Children of a low birth weight or born preterm also have an increased risk of febrile seizure (13).

<table>
<thead>
<tr>
<th>Preterm (28–36 weeks)</th>
<th>Term (37–41 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of person-years at risk</td>
<td>No. of cases</td>
</tr>
<tr>
<td>All children</td>
<td>362,338</td>
</tr>
<tr>
<td>z score</td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>13,808</td>
</tr>
<tr>
<td>5–9.9%</td>
<td>15,480</td>
</tr>
<tr>
<td>10–14.9%</td>
<td>15,721</td>
</tr>
<tr>
<td>≥15%</td>
<td>317,329</td>
</tr>
<tr>
<td>Second-born children</td>
<td>66,667</td>
</tr>
<tr>
<td>z score</td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>2,010</td>
</tr>
<tr>
<td>5–9.9%</td>
<td>2,351</td>
</tr>
<tr>
<td>10–14.9%</td>
<td>2,484</td>
</tr>
<tr>
<td>≥15%</td>
<td>59,822</td>
</tr>
<tr>
<td>Birth-weight ratio</td>
<td></td>
</tr>
<tr>
<td>&lt;5%</td>
<td>3,099</td>
</tr>
<tr>
<td>5–9.9%</td>
<td>3,266</td>
</tr>
<tr>
<td>10–14.9%</td>
<td>3,340</td>
</tr>
<tr>
<td>≥15%</td>
<td>56,963</td>
</tr>
</tbody>
</table>

* Crude incidence rate (IR) per 100,000 person-years.
† Incidence rate ratio (IRR) adjusted for calendar year, age, and the interaction between age and sex.
‡ CI, confidence interval.
We cannot exclude the possibility that some of those febrile seizures were miscoded as epilepsy, although this bias is likely small.

In this study, we focused on children born with a short gestational age or children who did not fulfill their growth potential, but postterm delivery is also a risk factor for perinatal complications. A recent study showed that children born postterm had an increased risk of epilepsy in the first year of life (43), but we were unable to confirm these findings when using the entire Danish population and adjusting for age and calendar period. The authors of that study used the data from three counties in Denmark, which may have characteristics different from those in the whole population in our study, and followed up the children from birth. Furthermore, we excluded the uncertain diagnoses of epilepsy.

Our study was based on a large, population-based cohort that was followed up to 24 years with virtually no loss to follow-up (23). Thus, bias due to selection of study participants cannot explain our findings. The quality of the gestational age assessment was not optimal, however; estimates of last menstrual period may be biased by early pregnancy bleeding, irregular periods, use of contraceptives, and recall problems (44), and estimates from ultrasound may be biased by exposures that impair early fetal growth (45). A validation study in Denmark showed that, between 1982 and 1987, 64 percent of gestational-age estimates from the medical records were based on the last menstrual period, 35 percent on early ultrasound, and 1 percent on clinical estimates (46), but, in recent years, ultrasound measurements have been increasingly used (47). On the other hand, information on gestational age was recorded before epilepsy was diagnosed, and misclassification was thus most likely to be non-differential, which often attenuates effect measures (48). It is possible, however, that children born preterm or small may have been more likely to receive a diagnosis of epilepsy compared with those born at term or of normal growth, especially if these factors increased their probability of being hospitalized or diagnosed with seizures. On the other hand, it is also possible that the diagnosis could be false positive.

This study included only singletons. Thus, the results cannot be applied to children born of multiple deliveries, for whom the significance of preterm and low birth weight are likely to be different.

Diagnoses of epilepsy were obtained from the Danish National Hospital Register, which has included information on discharge diagnoses from Danish hospitals for all inpatients since 1977 and all outpatients since 1995. The positive predictive value of the diagnosis of epilepsy in the Danish National Hospital Register has been assessed according to the criteria (which requires two or more unprovoked seizure episodes) of the International League Against Epilepsy and found to be 81 percent (95 percent CI: 75, 87) (49). Unfortunately, we did not have information on completeness of the epilepsy diagnosis in the Danish National Hospital Register. We believe that cases with more severe epilepsy are more likely to be hospitalized. Including outpatients in the register in 1995 was followed by a 17 percent increase in the

### TABLE 3. Incidence rate ratios of epilepsy during the first 5 years of life according to gestational age and birth weight among second-born children who achieved their expected birth weight,* Denmark, 1979–2002

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>No. of person-years at risk</th>
<th>No. of cases</th>
<th>IR †</th>
<th>IRR‡</th>
<th>95% CI§</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–32</td>
<td>4,385</td>
<td>20</td>
<td>456.2</td>
<td>5.23</td>
<td>3.35, 8.16</td>
</tr>
<tr>
<td>33–36</td>
<td>29,405</td>
<td>48</td>
<td>163.2</td>
<td>1.86</td>
<td>1.39, 2.50</td>
</tr>
<tr>
<td>37–38</td>
<td>164,003</td>
<td>174</td>
<td>106.1</td>
<td>1.20</td>
<td>1.01, 1.41</td>
</tr>
<tr>
<td>39–41</td>
<td>757,611</td>
<td>659</td>
<td>87.0</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>≥42</td>
<td>368,799</td>
<td>332</td>
<td>90.0</td>
<td>1.04</td>
<td>0.91, 1.08</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>No. of cases</th>
<th>IR †</th>
<th>IRR‡</th>
<th>95% CI§</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,500</td>
<td>1,613</td>
<td>13</td>
<td>806.0</td>
<td>9.37</td>
</tr>
<tr>
<td>1,500–1,999</td>
<td>3,651</td>
<td>8</td>
<td>219.1</td>
<td>2.51</td>
</tr>
<tr>
<td>2,000–2,499</td>
<td>9,833</td>
<td>18</td>
<td>183.1</td>
<td>2.11</td>
</tr>
<tr>
<td>2,500–2,999</td>
<td>61,248</td>
<td>84</td>
<td>137.1</td>
<td>1.60</td>
</tr>
<tr>
<td>3,000–3,499</td>
<td>440,613</td>
<td>406</td>
<td>92.1</td>
<td>1.06</td>
</tr>
<tr>
<td>3,500–3,999</td>
<td>616,925</td>
<td>548</td>
<td>88.8</td>
<td>1.00</td>
</tr>
<tr>
<td>≥4,000</td>
<td>190,320</td>
<td>156</td>
<td>82.0</td>
<td>0.89</td>
</tr>
</tbody>
</table>

* Refers to children whose observed birth weight was between 90% and 109% of the expected birth weight.
† Crude incidence rate (IR) per 100,000 person-years.
‡ Incidence rate ratio (IRR) adjusted for calendar year, age, and the interaction between age and sex.
§ CI, confidence interval.
incidence rates of epilepsy (3). When we restricted the analyses to data from 1995–2002, we found the same trend regarding the association of gestational age and birth weight with the risk of epilepsy. Incomplete registration of epilepsy would cause underestimation of the cumulative incidence of epilepsy, but rate ratios would be affected only if the registration of epilepsy depended on exposure status, which is possible. However, this mechanism would result in higher IRR estimates of epilepsy during early childhood but is unlikely to explain the long-term impact of gestational age and birth weight on the risk of epilepsy.

Our study was limited by lack of detailed clinical data on types of epilepsy. Our validation study showed that the data on epilepsy classification were imprecise (49), and more than half of the epilepsy cases in the first year of life received a code of “unspecified” or “other” (43). Thus, more studies are needed to evaluate whether the association with birth weight, gestational age, and intrauterine growth is restricted to certain types of epilepsy.

This study showed that gestational age at birth and intrauterine growth restriction are associated with subsequent risk of epilepsy. Environmental factors operating in fetal life or short gestation in itself may play a causal role in the development of epilepsy, especially in young children.

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