In Utero Exposure to Ischemic-Hypoxic Conditions and Attention-Deficit/Hyperactivity Disorder

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KEY WORDS: pregnancy, ischemic-hypoxic conditions, asphyxia, hypoxia, ischemia, preeclampsia, attention deficit hyperactivity disorder, race, ethnicity

ABBREVIATIONS:
ADHD—attention-deficit/hyperactivity disorder
IHC—ischemic-hypoxic condition
ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification
KPSC—Kaiser Permanente Southern California
OR—odds ratio
RDS—respiratory distress syndrome

WHAT’S KNOWN ON THIS SUBJECT: Although previous studies indicate that perinatal factors are associated with altered neurodevelopment, data on the association between ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder in children are sparse.

WHAT THIS STUDY ADDS: This study demonstrates that preeclampsia, birth asphyxia, and respiratory distress syndrome are independently associated with increased risk of attention-deficit/hyperactivity disorder in a large population-based study.

OBJECTIVE: To examine the association between ischemic-hypoxic conditions (IHCs) and attention-deficit/hyperactivity disorder (ADHD) by gestational age and race/ethnicity.

METHODS: Nested case-control study using the Kaiser Permanente Southern California (KPSC) medical records. The study cohort included children aged 5 to 11 years who were delivered and cared for in the KPSC between 1995 and 2010 (N = 308,634). Case children had a diagnosis of ADHD and received ≥2 prescriptions specific to ADHD during the follow-up period. For each case, 5 control children were matched by age at diagnosis. Exposures were defined by using International Classification of Diseases, Ninth Revision codes. A conditional regression model was used to estimate adjusted odds ratios (ORs).

RESULTS: Among eligible children, 13,613 (4.3%) had a diagnosis of ADHD. Compared with control children, case children were more likely to be male and of white or African American race/ethnicity. Case children were more likely to be exposed to IHCs (OR = 1.16, 95% confidence interval [CI] 1.11–1.21). When stratified by gestational age, cases born at 28 to 33, 34 to 36, and 37 to 42 weeks of gestation, were more likely to be exposed to IHCs (ORs, 1.6 [95% CI 1.2–2.1], 1.2 [95% CI 1.1–1.3], and 1.1 [95% CI 1.0–1.2], respectively) compared with controls. IHC was associated with increased odds of ADHD across all race/ethnicity groups.

CONCLUSIONS: These findings suggest that IHCs, especially birth asphyxia, respiratory distress syndrome, and preeclampsia, are independently associated with ADHD. This association was strongest in preterm births. Pediatrics 2013;131:e53–e61

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Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent chronic childhood disease characterized by hyperactivity, inattention/distractability, and impulsivity that persists into adulthood for approximately half of affected children. In the United States, 4% to 12% of all children aged 5 to 17 years had ADHD in 2008. Children with ADHD are also likely to develop other mental and physical conditions, often requiring intensive medical care and special social and educational services. Nationally, the annual cost of ADHD-related illness in children aged 5 to 18 years is estimated to be between $36 and $52.4 billion, in 2005 dollars. The high prevalence and chronic nature of ADHD combined with its rising health care costs make it a public health priority.

Previous studies have suggested that genetic, environmental, and prenatal and postnatal factors may be associated with altered neurodevelopment. Emerging evidence suggests that ischemic-hypoxic conditions (IHCs) in pregnancy resulting from acute and chronic perinatal events have adverse consequences on fetal brain development that are not apparent at birth. Although previous studies noted that in utero exposure to IHC is associated with fetal brain injury, the role of IHCs in the development of ADHD is unexplored. Thus, we hypothesize that IHC is an independent risk factor for childhood ADHD. If true, this could have important clinical implications because preeclampsia and fetal asphyxia may be modifiable risk factors for ADHD. Moreover, it could help identify newborns at risk who could benefit from surveillance and early diagnosis, when treatment is more effective.

METHODS

This study used population-based data from children born in Kaiser Permanente Southern California (KPSC) hospitals during 1991–2005 (N = 464,317). For each study subject, we compiled data from the perinatal service system, hospital inpatient records, outpatient physician encounters, and laboratory and pharmacy records. Information extracted from perinatal service system records included maternal sociodemographic and behavioral characteristics, perinatal complications, and child race/ethnicity, age, and gender. Inpatient and outpatient encounter records included maternal obstetrical complications and procedures as well as child medical history. Pharmacy records provided data on ADHD-specific medications.

This study used a case-control approach within an established cohort of children. To be included in the cohort, children must have been born to KPSC members, have been a singleton birth between 28 and 42 weeks of gestation in a KPSC hospital between January 1, 1991, and December 31, 2005, and have been a KPSC health plan member at least for 3 months between the ages of 5 to 11 years, during 1995–2010. Children born at <28 weeks of gestation were excluded because of their high morbidity and mortality, as were children with a diagnosis of autism because of its overlap with ADHD. The total number of children in the resulting cohort was 308,634 (Fig 1).

Gestational age was based on clinical estimates. Potential confounders included child gender (male/female), family household income based on census tract of residence (<$29,999, $30,000–$49,999, $50,000–$69,999, $70,000–$89,999, ≥$90,000), maternal age (<20, 20–29, 30–34, ≥35 years) and education (<12, 12, ≥13 years of completed schooling), prenatal care (first trimester and none/late initiation), smoking (yes/no), and psychosocial disorders during pregnancy (yes/no). Child race/ethnicity was based on...
maternal and paternal race/ethnicity and categorized as non-Hispanic white (white), non-Hispanic black (African American), Hispanic, Asian/Pacific Islander, or other/mixed racial/ethnic groups. Children of unknown or missing race were excluded from all race/ethnicity–specific analyses because of their small number (<3.3%).

Definition of the exposure (IHC) required presence of at least one of the following: (1) acute (placental abruption [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 641.2X, 762.1], birth asphyxia [ICD-9-CM codes 768.X, which included Apgar score <7 at 5 minutes and neonatal resuscitation], breech/transverse presentation of the fetus [ICD-9-CM codes 652.2X, 652.3X, 669.6X, 763.0, 72.X], dystocia [ICD-9-CM codes 660.4X], prolapsed/nuclal cord [ICD-9-CM codes 762.4, 762.5, 73.92], and respiratory distress syndrome [RDS; ICD-9-CM codes 769.X]),37–39 or (2) chronic (preeclampsia [ICD-9-CM codes 642.X])40,43 perinatal conditions. We validated the accuracy of the ICD-9-CM coding by comparing it with diagnoses abstracted from a random sample of 400 medical records. For our validation study, pregnancies resulting in low birth weight or preterm births were oversampled to ensure adequate representation of subjects with obstetric risk factors. After adjusting for sampling fractions, the estimated sensitivity, specificity, positive, and negative predictive values for placental abruption, intrauterine growth restriction, fetal distress, Apgar score <7 at 5 minutes, and preeclampsia were 97%, 100%, 100%, and 100%; 80%, 99%, 95%, and 100%; 91%, 96%, 69%, and 97%; 100%, 98%, 100%, and 100%; and 94%, 97%, 68%, and 100%, respectively. These findings support the validity of the diagnosis codes in our study.

Case children had to have clinically diagnosed ADHD (ICD-9-CM codes 314.X) on at least 2 separate visits or a diagnosis on 1 visit and at least 2 refills of ADHD-specific medications (including amphetamine aspartate, amphetamine sulfate, dextroamphetamine aspartate, dextroamphetamine sulfate, or methylphenidate hydrochloride) during the follow-up period. This approach increases the specificity of case ascertainment. Per KPSC guidelines, a clinical diagnosis of ADHD was based on a child behavior checklist completed by parents and teachers and a clinical interview performed by a qualified mental health professional. In a preliminary analysis for this project, 96% of children with ADHD were diagnosed by child/adolescent psychiatrists, developmental/behavioral pediatricians, child psychologists, or neurologists. Incidence density (risk set) sampling was used to sample the comparison group (controls). For each case child, 5 control children without ADHD at the time of case diagnosis were selected at random from all those matched by age at diagnosis. These control children were at risk of subsequently being diagnosed with ADHD, and ~1000 (1.5%) were later diagnosed. They were retained in the control group in conformance with the at-risk sampling plan.45 Subjects were eligible for participation in the control sample for more than 1 case, so that the group of 68 065 matched control subjects was actually composed of 59 210 separate individuals.

We first analyzed trends in IHCs across the study period. We then performed a nested case-control analysis to examine the association between IHC and ADHD diagnosis. Statistical analyses were performed in 4 steps: (1) we examined the distributions of maternal and child characteristics by case status, (2) a conditional logistic regression model was fitted to examine the association between IHC and ADHD before and after controlling for confounding variables. Exact conditional logistic regression models were used when expected cell counts were <5. IHCs were examined both individually and as part of a cumulative risk index. Confounding variables were chosen a priori. (3) We repeated the analysis by using conditional logistic regression in cases and controls that were matched (1:5 ratio) by gestational age and by child race/ethnicity. ORs and 95% CIs were used to quantify associations. (4) The impact of IHC on ADHD was evaluated by using the population-attributable fraction using the following formula: population-attributable fraction = proportion of cases in the population [(adjusted OR – 1)/adjusted OR], where adjusted OR is for the exposure category and the proportion of cases in the population is from the 4th exposure category.46 Analyses were performed by using SAS version 9.2 (SAS Institute, Cary, SC). This study was approved by the KPSC Institutional Review Board.

RESULTS

There were 13 613 children born in KPSC hospitals and diagnosed with ADHD between the age of 5 and 11 years. They were individually matched to 68 065 control children (Fig 1). During the study period, the incidence of ADHD was 4.3 per 100 children. The mean age at first diagnosis was ~8 years (SD 1.7). The rate of IHC diagnoses per 100 singleton births increased from 17.8% in 1991% to 22.6% in 2005 (P for trends <.001; Fig 2).

Characteristics of mothers and children in the case and control groups are shown in Table 1. Compared with control mothers, case mothers were more likely to be older, have ≥12 years education, and have a high household income, history of smoking, and psychosocial disorders during pregnancy. The rate of ADHD diagnosis varied substantially by race/ethnicity. By using non-Hispanic whites as the reference, the ORs for ADHD were 0.81, 0.50,
0.26, and 0.83 for African Americans, Hispanics, Asian/Pacific Islanders, and others, respectively ADHD was diagnosed 3 times more frequently in boys as in girls.

The proportion of case children exposed to IHCs in utero was significantly higher (24.0%) than that of control children (20.9%; OR 1.16, 95% CI 1.11–1.21; Table 2). Although we observed a significant association between each component of IHC and childhood ADHD in unadjusted analysis, the association between placental abruption (OR 1.16, 95% CI 0.96–1.42), fetal dystocia (OR 1.11, 95% CI 0.94–1.31), and ADHD attenuated and became nonsignificant after accounting for potential confounding factors listed in Table 1. Further adjustment for gestational age did not change this result (data not shown). In contrast, birth asphyxia was associated with 1.26-fold (95% CI 1.13–1.40) increased risk. Infants with an Apgar score of <7 at 5 minutes (OR 1.31, 95% CI 1.08–1.57) and those requiring resuscitation (OR 2.75, 95% CI 2.04–3.72) were at significantly increased risk. Breech/transverse presentations (OR 1.13, 95% CI 1.05–1.23) and cord complications (OR 1.13, 95% CI 1.08–1.19) were noted to be associated with a moderately increased risk of ADHD. Preeclampsia (OR 1.34, 95% CI 1.25–1.44) had a stronger association with ADHD and remained significant after accounting for potential confounding factors. The estimated adjusted population fraction of ADHD attributable to IHC was 3.3%. Approximately two-thirds of this attributable risk was related to preeclampsia.

Table 3 shows rates of IHC for case and control children and its association with ADHD based on gestational age at birth and IHC subtypes. Among children born at 28 to 33 weeks of gestation, case children were more likely (OR 1.6, 95% CI 1.2–2.1) than control children to be exposed to IHCs. The magnitude of this association decreased with greater gestational age. Children exposed to placental abruption experienced significantly increased risk of ADHD (OR 2.1, 95% CI 1.4–3.3) only if the abruption occurred before 34 weeks. Birth asphyxia, breech/transverse presentations, and prolapsed/nuchal cord were strongly associated with ADHD at 28 to 33 and 37 to 42 weeks of gestations, and neonatal RDS was important risk factor for ADHD at preterm gestation. On the other hand, preeclampsia remained significant as a risk factor regardless of gestational age. The findings were largely unchanged after adjustment for gestational age (data not shown).

The race/ethnicity–specific frequency of IHC in ADHD cases and controls is shown in Table 4. Birth asphyxia and preeclampsia accounted for most of the IHC exposures in all groups. ORs for the association of IHC with ADHD, adjusted for major confounders, are shown by race/ethnicity in Table 5 and were fairly consistent for birth asphyxia and for preeclampsia across race/ethnicity groups. These findings were not affected by adjustment for gestational age (data not shown).
TABLE 2 Associations Between IHCs and ADHD

<table>
<thead>
<tr>
<th>Conditions</th>
<th>ADHD</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
<th>PAF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n = 13 613, No. (%)</td>
<td>Controls n = 68 065, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No IHC</td>
<td>10 342 (76.0)</td>
<td>1.00 (Reference)</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>IHC</td>
<td>3271 (24.0)</td>
<td>1.20 (1.15–1.25)</td>
<td>1.16 (1.11–1.21)</td>
<td>3.3</td>
</tr>
<tr>
<td>Acute conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td>135 (1.11)</td>
<td>0.97 (0.93–1.00)</td>
<td>0.96 (0.93–1.00)</td>
<td>0.2</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>441 (3.53)</td>
<td>1.54 (1.50–1.59)</td>
<td>1.51 (1.48–1.55)</td>
<td>0.3</td>
</tr>
<tr>
<td>Apgar score of &lt;7 at 5 min</td>
<td>150 (1.23)</td>
<td>1.37 (1.34–1.40)</td>
<td>1.34 (1.31–1.37)</td>
<td>0.4</td>
</tr>
<tr>
<td>Neonatal resuscitation</td>
<td>74 (0.61)</td>
<td>2.88 (2.83–3.93)</td>
<td>2.84 (2.79–3.89)</td>
<td>0.7</td>
</tr>
<tr>
<td>Breech/transverse presentations</td>
<td>808 (7.20)</td>
<td>1.12 (1.09–1.15)</td>
<td>1.10 (1.07–1.14)</td>
<td>0.2</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>2257 (17.8)</td>
<td>1.16 (1.12–1.20)</td>
<td>1.14 (1.10–1.18)</td>
<td>0.2</td>
</tr>
<tr>
<td>Fetal dystocia</td>
<td>187 (1.77)</td>
<td>1.19 (1.16–1.22)</td>
<td>1.17 (1.14–1.21)</td>
<td>0.2</td>
</tr>
<tr>
<td>RDS</td>
<td>185 (1.75)</td>
<td>1.62 (1.59–1.65)</td>
<td>1.59 (1.56–1.62)</td>
<td>0.6</td>
</tr>
<tr>
<td>Chronic conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1105 (9.65)</td>
<td>1.36 (1.32–1.40)</td>
<td>1.34 (1.31–1.37)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

The number of women with acute conditions and chronic conditions may not add up to the total of IHCs because a woman may have received a diagnosis with >1 acute condition. PAF, population-attributable fraction.

* ORs were adjusted for maternal age, education, smoking during pregnancy, parity, prenatal care, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender.

Cesarean delivery also was strongly associated with IHC in bivariate analyses but was not an independent risk factor in the final model (data not shown). In an attempt to clarify whether the observed associations between IHCs and ADHD are modified by child’s neonatal jaundice status, we repeated the analysis stratified by the presence of neonatal jaundice and found a negligible difference (data not shown).

**DISCUSSION**

In this nested case-control study, we found that children with ADHD were more likely than those without ADHD to be exposed to IHCs in utero. This association persisted after adjustment for maternal sociodemographic and behavioral characteristics, psychosocial disorder status, and child gender and race/ethnicity. Much of the hypoxia-associated increase in ADHD risk can be explained by exposure to birth asphyxia, neonatal RDS, and preeclampsia. Children exposed to birth asphyxia, neonatal RDS, and preeclampsia had a significantly higher risk (26%, 47%, and 34%, respectively) of ADHD compared with unexposed children. Additional analysis by gestational age revealed that preeclampsia remained a significant predictor of ADHD regardless of the

TABLE 3 Associations Between IHCs and ADHD by Gestational Age

<table>
<thead>
<tr>
<th>Conditions</th>
<th>28–33 wk</th>
<th>Gestational Age–Specific Rates and ORs (95% CIs)* for ADHD</th>
<th>34–36 wk</th>
<th>37–42 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n = 275, No. (%)</td>
<td>Controls n = 1375, No. (%)</td>
<td>Adjusted OR (95% CI)*</td>
<td>Cases n = 881, No. (%)</td>
</tr>
<tr>
<td>No IHC</td>
<td>85 (30.9)</td>
<td>553 (40.2)</td>
<td>1.0 (Ref.)</td>
<td>560 (63.6)</td>
</tr>
<tr>
<td>IHC</td>
<td>190 (69.1)</td>
<td>822 (59.8)</td>
<td>1.6 (1.2–2.1)</td>
<td>321 (36.4)</td>
</tr>
<tr>
<td>Acute conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td>40 (25.0)</td>
<td>134 (14.1)</td>
<td>2.1 (1.4–3.3)</td>
<td>30 (4.3)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>45 (25.0)</td>
<td>153 (15.7)</td>
<td>2.0 (1.3–2.9)</td>
<td>40 (5.7)</td>
</tr>
<tr>
<td>Apgar score &lt;7 at 5 min</td>
<td>17 (11.2)</td>
<td>62 (7.3)</td>
<td>1.9 (1.6–2.5)</td>
<td>18 (2.7)</td>
</tr>
<tr>
<td>Neonatal resuscitation</td>
<td>7 (4.9)</td>
<td>12 (1.4)</td>
<td>3.4 (2.4–4.9)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Breech/transverse presentations</td>
<td>70 (40.0)</td>
<td>251 (27.5)</td>
<td>1.7 (1.2–2.4)</td>
<td>76 (11.2)</td>
</tr>
<tr>
<td>Prolapsed/nuchal cord</td>
<td>63 (37.5)</td>
<td>234 (26.2)</td>
<td>1.6 (1.1–2.3)</td>
<td>181 (25.1)</td>
</tr>
<tr>
<td>Fetal dystocia</td>
<td>1 (0.94)</td>
<td>3 (0.5)</td>
<td>2.1 (0.2–23.7)*</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>RDS</td>
<td>93 (43.0)</td>
<td>408 (58.2)</td>
<td>1.4 (1.0–2.0)</td>
<td>48 (7.4)</td>
</tr>
<tr>
<td>Chronic conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>87 (50.6)</td>
<td>372 (40.2)</td>
<td>1.6 (1.1–2.3)</td>
<td>175 (23.8)</td>
</tr>
</tbody>
</table>

The number of women with acute conditions and chronic conditions may not add up to the total of IHCs because a woman may have received a diagnosis with >1 acute condition.

* ORs derived from unconditional logistic regression models adjusted for maternal age, education, smoking during pregnancy, prenatal care, parity, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender.

* Estimates were based on exact conditional analysis.
gestational age at delivery. Birth asphyxia, breech/transverse presentation, and prolapsed/nuchal cord were significant risk factors at 28 to 33 and 37 to 42 weeks of gestation, but placental abruption and neonatal RDS conferred slight or absent risk for ADHD at term gestation. The estimated proportion of ADHD attributable to IHC is small (population-attributable fraction, 3.3%) because of modest association between IHC and ADHD. Therefore, efforts to reduce IHC would not have a substantial impact on ADHD rates.

The cause of ADHD remains largely unknown. However, there is strong evidence for genetic influences on risk of ADHD from twin and family studies.\(^{11,12}\) Monozygotic twins are more strongly concordant than are dizygotic twins for ADHD. In addition, evidence from human and animal studies suggests that antenatal psychosocial disorder,\(^{20,21}\) prenatal and postnatal tobacco exposure,\(^{47}\) viral infection during pregnancy,\(^{48}\) prenatal and postnatal drug exposures,\(^{49,50}\) and postnatal factors such as environmental lead exposure\(^{51,52}\) and type 1 diabetes before age 5\(^{53}\) are associated with increased risk of ADHD. Although the cause and pathophysiological underpinnings of the IHCs remain elusive, they pose significant risks to the unborn child through common pathophysiological mechanisms, namely, uteroplacental underperfusion, placental ischemia, and hypoxia. Therefore, during critical periods of fetal organ development, IHCs may result in suboptimal oxygen and nutrient transport from the mother’s blood to fetal circulation, which results in compromised

### TABLE 4  Rates of IHCs by ADHD Status and Child’s Race/Ethnicity

<table>
<thead>
<tr>
<th>Conditions</th>
<th>White Cases</th>
<th>White Controls</th>
<th>African American Cases</th>
<th>African American Controls</th>
<th>Hispanic Cases</th>
<th>Hispanic Controls</th>
<th>Asian/Pacific Islander Cases</th>
<th>Asian/Pacific Islander Controls</th>
<th>Others Cases</th>
<th>Others Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IHC</td>
<td>n = 4548, No. (%)</td>
<td>n = 21,740, No. (%)</td>
<td>n = 1583, No. (%)</td>
<td>n = 7815, No. (%)</td>
<td>n = 3559, No. (%)</td>
<td>n = 17,795, No. (%)</td>
<td>n = 373, No. (%)</td>
<td>n = 1865, No. (%)</td>
<td>n = 337, No. (%)</td>
<td>n = 16,983, No. (%)</td>
</tr>
<tr>
<td>IHC</td>
<td>3296 (75.8)</td>
<td>1729 (79.5)</td>
<td>1125 (72.0)</td>
<td>6026 (71.1)</td>
<td>2722 (77.9)</td>
<td>14,156 (78.6)</td>
<td>278 (74.5)</td>
<td>1476 (78.1)</td>
<td>2567 (76.1)</td>
<td>1337 (79.3)</td>
</tr>
</tbody>
</table>

Acute conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental abruption</td>
<td>3.6 (0.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>1.2 (0.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>Birth asphyxia &lt; 7 at 5 min</td>
<td>3.6 (0.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Neonatal resuscitation</td>
<td>1.9 (0.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>breech/transverse presentations</td>
<td>2.84 (0.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Prolapsed/mucal cord</td>
<td>7.42 (18.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fetal dystocia</td>
<td>5.8 (1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>RDS</td>
<td>5.5 (1.7)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Chronic conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>352 (9.7)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The number of women with acute conditions and chronic conditions may not add up to the total of IHCs because a woman may have received a diagnosis with >1 acute condition.

### TABLE 5  Associations Between IHCs and ADHD by Child’s Race/Ethnicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted ORs (95% CIs) for ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IHC</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>IHC</td>
<td>1.24 (1.15–1.34)</td>
</tr>
</tbody>
</table>

Acute conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted ORs (95% CIs) for ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placental abruption</td>
<td>0.95 (0.67–1.36)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>1.08 (0.88–1.32)</td>
</tr>
<tr>
<td>Birth asphyxia &lt; 7 at 5 min</td>
<td>1.03 (0.72–1.48)</td>
</tr>
<tr>
<td>Asphyxia requiring resuscitation</td>
<td>1.65 (0.99–2.78)</td>
</tr>
<tr>
<td>Breech/transverse presentations</td>
<td>1.08 (0.84–1.34)</td>
</tr>
<tr>
<td>Prolapsed/mucoal cord</td>
<td>1.23 (1.13–1.35)</td>
</tr>
<tr>
<td>Fetal dystocia</td>
<td>0.96 (0.72–1.27)</td>
</tr>
<tr>
<td>RDS</td>
<td>1.40 (1.04–1.89)</td>
</tr>
</tbody>
</table>

The number of women with acute conditions and chronic conditions may not add up to the total of IHCs because a woman may have received a diagnosis with >1 acute condition.

- Others, non-Hispanic children with multiple recorded races.
- Asian/Pacific Islanders and non-Hispanic children with multiple recorded races.
- Estimates were based on exact conditional analysis.
oxygen delivery to tissues and cerebrovascular complications. In particular, it has long been known that hypoxic injury during fetal development leads to significant structural and functional brain injuries in the offspring.\textsuperscript{26–35} Selective vulnerability of striatal neurons has been described in children born after a pregnancy complicated by asphyxia.\textsuperscript{54} Lower concentrations of |acetylaspartate and creatine levels have also been found in the central nervous system tissue of fetuses affected by hypoxic conditions indicating neuronal loss or damage.\textsuperscript{54,55} Also, evidence from imaging studies demonstrated that placental ischemic injury and resulting hypoxia alter brain development and cause structural changes such as a marked reduction in absolute gray matter volume, intraventricular volume, and periventricular leukomalacia.\textsuperscript{31,35,56} Studies based on animal models and human subjects have also reported detrimental effects of chronic fetal hypoxia on the brain.\textsuperscript{29,57,58}

Although the above-mentioned epidemiologic, animal model and imaging studies demonstrated an adverse impact of IHCs on fetal brain development, it is unknown whether this condition may lead to the development of ADHD. Our data suggest that the adverse effect of hypoxia on prenatal brain development may lead to functional problems, including ADHD.

The strengths of the current study include a large sample size and ability to control for potential confounding factors. KPSC’s integrated electronic medical record system provides access to comprehensive patient and treatment information. Thus, the pitfalls of incomplete, missing, or unreadable charts that confound epidemiologic health studies are minimized.

For case ascertainment, we used the combination of (1) diagnoses made by physicians who specialized in the diagnosis and treatment of ADHD and (2) use of prescriptions specific to ADHD during the follow-up period. Similar to a previous report,\textsuperscript{59} this approach increased the specificity of case ascertainment. Moreover, KPSC has stringent criteria that must be met for the diagnosis of ADHD: (1) every child has a standardized form, “The Child Behavior Checklist,” that parents and teachers fill out to describe the child’s behavioral and emotional problems and (2) a clinical interview is conducted by a qualified child mental health professional. The Kaiser Permanente ADHD guideline recommends the use of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria and the Vanderbilt ADHD Diagnostic Parent (VADPRS) and Teacher (VADTRS) Rating Scales for the diagnosis and evaluation of ADHD in children and adolescents.\textsuperscript{50} Scales such as Conners’ Parent (CPRS-R) and Teacher (CTRS-R) Rating Scales and Achenbach’s (Child Behavior Checklist [CBCL], Teachers Report Form [TRF], and Youth Self-Report [YSRI] rating scales are optional and can be used in addition to the initial evaluation. The stringent criteria used in the KPSC health plan in diagnosing ADHD are likely more valid than parental or teacher reports or reports by other health professionals. Previous studies have suggested rates are overestimated by parents and teachers.\textsuperscript{61,62} Although one may argue that the diagnosis of ADHD by health care professionals with appropriate expertise to diagnose and treat the condition is a reflection of validity, here we would also like to underline that we have not compared whether the diagnostic validity has increased by the KPSC approach or whether it is any better than a diagnosis made by parent and teacher reports with rapid pediatrician assessment. Moreover, in the database used for this study, among 100 randomly selected ADHD cases, all children were routinely screened for developmental and emotional status. Only 3% of the children with the diagnosis of ADHD also had an autism spectrum disorder, and they were excluded from the study.

An additional strength of the study is the validation of the accuracy of hospital-based diagnosis codes for IHCs against the electronic medical records and excellent ascertainment of exposure diagnosis. The nested case-control study approach allowed us to limit the number of laboratory records required to ascertain neonatal bilirubin levels.

Our study is not without limitations. There were wide differences in the frequency of ADHD in different racial/ethnic groups, and it is not known if these differences are real or whether they reflect cultural perceptions that bias the likelihood of diagnosis. Also, it is likely that our study manifests an ascertainment bias, particularly as minority children are less likely to be diagnosed with ADHD and at the same time mothers of these children are more likely to have pregnancy complications. We used the birth certificate records to extract information on maternal smoking during pregnancy with its known underreporting of this factor. The positive predictive value for a diagnosis of preeclampsia in our validity study was 88%, suggesting some misclassification of this risk variable. In our study, residual confounding is possible due to unmeasured factors such as in utero exposure to illicit drugs, lead, and environmental agents.\textsuperscript{51,52}

Although the findings of this study certainly add to our understanding about the perinatal circumstances in which childhood ADHD is more likely to occur, this should not be considered evidence of causation. Surveillance bias related to the diagnosis of ADHD is also possible. This nonrandom type of information bias can occur when subjects differ in the likelihood that they will report a problem to their physician or in the manner in which they describe their symptoms and concerns.
The findings of this study suggest that IHCs, especially birth asphyxia, neonatal RDS, and preeclampsia, are associated with ADHD in childhood even after accounting for gestational age and other potential risk factors. This association was strongest in preterm births. This suggests that events in pregnancy contribute to the etiology of this condition over and above the well-known familial/genetic influences.

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In Utero Exposure to Ischemic-Hypoxic Conditions and Attention-Deficit/Hyperactivity Disorder

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