Caffeine Intake During Pregnancy and Risk of Problem Behavior in 5- to 6-Year-Old Children

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KEY WORDS
pregnancy, caffeine, prenatal exposure, preschool age, behavior problems

ABBREVIATIONS
ABCD study—the Amsterdam Born Children and their Development study
SDQ—Strengths and Difficulties Questionnaire
Drs van der Wal and Vrijkotte designed and implemented the study; Ms Loomans and Ms Hofland conducted research; analyzed the data; Ms Loomans wrote the article, and Drs van der Stelt, van der Wal, Van den Bergh, Koot, and Vrijkotte contributed substantially to the interpretation of the data, revision of the manuscript and have read and approved the final version.

WHAT’S KNOWN ON THIS SUBJECT: In humans, evidence for an association between maternal caffeine intake during pregnancy and alterations in fetal brain development with persistent alterations in the offspring’s brain and behavior in later life is inconclusive.

WHAT THIS STUDY ADDS: Prenatal caffeine intake is not associated with a higher risk for behavior problems in young children. Results do not provide evidence to advise pregnant women to reduce their caffeine intake to prevent problem behavior in their children.

abstract

BACKGROUND AND OBJECTIVE: Human studies that have investigated the association between caffeine intake during pregnancy and offspring’s behavioral outcomes are scant and inconclusive. We prospectively investigated the association between maternal caffeine intake during pregnancy and children’s problem behavior at age 5 to 6 years. Mediation by fetal growth restriction and gestational age as well as effect modification by the child’s gender and maternal smoking was tested.

METHODS: In a community based multiethnic birth cohort, dietary caffeine intake (coffee, caffeinated tea, and cola) was measured (maternal self-report, n = 8202) around the 16th week of gestation. At age 5, children’s overall problem behavior, emotional problems, conduct problems, hyperactivity/inattention problems, peer relationship problems, and prosocial behavior were rated by both mother and teacher (n = 3439) with the Strengths and Difficulties Questionnaire. Analyses were adjusted for maternal age, ethnicity, cohabitant status, education, smoking and alcohol consumption during pregnancy, child’s gender, family size, and prenatal maternal anxiety.

RESULTS: Caffeine intake was not associated with a higher risk for behavior problems or with suboptimal prosocial behavior. No evidence was found for mediation by fetal growth restriction or gestational age, nor for effect modification by the child’s gender.

CONCLUSIONS: Results did not provide evidence for developmental programming influences of intrauterine exposure to caffeine on offspring’s problem behavior at age 5. Present results give no indication to advise pregnant women to reduce their caffeine intake to prevent behavior problems in their children. Pediatrics 2012;130:e305–e313
Caffeinated drinks like coffee, tea, and soft drinks are frequently consumed throughout the world.\(^1\)\(^2\) Moderate amounts of caffeine act as a central nervous system stimulant\(^2\) by blocking adenosine receptors that inhibit neuronal activity of cholinergic, glutamatergic, and GABAergic neurons in the brain.\(^3\)\(^5\) Daily caffeine intake is common among 75% to 93% of pregnant women,\(^6\)\(^7\) which has raised concerns about its potential influence on offspring’s neurodevelopment, because caffeine reaches the fetal brain by crossing the placenta\(^8\) and fetal blood-brain barrier.\(^9\) Moreover, caffeine metabolism during gestation is slowed down in the mother and has an extended half-life in the fetus;\(^5\) therefore, its potential programming influence on the developing fetal brain may be lengthened.

Evidence for an association between prenatal exposure to caffeine and alterations in fetal brain development with persistent impairments in offspring’s brain and behavior in later life comes mainly from animal studies.\(^5\)\(^10\)\(^12\) Caffeine ingestion during pregnancy is associated with a reduction of fetal cerebral weight,\(^13\) long-term biochemical alterations in the brain, heightened locomotive activity,\(^11\) increased emotional reactivity, impulsivity,\(^16\) and impaired cognitive functioning\(^2\) in rodent offspring. Human studies that have investigated gestational caffeine consumption and (long-term) neurodevelopmental and behavioral outcomes in offspring are scant, and results are inconclusive. Prenatal caffeine exposure was related to altered neuromuscular development, reflex functioning, heightened arousal, and irritability in newborns,\(^14\) neural tube defects (ie, spina bifida),\(^15\) hyperactivity in 18-month-olds,\(^16\) and social problems in middle childhood.\(^17\) Conversely, no associations were found with mental and motor development at 8 months,\(^18\) IQ and attention at age 7,\(^19\) and a clinically verified hyperkinetic disorder and attention-deficit hyperactivity disorder.\(^20\) The fact that findings vary among studies is most likely due to differences in study design, such as behavioral reports that were solely based on maternal ratings, limited control for important confounding factors, and retrospective information on caffeine intake.

Caffeine intake during pregnancy might also affect offspring’s neurodevelopment and subsequent behavioral outcomes indirectly via fetal growth restriction and gestational age, because it decreases placental blood flow and fetal heart rate,\(^21\) which may alter fetal growth. In turn, fetal growth restriction\(^22\)\(^25\) and gestational age\(^26\) have been linked to an increased risk for problem behavior in offspring. Results from animal studies have indicated gender differences in the programming effects of intrauterine caffeine exposure with a heightened susceptibility for adverse developmental outcomes in male offspring.\(^27\)\(^28\) In humans, evidence for effect modification by the child’s gender is lacking, although 1 study has reported an increased risk for fetal growth retardation in boys, related to high caffeine intake in the third trimester.\(^20\) Tobacco smoking induces the CYP1A2 liver enzyme that accelerates caffeine metabolism.\(^31\) Hence, smoking could moderate the association between caffeine intake and offspring’s neurodevelopmental outcomes.

The aim of the current study was to prospectively investigate the association between prenatal maternal dietary caffeine intake and children’s problem behavior in a large multietnic, community-based birth cohort. We were able to take into account a large number of potential confounding factors, and we included mothers’ as well as teachers’ ratings on multiple dimensions of children’s behavior. Mediation by fetal growth restriction and gestational age as well as effect modification by prenatal smoking and the child’s gender were taken into account.

**METHODS**

**Design**

The current study is part of the Amsterdam Born Children and their Development (ABCD) study, a large multietnic, community-based birth cohort. Extensive information about the cohort and procedures regarding data collection is provided elsewhere.\(^32\) In short, pregnant women living in Amsterdam were approached for their participation between January 2003 and March 2004 during their first visit with an obstetric care provider. All women (12 373, ie, \sim99% of target population) received a questionnaire covering sociodemographic, obstetric, lifestyle, and psychosocial conditions, which was filled out by 8266 of them (67%). These data were completed with information on pregnancy outcome from Youth Health Care Registration and the Dutch Perinatal Registration. Currently, 6161 mothers who gave permission for follow-up of their child were eligible for the fifth-year measurement of their child. Attrition in this follow-up number is due to withdrawal, infant or maternal death, and loss to follow-up as a result of unknown current address or emigration. To be included in the current study, complete data on both maternal caffeine intake and children’s behavioral assessment (both mother and teacher reports) had to be available (\(n = 3439\)). Additional information about inclusion criteria is provided in Fig 1. All participating mothers gave their written informed consent. Approval of the study was obtained from the Central Committee on Research involving Human Subjects in The Netherlands, the Medical Ethical Committees of participating hospitals, and from the Registration Committee of the Municipality of Amsterdam.

**Maternal Caffeine Intake**

Information on women’s dietary caffeine intake during pregnancy was obtained from items in the pregnancy...
questionnaire that was filled in during the 16th week of gestation (interquartile range, 14–18 weeks). Pregnant women were asked whether they drank coffee, tea, and cola in the past week. In addition, they were asked about the amount and type of coffee, tea, and cola (caffeinated, decaffeinated, both, or herbal tea) they consumed. Total caffeine intake per day was calculated by using the Dutch Food Composition Database33 that contains data on the nutritional composition and caffeine content of food and beverages. The type of coffee, tea, or cola (a regular coffee or tea contains 125 mL, a regular cola 150 mL) determined the total caffeine intake in milligrams per day (one regular coffee = 85 mg; decaffeinated coffee = 3 mg; both regular and decaffeinated coffee = 44 mg; regular tea = 45 mg; regular cola = 35 mg; decaffeinated cola = 0 mg; regular and decaffeinated cola = 17 mg; no cola, coffee, tea, only herbal tea = 0 mg). To explore the influence of high doses of caffeine, total caffeine intake was categorized in 4 groups (I: 0–85 mg/d, II: 86–255 mg/d, III: 256–425 mg/d, IV: ≥ 425 mg/day), that correspond to the number of cups of coffee per day (I: 0–1, II: 2–3, III: 4–5, IV: >5 cups).

Children’s Problem Behavior

Children’s problem behavior was reported by their mothers and primary school teachers by using the Strengths and Difficulties Questionnaire (SDQ), a short behavioral screening questionnaire suitable for 4- to 16-year-olds.34 This questionnaire consists of 25 items that are divided in 5 subscales: emotional symptoms, conduct problems, hyperactivity/inattention problems, peer relationship problems, and prosocial behavior. All items (without prosocial behavior items) added together form a total difficulties score that represents children’s overall problem behavior. Behavioral outcomes were dichotomized (“no behavior problems” or “at risk for problem behavior”).35 Children with SDQ (subscale) scores by both mother and teacher below the 83rd percentile were not considered to be at risk for problem behavior. In accordance, children with a score above the 83rd percentile reported by either mother or teacher were also not considered to be at risk for problem behavior. Only children with a mean (subscale) score above the 83rd percentile reported both by their mother and their teacher were considered to be at risk for behavior problems. For prosocial behavior, children with SDQ (subscale) scores by both mother and teacher above the 17th percentile were not considered to show suboptimal prosocial behavior. Children with a score below the 17th percentile reported by either mother or teacher were also not considered to be at risk for suboptimal prosocial behavior. Only children with a score below the 17th percentile reported both by their mother and their teacher were considered to be at risk for suboptimal prosocial behavior. The reliability and validity of the SDQ have been established in a Dutch population with satisfactory psychometric characteristics comparable to those of the Child Behavior Checklist.36

Data Analysis

Descriptive statistics were used to explore the association between maternal characteristics and caffeine intake; statistical differences were tested with analysis of variance for continuous variables and $\chi^2$ tests for categorical variables (Table 1). The association between maternal prenatal caffeine intake and problem behavior was analyzed by multiple logistic regression analysis (Table 2). Potential covariates were selected a priori on a theoretical basis and were included in the regression model at once by using a forced-entry method. First, associations were tested in a crude (unadjusted) model and subsequently maternal age (years), ethnicity (Dutch, Surinamese, Mediterranean, etc.) were considered.
and others), maternal education (years after primary school), maternal state-anxiety (low/high), cohabitant status (yes/no), smoking (yes/no), alcohol (yes/no), child's gender, family size (child plus brothers or sisters) were added to the unadjusted model. Thereafter, in the third step, birth weight standardized for gender, gestational age, and parity based on the most recent Dutch reference values, and gestational age (based on ultrasound, when unavailable (<10%) on the first day of the last menstrual period) were added to examine potential mediation. Interaction terms with the child's gender and maternal smoking were added to the fully adjusted models to investigate effect modification. Analyses were conducted by using SPSS 17.0 (SPSS Inc, Chicago, IL).

## RESULTS

### Subject Characteristics

Attrition analysis on key variables revealed that mothers who filled in the pregnancy questionnaire and rated their child's behavior at age 5 were somewhat older ($F_{[1, 7808]} = 338.14, P < .001$), more often highly educated ($F_{[1, 7736]} = 539.50, P < .001$), had a Dutch background ($x^2_{[3]} = 529.9, P < .001$), were less anxious ($F_{[1, 7678]} = 136.38, P < .001$), had fewer premature ($x^2_{[1]} = 7.8, P < .01$) and heavier babies ($F_{[1, 7755]} = 52.13, P < .001$), and fewer babies that were small for gestational age ($x^2_{[1]} = 11.2, P < .01$) in comparison with mothers in the nonresponse group who gave birth to a viable singleton infant ($n = 4371$). Mothers in the response group had taken more caffeine during pregnancy ($mean = 174.9 \text{ mg}, SD = 131.0$) in comparison with nonresponders (mean = 144.5, SD = 125.2), $F_{(1, 7808)} = 108.97, P < .001$.

Demographic characteristics about the participating mothers and children are presented in Table 1. The mean age of the mothers in this sample was 31.9 (SD = 4.5) years. Almost 77% of the mothers were Dutch, 3% were Surinamese, 6% were either Turkish or Moroccan, and 14% had another ethnical background. Dutch mothers consumed more caffeine compared with non-Dutch mothers (most women who consumed no or little caffeine were non-Dutch).

### Table 1: Demographic Characteristics of 3439 Women and Their Children According to Caffeine Intake

<table>
<thead>
<tr>
<th>Caffeine Intake, mg/d</th>
<th>n</th>
<th>0–85, n = 963</th>
<th>86–255, n = 1614</th>
<th>256–425, n = 719</th>
<th>&gt;425, n = 143</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>3439</td>
<td>31.1 (5.0)</td>
<td>31.9 (4.4)***</td>
<td>32.8 (3.8)***</td>
<td>33.1 (4.2)***</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>1972</td>
<td>59.9</td>
<td>55.9</td>
<td>56.7</td>
<td>58.4</td>
</tr>
<tr>
<td>Dutch</td>
<td>2630</td>
<td>59.1</td>
<td>80.1***</td>
<td>88.2***</td>
<td>93.7***</td>
</tr>
<tr>
<td>Surinamese</td>
<td>117</td>
<td>6.2</td>
<td>2.8***</td>
<td>1.5***</td>
<td>0.7***</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>202</td>
<td>10.5</td>
<td>5.1***</td>
<td>2.5***</td>
<td>2.1***</td>
</tr>
<tr>
<td>Other</td>
<td>490</td>
<td>24.4</td>
<td>12.0***</td>
<td>7.9***</td>
<td>3.5***</td>
</tr>
<tr>
<td>Education, y, mean (SD)</td>
<td>3425</td>
<td>9.1 (3.9)</td>
<td>10.0 (3.8)***</td>
<td>10.6 (3.1)***</td>
<td>10.1 (3.6)***</td>
</tr>
<tr>
<td>Living with partner</td>
<td>3120</td>
<td>88.7</td>
<td>90.8</td>
<td>93.0</td>
<td>91.6</td>
</tr>
<tr>
<td>High levels of anxiety</td>
<td>256</td>
<td>9.3</td>
<td>7.3</td>
<td>5.4**</td>
<td>7.7</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>911</td>
<td>16.2</td>
<td>25.7***</td>
<td>39.2 ***</td>
<td>41.3***</td>
</tr>
<tr>
<td>Smoking</td>
<td>285</td>
<td>5.8</td>
<td>6.8</td>
<td>12.8***</td>
<td>19.6***</td>
</tr>
<tr>
<td>Gestational age, wk, mean (SD)</td>
<td>3417</td>
<td>39.7 (1.7)</td>
<td>39.9 (1.6)*</td>
<td>40.0 (1.7)**</td>
<td>40.0 (1.4)</td>
</tr>
<tr>
<td>Child characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td>156</td>
<td>5.9</td>
<td>4.1*</td>
<td>4.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Standardized birth weight, mean (SD)</td>
<td>3415</td>
<td>1.01 (0.1)</td>
<td>1.01 (0.1)</td>
<td>1.01 (0.1)</td>
<td>1.01 (0.1)</td>
</tr>
<tr>
<td>Small for gestational ageb</td>
<td>293</td>
<td>10.1</td>
<td>7.0**</td>
<td>10.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Female</td>
<td>1684</td>
<td>50.2</td>
<td>48.4</td>
<td>50.9</td>
<td>44.8</td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2406</td>
<td>75.0</td>
<td>75.0*</td>
<td>71.3**</td>
<td>79.6</td>
</tr>
<tr>
<td>2</td>
<td>684</td>
<td>19.3</td>
<td>21.3*</td>
<td>25.3**</td>
<td>19.0</td>
</tr>
<tr>
<td>3 or more</td>
<td>132</td>
<td>5.7</td>
<td>3.7*</td>
<td>3.4**</td>
<td>1.5</td>
</tr>
<tr>
<td>SDQ scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall problem behavior</td>
<td>3439</td>
<td>5.2 (4.0)***</td>
<td>5.3 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity/inattention</td>
<td>3439</td>
<td>2.4 (2.2)***</td>
<td>2.3 (2.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>3439</td>
<td>1.0 (1.3)***</td>
<td>1.2 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct problems</td>
<td>3439</td>
<td>1.0 (1.2)***</td>
<td>0.8 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>3439</td>
<td>0.8 (1.2)***</td>
<td>1.0 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosocial behavior</td>
<td>3431</td>
<td>8.0 (1.8)***</td>
<td>7.6 (2.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are numbers (percentages) unless stated otherwise.

* Reference group

b Small for gestational age (birth weight ≤ 10th percentile for gestational age).

* $P < .05$; ** $P < .01$; *** $P < .001$ (significantly different from reference group).
mothers who consumed more caffeine tended to be older, worked more during pregnancy, and were more highly educated. They were more frequently smokers and alcohol consumers. The sample consisted of 8.5% children (n = 293) who were small for gestational age and 4.5% (n = 156) who were born premature. The mean gestational age of the children was 39.9 (SD = 1.6) weeks, and the mean birth weight was 3485.6 g (SD = 540.7). The children’s mean age at the time of the behavioral assessment was 5.1 years (SD = 0.15). The mean SDQ scores by both mother and teacher are presented in Table 1, and the prevalence of problem behavior in children is reported in Table 2. Bivariate correlations between mother and teacher behavior ratings were r = 0.44 (hyperactivity/inattention problems), r = 0.28 (emotional symptoms), r = 0.30 (conduct problems), r = 0.32 (peer relationship problems), r = 0.22 (prosocial behavior), and r = 0.40 (overall problem behavior), which compares with parent-teacher agreement on behavioral/emotional problems in general.38

**TABLE 2 Risk of Problem Behavior in 5-Year-Old Children According to Maternal Caffeine Intake During Pregnancy**

<table>
<thead>
<tr>
<th>Problem Behavior</th>
<th>Overall problem behavior n = 224</th>
<th>I. 0–85 mg/d</th>
<th>II. 86–255 mg/d</th>
<th>III. 256–425 mg/d</th>
<th>IV. &gt;425 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude Model, Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 1: Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 1: Odds Ratio (95% CI)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

Prenatal maternal dietary caffeine intake was not associated with a higher risk for hyperactivity/inattention problems, emotional symptoms, conduct problems, peer relationship problems, overall problem behavior, or suboptimal prosocial behavior in the adjusted models. Furthermore, no evidence was found for mediation by fetal growth restriction and gestational age, because no consistent associations were found between caffeine intake and these perinatal outcomes (Table 1). Moreover, fetal growth restriction and gestational age were not related to children’s problem behavior, with the exception of hyperactivity/inattention problems (Table 3). Children with hyperactivity/inattention problems were more often born preterm, had a lower standardized birth weight, and a shorter gestational age, but these associations did not depend on the level of caffeine intake.

We did not find evidence for effect modification by the child’s gender (tests for interaction, all \( P > 0.05 \)). However, maternal smoking during pregnancy moderated the association between caffeine intake and peer relationship problems (test for interaction, \( P = 0.02 \)). Caffeine intake >425 mg/d compared with an intake of 0–85 mg/d increased the risk for offspring’s peer relationship problems in women who smoked, whereas an inverse trend was found in women who did not smoke (Table 4).
TABLE 3 Association Between Children's Problem Behavior and Perinatal Adversities

<table>
<thead>
<tr>
<th>Problem Behavior</th>
<th>Gestational Age, wk</th>
<th>Preterm Birtha</th>
<th>Standardized Birth Weightb</th>
<th>SGAc (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Overall problem behavior</td>
<td>224</td>
<td>39.7 (1.7)</td>
<td>3185</td>
<td>39.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>143</td>
<td>9.5 (7.1)</td>
<td>8</td>
</tr>
<tr>
<td>Hyperactivity/inattention</td>
<td>255</td>
<td>39.7 (2.7)</td>
<td>3162</td>
<td>39.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>138</td>
<td>10.10 (0.17)</td>
<td>20</td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>145</td>
<td>40.0 (1.7)</td>
<td>3272</td>
<td>39.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>149</td>
<td>1.01 (0.13)</td>
<td>18</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>109</td>
<td>39.7 (1.6)</td>
<td>3308</td>
<td>39.9 (1.7)</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>149</td>
<td>1.00 (0.12)</td>
<td>18</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>204</td>
<td>39.8 (1.8)</td>
<td>3213</td>
<td>39.9 (1.6)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>149</td>
<td>1.00 (0.13)</td>
<td>23</td>
</tr>
<tr>
<td>Pro social behavior</td>
<td>63</td>
<td>40.2 (1.5)</td>
<td>3354</td>
<td>39.9 (1.7)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>154</td>
<td>9.5 (7.4)</td>
<td>8</td>
</tr>
</tbody>
</table>

M, mean; SD, standard deviation; SGA, small for gestational age.

a Delivery between 24 and 36.6 weeks of gestation.
b Birth weight standardized for gender, pregnancy duration, and parity.
c Small for gestational age (birth weight < 10th percentile for gestational age).

M * P < .05; ** P < .01; *** P < .001.

TABLE 4 Risk for Peer Relationship Problems According to Maternal Caffeine Intake During Pregnancy Stratified for Maternal Smoking Status

<table>
<thead>
<tr>
<th>Peer Relationship Problems</th>
<th>Crude Model, Odds Ratio (95% CI)</th>
<th>Model 1, b Odds Ratio (95% CI)</th>
<th>Model 1, c Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. 0–85 mg/d</td>
<td>1</td>
<td>6.50 (0.56–75.43)</td>
<td>54.73 (3.48–860.32)</td>
</tr>
<tr>
<td>II. 86–255 mg/d</td>
<td>6</td>
<td>3.64 (0.37–38.28)</td>
<td>2.53 (0.17–38.13)</td>
</tr>
<tr>
<td>III. 256–425 mg/d</td>
<td>3</td>
<td>2.76 (0.31–24.25)</td>
<td>1.97 (0.15–26.80)</td>
</tr>
<tr>
<td>IV. &gt;425 mg/d</td>
<td>4</td>
<td>1.22 (0.11–15.77)</td>
<td>0.77 (0.07–8.60)</td>
</tr>
</tbody>
</table>

Non-smokers

<table>
<thead>
<tr>
<th>Peer Relationship Problems</th>
<th>Crude Model, Odds Ratio (95% CI)</th>
<th>Model 1, b Odds Ratio (95% CI)</th>
<th>Model 1, c Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. 0–85 mg/d</td>
<td>1</td>
<td>6.50 (0.56–75.43)</td>
<td>54.73 (3.48–860.32)</td>
</tr>
<tr>
<td>II. 86–255 mg/d</td>
<td>6</td>
<td>3.64 (0.37–38.28)</td>
<td>2.53 (0.17–38.13)</td>
</tr>
<tr>
<td>III. 256–425 mg/d</td>
<td>3</td>
<td>2.76 (0.31–24.25)</td>
<td>1.97 (0.15–26.80)</td>
</tr>
<tr>
<td>IV. &gt;425 mg/d</td>
<td>4</td>
<td>1.22 (0.11–15.77)</td>
<td>0.77 (0.07–8.60)</td>
</tr>
</tbody>
</table>

CI, 95% confidence interval.

a Adjusted for maternal age, ethnicity, maternal education, maternal anxiety, cohabitant status, smoking, alcohol, child's gender, family size.
b Additionally adjusted for standardized birth weight and gestational age (potential mediators).
c Reference group.

* P < .05; ** P < .01; *** P < .001 (significantly different from reference group).

moderated the association between caffeine intake and peer relationship problems.

A number of this study’s limitations need to be addressed. First, attrition analysis on key variables revealed that mothers who filled in the pregnancy questionnaire and rated their child’s behavior differed from mothers in the nonresponse group. This may have resulted in an underestimation of the prevalence of behavioral problems, because children of nonresponding women might be more prone to develop problem behavior; because low socioeconomic status is associated with behavioral difficulties. However, the prevalence of problem behavior in the response group (eg, hyperactivity/inattention, 7.5%) is in line with prevalence rates from previous studies that varied between 3% and 10%. Furthermore, mean SDQ (subscale) scores on problem behavior by mothers and teachers in our sample were somewhat lower, whereas scores on prosocial behavior were slightly higher compared with scores from a Dutch norm population that consisted of older children. Second, caffeine intake was measured by self-report, which is considered to be the most valid measure of antenatal caffeine exposure by use of the best available estimates of caffeine content from coffee, tea, and soft drinks. Multiple assessments of caffeine consumption would have given insight in potential sensitive or critical periods in pregnancy during which the fetus might be more susceptible to potential programming effects of caffeine intake. Although intake levels remained fairly stable after the first trimester in a large observational study, it is known that caffeine half-life is extended during the last trimester of pregnancy, which could lead to a decreased caffeine intake and hence overestimation of caffeine intake over the course of pregnancy in the current study. Third, no information about caffeine intake via chocolate, energy drinks, and medication was available, which may have led to an underestimation of caffeine intake. We do not expect this limitation to lessen the validity of our findings, because it is known that caffeine ingestion in pregnant women stems mainly from coffee and tea. Individual differences in preparation and portion size may have also induced unaccounted variability in estimated caffeine content. Furthermore, no data on caffeine metabolism were available.

Fourth, nausea is a common symptom in the first trimester of healthy pregnancies. Nausea (n = 1586 women reported nausea) did reduce caffeine intake significantly in our sample; nevertheless, findings (not presented) in a subsample of only nonnauseous women did not differ from results shown in Table 2.
A major strength of the current study is that we assessed multiple domains of children’s problem behavior in the (pre) school age, by using a validated questionnaire with good psychometric properties, filled in by both mother and teacher, because children tend to behave differently in their home and school environment. Previous studies were solely based on maternal reports of child behavior and hence are at risk for a maternal bias (overrated problem behavior). Furthermore, by using multiple informants on children’s behavior, we have implemented an accurate as well as conservative approach to identify potential problem behavior. In addition, most studies considered 3 or more cups of coffee per day (>255 mg/d) as high intake. Because a relatively large group of women in our study reported to consume comparable or even higher amounts of caffeine, we were able to fully explore the effect of high doses of caffeine. Current analyses were conducted in a large, community-based, multiethnic birth cohort, which is a clear advantage in terms of statistical power and generalizability. In addition, we were able to control for a large number of potential confounding factors such as maternal ethnic background, which appeared to be an important confounder, because non-Dutch women drank significantly less coffee compared with Dutch women (Table 1). In addition, ethnic differences in reports on offspring’s mental health problems have been found. However, neither statistical control for confounding by ethnic background nor analyses within a sample that consisted of only Dutch women (n = 2630) led to different results (data not shown).

Current findings are in accordance with previous studies that have reported no association between prenatal caffeine consumption and neurodevelopmental outcomes in the offspring. No long-term neurobehavioral consequences assessed in the first 7 years of life that were related to prenatal maternal caffeine consumption were found in a large cohort. Caffeine intake examined during a similar period early in pregnancy (16th week) was not associated with hyperkinetic disorder and attention-deficit hyperactivity disorder in children in another prospective cohort study. In contrast, some studies did find evidence for an increased risk for neurodevelopmental adversities. However, the explained variance in inattention/hyperactivity by prenatal caffeine intake was very low. An increased risk for social problems related to retrospectively assessed coffee consumption (no information on quantity and caffeine content was taken into account) during pregnancy was found. However, the number of women that had reported to consume coffee on a regular basis was very low (n = 19). We did not find evidence for mediation by gestational age and fetal growth restriction. As such, the current study did not replicate previous studies that have found significant associations between high caffeine intake and shorter gestational age and fetal growth restriction. Fetal growth restriction and gestational age were not related to children’s problem behavior, with the exception of hyperactivity/inattention problems, which is in line with findings from a previous study. The child’s gender did not moderate the association between prenatal caffeine intake and children’s problem behavior, which is not in accordance with findings in animal studies. However, in human studies the child’s gender has not been reported to moderate the association up until now. Interpretation of the effect modification by maternal smoking could only be based on findings in the crude model because the ratio of cases to the number of predictors in the adjusted models was too small. Therefore, this association should be interpreted with caution, because confounding by, for example, socioeconomic status or ethnic background might be present.

CONCLUSIONS
To conclude, this study has provided insight into what extent caffeine consumption during pregnancy contributes to the development of problem behavior. Our results did not provide evidence to advise pregnant women to reduce their caffeine intake to prevent problem behavior in their children.

ACKNOWLEDGMENTS
The Amsterdam Born Children and their Development Study (www.abcd-studie.nl) is conducted by the Department of Epidemiology, Documentation and Health Promotion, Public Health Service Amsterdam, and the Department of Public Health, Academic Medical Centre, University of Amsterdam; in collaboration with the Department of Psychology, Tilburg University, Netherlands. The authors especially thank all participating mothers and their children and are grateful to all obstetric care providers and YHC centers for assisting in the implementation of the ABCD study. The authors also thank all members of the ABCD study team for their dedication and support.

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Pediatrics 2012;130:e305; originally published online July 9, 2012;
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