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Prenatal Caffeine Exposure and Child IQ at Age 5.5 Years: The EDEN Mother-Child Cohort

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ABSTRACT

BACKGROUND: Evidence from animal studies suggests maternal caffeine intake during pregnancy has detrimental effects on subsequent brain development in offspring. However, human data in this area are limited. The aim of this study was to assess whether caffeine intake by women during pregnancy is associated with impaired cognitive development in offspring at age 5.5 years.

METHODS: Multivariate modeling was conducted using data of 1083 mother-child pairs from a population-based birth cohort in France followed from pregnancy to age 5.5 years of the children. Measures included an estimate of maternal caffeine intake during pregnancy, children's IQ at age 5.5, and individual and family characteristics.

RESULTS: Prenatal caffeine exposure was common in the sample (91%) with 12% displaying an intake ≥200 mg/day (high). Multivariable modeling showed a significant negative relationship between caffeine intake and children's IQ at 5.5 years (−.94 [95% confidence interval = −1.70, −.17] full IQ unit per 100 mg daily caffeine intake). In particular, children of mothers consuming ≥200 mg/day were more likely to have borderline or lower IQ compared with children of mothers consuming <100 mg/day (13.5% vs. 7.3%; odds ratio = 2.30, 95% confidence interval = 1.13, 4.69).

CONCLUSIONS: We found an association between caffeine intake during pregnancy and impaired cognitive development in offspring, a result in line with animal data. More epidemiologic and biologically grounded research is needed to determine whether this association is causal. This finding suggests that conservative guidelines regarding the maximum caffeine intake recommended in pregnancy (i.e., 200 mg/day) should be maintained.

Keywords: Caffeine, Cohort studies, Cognition, IQ, Pregnancy, Prenatal exposure, Preschool age

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Pregnant women represent a priority subpopulation for policies aiming to improve public health in the next generation. Specifically, the reduction of exposure to drugs and toxins during gestation has become a central issue as a result of numerous interventions promoting healthy behaviors. Among legally available substances, tobacco and alcohol are shown to have adverse effects on fetal development (e.g., risk of prematurity, low birth weight, fetal alcohol syndrome), justifying the need for such interventions. However, the impact of caffeine and other methylxanthines on the fetus remains poorly understood. Meanwhile, the magnitude of coffee, tea, and cola consumption makes caffeine the most common pharmacologically active substance ingested by pregnant women worldwide.

Animal studies (e.g., rodents and chicks) showed concerning results regarding the effects of prenatal caffeine exposure on pregnancy and offspring outcomes. Caffeine administered in large amounts was associated with teratogenic effects (i.e., neural tube, eye, cleft, cardiovascular, and angiogenesis malformations) (1–5). Prenatal caffeine exposure can also lead to postnatal cognitive and behavioral changes in adult rodent offspring. These long-lasting modifications include spatial and recognition memory impairments, variations in motor activity, and emotional hyperreactivity (6). A more recent study suggested that a range of neuronal and brain alterations induced by caffeine antagonism of adenosine receptors may lead to a deficit in cognitive functioning in mice (7). However, extrapolating such animal data to humans is not straightforward. First, evolutionary and developmental biology suggests that the complexity of humans precludes direct and simplistic inferences from animal models. Second, caffeine doses tested in animals often exceed what humans ingest, even for the heaviest consumers. Third, evidence from animal studies has not consistently been replicated in human samples. Epidemiologic studies reported mixed findings by showing inconsistent adverse effects associated with high prenatal caffeine intake (e.g., miscarriage, stillbirth, teratogenicity, low birth weight, prematurity) (6,8–13) as well as potential benefits of moderate caffeine intake during pregnancy on the risk of gestational diabetes mellitus (14). Cognitive development in children has received little attention, and only a few underpowered studies are available (15). Nevertheless, general cognitive ability as measured by IQ is a key indicator that can have lifelong repercussions on individuals' health and socioeconomic status.

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The possibility that caffeine might be detrimental to fetal brain development, as suggested by animal studies, makes it necessary to explore cognitive outcomes of prenatally exposed children further as they grow up.

Owing to possible associations with adverse outcomes, current guidelines for pregnant women advocate a conservative approach by recommending a daily caffeine intake <200 mg (16,17) or <300 mg (18). To guide prevention policies related to prenatal caffeine exposure (a modifiable risk factor) and its association with children's IQ, we conducted analyses on data from the EDEN (Etude des Déterminants pré- et postnatals précoces du développement et de la santé de l'ENfant) birth cohort study; this study in France was specifically designed to investigate the impact of prenatal nutrition on child development. The aim was to examine whether caffeine intake by women during pregnancy is associated with impaired cognitive development in offspring at age 5.5 years.

METHODS AND MATERIALS

Study Design and Setting

The EDEN mother-child cohort study primarily aims to assess prenatal and postnatal determinants of child growth, development, and health, particularly nutrition. Recruitment of pregnant women (before 24 weeks of amenorrhea) was conducted during prenatal visits to the Department of Obstetrics and Gynecology in two French university hospitals (Nancy and Poitiers) during the period 2003–2005. Exclusion criteria were multiple pregnancy (i.e., more than one fetus), a diabetes diagnosis before pregnancy, illiteracy, and planned move outside the region in the following 3 years. Data collection was conducted at multiple study points (pregnancy; at the child's birth; at 4, 8, 12, and 24 months; and at 3 and 5.5 years). Data were collected by trained interviewers at pregnancy, birth, and 3 and 5.5 years; by mothers' and fathers' self-reports at all study points; and from medical records at pregnancy, birth, and 3 and 5.5 years.

Participants

Among the 2002 women included in the cohort, 1907 pairs of mothers and newborns were followed up at delivery; pairs were excluded for the following reasons: miscarriages (n = 11), in utero deaths (n = 7), abortions for medical reasons (n = 2), loss to follow-up (n = 14), moving away (n = 8), mothers changing their mind (n = 51), and not meeting inclusion criteria (n = 2). Among these, 1849 mother-child pairs had dietary assessments during pregnancy, making it possible to estimate maternal caffeine consumption in 1838 mother-child pairs. Among them, 1111 children were still followed at 5.5 years and received a clinical and neuropsychological assessment; 1083 children had a complete IQ test. Compared with a nationally representative sample of pregnant women in France in 2003, EDEN study participants had similar parental sociodemographic characteristics (except for educational attainment, which was higher in the study), offsprings birth weight, and prematurity rate. Over the follow-up period, attrition rates were highest in families in which the mother was young, had a low educational level and low income, did not live with the child's father, presented higher levels of caffeine intake, smoked during pregnancy, had psychological difficulties in pregnancy, and whose child did not have low birth weight. Informed written consent for the parents was obtained at enrollment, and consent for the child was obtained from both parents after the child's birth. The EDEN cohort received approval from the Bicêtre Hospital ethics committee and the Commission Nationale Informatique et Libertés, which oversees ethical aspects of data collection in France.

Outcome Variable: Cognition in the Offspring

The Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) was administered by trained psychologists to assess IQ when the child was 5.5 years old (19). The core subtests of the battery were assessed (Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding) to obtain the composite scores: verbal IQ, performance IQ, and full-scale IQ. IQ was defined as a continuous variable and in categories (IQ <85 [borderline or lower intellectual functioning] vs. IQ ≥85). We used the threshold of 85 (borderline intellectual functioning; 1 SD below the mean of the IQ score distribution) to appreciate the clinical significance of cognitive impairments and to balance group sizes. Moreover, below this cutoff, rates of poor adaptive functioning and life hardships (e.g., neurocognitive, social, and mental health problems) are elevated (20).

Main Exposure: Prenatal Caffeine Consumption

At enrollment and after delivery, mothers completed a validated food frequency questionnaire including beverage consumption (21). The food frequency questionnaire encompassed the year before pregnancy and the last trimester of pregnancy (main exposure). Questions on beverages containing caffeine included the number of cups/glasses of caffeinated or regular coffee, tea, and caffeinated soda/soft drink consumed by the mothers (none, <1/month, 1–3/month, 1/week, 2–5/week, 1/day, 2–4/day, >4/day). To estimate the mean caffeine intake per day, we applied the criteria of Bracken *et al.* (22): one cup of coffee was estimated to contain 100 mg of caffeine, and one cup of tea was estimated to contain 37 mg of caffeine. One glass of caffeinated soda/soft drink was estimated to contain 37 mg. Coffee represented the main source of caffeine (73% of total caffeine intake). Total caffeine intake was considered either as a continuous variable or in categories. Categorization comprised three levels: low, 0 to <100 mg/day; moderate, 100 to <200 mg/day; and high, ≥200 mg/day. We chose the threshold of 200 mg/day to define high intake because several health guidelines advise pregnant women to limit their caffeine consumption to <200 mg/day (16,17). Questions on paternal coffee consumption during pregnancy were also available (number of cups/day: none, 1–2, 3–4, >4).

Covariates

Parental characteristics at baseline included parental education (mean of maternal and paternal school years), maternal age at inclusion (years), maternal prepregnancy body mass index (kg/m^2), and parental separation before the child's birth. Pregnancy characteristics included maternal alcohol consumption (>2 glasses/week vs. no or ≤2 glasses/week), maternal daily