Maternal Caffeine Consumption during Pregnancy and Behavioral Disorders in 11-Year-Old Offspring: A Danish National Birth Cohort Study

Susanne Hvolgaard Mikkelsen, PhD[1], Carsten Obel, MD, PhD[1], Jørn Olsen, MD, PhD[2,3], Janni Niclasen, PhD[4], and Bodil Hammer Bech, MD, PhD[5]

Objective To examine the association between maternal caffeine consumption from coffee and tea during pregnancy and offspring behavioral disorders.

Study design We studied 47 491 children enrolled in the Danish National Birth Cohort between 1996 and 2002. Data on maternal coffee and tea consumption was collected at 15 and 30 weeks of gestation. When the child was 11 years old, the Strength and Difficulties Questionnaire was filled in by children, parents, and teachers. We estimated risk ratios (RRs) for offspring behavioral disorders.

Results At 15 weeks of gestation 3% and 4% of the pregnant women consumed ≥8 cups/d of coffee or tea, respectively. Maternal coffee consumption ≥8 cups/d at 15 weeks of gestation was associated with increased risk of hyperactivity-inattention disorder (RR 1.47; 95% CI 1.18-1.83), conduct-oppositional disorders (RR 1.22; 95% CI 1.01-1.48), and any psychiatric disorder (RR 1.23; 95% CI 1.08-1.40). Maternal tea consumption ≥8 cups/d at 15 weeks of gestation was associated with increased risk of anxiety-depressive disorders (RR 1.28; 95% CI 1.09-1.52) and any psychiatric disorder (RR 1.24; 95% CI 1.11-1.40). An increased risk of hyperactivity-inattention disorder was observed with increasing daily caffeine consumption at 15 weeks of gestation.

Conclusion High maternal caffeine consumption from coffee and tea at 15 weeks of gestation was associated with behavioral disorders in 11-year-old offspring. We hypothesize that caffeine exposure may affect the fetal brain and program for behavioral disorders later in life. The fetal brain seems to be more sensitive to caffeine exposure at 15 weeks of pregnancy compared with 30 weeks of gestation. *(J Pediatr 2017;189:120-7).*

During the last decade, the incidence of the most common childhood mental disorders (attention-deficit hyperactivity disorder [ADHD], autism spectrum disorders, and emotional disorders) has increased.[1-3] This has resulted in a greater focus on potential perinatal factors as predictors of mental health problems.[4,5] Maternal lifestyle and risky behavior during pregnancy have been suggested to play a role in the etiology of ADHD.[6] Exposure to tobacco smoke and alcohol in utero has been suggested as risk factors for ADHD in some, but not all, studies.[7-9] Another stimulant habitually consumed among women of reproductive age is caffeine, and the potential effect during pregnancy is of interest, because caffeine reaches the fetal brain by crossing the placenta and the fetal blood–brain barrier.[10] In addition, the caffeine metabolism is delayed during pregnancy,[11] allowing longer opportunities for absorption.

Caffeine increases dopamine levels by slowing down the rate of dopamine reabsorption, and this dysfunction of the dopaminergic system is thought to explain part of the association between caffeine consumption and offspring behavioral disorders. In animal studies, associations between exposure to high dosages of caffeine and increased motor activity in the offspring have been found,[12,13] but the association has not been studied much in humans, and the few studies report conflicting results.[14-17]

It is known that people with ADHD often have a high consumption of coffee used as self-medication due to the effect of caffeine on the dopamine system.[18,19] The tendency of increased risk of offspring behavioral disorders with increased caffeine consumption during pregnancy reported in some studies may be a result of confounding by genetic factors. In a large national birth cohort, we aimed to study behavioral disorders in 11-year-old offspring according to maternal caffeine consumption from coffee and tea at both 15 and 30 weeks of gestation.

Materials and Methods

We used data from the Danish National Birth Cohort (DNBC). Women were recruited at their first pregnancy visit by the general practitioners between 1996 and 2002. Once enrolled, the women were offered 4 computer-assisted telephone

ADHD	Attention-deficit hyperactivity disorder
DNBC	Danish National Birth Cohort
RR	Risk ratio
SDQ	Strength and Difficulties Questionnaire

From the [1]Department of Public Health, Section for General Medical Practice; [2]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [3]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA; [4]Department of Psychology, University of Copenhagen, Copenhagen; and [5]Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark

interviews, twice during pregnancy (at approximately 15 and 30 weeks of gestation) and twice after delivery, when the child was approximately 6 and 18 months old. The DNBC has been described in detail elsewhere.[20] Self-reported data on daily coffee and tea consumption was collected at both first and second pregnancy interview.

A total of 101 033 pregnancies were recruited to the DNBC. For this study, we included only live born singletons and pregnancies with complete data on coffee and tea consumption, resulting in 86 642 children.

When the child was 11 years old, a follow-up questionnaire including the Strength and Difficulties Questionnaire (SDQ) was filled in by 3 informants: children, parents, and teachers. By linking the 11-year follow-up data (n = 51 056) with the pregnancy interviews, we finally had 47 491 children with complete data on maternal consumption from coffee and tea and SDQ.

We studied caffeine consumption from coffee and tea at 15 and 30 weeks of gestation. The participants were asked "How many cups of coffee do you drink daily?" Answers were coded in number of cups per day; a mug was coded as 2 cups. Similar questions were asked about consumption of tea. If the woman answered drinking less than one cup per day, it was coded as 0.5 cup per day. Coffee and tea consumption were studied separately categorized into 4 groups: (0; 0.5-3; 4-7; ≥8 cups per day), with 0 cups as the referent group.

Furthermore, we studied total daily caffeine consumption from both coffee and tea. One cup of coffee was coded as 100 mg of caffeine, and one cup of tea as 50 mg. The total daily caffeine consumption was studied as a continuous variable, expressed as cubic splines with 0 mg/d of caffeine from coffee or tea as the referent.

Outcome

The Strengths and Difficulties Questionnaire. The SDQ questionnaire is a measure of emotional, behavioral, and social functioning in children and adolescents. It can be administered to parents and teachers of 4- to 17-year-old subjects and to 11- to 17-year-old subjects themselves.[21,22]

The SDQ comprises 25 questions generating 5 subscale scores for hyperactivity, emotional symptoms, peer problems, conduct problems, and prosocial behaviors. It is rated on a 3-point Likert scale with the following response choices: 0 (not true), 1 (somewhat true), and 2 (certainly true) (http://www.sdqinfo.org). In addition, an impact supplement asks whether the respondent thinks the young person has a problem, and, if so, enquires further about chronicity, distress, social impairment, and burden to others.[23]

In the present study, we used computerized algorithms for predicting psychiatric disorder by bringing together information on symptoms and impact from the SDQ completed by multiple informants.[24] The computerized algorithms have been found to have good psychometric properties. In a general child population, it has been suggested to predict the presence of a psychiatric disorder with good specificity (80%) and sensitivity (85%).[21]

The algorithm makes separate predictions for 3 groups of disorders: conduct-oppositional disorders, hyperactivity-inattention disorders, and anxiety-depressive disorders. Each is predicted to be unlikely, possible, or probable.

Prediction of the 3 groups of disorders is combined to generate an overall prediction about the presence of any psychiatric disorder. The outcomes: conduct-oppositional disorders, hyperactivity-inattention disorders, anxiety-depressive disorders, and any psychiatric disorder were dichotomized into "unlikely" and "possible/probable." Potential confounders and mediators were chosen a priori based on previous studies on associations between maternal caffeine consumption during pregnancy and child development.

Measured covariates included maternal age at birth (<20, 20-24, 25-29, 30-34, 35-39, ≥40 years), maternal prepregnancy body mass index (underweight/normal, overweight, obese), parity (0, 1+), maternal smoking during pregnancy (0, >0-9, 10+ cigarettes/d), maternal socioeconomic status at first interview (high, medium, low), maternal marital status at first interview (cohabiting/married, single), birth year (1997-1999, 2000-2001, 2002-2003), and sex (girl, boy). Gestational age and birth weight are assumed to be potential intermediate factors and were therefore not adjusted for.

Statistical Analyses

Using binomial regression analyses, we estimated risk ratios (RR) with corresponding 95% CIs for the associations between maternal coffee and tea consumption during pregnancy with offspring SDQ outcomes including conduct-oppositional disorders, hyperactivity-inattention disorders, anxiety-depressive disorders, and any psychiatric disorder. The exposures, coffee and tea, were analyzed in unadjusted and adjusted models, with 0 cups/d as the reference category. Coffee and tea consumption were adjusted mutually. In subanalyses, we stratified the results on maternal smoking during pregnancy and socioeconomic status to evaluate possible effect modification.

To examine the total daily caffeine consumption from coffee and tea at 15 and 30 weeks of gestation, caffeine consumption in the range 0-1500 mg/d was studied as a continuous variable expressed as cubic splines with 5 knots, which are the default knot values based on Harrell-recommended percentiles.[25] Caffeine consumption 0 mg/d was used as the reference.

We examined the same outcome, conduct-oppositional disorders, hyperactivity-inattention disorders, anxiety-depressive disorders, and any psychiatric disorder, as done for maternal coffee and tea consumption when expressed categorically and likewise we did unadjusted and adjusted models. As few women (less than 3%) contributed with 2 children to the cohort, we used robust variance estimators to calculate the 95% CI to control for the lack of independence of children within the same family.

P values < .05 were considered statistically significant. All statistical analyses were conducted with Stata 13.0 statistical software (Stata Corporation, College Station, Texas).

Results

At 15 weeks of gestation, 11.9% of the pregnant women consumed more than 3 cups/d of coffee, with 2.7% consuming 8