The Journal of Nutrition
Nutrition and Disease

Intake of Caffeinated Soft Drinks before and during Pregnancy, but Not Total Caffeine Intake, Is Associated with Increased Cerebral Palsy Risk in the Norwegian Mother and Child Cohort Study[1–3]

Mette C Tollånes,[4,5]* Katrine Strandberg-Larsen,[6] Kacey Y Eichelberger,[7] Dag Moster,[4,5,8] Rolv Terje Lie,[4] Anne Lise Brantsæter,[9] Helle Margrete Meltzer,[9] Camilla Stoltenberg,[4,10] and Allen J Wilcox[11]

[4]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [5]Domain for Health Data and Digitalisation, Norwegian Institute of Public Health, Bergen, Norway; [6]Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [7]Department of Obstetrics and Gynecology, Greenville Health System, University of South Carolina School of Medicine Greenville, Greenville, SC; [8]Department of Pediatrics, Haukeland University Hospital, Bergen, Norway; [9]Domain for Infection Control and Environmental Health and [10]Director General, Norwegian Institute of Public Health, Oslo, Norway; and [11]National Institutes of Environmental Health Sciences, Durham, NC

Abstract

Background: Postnatal administration of caffeine may reduce the risk of cerebral palsy (CP) in vulnerable low-birth-weight neonates. The effect of antenatal caffeine exposure remains unknown.

Objective: We investigated the association of intake of caffeine by pregnant women and risk of CP in their children.

Methods: The study was based on The Norwegian Mother and Child Cohort Study, comprising >100,000 live-born children, of whom 222 were subsequently diagnosed with CP. Mothers reported their caffeine consumption in questionnaires completed around pregnancy week 17 (102,986 mother–child pairs), week 22 (87,987 mother–child pairs), and week 30 (94,372 mother–child pairs). At week 17, participants were asked about present and prepregnancy consumption. We used Cox regression models to estimate associations between exposure [daily servings (1 serving = 125 mL) of caffeinated coffee, tea, and soft drinks and total caffeine consumption] and CP in children, with nonconsumers as the reference group. Models included adjustment for maternal age and education, medically assisted reproduction, and smoking, and for each source of caffeine, adjustments were made for the other sources.

Results: Total daily caffeine intake before and during pregnancy was not associated with CP risk. High consumption (≥6 servings/d) of caffeinated soft drinks before pregnancy was associated with an increased CP risk (HR: 1.9; 95% CI: 1.2, 3.1), and children of women consuming 3–5 daily servings of caffeinated soft drinks during pregnancy weeks 13–30 also had an increased CP risk (HR: 1.7; 95% CI: 1.1, 2.8). A mean daily consumption of 51–100 mg caffeine from soft drinks during the first half of pregnancy was associated with a 1.9-fold increased risk of CP in children (HR: 1.9; 95% CI: 1.1, 3.6).

Conclusions: Maternal total daily caffeine consumption before and during pregnancy was not associated with CP risk in children. The observed increased risk with caffeinated soft drinks warrants further investigation. *J Nutr* 2016;146:1701–6.

Keywords: Cerebral palsy, antenatal caffeine exposure, caffeine consumption, caffeinated soft drinks, pregnancy, prospective cohort study

Introduction

Cerebral palsy (CP) affects ~2 in 1000 live-born children and is the most common cause of childhood physical disability (1). CP is an umbrella term, including various subtypes of disease. In addition to a wide spectrum of motor impairments, many

[1] Supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (NIEHS). The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract N01-ES-75558), NIH/National Institute of Neurological Disorders and Stroke (grants UO1 NS 047537-01 and UO1 NS 047537-06A1).

[2] Author disclosures: MC Tollånes, K Strandberg-Larsen, KY Eichelberger, D Moster, RT Lie, AL Brantsæter, HM Meltzer, C Stoltenberg, and AJ Wilcox, no conflicts of interest.

[3] Supplemental Appendix, Supplemental Figure 1, and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of this article and from the same link in the online table of contents at http://jn.nutrition.org.

*To whom correspondence should be addressed. E-mail: mette.tollanes@uib.no.

Manuscript received March 8, 2016. Initial review completed March 28, 2016. Revision accepted June 24, 2016.
First published online August 3, 2016; doi:10.3945/jn.116.232272.

children affected with CP also suffer from visual impairment, hearing loss, seizures, and cognitive impairment (2). CP is believed to originate from in utero or peripartum damage to the immature brain. Although preterm birth is strongly associated with CP, and factors such as birth defects and fetal growth restriction have been identified as risk factors for CP in singletons born at term (3), the underlying causes of CP remain largely unknown.

Caffeine metabolism is substantially slowed in pregnancy (4), and caffeine and its metabolites readily cross the placental barrier, exposing the fetus for a prolonged time (5). Caffeine intake in pregnancy has in observational studies been associated with miscarriage, stillbirth, intrauterine growth restriction, low birth weight, oral clefts, and neural tube defects (6–8), although critics have claimed that the findings may result from flawed methodology (9). Antenatal caffeine exposure has been more tentatively linked to later effects in children, such as problem behavior and attention deficit hyperkinetic disorder (10–12). A recent report from the European Food Safety Authority concluded that pregnant women should limit their daily caffeine intake to <200 mg (13). In contrast, a recent Cochrane review of caffeine intervention studies concluded that "There is insufficient evidence to confirm or refute the effectiveness of caffeine avoidance on birthweight or other pregnancy outcomes" (14).

There are data to suggest that caffeine administration may actually be beneficial in the prevention of CP. In a study of newborn rats in a hypoxic environment, caffeine prevented the development of periventricular white matter injury (15), a pathologic condition associated with CP in humans (16). In a randomized controlled trial of premature newborns, caffeine used to treat apnea was found at follow-up at age 18–21 mo to significantly improve an infant's chance of survival with no neurological disability (17). Although the difference was no longer statistically significant at age 5 y (18), caffeine-treated children still displayed reduced risk of developmental coordination disorder (19).

It is not clear whether antenatal caffeine exposure affects the fetal human brain in any way, either negatively or positively. Our aim was to investigate the association of mothers' intake of caffeine in pregnancy and risk of CP in their children.

Methods

Study population and case ascertainment. The Norwegian Mother and Child cohort study (MoBa) is a prospective, population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (20). Participants were recruited from all over Norway during 1999–2008. Forty-one percent of contacted women consented to participate. The cohort includes 114,500 children, 95,200 mothers (some with >1 pregnancy), and 75,200 fathers. The women were followed through pregnancy with 3 questionnaires: the first filled in around week 17 (median: 120 d gestational age, 80% within 105–147 d), an FFQ filled in around week 22 (median: 158 d gestational age, 80% within 150–185 d), and a third questionnaire filled in around week 30 (median: 212 d gestational age, 80% within 205–230 d). Extensive information was collected about maternal physical and mental health before and during pregnancy, reproductive history, occupation, socioeconomic status, and environmental exposures. Analyses were restricted to the 102,986 live-born children for whom data were available from the first pregnancy questionnaire. To investigate effects of exposure to caffeine at later time points in pregnancy, we used the subcohorts of 87,978 children with data available also from the FFQ and 94,372 children with data available from the third pregnancy questionnaire. The current study is based on version 8 of the quality-assured data files released for research in February 2014.

Information on CP diagnosis, including subtype information (spastic unilateral, spastic bilateral, ataxic, and dyskinetic), was obtained through record linkage with the Norwegian CP registry (21), which covered ~90% of CP cases in the cohort. Additional children with CP were identified through record linkage with the Norwegian Patient Registry (22). The additional CP cases were validated by 2 trained pediatric neurologists by review of medical records, from which information on CP subtype was also extracted (23).

Exposures and covariates. The **Supplemental Appendix** describes in detail the wording and format of the items in the 3 questionnaires regarding caffeine exposure. In summary, in the first pregnancy questionnaire (around week 17), caffeine exposures were reported as prepregnancy and present mean daily intake of servings (1 serving = 125 mL) of caffeinated coffee, tea, and soft drinks ("Coca Cola, Pepsi, or similar," sugar-sweetened, and artificially sweetened). In the third questionnaire (around week 30), women were asked about mean daily intake since pregnancy week 13, indicating overlap in exposure window with the first questionnaire. Exposures to daily servings of caffeinated coffee, tea, and soft drinks were evaluated in the models in categories of 0 (reference category), 1–2, 3–5, and ≥6 servings/d and during 3 windows of exposure: prepregnancy (a surrogate for consumption during the earliest weeks of pregnancy, before a woman is necessarily aware of pregnancy), early pregnancy (around week 17), and late pregnancy (weeks 13–30). Using previously published data on mean caffeine content in various beverages (24), we calculated an estimated total daily caffeine intake from caffeinated beverages in milligrams. Total caffeine intake was evaluated for prepregnancy and in early and late pregnancy in the models in categories of 0 (reference category), <101, 101–200, 201–300, and >300 mg/d. We also investigated associations between CP and total caffeine intake as a continuous variable, using cubic splines.

In the comprehensive FFQ answered around week 22 of pregnancy, women were asked about mean intake of beverages and food items since the beginning of pregnancy (25, 26), again indicating overlap in exposure windows with the first and third questionnaires. The FFQ has been extensively validated in a MoBa subpopulation (n = 119) by using a 4-d weighed food diary and biological markers in blood and urine as reference measures. The agreement between the FFQ and the food diary was particularly high for coffee (r = 0.80, 95% CI: 0.72, 0.86) and was moderate for tea (r = 0.53, 95% CI: 0.39. 0.65) and soft drinks (r = 0.48, 95% CI: 0.33, 0.61). When caffeine concentrations were combined with consumption data, high agreement was observed between the FFQ and the food diary for total caffeine (r = 0.70, 95% CI: 0.59, 0.78) (24). In addition to caffeinated beverages (including energy drinks and sugar-sweetened and artificially sweetened cola drinks), caffeine intake from other dietary sources, primarily chocolate and desserts or cake, was calculated. This information has previously been compiled in an extensive caffeine database, enabling calculation of mean daily caffeine intake during the first half of pregnancy for each participating mother (24). The calculated total caffeine intake was ranked into categories of 0–50 (reference category), 51–100, 101–200, 201–300, and >300 mg/d. In addition, we investigated associations between CP and caffeine from various sources of caffeinated beverages reported in the FFQ. Coffee caffeine was evaluated in the models in categories of 0 (reference category), <101, 101–200, 201–300, and >300 mg/d and tea and soft-drink caffeine in categories of 0 (reference category), <51, 51–100, and >100 mg/d.

As post hoc secondary analyses, we also investigated whether intake of decaffeinated coffee reported in the FFQ (any compared with none) or intake of noncaffeinated soft drinks reported in the first and third pregnancy questionnaires [0 (reference), 1–2, or ≥3 daily servings] was associated with CP.

The following data on potential confounders (obtained from the first pregnancy questionnaire) were included in the models as categorical variables: maternal age (<25, 25–29, 30–34, or ≥35 y), medically assisted reproductive therapy (yes or no), and smoking status (none, stopped in pregnancy, <10 cigarettes/d, ≥10 cigarettes/d, or missing). We also included maternal educational level (less than high school, high school, more than high school, or missing) as a proxy of socioeconomic status.

Statistical analyses. Associations between intake of caffeinated beverages and total caffeine in pregnancy (see detailed description above) and CP in children were investigated by using Cox proportional hazards models in STATA version 12.1 (StataCorp), with separate models for each exposure window. Entry time into the model was set at birth. Exit time was the child's age in months at diagnosis of CP, death, emigration, or age in May 2014, whichever came first. The proportional hazards assumptions were evaluated graphically for each covariate; no obvious deviations were found. To account for dependency between pregnancies by the same mother, robust variances were used. $P < 0.05$ was considered statistically significant, and we made no formal adjustment for multiple comparisons. Using log-binomial regression models instead yielded very similar results and did not affect interpretation.

We investigated possible statistically significant interactions between caffeine exposures and potential confounders by including interaction terms in the models; none was found.

Although with limited statistical power, we investigated whether caffeine differentially affected risks of the major CP subtypes (spastic bilateral and spastic unilateral CP). Finally, we conducted sensitivity analyses by repeating all analyses restricted to singletons only, to term-born children only (37 wk of gestation or more), and to first-born children only.

Ethical considerations. Written, informed consent was obtained from all participating mothers in MoBa at the time of enrollment, and license from the Norwegian Data Inspectorate was obtained. Linkage of MoBa with the National CP registry of Norway and the Norwegian Patient register was further approved by the Regional committees for Medical and Health Research Ethics (2012/1738).

Results

We identified 222 children with CP (2.2/1000). Mean daily caffeine consumption before pregnancy was 169 mg (median: 120 mg, IQR: 35–253 mg). Daily consumption was lower during pregnancy: mean 72 mg (median: 40 mg, IQR: 0–100 mg) at the time of the first pregnancy questionnaire, 90 mg (median: 60 mg, IQR: 23–125 mg) up to the time of the FFQ, and 97 mg (median: 70 mg, IQR: 20–143 mg) from week 13 until the time of the third pregnancy questionnaire (data not shown). In the FFQ, 56% of total caffeine intake in the cohort was from coffee, 22% from tea, 14% from soft drinks, and only 8% from other sources, mainly chocolate (24).

Approximately one-quarter of participants consumed no caffeine early in pregnancy, one-half consumed ≤100 mg daily, and one-quarter consumed more (**Table 1**). Consumption was lower in younger mothers, mothers who had used medically assisted reproductive therapy, and nonsmokers.

Daily servings of caffeinated coffee prepregnancy and around pregnancy week 17 were not associated with CP (**Table 2**). Children of the heaviest coffee consumers (≥6 daily servings) during pregnancy weeks 13–30 had, compared with children of coffee-abstainers, a 2-fold increased risk of CP (HR: 2.3; 95% CI: 1.1, 5.0) (Table 2). However, there was no dose-response relation; consumption of 1–2 or 3–5 daily servings of coffee during this window was not associated with CP risk (HR: 0.9; 95% CI: 0.6, –1.2 and HR: 0.7; 95% CI: 0.4, 1.3, respectively, *P*-trend = 0.79).

Compared with children of nonconsumers of caffeinated soft drinks, children of women who consumed on average ≥6 daily servings before pregnancy had a 1.9-fold increased risk of CP (HR: 1.9; 95% CI: 1.2, 3.0) (Table 2). Maternal consumption of 3–5 daily servings of caffeinated soft drinks during pregnancy weeks 13–30 was associated with a 1.7-times increased risk of CP in children (HR: 1.7; 95% CI: 1.1, 2.8). Before pregnancy, around pregnancy week 17, and during pregnancy weeks 13–30, there were statistically significant or borderline significant trends of higher risks of CP with higher maternal consumption of caffeinated soft drinks (Table 2).

TABLE 1 Maternal characteristics by daily caffeine consumption from caffeinated beverages around week 17 of pregnancy[1]

	Caffeine consumption, mg					
	None	1–100	101–200	201–300	>300	Total
n	27,684 (27)	48,487 (48)	16,686 (17)	5334 (5)	2969 (3)	101,160 (100)
Age, y						
<25	4070 (36)	5373 (48)	1166 (10)	384 (3)	241 (2)	11,234 (100)
25–29	10,319 (31)	16,456 (49)	4576 (14)	1128 (4)	676 (2)	33,255 (100)
30–34	9672 (25)	18,913 (48)	7091 (18)	2190 (6)	1146 (3)	39,012 (100)
≥35	3623 (21)	7745 (44)	3853 (22)	1532 (9)	906 (5)	17,659 (100)
Education, y						
<12	2192 (28)	3206 (42)	1173 (15)	599 (8)	549 (7)	7719 (100)
12	7818 (29)	12,183 (46)	4164 (16)	1545 (6)	1045 (4)	26,755 (100)
13–16	10,777 (28)	19,249 (49)	6267 (16)	1930 (5)	886 (2)	39,109 (100)
≥17	5252 (23)	11,455 (51)	4286 (19)	1021 (5)	367 (2)	22,381 (100)
Missing	1645 (32)	2394 (46)	796 (15)	239 (5)	122 (2)	5196 (100)
Medically assisted reproduction						
No	28,835 (27)	47,161 (48)	16,244 (17)	5225 (5)	2916 (3)	98,381 (100)
Yes	849 (31)	1326 (48)	442 (16)	109 (4)	53 (2)	2779 (100)
Smoking						
No	22,747 (29)	39,081 (50)	11,681 (15)	2975 (4)	1088 (1)	77,572 (100)
Quit in pregnancy	3186 (22)	6480 (45)	3122 (22)	1075 (7)	551 (4)	14,414 (100)
1–9 cigarettes/d	976 (15)	2307 (36)	1454 (22)	959 (15)	771 (12)	6467 (100)
≥10 cigarettes/d	233 (12)	484 (25)	371 (19)	291 (15)	530 (28)	1909 (100)
Missing	542 (68)	135 (17)	58 (7)	34 (4)	29 (4)	798 (100)

[1] Values are *n* (%).

TABLE 2 Crude and adjusted HRs (95% CIs) for cerebral palsy in live-born children according to maternal daily caffeinated coffee, tea, soft drinks (cola), and total caffeine consumption

	Prepregnancy[1]		Week 17[1]		Week 30[2]	
	Crude	Adjusted[3]	Crude	Adjusted[3]	Crude	Adjusted[3]
Coffee servings[4]						
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1–2	0.9 (0.6, 1.3)	1.0 (0.7, 1.4)	0.8 (0.6, 1.2)	0.9 (0.6, 1.2)	0.8 (0.6, 1.2)	0.9 (0.6, 1.2)
3–5	0.9 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.6, 1.8)	1.1 (0.6, 1.9)	0.7 (0.4, 1.2)	0.7 (0.4, 1.3)
≥6	1.3 (0.8, 2.0)	1.4 (0.9, 2.1)	0.4 (0.1, 2.7)	0.4 (0.1, 2.6)	2.2 (1.0, 4.7)	2.3 (1.1, 5.0)
P-trend		0.40		0.58		0.79
Tea servings[4]						
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1–2	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	0.9 (0.7, 1.3)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
3–5	0.9 (0.5, 1.5)	0.9 (0.5, 1.5)	0.8 (0.4, 1.5)	0.8 (0.4, 1.5)	0.8 (0.4, 1.6)	0.8 (0.4, 1.5)
≥6	0.9 (0.3, 2.5)	0.9 (0.3, 2.4)	1.3 (0.4, 4.0)	1.3 (0.4, 4.0)	0.4 (0.1, 2.6)	0.3 (0.1, 2.3)
P-trend		0.54		0.68		0.24
Cola servings[4]						
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1–2	1.2 (0.8, 1.6)	1.2 (0.9, 1.7)	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)	1.1 (0.8, 1.5)	1.1 (0.8, 1.6)
3–5	1.3 (0.8, 1.9)	1.3 (0.8, 2.0)	1.4 (0.8, 2.3)	1.4 (0.8, 2.3)	1.7 (1.1, 2.7)	1.7 (1.1, 2.8)
≥6	1.9 (1.2, 3.0)	1.9 (1.2, 3.1)	1.5 (0.7, 3.2)	1.5 (0.7, 3.3)	1.0 (0.4, 2.4)	0.9 (0.4, 2.3)
P-trend		0.01		0.11		0.12
Total caffeine,[5] mg/d						
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1–100	1.0 (0.7, 1.6)	1.0 (0.7, 1.6)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)
101–200	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)
201–300	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)	0.8 (0.4, 1.6)	0.8 (0.4, 1.6)	0.7 (0.4, 1.4)	0.7 (0.4, 1.4)
>300	1.2 (0.8, 1.9)	1.2 (0.8, 1.9)	0.9 (0.4, 2.2)	1.0 (0.4, 2.2)	1.0 (0.5, 2.0)	0.9 (0.5, 1.9)
P-trend		0.49		0.92		0.30

[1] Around pregnancy week 17, women were asked about present and prepregnancy intake of caffeinated beverages.
[2] Around pregnancy week 30, women were asked about mean intake of caffeinated beverages since week 13 of pregnancy.
[3] Adjusted for maternal age (<25, 25–29, 30–34, or ≥35 y), maternal education (<12, 12, 13–16, or >16 y or missing), medically assisted reproduction (yes or no), and smoking (none, quit in pregnancy, <10 cigarettes/d, ≥10 cigarettes/d, or missing) and for each source of caffeine; adjustments were made for the others (i.e., in coffee analyses, adjusted for servings of tea and servings of cola, etc.).
[4] Serving defined as 125 mL.
[5] From caffeinated beverages.

No associations were observed between intake of caffeinated tea in pregnancy and CP risk in children (Table 2). Similarly, total maternal caffeine consumption (from caffeinated beverages) before pregnancy, around week 17, and during pregnancy weeks 13–30 was not associated with CP risk (Table 2). Using cubic splines to investigate the relation between total caffeine intake and CP during the same exposure windows did not reveal any associations (**Supplemental Figure 1**).

The results in which caffeine exposures were derived from the FFQ were in line with results from the other exposure windows: coffee caffeine, tea caffeine, and total caffeine (from beverages and food) were not associated with CP risk (**Table 3**). However, a mean daily consumption of 51–100 mg caffeine from soft drinks was associated with a 1.9-fold increased risk of CP in children (HR: 1.9; 95% CI: 1.1, 3.6). Although daily intake of >100 mg caffeine from soft drinks was not significantly associated with CP risk (HR: 1.5; 95% CI: 0.7, 3.5), the *P*-trend was close to significant (0.06).

Children of mothers who reported any caffeine intake from decaffeinated coffee in the FFQ had no increased risk of CP compared with children of mothers who did not drink decaffeinated coffee (HR: 1.2; 95% CI: 0.7, 2.2, data not shown). Children of women consuming ≥3 daily servings of noncaffeinated soft drinks before pregnancy, around pregnancy week 17, and during pregnancy weeks 13–30 had increased, although not statistically significant, risks of CP (HR: 1.7; 95% CI: 1.0, 2.8; HR: 1.7; 95% CI: 0.9, 3.0; and HR: 1.6; 95% CI: 0.9, 2.9, respectively, **Supplemental Table 1**).

Because different subtypes of CP may have different risk factors (27), analyses were repeated with unilateral and bilateral spastic CP as separate outcomes. The effects of caffeine exposure on these 2 outcomes did not differ substantially, although low power due to few cases limited the interpretation of these results (data not shown).

Restricting analyses to singletons, term-born children (≥37 wk of gestation), or first-born children did not change results.

Discussion

Consumption of caffeinated soft drinks before and during pregnancy was associated with increased risk of CP in children, and with significant or borderline significant trends suggesting higher risk of CP with higher consumption. However, maternal total daily caffeine consumption before and during pregnancy was not associated with CP risk in children.

Comparison with other studies. To our knowledge, no previously published studies have investigated whether maternal caffeine intake during pregnancy is a risk factor for CP in

TABLE 3 Crude and adjusted HRs (95% CIs) for cerebral palsy in live-born children according to maternal mean caffeine consumption from beverages and other dietary sources in the first half of pregnancy

	Crude	Adjusted[1]
Coffee caffeine, mg/d		
0	1 (reference)	1 (reference)
<101	1.1 (0.8, 1.5)	1.1 (0.8, 1.5)
101–200	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)
201–300	0.3 (0.1, 2.4)	0.3 (0.1, 2.4)
>300	0.9 (0.3, 2.4)	0.8 (0.3, 2.4)
P-trend		0.64
Tea caffeine, mg/d		
0	1 (reference)	1 (reference)
<51	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
51–100	1.2 (0.7, 2.0)	1.1 (0.7, 2.0)
>100	1.0 (0.2, 4.0)	1.0 (0.2, 3.9)
P-trend		0.75
Soft-drink caffeine, mg/d		
0	1 (reference)	1 (reference)
<51	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)
51–100	1.9 (1.0, 3.5)	1.9 (1.1, 3.6)
>100	1.5 (0.7, 3.4)	1.5 (0.7, 3.5)
P-trend		0.06
Total caffeine,[2] mg/d		
0–50	1 (reference)	1 (reference)
51–100	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)
101–200	1.4 (0.9, 1.9)	1.4 (0.9, 2.0)
201–300	0.6 (0.3, 1.3)	0.6 (0.3, 1.3)
>300	1.0 (0.4, 2.4)	1.0 (0.4, 2.4)
P-trend		0.81

[1] Adjusted for maternal age (<25, 25–29, 30–34, or ≥35 y), maternal education (<12, 12, 13–16, or >16 y or missing), medically assisted reproduction (yes or no), and smoking (none, quit in pregnancy, <10 cigarettes/d, or ≥10 cigarettes/d or missing), and for each source of caffeine, adjustments were made for the others (i.e., in coffee analyses, adjusted for milligrams of tea and cola, etc.).
[2] From caffeinated beverages and foods such as chocolates, desserts, etc.

children. However, a few previous studies have evaluated whether antenatal exposure to caffeine is a risk factor for other neurodevelopmental disorders. This may be relevant if neurodevelopmental disorders share causes of early negative influence on brain development (28). Partially consistent with our findings, a study using data on MoBa children at age 18 mo reported that total caffeine intake in pregnancy, and in particular caffeinated soft drinks, was positively associated with inattention/hyperkinetic symptoms, whereas intake of coffee and tea was not (10). A Dutch study found no association between total caffeine intake reported in week 16 of pregnancy and problem behavior in 5-y-olds (12). However, the Dutch cohort was small (~3500 participants) and could not investigate various sources of caffeine separately. A larger Danish study of >24,000 singletons reported a positive association between intake of ≥10 daily servings of coffee in early pregnancy and hyperkinetic disorder and attention deficit hyperkinetic disorder in children (11). The association weakened after adjustment for potential confounders. The study reported similar findings for total caffeine intake but did not report separate results for tea or soft-drink intake. A recent US study of >2000 mother–child pairs reported "no meaningful associations" between paraxanthine levels in serum (a metabolite of caffeine) measured twice in pregnancy and problem behavior in 4- to 7-y-old children (29).

Strengths and limitations. The considerable size of the present study is an important strength. CP is a rare condition, and few cohort studies, which allow prospective exposure measurements, have adequate power to study CP risk factors. In MoBa, with >100,000 children, we identified 222 children diagnosed with CP, all ascertained through record linkage with national registries. All CP cases were validated by neuropediatricians' assessments of medical records, independent of the hypothesis addressed in the present study. The prospective and repeated assessment of caffeine intake during various exposure windows in pregnancy is another considerable strength of this study. The design ensures differential misclassifications of exposures and outcomes are unlikely.

A limitation is that the study population is not a random sample of the source populations. MoBa participants are older, healthier, and better educated than the general population (30). Analyses of possible selection bias have demonstrated that known associations between risk factors and outcomes are preserved within MoBa (30, 31). However, a bias due to self-selection of participants into the cohorts may affect the generalizability of our results. Also, although adjustment for potential confounders had little impact, our results may still be influenced by unmeasured confounding.

Inaccuracy in timing of data collection and overlap between exposure windows captured by the different questionnaires limit our ability to draw conclusions about potential differentiated effects of caffeine in different exposure windows. However, because data collection was prospective, any bias thus created should be nondifferential, biasing our findings toward the null hypothesis, meaning any "true" associations may be stronger than observed.

The pregnancy questionnaire around week 30 may be missed by the women who give birth prematurely, and this selection is not independent of our outcome because preterm birth is an important risk factor for CP (32). However, restricting analyses to term-born children did not change our results.

Interpretation of results. We found an association between intake of caffeinated soft drinks before and during pregnancy and risk of CP in children, with significant or borderline significant trends of higher risk of CP with higher consumption. Because soft drinks constituted only a minor part of total caffeine intake, and total caffeine intake before and during pregnancy in itself was not associated with CP, this association is probably not related to the caffeine in soft drinks. This is further supported by the fact that findings were similar also for noncaffeinated soft drinks. There may be other constituents in soft drinks that could be harmful to early brain development: sugar or caloric content, artificial sweeteners, or other ingredients. The association may also be the result of unmeasured confounding. Aspects of the lifestyle of women who consume a lot of soft drinks could possibly affect their children's risk of CP. It has previously been shown in both MoBa and the British cohort study Avon Longitudinal Study of Parents and Children that intake of soft drinks in pregnancy was related to generally unhealthy dietary patterns and associated with unfavorable socioeconomic determinants such as young age, low education, and low income (33, 34), some of which have been associated with risk of CP (35).

A 2-fold increased risk for CP was observed in children of the heaviest caffeinated coffee consumers during pregnancy weeks 13–30. However, there was no dose-response relation and no increased risk during any other exposure window before or during pregnancy. Given the multiple comparisons in our analysis and the general lack of consistency for a coffee effect, a type 1 error is considered likely.

We found no evidence that total caffeine intake before or during pregnancy was associated with CP in children. However, we observed an increased risk with caffeinated soft drinks, which warrants further investigation.

Acknowledgments

MCT, KS-L, KYE, DM, RTL, CS, and AJW designed the research; ALB and HMM provided essential data; MCT analyzed data, drafted the manuscript, and had primary responsibility for the final content. All authors contributed to the interpretation of the results and critically reviewed, read, and approved the final manuscript.

References

1. Blair E, Watson L. Epidemiology of cerebral palsy. Semin Fetal Neonatal Med 2006;11:117–25.
2. Krägeloh-Mann I, Cans C. Cerebral palsy update. Brain Dev 2009; 31:537–44.
3. Nelson KB, Blair E. Prenatal factors in singletons with cerebral palsy born at or near term. N Engl J Med 2015;373:946–53.
4. Yu T, Campbell S, Stockmann C, Tak C, Schoen K, Clark EA, Varner MW, Spigarelli MG, Sherwin CM. Pregnancy-induced changes in the pharmacokinetics of caffeine and its metabolites. J Clin Pharmacol 2016;56:590–6.
5. Grosso LM, Bracken MB. Caffeine metabolism, genetics, and perinatal outcomes: a review of exposure assessment considerations during pregnancy. Ann Epidemiol 2005;15:460–6.
6. Schmidt RJ, Romitti PA, Burns TL, Murray JC, Browne ML, Druschel CM, Olney RS; National Birth Defects Prevention Study. Caffeine, selected metabolic gene variants, and risk for neural tube defects. Birth Defects Res A Clin Mol Teratol 2010;88:560–9.
7. Greenwood DC, Thatcher NJ, Ye J, Garrard L, Keogh G, King LG, Cade JE. Caffeine intake during pregnancy and adverse birth outcomes: a systematic review and dose-response meta-analysis. Eur J Epidemiol 2014;29:725–34.
8. Johansen AM, Wilcox AJ, Lie RT, Andersen LF, Drevon CA. Maternal consumption of coffee and caffeine-containing beverages and oral clefts: a population-based case-control study in Norway. Am J Epidemiol 2009;169:1216–22.
9. Peck JD, Leviton A, Cowan LD. A review of the epidemiologic evidence concerning the reproductive health effects of caffeine consumption: a 2000–2009 update. Food Chem Toxicol 2010;48:2549–76.
10. Bekkhus M, Skjothaug T, Nordhagen R, Borge AI. Intrauterine exposure to caffeine and inattention/overactivity in children. Acta Paediatr 2010;99:925–8.
11. Linnet KM, Wisborg K, Secher NJ, Thomsen PH, Obel C, Dalsgaard S, Henriksen TB. Coffee consumption during pregnancy and the risk of hyperkinetic disorder and ADHD: a prospective cohort study. Acta Paediatr 2009;98:173–9.
12. Loomans EM, Hofland L, van der Stelt O, van der Wal MF, Koot HM, Van den Bergh BR, Vrijkotte TG. Caffeine intake during pregnancy and risk of problem behavior in 5- to 6-year-old children. Pediatrics 2012;130:e305–13.
13. EFSA Panel on Dietetic Products Nutrition and Allergies. Scientific opinion on the safety of caffeine. EFSA Journal 2015;13:4102.
14. Jahanfar S, Jaafar SH. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcomes. Cochrane Database Syst Rev 2015;6:CD006965.
15. Back SA, Craig A, Luo NL, Ren J, Akundi RS, Ribeiro I, Rivkees SA. Protective effects of caffeine on chronic hypoxia-induced perinatal white matter injury. Ann Neurol 2006;60:696–705.
16. Korzeniewski SJ, Birbeck G, DeLano MC, Potchen MJ, Paneth N. A systematic review of neuroimaging for cerebral palsy. J Child Neurol 2008;23:216–27.
17. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893–902.
18. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, Davis PG, Tin W, Moddemann D, Solimano A, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275–82.
19. Doyle LW, Schmidt B, Anderson PJ, Davis PG, Moddemann D, Grunau RE, O'Brien K, Sankaran K, Herlenius E, Roberts R, et al. Reduction in developmental coordination disorder with neonatal caffeine therapy. J Pediatr 2014;165:356–9.e2.
20. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C; MoBa Study Group. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 2006;35:1146–50.
21. Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. Cerebral palsy in Norway: prevalence, subtypes and severity. Eur J Paediatr Neurol 2008;12:4–13.
22. The Norwegian Patient register [Internet]. Oslo, Norway: Helsedirektoratet [cited 2016 May 18]. Available from: https://helsedirektoratet.no/english/norwegian-patient-registry.
23. Dokumentkontroll av pasientjournaler med ICD-10 kode for cerebral parese [Internet]. Oslo, Norway: Helsedirektoratet [cited 2016 May 18]. Available from: https://helsedirektoratet.no/publikasjoner/dokumentkontroll-av-pasientjournaler-med-icd-10-kode-for-cerebral-parese-validering-av-resultater-fra-dekningsgradsanalyse-for-cerebral-pareseregisteret-i-norge-og-norsk-pasientregister.
24. Sengpiel V, Elind E, Bacelis J, Nilsson S, Grove J, Myhre R, Haugen M, Meltzer HM, Alexander J, Jacobsson B, et al. Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. BMC Med 2013;11:42.
25. Meltzer HM, Brantsaeter AL, Ydersbond TA, Alexander J, Haugen M. Methodological challenges when monitoring the diet of pregnant women in a large study: experiences from the Norwegian Mother and Child Cohort Study (MoBa). Matern Child Nutr 2008;4:14–27.
26. Brantsaeter AL, Haugen M, Alexander J, Meltzer HM. Validity of a new food frequency questionnaire for pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). Matern Child Nutr 2008;4:28–43.
27. Nelson KB. Causative factors in cerebral palsy. Clin Obstet Gynecol 2008;51:749–62.
28. Strickland AD. Prevention of cerebral palsy, autism spectrum disorder, and attention deficit-hyperactivity disorder. Med Hypotheses 2014;82:522–8.
29. Klebanoff MA, Keim SA. Maternal caffeine intake during pregnancy and child cognition and behavior at 4 and 7 years of age. Am J Epidemiol 2015;182:1023–32.
30. Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, Alsaker ER, Haug K, Daltveit AK, Magnus P. Self-selection and bias in a large prospective pregnancy cohort in Norway. Paediatr Perinat Epidemiol 2009;23:597–608.
31. Nilsen RM, Suren P, Gunnes N, Alsaker ER, Bresnahan M, Hirtz D, Hornig M, Lie KK, Lipkin WI, Reichborn-Kjennerud T, et al. Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders. Paediatr Perinat Epidemiol 2013;27:553–63.
32. Trønnes H, Wilcox AJ, Lie RT, Markestad T, Moster D. Risk of cerebral palsy in relation to pregnancy disorders and preterm birth: a national cohort study. Dev Med Child Neurol 2014;56:779–85.
33. Englund-Ögge L, Brantsæter AL, Sengpiel V, Haugen M, Birgisdottir BE, Myhre R, Meltzer HM, Jacobsson B. Maternal dietary patterns and preterm delivery: results from large prospective cohort study. BMJ 2014;348:g1446.
34. Northstone K, Emmett P, Rogers I. Dietary patterns in pregnancy and associations with socio-demographic and lifestyle factors. Eur J Clin Nutr 2008;62:471–9.
35. Solaski M, Majnemer A, Oskoui M. Contribution of socio-economic status on the prevalence of cerebral palsy: a systematic search and review. Dev Med Child Neurol 2014;56:1043–51.