2016

Article 1

Maternal Consumption of Coffee and Caffeine-containing Beverages and Oral Clefts : A Population-based Case-Control Study in Norway

1 **Il s'agit d'une étude :**

a. Randomisée
b. Rétrospective
c. Observationnelle
d. Étiologique
e. Prospective

2 **Dans cette étude, les cas sont les nouveau-nés :**

a. Présentant une fente labio-palatine à la naissance opérés dans les centres hospitaliers universitaires d'Oslo et de Bergen
b. De mère qui consommaient plus de 3 tasses de café par jour au premier trimestre de grossesse
c. Dont la mère a accouché dans les maternités des centres hospitaliers universitaires d'Oslo ou de Bergen
d. Indemnes de fente labio-palatine à l'issue de la grossesse
e. Décédés après la naissance

3 **Dans cet article, les facteurs d'exposition d'intérêt incluent :**

a. La consommation de thé au cours du troisième trimestre de la grossesse
b. La supplémentation vitaminique, au cours du premier trimestre de la grossesse
c. La consommation de boissons contenant de la caféine au cours du premier trimestre de grossesse
d. Le tabagisme au cours du premier trimestre de grossesse
e. La consommation de café au cours du premier trimestre de grossesse

4 **L'information sur la consommation quotidienne de café au cours du premier trimestre de grossesse :**

a. A été de nature déclarative
b. A été recueillie de manière prospective
c. A été extraite de la base de données du registre national des naissances
d. A été quantifiée au nombre de tasses
e. A été recueillie uniquement chez les mères de nouveau-nés avec une fente labio-palatine

5 **Le choix d'une étude de type cas-témoin a été guidé par le fait ou les faits suivants :**

a. La prévalence de la fente labio-palatine à la naissance est faible
b. Ce type d'étude permet de montrer une relation causale
c. Ce type d'étude ne présente généralement pas de biais
d. La consommation de café au cours du premier trimestre de grossesse est fréquente
e. Le niveau d'exposition aux facteurs de risque étudiés peut être déterminé précisément

6 **Dans cette étude, approximativement deux témoins ont été recrutés pour un cas de fente labiale (avec ou sans fente palatine) dans le but :**

a. De limiter un potentiel biais de sélection lié aux sujets perdus de vue au cours du suivi
b. De calculer des risques relatifs
c. De réduire la largeur de l'intervalle de confiance des odds ratio estimés
d. D'augmenter les chances de mettre une différence entre les cas et les témoins
e. De procéder à un appariement sur les facteurs de confusion potentiels

7 **D'après le tableau 1 :**

a. Avant la grossesse 75 % des femmes consommaient au moins une tasse de café par jour
b. La fréquence du tabagisme maternel actif au cours du premier trimestre de grossesse était de 31,9 % dans le groupe témoin
c. 79,5 % des mères travaillant durant le premier trimestre de grossesse ont donné naissance à un nouveau-né avec une fente palatine seule (FPS)
d. 50 % des mères du groupe témoin consommaient au moins deux tasses de café quotidiennement pendant le premier trimestre de grossesse
e. 573 cas de fente labio-palatine (FLP) ou fente palatine seule (FPS) ont été inclus au total dans cette étude

8 **Pourquoi le tabagisme actif est-il un facteur de confusion potentiel de l'association observée entre la consommation de café au cours du premier trimestre de grossesse et le diagnostic de fente labio-palatine à la naissance dans cette étude ?**

a. Car la prévalence du tabagisme actif au premier trimestre de grossesse diffère entre les cas et les témoins dans cette étude
b. Car le tabagisme est un facteur de risque des fentes labio-palatines identifié dans la littérature
c. Car il est possible que les femmes fumeuses consomment plus de café que les non fumeuses
d. Car l'information sur le tabagisme a été recueillie rétrospectivement par questionnaire dans cette étude
e. Car le tabagisme passif et l'absence de tabagisme ont été regroupés au sein d'une seule et même catégorie dans cette étude

9 **Quelle(s) stratégie(s) ont utilisée(s) les auteurs pour s'affranchir de l'effet du facteur de confusion « tabagisme actif au cours du premier trimestre de grossesse » dans cette étude ?**

a. L'estimation d'odds ratios bruts
b. Un test de tendance sur la consommation de café
c. L'appariement de témoins à chaque cas
d. La restriction aux mères non-fumeuses
e. L'ajustement à l'aide d'un modèle de régression logistique multivariée non-conditionnelle

10 **En analyse multivariée (Tableau 2), les auteurs indiquent qu'il existe une relation croissante entre l'odds ratio de fente labiale (avec ou sans fente palatine, FPL) et la consommation de café codée en tasses par jour. Sur quelle(s) preuve(s) repose cette affirmation ?**

a. Le recouvrement partiel des intervalles de confiance à 95 % des odds ratios ajustés pour les catégories > 0 – < 3 tasses et 3 tasses et plus, respectivement
b. L'exclusion de l'échantillon d'analyse des mères ne consommant pas de café pendant le premier trimestre de grossesse
c. L'odds ratio de fente labiale chez les femmes consommant 3 tasses par jour ou plus de café par rapport aux femmes consommant moins de 3 tasses par jour est de 1,59 (IC95 % 1,05 - 2,39)
d. L'estimation ponctuelle de l'odds ratio ajusté égale, respectivement, à 1,00 pour 0 tasse, 1,39 pour > 0 – < 3 tasses, et 1,59 pour 3 tasses et plus
e. Le degré de signification (valeur de p) du test de tendance (soit 0,013)

11 **Le risque de conclure à tort à la responsabilité de la consommation de café au cours du premier trimestre de la grossesse dans cette étude peut s'expliquer par :**

a. Le risque d'erreur statistique de première espèce (alpha)
b. Le caractère rétrospectif du recueil des données
c. L'existence d'une relation entre la dose de caféine ingérée quotidiennement et L'odds ratio de fente labiale
d. L'existence de facteurs de confusion résiduels méconnus
e. Un défaut de puissance statistique

12 **Sur la base des informations données dans cet article, quel(s) facteur(s) de confusion potentiel(s) supplémentaire(s) les auteurs auraient-ils pu prendre en compte ?**

a. Les antécédents familiaux
b. La consommation de café au deuxième trimestre
c. L'homocystéinémie chez la mère
d. L'âge gestationnel
e. L'activité physique

13 **Quels sont les biais potentiels de cette étude ?**

a. Biais de sélection des populations étudiées
b. Biais lié à la présence de facteurs de confusion
c. Biais de classement sur les critères définissant les cas
d. Biais de classement sur l'exposition, lié à l'absence de souvenir
e. Biais d'attrition des populations étudiées

14 **Citez le(s) argument(s) en faveur de la nature causale de l'association, retrouvée dans cette étude, entre la consommation de café pendant le premier trimestre de grossesse et le risque accru de fente labiale (avec ou sans fente palatine, FLP) à la naissance :**

a. L'ajustement sur les facteurs de confusion connus
b. L'existence d'une relation dose-effet statistiquement significative
c. La séquence temporelle entre l'exposition et l'événement de santé étudié
d. Le risque de fente labio-palatine induit par l'exposition à une dose unique élevée de caféine chez l'animal
e. L'absence d'association similaire entre la consommation de café et la fente palatine seule

15 **Parmi les implications potentielles de cette étude pour la prévention des fentes labio-palatines, il paraît pertinent :**

a. De réaliser une étude randomisée portant sur la consommation de thé versus café chez les femmes enceintes
b. D'inciter les femmes enceintes à consommer plus de trois tasses de thé par jour pendant le premier trimestre de grossesse
c. De renforcer la surveillance échographique morphologique de l'extrémité céphalique chez les femmes enceintes consommant plus de trois tasses de café par jour
d. De conseiller d'éviter les boissons contenant de la caféine au cours du premier trimestre de grossesse
e. D'informer les femmes enceintes concernées sur l'absence de preuve de l'innocuité d'une consommation de café supérieure à trois tasses par jour

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Original Contribution

Maternal Consumption of Coffee and Caffeine-containing Beverages and Oral Clefts: A Population-based Case-Control Study in Norway

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A large, population-based case-control study of facial clefts was carried out in Norway between 1996 and 2001. The study included 573 cases—377 with cleft lip with or without cleft palate and 196 with cleft palate only—and 763 randomly selected controls. Maternal consumption of coffee and other caffeine-containing beverages in early pregnancy was recorded shortly after birth. Compared with that for no coffee consumption, the adjusted odds ratios for cleft lip with or without cleft palate were 1.39 (95% confidence interval: 1.01, 1.92) for less than 3 cups a day and 1.59 (95% confidence interval: 1.05, 2.39) for 3 cups or more. Coffee consumption was not associated with risk of cleft palate only (for $\geq$3 cups vs. none, adjusted odds ratio = 0.96, 95% confidence interval: 0.55, 1.67). Tea consumption was associated with a reduced odds ratio of both cleft lip with or without cleft palate and cleft palate only. There was little evidence of an association between caffeine exposure and clefts when all sources of caffeine were considered. Adjustment for known confounding factors in general had minor effects on risk estimates. Still, the authors could not rule out the possibility of uncontrolled confounding by factors associated with the habit of drinking coffee.

caffeine; cleft lip; cleft palate; coffee; pregnancy

Abbreviations: CI, confidence interval; CLP, cleft lip with or without cleft palate; CPO, cleft palate only.

Orofacial clefts are among the most common birth defects, and the prevalence in Norway (2.2 per 1,000 livebirths) is particularly high. The etiology of clefts is complex and largely unknown. The high risk of recurrence of clefts among first-degree relatives (as much as 56 times the background prevalence) suggests a strong genetic component (1). However, environmental factors such as maternal nutrition (2–4), vitamin supplements (5), smoking (6), and binge alcohol consumption (7) also appear to contribute.

Coffee consumption is relatively high in Norway. In the latest nationwide study, average coffee intake was half a liter a day, with peak intake among those aged 40–60 years (8). Data from animal studies suggest that large single doses of caffeine may cause palatal clefts as well as other birth defects (9), although studies of coffee consumption in humans have provided little evidence of teratogenic effects (10). In a systematic review of 3 studies of orofacial clefts and caffeine, high coffee intake was associated with a slight increase in risk (11). According to a recently published article, maternal caffeine intake during pregnancy was associated with fetal growth restriction (12).

Coffee is a commonly consumed beverage among pregnant women, and even a small increase in malformation risk could be a matter of concern. We used data from a population-based case-control study to evaluate the association of maternal consumption of coffee and caffeinated beverages in early pregnancy with the risk of delivering an infant with an orofacial cleft.

MATERIALS AND METHODS

All infants born with facial clefts in Norway are treated at government expense in surgical centers at university hospitals located in Oslo and Bergen. In collaboration with these 2 centers, we identified all babies born from 1996 to 2001 who were referred for treatment for either cleft lip with or

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without cleft palate (CLP) or cleft palate only (CPO). Controls were recruited during the same period by randomly selecting approximately 4 births per 1,000 from the National Medical Birth Registry (which includes all births in the country). These births served as controls for both case groups, with the target of 2 controls per case of CLP (nearly 4 controls for each case of CPO). Both cases and controls were recruited during their first weeks of life.

Our present study was approved by the regional ethics review board, the Norwegian Data Inspectorate, and the US National Institute of Environmental Health Sciences Review Board. All participating mothers provided informed consent.

Participants

There were 676 women in Norway who delivered infants requiring surgery for orofacial clefts during 1996–2001. We excluded 24 mothers who did not speak Norwegian or whose infant died after birth, leaving 652 eligible mothers. Of these, 88% ($n = 573$) agreed to participate. We randomly selected 1,022 control mothers of livebirths via the national Medical Birth Registry within 6 weeks of delivery. After excluding 16 who were not Norwegian speakers or whose infant died, 1,006 mothers of controls were eligible, of whom 76% ($n = 763$) agreed to participate. Data on intake of coffee and other caffeinated beverages were available for all participating mothers of cases and controls. We identified other birth defects among the cleft cases by using 3 data sources: the Medical Birth Registry (based on delivery records and hospital records from the first week of life), medical records at the hospital performing the corrective surgery, and mother's questionnaire. Accompanying defects were reported for 17% of CLP cases and 40% of CPO cases. Cases of clefts without accompanying defects have been categorized as isolated clefts.

Data collection

Mothers completed a 32-page questionnaire covering demographic characteristics, reproductive history, and exposures during pregnancy (including smoking, alcohol consumption, coffee intake, medication use, and occupational and household exposures). Median time from delivery to completion of the questionnaire was 14 weeks for cases and 15 weeks for controls. The questionnaire included items on maternal consumption of caffeine-containing beverages (coffee, tea, and soft drinks) during the first 3 months of pregnancy. For each beverage, there was 1 question with 5 response categories: none, number of cups per day, number of cups per week, number of cups per month, and number of cups per year (without specifying the size of the cup). An English translation of the questionnaire is available online (http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/ncl/ncl_pregnancy_en.pdf).

Statistical methods

The risk of delivering offspring with an orofacial cleft was estimated by odds ratios with 95% confidence intervals in unconditional logistic regression models. All beverages were summarized and were analyzed in the same way, as follows. "Cups per day" was computed from reported number of cups consumed per day, per week (divided by 7), or per month (divided by 30). Women who reported consuming less than 1 cup per month were categorized as consuming zero. The cups-per-day variable was analyzed as a continuous variable. Finally, a 3-category variable was created: 0 cups per day (reference category), more than 0 but less than 3 cups per day, and 3 or more cups per day. Trends across the categories were evaluated, with zero as the reference.

An estimate of caffeine from all sources was computed from the data on coffee, tea, and caffeinated soft drinks. Caffeine content was estimated as 100 mg per cup of coffee, 40 mg per cup of tea, and 20 mg per cup of caffeinated soft drink based on values from the Norwegian Health Authorities Web page (http://www.matportalen.no/Emner/Gravide (in Norwegian)). Risk of clefts was evaluated per 100-mg increase in caffeine intake (continuous variable) and for the categories $>100–<500$ mg and ≥ 500 mg of caffeine relative to 0–100 mg.

Adjustments were made for potential confounders (factors associated with clefts in other studies, most of which were also associated in our study), namely, dietary vitamin A (quartiles), dietary folate (quartiles), folic acid supplement (400 μg/day, yes or no), vitamin supplement use (yes or no), consumption of alcohol in early pregnancy (number of drinks per sitting), smoking (ordinal linear with 5 categories: none; passive only; and 1–5, 6–10, and ≥ 11 cigarettes a day), nausea during the first trimester (yes or no), employment in early pregnancy (yes or no), education (ordinal linear with 6 categories), father's income (ordinal linear with 3 categories), and year of birth. Evaluations of possible interactions with coffee intake were carried out for use of folic acid supplements and smoking. In evaluating the effects of coffee or tea separately, we adjusted for the other (categorized as number of cups per day). Because CLP and CPO are considered etiologically distinct outcomes, we conducted separate analyses for each (1). Separate analyses were also performed for isolated clefts (i.e., excluding those with accompanying defects). Because oral clefts are relatively rare birth defects, odds ratios are close approximations of relative risks. All statistical analyses were performed by using SPSS 14.0 software (SPSS Inc., Chicago, Illinois).

RESULTS

Women who gave birth to infants with CLP were taller, less educated, and less likely to work during the first trimester compared with mothers who gave birth to healthy controls (Table 1). Compared with mothers of controls, fewer mothers of CLP cases used a folic acid supplement, and they were more often coffee consumers and smokers. Fewer mothers of CLP and CPO cases drank tea compared with mothers of controls (Table 1).

Maternal coffee consumption was associated with an increased risk of CLP. In the adjusted analyses, the odds ratio

Table 1. Demographic and Other Characteristics of Participants in the Case-Control Study of Maternal Consumption of Caffeine-containing Beverages and Oral Clefts, Norway, 1996–2001

	Cleft Lip With or Without Cleft Palate (n = 377)			Cleft Palate Only (n = 196)			Control Group (n = 763)		
	Median (25th, 75th percentile)[a]	%	Mean (SD)	Median (25th, 75th percentile)[a]	%	Mean (SD)	Median (25th, 75th percentile)[a]	%	Mean (SD)
Mother's characteristics									
Coffee consumption before pregnancy, cups/day	3.0 (1.0, 4.1)			3.0 (1.0, 5.0)			3.0 (1.0, 4.3)		
Coffee consumption during the first trimester, cups/day	2.0 (0.7, 4.0)			2.0 (0.4, 3.0)			2.0 (0.7, 3.0)		
Coffee consumers during the first trimester		56.0			49.0			45.7	
Tea consumption during the first trimester, cups/day	1.0 (0.4, 2.0)			1.0 (0.3, 2.0)			1.0 (0.4, 2.0)		
Tea consumers during the first trimester		62.1			62.2			71.7	
Soft drink consumption in the first trimester, cups/day	0.6 (0.3, 2.0)			0.6 (0.3, 1.0)			0.6 (0.3,1.5)		
Soft drink consumers during the first trimester		77.1			70.9			73.1	
Folic acid supplement use during the first trimester ($\geq$400 μg)		13.1			15.8			19.0	
Multivitamin use during the first trimester		32.6			36.2			36.6	
Smoking during the first trimester[b]		44.1			36.8			31.9	
Alcohol consumption, drinks/sitting	2.0 (1.0, 2.0)			1.0 (1.0, 2.0)			1.0 (1.0, 2.0)		
Age at delivery, years			28.9 (4.9)			28.9 (5.1)			29.2 (4.8)
Height, cm			168.6 (5.7)			166.9 (6.6)			167.7 (6.0)
Prepregnancy weight, kg			67.2 (12.9)			66.2 (13.6)			66.0 (11.3)
Body mass index, kg/m^2			23.6 (4.3)			23.8 (4.5)			23.4 (3.7)
Education less than high school		18.8			11.2			11.0	
Working during the first trimester		76.3			79.5			83.1	
Father's income <250,000 Norwegian kroner		52.6			54.5			47.3	
Other birth defects		16.7			39.8			5.0	

Abbreviation: SD, standard deviation.
[a] Intake among consumers only.
[b] All levels of active smoking versus nonsmoking and passive smoking.

of CLP increased by 7% per-cup increase in daily coffee intake (adjusted odds ratio = 1.07, 95% confidence interval (CI): 1.00, 1.16). Compared with those for women with zero coffee consumption, the adjusted odds ratios of CLP were 1.39 (95% CI: 1.01, 1.92) for daily coffee consumption of less than 3 cups a day and 1.59 (95% CI: 1.05, 2.39) for consumption of 3 or more cups a day (Table 2), and inspection of categories of coffee intake confirmed that there was a trend in risk by dose ($P_{\text{trend}} = 0.013$ in the adjusted analyses). The association between coffee consumption and CLP persisted among nonsmokers (among whom there would presumably be no residual confounding by smoking) and among mothers of isolated cleft cases (Table 2). We found no evidence of an association between maternal coffee consumption during the first trimester and the risk of CPO (Table 2).

Consumption of caffeine-containing tea was associated with a decrease in the odds ratio of both CLP and CPO (Table 2). Compared with no tea intake, daily tea intake of 3 or more cups gave adjusted odds ratios of 0.55 (95% CI: 0.32, 0.95) for CLP and 0.58 (95% CI: 0.31, 1.07) for CPO. Soft drinks that contain caffeine were positively associated with both types of facial clefts, although with confidence intervals that did not exclude 1 (Table 2).

Table 3 shows maternal intake of caffeine from all beverages in relation to cleft risk. Although there was

Table 2. Maternal Consumption of Caffeine-containing Coffee, Tea, and Soft Drinks During the First Trimester and Odds Ratios of Cleft Lip With or Without Cleft Palate and Cleft Palate Only, Norway, 1996–2001

	Cleft Lip With or Without Cleft Palate								Cleft Palate Only							
	All Cases				Isolated[a] Cases				All Cases				Isolated[a] Cases			
	Crude Analysis (*n* = 377/763)[b]		Adjusted[c] Analysis (*n* = 318/653)		Crude Analysis (*n* = 314/763)		Adjusted[c] Analysis (*n* = 263/653)		Crude Analysis (*n* = 196/763)		Adjusted[c] Analysis (*n* = 178/653)		Crude Analysis (*n* = 118/763)		Adjusted[c] Analysis (*n* = 108/653)	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Coffee, per-cup increase	1.11	1.04, 1.18	1.07	1.00, 1.16	1.09	1.00, 1.17	1.09	1.00, 1.17	1.00	0.92, 1.09	0.98	0.88, 1.09	0.95	0.84, 1.07	0.94	0.82, 1.09
Coffee, categorical[d]																
>0–<3 cups/day	1.37	1.03, 1.81	1.39	1.01, 1.92	1.41	1.05, 1.90	1.47	1.05, 2.07	1.17	0.83, 1.66	1.26	0.85, 1.86	1.11	0.72, 1.70	1.24	0.77, 1.99
≥3 cups/day	1.80	1.29, 2.53	1.59	1.05, 2.39	1.85	1.29, 2.64	1.67	1.08, 2.58	1.07	0.68, 1.70	0.96	0.55, 1.67	0.88	0.48, 1.61	0.91	0.45, 1.85
P for trend	<0.001		0.013		<0.001		<0.001		0.566		0.760		0.879		0.877	
Tea, per-cup increase	0.85	0.76, 0.94	0.86	0.76, 0.98	1.01	0.97, 1.05	1.01	0.97, 1.05	0.86	0.75, 0.99	0.82	0.70, 0.96	0.81	0.67, 0.98	0.79	0.64, 0.97
Tea, categorical[d]																
>0–<3 cups/day	0.68	0.52, 0.88	0.74	0.55, 1.01	0.65	0.49, 0.86	0.72	0.52, 0.99	0.65	0.46, 0.91	0.66	0.45, 0.95	0.64	0.43, 0.97	0.64	0.41, 1.01
≥3 cups/day	0.50	0.31, 0.80	0.55	0.32, 0.95	0.49	0.30, 0.82	0.53	0.30, 0.94	0.68	0.39, 1.18	0.58	0.31, 1.07	0.49	0.23, 1.05	0.45	0.20, 1.01
P for trend	0.001		0.014		0.001		0.011		0.033		0.025		0.018		0.020	
Soft drinks, per-cup increase	1.04	0.97, 1.11	1.05	0.96, 1.14	1.04	0.97, 1.11	1.04	0.95, 1.14	1.03	0.96, 1.12	1.05	0.95, 1.15	1.06	0.97, 1.15	1.06	0.96, 1.18
Soft drinks, categorical[d]																
>0–<3 cups/day	1.20	0.90, 1.62	1.16	0.84, 1.62	1.23	0.90, 1.69	1.17	0.82, 1.67	0.85	0.60, 1.22	0.84	0.56, 1.24	1.15	0.72, 1.83	1.14	0.69, 1.89
≥3 cups/day	1.44	0.93, 2.23	1.48	0.88, 2.49	1.43	0.90, 2.27	1.44	0.82, 2.51	1.15	0.68, 1.96	1.30	0.70, 2.40	1.36	0.69, 2.67	1.43	0.65, 3.13
P for trend	0.086		0.144		0.107		0.193		0.928		0.788		0.371		0.384	

Abbreviation: CI, confidence interval.

[a] No accompanying malformations.

[b] All parenthetical information is expressed as number of mothers of cases/number of mothers of controls.

[c] Odds ratios were adjusted for maternal nausea, smoking, alcohol consumption, folic acid supplement use, multivitamin supplement use, coffee consumption (in the analysis of tea and soft drinks), tea consumption (in the analysis of coffee and soft drinks), dietary folate, dietary vitamin A, work status during the first trimester, educational level, income level (father), and year of birth.

[d] Reference category: 0 cups/day.