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MATERNAL COFFEE AND ALCOHOL CONSUMPTION DURING PREGNANCY, PARENTAL SMOKING AND RISK OF CHILDHOOH ACUTE LEUKEMIA

Short title: Maternal coffee and alcohol consumption, parental smoking and childhood leukemia

Category : Original article

Condensed abstract : Maternal habits during pregnancy, as maternal smoking and maternal beverage consumption, were obtained for 280 cases of childhood acute leukemia and 280 frequency matched controls. The results suggest an association between maternal alcohol and coffee consumption during pregnancy.

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Abstract

We investigated the role of maternal alcohol and coffee drinking and parental smoking on the risk of childhood acute leukemia in a multicenter case-control study. The study included 280 incident cases and 288 hospitalized controls, frequency matched with the cases by age, gender and center. Data collection was completed by face-to-face standardized interviews of the case and control mothers. An association with maternal alcohol consumption during pregnancy was observed with acute lymphoid leukemia (ALL) (OR=2.0 [1.4-3.0]) and acute non-lymphoid leukemia (ANLL) (OR=2.6 [1.2-5.8]). Maternal coffee consumption during pregnancy was associated with childhood acute leukemia, ORs increasing in ALL with coffee consumption (OR=1.1 [0.7-1.8], OR=2.4 [1.3-4.7] and OR=3.1 [1.0-9.5], respectively for ≤ 3, 4-8 and > 8 cups/day). No association with maternal smoking during pregnancy or parental smoking before or after the index child's birth was observed. Our results suggest an association with maternal alcohol and coffee drinking during pregnancy and call for further investigations. Besides, the present study does not support the hypothesis of an increase in the risk of childhood leukemia related to parental smoking.

Key words: Case-control study, childhood leukemia, alcohol, coffee, smoking

Introduction

To our knowledge, seven studies investigated the role of maternal alcohol drinking during pregnancy and childhood leukemia [1-7]. The three of them which published on acute myeloid leukemia, showed positive associations [2-4]. One, on ALL, found also an association [4], three found no association [1, 5-6] and one found a negative association [7]. In the eyes of those studies, the role of maternal alcohol consumption during pregnancy and childhood acute leukemia remains unclear.

Maternal coffee drinking has been even less investigated [5, 8, 9]. Ross et al. showed an association between coffee drinking and infant leukemia [9]. They suggested that coffee may act as an inhibitor of DNA topoisomerase II and induce abnormalities of chromosome 11q23, similar to those induced by epipodophyllotoxins.

The influence of maternal smoking on the risk of leukemia has been investigated in many studies, most of which have generated arguments against a strong association, or even against any association [1-5, 10-19]. Studies on passive smoking during childhood, although less numerous, have also yielded negative results [20]. Although the negative results seem consistent at present, smoking remains an exposure of interest because of its known carcinogenicity to many organs [21], the ability of many smoke constituents to cross the placental barrier and its rather high prevalence during pregnancy.

The present paper reports a detailed analysis of the role of maternal beverage consumption during pregnancy and parental smoking in the etiology of childhood leukemia. Data are obtained from a hospital-based case-control study designed to investigate environmental and genetic factors of childhood acute leukemia.

Methods

Selection of cases and controls

Data were obtained from a hospital-based case-control study conducted in Paris, Lille, Lyon, and Nancy between January 1995 and December 1999. The design of the study has been described elsewhere [22]. Briefly, eligible cases were all children newly diagnosed with acute leukemia before the age of 15, whom the interviewers were authorized to contact by the physician. The controls were children hospitalized in the same hospital as the cases for diseases other than cancer or birth defects. The controls were mainly recruited in orthopedic departments to which they had been admitted for a variety of reasons. The choice of control departments was guided both by the necessity of targeting the same age bracket as that of the cases, without selecting particular risk factors or socioeconomic status, and by the need to restrict blood samplings to a limited number of centers. The mothers of two cases and two controls refused to participate. Physicians did not allow the interviewers to make contact with the mothers of 13 cases (9 ALL and 4 ANLL) who were in critical conditions. There were no physician refusals for the controls. Thus, a total of 280 incident cases of acute leukemia (AL) and 288 controls were included in the study. The recruitment was stratified by age, gender, hospital, and ethnic origin (Caucasian, North African, others). Blood-samples were obtained in a subset of 219 cases (78%) and 105 controls (36%) to investigate several metabolic polymorphisms (analysis in progress).

Data collection

Medical interviewers conducted face-to-face interviews of the mothers, using standardized questionnaires. The cases' mothers were interviewed 1 or 2 months after the diagnosis, when the children were in improved condition. The questionnaire included questions on the parents' socio-demographic characteristics and medical history, the child's perinatal characteristics, the familial history of cancer and auto-immune disease, contacts with animals (pets, breeding cattle), and the parents' occupations and habits.

Mothers of cases and controls were asked about alcohol, coffee, tea and cola consumption during the index pregnancy (in any period of the pregnancy without distinction) and breastfeeding. The daily alcohol intake during pregnancy was estimated as the total number of drinks of any type of alcohol (wine, beer, spirits).

Maternal smoking history included smoking status (never, past and current), intensity of smoking (number of cigarettes per day or per week), duration of smoking (years) and the timing of smoking (before the index pregnancy, during the index pregnancy with each.

Paternal smoking history included the same questions as maternal smoking excepted for the timing of smoking (before the index pregnancy, during the index pregnancy, and after birth. Mothers were asked whether the atmosphere at home and at the nanny's home was smoky.

Study power

With a power of 80% and α=5%, the size of the study enabled to detect minimum odds ratios of 1.6, 1.9 and 2.2 for exposure prevalences among controls of 20%, 10% and 5% respectively.

Statistical analysis

Statistical analysis was performed using unconditional logistic regression models including the stratification variables, age, gender, hospital and ethnic origin, with positive [22-23] or negative [23-24] adjustment on socio-demographic characteristics and the other factors associated with leukemia risk under study. Separate analyses and regressions were also used to estimate specific odds ratios for acute lymphocytic leukemia (ALL) and acute non-lymphocytic leukemia (ANLL). We also considered the subgroup of cases with 11q23 abnormalities which are characteristic of acute leukemia induced by topoisomerase II inhibitors.

Results

Out of the 280 cases included in the study, 240 (86%) had a diagnosis of ALL and 40 (14%) a diagnosis of ANLL with the following morphological type: 4 acute myeloid leukemia (AML) with minimal evidenece of myeloid differenciation (M0), 3 acute myeloblastic leukemia without maturation (M1), 7 acute myeloblastic leukemia with maturation (M2), 1 acute promyelocytic leukemia (M3), 6 acute myelomonocytic leukemia (M4), 12 acute monocytic/monoblastic leukemia (M5), 2 acute erythroleukemia (M6), 1 unspecified AML and 4 acute mixed-lineage leukemias. Seven cases had a cytogenetic abnormality of the long arm of chromosome 11 (3 t(4;11), 2 t(9;11), 1 t(10;11)). Out of the 288 controls, 154 (54%) were admitted for a traumatic lesion (fracture, wound, burn), 100 (35%) for an osteoarticular diseases (infectious arthritis, osteomyelitis, juvenile osteochondritis), 17 (6%) for gastrointestinal or genitourinary symptoms (appendicitis, pyelonephritis, urinary tract infection, testicular torsion), 6 (2%) for a minor congenital malformation (clubfoot, etc.) and 11 (4%) for other symptoms (ingrown toenail, dental abscess, drug poisoning).

Case-control comparability

The distribution of cases and controls by stratification and socio-economic variables is shown in Table 1. The recruitment of controls aged 2-6 years, the peak childhood leukemia incidence age group, was difficult, resulting in a significant difference between cases and controls for age. The other stratification variables were similarly distributed among the cases and controls. Good comparability of maternal and paternal schooling was obtained after adjustment for stratification variables. The case and control groups had the same proportion of active mothers, and similar socio-professional category distributions.

Maternal beverage consumption during pregnancy

Maternal coffee consumption during pregnancy was associated with acute leukemia, with odds ratios (OR) increasing with the amount of coffee (OR=1.0 [0.7-1.5] for daily intakes of ≤

3 cups, 2.1 [1.2-3.8] for 4-8 cups and 2.8 [0.9-8.1] for > 8 cups, p trend < 0.05). The similar estimates observed for ALL and ANLL are shown in table 2. There was no association between childhood leukemia and tea or cola consumption during pregnancy, for either type of leukemia. Out of the 7 case mothers with an abnormality of chromosome 11, 6 reported having drunk more than 3 cups of coffee per day during pregnancy.

Significant associations between alcoholic beverage consumption during pregnancy and childhood leukemia, of comparable strengths, were found for ALL and ANLL (OR=2.0 [1.4-3.0] and OR=2.6 [1.2-5.8], respectively). Even higher ORs were observed for children less than 2 years old at diagnosis (OR=5.1 [1.5-17.5]). The estimates were almost the same depending on the type of alcohol consumed even if our results for spirits seemed slightly more pronounced in ALL (OR=1.8 [1.3-2.9]) than for wine (OR=1.4 [1.0-2.1]) or beer (OR=1.4 [0.9-2.3]).

Parental smoking

The same proportion (26%) of case and control mothers smoked during a period (any trimester) of pregnancy. The odds ratios were around 1.0, independently of the trimester of pregnancy, and did not vary with the number of cigarettes smoked daily. Seven percent of the case mothers and 8% of the control mothers reported having smoked 10 cigarettes or more daily during pregnancy. All smoking mothers smoked filter cigarettes of blond tobacco. The results are shown separately for ALL and ANLL in table 3, but did not differ for the two types of leukemia. Smoking during breastfeeding was less frequent than during pregnancy for both case and control mothers and was not associated with AL, ALL or ANLL (Table 4).

Paternal smoking was associated with AL neither before pregnancy (OR=0.9 [0.6-1.3]), nor during pregnancy (OR=1.0 [0.7-1.4]). Results were similar in ALL and ANLL.

Passive smoking during childhood is described in table 4. No association has been observed between ALL or ANLL and either paternal smoking after birth, passive smoking at home or passive smoking at nanny's home.

The odds ratios associated with maternal coffee drinking of at least 3 cups per day were of the same order of magnitude for smoker (2.7 [0.7-10.6]) and non-smoker (3.5 [1.6-7.4]) mothers.

Multivariate models

Adjustments for socio-professional category or educational level did not modify any of the above results. The odds ratios associated with alcohol and coffee drinking and parental smoking did not change after mutual adjustments. Lastly, inclusion of early infection history, breast-feeding, maternal history of fetal loss or familial history of cancer did not modify the results.

Discussion

The present study evidenced an association between maternal alcohol consumption and childhood leukemia, especially in children aged less than 2 years. The study also showed an association between maternal coffee consumption during pregnancy and both ANLL and ALL, with odds ratios that increased with the amount of coffee consumed. Any association with smoking, either maternal smoking during any trimester of pregnancy, or exposure to tobacco smoke during childhood has been observed.

The size of the present study enabled to detect minimum odds ratios of 1.6, 1.9 and 2.2 for exposure prevalences among controls of 20%, 10% and 5% respectively. These prevalences are in the order of magnitude of maternal smoking during pregnancy (25%) and maternal alcohol (36% for 1 glass/week) and coffee (12% for more than 4 cups/day) consumption during pregnancy.

The case and control mothers were very similar with respect to their education, activity, socio-economic status and smoking status. Thus, control selection is unlikely to explain the association with coffee and alcohol drinking. In addition, the results were unchanged after additional adjustment for both parents' socio-professional categories and educational levels. An information bias may have operated although the use of standardized questionnaires, and the similar interviewing conditions for case and control mothers, reduced potential differential misclassifications. Nevertheless, a recall bias cannot strictly ruled out, although there is no specific public concern about a possible role of maternal smoking or drinking in childhood leukemia or the control diseases. No controls admitted for a neonatal pathology directly related to maternal smoking or alcohol drinking was included.

The general feeling of guilt associated with smoking and alcohol drinking may be stronger in mothers of children with AL than in mothers of children hospitalized for less serious diseases. The recent UKCSS [19] findings support this hypothesis. Induced recall bias is likely to

influence the pattern of the relationships with the highest levels of consumption rather than the ever/never relationships. Such a bias seems unable to explain an absence of relationship with smoking. If the same guilt feeling had existed for coffee drinking during pregnancy, it would have tended to underestimate the association. Conversely, non-differential misclassifications with respect to the number of cigarettes smoked, or the quantities of coffee or alcohol consumed during pregnancy are likely to have occurred.

The maternal alcohol consumption during pregnancy was similar in the control group and in the national perinatal survey of 1998, based on a representative sample of 13718 deliveries [25]. Given the public concern with respect to alcohol, a non-differential underreporting of drinking is likely, and would probably be more marked for the quantities of alcohol drunk than for the ever/never variable. The questionnaire did not describe alcohol consumption by period of gestation. The results of the studies of alcohol consumption remain inconsistent. No association was reported by Van Steensel-Moll et al, Petridou et al and Schuz et al [1, 5-6]. Infante-Rivard et al. even observed an inverse association with ALL, but they also reported a positive association with maternal alcohol drinking during the second or third trimester of pregnancy with children with a null GSTM1 genotype or a CYP2E1*5 mutation [7]. Although very few in number, all the studies on AML evidenced a positive association with alcohol consumption [2-4], restricted to children younger than 3 years or M5 cases [2].

The association with maternal coffee drinking found in the present study is interesting, since Ross et al. have suggested that coffee may act as an inhibitor of DNA topoisomerase II and induce abnormalities of chromosome 11q23, resembling those induced by epipodophyllotoxins [9]. There was no confounding by the factors previously associated with AL in the present study and there is no obvious candidate for confounding, liable to increase the odds ratios with the number of cups drunk. To the best of the authors' knowledge, only 3 studies have investigated for an association between maternal coffee drinking and childhood leukemia [5, 8-9]. An association was reported by Ross et al., whose study was restricted to infantile leukemia, with elevated odds ratios associated with both ALL and ANLL [9].

Control mothers had similar smoking habits during their pregnancy to that of the population-based survey [25] (21% of smokers in controls vs 25% of smokers in the French population). The numbers of mothers smoking during pregnancy hardly changed from first trimester through to third trimester in both case and control mothers, as observed in other studies [17,19]. Lack of memory may have induced a non-differential underestimation of smoking during the first trimester of pregnancy. There are currently no arguments in support of an influence of maternal smoking during pregnancy on the risk of childhood leukemia and the present results are consistent with that fact. Most of the studies on childhood acute leukemia produced negative results [1-5, 10-19]. In only a few studies [26-28], was maternal smoking significantly associated with the risk of ALL. A dose-response relationship was observed in one of those studies [28]. A meta-analysis estimated the odds ratio for the association between childhood leukemia and maternal smoking to be 1.05 [0.82-1.34] [29]. Interestingly, Infante-Rivard et al. reported an association with maternal smoking restricted to children presenting with the CYP1A1*1 mutant genotype [16].

Data on paternal smoking were collected through maternal interview for both cases and controls, which may induce non-differential information bias. Missing values were few and in the same range for cases (1% to 6%) and controls (0.3% to 6%). In the literature, the role of paternal smoking during childhood has been much less investigated than the role of maternal smoking. Again, most of the studies are negative [4, 6, 12, 16, 19, 26, 30].

In conclusion, the present results suggest that maternal alcohol and coffee consumptions during pregnancy might be risk factors of childhood acute leukemia. Better understanding these associations, sparsely documented so far, is important for prevention purposes and need further investigations. The present study also provides additional evidences against a role of parental smoking in childhood leukemia.

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Table 1: Description of cases and controls

	Cases n=280		Controls n=288		p
Age (years) [1]					<0.01
< 2	33	(12%)	51	(18%)	
2-3	85	(30%)	53	(18%)	
4-6	83	(30%)	79	(27%)	
7-10	41	(15%)	63	(22%)	
≥ 11	38	(14%)	42	(15%)	
Gender[1]					ns
Male	166	(59%)	168	(58%)	
Hospital[1]					ns
Paris	182	(65%)	205	(71%)	
Lyon	36	(13%)	35	(12%)	
Lille	39	(14%)	26	(9%)	
Nancy	23	(8%)	22	(8%)	
Ethnic origin[1]					ns
Caucasian	259	(92%)	261	(91%)	
Caribbean	4	(1%)	5	(2%)	
African	2	(1%)	6	(2%)	
Asian, Middle Eastern	2	(1%)	6	(2%)	
Mixed, others	13	(5%)	10	(3%)	
Parental education					ns
Mother > high school	90	(32%)	108	(38%)	
Father > high school	87	(32%)	99	(37%)	
Maternal occupational activity at time of interview					ns
Yes *vs*. No	173	(62%)	191	(67%)	
Parental socio-professional category at time of interview[2]					ns
Professional, technical workers Administrators, managers	147	(52%)	160	(56%)	
Clerical, sales and services workers	55	(20%)	49	(17%)	
Factory and agricultural workers	78	(28%)	76	(27%)	
missing	0		3		

[1] Stratification variables; [2] Highest of mother's and father's categories

Table 2: Maternal coffee, tea and alcohol consumption during pregnancy

	ALL						ANLL					
	Cases (n=240)		Controls (n=288)		**OR[1]**	**95% CI**	Cases (n=40)		Controls (n=288)		**OR[1]**	**95% CI**
Maternal coffee drinking during pregnancy												
Never	50	(21%)	71	(25%)	**1.0**	Ref.	6	(15%)	71	(25%)	**1.0**	Ref.
≤ 3 cups/d	137	(57%)	180	(63%)	**1.1**	[0.7-1.8]	25	(63%)	180	(63%)	**1.6**	[0.6-4.3]
4-8 cups/d	41	(17%)	29	(10%)	**2.4**	[1.3-4.7]	8	(20%)	29	(10%)	**2.8**	[0.7-10.4]
> 8 cups/d	12	(5%)	7	(2%)	**3.1**	[1.0-9.5]	1	(3%)	7	(2%)	**3.0**	[0.3-35.1]
missing	0		1				0		1			
Maternal tea drinking during pregnancy												
Never	104	(44%)	138	(48%)	**1.0**	Ref.	25	(63%)	138	(48%)	**1.0**	Ref.
≤ 3 cups/d	117	(49%)	131	(45%)	**1.2**	[0.8-1.9]	15	(38%)	131	(45%)	**0.6**	[0.3-1.4]
> 3 cups/d	18	(8%)	19	(7%)	**1.2**	[0.6-2.6]	0	(0%)	19	(7%)	**-**	-
missing	1		0				0		0			
Alcohol during pregnancy												
Never	87	(36%)	144	(50%)	1.0	Ref.	12	(30%)	144	(50%)	1.0	Ref.
Ever	153	(64%)	143	(50%)	2.0	[1.4-3.0]	28	(70%)	143	(50%)	2.6	[1.2-5.8]
missing	0		1				0		1			
Wine (Ever *vs* never)	99	(41%)	97	(34%)	1.4	[1.0-2.1]	15	(38%)	97	(34%)	1.4	[0.7-3.0]
Beer (Ever *vs* never)	45	(16%)	45	(16%)	1.4	[0.9-2.3]	5	(13%)	45	(16%)	0.7	[0.3-2.1]
Spirits (Ever *vs* never)	92	(38%)	71	(25%)	1.8	[1.3-2.9]	14	(35%)	71	(25%)	1.4	[0.7-3.1]
Daily alcohol consumption during pregnancy												
Never	87	(36%)	144	(50%)	1.0	Ref.	12	(30%)	144	(50%)	1.0	Ref.
1 glass/week	103	(43%)	103	(36%)	2.0	[1.3-3.0]	21	(53%)	103	(36%)	2.8	[1.2-6.6]
2 glasses/week	25	(10%)	14	(5%)	2.8	[1.3-6.0]	7	(18%)	39	(14%)	2.4	[0.8-7.1]
≥ 3 glasses/week	25	(10%)	25	(9%)	1.9	[0.9-3.5]						
missing	0		2				0		2			

[1] Odds ratios estimated by unconditional logistic regression including age, gender, center, origin

Table 3: Exposure to maternal smoking during pregnancy

	ALL						ANLL					
	Cases (n=240)		Controls (n=288)		**OR[1]**	**95% CI**	Cases (n=40)		Controls (n=288)		**OR[1]**	**95% CI**
Maternal smoking during pregnancy												
Never	177	(74%)	212	(74%)	1.0	Ref.	30	(73%)	212	(74%)	1.0	Ref.
Ever	62	(26%)	76	(26%)	0.9	[0.6-1.4]	10	(24%)	76	(26%)	1.0	[0.4-2.3]
missing	1		0				0		0			
Period of smoking												
First trimester vs never	59	(25%)	64	(23%)	1.0	[0.7-1.6]	8	(21%)	64	(23%)	0.9	[0.4-2.2]
Second trimester vs never	54	(23%)	59	(21%)	1.0	[0.6-1.6]	7	(18%)	59	(21%)	0.9	[0.3-2.2]
Third trimester vs never	51	(21%)	58	(21%)	1.0	[0.6-1.5]	7	(18%)	58	(21%)	0.9	[0.3-2.3]
Daily cigarette consumption during pregnancy												
Never	177	(74%)	212	(76%)	1.0	Ref.	30	(79%)	212	(76%)	1.0	Ref.
< 5 cig/d	22	(9%)	23	(8%)	0.9	[0.5-1.8]	4	(11%)	23	(8%)	1.5	[0.4-5.0]
5- 9 cig/d	19	(8%)	23	(8%)	0.8	[0.4-1.6]	4	(11%)	23	(8%)	1.4	[0.4-4.8]
≥ 10 cig/d	20	(8%)	21	(8%)	1.3	[0.7-2.7]	0	(0%)	21	(8%)	-	-
missing	2		9				2		9			

[1] Odds ratios estimated by unconditional logistic regression including age, gender, center, origin

Table 4: Passive smoking during childhood

	ALL						ANLL					
	Cases (n=240		Controls (n=288		**OR[1]**	**95% CI**	Cases (n=40		Controls (n=288		**OR[1]**	**95% CI**
Exposure to maternal smoking during breast feeding[2]												
Never	127	(89%)	146	(85%)	**1.0**	Ref.	19	(86%)	146	(85%)	**1.0**	Ref.
Ever	15	(11%)	26	(15%)	**0.7**	[0.3-1.5]	3	(14%)	26	(15%)	**1.0**	[0.3-4.1]
Maternal smoking from birth to interview												
Never	139	(59%)	168	(60%)	**1.0**	Ref.	24	(60%)	168	(60%)	**1.0**	Ref.
Ever	97	(41%)	110	(40%)	**1.1**	[0.7-1.6]	14	(37%)	110	(40%)	**1.0**	[0.5-2.1]
< 10 cig/d	29	(12%)	34	(12%)	**1.0**	[0.6-1.8]	7	(18%)	34	(12%)	**1.6**	[0.6-4.3]
10-19 cig/d	39	(17%)	37	(13%)	**1.4**	[0.8-2.3]	5	(13%)	37	(13%)	**1.1**	[0.4-3.1]
≥ 20 cig/d	29	(12%)	39	(14%)	**0.6**	[0.5-1.6]	2	(5%)	39	(14%)	**0.4**	[0.1-2.0]
missing	4		10				2		10			
Paternal smoking during childhood from birth to interview												
Never	121	(52%)	142	(53%)	**1.0**	Ref.	18	(49%)	142	(49%)	**1.0**	Ref.
Ever	111	(48%)	128	(47%)	**1.1**	[0.7-1.5]	19	(51%)	128	(44%)	**1.3**	[0.6-2.7]
< 10 cig/d	16	(7%)	22	(8%)	**0.9**	[0.4-1.9]	3	(8%)	22	(8%)	**0.9**	[0.2-3.8]
10-19 cig/d	30	(13%)	34	(13%)	**1.2**	[0.7-2.2]	8	(22%)	34	(12%)	**2.0**	[0.8-5.2]
≥ 20 cig/d	65	(28%)	72	(27%)	**1.0**	[0.7-1.6]	8	(22%)	72	(25%)	**1.0**	[0.4-2.7]
missing	8		18				3		18			
Passive smoking at home												
Never smoky	152	(63%)	182	(65%)	**1.0**	Ref	26	(67%)	182	(65%)	**1.0**	Ref
Sometimes smoky	63	(26%)	66	(24%)	**1.2**	[0.8-1.9]	10	(26%)	66	(24%)	**1.4**	[0.6-3.2]
Often smoky	23	(10%)	31	(11%)	**0.9**	[0.5-1.8]	3	(8%)	31	(11%)	**0.7**	[0.2-2.8]
missing	2		9				1		6			
Passive smoking at nanny's home[3]												
Never exposed	88	(75%)	87	(75%)	**1.0**	Ref.	15	(79%)	87	(75%)	**1.0**	Ref.
Sometimes smoky	20	(17%)	24	(21%)	**0.9**	[0.4-1.8]	3	(16%)	24	(21%)	**0.7**	[0.1-3.2]
Often smoky	9	(8%)	5	(4%)	**1.8**	[0.5-6.1]	1	(5%)	5	(4%)	**0.5**	[0.02-9.5]

[1] Odds ratios estimated by unconditional logistic regression including age, gender, center, origin [2] Among children who were breastfed [3] Among children who received childcare