American Journal of Epidemiology
Published by the Johns Hopkins Bloomberg School of Public Health 2008.

Vol. 168, No. 6
DOI: 10.1093/aje/kwn186
Advance Access publication July 30, 2008

Original Contribution

First-Trimester Maternal Alcohol Consumption and the Risk of Infant Oral Clefts in Norway: A Population-based Case-Control Study

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Received for publication November 25, 2007; accepted for publication May 22, 2008.

Although alcohol is a recognized teratogen, evidence is limited on alcohol intake and oral cleft risk. The authors examined the association between maternal alcohol consumption and oral clefts in a national, population-based case-control study of infants born in 1996–2001 in Norway. Participants were 377 infants with cleft lip with or without cleft palate, 196 with cleft palate only, and 763 controls. Mothers reported first-trimester alcohol consumption in self-administered questionnaires completed within a few months after delivery. Logistic regression was used to calculate odds ratios and 95% confidence intervals, adjusting for confounders. Compared with nondrinkers, women who reported binge-level drinking ($\geq$5 drinks per sitting) were more likely to have an infant with cleft lip with or without cleft palate (odds ratio = 2.2, 95% confidence interval: 1.1, 4.2) and cleft palate only (odds ratio = 2.6, 95% confidence interval: 1.2, 5.6). Odds ratios were higher among women who binged on three or more occasions: odds ratio = 3.2 for cleft lip with or without cleft palate (95% confidence interval: 1.0, 10.2) and odds ratio = 3.0 for cleft palate only (95% confidence interval: 0.7, 13.0). Maternal binge-level drinking may increase the risk of infant clefts.

alcohol drinking; cleft lip; cleft palate

Alcohol is a human teratogen that produces a range of effects depending on the timing of exposure and the amount of alcohol consumed (1). One of the best-described and most severe outcomes of heavy maternal drinking is fetal alcohol syndrome, characterized by a specific pattern of craniofacial malformations, prenatal and postnatal growth retardation, and central nervous system disorders (2). It is less clear that women's alcohol consumption during pregnancy is related to individual congenital malformations such as oral clefts (3). Cleft lip with or without cleft palate occurs in about 9–18 percent of infants with fetal alcohol syndrome but is not diagnostic of the syndrome (4).

Some evidence exists that women who drink alcohol during pregnancy are more likely than nondrinkers to have infants with facial clefts (5–8), but summarizing previous findings is hampered by different categories of drinks and time points of reference across studies. Few studies have examined binge-level drinking (7–10), usually defined as the consumption of five or more drinks per sitting (11). Maternal drinking is uncommon in some populations, and the small numbers of exposed women in many studies have made it difficult to assess this association.

In Norway and other Nordic countries, weekend binge drinking is a common pattern of alcohol consumption (12, 13). In a population-based survey, 25 percent of Norwegian women reported at least one binge drinking episode during early pregnancy (14). We examined the relation between maternal alcohol consumption, including binge-level drinking, and infant oral clefts in Norway by using a population-based case-control study.

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MATERIALS AND METHODS

Eligible cases were all newborn infants with orofacial cleft defects born in Norway in May 1996 to October 2001 and referred for surgical treatment. In Norway, all surgery for clefts is paid for by the government and takes place at one of two surgical centers (Oslo and Bergen). An infant with a cleft is routinely referred for surgery shortly after birth. Our study office was notified of all referrals, at which time a letter of invitation was sent to the family. We randomly selected controls (with a probability of about 4 per 1,000) from all livebirths recorded in the Medical Birth Registry of Norway from September 1996 to April 2001. Families of selected controls were mailed an invitation to participate. These infants served as controls for both cleft case groups, with control-case ratios of about 2:1 for cleft lip with or without cleft palate and 4:1 for cleft palate. Study materials were in Norwegian; mothers who did not speak Norwegian were excluded. The study was approved by the Norwegian Data Inspectorate, the Regional Medical Ethics Committee of Western Norway, and the Institutional Review Board of the US National Institute of Environmental Health Sciences. Parents provided informed consent.

Mothers completed a self-administered, mailed questionnaire on demographic characteristics, medical history, family history of clefts, cigarette smoking, alcohol consumption, and other exposures during pregnancy. Questions pertaining to maternal exposures and diet were asked specifically for the first 3 months of pregnancy, the relevant exposure period for early facial development. During this time period, the structures that form the embryonic lip and palate fuse: closure of the lip occurs during weeks 5 and 6 postconception, followed by closure of the palatal shelves during weeks 7–10 (15). Median time from the infant's delivery to the mother's completion of the main questionnaire was 14 weeks for cases and 15 weeks for controls. After returning the main questionnaire, mothers completed a quantitative food frequency questionnaire (16–18) on dietary habits during the first 3 months of pregnancy, including the types of alcoholic beverages (beer, wine, and liquor) consumed. The study questionnaires (with English translations) are available online at http://www.niehs.nih.gov/research/atniehs/labs/epi/studies/ncl/question.cfm.

Information on noncleft birth defects was collected from three sources: the mother's questionnaire, the infant's medical records at the time of cleft repair surgery, and the Medical Birth Registry, which contains information from the infant's delivery records and hospital records during the first week of life. Cases with any accompanying birth defect or syndrome were categorized as nonisolated.

Information on maternal alcohol consumption was collected for the first 3 months of pregnancy and the time period before the pregnancy. Mothers were asked to recall the average number of days per week or month they drank alcohol, and the average number of drinks consumed on each occasion. Total number of drinking days in the first trimester was estimated by extrapolating weekly or monthly drinking frequency over the 3-month period. Total number of alcoholic beverages consumed in the first trimester was estimated by multiplying the total number of drinking days by the average number of drinks per occasion. Categorical variables were used to summarize total drinks (1–3, 4–6, $\geq$7), number of drinking days (1–2, 3–6, $\geq$7), and average number of drinks per occasion (1, 2–4, $\geq$5) in the first trimester. The categories were defined to ensure adequate case numbers within categories and to capture binge-level drinking (defined as an average of $\geq$5 drinks per sitting.) An additional categorical variable was used to examine number of drinks and frequency of consumption simultaneously: one to four drinks on one to two occasions, one to four drinks on three or more occasions, five or more drinks on one to two occasions, and five or more drinks on three or more occasions. Nondrinkers served as the referent group for all measures of first-trimester alcohol exposure.

We calculated odds ratios and 95 percent confidence intervals for the associations between infant clefts and maternal alcohol consumption. Because cleft outcomes are rare, the odds ratios are close approximations of risk ratios and can be interpreted as such. We conducted separate analyses of cleft lip with or without cleft palate, and cleft palate only. We calculated separate estimates for infants with isolated and with nonisolated cleft defects. Multivariable logistic regression models were used to estimate odds ratios adjusted for child's year of birth, mother's age group ($<$25, 25–29, 30–34, $\geq$35 years), education (less than high school, high school, technical college, 2–4-year college, university), first-trimester smoking (none; passive only; active, 1–5 cigarettes per day; active, 6–10 cigarettes per day; active, $\geq$11 cigarettes per day), household per capita income ($\leq$50,000, 50,001–75,000, 75,001–100,000, 100,001–150,000, $\geq$150,001 kroner), and family history of clefts among parents or grandparents (yes/no). Dummy variables were used for variables with more than two levels. Further adjustment for mother's marital status, parity, employment during the first trimester, folic acid supplement use, dietary folate, multivitamin use, and prepregnancy body mass index did not substantially change the estimates.

We explored the possible effect of heavy drinking before the pregnancy by restricting analysis to mothers who drank an average of five or more alcoholic beverages per sitting before pregnancy but reported no drinking during pregnancy. We calculated the risk of infant clefts among these women compared with women who abstained from drinking alcohol both before and during their pregnancies.

Pearson chi-square tests were used to compare the percentages of beer, wine, and liquor drinkers among the women who reported an average of five or more drinks per sitting and those who reported four or fewer. To assess possible differences in infant cleft risk by the type(s) of alcohol the mothers consumed, separate multivariable logistic regression models were conducted to examine beer/wine consumption (alone or in combination) and liquor consumption (alone or in combination with beer or wine).

RESULTS

Participants

There were 676 infants referred for orofacial cleft surgery during the study recruitment period (May 1996–October 2001). Excluding 24 mothers who did not speak Norwegian

TABLE 1. Characteristics of mothers of cases and controls and of their infants studied regarding first-trimester alcohol consumption and oral clefts, Norway, 1996–2001

	Cases				Controls ($n = 763$)	
	Cleft lip with or without cleft palate ($n = 377$)		Cleft palate only ($n = 196$)			
	No.	%	No.	%	No.	%
Current marital status						
Married	182	48	91	47	405	53
Living as married	177	47	96	49	329	43
Single*	18	5	8	4	28	4
Missing	0		1		1	
Maternal age (years)						
<25	71	19	36	18	125	16
25–29	136	36	75	38	295	39
30–34	120	32	55	28	231	30
≥35	50	13	30	15	112	15
Parity						
1	151	40	88	45	292	38
2	138	37	63	32	290	38
3	63	17	36	18	132	17
≥4	25	7	9	5	49	6
Education						
<High school	71	19	23	12	87	11
High school	94	25	48	25	211	28
Technical college	69	18	41	21	153	20
2–4-year college	124	33	72	37	265	35
University	19	5	12	6	46	6
Missing	0		0		1	
Employment†						
Yes	287	76	155	79	634	83
Missing	1		1		0	
Cigarette smoking†						
No exposure	152	40	92	47	414	54
Passive only	58	15	32	16	106	14
Active, 1–5 cigarettes/day	93	25	36	18	142	19
Active, 6–10 cigarettes/day	49	13	31	16	73	10
Active, ≥11 cigarettes/day	25	7	5	3	28	4
Total no. of alcoholic beverages consumed†						
0	230	62	120	61	527	70
1–3	70	19	37	19	123	16
4–6	26	7	17	9	40	5
≥7	45	12	22	11	68	9
Missing	6		0		5	
No. of drinking days†						
0	230	61	120	61	527	69
1–2	104	28	54	28	164	21
3–6	24	6	14	7	30	4
≥7	19	5	8	4	42	6

Table continues

or whose infants died after birth left 652 eligible mothers of cases. Of these, 573 (88 percent) agreed to participate (377 infants with cleft lip with or without cleft palate, 196 with cleft palate only). A total of 1,022 controls were randomly selected within 6 weeks of their deliveries in September 1996–April 2001. After excluding 16 mothers who did not speak Norwegian or whose infants had died, 1,006 mothers of controls were eligible, of whom 763 (76 percent) agreed to participate.

Ninety-five percent of mothers were married or living as married (table 1). The mean age of mothers was 29 years, and about 40 percent were primiparous. Thirty percent of mothers of controls reported drinking alcohol during the

TABLE 1. Continued

	Cases				Controls ($n = 763$)	
	Cleft lip with or without cleft palate ($n = 377$)		Cleft palate only ($n = 196$)			
	No.	%	No.	%	No.	%
Average no. of drinks per sitting†						
0	230	62	120	61	527	69
1	64	17	41	21	126	17
2–4	52	14	23	12	81	11
≥5	25	7	12	6	24	3
Missing	6		0		5	
Average no. of drinks per sitting/no. of drinking days†						
Nondrinker	230	62	120	61	527	69
1–4 drinks/1–2 days	84	23	45	23	143	19
1–4 drinks/≥3 days	32	9	19	10	64	8
≥5 drinks/1–2 days	15	4	9	5	17	2
≥5 drinks/≥3 days	10	3	3	2	7	1
Missing	6		0		5	
Folic acid supplement (mcg)‡						
No supplement	240	64	119	61	453	59
1–399	86	23	46	23	165	22
≥400	51	14	31	16	145	19
Dietary folate (mcg) quartile†						
0–171	111	31	62	33	176	25
172–214	88	25	44	23	177	25
215–264	81	23	36	19	177	25
≥265	74	21	46	24	174	25
Missing	23		8		59	
Used multivitamins§	123	33	71	36	279	37
Prepregnancy body mass index						
Underweight	15	4	10	5	28	4
Normal	256	68	126	65	533	70
Overweight	67	18	47	24	144	19
Obese	36	10	11	6	54	7
Missing	3		2		4	
Household per capita income (kroner)						
≤50,000	42	11	17	9	73	10
50,001–75,000	67	18	28	15	110	15
75,001–100,000	81	22	41	21	161	21
100,001–150,000	107	29	76	39	273	36
≥150,001	69	19	31	16	136	18
Missing	11		3		10	
Infant's parent or grandparent had an oral cleft						
Yes	31	8	17	9	8	1
Missing	6		2		8	
Infant had a noncleft birth defect	63	17	78	40	38	5

* Includes never married, divorced, and separated.

† During the first 3 months of pregnancy.

‡ Any intake of folic acid supplements (either alone or with multivitamins) during the month prior to pregnancy and the first 2 months of pregnancy.

§ Intake during the month prior to pregnancy and the first 2 months of pregnancy.

first trimester, with a median of three drinks total (range, 1.5–780 drinks); 3 percent reported binge-level drinking of an average of five or more drinks per occasion.

Among the cases, noncleft birth defects were present in 17 percent of infants with cleft lip with or without cleft palate and 40 percent of infants with cleft palate only.

The associations between cleft defects and maternal alcohol consumption did not differ substantially by the presence of noncleft defects (appendix table 1), and we therefore present the results for isolated and nonisolated clefts combined.

Maternal alcohol consumption in the first trimester

Total drinks and number of drinking days. There were no clear patterns of increased infant cleft risk for categories of total drinks or number of drinking sessions (table 2). Mothers who drank between four and six drinks total were twice as likely as nondrinkers to have an infant with cleft palate (odds ratio = 2.0, 95 percent confidence interval: 1.1, 3.7), but risk declined with seven or more drinks. For both cleft types, odds ratios rose among women who reported 1–2 or 3–6 drinking days, but they decreased among those who drank on 7 or more days.

Average drinks per sitting. Women who reported drinking five or more drinks per occasion were more than twice as likely to have an infant with either of the cleft types: for cleft lip with or without cleft palate, odds ratio = 2.2 (95 percent confidence interval: 1.1, 4.2); for cleft palate only, odds ratio = 2.6 (95 percent confidence interval: 1.2, 5.6) (table 2). The odds ratios ranged from 1.1 to 1.6 for lower levels of alcohol consumption.

Average drinks per sitting by drinking days. Odds ratios for mothers who consumed an average of five or more drinks per sitting during one or two drinking days were 1.8 (95 percent confidence interval: 0.8, 4.0) for infant cleft lip with or without cleft palate and 2.5 (95 percent confidence interval: 1.0, 6.0) for cleft palate only (table 2). The odds ratios were further increased among women who drank this amount on three or more occasions: for cleft lip with or without cleft palate, odds ratio = 3.2 (95% confidence interval: 1.0, 10.2) and cleft palate only, odds ratio = 3.0 (95 percent confidence interval: 0.7, 13.0).

Binge-level drinking before pregnancy. Among the women who drank an average of five or more drinks per occasion before pregnancy, two thirds reported no alcohol consumption during the first trimester of pregnancy. These women showed no evidence of increased risk of infant clefts compared with women who reported no alcohol consumption before or during their pregnancies (table 3). Those who continued to drink during the first trimester but reduced the amount to one to four drinks per sitting also showed little evidence of increased risk of clefts in their offspring. Odds ratios were increased, however, among the women who maintained binge-level drinking of an average of five or more drinks per occasion in the first trimester.

Types of alcoholic beverages consumed. The types of alcohol consumed were available for 69 percent of the mothers who drank an average of five or more drinks per session and 80 percent of the other drinkers. A higher percentage of the binge-level drinkers reported consuming liquor compared with the lighter drinkers (36 percent vs. 14 percent; chi-square $p < 0.001$), whereas a lower percentage reported drinking wine (52 percent vs. 70 percent; chi-square $p = 0.005$). The percentage of beer drinkers was the same for the two groups (54 percent). Infant cleft risk did not appear to differ for beer/wine and liquor drinkers, but small numbers of women in some drinking categories precluded a definite conclusion (appendix table 2).

DISCUSSION

We found increased risks of orofacial clefts among infants whose mothers reported binge-level drinking of an average of five or more drinks per occasion during the first trimester compared with nondrinkers. Risk was further increased for women who drank at this level most frequently. The evidence was weaker for increased risk of infant clefts at lower levels of maternal alcohol consumption. The risk for women who reported habitual binge-level drinking before their pregnancies but who reduced or stopped drinking during their pregnancies was similar to that for women who abstained before and during pregnancy. The higher percentage of liquor drinkers and lower percentage of wine drinkers among women who drank at binge levels compared with the other drinkers may reflect greater alcohol dependence or different social patterns of drinking among heavy drinkers.

Associations were weaker when measuring alcohol consumption as total drinks or number of drinking days. Both animal and human studies suggest that the dose of alcohol consumed per episode, rather than the frequency or total amount over time, is the most relevant alcohol measurement for assessing potential adverse fetal outcomes (11). Maternal binge drinking may be particularly harmful because it results in greater peak blood alcohol concentrations and prolonged fetal alcohol exposure compared with drinking fewer drinks over more occasions (19). The body's rate of alcohol metabolism remains relatively constant regardless of the amount of alcohol consumed. The greater the blood alcohol concentration, the longer it takes to clear the alcohol, resulting in longer fetal exposure (19). The crucial stages of embryonic development for lip and palate are relatively brief. Even a single binge episode at the crucial time would presumably be enough to result in harm.

Strengths of this study include the virtually complete ascertainment of cleft cases drawn from a large, well-defined population; the high participation rate among mothers of cases (88 percent); and the clinical confirmation of cleft malformations. The participation rate for controls was lower (76 percent), although with the advantage of being drawn from a random sample of the entire population of births. The study collected extensive data on relevant maternal characteristics assessed as potential confounders.

This study has some possible limitations that should be considered. We relied on retrospective self-report of alcohol consumption, which is generally considered less valid than concurrent reports. Some studies, however, have shown that mothers' recall of prenatal alcohol consumption after pregnancy revealed greater intake than concurrent reports (20, 21), perhaps because it was easier for women to disclose socially sensitive behavior when it occurred in the past. This situation was found in Norway, where Alvik et al. (22) reported that women tended to report less drinking when asked during pregnancy than when asked about the same period later in the pregnancy or 6 months postnatally. Self-administered questionnaires tend to reveal greater consumption of alcohol than interview-administered

TABLE 2. Association between maternal alcohol consumption during the first trimester and risk of infant clefts, Norway, 1996–2001

Maternal alcohol consumption in the first trimester	Cleft lip with or without cleft palate ($n = 377$)				Cleft palate only ($n = 196$)			
	Crude		Adjusted*		Crude		Adjusted*	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI
Total no. of drinks								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–3	1.3	0.9, 1.8	1.2	0.9, 1.8	1.3	0.9, 2.0	1.4	0.9, 2.2
4–6	1.5	0.9, 2.5	1.4	0.8, 2.4	1.9	1.0, 3.4	2.0	1.1, 3.7
≥7	1.5	1.0, 2.3	1.2	0.8, 1.9	1.4	0.8, 2.4	1.5	0.9, 2.7
Test for linear trend			$p = 0.99$				$p = 0.81$	
No. of drinking days								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–2	1.5	1.1, 1.9	1.4	1.0, 1.9	1.4	1.0, 2.1	1.5	1.0, 2.3
3–6	1.8	1.1, 3.2	1.6	0.9, 2.9	2.1	1.1, 4.0	2.4	1.2, 4.8
≥7	1.0	0.6, 1.8	0.8	0.4, 1.5	0.8	0.4, 1.8	0.9	0.4, 2.0
Test for linear trend			$p = 0.13$				$p = 0.21$	
Average no. of drinks per sitting								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1	1.2	0.8, 1.6	1.1	0.8, 1.6	1.4	1.0, 2.1	1.6	1.0, 2.4
2–4	1.5	1.0, 2.2	1.2	0.8, 1.8	1.3	0.8, 2.1	1.3	0.8, 2.2
≥5	2.4	1.3, 4.3	2.2	1.1, 4.2	2.2	1.1, 4.5	2.6	1.2, 5.6
Test for linear trend			$p = 0.07$				$p = 0.23$	
Average no. of drinks per sitting/no. of drinking days								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–4 drinks/1–2 days	1.4	1.0, 1.8	1.3	0.9, 1.8	1.4	0.9, 2.0	1.5	1.0, 2.2
1–4 drinks/≥3 days	1.2	0.7, 1.8	0.9	0.6, 1.6	1.3	0.8, 2.3	1.4	0.8, 2.6
≥5 drinks/1–2 days	2.0	1.0, 4.1	1.8	0.8, 4.0	2.3	1.0, 5.3	2.5	1.0, 6.0
≥5 drinks/≥3 days	3.3	1.2, 8.7	3.2	1.0, 10.2	1.9	0.5, 7.4	3.0	0.7, 13.0
Test for linear trend			$p = 0.06$				$p = 0.26$	

* Adjusted for child's year of birth, mother's age group, prenatal smoking, education, household income, and family history of clefts.

† OR, odds ratio; CI, confidence interval.

questionnaires (23), suggesting that our data collection methods were appropriate for prenatal alcohol consumption.

Mothers of controls may be more likely than mothers who have an affected child to admit drinking alcohol during pregnancy after giving birth to a healthy infant. This possibility would tend to underestimate the association between maternal prenatal alcohol consumption and infant clefts. Conversely, the effect may have been overestimated if mothers of cases were more likely to remember past drinking, perhaps in an effort to explain the occurrence of the malformation. In a prospective study, Verkerk et al. (24) compared concurrent and retrospective reports of alcohol consumption during pregnancy among women whose infants had congenital malformations and those who did not. The differences in reporting for the two groups did not substantially change risk estimates. Their findings suggest that recall bias may not have a large impact on effect estimates in studies using retrospective alcohol information; however, we cannot rule it out in our study.

Confounding is always a potential concern in observational studies, but we were able to adjust for confounders including mother's smoking, education, household income, and other important variables. Such adjustments tended to weaken the associations with cleft lip with or without cleft palate, whereas they strengthened the associations with cleft palate only (table 2). Further adjustment for other variables had little impact on the estimates.

Selection bias may have resulted if heavy drinkers selected as mothers of controls were less likely to participate in the study than heavy drinkers whose infants had clefts. Restriction of the analysis to mothers of cases and controls who were heavy drinkers before pregnancy led to the same general finding of increased infant cleft risk for the mothers who continued to drink at high levels in the first trimester,

TABLE 3. Risk of infant clefts among mothers who reported binge-level drinking before pregnancy compared with nondrinkers,* by first-trimester drinking status, Norway, 1996–2001

Average alcohol consumption before pregnancy	Average alcohol consumption during pregnancy	Cases		Controls		Unadjusted		Adjusted†	
		No.	%	No.	%	OR‡	95% CI‡	OR	95% CI
Cleft lip with or without cleft palate									
None	None	36	24	65	25	1.0	Referent	1.0	Referent
≥5 drinks per sitting	None	70	46	135	53	0.9	0.6, 1.5	0.9	0.4, 1.7
	<5 drinks	25	17	40	16	1.1	0.6, 2.2	0.8	0.4, 1.9
	≥5 drinks/1–2 sittings	10	7	10	4	1.8	0.7, 4.8	1.3	0.4, 4.2
	≥5 drinks/≥3 sittings	10	7	6	2	3.0	1.0, 9.0	3.6	0.9, 14.6
Cleft palate only									
None	None	26	31	65	25	1.0	Referent	1.0	Referent
≥5 drinks per sitting	None	36	42	135	53	0.7	0.4, 1.2	0.7	0.3, 1.5
	<5 drinks	14	17	40	16	0.9	0.4, 1.9	1.1	0.4, 3.0
	≥5 drinks/1–2 sittings	7	8	10	4	1.8	0.6, 5.1	2.2	0.6, 8.1
	≥5 drinks/≥3 sittings	2	2	6	2	0.8	0.2, 4.4	1.7	0.2, 12.6

* The referent group consisted of mothers who abstained from alcohol both before and during the first trimester (cases: $n = 62$; controls: $n = 65$).

† Adjusted for child's year of birth, mother's age group, prenatal smoking, education, household income, and family history of clefts.

‡ OR, odds ratio; CI, confidence interval.

giving some reassurance that differential participation was not responsible for the results in the full analysis.

The structure of our questionnaire did not enable us to measure the number of binge drinking episodes or to capture sporadic binge drinking (defined as periods of no or little drinking punctuated by episodes of drinking large quantities of alcohol) (11). When answering our alcohol consumption questions, a woman who drank one alcoholic beverage a day during 6 drinking days and had one binge episode of eight drinks would have reported an average consumption of two drinks per sitting (14 drinks total/seven sittings). The women who make up our category of an average of five or more drinks per occasion are therefore probably a mixture of chronic heavy drinkers and episodic binge drinkers. This group experienced a high level of alcohol consumption on average, but we were unable to assess in more detail the effect of periodic binge drinking. Missing data in the food frequency questionnaire on the types of alcoholic beverages the mothers consumed hindered our ability to assess infant cleft risk by alcohol type. We were also unable to determine the type(s) of alcohol consumed specifically during binge drinking episodes, if that differed from usual drinking. Respondents may have miscalculated average drinks per sitting (and underreported consumption) if they interpreted the question as usual (modal rather than mean) number of drinks and did not incorporate drinks consumed during atypical drinking sessions (25). We would not expect this factor to differ for mothers of cases and controls.

Previous studies on maternal alcohol consumption and infant clefts have reported conflicting results (5–10, 26–28) probably in part because of differences in ascertaining and classifying subjects, measuring the amount and timing of exposure, and evaluating confounders. All of the previous studies used case-control designs, although Bille et al. (27) conducted a case-control study nested within a cohort, thus avoiding recall bias by collecting exposure information prospectively. Their results based on 192 cases suggested an increased risk of infant cleft lip (odds ratio = 1.48, 95 percent confidence interval: 0.68, 3.19) and cleft palate (odds ratio = 1.36, 95 percent confidence interval: 0.45, 4.15) among women who drank three or more drinks per week, but the confidence limits were wide.

Our findings are consistent with four studies reporting risks ranging from 2.8 to 4.0 for cleft lip with or without cleft palate among mothers in the highest drinking categories (ranging from ≥4 drinks per month to ≥5 drinks per drinking day) (5–8). Some studies reported increased risks of infant cleft palate among women in the highest drinking categories, although a lack of power limits their interpretation (5, 6, 28). Four previous papers examined binge-level drinking. Two studies used the same definition of binge drinking as ours (average of ≥5 drinks per sitting), and both reported threefold increases in cleft lip with or without cleft palate among the binge-level drinkers compared with nondrinkers but did not find increased risks for cleft palate (7, 8). The other two studies based their definition on the maximum number of drinks consumed at one sitting and categorized women who reported drinking a maximum of five or more drinks as binge drinkers. These studies did not find an increased risk of infant clefts among binge drinkers, but the women who drank a ''maximum'' of five or more drinks on any occasion may have consumed less alcohol than the women in our study who drank an average of five or more drinks per sitting (9, 10).

Many previous studies have examined isolated and nonisolated clefts separately, or only one or the other. We found little difference in our results for infants with isolated and nonisolated clefts. By studying the combined groups, we increased statistical power to detect associations. There has been debate in oral cleft research on whether cases with associated anomalies should be included in etiologic studies (29). Combining groups for analysis makes sense when the exposure of interest may be an etiologic factor in both nonsyndromic and syndromic cases. This seems likely for alcohol, which may act through different mechanisms to cause a variety of teratogenic effects. Besides oral clefts, children diagnosed with fetal alcohol syndrome often have other anomalies suspected to be related to alcohol exposure, including those of the limb and joints, heart, kidney, and reproductive organs (30).

In summary, our findings suggest that maternal binge-level drinking (an average of $\geq$5drinks per occasion) in the first trimester increases the risk of infant oral clefts. These data on possible further teratogenic effects of alcohol reinforce the public health message that women should not drink alcohol during pregnancy.

ACKNOWLEDGMENTS

This research was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences.

Conflict of interest: none declared.

REFERENCES

1. Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. JAMA 2003;290:2996–9.
2. Clarren SK, Smith DW. The fetal alcohol syndrome. N Engl J Med 1978;298:1063–7.
3. Wyszynski DF, Beaty TH. Review of the role of potential teratogens in the origin of human nonsyndromic oral clefts. Teratology 1996;53:309–17.
4. Abel EL. Craniofacial anomalies. Fetal alcohol abuse syndrome. New York, NY: Plenum Press, 1998:71–87.
5. Munger RG, Romitti PA, Daack-Hirsch S, et al. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996;54:27–33.
6. Romitti PA, Lidral AC, Munger RG, et al. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts. Teratology 1999;59:39–50.
7. Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. J Pediatr 1999;134:298–303.
8. Werler MM, Lammer EJ, Rosenberg L, et al. Maternal alcohol use in relation to selected birth defects. Am J Epidemiol 1991;134:691–8.
9. Meyer KA, Werler MM, Hayes C, et al. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study. Birth Defects Res A Clin Mol Teratol 2003;67:509–14.
10. Romitti PA, Sun L, Honein MA, et al. Maternal periconceptional alcohol consumption and risk of orofacial clefts. Am J Epidemiol 2007;166:775–85.
11. Gladstone J, Nulman I, Koren G. Reproductive risks of binge drinking during pregnancy. Reprod Toxicol 1996;10:3–13.
12. Brathen G, Brodtkorb E, Sand T, et al. Weekday distribution of alcohol consumption in Norway: influence on the occurrence of epileptic seizures and stroke? Eur J Neurol 2000;7:413–21.
13. Makela P, Fonager K, Hibell B, et al. Episodic heavy drinking in four Nordic countries: a comparative survey. Addiction 2001;96:1575–88.
14. Alvik A, Heyerdahl S, Haldorsen T, et al. Alcohol use before and during pregnancy: a population-based study. Acta Obstet Gynecol Scand 2006;85:1292–8.
15. Diewert VM. Development of human craniofacial morphology during the late embryonic and early fetal periods. Am J Orthod 1985;88:64–76.
16. Andersen LF, Solvoll K, Drevon CA. Very-long-chain n-3 fatty acids as biomarkers for intake of fish and n-3 fatty acid concentrates. Am J Clin Nutr 1996;64:305–11.
17. Andersen LF, Solvoll K, Johansson LR, et al. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999;150:75–87.
18. Nes M, Frost Andersen L, Solvoll K, et al. Accuracy of a quantitative food frequency questionnaire applied in elderly Norwegian women. Eur J Clin Nutr 1992;46:809–21.
19. Maier SE, West JR. Drinking patterns and alcohol-related birth defects. Alcohol Res Health 2001;25:168–74.
20. Ernhart CB, Morrow-Tlucak M, Sokol RJ, et al. Underreporting of alcohol use in pregnancy. Alcohol Clin Exp Res 1988;12:506–11.
21. Jacobson SW, Jacobson JL, Sokol RJ, et al. Maternal recall of alcohol, cocaine, and marijuana use during pregnancy. Neurotoxicol Teratol 1991;13:535–40.
22. Alvik A, Haldorsen T, Groholt B, et al. Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. Alcohol Clin Exp Res 2006;30:510–15.
23. Rogers SM, Miller HG, Turner CF. Effects of interview mode on bias in survey measurements of drug use: do respondent characteristics make a difference? Subst Use Misuse 1998;33:2179–200.
24. Verkerk PH, Buitendijk SE, Verloove-Vanhorick SP. Differential misclassification of alcohol and cigarette consumption by pregnancy outcome. Int J Epidemiol 1994;23:1218–25.
25. Stahre M, Naimi T, Brewer R, et al. Measuring average alcohol consumption: the impact of including binge drinks in quantity-frequency calculations. Addiction 2006;101:1711–18.
26. Beaty TH, Wang H, Hetmanski JB, et al. A case-control study of nonsyndromic oral clefts in Maryland. Ann Epidemiol 2001;11:434–42.
27. Bille C, Olsen J, Vach W, et al. Oral clefts and life style factors—a case-cohort study based on prospective Danish data. Eur J Epidemiol 2007;22:173–81.
28. Lorente C, Cordier S, Goujard J, et al. Tobacco and alcohol use during pregnancy and risk of oral clefts. Occupational Exposure and Congenital Malformation Working Group. Am J Public Health 2000;90:415–19.
29. Christensen K. Methodological issues in epidemiological studies of oral clefts. In: Wyszynski DF, ed. Cleft lip and palate: from origin to treatment. Oxford, United Kingdom: Oxford University Press, 2002:101–7.
30. Abel EL. Alcohol-abuse-related malformations. Fetal alcohol abuse syndrome. New York, NY: Plenum Press, 1998:89–99.

APPENDIX TABLE 1. Unadjusted associations between maternal alcohol consumption during the first trimester and isolated and nonisolated infant clefts, Norway, 1996–2001

Maternal alcohol consumption in the first trimester	Cleft lip with or without cleft palate				Cleft palate only			
	Isolated ($n = 314$)		Nonisolated ($n = 63$)		Isolated ($n = 118$)		Nonisolated ($n = 78$)	
	OR*	95% CI*	OR	95% CI	OR	95% CI	OR	95% CI
Total no. of drinks								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–3	1.3	0.9, 1.9	1.3	0.7, 2.6	1.1	0.6, 1.9	1.7	0.9, 3.0
4–6	1.5	0.8, 2.5	1.7	0.6, 4.5	2.0	1.0, 4.0	1.7	0.7, 4.3
≥7	1.5	1.0, 2.4	1.4	0.6, 3.2	1.5	0.8, 2.7	1.3	0.6, 3.0
No. of drinking days								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–2	1.4	1.1, 2.0	1.5	0.8, 2.7	1.2	0.8, 1.9	1.8	1.1, 3.0
3–6	1.9	1.1, 3.4	1.4	0.4, 4.6	2.6	1.3, 5.4	1.1	0.3, 3.9
≥7	1.0	0.6, 1.9	1.0	0.3, 3.3	0.9	0.3, 2.2	0.8	0.2, 2.7
Average no. of drinks per sitting								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1	1.2	0.9, 1.8	0.8	0.3, 1.7	1.4	0.8, 2.2	1.5	0.9, 2.8
2–4	1.3	0.9, 2.0	2.2	1.1, 4.2	1.2	0.7, 2.3	1.3	0.6, 2.7
≥5	2.4	1.3, 4.4	2.3	0.7, 6.8	1.8	0.7, 4.5	2.9	1.1, 7.4
Average no. of drinks per sitting/no. of drinking days								
None	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–4 drinks/1–2 days	1.3	0.9, 1.8	1.5	0.5, 4.4	1.2	0.7, 1.9	1.8	1.0, 3.0
1–4 drinks/≥3 days	1.2	0.8, 1.9	0.8	0.1, 5.4	1.7	0.9, 3.1	0.7	0.2, 2.2
≥5 drinks/1–2 days	2.1	1.0, 4.4	1.6	0.3, 21.0	2.1	0.8, 5.8	2.7	0.9, 8.3
≥5 drinks/≥3 days	3.1	1.1, 8.8	3.9	0.8, 19.2	1.0	0.1, 8.4	3.3	0.7, 16.2

* OR, odds ratio; CI, confidence interval.

APPENDIX TABLE 2. Association between type and amount of maternal alcohol consumption during the first trimester and the risk of infant clefts, Norway, 1996–2001

Average no. of drinks per sitting	Type of alcohol*	Cases		Controls		Unadjusted		Adjusted†	
		No.	%	No.	%	OR‡	95% CI‡	OR	95% CI
Cleft lip with or without cleft palate									
None	None	230	69	527	75	1.0	Referent	1.0	Referent
1–4 drinks	Beer/wine§	76	23	133	19	1.3	0.9, 1.8	1.3	0.9, 1.8
	Liquor plus¶	12	4	31	4	0.9	0.4, 1.8	0.6	0.3, 1.3
≥5 drinks	Beer/wine	6	2	9	1	1.5	0.5, 4.3	1.7	0.6, 5.2
	Liquor plus¶	10	3	7	1	3.3	1.2, 8.7	2.5	0.9, 7.4
Cleft palate only									
None	None	120	64	527	75	1.0	Referent	1.0	Referent
1–4 drinks	Beer/wine	50	27	133	19	1.7	1.1, 2.4	1.8	1.2, 2.8
	Liquor plus¶	7	4	31	4	1.0	0.4, 2.3	0.9	0.4, 2.3
≥5 drinks	Beer/wine	7	4	9	1	3.4	1.2, 9.4	4.9	1.7, 14.3
	Liquor plus¶	3	2	7	1	1.9	0.5, 7.4	1.8	0.4, 8.0
All clefts									
None	None	350	67	527	75	1.0	Referent	1.0	Referent
1–4 drinks	Beer/wine	126	24	133	19	1.4	1.1, 1.9	1.5	1.1, 2.0
	Liquor plus¶	19	4	31	4	0.9	0.5, 1.7	0.8	0.4, 1.4
≥5 drinks	Beer/wine	13	3	9	1	2.2	0.9, 5.1	2.5	1.0, 6.4
	Liquor plus¶	13	3	7	1	2.8	1.1, 7.1	2.3	0.8, 6.1

* Missing for 20% of women reporting 1–4 drinks per sitting and 31% of women reporting ≥5 drinks per sitting.

† Adjusted for child's year of birth, mother's age group, prenatal smoking, education, household income, and family history of clefts.

‡ OR, odds ratio; CI, confidence interval.

§ Beer or wine alone or in combination.

¶ Liquor alone or in combination with beer or wine.