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## Original Contribution

# Maternal Periconceptional Alcohol Consumption and Risk of Orofacial Clefts

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Using data from the National Birth Defects Prevention Study, the authors investigated the association between maternal reports of periconceptional alcohol consumption and clefting. Cases with a cleft lip, cleft palate, or both and unaffected controls delivered from 1997 through 2002 were ascertained. Interview reports of alcohol consumption were obtained from 1,749 (75.1%) case and 4,094 (68.2%) control mothers. Adjusted odds ratios and 95% confidence intervals were calculated to assess associations. Compared with odds ratios for mothers with no reported consumption, those for mothers who consumed alcohol tended to be near to (cleft lip, cleft lip with cleft palate) or to exceed (cleft palate) unity. The odds ratios associated with binge drinking were elevated but did not demonstrate significantly increased risk for any phenotype; however, the odds ratios differed by the type of alcohol consumed, particularly for cleft palate (distilled spirits > wine > beer). These odds ratios were further increased among mothers with no reported folic acid intake. Although these findings suggest that the association between alcohol consumption and clefting might be most influenced by the type of beverage consumed and folic acid intake, they are preliminary and might reflect chance associations. Such findings need exploration in additional, large studies.

alcohol drinking; case-control studies; cleft lip; cleft palate; folic acid; pregnancy

Abbreviation: CDC, Centers for Disease Control and Prevention.

Orofacial clefts are common human malformations that comprise the phenotypes cleft lip, cleft palate, and cleft lip with cleft palate. Collectively, the prevalence of these phenotypes is estimated at one per 700 births, with variability identified by race/ethnicity (1). Within these phenotypes, patients can present with a cleft alone or in combination with additional malformations (2, 3), including those that comprise recognizable syndromes (4).

Identification of etiologic explanations for clefting has included extensive evaluation of genes (5, 6). Such efforts have largely been successful in identifying single-gene effects that contribute to recognized syndromes (7); however, an estimated 70 percent of deliveries with clefts occur as isolated defects or in combination with other malformations, but not part of a recognized syndrome (6). Animal studies have provided insights into both genetic and environmental risk factors for these ''nonsyndromic'' clefts, although few have demonstrated consistent effects in humans (5–10).

Results of studies of alcohol consumption reflect the inconsistencies between animal and human studies. In animals, gestational exposure to alcohol has been shown to disrupt formation of the cranial neural crest, embryonic cells that contribute to the development of the face (11–14). In humans, case reports have described the fetal alcohol syndrome (15, 16) and other recognized phenotypes that include clefts (17, 18) among the birth outcomes of mothers who reported heavy periconceptional alcohol consumption. Likewise, some case-control studies (19–21) have identified

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elevated risks for clefting associated with heavy consumption, whereas others have demonstrated such associations with more moderate consumption levels (22–29) or failed to find an association (30–35). Contributing to the discordant results in human studies have been variability in sample size, subject ascertainment and classification, amount and timing of exposure, and level of evaluation of covariates. Moreover, analyses incorporating the type of alcoholic beverages consumed have been limited. Further, alcohol consumption has been associated with lower folate and higher homocysteine levels (36), but the impact of folic acid intake on the risk of clefting associated with alcohol consumption has been largely unexplored.

Because of the high prevalence of alcohol consumption among US women of childbearing age (37), the relation between maternal periconceptional alcohol consumption and orofacial clefts was examined by use of data from the National Birth Defects Prevention Study, a large, population-based case-control study. Associations between amount, timing, and type of alcohol exposure and individual phenotypes were examined.

## MATERIALS AND METHODS

The National Birth Defects Prevention Study is an ongoing, multicenter, case-control study designed to investigate genetic and environmental risk factors for over 30 major birth defects (38–40). Centers that participated in the current analysis represented birth defect surveillance systems in seven states (Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas), as well as the Centers for Disease Control and Prevention (CDC) in Georgia. Each center obtained institutional review board approval for the National Birth Defects Prevention Study.

Cases included livebirths (all centers), fetal deaths (Arkansas, California, CDC, Iowa, Massachusetts, Texas), and elective terminations (Arkansas, California, CDC, Iowa, Texas) with deliveries on or after October 1, 1997 (California, CDC, Iowa, Massachusetts, New York, Texas), or January 1, 1998 (Arkansas, New Jersey); estimated dates of delivery on or before December 31, 2002; and diagnosis of at least one eligible birth defect. Cases with defects of known etiology (single-gene disorders and chromosome abnormalities) were excluded. Controls were livebirths, without a major birth defect and with estimated dates of delivery during the same time frames, randomly selected from hospital delivery logs (Arkansas, California, CDC through 2000, New York, Texas) or birth certificate files (CDC 2001–2002, Iowa, Massachusetts, New Jersey). A liveborn child not in the custody of or not residing with the birth mother or any delivery whose birth mother did not speak English or Spanish was excluded.

Clinical geneticists at each center reviewed clinical information to determine case eligibility using standard case definitions for the study (40). Clinical information from each center was also evaluated by one of us (S. A. R.) to classify cases as isolated (no additional major, unrelated defects) or multiple (two or more major, unrelated defects). Cases with clefts likely related to another defect (e.g., holoprosencephaly) were excluded. Eligible cases were analyzed by phenotype, cleft lip, cleft palate, or cleft lip with cleft palate, and by the presence of accompanying defects, isolated, multiple, or the Pierre-Robin syndrome (cleft palate, micrognathia, and glossoptosis). Laterality was also analyzed separately.

Structured, computer-assisted telephone interviews were conducted with birth mothers of cases and controls (38). Interviews were conducted from 6 weeks to 2 years following the estimated date of delivery. Mothers were asked to provide preconceptional and postconceptional reports of illness, medications, vitamin supplements, residence, occupation(s) (maternal and paternal), substance use (maternal and paternal), and information on pregnancy and family history. Reports of alcohol consumption were collected for the period from 3 months before conception to the delivery date. Mothers who reported consumption of an alcoholic beverage (beer, wine, mixed drinks, or shots of liquor) during this time period were queried about the month(s) during which they drank, the average number of drinking days per month (frequency), the average number of drinks per drinking day (quantity), the maximum number of drinks on one occasion per drinking month (variability), and the type(s) of alcohol consumed.

Mothers were classified as exposed if they reported drinking during one or more periconceptional months defined as 1 month before conception (B1) through the first 3 months following conception (M1, M2, and M3, respectively). Including reported consumption in B1 allowed for analysis of mothers with unrecognized or unintended pregnancies who might have extended consumption behaviors (unreported) into pregnancy. Including only M1–M3 during pregnancy is consistent with the developmentally relevant time period for the lip and palate. Two approaches were used to evaluate the effect of drinking months. The first was to categorize reported patterns of consumption as B1 only, B1–M1, B1–M2, B1–M3, and other (e.g., M1 only). The second was to categorize the number of drinking months as 0 through 4, considering each month to be of equal exposure value; thus, duration was assigned a value of one whether a mother reported drinking during B1, M1, M2, or M3 only. Comparison of the two approaches among mothers with 3 or fewer drinking months showed that duration largely reflected pattern of consumption, with 69 percent of mothers assigned a duration of 1 month represented by those with a pattern of B1 only, 92 percent with a duration of 2 months represented by B1–M1, and 89 percent with a duration of 3 months represented by B1–M2.

The average number of drinks per drinking month was calculated by multiplying the frequency and quantity values reported for that month. To account for changes in consumption between months, periconceptional average and maximum average amounts were calculated for drinking months. For example, if a mother reported consuming eight drinks per month in B1, six in M1, six in M2, and four in M3, her average consumption was calculated as six drinks per month $((8 + 6 + 6 + 4)/4)$ and her maximum average consumption as eight drinks per month. By use of a 30-day month, four categories of consumption rates were created: monthly to weekly (1–4 drinks per month); weekly to every other day (5–15 drinks per month); every other day to daily (16–30

drinks per month); and daily with more than one drink per day (>30 drinks per month).

Variability of consumption within a drinking month was defined with both sex-neutral (41) and sex-specific (42) norms. Sex-neutral norms used five or more drinks per day on average or on one occasion, or both, to define binge drinking, whereas sex-specific norms used four or more drinks. Mothers were also classified by the reported type(s) of alcohol consumed, beer only, wine only, distilled spirits (mixed drinks plus shots of liquor) only, or a combination of two or more types. Because mothers were not queried about drink volume, a standard drink volume was assumed, 0.5 fluid ounces (approximately 12 g) of alcohol per 12 fluid ounces of beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits (43).

Odds ratios and 95 percent confidence intervals were used to assess the association between phenotypes and maternal periconceptional quantity-frequency (average drinks per month) and variability (number of binge episodes) of consumption. Descriptive analyses using the chi-squared test were conducted comparing case phenotypes with controls for child's sex, gestational age, and family history of clefts; maternal age, education, race/ethnicity, gravidity, prepregnancy body mass index, periconceptional cigarette smoking, and folic acid intake from vitamin supplements; and National Birth Defects Prevention Study center. For each characteristic evaluated, bivariate analysis, including an interaction term, was conducted with level of maternal alcohol consumption to assess risk for confounding and effect modification. Results of descriptive and bivariate analyses were used to construct the most parsimonious models for each phenotype, including use of categorical (child's sex and family history; maternal race/ethnicity and cigarette smoking; and National Birth Defects Prevention Study center) and continuous (maternal age, education, and prepregnancy body mass index) variables to calculate adjusted estimates of the odds ratios using multiple logistic regression analyses. Each logistic model also included a variable to account for reported duration of periconceptional consumption. Multivariate analyses for quantity-frequency and variability of consumption were extended to include evaluation of type of alcohol on risk of clefting. In addition, the associations between type of alcohol and quantity-frequency of consumption, variability of consumption, and maternal folic acid intake were examined. All analyses were conducted using SAS, version 9.1.3, software (44).

## RESULTS

Birth mothers of 2,329 eligible cases and 6,004 eligible controls were identified, and 1,770 and 4,143 mothers, respectively, consented to interview. Of these, partial interviews were completed with 21 case and 49 control mothers; therefore, analyses were limited to reports for 1,749 (75.1 percent) cases and 4,094 (68.2 percent) controls. The median time between the estimated dates of delivery and completed interviews was 9.3 months for cases and 7.3 months for controls.

Among cases, those with cleft palate were more likely to have additional malformations, and those with cleft lip were more likely to be unilateral clefts (table 1). Compared with controls, an excess of males was found for cases with cleft lip or cleft lip with cleft palate, and each case phenotype was more likely to have a reported family history of clefting. Among mothers, those of cleft lip or cleft palate cases differed little from controls except that they were more likely to be non-Hispanic White and to smoke cigarettes. In contrast, mothers of cleft lip with cleft palate cases tended to be younger, less educated, non-Hispanic White, and obese and to have smoked cigarettes. Differences in the proportions of case phenotypes and controls recruited were also found across centers.

Any preconceptional or postconceptional alcohol consumption, or both, was reported by 841 (48.1 percent) case and 1,978 (48.3 percent) control mothers, with 695 (39.8 percent) case and 1,580 (38.6 percent) control mothers reporting periconceptional consumption (table 2). Stratification of periconceptional reports by 6-month intervals for time between the estimated date of delivery and the interview showed little difference between case mothers and control mothers (data not shown). Duration of periconceptional use tended to differ between control mothers and those of cases with cleft lip or cleft lip with cleft palate, although the type(s) of alcohol consumed tended to be similar. Mothers with missing or incomplete reports, that is, cases ($n = 15$) and controls ($n = 30$), or questionable reports (e.g., 600 drinks per month) of consumption, that is, cases ($n = 4$) and controls ($n = 7$), were excluded.

Table 3 shows the odds ratios associated with maximum average alcoholic drinks consumed per drinking month; estimates calculated for average drinks consumed did not materially change the estimates presented (data not shown). Compared with those for mothers who reported no periconceptional consumption, the odds ratios for all cases combined were near unity, with the highest estimate found for mothers who consumed 1–4 drinks per month. A similar pattern was identified within each phenotype for all cases and isolated cases. Among cases with multiple defects or Pierre-Robin syndrome, odds ratios were elevated but did not approach statistical significance, although several estimates were imprecise because of the small number of exposed cases. The odds ratios for unilateral cleft lip and cleft lip with cleft palate tended to be near unity, and those for bilateral cleft lip and cleft lip with cleft palate tended to exceed unity but were not significant (data not shown). Restriction of reports of consumption to P1–P3 did not materially change the odds ratios (data not shown). In addition, analyses stratified by the child's sex or gestational age did not show appreciable differences in risk (data not shown).

For all phenotypes, odds ratios tended to be near unity among mothers who reported consumption but no binge episodes (≥5 drinks/episode), and similar estimates were found for mothers who reported one or more binge episodes (table 4). Applying sex-specific norms (≥4 drinks/episode) revealed marginally stronger associations for no reported binge episodes and similar but slightly attenuated associations for mothers with binge episodes (data not shown). Because reports of variability of consumption were limited to a single report of maximum number of drinks per drinking month, multiple binge episodes per drinking month

**TABLE 1. Selected characteristics of children and birth mothers by child phenotype, National Birth Defects Prevention Study, 1997–2002**

| Characteristic | Cleft lip only ($n = 384$) | | Cleft lip with cleft palate ($n = 744$) | | Cleft palate only ($n = 621$) | | Controls ($n = 4,094$) | |
|---|---|---|---|---|---|---|---|---|
| | No.* | %† | No. | % | No. | % | No. | % |
| Child | | | | | | | | |
| Sex | | | | | | | | |
| Male | 255 | 66.6 | 487 | 65.7 | 280 | 45.2 | 2,049 | 50.1 |
| Female | 128 | 33.4 | 254 | 34.3 | 340 | 54.8 | 2,040 | 49.9 |
| Defect status | | | | | | | | |
| Isolated | 359 | 93.5 | 635 | 85.4 | 375 | 60.4 | NA‡ | NA |
| Multiple | 25 | 6.5 | 109 | 14.7 | 82 | 13.2 | | |
| Pierre-Robin syndrome | | | | | 164 | 26.4 | | |
| Laterality | | | | | | | | |
| Unilateral | 308 | 80.2 | 446 | 60.0 | NA | NA | NA | NA |
| Bilateral | 30 | 7.8 | 220 | 29.6 | | | | |
| Central | 7 | 1.8 | 2 | 0.3 | | | | |
| Unknown | 39 | 10.2 | 76 | 10.2 | | | | |
| Gestational age (weeks) | | | | | | | | |
| Preterm (<37) | 41 | 10.7 | 132 | 17.7 | 118 | 19.0 | 365 | 8.9 |
| Term (37–45) | 343 | 89.3 | 612 | 82.3 | 502 | 81.0 | 3,726 | 91.1 |
| Family history of clefting | | | | | | | | |
| First-degree relative | 20 | 5.2 | 45 | 6.1 | 35 | 5.6 | 16 | 0.4 |
| Other relative | 46 | 12.0 | 126 | 16.9 | 59 | 9.5 | 38 | 0.9 |
| None | 318 | 82.8 | 573 | 77.0 | 527 | 84.9 | 4,040 | 98.7 |
| Mother | | | | | | | | |
| Age at delivery (years) | | | | | | | | |
| <21 | 71 | 18.5 | 148 | 19.9 | 86 | 13.9 | 632 | 15.4 |
| 21–25 | 90 | 23.4 | 197 | 26.5 | 136 | 21.9 | 913 | 22.3 |
| 26–30 | 89 | 23.2 | 187 | 25.1 | 149 | 24.0 | 1,129 | 27.6 |
| 31–35 | 97 | 25.3 | 130 | 17.5 | 165 | 26.6 | 984 | 24.0 |
| >35 | 37 | 9.6 | 82 | 11.0 | 85 | 13.7 | 436 | 10.7 |
| Education (years) | | | | | | | | |
| <12 | 64 | 16.7 | 179 | 24.1 | 104 | 16.8 | 676 | 16.5 |
| 12 | 101 | 26.4 | 215 | 28.9 | 163 | 26.3 | 1,030 | 25.2 |
| 13–15 | 102 | 26.6 | 186 | 25.0 | 181 | 29.2 | 1,105 | 27.0 |
| ≥16 | 116 | 30.3 | 164 | 22.0 | 173 | 27.9 | 1,275 | 31.2 |

**Table continues**



could be calculated only for mothers who reported an average consumption of five or more drinks/drinking day. Those who reported an average quantity of less than five drinks/drinking day, but a maximum of five or more drinks/drinking day, were categorized as having one binge episode per month.

Examination of odds ratios stratified by type of alcohol differed by phenotype (table 5). For cleft lip, consumption of distilled spirits tended to be associated with the highest risk for each amount of consumption, whereas no clear pattern was observed for cleft lip with cleft palate. For cleft palate, the strongest associations were found for consumption of distilled spirits for most drinking levels, particularly among mothers who consumed 1–4 drinks/month; however, wine was associated with the highest risk among mothers who consumed more than 30 drinks/month. This pattern for cleft palate was also reflected in associations identified for type of alcohol stratified by binge episodes. The impact of folic acid intake on the type of alcohol consumed was also examined. Compared with mothers with no alcohol consumption but folic acid intake, mothers of cleft lip and cleft lip with cleft palate cases who reported consumption but no folic acid intake had elevated but nonsignificant odds ratios. Mothers who reported consumption of distilled spirits but no folic acid intake had a greater than threefold risk of delivering a child with cleft palate, with the suggestion of

**TABLE 1. Continued**

| Characteristic | Cleft lip only ($n = 384$) | | Cleft lip with cleft palate ($n = 744$) | | Cleft palate only ($n = 621$) | | Controls ($n = 4,094$) | |
|---|---|---|---|---|---|---|---|---|
| | No.* | %† | No. | % | No. | % | No. | % |
| Race/ethnicity | | | | | | | | |
| Non-Hispanic White | 259 | 67.5 | 447 | 60.2 | 425 | 68.6 | 2,456 | 60.2 |
| Non-Hispanic African American | 23 | 6.0 | 43 | 5.8 | 40 | 6.5 | 491 | 12.0 |
| Hispanic | 83 | 21.6 | 204 | 27.5 | 115 | 18.6 | 931 | 22.8 |
| Other | 19 | 5.0 | 49 | 6.6 | 40 | 6.5 | 205 | 5.0 |
| Gravidity | | | | | | | | |
| 1 | 123 | 32.0 | 238 | 32.0 | 184 | 29.6 | 1,171 | 28.6 |
| 2 | 119 | 31.0 | 212 | 28.5 | 184 | 29.6 | 1,237 | 30.2 |
| >2 | 142 | 37.0 | 294 | 39.5 | 253 | 40.7 | 1,684 | 41.2 |
| Prepregnancy body mass index (kg/m$^2$) | | | | | | | | |
| Underweight (<18.5) | 29 | 7.9 | 63 | 8.8 | 33 | 5.5 | 233 | 5.9 |
| Normal weight (18.5–24.9) | 218 | 59.2 | 380 | 53.2 | 333 | 55.4 | 2,254 | 57.3 |
| Overweight (25.0–29.9) | 74 | 20.1 | 144 | 20.2 | 127 | 21.1 | 862 | 21.9 |
| Obese (≥30) | 47 | 12.8 | 127 | 17.8 | 108 | 18.0 | 584 | 14.9 |
| Cigarette smoking (cigarettes/day) | | | | | | | | |
| 0 | 288 | 75.2 | 550 | 73.9 | 473 | 76.2 | 3,295 | 80.5 |
| 1–14 | 70 | 18.3 | 121 | 16.3 | 95 | 15.3 | 541 | 13.2 |
| ≥15 | 25 | 6.5 | 73 | 9.8 | 52 | 8.4 | 256 | 6.3 |
| Folic acid intake | | | | | | | | |
| Yes | 328 | 85.4 | 618 | 83.1 | 530 | 85.4 | 3,488 | 85.2 |
| No | 56 | 14.6 | 126 | 16.9 | 91 | 14.7 | 606 | 14.8 |
| Center | | | | | | | | |
| Arkansas | 33 | 8.6 | 84 | 11.3 | 62 | 10.0 | 499 | 12.2 |
| California | 66 | 17.2 | 128 | 17.2 | 75 | 12.1 | 597 | 14.6 |
| Iowa | 56 | 14.6 | 79 | 10.6 | 60 | 9.7 | 479 | 11.7 |
| Massachusetts | 57 | 14.8 | 92 | 12.4 | 112 | 18.0 | 535 | 13.1 |
| New Jersey | 45 | 11.7 | 72 | 9.7 | 74 | 11.9 | 575 | 14.0 |
| New York | 42 | 10.9 | 74 | 10.0 | 74 | 11.9 | 448 | 10.9 |
| Texas | 51 | 13.3 | 130 | 17.5 | 77 | 12.4 | 503 | 12.3 |
| CDC‡/Atlanta, GA | 34 | 8.9 | 85 | 11.4 | 87 | 14.0 | 458 | 11.2 |

* Numbers vary because of incomplete or missing data.
† Because of rounding, percentages might not total 100.
‡ NA, not applicable; CDC, Centers for Disease Control and Prevention.

statistical interaction between the two exposures ($p = 0.06$). Restriction of cases to isolated cleft palate also revealed a significantly increased risk (data not shown). No additional interactions were noted between type of alcohol consumed and folic acid intake; thus, given the number of associations examined, the elevated risk for cleft palate may simply be due to chance.

## DISCUSSION

Data from the National Birth Defects Prevention Study were used to investigate the association between maternal periconceptional alcohol consumption and orofacial clefts. Weak associations were found for average consumption for all clefts combined and isolated clefts, and somewhat moderate associations were identified for multiple clefts and the Pierre-Robin syndrome; however, estimates for these latter phenotypes were based on small numbers reflecting the study criteria to exclude cases of known etiology. For binge drinking (≥5 drinks/episode), the odds ratios associated with one or more reported episodes were found to be near unity for each phenotype, and sex-specific norms (≥4 drinks/episode) produced similar associations. Reported consumption of beverages with higher alcohol content by volume (e.g., distilled spirits) tended to produce the strongest associations.

Results for average consumption and all clefts combined were consistent with those of some previous studies

**TABLE 2. Reported patterns of maternal alcohol consumption and type(s) of alcohol consumed by child phenotype, National Birth Defects Prevention Study, 1997–2002*,†**

| | All cases | | Cleft lip only | | Cleft lip with cleft palate | | Cleft palate only | | Controls | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No.‡ | %§ | No. | % | No. | % | No. | % | No. | % |
| Total | 1,749 | | 384 | | 744 | | 621 | | 4,094 | |
| Reported pattern of consumption | | | | | | | | | | |
| Any preconceptional or postconceptional use | 841 | 48.1 | 192 | 50.5 | 348 | 46.7 | 301 | 48.3 | 1,978 | 48.3 |
| Any periconceptional use (months) | 695 | 39.8 | 155 | 40.8 | 283 | 37.9 | 257 | 41.4 | 1,580 | 38.6 |
| 1 | 369 | 21.3 | 87 | 22.7 | 150 | 20.4 | 132 | 21.4 | 804 | 19.8 |
| 2 | 204 | 11.8 | 38 | 10.0 | 78 | 10.6 | 88 | 14.3 | 502 | 12.4 |
| 3 | 75 | 4.3 | 19 | 5.0 | 36 | 4.9 | 20 | 3.3 | 118 | 2.9 |
| 4 | 47 | 2.7 | 11 | 2.9 | 19 | 2.6 | 17 | 2.8 | 156 | 3.8 |
| Reported type(s) of alcohol consumed | | | | | | | | | | |
| Beer only | 147 | 8.5 | 31 | 8.1 | 67 | 9.1 | 49 | 8.0 | 322 | 7.9 |
| Wine only | 192 | 11.1 | 45 | 11.8 | 76 | 10.3 | 71 | 11.5 | 442 | 10.9 |
| Distilled spirits only | 132 | 7.6 | 30 | 7.9 | 50 | 6.8 | 50 | 8.1 | 262 | 6.5 |
| Beer + wine | 89 | 5.1 | 23 | 6.0 | 33 | 4.5 | 33 | 5.4 | 211 | 5.2 |
| Beer + distilled spirits | 55 | 3.2 | 10 | 2.6 | 29 | 4.0 | 17 | 2.8 | 136 | 3.4 |
| Wine + distilled spirits | 55 | 3.2 | 10 | 2.6 | 21 | 2.9 | 24 | 3.9 | 121 | 3.0 |
| Beer + wine + distilled spirits | 25 | 1.4 | 6 | 1.6 | 6 | 0.8 | 13 | 2.1 | 83 | 2.0 |

* Missing or incomplete data for consumption were distributed as follows: all cases ($n = 15$); cleft lip only ($n = 2$); cleft lip with cleft palate ($n = 8$); cleft palate only ($n = 5$); and controls ($n = 30$).

† Questionable reports were distributed as follows: all cases ($n = 4$); cleft lip with cleft palate ($n = 2$); cleft palate only ($n = 2$); and controls ($n = 7$).

‡ Numbers vary because of incomplete or missing data.

§ Percentage of total. Because of rounding, percentages might not total 100.

**TABLE 3. Adjusted odds ratio estimates for child phenotype associated with maternal reports of maximum average alcoholic drinks consumed per month, National Birth Defects Prevention Study, 1997–2002***

| Child phenotype | 0 drinks/month (no.) | 1–4 drinks/month | | | 5–15 drinks/month | | | 16–30 drinks/month | | | >30 drinks/month | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval |
| Controls | 2,484 | 726 | | | 503 | | | 221 | | | 119 | | |
| All cases | 1,039 | 347 | 1.2 | 0.9, 1.5 | 207 | 1.0 | 0.7, 1.3 | 81 | 0.9 | 0.6, 1.3 | 54 | 1.0 | 0.6, 1.5 |
| Cleft lip only† | 227 | 84 | 1.2 | 0.8, 1.7 | 46 | 0.9 | 0.5, 1.4 | 11 | 0.4 | 0.2, 0.9 | 13 | 1.0 | 0.5, 2.1 |
| Isolated | 209 | 79 | 1.1 | 0.8, 1.7 | 45 | 0.9 | 0.5, 1.5 | 11 | 0.4 | 0.2, 1.0 | 12 | 0.9 | 0.4, 2.1 |
| Multiple | 18 | 5 | 1.6 | 0.3, 8.7 | 1 | NC‡ | NC | 0 | NC | NC | 1 | NC | NC |
| Cleft lip with cleft palate§ | 453 | 137 | 1.0 | 0.7, 1.5 | 82 | 0.8 | 0.6, 1.2 | 39 | 1.0 | 0.6, 1.6 | 24 | 0.8 | 0.5, 1.6 |
| Isolated | 387 | 119 | 1.0 | 0.7, 1.4 | 66 | 0.7 | 0.5, 1.1 | 36 | 1.0 | 0.6, 1.7 | 21 | 0.8 | 0.4, 1.6 |
| Multiple | 66 | 18 | 1.3 | 0.6, 2.8 | 16 | 1.7 | 0.7, 4.1 | 3 | 0.8 | 0.2, 3.4 | 3 | 1.3 | 0.3, 5.4 |
| Cleft palate only¶ | 359 | 126 | 1.3 | 1.0, 1.9 | 79 | 1.1 | 0.8, 1.7 | 31 | 1.1 | 0.6, 1.8 | 17 | 1.1 | 0.6, 2.2 |
| Isolated | 209 | 75 | 1.4 | 0.9, 2.1 | 57 | 1.4 | 0.9, 2.3 | 19 | 1.2 | 0.6, 2.2 | 10 | 1.1 | 0.5, 2.5 |
| Multiple | 54 | 15 | 0.9 | 0.4, 2.2 | 5 | 0.4 | 0.1, 1.4 | 2 | 0.4 | 0.1, 2.0 | 4 | 1.5 | 0.3, 6.4 |
| Pierre-Robin syndrome | 96 | 36 | 1.5 | 0.8, 2.7 | 17 | 0.9 | 0.4, 1.9 | 10 | 1.1 | 0.5, 2.9 | 3 | 0.7 | 0.2, 2.9 |

* Missing or incomplete data for consumption were distributed as follows: all cases ($n = 21$); cleft lip only ($n = 3$); cleft lip with cleft palate ($n = 9$); cleft palate only ($n = 9$); and controls ($n = 41$).

† Adjusted for family history, maternal race/ethnicity, cigarette smoking, center, and duration of alcohol exposure.

‡ NC, not calculated.

§ Adjusted for family history, maternal age, education, race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

¶ Adjusted for family history, maternal race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

**TABLE 4. Adjusted odds ratio estimates for child phenotype associated with maternal reports of binge episodes per month (≥5 drinks/episode), National Birth Defects Prevention Study, 1997–2002***

| Child phenotype | 0 drinks/ month (no.) | No episodes | | | One or more episodes | | |
|---|---|---|---|---|---|---|---|
| | | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval |
| Controls | 2,484 | 1,215 | | | 352 | | |
| All cases | 1,039 | 532 | 1.1 | 0.9, 1.4 | 155 | 1.0 | 0.7, 1.4 |
| Cleft lip only† | 227 | 122 | 1.1 | 0.7, 1.6 | 32 | 0.9 | 0.5, 1.6 |
| Isolated | 209 | 116 | 1.1 | 0.7, 1.6 | 31 | 0.9 | 0.5, 1.6 |
| Multiple | 18 | 6 | 1.6 | 0.2, 10.3 | 1 | NC‡ | NC |
| Cleft lip with cleft palate§ | 453 | 210 | 1.0 | 0.7, 1.3 | 71 | 0.9 | 0.6, 1.4 |
| Isolated | 387 | 183 | 0.9 | 0.7, 1.3 | 59 | 0.9 | 0.5, 1.4 |
| Multiple | 66 | 27 | 1.4 | 0.7, 3.0 | 12 | 1.9 | 0.7, 5.2 |
| Cleft palate only¶ | 359 | 200 | 1.3 | 0.9, 1.8 | 52 | 1.1 | 0.7, 1.8 |
| Isolated | 209 | 127 | 1.4 | 0.9, 2.0 | 33 | 1.2 | 0.7, 2.1 |
| Multiple | 54 | 18 | 0.6 | 0.3, 1.6 | 8 | 1.0 | 0.3, 3.2 |
| Pierre-Robin syndrome | 96 | 55 | 1.3 | 0.7, 2.3 | 11 | 1.0 | 0.4, 2.3 |

* Missing or incomplete data for consumption were distributed as follows: all cases ($n = 23$), cleft lip only ($n = 3$), cleft lip with cleft palate ($n = 10$), cleft palate only ($n = 10$), and controls ($n = 43$).

† Adjusted for family history, maternal race/ethnicity, cigarette smoking, center, and duration of alcohol exposure.

‡ NC, not calculated.

§ Adjusted for family history, maternal age, education, race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

¶ Adjusted for family history, maternal race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

(30–32), but less so with others (23, 28, 29) that found statistically significant associations among all isolated clefts combined. Similarly, findings for average consumption and cleft palate supported several (19–21, 24, 25, 27, 33, 34), but not all (26, 45), previous studies, including that of Meyer et al. (27) of an increased risk of Pierre-Robin syndrome. In contrast, findings for isolated cleft lip and cleft lip with cleft palate were similar to those of Meyer et al. (27) but not directly comparable with most previous studies, which evaluated the risk for cleft lip and cleft lip with cleft palate combined. This report is the first to identify an interaction between the type of alcohol and folic acid intake as risk factors for cleft palate; an elevated risk for cleft lip and cleft lip with cleft palate associated with any maternal alcohol consumption without multivitamin use had been suggested (46) but not confirmed (27). No published reports of alcohol consumption and multiple, bilateral, and/or unilateral cleft lip or cleft lip with cleft palate were identified.

Both chick (11) and mouse (12) models have suggested that orofacial clefts associated with alcohol exposure could be related to the effect of alcohol on embryonic cells of the cranial neural crest. Several mechanisms have been proposed to explain this, including decreased cell proliferation and excessive cell death. Using a mouse model, Kotch and Sulik (12) found that prenatal exposure to ethanol resulted in excessive cell death leading to facial and brain abnormalities, and additional work suggested that such exposure led to changes in membrane fluidity (13) and reduced activity of selected antioxidant enzymes (14). The teratogenic insults of alcohol might be further increased by insufficient intake of folic acid. Alcohol is a known folic acid antagonist (47), and such antagonists have been shown in humans (48) to be associated with an increased risk of clefting.

The design of the National Birth Defects Prevention Study included a large sample, systematic case review, and a detailed interview instrument. Population-based selection of cases and controls offered the potential for reduced selection bias; in particular, comparison of control participants with all livebirths at each center showed that participants tended to be similar to all livebirths for several maternal characteristics (data not shown). The analyses used also attempted to address limitations identified in previous studies. Risks for cleft lip and cleft lip with cleft palate were examined separately on the basis of increasing evidence that these phenotypes might not share similar etiologies (49–51). Related to this, risks for isolated and multiple cases were analyzed separately, because, even with systematic case review, some multiple cases might have had undiagnosed genetic disorders not identified by a participating surveillance system or by the case's health-care provider. The risk of clefting was also examined by use of both sex-specific and sex-neutral binge groups, as suggested by findings of sex differences in alcohol metabolism (52) and evaluation of sex-specific measures of binge drinking (42). In addition, the risk by type(s) of alcohol consumed was evaluated given the different alcohol concentrations among beverages and the increased risk of selected birth defects associated with increasing levels of alcohol consumed (53).

**TABLE 5. Adjusted odds ratio estimates for maternal reports of maximum average alcoholic drinks consumed per month,* binge episodes per month,† and folic acid intake‡ by reports of alcohol type(s) consumed by child phenotype, National Birth Defects Prevention Study, 1997–2002**

| Alcohol type | Controls (no.) | Cleft lip only§ | | | Cleft lip with cleft palate¶ | | | Cleft palate only# | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval |
| Drinks/month | | | | | | | | | | |
| No alcohol | 2,484 | 227 | Referent | | 453 | Referent | | 359 | Referent | |
| 1–4 drinks | | | | | | | | | | |
| Beer | 134 | 16 | 1.2 | 0.6, 2.2 | 27 | 1.3 | 0.8, 2.1 | 16 | 1.0 | 0.6, 1.9 |
| Wine | 278 | 30 | 1.1 | 0.7, 1.9 | 50 | 1.0 | 0.6, 1.5 | 43 | 1.2 | 0.8, 1.9 |
| Distilled spirits | 149 | 21 | 1.4 | 0.8, 2.5 | 32 | 1.0 | 0.6, 1.7 | 30 | 1.5 | 0.9, 2.4 |
| Two or more** | 164 | 17 | 0.9 | 0.5, 1.7 | 28 | 0.9 | 0.6, 1.6 | 37 | 1.7 | 1.1, 2.8 |
| 5–15 drinks | | | | | | | | | | |
| Beer | 112 | 8 | 0.5 | 0.2, 1.3 | 24 | 1.0 | 0.6, 1.8 | 21 | 1.4 | 0.8, 2.4 |
| Wine | 106 | 10 | 0.9 | 0.4, 1.9 | 16 | 0.8 | 0.4, 1.6 | 13 | 0.9 | 0.5, 1.8 |
| Distilled spirits | 76 | 3 | 0.4 | 0.1, 1.5 | 11 | 0.8 | 0.4, 1.6 | 14 | 1.6 | 0.8, 3.0 |
| Two or more | 209 | 25 | 1.1 | 0.6, 2.0 | 30 | 0.7 | 0.4, 1.2 | 31 | 1.0 | 0.6, 1.7 |
| 16–30 drinks | | | | | | | | | | |
| Beer | 45 | 3 | 0.6 | 0.2, 2.1 | 7 | 0.7 | 0.3, 1.9 | 8 | 1.7 | 0.7, 4.1 |
| Wine | 47 | 3 | 0.6 | 0.2, 2.1 | 8 | 1.1 | 0.5, 2.7 | 10 | 1.7 | 0.8, 3.8 |
| Distilled spirits | 25 | 3 | 1.2 | 0.3, 4.4 | 4 | 0.9 | 0.3, 2.8 | 3 | 1.1 | 0.3, 3.7 |
| Two or more | 104 | 2 | 0.1 | 0.03, 0.6 | 20 | 1.0 | 0.5, 1.8 | 10 | 0.6 | 0.3, 1.4 |
| >30 drinks | | | | | | | | | | |
| Beer | 29 | 4 | 1.0 | 0.3, 3.4 | 8 | 1.0 | 0.4, 2.5 | 2 | 0.6 | 0.1, 2.6 |
| Wine | 9 | 2 | 1.7 | 0.3, 9.8 | 2 | 0.5 | 0.1, 4.5 | 5 | 4.5 | 1.4, 14.6 |
| Distilled spirits | 8 | 3 | 4.3 | 1.0, 17.8 | 3 | 2.3 | 0.6, 9.5 | 1 | NC†† | NC |
| Two or more | 72 | 4 | 0.6 | 0.2, 1.7 | 11 | 0.7 | 0.3, 1.5 | 9 | 1.0 | 0.4, 2.2 |
| Binge episodes | | | | | | | | | | |
| No alcohol | 2,484 | 227 | Referent | | 453 | Referent | | 359 | Referent | |
| No episodes | | | | | | | | | | |
| Beer | 216 | 21 | 1.0 | 0.5, 1.7 | 44 | 1.2 | 0.8, 1.8 | 29 | 1.0 | 0.6, 1.7 |
| Wine | 420 | 43 | 1.1 | 0.7, 1.8 | 72 | 0.9 | 0.6, 1.4 | 61 | 1.1 | 0.8, 1.7 |
| Distilled spirits | 200 | 26 | 1.4 | 0.8, 2.4 | 40 | 1.0 | 0.6, 1.5 | 38 | 1.4 | 0.9, 2.2 |
| Two or more | 377 | 32 | 0.8 | 0.5, 1.4 | 54 | 0.8 | 0.5, 1.2 | 72 | 1.4 | 0.9, 2.1 |

**Table continues**

Despite efforts to improve upon the quality of previous studies, these findings need to be interpreted cautiously, as methods used for case ascertainment, subject exclusion, and reports of alcohol consumption may have limited the number of alcohol-affected pregnancies identified. Evidence suggests that the risk of developing clefts is three times as frequent among fetal deaths and abortions than among livebirths (1), and although several centers ascertained elective terminations and fetal deaths, it is likely that some pregnancy terminations and fetal deaths affected with a cleft were not identified. Also, exclusion of case and control mothers whose children were in foster care might have potentially biased recruitment toward less heavy drinkers; however, the reasons for placement of the children were unavailable. Similarly, even with participation rates of 75 percent for cases and 68 percent for controls, some selection bias might have occurred if participants were more or less likely to consume alcohol during pregnancy than were nonparticipants. With regard to collection of reports of alcohol consumption, retrospective assessment of consumption might have led to differential recall between case and control mothers; however, Verkerk et al. (54) found that prospective and retrospective prenatal reports of cigarette and alcohol use from mothers tended to produce similar levels of exposure. Another limitation, mentioned previously, was the interview item regarding variability of consumption that identified the maximum number of drinks on one occasion per drinking month, but not the number of episodes for

**TABLE 5. Continued**

| Alcohol type | Controls (no.) | Cleft lip only§ | | | Cleft lip with cleft palate¶ | | | Cleft palate only# | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval | No. | Odds ratio | 95% confidence interval |
| 1 or more | | | | | | | | | | |
| Beer | 104 | 9 | 0.7 | 0.3, 1.7 | 22 | 0.9 | 0.5, 1.6 | 18 | 1.5 | 0.8, 2.7 |
| Wine | 22 | 2 | 0.7 | 0.2, 3.6 | 4 | 0.9 | 0.3, 2.9 | 9 | 2.7 | 1.1, 6.5 |
| Distilled spirits | 59 | 4 | 0.8 | 0.3, 2.4 | 10 | 0.9 | 0.4, 2.0 | 10 | 1.5 | 0.7, 3.2 |
| Two or more | 167 | 17 | 1.0 | 0.5, 2.0 | 34 | 0.9 | 0.4, 1.5 | 15 | 0.6 | 0.3, 1.2 |
| Folic acid intake | | | | | | | | | | |
| Yes | | | | | | | | | | |
| No alcohol | 2,077 | 191 | Referent | | 368 | Referent | | 297 | Referent | |
| Beer | 273 | 22 | 0.8 | 0.4, 1.4 | 57 | 1.1 | 0.7, 1.7 | 43 | 1.3 | 0.8, 2.0 |
| Wine | 400 | 44 | 1.2 | 0.7, 1.9 | 63 | 0.9 | 0.6, 1.4 | 68 | 1.3 | 0.9, 2.0 |
| Distilled spirits | 228 | 25 | 1.2 | 0.7, 2.0 | 40 | 0.9 | 0.6, 1.4 | 37 | 1.2 | 0.8, 1.9 |
| Two or more | 485 | 45 | 0.9 | 0.6, 1.5 | 79 | 0.9 | 0.6, 1.3 | 78 | 1.1 | 0.7, 1.7 |
| No | | | | | | | | | | |
| No alcohol | 407 | 36 | 1.0 | 0.7, 1.5 | 85 | 1.2 | 0.9, 1.6 | 62 | 1.4 | 1.0, 1.9 |
| Beer | 49 | 9 | 1.7 | 0.7, 4.0 | 10 | 1.1 | 0.5, 2.5 | 6 | 1.2 | 0.5, 3.2 |
| Wine | 42 | 1 | NC | NC | 13 | 1.5 | 0.7, 3.1 | 3 | 0.6 | 0.2, 2.1 |
| Distilled spirits | 34 | 5 | 1.8 | 0.7, 5.0 | 10 | 1.6 | 0.7, 3.6 | 13 | 3.6 | 1.7, 7.4 |
| Two or more | 67 | 4 | 0.6 | 0.2, 1.8 | 10 | 0.6 | 0.2, 1.4 | 9 | 1.2 | 0.5, 2.6 |

* Missing or incomplete data for consumption were distributed as follows: all cases ($n = 22$), cleft lip only ($n = 3$), cleft lip with cleft palate ($n = 10$), cleft palate only ($n = 9$), and controls ($n = 43$).

† Missing or incomplete data for consumption were distributed as follows: all cases ($n = 24$), cleft lip only ($n = 3$), cleft lip with cleft palate ($n = 11$), cleft palate only ($n = 10$), and controls ($n = 45$).

‡ Missing or incomplete data for consumption were distributed as follows: all cases ($n = 16$), cleft lip only ($n = 2$), cleft lip with cleft palate ($n = 9$), cleft palate only ($n = 5$), and controls ($n = 32$).

§ Adjusted for family history, maternal race/ethnicity, cigarette smoking, center, and duration of alcohol exposure.

¶ Adjusted for family history, maternal age, education, race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

# Adjusted for family history, maternal race/ethnicity, prepregnancy body mass index, cigarette smoking, center, and duration of alcohol exposure.

** Includes beer + wine, beer + distilled spirits, wine + distilled spirits, and beer + wine + distilled spirits.

†† NC, not calculated.

women with reported average monthly frequencies of less than five (or less than four) drinks/drinking day; therefore, the number of binge episodes reported for such women might have been an underestimate. Also, because mothers were not requested to report the volume of drink consumed, findings might have been attenuated using the assumption of alcohol concentration in a standard drink. The volume of alcohol consumed might have varied among the types of alcohol, among exposed women, or both. Further, over 50 percent of women who consumed alcohol reported not being aware of their pregnancy until the second month past conception (data not shown); thus, the periconceptional period was defined to include the month before conception to capture women who reported only preconceptional consumption (B1 only) but whose drinking might have continued unreported into the early months of pregnancy. Finally, alcohol consumption during pregnancy may have been underreported by both case and control mothers because of the social stigma of the known association between alcohol consumption and fetal alcohol syndrome (55).

In summary, data from a large, population-based study were used to investigate the association between maternal periconceptional alcohol consumption and orofacial clefts. Analyses identified increased risks associated with the varying amounts, patterns, and types of alcohol consumed. In addition, alcohol risk was found to be modified by folic acid intake; however, these findings are preliminary and require replication in future, large investigations. Future investigations should also consider evaluation of genetic predisposition to differences in facial development (25), alcohol metabolism (29), or folate metabolism (56), which might influence the risk of clefting associated with alcohol consumption.

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