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Maternal Periconceptional Exposure to Cigarette Smoking and Alcohol and Esophageal Atresia ± Tracheo-Esophageal Fistula

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Abstract

BACKGROUND: Esophageal atresia (EA) is a moderately frequent birth defect that often occurs with tracheoesophageal fistula (TEF). Etiologic studies for EA ± TEF have produced inconsistent results.

METHODS: This study used data from the National Birth Defects Prevention Study (NBDPS) to examine the association between maternal periconceptional exposure to cigarette smoking and alcohol and EA ± TEF. Cases of EA ± TEF and unaffected controls with an estimated date of delivery from October 1997 through December 2003 were identified, and telephone interview reports for smoking and alcohol exposure were obtained from birth mothers of 334 cases and 4,967 controls. Odds ratios (OR)s and 95% confidence intervals (CI)s, adjusted for several covariates, were calculated to assess associations.

RESULTS: ORs were near unity for all EA ± TEF cases combined and any periconceptional exposure to cigarette smoking (OR = 1.1; CI = 0.8,1.6) or alcohol (OR = 1.2; CI = 0.8,1.8). For cigarette smoking, some elevated ORs were found but varied by type of smoking exposure. No consistent patterns were identified for number of cigarettes smoked per day. For alcohol, ORs were weak to moderately elevated with increasing number of drinks consumed and for binge drinkers compared to non-binge drinkers. ORs were further elevated among mothers who reported active + passive exposure to cigarette smoking and alcohol (OR = 2.5; CI = 1.1,5.6). For both exposures, ORs were higher for cases with additional major defects compared to isolated cases.

CONCLUSIONS: These results, based on one of the largest published samples of EA ± TEF cases, suggest a role for these exposures in the etiology of EA ± TEF, although further study is needed to replicate the observed associations.

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Keywords

alcohol drinking; case-control study; cigarette smoking; esophageal atresia; pregnancy; tracheo-esophageal fistula

INTRODUCTION

Esophageal atresia (EA) is characterized by a complete discontinuity of the lumen of the esophagus resulting in a blind esophageal pouch (Bianca and Ettore, 2003; Torfs et al., 1995). In approximately 90% of cases (Kovesi and Rubin, 2004), EA has been estimated to co-occur with tracheo-esophageal fistula (TEF), an abnormal connection between the esophagus and trachea (Torfs et al., 1995). Overall, prevalence estimates for EA $\pm$ TEF range from 2 to 4 per 10,000 births (Robert et al., 1993; Bianca and Ettore, 2003; CDC, 2006; Spitz, 2007). EA $\pm$ TEF may present as an isolated defect or in combination with other defects, and is a major phenotypic component of the VATER association (Vertebral anomalies, Anorectal atresia, Tracheo-esophageal fistula, Esophageal atresia, Renal anomalies) (Robert et al., 1993).

The etiology of EA $\pm$ TEF is not well understood. Several previously published studies examined selected birth and maternal characteristics as risk factors for EA $\pm$ TEF. Positive associations were found for low birth weight and multiple births (Robert et al., 1993; Bianca and Ettore, 2003; Forrester and Merz, 2005) and preterm birth (Robert et al., 1993; Rasmussen et al., 2001; Forrester and Merz, 2005). Among maternal characteristics examined, positive associations were found for advanced maternal age (>35 years) (Torfs et al., 1995; Forrester and Merz, 2005; Felix et al., 2008), younger maternal age (<20 years) (Depaepe et al., 1993), both advanced and younger ages (Szendrey et al., 1985; David and O'Callaghan, 1975), as well as white race (Forrester and Merz, 2005) and low parity (Robert et al., 1993; Bianca and Ettore, 2003).

In contrast to birth and maternal characteristics, common pregnancy exposures, such as maternal exposure to cigarette smoking and/or alcohol, have been less well studied. Of the five published reports identified, two were case reports (Angerpointner et al., 1981, Martinez-Frias and Rodriguez-Pinilla, 1991), one included these exposures as covariates for analyses on the association between illicit drug use during pregnancy and EA $\pm$ TEF (Martínez-Frías, 1999), and the remaining two studies evaluated each exposure only as a dichotomous variable (yes/no) (Szendrey et al., 1985; Felix et al., 2008).

The paucity of comprehensive studies of the relation between maternal smoking and alcohol exposure and EA $\pm$ TEF is of concern as the prevalence of cigarette smoking among pregnant women was reported to be 11.0% (Martin et al., 2003) and the prevalence of any alcohol consumption among pregnant women was 10.1% (Tsai and Floyd, 2004.). To address this deficiency, we analyzed data from the National Birth Defects Prevention Study (NBDPS). The NBDPS is the largest population-based case-control study of birth defects in the United States and collects detailed maternal interview reports of periconceptional exposure to cigarette smoking and alcohol. Using data collected through these interviews, we examined the contribution of maternal cigarette smoking, maternal exposure to passive

cigarette smoke, maternal alcohol consumption, and the combined effects of these exposures to the risk of EA $\pm$ TEF.

METHODS

National Birth Defects Prevention Study (NBDPS)

The NBDPS is an ongoing, multi-center, case-control study designed to investigate genetic and environmental risk factors for more than 30 major structural birth defects through the collection of interview data and biological samples. Initial centers for the NBDPS included birth defect surveillance systems in seven states: Arkansas (AR), California (CA), Iowa (IA), Massachusetts (MA), New Jersey (NJ), New York (NY), and Texas (TX), along with the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. In 2002, surveillance systems in two additional states, North Carolina (NC) and Utah (UT), were included in the NBDPS. Each center has obtained institutional review board approval for the NBDPS. A brief description of study methods is presented below. Additional detail is reported elsewhere (Yoon et al., 2001; Rasmussen et al., 2002, 2003).

Subject Selection

Cases diagnosed with EA $\pm$ TEF were identified from live births (all centers), fetal deaths (AR, CA, CDC, IA, MA, TX), and elective terminations (AR, CA, CDC, IA, TX) with an estimated date of delivery (EDD) on or after October 1, 1997 (CA, CDC, IA, MA, NY, TX), January 1, 1998 (AR, NJ), or January 1, 2003 (NC, UT) and on or before December 31, 2003. Cases with defects of known etiology (single gene disorders and chromosome abnormalities) were excluded. Controls included live births without a major birth defect and with an EDD during the same time frames randomly selected from either hospital delivery logs (AR, CA, CDC, 1997–2000, NY, TX) or birth certificate files (CDC, 2001–2003, IA, MA, NC, NJ, UT). A live born case or control child who was not in the custody of and residing with the birth mother, or any delivery whose birth mother did not speak English or Spanish, was excluded.

Case Classification

Clinical geneticists at each center reviewed clinical information to determine case eligibility using standard case definitions (Rasmussen et al., 2003). Information abstracted from medical records was reviewed by one NBDPS clinical geneticist to further classify eligible EA $\pm$ TEF cases as isolated or multiple. Cases were classified as isolated if the EA $\pm$ TEF occurred as a solitary major defect, with an additional minor defect(s), or as a sequence (EA $\pm$ TEF was presumed to be the primary defect) (Rasmussen et al., 2003). Otherwise, cases with accompanying major defects were classified as multiple. These multiple cases were also reviewed to identify infants with the VATER association. The VATER association was defined as the presence of three or more major defects in selected defect groups within the VATER spectrum including those of the axial skeleton, radial ray, kidney, upper and lower gastrointestinal tract, and heart (Botto et al., 1997). All infants identified as having the VATER association were independently classified by two clinical geneticists. Defects that showed a statistically significant association in the study by Botto et al. (1997) were

included in the VATER association group; infants with other additional defects were excluded from the VATER association group and analyzed with the multiple cases.

Exposure Assessment

Structured, computer-assisted telephone interviews were conducted with birth mothers of cases and controls (Yoon et al., 2001). These interviews were conducted between 6 weeks and 2 years following the EDD. Included in the interview were detailed questions regarding maternal exposure to cigarette smoking and alcohol during the 3 months prior to conception and the duration of the pregnancy.

Maternal reports of cigarette smoking were classified as active smoking, and reports of exposure to cigarette smoke in the household or workplace were classified as passive smoking. Information on maternal exposure to cigarette smoke was collected monthly for the 3 months prior to pregnancy (labeled B3, B2, and B1) and for the first 3 months of pregnancy (labeled M1, M2, and M3) and by trimester for months 4–6 and 7–9 of pregnancy (labeled T2 and T3, respectively). If mothers reported smoking during any of these time periods, further information was requested regarding the number of cigarettes smoked per day and categorized as <1, 1, 2–4, 5–14 (one-half pack), 15–24 (one pack), 25–34 (one and one-half packs), 35–44 (two packs), and >45. If mothers reported passive exposure to smoking, information was requested for the location at which exposure occurred (household or workplace) and the month(s) during which exposure occurred.

For alcohol exposure, mothers were asked if they consumed an alcoholic beverage (beer, wine, mixed drinks or shots of liquor) during the 3 months prior to conception and each month of the pregnancy. If mothers reported consumption, further information was requested for the month(s) during which they drank, average number of drinking days per month (frequency), average number of drinks per drinking day (quantity), and maximum number of drinks on one occasion per drinking month (variability). As with items on cigarette smoking, mothers were asked to report exposure for each month prior to conception (B3–B1), each month during the first trimester (M1–M3), and for each of the remaining trimesters (T2 and T3). Incomplete reports of either smoking exposure or alcohol consumption were excluded from their respective analyses.

To examine the association between maternal exposure to cigarette smoking and alcohol consumption and EA $\pm$ TEF, mothers were classified as exposed if they reported active or passive smoking or alcohol consumption during the periconceptional period defined as 1 month before conception (B1) through the first 3 months following conception (M1, M2, and M3). Since development of the foregut begins during week 4 of embryonic life and is completed by weeks 6–7 (Felix et al., 2004), this periconceptional period includes the biologically relevant time frame for disruption of esophageal formation. Reported exposure to cigarette smoking was classified as any exposure (none vs. active and/or passive), and also as active exposure only, passive exposure only, or active + passive exposure. Among mothers who reported active smoking, exposure was further classified by number of cigarettes per day. To evaluate the effect of changes in number of reported cigarettes smoked across months, odds ratios (OR)s were calculated using both minimum and maximum reported monthly values. To evaluate the effect of variation in number of periconceptional months

exposed, mothers were classified by reported patterns of exposure as B1 only, B1–M1, B1–M2, B1–M3, and other (e.g., M1 only). They were also classified by duration of exposure (number of months exposed, 0–4) considering each month to be of equal exposure value; thus, duration was assigned a value of 1 whether a mother reported exposure during B1, M1, M2, or M3 only. Comparison of values for duration and pattern of exposure showed a high concordance. Of the mothers who reported 1 periconceptional month of exposure, 86% reported smoking in B1 only. Of mothers who reported 2 or 3 periconceptional months of exposure, 98% reported smoking in B1–M1 and B1–M2, respectively.

For alcohol exposure, reported consumption was classified as any drinking, and was analyzed by quantity, frequency, and variability of consumption as described elsewhere (Romitti et al., 2007). Because reports of average number of drinks per day were recorded as continuous variables, unlike cigarette smoking in which responses were recorded in categories, average and maximum average values were calculated for each mother as described (Romitti et al., 2007). Similar to smoking exposure, both duration and pattern of periconceptional alcohol consumption were calculated and compared. Duration largely reflected reported patterns of exposure with reports of 1, 2, and 3 periconceptional months of exposure corresponding to patterns of B1 only, B1–M1, and B1–M2 for 70%, 92%, and 87% of mothers, respectively. In addition, binge drinking was evaluated using both sex-neutral (≥ 5 drinks per day) (Naimi et al., 2003) and sex-specific (≥ 4 drinks per day) (Wechsler et al., 1995) criteria.

Statistical Analysis

Analyses were conducted using SAS, version 9.1.3 (SAS, Cary, NC). Selected characteristics of children and their birth mothers were compared using the Pearson chi-square or, where appropriate, the Fisher exact test. Crude odds ratios (OR)s and 95% confidence intervals (CI)s were calculated to determine the risk of EA ± TEF associated with maternal exposure to active smoking, passive smoking, and alcohol. Bivariate analyses were conducted for each exposure and index child sex, gestational age, plurality, and maternal age, race and ethnicity, education, gravidity, pre-pregnancy body mass index, pre-pregnancy diabetes (either type 1 or type 2), infertility treatment (use of in vitro fertilization, intracytoplasmic sperm injection, or clomiphene citrate vs. no fertility treatment), periconceptional intake of folic acid-containing supplements, duration of smoking or alcohol exposure, and study center. Results of bivariate analyses were used to guide model development for multivariate logistic regression analyses. Models for smoking exposure were adjusted for alcohol consumption, whereas those for alcohol consumption were adjusted for smoking exposure. Also, models were constructed to examine the joint effects of periconceptional exposure to both cigarette smoking and alcohol relative to no exposure to either source. In addition, both cigarette smoking and alcohol consumption have been associated with lower folate and higher homocysteine levels (Chiuve et al., 2005); thus, risk associated with each exposure was stratified by reported intake of folic acid-containing supplements.

RESULTS

Birth mothers of 437 eligible case and 7,258 control infants were identified, and interviews were completed with 334 (76.4%) case and 4,967 (68.4%) control mothers. The median time between EDD and interview was 8.9 months for case mothers and 7.5 months for control mothers.

As shown in Table 1, the proportion of males and females was similar between cases and controls. Both the occurrence of preterm births and plural births were more common among cases than controls, and no case and a small number of controls had a reported family history of EA $\pm$ TEF. In addition, more than one-half of cases were classified with either the multiple phenotype or the VATER association.

Mothers of cases compared to those of controls tended to be older, non-Hispanic white, more educated, and to have had only one previous pregnancy, pre-pregnancy diabetes, and infertility treatments (Table 1). Little difference was found between case and control mothers for pre-pregnancy body mass index or periconceptional intake of folic acid-containing supplements, although differences among centers in the proportions of cases and controls recruited were identified.

Overall, 112 (33.5%) case mothers and 1,718 (34.6%) control mothers reported periconceptional exposure to cigarette smoking with similar proportions found between groups for type of exposure, but less similar reports for duration of exposure (Table 2). Any periconceptional alcohol consumption was reported by 145 (43.4%) case mothers and 1,857 (37.4%) control mothers, with some variation between groups in the reported duration and types of alcohol consumed. Stratification of periconceptional reports by 6-month intervals for time between EDD and interview showed little difference in exposure between case and control mothers (data not shown). Mothers with incomplete information for smoking exposure (controls = 15) or alcohol consumption (cases = 3; controls = 39) were excluded from analyses of the respective exposure.

The adjusted OR for any reported periconceptional exposure to cigarette smoking and all EA $\pm$ TEF cases combined was near 1 and was elevated when stratified by type of smoking or number of cigarettes per day among active smokers (Table 3). Respective ORs for isolated cases tended to be reduced, whereas those for the multiple phenotype or the VATER association tended to be elevated, but imprecise. Most elevated were ORs for cases with the VATER association whose mothers reported active smoking with or without passive smoking.

A very weak increase in the OR was found for any periconceptional alcohol consumption and all EA $\pm$ TEF cases combined (Table 3). ORs were increased with increasing consumption and tended to be weakly elevated but marginally higher for mothers who reported one or more binge episodes (≥ 5 drinks per day) compared to those who reported consumption but no binge episodes; application of sex-specific norms (≥ 4 drinks per day) for binge drinking produced no appreciable differences in the ORs (data not shown). In addition, ORs were elevated for mothers who reported consumption of wine or distilled spirits compared to those who consumed beer or two or more types of alcohol. Examination

of ORs by phenotypes showed no clear patterns for isolated or multiple cases, although ORs for cases with the VATER association tended to be the most elevated, but also the most imprecise. Because center was included in the multivariate models, these latter ORs excluded controls from NC and UT as neither center conducted a telephone interview with the mother of a case with the VATER association.

The ORs for combined exposure to cigarette smoking and alcohol are presented in Table 4. Any periconceptional exposure to both cigarette smoking and alcohol produced elevated ORs, particularly for cases with the VATER association. Such ORs remained elevated when stratified by type of exposure to cigarette smoking or quantity of cigarettes smoked per day among active smokers. Among mothers with any exposure to cigarette smoking, examination of ORs by number of drinks consumed per month tended to show increasing ORs with increasing number of drinks consumed. For most phenotypes, modestly elevated ORs, but no clear patterns of associations were observed for reports of consumption with or without binge episodes; however, a near three-fold increase in risk was found for mothers of cases with the VATER association who reported one or more binge episodes per month regardless of exposure to cigarette smoking. Similarly, no clear pattern of associations was identified for type of alcohol consumed when stratified by any periconceptional exposure to cigarette smoking. For all associations examined, adjusted ORs tended to be either somewhat elevated or attenuated compared to crude ORs, but did not appreciably change the conclusions. Also, for all associations examined, exclusion of controls with a positive family history of EA $\pm$ TEF did not materially change the ORs presented. In addition, for mothers of cases with the VATER association, use of all available control subjects and excluding adjustment for study center did not appreciably change the conclusions (data not shown).

For any periconceptional smoking exposure, ORs for mothers who reported intake of folic acid-containing supplements were similar to those shown in Table 3; data were too sparse to precisely evaluate risk associated with smoking exposure among mothers without reported intake of folic acid-containing supplements. Similar findings for any periconceptional alcohol consumption were identified for mothers who reported folic acid-containing supplement intake; however, among mothers without reported intake, ORs associated with alcohol consumption tended to be higher, particularly for cases with the multiple phenotype (data not shown).

DISCUSSION

This study represents the most comprehensive evaluation to date of the relation between maternal periconceptional exposure to cigarette smoking and/or alcohol and EA $\pm$ TEF. Weak associations were identified between any periconceptional exposure to smoking and each case phenotype. Elevated ORs were found when risk was evaluated by type of smoking or average number of cigarettes smoked per day; the highest ORs were found for mothers with active cigarette smoking (with or without passive smoking) exposure and whose child had the VATER association. Similarly, no associations or weak associations were identified between maternal periconceptional alcohol consumption and each phenotype, although increasing, but non-significant associations were found for increasing average number of drinks consumed per month and for mothers who reported one or more binge drinking

episodes compared to those who did not report such episodes. Examination of combined exposure to smoking and alcohol also did not identify clear patterns of association for EA $\pm$ TEF, although several elevated ORs were found, particularly for cases with the VATER association.

Univariate analyses of selected infant and maternal characteristics for EA $\pm$ TEF tended to support previously reported associations with preterm birth (Robert et al., 1993; Rasmussen et al., 2001; Forrester and Merz, 2005), older maternal age (Torfs et al., 1995; Forrester and Merz, 2005), white race (Forrester and Merz, 2005), and low parity (Robert et al., 1993; Bianca and Ettore, 2003). For all EA $\pm$ TEF cases combined, any maternal periconceptional exposure to active cigarette smoking was associated with a moderate increase in risk, which differed from previous reports of no association (Angerpointner, 1981; Szendrey et al., 1985; Felix et al., 2008). In contrast, periconceptional exposure to passive cigarette smoking showed no association in the current study, but an elevated association in a previous case-control study (Felix et al., 2008). Similarly, the association between all EA $\pm$ TEF cases combined and any maternal periconceptional exposure to alcohol showed only a weak association in the current study, but a more elevated association in a previous report (Felix et al., 2008). With the detailed exposure data collected in the NBDPS for cigarette smoking and alcohol consumption, the current study was able to further analyze patterns and extent of exposure to identify elevations in risk for several stratifications. Classification of cases into isolated and multiple phenotypes and the VATER association allowed more detailed analyses and showed elevated risks, particularly for higher levels of smoking exposure. Likewise, stratification of alcohol exposure and classification of cases by isolated or multiple phenotypes suggested a tendency for increased risk among mothers of cases with the VATER association and number of drinks, binge drinking, and wine or distilled spirits, although these estimates were often imprecise.

As others have noted (Brunner and van Bokhoven, 2005; Spitz, 2007), EA $\pm$ TEF is most likely multifactorial in origin with both environmental and genetic risk factors. Animal studies and preliminary human studies have identified a number of candidate genes suggested to play a role in the abnormal development of the esophagus including retinoic acid receptor (*RAR*) and Sonic hedgehog (*shh*) (reviewed in Felix et al., 2004). Other studies have focused on the embryogenesis of EA $\pm$ TEF in animal models (Merei et al., 1997, 1998), but these studies have not explored mechanisms by which this defect occurs. Also, some genetic pathways such as Sonic hedgehog (*shh*) may be shared by EA $\pm$ TEF (Felix et al., 2004; Spitz, 2007) and some esophageal cancers (Ma et al., 2006).

Despite systematic methods for identification, some cases of EA $\pm$ TEF may not have been identified due to the inability of some centers to ascertain fetal deaths or elective terminations. Also, some selection bias might have occurred if participants were more or less likely to have exposure to cigarette smoking or alcohol during pregnancy than nonparticipants. Related to this is the social stigma of smoking cigarettes and drinking alcohol during pregnancy, which may have led to an underreporting of each exposure. In addition, retrospective collection of reports of exposure to cigarette smoking or alcohol might have led to differential recall between case and control mothers; however, in the current study, stratification of periconceptional reports by 6-month intervals for time

between EDD and interview showed little difference in exposure between case and control mothers. Moreover, Verkerk et al. (1994) found that prospective and retrospective prenatal reports of cigarette and alcohol use from mothers tended to produce similar levels of exposure.

Along with the potential bias introduced by retrospective data collection, limitations exist in the information collected in the NBDPS interview. One limitation was the lack of detailed information collected regarding passive smoking exposure. Interview items asked during which months passive exposure occurred and the type of exposure (household or workplace) but did not include additional information such as the length of time for which exposure occurred or the quantity of exposure. Another limitation was information collected on binge episodes. The interview item identified the maximum number of drinks on one occasion per drinking month, but not the number of occasions that this maximum was reached per month; thus, women whose reported monthly average was <5 (or <4 for sex-specific norms) drinks/drinking day may have underreported binge episodes. A third limitation was the use of alcohol concentration in a standard drink rather than request for volume of drinks consumed. Given the different alcohol concentrations among types of alcohol, this assumption might have attenuated risks associated with different types of alcohol.

One of the challenges of studying etiologic factors for EA $\pm$ TEF is the birth prevalence of the defect. Even in a large study, such as the NBDPS, fewer than 400 cases of EA $\pm$ TEF have been identified and when considering some exposures and case subgroups, our effect estimates were imprecise. Despite this limitation, this study identified elevated risk for cigarette smoking and alcohol consumption, particularly among mothers of cases with the VATER association. Although the modest numbers of cases available for some analyses suggest caution in interpreting these results, these findings provide preliminary evidence and suggest that more detailed study of the association between EA $\pm$ TEF and cigarette smoking and alcohol consumption is needed.

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REFERENCES

- Angerpointner T, Radtke W, Murken J. Catamnestic investigations in children with malformations of the gastrointestinal tract and the abdominal wall. *Z Kinderchir.* 1981; 32:129–144. [PubMed: 6456621]
- Bianca S, Ettore G. Isolated esophageal atresia and perinatal risk factors. *Dis Esophagus.* 2003; 16:39–40. [PubMed: 12581253]
- Botto LD, Khoury MJ, Mastroiacovo P. The spectrum of congenital anomalies of the VATER association: an international study. *Am J Med Genet.* 1997; 71:8–15. [PubMed: 9215761]

- Brunner HG, van Bokhoven H. Genetic players in esophageal atresia and tracheoesophageal fistula. *Curr Opin Genet Dev.* 2005; 15:341–347. [PubMed: 15917211]
- Centers for Disease Control and Prevention (CDC). Improved national prevalence estimates for 18 selected major birth defects—United States, 1999–2001. *MMWR.* 2006; 54:1301–1305. [PubMed: 16397457]
- Chiuvè SE, Giovannucci EL, Hankinson SE. Alcohol intake and methylenetetrahydrofolate reductase polymorphism modify the relation of folate intake to plasma homocysteine. *Am J Clin Nutr.* 2005; 82:155–162. [PubMed: 16002814]
- David T, O’Callaghan S. Oesophageal atresia in the South West of England. *J Med Genet.* 1975; 12:1–11. [PubMed: 1121014]
- Depaëpe A, Dolk H, Lechat M. The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT Working Group. *Arch Dis Child.* 1993; 68:743–748. [PubMed: 8333763]
- Felix JF, Keijzer R, van Dooren MF. Genetics and developmental biology of oesophageal atresia and tracheo-oesophageal fistula: lessons from mice relevant for paediatric surgeons. *Pediatr Surg Int.* 2004; 20:731–736. [PubMed: 15517294]
- Felix JF, van Dooren MF, Klaassens M. Environmental factors in the etiology of esophageal atresia and congenital diaphragmatic hernia: results of a case-control study. *Birth Defects Res A Clin Mol Teratol.* 2008; 82:98–105. [PubMed: 18172903]
- Forrester MB, Merz RD. Epidemiology of oesophageal atresia and tracheo-oesophageal fistula in Hawaii, 1986–2000. *Public Health.* 2005; 119:483–488. [PubMed: 15826889]
- Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest.* 2004; 126:915–925. [PubMed: 15364774]
- Ma X, Sheng T, Zhang Y. Hedgehog signaling is activated in subsets of esophageal cancers. *Int J Cancer.* 2006; 118:139–148. [PubMed: 16003737]
- Martin JA, Hamilton BE, Sutton PD. Births: final data for 2002. *Natl Vital Stat Rep.* 2003; 52:1–113.
- Martínez-Frías ML. A risk analysis of congenital defects due to drug intake during pregnancy. Spanish Collaborative Study of Congenital Malformations. *Med Clin (Barc).* 1999; 112:41–44. [PubMed: 10065427]
- Martínez-Frías ML, Rodríguez-Pinilla E. Tracheoesophageal and anal atresia in prenatal children exposed to a high dose of alcohol. *Am J Med Genet.* 1991; 40:128. [PubMed: 1887844]
- Merei JM, Farmer P, Hasthorpe S. Timing and embryology of esophageal atresia and tracheo-oesophageal fistula. *Anat Rec.* 1997; 249:240–248. [PubMed: 9335470]
- Merei JM, Hasthorpe S, Farmer P, Hutson JM. Embryogenesis of tracheal fistula. *Anat Rec.* 1998; 252:271–275. [PubMed: 9776081]
- Naimi TS, Brewer RD, Mokdad A. Binge drinking among U.S. adults. *JAMA.* 2003; 289:70–75. [PubMed: 12503979]
- Rasmussen SA, Moore CA, Paulozzi LJ, Rhodenhiser EP. Risk for birth defects among premature infants: a population-based study. *J Pediatr.* 2001; 138:668–673. [PubMed: 11343041]
- Rasmussen SA, Lammer EJ, Shaw GM. Integration of DNA sample collection into a multi-site birth defects case-control study. *Teratology.* 2002; 66:177–184. [PubMed: 12353214]
- Rasmussen SA, Olney RS, Holmes LB. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defects Res A Clin Mol Teratol.* 2003; 67:193–201. [PubMed: 12797461]
- Robert E, Mutchinick O, Mastroiacovo P. An international collaborative study of the epidemiology of esophageal atresia or stenosis. *Reprod Toxicol.* 1993; 7:405–421. [PubMed: 8274816]
- Romitti PA, Sun L, Honein MA. Maternal periconceptional alcohol consumption and risk of orofacial clefts. *Am J Epidemiol.* 2007; 166:775–785. [PubMed: 17609516]
- Spitz L. Oesophageal atresia. *Orphanet J Rare Dis.* 2007; 2:24. [PubMed: 17498283]
- Szendrey T, Danyi G, Czeizel A. Etiological study on isolated esophageal atresia. *Hum Genet.* 1985; 70:51–58. [PubMed: 3997151]
- Torfs CP, Curry CJR, Bateson TF. Population-based study of tracheoesophageal fistula and esophageal atresia. *Teratology.* 1995; 52:220–232. [PubMed: 8838292]

- Tsai J, Floyd R. Alcohol consumption among women who are pregnant or who might become pregnant—United States, 2002. *MMWR*. 2004; 53:1178–1181. [PubMed: 15614234]
- Verkerk PH, Buitendijk SE, Verloove-Vanhorick SP. Differential mis-classification of alcohol and cigarette consumption by pregnancy outcome. *Int J Epidemiol*. 1994; 23:1218–1225. [PubMed: 7721524]
- Wechsler H, Dowdall GW, Davenport A, Rimm EB. A gender-specific measure of binge drinking among college students. *Am J Public Health*. 1995; 85:982–985. [PubMed: 7604925]
- Yoon PW, Rasmussen SA, Lynberg MC. The National Birth Defects Prevention Study. *Public Health Rep*. 2001; 116(Suppl 1):32–40.

Table 1

Selected Characteristics of Case and Control Children and Birth Mothers, National Birth Defects Prevention Study 1997–2003

Characteristic	EA ± TEF		Controls	
	(N = 334)		(N = 4,967)	
Child	<i>n</i> ^a	% ^b	<i>n</i> ^a	% ^b
Sex				
Female	168	50.3	2,456	49.5
Male	166	49.7	2,506	50.5
Gestational age ^c				
Term (37–45 weeks)	205	61.4	4,499	90.6
Preterm (<37 weeks)	129	38.6	465	9.4
Plurality ^c				
1	295	88.3	4,810	96.9
2 or more	39	11.7	152	3.1
Family history of EA ± TEF				
First-degree relative	0	0.0	5	0.1
Other relative	0	0.0	3	0.1
None	334	100.0	4,959	99.8
Malformation status				
Isolated	138	41.3	—	—
Multiple	142	42.5	—	—
VATER	54	16.2	—	—
Mother	<i>n</i> ^a	% ^b	<i>n</i> ^a	% ^b
Age at delivery (years) ^d				
<21	41	12.3	763	15.4
21–25	67	20.1	1,142	23.0
26–30	81	24.3	1,362	27.4
31–35	95	28.4	1,182	23.8
>35	50	15.0	518	10.4
Race and ethnicity ^e				
Non-Hispanic white	233	69.8	2,995	60.4
Non-Hispanic black	15	4.5	580	11.7
Other	20	6.0	266	5.4
Hispanic	66	19.8	1,114	22.5
Education (years) ^d				
<12	49	14.7	836	16.9
12	73	21.9	1,236	24.9
13–15	77	23.1	1,315	26.5
16 or more	135	40.4	1,572	31.7

Characteristic	EA ± TEF		Controls	
	(N = 334)		(N = 4,967)	
Gravidity ^e				
1	123	36.8	1,446	29.1
2	103	30.8	1,487	30.0
>2	108	32.3	2,032	40.9
Pre-pregnancy body mass index				
Underweight (<18.5)	19	6.0	284	6.0
Normal weight (18.5–24.9)	185	58.0	2,695	56.5
Overweight (25.0–29.9)	64	20.1	1,055	22.1
Obese (≥ 30)	51	16.0	734	15.4
Pre-pregnancy diabetes ^d				
Yes	6	1.8	25	0.5
No	328	98.2	4,942	99.5
Infertility treatment ^c				
Yes	34	10.8	106	2.2
No	280	89.2	4,734	97.8
Folic acid intake				
Yes	294	88.0	4,246	85.5
No	40	12.0	721	14.5
Study center ^d				
Arkansas	35	10.5	587	11.8
California	39	11.7	685	13.8
Iowa	26	7.8	568	11.4
Massachusetts	57	17.1	643	13.0
New Jersey	55	16.5	575	11.6
New York	33	9.9	460	9.3
Texas	37	11.1	609	12.3
CDC/Atlanta	36	10.8	547	11.0
North Carolina	7	2.1	159	3.2
Utah	9	2.7	134	2.7

EA ± TEF, esophageal atresia with or without tracheo-esophageal fistula; VATER, vertebral anomalies, anorectal atresia, tracheo-esophageal fistula, esophageal atresia, renal anomalies.

^aNumbers vary due to incomplete or missing data.

^bDue to rounding, percentages may not total 100.

^c*p*-Value <0.001.

^d*p*-Value <0.05.

^e*p*-Value <0.01.

Table 2

Reported Patterns of Exposure for Cigarette Smoking and Alcohol for Case and Control Mothers, National Birth Defects Prevention Study 1997–2003

Exposure	EA ± TEF		Controls	
	<i>n</i>	% ^a	<i>n</i>	% ^a
Cigarette smoking ^b				
Total	334		4,967	
Any periconceptional exposure	112	33.5	1,718	34.6
Type of exposure				
Active + passive smoking	42	12.6	611	12.3
Active smoking only	22	6.6	349	7.0
Passive smoking only	48	14.4	758	15.3
Active smoking				
1 month	11	3.3	138	2.8
2 months	17	5.1	184	3.7
3 months	8	2.4	117	2.4
4 months	28	8.4	523	10.5
Alcohol ^c				
Total	334		4,967	
Any periconceptional exposure	145	43.4	1,857	37.4
1 month	67	20.2	962	19.5
2 months	54	16.3	575	11.7
3 months	13	3.9	138	2.8
4 months	11	3.3	182	3.7
Type(s) of alcohol				
Beer only	23	7.0	391	7.9
Wine only	52	15.7	513	10.4
Distilled spirits only	24	7.3	311	6.3
Beer + wine	20	6.0	248	5.0
Beer + distilled spirits	9	2.7	159	3.2
Wine + distilled spirits	9	2.7	140	2.8
Beer + wine + distilled spirits	8	2.4	93	1.9

EA ± TEF, esophageal atresia with or without tracheo-esophageal fistula.

^aPercentage of completed reports. Due to rounding, percentages may not total 100.

^bMissing or incomplete data for cigarette smoking distributed as follows: controls = 15 (missing data for active smoking, reported exposure to passive smoking = 1; no reported exposure to active smoking, missing data for passive smoking = 12, reported exposure to active smoking, missing data for passive smoking = 2).

^cMissing or incomplete data for alcohol consumption distributed as follows: cases = 3; controls = 39.

Table 3

Adjusted Odds Ratio Estimates for Child Phenotype Associated with Maternal Exposure to Cigarette Smoking^a or Alcohol,^b National Birth Defects Prevention Study 1997–2003

Exposure	EA ± TEF											
	Controls			All			Isolated			Multiple		
	N	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR
Cigarette smoking ^d												
None	3,234	222		ref	96		ref	3,010		ref	32	ref
Any periconceptual exposure	1,718	112	1.1	0.8, 1.6	42	0.9	0.5, 1.5	1,649		0.7, 1.8	22	1.8
Type of exposure ^d												
Active only	349	22	1.5	0.7, 3.1	9	0.3	0.1, 1.6	331		0.4, 4.4	8	8.0
Passive only	758	48	1.1	0.7, 1.5	18	1.1	0.6, 1.8	732		0.6, 1.7	8	1.2
Active + passive	611	42	1.9	0.9, 4.1	15	0.3	0.1, 1.4	586		1.5, 12.3	6	5.1
Cigarettes/day ^e												
No active smoking	4,004	270		ref	114		ref	3,754		ref	40	ref
1–14	658	45	1.6	0.8, 3.2	17	0.3	0.1, 1.4	631		0.9, 6.2	10	7.0
15	301	19	1.4	0.6, 3.5	7	0.1	0.02, 0.9	286		0.7, 9.9	4	nc
Alcohol ^{a,f}												
None	3,071	186		ref	77		ref	2,836		ref	26	ref
Any periconceptual exposure	1,857	145	1.2	0.8, 1.8	59	1.2	0.6, 2.2	1,798		0.6, 2.0	28	1.5
Drinks/month ^f												
1–15	1,461	111	1.2	0.8, 1.8	45	1.2	0.6, 2.2	1,414		0.6, 2.0	17	1.4
16–30	250	20	1.3	0.7, 2.5	7	1.1	0.4, 3.1	242		0.2, 2.2	8	4.1
>30	134	14	1.8	0.8, 3.7	7	2.1	0.7, 6.1	131		nc	3	nc
Binge episodes ^f												
Drinking, no binge episodes	1,433	112	1.2	0.8, 1.8	46	1.1	0.6, 2.1	1,388		0.6, 2.1	19	1.3
Drinking, 1 binge episodes	407	32	1.4	0.8, 2.3	13	1.4	0.6, 3.2	395		0.4, 2.3	9	2.5
Type(s) of alcohol ^f												
Beer only	391	23	1.0	0.6, 1.7	11	1.1	0.5, 2.6	382		0.3, 1.8	5	1.6

Exposure	EA ± TEF																	
	Controls			All			Isolated			Multiple			Controls ^c			VATER		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI			
Wine only	513	52	1.3	0.8, 2.1	21	1.3	0.6, 2.6	23	1.3	0.6, 2.7	494	8	1.3	0.4, 4.1				
Distilled spirits only	311	24	1.3	0.8, 2.3	9	1.3	0.6, 3.0	9	1.2	0.5, 2.7	300	6	1.8	0.5, 6.1				
Two or more types	640	46	1.1	0.7, 1.8	18	1.0	0.5, 2.1	19	1.1	0.5, 2.4	620	9	1.4	0.5, 4.5				

Ref, reference; nc, not calculated; EA ± TEF, esophageal atresia with or without tracheo-esophageal fistula; VATER, vertebral anomalies, anorectal atresia, tracheo-esophageal fistula, esophageal atresia, renal anomalies; OR, odds ratio; CI, confidence interval.

^aMissing or incomplete data for cigarette smoking distributed as follows: controls = 15.

^bMissing or incomplete data for alcohol distributed as follows: cases = 3; controls = 39.

^cNo mothers of VATER cases interviewed by NC or UT centers; thus control subjects excluded from analyses for these centers.

^dAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, alcohol consumption (yes/no), duration of cigarette smoking, and study center.

^eAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, passive cigarette smoking, alcohol consumption (yes/no), duration of cigarette smoking, and study center.

^fAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, cigarette smoking (yes/no), duration of alcohol consumption, and study center.

Table 4

Adjusted Odds Ratio Estimates for Child Phenotype Associated with Maternal Exposure to Both Cigarette Smoking^a and Alcohol,^b National Birth Defects Prevention Study 1997–2003

Exposure	EA ± TEF											
	Controls			All			Isolated			Multiple		
	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI
Alcohol												
Cigarette smoking ^d												
No	2,151	131	ref	56	ref	56	ref	56	ref	19	ref	
Yes	909	55	1.2 0.8, 1.7	21	1.0 0.6, 1.9	27	1.2 0.7, 2.2	867	7	1.1 0.4, 2.9		
No	1,068	89	1.2 0.8, 1.9	39	1.3 0.7, 2.5	37	1.2 0.6, 2.3	1,035	13	1.0 0.4, 3.0		
Yes	786	56	1.3 0.8, 2.2	20	1.0 0.4, 2.2	21	1.1 0.5, 2.6	760	15	2.9 1.0, 8.9		
Type of exposure ^d												
Active only	135	9	2.1 0.8, 5.3	4	0.5 0.1, 3.1	2	nc	126	3	nc		
Passive only	509	31	1.1 0.7, 1.7	10	1.0 0.5, 2.0	18	1.4 0.8, 2.4	488	3	nc		
Active + passive	265	15	1.8 0.7, 4.5	7	0.3 0.1, 2.2	7	3.3 0.9, 11.6	253	1	nc		
Active only	206	13	1.6 0.7, 3.6	5	0.4 0.1, 2.2	3	nc	197	5	6.4 1.5, 26.5		
Passive only	247	17	1.3 0.7, 2.2	8	1.7 0.8, 3.7	4	nc	242	5	2.2 0.8, 6.3		
Active + passive	333	26	2.5 1.1, 5.6	7	0.4 0.1, 2.1	14	4.9 1.7, 14.2	321	5	7.1 1.5, 33.8		
Cigarettes/day ^e												
1–14	278	15	1.3 0.5, 3.4	9	0.5 0.1, 3.0	4	nc	263	2	nc		
15	123	9	1.6 0.5, 5.1	2	nc	5	1.8 0.3, 9.4	117	2	nc		
1–14	369	30	1.8 0.9, 3.9	8	0.4 0.1, 2.0	14	1.5 0.4, 4.8	357	8	10.7 2.8, 41.4		
15	168	9	1.3 0.4, 3.7	4	nc	3	nc	160	2	nc		
Cigarette smoking												
Alcohol Drinks/month ^f												
1–15	903	76	1.3 0.9, 2.1	35	1.4 0.7, 2.8	34	1.3 0.7, 2.5	873	7	0.8 0.3, 2.6		
16–30	123	10	1.3 0.6, 3.1	3	nc	3	nc	121	4	nc		
>30	40	3	nc	1	nc	0	nc	39	2	nc		
1–15	555	35	1.1 0.7, 1.9	10	0.8 0.3, 1.8	15	1.0 0.4, 2.2	538	10	2.7 0.9, 8.0		
16–30	127	10	1.4 0.6, 3.2	4	nc	2	nc	121	4	nc		

EA ± TEF																			
Exposure		Controls			All			Isolated			Multiple			Controls ^c			VATER		
		N	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI	N	OR	95% CI		
	>30	94	11	2.3	1.0, 5.1	6	2.8	0.9, 8.8	4	nc		92	1	nc					
	Binge episodes ^f																		
No	None	929	75	1.2	0.7, 1.8	34	1.3	0.6, 2.5	32	1.1	0.6, 2.3	898	9	0.8	0.2, 2.4				
	1 or more	133	13	1.7	0.9, 3.5	5	1.5	0.5, 4.5	4	nc		132	4	nc					
Yes	None	501	37	1.2	0.7, 2.1	12	0.9	0.4, 2.2	15	1.1	0.5, 2.5	487	10	2.6	0.8, 7.9				
	1 or more	274	19	1.3	0.6, 2.3	8	1.2	0.5, 3.3	6	1.1	0.7, 1.9	263	5	2.7	0.7, 10.5				
	Type(s) of alcohol ^f																		
No	Beer only	186	11	1.0	0.5, 2.1	5	1.0	0.4, 2.9	5	1.1	0.4, 3.0	181	1	nc					
	Wine only	376	41	1.3	0.8, 2.3	18	1.4	0.7, 3.1	17	1.3	0.6, 2.8	361	6	1.1	0.3, 4.1				
	Distilled spirits only	151	12	1.4	0.7, 2.8	5	1.5	0.5, 4.2	5	1.5	0.5, 4.0	146	2	nc					
	Two or more types	353	25	1.1	0.6, 1.9	11	1.0	0.4, 2.5	10	1.1	0.4, 2.7	345	4	nc					
Yes	Beer only	205	12	1.1	0.5, 2.1	6	1.2	0.4, 3.4	2	nc		201	4	3.0	0.8, 11.7				
	Wine only	136	11	1.2	0.6, 2.6	3	0.8	0.2, 3.0	6	1.5	0.5, 4.4	132	2	nc					
	Distilled spirits only	159	12	1.3	0.7, 2.7	4	1.1	0.3, 3.4	4	1.0	0.3, 3.2	153	4	3.3	0.8, 13.1				
	Two or more types	286	21	1.2	0.6, 2.2	7	0.9	0.3, 2.4	9	1.2	0.5, 3.2	274	5	2.3	0.6, 8.7				

Ref, reference; nc, not calculated; EA ± TEF, esophageal atresia with or without tracheo-esophageal fistula; VATER, vertebral anomalies, anorectal atresia, tracheo-esophageal fistula, esophageal atresia, renal anomalies; OR, odds ratio; CI, confidence interval.

^aMissing or incomplete data for cigarette smoking distributed as follows: cases = 3; controls = 53.

^bMissing or incomplete data for alcohol distributed as follows: cases = 3; controls = 65.

^cNo VATER cases ascertained by NC or UT centers; thus control subjects excluded from analyses for these centers.

^dAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, duration of cigarette smoking, and study center.

^eAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, duration of alcohol exposure, passive smoking (yes/no), and study center.

^fAdjusted for plurality, maternal age, race and ethnicity, education, pre-pregnancy diabetes, infertility treatments, duration of alcohol consumption, and study center.