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Paternal occupation and birth defects: findings from the National Birth Defects Prevention Study

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Abstract

Objectives—Several epidemiologic studies have suggested that certain paternal occupations may be associated with an increased prevalence of birth defects in offspring. Using data from the National Birth Defects Prevention Study, we investigated the association between paternal occupation and birth defects in a case-control study of cases comprising over 60 different types of birth defects (n = 9998) and non-malformed controls (n = 4066) with dates of delivery between 1997 and 2004.

Methods—Using paternal occupational histories reported by mothers via telephone interview, jobs were systematically classified into 63 groups based on shared exposure profiles within occupation and industry. Data were analyzed using Bayesian logistic regression with a hierarchical prior for dependent shrinkage to stabilize estimation with sparse data.

Results—Several occupations were associated with an increased prevalence of various birth defect categories, including: mathematical, physical and computer scientists; artists; photographers and photo processors; food service workers; landscapers and groundskeepers; hairdressers and cosmetologists; office and administrative support workers; sawmill workers; petroleum and gas workers; chemical workers; printers; material moving equipment operators; and motor vehicle operators.

Conclusions—Findings from this study might be used to identify specific occupations worthy of further investigation, and to generate hypotheses about chemical or physical exposures common to such occupations.

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COMPETING INTERESTS None declared.

Keywords

Bayes theorem; congenital abnormalities; occupational exposure; occupations; paternal exposure

Birth defects are a leading cause of infant mortality and developmental disabilities in the United States, yet the causes of most birth defects are unknown.[1, 2] Previous epidemiologic studies have suggested that certain paternal occupations and workplace exposures may be associated with an increased prevalence of birth defects in offspring.[3-5] Occupations found to be associated with various defects include: agricultural and groundskeeping workers, electronic industry workers, forestry and logging workers, janitors and cleaners, laboratory workers, painters, printers, vehicle manufacturers and mechanics, welders, and woodworkers.[6-21]

Investigations of occupation as a risk factor for birth defects face a number of methodological challenges.[4] Many of these challenges stem primarily from small sample size, which is impacted by low exposure prevalence (e.g., diversity of occupations) and the rarity of individual phenotypes. To recover statistical power, investigators may group occupations or birth defects into larger categories, tolerating increased heterogeneity in order to increase sample sizes within groups. Conversely, study designs with more finely categorized (and thus more homogeneous) exposures and outcomes are prone to other issues such as imprecision and multiple hypotheses testing.

The objective of this study was to use data from a large national case-control study of birth defects to explore the relation between paternal occupation and various birth defects using analytic methods that specifically address the statistical challenges associated with analysis of sparsely distributed data across numerous occupational groups and birth defect categories. A complementary analysis of the association between maternal occupation and birth defects in this study population has been previously published.[22]

METHODS

All data are from the National Birth Defects Prevention Study (NBDPS), an ongoing, multi-center, population-based case-control study designed to investigate a range of potential risk factors for major birth defects. Detailed study methods have been previously published.[23] Briefly, eligible cases with one or more major birth defect were identified by 10 participating state birth defect surveillance systems (Arkansas; California; Georgia; Iowa; Massachusetts; New Jersey; North Carolina; New York; Texas; Utah) and included live births, fetal deaths and prenatally diagnosed elective terminations. Controls were randomly selected in each state among live births without major defects from either hospital records or birth certificates, with an approximate overall case:control ratio of 3:1. Between 6 weeks and 24 months after the estimated delivery date (EDD), mothers were enrolled and interviewed by telephone in either English or Spanish using a structured questionnaire that covers numerous demographic, behavioral and clinical factors before and during pregnancy.

This analysis includes cases and controls with EDDs between 01 October 1997 and 31 December 2004. Overall participation in the interview among case and control mothers during this time period was 69.4 and 66.1%, respectively.

Outcome classification

Clinical geneticists at each center performed standardized case review and coding to determine eligibility.[24] Eligible cases of major defects (those typically considered to have major medical or surgical significance) were centrally reviewed again by NBDPS clinicians

to confirm eligibility and to classify each case as having only one major birth defect ("isolated"), more than one major birth defect ("multiple"), or a pattern of defects that represent a complex developmental sequence. In general, only cases with non-syndromic isolated and multiple defects were considered for this analysis, which includes more than 60 distinct birth defect categories. The birth defects of interest in this study (Table 1) are grouped by the primary organ system affected; this grouping is for convenience of presentation only and is not indicative of shared etiology or embryological development.

Occupational classification

During the interview, mothers reported the job title, main activities and other details for each job held by the infant's father for at least 1 month duration from 3 months preceding the estimated date of conception (EDC) through the EDD. Jobs were then coded using the Standard Occupational Classification (SOC) Manual and North American Industry Classification System (NAICS).[25, 26]

We restricted the exposure period of interest to 3 months preceding the EDC through the first month of pregnancy, which corresponds to the primary critical window of susceptibility for male-mediated mechanisms of teratogenesis.[5, 27] All jobs held during this period were further grouped by SOC and NAICS codes into a modified occupational classification scheme which combines occupations considered to have similar physical and chemical exposure profiles.[22, 28] For example, the occupational group "farmers and farm workers" included agricultural workers, farmers and ranchers, and floral designers. Fathers who held more than 1 job during the critical period were assigned to more than 1 occupational group as appropriate (up to 2 groups per job). For example, Air Force pilots were assigned to "armed forces" as well as "aircraft operators."

Study sample

The overall study population included fathers of 14,920 singleton cases and 5,771 singleton controls conceived without donor sperm or embryo. We further excluded fathers with missing occupational histories (498 [3.3%] cases; 182 [3.2%] controls), fathers who did not work at all between 3 months before the EDC and the EDD (1024 [6.9%] cases; 321 [5.6%] controls), fathers who did not have a job or were students during the exposure period of interest (3318 [22.2%] cases; 1180 [20.4%] controls), and fathers who worked during the relevant period but whose job descriptions were insufficient for classification (82 [0.5%] cases; 22 [0.4%] controls). The final sample for analysis consisted of fathers of 9998 cases and 4066 controls.

Statistical analysis

Despite the large sample size overall, the data were sparsely distributed since the cross-classification of occupations and outcomes yielded over 5000 combinations, many of which were represented by very few or no father-infant pairs. Given this distribution as well as the underlying assumptions about common workplace exposures within occupational groups, we assumed that an occupation associated with one defect may be more likely to be associated with other defects, and likewise a birth defect associated with one occupation may be more likely to be associated with other occupations. Using Bayesian logistic regression with a heavy-tailed scale mixture of normals prior, we incorporated this data structure in a hierarchical prior for dependent shrinkage across coefficients for occupation. The prior corresponded to a *t*-distribution with low degrees of freedom, which is expressed as a *gamma* (*Ga*) precision mixture of normals centered at zero. In particular, we specify $\beta_{kj} \sim N(0, \lambda_j^{-1} \nu_k^{-1})$,over the occupations *k* and birth defects *j*, with λ_j and ν_k assigned $Ga(5,5)$ hyperpriors. Note that by fixing these parameters at their prior mean values $\lambda_j = \nu_k = 1$, this prior is simply a $N(0,1)$ prior which does not borrow any information across occupations or

outcomes. A $N(0,1)$ prior is relatively non-informative for log odds ratios (ORs), expressing our prior belief that ORs > 7.4 or < 0.14 are possible, but unlikely to be observed in our study. Closely-related priors are widely used due to their tendency for strong shrinkage of small coefficients towards zero, leading to a parsimonious model while limiting shrinkage of larger coefficients to reduce bias in estimating the signal.[29] These priors exhibit good performance in simulation studies and have previously been used to borrow information across related outcomes in high-dimensional regression.[30] In our study, shrinkage occurs in 2 dimensions: toward the typical OR for each birth defect and also toward the typical OR for each occupational group, accounting for multiplicities and dimensionality through an intrinsic Bayes correction via the hierarchical structure of the model. Thus, an advantage of this flexible modeling approach is that it is directly informed by the observed data: the degree of shrinkage is adaptively increased or decreased depending on the underlying data structure. Regression analyses were conducted using MATLAB version 7.7.0 (MathWorks Inc., Natick, MA; 2008).

An *a priori* set of potential confounding factors obtained from the interview included maternal residence at delivery (i.e., study center), maternal age, maternal race/ethnicity, maternal education, use of supplemental folic acid or prenatal vitamins, maternal smoking and alcohol use. Though some paternal characteristics were available (e.g., paternal race/ethnicity), maternal characteristics were chosen for adjustment because paternal information was often missing. For these covariates, we used independent $N(0,2)$ prior distributions, which are relatively non-informative.

The primary referent group was a fixed referent consisting of the combined occupational groups “managers, administrators” and “salesworkers,” which were considered to have little or no chemical exposure. Analyses were repeated using an alternative referent for each index occupational group consisting of all other groups combined, such that this revolving referent was different for each occupational group. Analyses were conducted first with all cases (cases with isolated or multiple defects) and then with cases of isolated defects only, since isolated and non-isolated defects may differ etiologically depending on the exposure and phenotype of interest. Adjusted posterior median ORs with 95% credible intervals (95% CI) are reported.

RESULTS

Table 2 presents the distribution of occupational groups among fathers by case-control status. The majority of fathers (90%) held only one job during the critical period of interest; thus most fathers (also 90%) were assigned to only one occupational group. Managers and administrators (10%), salesworkers (9%), and construction workers (9%) were the most common occupational groups for both cases and controls. Thirty-three groups were sparsely populated, each representing less than 1% of cases or controls. Of the 63 occupational groups in the coding scheme, only one group, metal miners, was unrepresented. Two groups, “managers and administrators” and “salesworkers,” were combined for subsequent analyses because job descriptions were similar and often resulted in assignment to both occupational groups (e.g., manager of an auto part sales department was assigned to both groups).

The main occupational analysis yielded over 20,000 effect measure estimates. A complete set of results is available from the corresponding author. To facilitate the presentation and interpretation of results, effect measure estimates are reported in Table 3 only for occupation-defect combinations with any exposed cases for which the 95% CI excluded the null (1.0) before rounding to 2 significant digits, or for which the observed effect estimate was ≥2.0 or ≤0.5 in either analyses with all cases (isolated and multiple defects) or with only cases of isolated defects. Thus, occupations were considered to be potentially associated

with a defect if the effect estimate met these specified criteria. Since very similar results were observed using either referent group, results are presented only for analyses using the fixed referent category consisting of managers, administrators and salesworkers.

Several occupations were positively associated with 3 or more birth defect categories: mathematical, physical and computer scientists; artists; photographers and photo processors; food service workers; landscapers and groundskeepers; hairdressers and cosmetologists; office and administrative support workers; sawmill workers; petroleum and gas workers; chemical workers not elsewhere classified (NEC); printers; material moving equipment operators; and motor vehicle operators.

Occupations associated with several different defects within the same anatomic system include artists, for which large effect estimates were observed for several defects of the oral cavity, eyes and ears, gastrointestinal system, limbs and heart. Photographers and photo processors were associated with 3 different eye defects: cataracts, anophthalmos/microphthalmos and glaucoma/anterior chamber defects. Motor vehicle operators were associated with anophthalmos/microphthalmos and glaucoma/anterior chamber defects. Landscapers and groundskeepers were associated with 3 gastrointestinal defects: esophageal atresia, duodenal atresia/stenosis and biliary atresia.

A number of occupations were associated with reduced odds of certain birth defects. For example, mathematical, physical and computer scientists were associated with reduced odds of anorectal atresia/stenosis as well as coarctation of the aorta. However, no occupation was associated with reduced odds of more than one defect within the same anatomic system.

Nearly one third of the occupational groups were not associated with any birth defect: architects, drafters and designers; biological scientists; entertainers and athletes; health care practitioners; dentists and dental assistants; firefighters; fishers, hunters and trappers; vehicle manufacturers; foundry and smelter workers; stone, glass and concrete workers; painters; paper workers; semiconductor processors; electronic equipment operators; plant and system operators; rail transportation workers; armed forces; and commercial divers.

DISCUSSION

This analysis provides a broad examination of the relation between paternal work in over 60 occupations and numerous birth defects. We observed over 100 occupation-defect combinations with effect measure estimates that met our pre-specified criteria for significance. Given the breadth of results and the potential for common etiologic pathways, one helpful summary approach is to examine the pattern of associated birth defects within each occupation. Several occupations were associated with more than one defect, suggesting the potential for diverse effects from a potential exposure or mixture of exposures represented by these paternal occupation categories. Some occupations were even associated with more than one defect within the same anatomic system, suggesting the possibility of varied effects from an early insult on morphogenesis, or perhaps differences in effects on components of an anatomic system depending upon timing or dose of a teratogenic exposure. For example, photographers and photo processing workers were associated with 3 distinct eye defects. Landscapers and groundskeepers were associated with 3 categories of gastrointestinal defects. Artists were associated with the most number of individual defects, including several eye/ear defects, oral clefts and defects of the gastrointestinal system. The artist group is particularly interesting as there are no exposed controls, which is reflected in the strikingly large odds ratios and upper limits of the credible intervals. To our knowledge, an increased prevalence of birth defects among offspring of artists has not been previously

reported. However, some artists' media may contain organic solvents or lead, both of which have been previously associated with birth defects in offspring of exposed fathers.[31, 32]

An alternative interpretive approach is to examine the pattern of associations across occupations that are thought to share specific exposures in the workplace. However, we did not have any information about specific agents to which fathers in our study population may have been occupationally exposed. Therefore, to better elucidate any potential patterns in exposures across occupational groups found to be associated with birth defects in these data, and to offer an additional perspective on interpreting our results, we employed an existing classification scheme determined by industrial hygienist review of job titles to identify occupations commonly exposed to solvents, wood and wood products, heavy metals and pesticides, which have each been associated with certain birth defects in previous studies of paternal occupation.[6] Occupations considered exposed to wood (e.g., sawmill workers) or metals (e.g., vehicle mechanics) were not observed to be associated with any consistent pattern of birth defects in our study. However, solvent-exposed occupations were significantly associated with an increased prevalence of numerous birth defects among NTDs, eye defects, oral clefts, gastrointestinal defects, limb deficiencies and heart defects. The following occupations were considered potentially exposed to solvents: artists, chemical workers, pharmacists, chemical engineers, electricians and electrical workers, janitors, mechanics, nurses, painters, dry cleaning and laundry workers, printers and plumbers. Associations between solvent-exposed paternal occupations and NTDs [12, 13, 32, 33] and other defects [6-8, 34]have been previously reported in many but not all [11, 15, 35] studies. We also observed an association between defects of the neural tube and both food processing workers andlandscapers/groundskeepers,, which is consistent with at least one other study reporting an association between pesticide-exposed occupations and NTDs.[16] In contrast to some previous studies, we did not observe an association with pesticide-exposed occupations and limb deficiencies.[21]

Only two population-based case-control studies in North America have previously examined a similar cross-classification of multiple paternal occupations and multiple birth defects. Olshan *et al.* [6] linked cases of birth defects from a Canadian surveillance registry to birth certificates, from which matched controls and information about paternal occupation were obtained. An occupational classification scheme similar to the one in our study was used, but there were important differences in the scope and definition of defects considered eligible. Standard statistical methods were applied and all results were presented without restriction by statistical significance or magnitude of the effect estimates. We did not observe any of the noted occupation-defect associations reported in the Canadian study such as janitors and ventricular septal defects (OR = 2.45; 95% CI = [1.10 to 5.45]; 13 exposed cases); forestry and logging workers and cataracts (2.28 [1.29, 4.02]; 30) and atrial septal defects (2.03 [1.35, 3.05]; 54); and painters and spina bifida (3.21 [0.91, 11.36]; 7) and cleft palate (3.36 [1.19, 9.46]; 9). However, our study yielded similar results for other elevated effects estimates (OR ≥ 1.5) observed by Olshan *et al.* such as shippers, messengers and cleft lip (1.50 [0.44, 5.12]; 5), chemical workers NEC and cleft lip (6.00 [0.62, 57.81]; 3), motor vehicle operators and cleft lip + cleft palate (1.49 [1.04, 2.11]; 58), and photographers, photo processors and hypospadias (2.00 [0.28, 14.23]; 2). These results, though consistent, are based on small numbers of exposed cases in both studies.

Schnitzer *et al.* [7] used self-reported job information from fathers in the Atlanta Birth Defects Case-Control Study, applied the same occupational classification scheme as Olshan *et al.,* but considered additional birth defect categories. The authors presented results from conditional logistic regression analyses with an OR greater than 1.5 and at least 3 exposed cases. We observed only one association consistent with this study: food processors and hydrocephaly (3.3 [1.2, 8.8]; 6). A large Norwegian study linking national birth and

occupation registries also examined multiple occupations and defects; the only common finding with this study was for vehicle mechanics and hypospadias (5.19 [1.31, 14.24]; 3). [36]

A recent analysis of maternal occupation and birth defects in the NBDPS (1997-2003) employed a similar study design and analytic approach.[22] Though the analysis of maternal occupation examined slightly different occupational groupings (given the different distribution of occupations between sexes), common findings are nevertheless potentially informative as they may point to teratogens encountered in the shared workplace. In both studies, solvent-exposed occupations were associated with defects of the neural tube, eye, limb, heart and gastrointestinal system as well as orofacial clefts. For example, the observed prevalence of amniotic bands and orofacial clefts was higher among offspring of both mothers and fathers who worked as janitors or cleaners. Admittedly, caution is warranted in making direct comparisons between studies of maternal and paternal occupation and occupational exposures. Given the expected variability in exposure patterns – even of the same physical or chemical agent – between men and women employed in the same occupation,[37] an association may be observed between a particular occupation and defect for one gender (e.g., the gender with the typically “higher” exposure level) but not the other. Further, because agents may demonstrate different mechanisms of teratogenesis and impact different target tissues following exposure during different time periods of susceptibility for men and women, it would not be unexpected if a particular occupational exposure had a true causal effect for one gender but not the other.

Direct comparison with other studies of paternal occupation and birth defects is also complicated by differences in study population, source and classification of occupation, and grouping of birth defects. For example, we cannot directly compare our results with studies that lump all birth defects together or that use very different occupational classifications. Further, this study is not designed to investigate any particular occupation-defect or exposure-defect relationship in depth, which would require an exposure assessment strategy beyond exclusive use of job titles. However, the results of our broad screening analysis suggested that paternal work in solvent-exposed occupations may be associated with an increase in the prevalence of several birth defects among offspring, including defects of the eye, NTDs and oral clefts. We also observed that a number of occupations (i.e., artists; photographers and photo processors; motor vehicle operators; landscapers and groundskeepers) were positively associated with several defects within the same anatomic system, which may suggest heterogeneity in effects depending on unmeasured exposure parameters such as timing or intensity.

Using the Bayesian shrinkage approach, we were able to improve upon many limitations of previous studies. For example, to reduce misclassification, we used finer, more homogenous groupings of both occupation and birth defects. Preserving the etiologic diversity of individual phenotypes is a major analytic challenge in birth defects research, and our adaptive methods use shrinkage in a manner that allows examination of more homogenous defect categories while also borrowing information across exposures and outcomes according to the presumed underlying structure of the observed data. Further, these methods address the problematic issues related to using a large number of finer exposure and outcome categories, such as decreased precision and multiple hypothesis testing.

Nonetheless, caution in the interpretation of the results is warranted. We found that when there were sufficient numbers of cases within a particular occupation, the model would allocate the coefficient for that occupation to the tails of the distribution and avoid shrinkage. However, when there were sufficient individuals in an occupation to rule out a zero log-odds ratio but not enough for reliable estimation of the coefficient, large point and

interval estimates were sometimes obtained. For example, all artists in the study were fathers of cases, leading to inflated effect measure estimates and large upper interval bounds for this occupation. Further, although large effect measure estimates (OR≥2.0) were observed for several occupation-defect combinations, most were based on few exposed cases.

Other limitations associated with exposure assessment in our study should be considered when interpreting the results. First, paternal occupational histories were reported by mothers via interview. Although use of maternal reports likely introduced some error in our occupational classification, agreement between maternal and paternal report of paternal occupation has been shown to be high (up to 80%) within two years after birth.[38, 39] Further, such misclassification has been demonstrated to be non-differential with respect to case status and thus will generally bias the effect measure estimates towards the null.[40] Despite the potential error associated with maternal report of paternal job, the quality and completeness of paternal occupational histories obtained by maternal interview exceeds that obtained from birth certificates.[41, 42] Second, the process of coding reported jobs by occupation and industry, and the further classification into 63 aggregate occupational groups, likely introduced non-differential misclassification that may have resulted in attenuation of observed effects for any given occupation. Ultimately, observed associations should be interpreted with caution, as our study is limited to using occupational groups as a surrogate measure for workplace exposures and exposure mixtures potentially encountered at each job.

Lastly, we acknowledge that the length of time between the infant's birth and the maternal interview could be a potential source of recall bias. Women were asked between 6 weeks and 24 months after the EDD to report on jobs held by their baby's father during their entire pregnancy and the 3 months before conception. Although a pregnancy calendar was used to aid recall, an extended time-to-interview could contribute to increased errors in reporting, and could further lead to recall bias if systematic differences in reporting accuracy due to time-to-interview exist between cases of different defects. However, the average time-to-interview in our study was less than one year (11 months for cases and 9 months for controls), and ranged from only 9 to 14 months among cases of different defects. Further, mothers were asked about the fathers' job title and general description of tasks, which is likely less susceptible to recall error than questions about specific chemical agents or other workplace exposures. Therefore, we do not expect time-to-interview to be a significant source of recall error or bias in our study.

Our exploratory study has a number of notable strengths that make it an important contribution to the existing literature on paternal occupation as a risk factor for birth defects. We used data from a national population-based case-control study with systematic case review and classification for a wide variety of birth defects among live-born infants, stillbirths and electively terminated pregnancies. We were able to examine more than 60 defect categories, many of which have not been previously investigated in relation to paternal occupation. Despite the aforementioned limitations related to classification of occupation, our study improves upon previous studies that have relied on data from birth certificates because we obtained detailed occupational histories by interview on multiple jobs held during the time window most etiologically relevant to male-mediated teratogenesis. We were able to account for potential confounding by several important covariates collected during the maternal interview. Further, consistency in observed effects across our 2 comparison groups – a fixed referent comprised of all managers, administrators and salesworkers, representing a set of jobs considered unlikely to have substantial chemical exposure; and a revolving referent consisting of all occupations other than the index occupation, an approach which is frequently used in similar studies – minimizes concern that our observed results are affected by residual confounding by factors such as

socioeconomic status.[15] Finally, our adaptive Bayesian analytic approach allows for the estimation of associations between numerous relatively homogenous occupational groups and etiologically distinct categories of birth defects, thereby addressing common small sample analytic limitations and avoiding the need for further aggregation of either exposure or outcomes into larger, less homogeneous groups.

Our study contributes evidence to the growing body of epidemiologic literature on male-mediated teratogenesis. Findings from this broad screening analysis can be used to inform further investigation of specific paternal occupations found to be associated with birth defects, and to generate hypotheses about chemical or physical exposures and exposure mixtures common to such occupations.

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What this paper adds

- Previous epidemiologic investigations of paternal occupation and birth defects in offspring have grouped etiologically distinct phenotypes together, which may introduce etiologic heterogeneity and dilute associations. Likewise, job titles with potentially different chemical and physical exposure profiles are often loosely grouped together by major industry rather than by shared exposures, leading to exposure misclassification.
- This large, population-based study was conducted to explore the relation between multiple paternal occupations and over 60 types of birth defects using Bayesian analytic methods that specifically address the statistical challenges associated with analysis of sparsely distributed data across numerous exposures and outcomes.
- Results from this study indicate that paternal work in a number of occupations may be associated with an increased prevalence of various birth defects in offspring. Findings can be used to inform future investigation of specific paternal occupations found to be associated with birth defects, or to generate hypotheses about chemical or physical exposures and exposure mixtures common to such occupations.

Table 1

Distribution of major birth defect categories eligible for analysis, by primary organ system, National Birth Defects Prevention Study, United States, 1997-2004

Birth defect categories[a]	Isolated and multiple (n)	Isolated only (n)
Non-heart defects		
Amniotic Band Syndrome and limb body wall defects		
Limb anomalies only	70	66
Craniofacial disruptions +/− limb anomalies	19	14
Body wall complex +/− limb anomalies and +/− craniofacial disruptions	15	13
Central nervous system defects		
Neural tube defects		
Anencephaly and craniorachischisis	192	176
Spina bifida	425	383
Encephalocele	83	60
Hydrocephaly	178	128
Cerebellar hypoplasia / Dandy-Walker malformation	61	36
Holoprosencephaly	46	33
Eye and ear defects		
Cataracts	99	92
Anophthalmos / microphthalmos	90	50
Glaucoma / anterior chamber defects	47	38
Anotia / microtia	242	184
Orofacial defects		
Oral clefts		
Cleft palate	562	455
Cleft lip	353	331
Cleft lip + cleft palate	658	574
Choanal atresia	55	27
Gastrointestinal defects		
Esophageal atresia	252	112
Duodenal atresia / stenosis	70	47
Jejunal or ileal atresia / stenosis	154	133
Colonic atresia / stenosis	16	14
Anorectal atresia / stenosis	366	181
Biliary atresia	66	58
Genitourinary defects		
Hypospadias (2^{nd} or 3^{rd} degree only)	751	689
Bilateral renal agenesis or hypoplasia	65	45
Musculoskeletal defects		
Bladder exstrophy	30	27
Limb deficiencies		

Birth defect categories[a]	Isolated and multiple (n)	Isolated only (n)
Longitudinal limb deficiency	153	84
Longitudinal preaxial limb deficiency	87	32
Transverse limb deficiency	247	213
Intercalary limb deficiency	24	18
NOS limb deficiency	9	7
Craniosynostosis	436	400
Diaphragmatic hernia	290	229
Omphalocele	147	94
Gastroschisis	379	350
Sacral agenesis or caudal dysplasia	21	3
Heart Defects		
Laterality defects with congenital heart disease[b]	113	
Conotruncal defects		
Truncus arteriosus	34	30
Interrupted aortic arch Type B	9	6
Interrupted aortic arch NOS	3	3
Tetralogy of Fallot	391	311
d-Transposition of the great arteries	250	239
Double outlet right ventricle - transposition of the great arteries	14	12
Double outlet right ventricle - other	15	10
Ventricular septal defect, conoventricular	31	25
Atrioventricular septal defect	68	56
Anomalous pulmonary venous return		
Total anomalous pulmonary venous return	94	86
Partial anomalous pulmonary venous return	15	13
Left-sided obstructions		
Hypoplastic left heart syndrome	195	179
Interrupted aortic arch Type A	6	5
Coarctation of the aorta	195	170
Aortic stenosis	109	102
Right-sided obstructions		
Pulmonary atresia	56	52
Pulmonary valve stenosis	363	345
Ebstein anomaly	43	41
Tricuspid atresia	25	21
Septal defects		
Ventricular septal defect, perimembranous	512	453
Ventricular septal defect, muscular	127	113
Ventricular septal defect, NOS	15	12
Ventricular septal defect, OS	9	7

Birth defect categories[a]	Isolated and multiple (n)	Isolated only (n)
Multiple ventricular septal defects	32	27
Atrial septal defect, secundum or NOS	614	473
Atrial septal defect, OS	3	1
Single ventricle[b]	146	
Associated heart defects		
AS + CoA	30	26
CoA + VSD	87	74
VSD + ASD	281	222
VSD + ASD + CoA	32	23
PVS + ASD	60	53
PVS + VSD	56	46

Abbreviation: NOS, not otherwise specified; OS, other specified; AS, aortic stenosis; CoA, coarctation of the aorta; VSD, ventricular septal defect; ASD, atrial septal defect; PVS, pulmonary valve stenosis.

[a]Defects are grouped by primary organ system and broad categories of heart defects for ease of presentation only; groupings do not necessarily represent shared etiology or embryological development.

[b]All cases are considered to be complex sequences; classification of “isolated *vs.* multiple” not applicable.

Table 2

Distribution of assigned occupational groups among fathers with one or more jobs during the critical exposure period[a], National Birth Defects Prevention Study, United States, 1997-2004

Occupational group	Cases n (%)[b]	Controls n (%)[b]	Total n[b]
Managers, administrators	973 (9.7)	436 (10.7)	1409
Business and financial specialists	355 (3.6)	184 (4.5)	539
Mathematical, physical, and computer scientists	440 (4.4)	191 (4.7)	631
Architects, drafters, designers	73 (0.7)	49 (1.2)	122
Surveyors, geologists, geoscientists	19 (0.2)	7 (0.2)	26
Engineers, science technicians	255 (2.6)	111 (2.7)	366
Biological scientists	80 (0.8)	28 (0.7)	108
Chemical scientists and pharmacists	32 (0.3)	20 (0.5)	52
Legal and social service workers	231 (2.3)	115 (2.8)	346
Teachers, librarians	227 (2.3)	120 (3.0)	347
Artists	8 (0.1)	0	8
Entertainers, athletes	106 (1.1)	44 (1.1)	150
Media and communication workers	42 (0.4)	22 (0.5)	64
Photographers, photo processors	20 (0.2)	3 (0.1)	23
Health care practitioners	85 (0.9)	43 (1.1)	128
Dentists, dental assistants	12 (0.1)	6 (0.1)	18
Nurses, therapists, health technicians	163 (1.6)	63 (1.5)	226
Police, guards	296 (3.0)	127 (3.1)	423
Firefighters	58 (0.6)	23 (0.6)	81
Food service workers	555 (5.6)	178 (4.4)	733
Landscapers, groundskeepers	273 (2.7)	87 (2.1)	360
Janitors, cleaners	257 (2.6)	90 (2.2)	347
Laundry and dry cleaning workers	13 (0.1)	6 (0.1)	19
Personal service workers	50 (0.5)	20 (0.5)	70
Hairdressers and cosmetologists	26 (0.3)	8 (0.2)	34
Salesworkers	874 (8.7)	360 (8.9)	1234
Office and administrative support workers	240 (2.4)	82 (2.0)	322
Messengers	58 (0.6)	29 (0.7)	87
Shippers	275 (2.8)	109 (2.7)	384
Farmers and farm workers	397 (4.0)	169 (4.2)	566
Fisher, hunters and trappers	2 (<0.1)	1 (<0.1)	3
Forestry and logging workers	20 (0.2)	6 (0.1)	26
Sawmill workers	57 (0.6)	16 (0.4)	73
Construction workers	884 (8.8)	345 (8.5)	1229
Carpenters, wood workers	233 (2.3)	103 (2.5)	336
Electricians, electrical, and electronics workers	395 (4.0)	138 (3.4)	533
Vehicle manufacturing	60 (0.6)	31 (0.8)	91

Occupational group	Cases	Controls	Total
	n (%)[b]	n (%)[b]	n[b]
Vehicle mechanics	315 (3.2)	112 (2.8)	427
Mechanics, NEC	441 (4.4)	156 (3.8)	597
Metal miners	0	0	0
Foundry and smelter workers	31 (0.3)	13 (0.3)	44
Petroleum and gas workers	71 (0.7)	20 (0.5)	91
Stone, glass, and concrete workers	37 (0.4)	21 (0.5)	58
Sheetmetal, iron, and other metal workers	126 (1.3)	55 (1.4)	181
Welders, cutters	111 (1.1)	35 (0.9)	146
Chemical workers, NEC	114 (1.1)	39 (1.0)	153
Food processing workers	231 (2.3)	88 (2.2)	319
Printers	54 (0.5)	23 (0.6)	77
Painters	156 (1.6)	80 (2.0)	236
Textile workers	35 (0.4)	16 (0.4)	51
Paper workers	38 (0.4)	14 (0.3)	52
Semiconductor processors	7 (0.1)	2 (<0.1)	9
Electronic equipment operators	79 (0.8)	29 (0.7)	108
Plant and system operators	18 (0.2)	9 (0.2)	27
Material moving equipment operators	251 (2.5)	93 (2.3)	344
Motor vehicle operators	538 (5.4)	200 (4.9)	738
Aircraft operators, air crew	30 (0.3)	8 (0.2)	38
Rail transportation workers	15 (0.2)	6 (0.1)	21
Water transportation workers	8 (0.1)	5 (0.1)	13
Transportation workers, NEC	15 (0.2)	3 (0.1)	18
Service station attendants	25 (0.3)	6 (0.1)	31
Armed forces	170 (1.7)	82 (2.0)	252
Commercial divers	1 (<0.1)	0	1

Abbreviation: NEC, not elsewhere classified.

[a]Three months preceding the estimated date of conception through the first month of pregnancy.

[b]The distribution does not add up to the total sample (9998 cases; 4066 controls) because each father may have more than one job, and each job may be assigned to more than one occupational group.

Table 3

Adjusted posterior median odds ratios and 95% credible intervals for birth defects associated with occupational groups assigned to fathers with one or more jobs during the critical exposure period[a], National Birth Defects Prevention Study, United States, 1997-2004

Occupational group	Associated defect category[b]	Isolated and multiple		Isolated only	
		n[b]	OR (95% CI)[d]	n[c]	OR (95% CI)[d]
Managers, administrators; salesworkers			REF [e]		REF [e]
Business and financial specialists	Cleft palate	14	0.8 (0.6, 1.0)	14	0.8 (0.6, 1.0)
	Jejunal or ileal atresia / stenosis	2	0.6 (0.4, 1.0)	2	0.6 (0.4, 1.0)
Mathematical, physical, and computer scientists	Anorectal atresia / stenosis	7	0.7 (0.5, 0.9)	7	0.7 (0.5, 0.9)
	Colonic atresia / stenosis	1	2.0 (0.8, 5.1)	1	2.0 (0.8, 5.1)
	Limb deficiency, intercalary	3	1.7 (0.9, 3.3)	3	1.7 (0.9, 3.3)
	Diaphragmatic hernia	21	1.2 (0.9, 1.6)	21	1.2 (0.9, 1.6)
	Coarctation of the aorta	3	0.6 (0.4, 0.9)	3	0.6 (0.4, 0.9)
Surveyors, geologists, geoscientists	Biliary atresia	1	1.9 (0.8, 4.8)	1	1.9 (0.8, 4.8)
Engineers, science technicians	Colonic atresia / stenosis	1	2.1 (0.9, 5.8)	1	2.1 (0.9, 5.8)
Chemical scientists and pharmacists	Interrupted aortic arch, Type B	1	2.4 (0.7, 8.5)	1	2.4 (0.7, 8.5)
Legal and social service workers	Esophageal atresia	14	1.3 (0.9, 1.7)	14	1.3 (0.9, 1.7)
	ASD, secundum or NOS	2	0.7 (0.5, 1.0)	2	0.7 (0.5, 1.0)
Teachers, librarians	Duodenal atresia / stenosis	5	1.3 (0.8, 2.0)	5	1.3 (0.8, 2.0)
Artists	Encephalocele	1	21 (1.8, 3000)	1	21 (1.8, 3000)
	Cataracts	1	17 (1.3, 5000)	1	17 (1.3, 5000)
	Anophthalmos / microphthalmos	1	25 (2.0, 7000)	1	25 (2.0, 7000)
	Anotia / microtia	1	14 (1.3, 1000)	1	14 (1.3, 1000)
	Cleft palate	2	11 (1.6, 609)	2	11 (1.6, 609)
	Cleft lip	1	10 (1.1, 687)	1	10 (1.1, 687)
	Anorectal atresia / stenosis	1	8.8 (0.9, 660)	1	8.8 (0.9, 660)
	Bilateral renal agenesis or hypoplasia	1	19 (1.6, 4000)	1	19 (1.6, 4000)
	Limb deficiency, transverse	1	15 (1.6, 1000)	1	15 (1.6, 1000)
	Hypoplastic left heart syndrome	2	18 (2.5, 1000)	2	18 (2.5, 1000)
	ASD, secundum or NOS	1	6.1 (0.7, 431)	1	6.1 (0.7, 431)
Media and communication workers	Colonic atresia / stenosis	1	2.8 (0.9, 9.6)	1	2.8 (0.9, 9.6)
Photographers, photo processors	ABS: limb anomalies only	1	2.1 (0.8, 6.7)	1	2.1 (0.8, 6.7)
	Cataracts	1	1.9 (0.6, 8.5)	1	1.9 (0.6, 8.5)
	Anophthalmos / microphthalmos	1	2.3 (0.8, 7.3)	1	2.3 (0.8, 7.3)
	Glaucoma / anterior chamber defects	1	3.2 (0.9, 16)	1	3.2 (0.9, 16)
	Hypospadias	4	2.0 (0.9, 4.6)	4	2.0 (0.9, 4.6)
Nurses, therapists, health technicians	Colonic atresia / stenosis	1	2.1 (0.8, 6.4)	1	2.1 (0.8, 6.4)
Police, guards	Diaphragmatic hernia	3	0.7 (0.5, 1.0)	3	0.7 (0.5, 1.0)
Food service workers	Anotia / microtia	20	1.3 (1.0, 1.8)	20	1.3 (1.0, 1.8)
	Biliary atresia	5	1.6 (1.0, 2.5)	5	1.6 (1.0, 2.5)

Occupational group	Associated defect category[b]	Isolated and multiple		Isolated only	
		n[b]	OR (95% CI)[d]	n[c]	OR (95% CI)[d]
	Limb deficiency, transverse	18	1.4 (1.0, 1.8)	18	1.4 (1.0, 1.8)
	Gastroschisis	49	1.4 (1.1, 1.8)	49	1.4 (1.1, 1.8)
	Sacral agenesis or caudal dysplasia	2	1.3 (0.7, 2.6)	2	1.3 (0.7, 2.6)
Landscapers, groundskeepers	ABS: Craniofacial disruptions +/− limb	2	1.9 (0.9, 4.4)	2	1.9 (0.9, 4.4)
	Anencephaly	8	1.4 (1.0, 2.1)	8	1.4 (1.0, 2.1)
	Esophageal atresia	8	1.2 (0.9, 1.8)	8	1.2 (0.9, 1.8)
	Duodenal atresia / stenosis	4	1.4 (0.8, 2.3)	4	1.4 (0.8, 2.3)
	Biliary atresia	3	1.7 (1.0, 2.8)	3	1.7 (1.0, 2.8)
	TAPVR	7	1.8 (1.2, 2.8)	7	1.8 (1.2, 2.8)
	ASD, secundum or NOS	18	1.3 (1.0, 1.7)	18	1.3 (1.0, 1.7)
Janitors, cleaners	ABS: Craniofacial disruptions +/− limb	3	2.3 (1.1, 5.1)	3	2.3 (1.1, 5.1)
	Cleft lip	12	1.4 (1.0, 2.0)	12	1.4 (1.0, 2.0)
Laundry and dry cleaning workers	Anophthalmos / microphthalmos	2	2.4 (1.0, 5.8)	2	2.4 (1.0, 5.8)
	AS + CoA	1	2.0 (0.7, 6.2)	1	2.0 (0.7, 6.2)
Personal service workers	Interrupted aortic arch Type B	1	2.0 (0.6, 6.8)	1	2.0 (0.6, 6.8)
Hairdressers and cosmetologists	Choanal atresia	1	2.0 (0.7, 5.2)	1	2.0 (0.7, 5.2)
	Limb deficiency, longitudinal preaxial	2	2.0 (0.9, 4.8)	2	2.0 (0.9, 4.8)
	Gastroschisis	3	2.0 (0.9, 4.3)	3	2.0 (0.9, 4.3)
	VSD, conoventricular	2	2.7 (1.0, 7.5)	2	2.7 (1.0, 7.5)
	AVSD	2	2.2 (0.9, 5.4)	2	2.2 (0.9, 5.4)
Office and administrative support workers	Glaucoma / anterior chamber defects	6	2.5 (1.5, 4.5)	6	2.5 (1.5, 4.5)
	Colonic atresia / stenosis	1	1.9 (0.7, 5.2)	1	1.9 (0.7, 5.2)
	Hypospadias	23	1.4 (1.0, 2.0)	23	1.4 (1.0, 2.0)
	Bladder exstrophy	3	2.0 (1.0, 3.6)	3	2.0 (1.0, 3.6)
	Omphalocele	8	1.5 (1.0, 2.2)	8	1.5 (1.0, 2.2)
Messengers	Choanal atresia	1	1.5 (0.7, 3.1)	1	1.5 (0.7, 3.1)
	VSD, NOS	2	2.6 (0.7, 12)	2	2.6 (0.7, 12)
Shippers	Cleft lip	14	1.4 (1.0, 1.9)	14	1.4 (1.0, 1.9)
	Anorectal atresia / stenosis	2	0.6 (0.4, 0.9)	2	0.6 (0.4, 0.9)
Farmers and farm workers	Anotia / microtia	28	1.4 (1.1, 1.9)	28	1.4 (1.1, 1.9)
	Gastroschisis	12	0.7 (0.5, 1.0)	12	0.7 (0.5, 1.0)
	VSD, muscular	1	0.5 (0.2, 1.0)	1	0.5 (0.2, 1.0)
Forestry and logging workers	ABS: Body wall complex	1	2.7 (0.7, 11)	1	2.7 (0.7, 11)
Sawmill workers	Glaucoma / anterior chamber defects	1	1.9 (0.7, 5.1)	1	1.9 (0.7, 5.1)
	Choanal atresia	1	2.0 (0.8, 4.8)	1	2.0 (0.8, 4.8)
	Hypospadias	5	1.8 (1.0, 3.3)	5	1.8 (1.0, 3.3)
	Interrupted aortic arch, Type B	1	2.6 (0.7, 9.8)	1	2.6 (0.7, 9.8)
	AVSD	2	1.8 (0.8, 3.9)	2	1.8 (0.8, 3.9)
Construction workers	Biliary atresia	9	1.6 (1.1, 2.4)	9	1.6 (1.1, 2.4)
Carpenters, wood workers	Colonic atresia / stenosis	1	1.9 (0.8, 5.1)	1	1.9 (0.8, 5.1)

Occupational group	Associated defect category[b]	Isolated and multiple		Isolated only	
		n[b]	OR (95% CI)[d]	n[c]	OR (95% CI)[d]
	Coarctation of the aorta	1	0.6 (0.4, 1.0)	1	0.6 (0.4, 1.0)
Electricians, electrical, and electronics workers	Cleft lip + cleft palate	37	1.3 (1.0, 1.6)	37	1.3 (1.0, 1.6)
Vehicle mechanics	Hypospadias	22	1.4 (1.0, 1.9)	22	1.4 (1.0, 1.9)
Mechanics, NEC	Biliary atresia	4	1.5 (1.0, 2.5)	4	1.5 (1.0, 2.5)
	VSD & ASD	23	1.5 (1.1, 1.9)	23	1.5 (1.1, 1.9)
Petroleum and gas workers	Glaucoma / anterior chamber defects	1	2.0 (0.8, 5.1)	1	2.0 (0.8, 5.1)
	Colonic atresia / stenosis	1	2.8 (0.9, 9.1)	1	2.8 (0.9, 9.1)
	Limb deficiency, intercalary	2	2.6 (1.1, 6.5)	2	2.6 (1.1, 6.5)
	ASD, secundum or NOS	11	1.6 (1.0, 2.4)	11	1.6 (1.0, 2.4)
Sheetmetal, iron, and other metal workers	Single ventricle	5	1.6 (1.0, 2.6)	5	1.6 (1.0, 2.6)
Welders, cutters	ABS: Body Wall Complex	2	2.2 (0.8, 5.7)	2	2.2 (0.8, 5.7)
	Laterality defects with CHD	5	2.1 (1.2, 3.5)	5	2.1 (1.2, 3.5)
Chemical workers, NEC	Anophthalmos / microphthalmos	3	1.6 (0.9, 2.9)	3	1.6 (0.9, 2.9)
	Cleft lip	8	1.6 (1.1, 2.4)	8	1.6 (1.1, 2.4)
	Pulmonary valve stenosis	10	1.5 (1.0, 2.2)	10	1.5 (1.0, 2.2)
Food processing workers	Encephalocele	7	1.6 (1.0, 2.5)	7	1.6 (1.0, 2.5)
	Hydrocephaly	10	1.5 (1.1, 2.2)	10	1.5 (1.1, 2.2)
Printers	Colonic atresia / stenosis	1	3.0 (1.0, 9.6)	1	3.0 (1.0, 9.6)
	Double outlet right ventricle - other	1	2.2 (0.8, 6.2)	1	2.2 (0.8, 6.2)
	Tricuspid atresia	2	2.4 (1.0, 5.4)	2	2.4 (1.0, 5.4)
	VSD, NOS	1	2.3 (0.5, 15)	1	2.3 (0.5, 15)
Textile workers	VSD, NOS	1	3.1 (0.7, 25)	1	3.1 (0.7, 25)
Material moving equipment operators	Cleft lip	13	1.4 (1.0, 1.9)	13	1.4 (1.0, 1.9)
	Craniosynostosis	18	1.4 (1.0, 1.9)	18	1.4 (1.0, 1.9)
	ASD, OS	1	2.3 (0.7, 9.8)	1	2.3 (0.7, 9.8)
Motor vehicle operators	Anencephaly	17	1.4 (1.1, 1.9)	17	1.4 (1.1, 1.9)
	Anophthalmos / microphthalmos	10	1.5 (1.1, 2.2)	10	1.5 (1.1, 2.2)
	Glaucoma / anterior chamber defects	5	1.7 (1.0, 2.8)	5	1.7 (1.0, 2.8)
	Cleft lip + cleft palate	42	1.2 (1.0, 1.5)	42	1.2 (1.0, 1.5)
	Hypospadias	35	1.3 (1.0, 1.7)	35	1.3 (1.0, 1.7)
	Limb deficiency, transverse	22	1.5 (1.1, 1.9)	22	1.5 (1.1, 1.9)
Aircraft operators, air crew	Anencephaly	3	2.2 (1.1, 4.5)	3	2.2 (1.1, 4.5)
Water transportation workers	ABS: Craniofacial disruptions +/− limb	1	3.2 (0.9, 15)	1	3.2 (0.9, 15)
Transportation workers, NEC	Colonic atresia / stenosis	1	4.0 (1.0, 19)	1	4.0 (1.0, 19)
Service station attendants	PVS & ASD	1	2.5 (0.9, 7.0)	1	2.5 (0.9, 7.0)

Abbreviations: ABS, amniotic band syndrome; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; CoA, coarctation of the aorta; CI, Credible Interval; NE, not estimated; NEC, not elsewhere NOS, not otherwise specified; classified; OR, Odds Ratio; OS, other specified; PVS, pulmonic valve stenosis; REF, referent; TAPVR, total anomalous pulmonary venous return; VSD, ventricular septal defect

[a]Three months preceding the estimated date of conception through the first month of pregnancy.

[b] Defect categories were considered to be associated with an occupation if the 95% credible interval around the odds ratio for occupation-defect combinations with any exposed cases excluded the null before rounding, or if the odds ratio was ≥2.0 or ≤0.5 for either isolated defects or for all cases combined.

[c] Number of exposed cases.

[d] Adjusted for maternal age at delivery, maternal race/ethnicity, maternal education, maternal smoking, maternal alcohol use, maternal vitamin/folic acid use, and maternal residence at delivery.

[e] Results presented for analyses with the common referent consisting of two occupational groups combined, “Managers, Administrators” and “Salesworkers”.