

Parental Lead Exposure and Total Anomalous Pulmonary Venous Return

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BACKGROUND: Investigators from the Baltimore-Washington Infant Study (BWIS) reported an association between self-reported maternal lead exposure and total anomalous pulmonary venous return (TAPVR) in their offspring. This association was further evaluated in the BWIS population using a more sensitive exposure estimate. **METHODS:** Cases included 54 live-born infants with TAPVR; controls were a stratified random sample of 522 live-born infants from the BWIS control group. Parental lead exposure was based on three assessment methods, including: an industrial hygiene assessment, an a priori job exposure matrix, and self-reported exposures. A parent was classified as exposed to lead if he/she was classified as exposed by any one of the assessment methods. **RESULTS:** Approximately 17% of case mothers and 11% of control mothers were classified as exposed to lead during the three months prior to conception through the first trimester (odds ratio [OR], 1.57; 95% confidence interval [CI], 0.64–3.47). Among fathers, 61% of case fathers and 46% of control fathers were classified as exposed to lead during the six months prior to conception (paternal critical period) (OR, 1.83; 95% CI, 1.00–3.42). During the paternal critical period, when only the father was exposed compared to neither parent exposed, the OR for any lead exposure and TAPVR was 1.65 (95% CI, 0.84–3.25). **CONCLUSIONS:** This study supports a possible association between paternal lead exposure and TAPVR. Further studies are warranted using validated assessment methods for occupational and nonoccupational lead exposures to corroborate this association and to elucidate the possible biological mechanism. *Birth Defects Research (Part A) 70:185–193, 2004.* © 2004 Wiley-Liss, Inc.

Key words: congenital heart defects; lead; occupational exposure

INTRODUCTION

Total anomalous pulmonary venous return (TAPVR) is a congenital cardiovascular malformation in which the pulmonary veins that bring oxygenated blood from the lungs to the heart connect to the right atrium or its tributaries instead of the left atrium. As a result, blood passing through the aorta to the rest of the body is inadequately oxygenated. It is a very rare malformation with a prevalence of approximately 6.5 cases per 100,000 live births and it is associated with an infant mortality rate greater than 80% when surgery is not undertaken (Grabitz et al., 1988; Krabill and Lucas, 1990; Ferencz et al., 1997).

Investigators in the Baltimore-Washington Infant Study (BWIS), a large case-control study of cardiovascular mal-

formations in live-born infants, found an association between self-reported maternal lead exposure and TAPVR in earlier analyses of the data (Correa-Villaseñor et al., 1991; Ferencz et al., 1997). Lead is a concern, as it is a relatively

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common occupational exposure and it is ubiquitous in the environment. Furthermore, lead has been associated with other congenital malformations (Sallmén et al., 1992; Kristensen et al., 1993; Alexander et al., 1996a; Irgens et al., 1998; Dawson et al., 1999; Vinceti et al., 2001), as well as several adverse reproductive outcomes, including: spontaneous abortions (Nordström et al., 1979; Lindbohm et al., 1991; Kristensen et al., 1993; Borja-Aburto et al., 1999); decreased fertility (Gennart et al., 1992; Lin et al., 1996; Apostoli et al., 2000); and decreased sperm quantity and quality (Lancranjan et al., 1975; Lerda, 1992; Alexander et al., 1996b; Robins et al., 1997; Bonde et al., 2002). Therefore, we were motivated to further explore the association between maternal (and paternal) lead exposure and TAPVR within the BWIS using data on self-reported lead exposures (occupational and nonoccupational), as well as an assessment of job histories for occupational lead exposure using an industrial hygiene assessment and a job exposure matrix. The addition of the industrial hygiene assessment and the job exposure matrix should provide a more accurate estimate of occupational exposures than self-reports alone and, as a result, increase the probability of finding an association if an association truly exists (Bouyer et al., 1995; Fritschi et al., 1996; Tielemans et al., 1999).

MATERIALS AND METHODS

Study Population

A case-control study was designed within the BWIS to investigate the association between parental lead exposure and total anomalous pulmonary venous return in children. Recruitment of children and their parents was carried out from January 1, 1981, through December 31, 1989. All infants were delivered in participating hospitals within the District of Columbia, Northern Virginia, and the state of Maryland. Details of the BWIS methods can be found in Ferencz et al. (1993).

Cases were confirmed before one year of age by echocardiography, cardiac catheterization, surgery, and/or autopsy, and their diagnosis and vital status were updated at one year of age. Each infant was given a primary diagnosis based upon the cardiovascular malformation that occurred the earliest in embryogenesis. There were 60 cases with a primary diagnosis of TAPVR, 56 (93%) of whose parents completed an interview, including two twins from different families. The current study includes only the 54 singleton infants. Approximately 24% of cases had a secondary noncardiac anomaly, including two with chromosomal abnormalities, five with organ defects, four with recognized syndromes, and one with multiple, nonclassified anomalies.

In the original study, controls ($n = 3572$) were a random sample of all live-born infants without cardiovascular malformations that were delivered in the participating hospitals, stratified by month, year, and hospital of birth. The number of controls selected from each hospital was proportional to the number of births the hospital contributed to all regional deliveries. Participation among controls was high, with first choices representing 78% of all controls participating in the study and second choices 17% (Rubin and Ferencz, 1993). Controls were similar to all area births during the study period by infant gender, race, birthweight, and multiplicity of birth, as well as season of birth and maternal age (Rubin and Ferencz, 1993).

Controls for the current study were originally identified for a study of occupational lead exposure and low birthweight within the BWIS (Min et al., 1996). They were selected from a subset ($n = 3140$) of the original control population that excluded twins ($n = 53$), infants with noncardiac birth defects ($n = 61$), infants of race other than "Black" or "White" ($n = 98$), and low birthweight infants ($n = 220$). Stratified random sampling was used to select 522 controls from the 3140-infant subset, stratified by year of birth.

A questionnaire including questions on infant health, demographic and socioeconomic factors, maternal medical history, family genetic factors, use of therapeutic drugs, medical exposures, personal habits, home environment, work histories, and avocational and occupational exposures was administered to parents of cases and controls by a trained interviewer. The mean time from infant birth to interview was 5.6 months (standard deviation [SD], 6.7 months) for cases and 6.0 months (SD, 3.6 months) for controls.

Exposure Assessment

Three different methods of exposure assessment were employed in the current study to determine occupational sources of lead exposure. These included an industrial hygiene assessment, an a priori job exposure matrix, and self-reported exposures. The industrial hygiene assessment was based upon information from the work histories, including job title, dates of employment, employer, and type of work, for both paternal and maternal jobs held from six months prior to conception through birth. Five screeners (industrial hygienists and occupational epidemiologists), blinded to case-control status, reviewed all jobs ($n = 1138$) to determine if there was potential lead exposure. When all five screeners agreed no lead was present, the job was considered to have no lead exposure. If any one of the screeners believed there was lead exposure in a job, an industrial hygienist who was not one of the original screeners further evaluated the job ($n = 247$). The industrial hygienist, blinded to case-control status, assessed these jobs for direct and indirect lead exposure. A parent was considered exposed if the industrial hygienist assigned either direct or indirect lead exposure for a job.

Occupational exposures were also assessed using the National Occupational Exposure Survey (NOES) job exposure matrix (JEM), which was based upon a survey carried out between November 1980 and June 1983 by the National Institute for Occupational Safety and Health (NIOSH) (Seta et al., 1988). The use of the NOES JEM was optimal in this study, as the survey period overlapped with the BWIS study period. The survey was representative of all businesses that were covered by the Occupational Safety and Health Act of 1970 and that employed eight or more employees, with the exception of businesses related to agricultural production; any mining activity, except oil and gas extraction; railroad transportation; private households; financial institutions; and public administration (Sieber, 1990). Trained surveyors inspected a total of 4490 establishments during the study.

The NOES JEM is a three-level classification system, with each classification nested within the previous one, including industry, occupation, and hazard, respectively (Sieber et al., 1991). The JEM contains information on 121 industries, 6301 industry/occupation pairs, and 483,201

industry/occupation/hazard groups. A total of 69 inorganic lead exposures, including alloys, compounds, ores, and lead used in welding, brazing, and soldering are included in the JEM, as well as 24 organic lead compounds. An occupational epidemiologist and industrial hygienist assigned 1980 industry and occupation codes (Bureau of the Census, 1982) to all BWIS jobs in the study, which were then compared to the NOES JEM to determine lead exposure. A parent was considered exposed by the NOES JEM if the probability of lead exposure (defined as the ratio of the national estimate of total number of employees potentially exposed to lead in the industry/occupation pair over the national estimate of total number of employees in the industry/occupation pair) was greater than zero for any job held by the parent.

During the BWIS interview, respondents were queried on 35 different occupational and environmental exposures to which the mother and father may have been in "direct contact" during the period of interest. BWIS staff having environmental or toxicological expertise reviewed all questionnaires to ensure reported exposures were consistent with verbatim descriptions of the activities provided by parents (Magee et al., 1993). When an inconsistency was found, appropriate corrections were made to the data. Determination of self-reported lead exposure was based on reports of one or more of the following activities: "paint stripping or sanding old paint which might have lead in it," "soldering with lead or any other work with lead scrap or battery smelting," "welding," "doing body repair work on vehicles," "degreasing motors or cleaning guns with solvents" (lead exposure from gun cleaning), "making jewelry (professionally or as a hobby)," and "doing arts and crafts with stained glass." For each reported activity, the respective parent was asked whether the exposure had been occupational or not.

Critical periods of exposure for both mothers and fathers were established a priori and were based upon the kinetics of lead in the body, as well as the timing of embryogenesis and spermatogenesis. For mothers, the critical period included the three months preceding pregnancy through the first trimester, so as to include the period of embryogenesis. Among fathers, the critical period was defined as the six months prior to pregnancy, which included the relevant period of spermatogenesis. Both critical periods permit exposure prior to embryogenesis and spermatogenesis, respectively, to capture recent lead exposures that may have been stored in parental tissues.

A parent was classified as having had occupational lead exposure during his/her critical period if he/she was classified as exposed by any one of the three exposure assessments methods during that period. A parent was classified as having had nonoccupational lead exposure during his/her critical period if he/she was classified as such by the self-report.

Analysis

Cases and controls were compared on selected infant, maternal, and paternal characteristics, including demographic, health, and exposure variables. Given the small number of observations in some cells, Fisher's exact test was used to determine if the distribution of cases and controls differed significantly for each of these factors (Fisher, 1935).

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare the odds of exposure for cases and controls. Due to the small number of observations in some cells, exact confidence intervals were calculated using the Epi Info Version 2000 software (Centers for Disease Control and Prevention, Atlanta, GA; <http://www.cdc.gov/epiinfo/index.htm>) (Mehta et al., 1985). As very few case mothers were exposed to lead, no adjustment for potential confounders was carried out for this group. Multiple logistic regression was used to adjust for potential confounders among fathers.

Given a sample size of 54 cases and 522 controls, the study had 87% power to detect an OR of 2.5 if the prevalence of exposure in the controls was as high as 20%. If the prevalence of exposure among controls was as low as 1%, the power to detect an OR of 2.5 decreased to 16%. The prevalence of lead exposure was estimated using the prior BWIS analysis (Correa-Villaseñor et al., 1991), as well as another community-based case-control study in Baltimore, which found among controls that the prevalence of maternal occupational lead exposure was approximately 1% and the prevalence of paternal occupational lead exposure was 22% (Hakim et al., 1991). Power was based upon an alpha = 0.05 (two-sided).

The current study was approved by the Committee on Human Research, Johns Hopkins Bloomberg School of Public Health.

RESULTS

Population Characteristics

Cases and controls differed significantly by low birth-weight and the presence of noncardiac defects due to the selection of controls (Table 1). Cases were more likely than controls to be female, of white or "other" race, to have been born between January and March, and to have a family history of cardiac defects, as well as noncardiac defects; however, these differences were not statistically significant.

Case mothers were more likely to be younger than 20 years of age or 30 years of age or older, unmarried, less educated, have an annual household income less than \$20,000, and live in an urban area compared to control mothers; however, these differences were small and not statistically significant (Table 2). Case and control mothers did not differ by maternal body mass index >26.0, previous pregnancy, or previous miscarriage. Maternal alcohol consumption and cigarette smoking did not differ significantly between cases and controls; however, control mothers were more likely to report cigarette smoking than case mothers. Case mothers were significantly less likely to be employed during the critical period ($p = 0.047$) and more likely to report pesticide exposure during the critical period ($p = 0.005$). Case fathers were more likely to be over 30 years of age at the time of the interview than control fathers (cases: 53.7% and controls: 44.4%; $p = 0.20$) and were less likely to be employed during the critical period (cases: 87.0% and controls: 92.5%; $p = 0.18$) (data not shown).

Parental Lead Exposure

The prevalence of any lead exposure was moderate among case and control mothers (16.7% and 11.3%, respectively) (Table 3). Approximately 7.5% of case and control mothers were categorized as having occupational lead ex-

posure; however, case mothers (9.3%) were twice as likely to report nonoccupational lead exposures compared to control mothers (4.4%). TAPVR was associated with an OR of 1.57 (95% CI, 0.64–3.47) for maternal lead exposure between three months prior to pregnancy through the first trimester. Nonoccupational self-reported exposures among case mothers explained this association. The most common nonoccupational self-reported lead exposure among mothers was “paint stripping or sanding old paint which might have lead in it,” with 7.4% of case mothers and 2.7% of control mothers reporting this exposure ($p = 0.08$) (Table 4).

The prevalence of any lead exposure among fathers was high, with 61.1% of case fathers and 46.2% of control fathers exposed during the six months prior to conception (Table 3). TAPVR was associated with an OR of 1.83 (95% CI, 1.00–3.42) for any paternal lead exposure during the respective critical period. More fathers reported occupational exposures (cases: 44.4% and controls: 36.2%) than nonoccupational exposures (cases: 27.8% and controls: 18.4%), with the OR for occupational exposures 1.41 (95% CI, 0.76–2.57) and the OR for nonoccupational exposures 1.71 (95% CI, 0.84–3.32). The most common lead-related, nonoccupational self-reported exposure among fathers was “solvents or chemicals used for degreasing or cleaning guns” (cases: 14.8% and controls: 10.3%; $p = 0.35$), which is

Table 1
Demographic and Birth Characteristics of Total Anomalous Pulmonary Venous Return Cases and Controls

Variable	Cases (<i>n</i> = 54)		Controls (<i>n</i> = 522)		<i>p</i> -value ^c
	<i>n</i>	%	<i>n</i>	%	
Gender					
Male	25	46.3	266	51.0	
Female	29	53.7	256	49.0	0.57
Race ^a					
White/other	45	83.3	372	71.3	
Black	9	16.7	150	28.7	0.08
Birth quarter					
January–March	16	29.6	109	20.9	
April–June	15	27.8	137	26.3	
July–September	13	24.1	138	26.4	
October–December	10	18.5	138	26.4	0.39
Low birth weight (<2500 gm)	8	14.8	0	0.0	<0.001
Noncardiac malformation present					
None	41	75.9	522	100.0	
Chromosomal anomalies	2	3.7	0	0.0	
Syndromes	6	11.1	0	0.0	
Organ defects	5	9.3	0	0.0	<0.001
Family history of cardiac malformations ^b					
Yes	2	3.7	9	1.7	0.28
Family history of noncardiac malformations ^b					
Yes	6	11.1	28	5.4	0.12

^aControls were sampled to be only of white or black race, five cases are “other.”

^b1st degree relatives only.

^c*p*-value for Fisher’s exact test.

Table 2
Maternal Characteristics of Total Anomalous Pulmonary Venous Return Cases and Controls

Variable	Cases (<i>n</i> = 54)		Controls (<i>n</i> = 522)		<i>p</i> -value ^a
	<i>n</i>	%	<i>n</i>	%	
Maternal age at conception (years)					
<20	9	16.7	71	13.6	
20–29	26	48.1	302	57.8	
≥ 30	19	35.2	149	28.5	0.38
Marital status					
Married	39	72.2	402	77.0	
Unmarried	15	27.8	120	23.0	0.41
Maternal education					
< High school degree	12	22.2	90	17.2	
≥ High school degree	42	77.8	432	82.8	0.35
Annual household income					
< \$20,000	24	44.4	179	35.1	
≥ \$20,000	30	55.6	331	64.9	0.18
Maternal residence at delivery					
Urban	17	32.1	132	25.3	
Suburban or rural	36	67.9	390	74.7	0.32
Maternal health					
Body mass index > 26.0	8	14.8	87	16.8	0.85
Pre-existing diabetes	1	1.9	1	0.2	0.18
Previous pregnancy	39	72.2	362	69.4	0.76
Previous miscarriage	11	20.4	95	18.2	0.71
Maternal smoking during critical period					
Never	37	68.5	328	62.8	
One or more cigarettes/day	17	31.5	194	37.2	0.46
Maternal alcohol consumption during critical period					
< Once/week excluding binge drinking	40	74.1	378	72.4	
Once/week or binge drinking	14	25.9	144	27.6	0.87
Maternal employment during the critical period	30	55.6	360	69.1	0.047
Self-reported maternal pesticide exposure	26	48.2	149	28.5	0.005

^a*p*-value for Fisher’s exact test.

a concern due to lead dust associated with cleaning guns (Table 4). Case fathers were significantly more likely to report nonoccupational exposure to “paint stripping or sanding old paint which might have lead in it” than control fathers ($p = 0.046$). After adjusting for maternal employment during the critical period, maternal pesticide exposure during the critical period, maternal residence at delivery (urban vs. suburban or rural), and infant race (white and “other” vs. black), the OR for any paternal lead exposure and TAPVR decreased only slightly (OR, 1.79; 95% CI, 0.99–3.23). Maternal residence (urban vs. rural/suburban) was included as a potential confounder, as it was a possible proxy measure for environmental lead exposure from lead paint in older urban housing and from urban air pollution containing lead. While not significant in the univariate analysis, it was statistically significant in the multivariate model (OR, 2.14; 95% CI, 1.06–4.34).

Table 3
Unadjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for Total Anomalous Pulmonary Venous Return and Parental Lead Exposure During the Critical Period by Parent and Source of Exposure

Parent	Cases (n = 54)		Controls (n = 522)		p-value ^e	OR	95% CI ^f
	n	%	n	%			
Any maternal lead exposure ^a	9	16.7	59	11.3	0.27	1.57	0.64–3.47
Occupational ^b	4	7.4	41	7.9	1.00	0.94	0.23–2.75
Nonoccupational ^c	5	9.3	23	4.4	0.17	2.21	0.63–6.31
Any paternal lead exposure ^d	33	61.1	241	46.2	0.045	1.83	1.00–3.42
Occupational ^b	24	44.4	189	36.2	0.24	1.41	0.76–2.57
Nonoccupational ^c	15	27.8	96	18.4	0.10	1.71	0.84–3.32

^aLimited to exposure during maternal critical period (three months prior to conception through first trimester).

^bData from industrial hygiene assessment, job exposure matrix, and self-report.

^cData only from self-report.

^dLimited to exposure during paternal critical period (the six months prior to conception).

^ep-value for Fisher's exact test.

^f95% exact confidence intervals.

In order to identify the parental pathway by which lead may cause TAPVR, we looked at the independent effects of maternal and paternal lead exposure by the critical period of exposure. During the paternal critical period, when only the father was exposed compared to neither parent exposed, the odds of TAPVR was 1.65 (95% CI, 0.84–3.25) (Table 5). During the maternal critical period, when only the mother was exposed compared to neither parent being exposed, there was no increased odds of TAPVR; however, this was based upon one exposed case mother. In Table 6, we further evaluated the parental mechanism by examining the joint effects of maternal and paternal lead exposure during their relevant critical periods. When the father was exposed to lead during the paternal critical period, but the mother was not exposed during the maternal critical period, the OR was 1.56 (95% CI, 0.81–3.05) when compared to neither parent having been exposed during their relevant critical period. The OR increased further and was

statistically significant when both parents were exposed to lead during their respective, relevant critical periods (OR, 2.94; 95% CI, 1.03–7.60).

DISCUSSION

Investigators in the BWIS found an association between self-reported maternal lead exposure and TAPVR in earlier analyses of the data (Correa-Villaseñor et al., 1991; Ferencz et al., 1997). The current report is a more detailed analysis, in which we used a more sensitive exposure estimate based upon self-reported exposures, and an industrial hygiene assessment and job exposure matrix to reassess the association for maternal lead exposure and to determine if an association existed for paternal exposure. We observed a possible association between TAPVR and paternal lead exposure when the father was exposed during the six months prior to conception. Maternal lead exposure be-

Table 4
Self-Reported Nonoccupational Lead Activities during the Respective Critical Periods of Exposure for Mothers and Fathers of Total Anomalous Pulmonary Venous Return Cases and Controls

Activity	Mothers ^a					Fathers ^b				
	Cases (n = 54)		Controls (n = 522)		p-value ^c	Cases (n = 54)		Controls (n = 522)		p-value ^c
	n	%	n	%		n	%	n	%	
Paint stripping or sanding old paint which might have lead in it	4	7.4	14	2.7	0.08	5	9.3	17	3.3	0.046
Soldering with lead or any other work with lead scrap or battery smelting	1	1.9	1	0.2	0.18	0	0.0	16	3.1	0.39
Welding	0	0.0	1	0.2	1.00	2	3.7	7	1.3	0.20
Body repair work of vehicles	0	0.0	0	0.0	—	5	9.3	31	5.9	0.37
Solvents for degreasing motors or cleaning guns	0	0.0	5	1.0	1.00	8	14.8	54	10.3	0.35
Jewelry making, professionally or as a hobby	0	0.0	1	0.2	1.00	1	1.9	1	0.2	0.18
Arts and crafts with stained glass	0	0.0	1	0.2	1.00	0	0.0	1	0.2	1.00

^aMaternal critical period is defined as the three months prior to conception through first trimester.

^bPaternal critical period is defined as the six months prior to conception.

^cp-value for Fisher's exact test.

Table 5
Unadjusted Odds Ratio (OR) and 95% Confidence Intervals (CI) for Total Anomalous Pulmonary Venous Return and Parental Lead Exposure during the Paternal and Maternal Critical Periods for Mothers and Fathers Independently*

	Cases		Controls		OR	95% CI ^d
	<i>n</i>	% ^c	<i>n</i>	% ^c		
Paternal critical period ^a						
Neither parent exposed	19	41.3	259	53.1	1.00	
Mother only exposed	2	4.3	22	4.5	1.24	0.13–5.71
Father only exposed	25	54.3	207	42.4	1.65	0.84–3.25
Maternal critical period ^b						
Neither parent exposed	20	43.5	249	51.2	1.00	
Mother only exposed	1	2.2	23	4.7	0.54	0.01–3.72
Father only exposed	25	54.3	214	44.0	1.45	0.75–2.84

*Lead exposure as determined by industrial hygiene assessment, job exposure matrix, or self-report (occupational and nonoccupational).

^aEight cases and 34 controls had both parents exposed to lead during the paternal critical period and are not included in the analysis. The paternal critical period is defined as the six months prior to conception.

^bEight cases and 36 controls had both parents exposed to lead during the maternal critical period and are not included in the analysis. The maternal critical period is defined as the three months prior to conception through first trimester.

^cPercents do not add up to 100% due to rounding.

^d95% exact confidence intervals.

tween the three months prior to conception through the first trimester did not appear to be associated with the presence of TAPVR in infants; however, when both parents were exposed during their relevant critical periods compared to neither parent having been exposed, there was a statistically significant association between lead exposure and TAPVR.

The results of the current analysis should be interpreted with caution for several reasons. First, the number of cases was small, thereby limiting the power of the study to detect an association. Second, there was little variation in exposure over time, making it difficult to interpret the findings regarding a maternal or paternal mechanism. Furthermore, these results are based upon a dichotomous exposure measure (yes/no) and do not take into consideration internal dose (blood lead level and bone lead level), which would capture both estimated and unestimated, past and present sources of lead exposure. As a result, exposure may be misclassified in the current study.

Misclassification of exposure is a common concern in population-based case-control studies, because exposures must be estimated retrospectively. Misclassification of ex-

posure reduces the power to detect an association and can lead to biased estimates (Kelsey et al., 1986; Hemminki et al., 1995). The current study combined three different exposure-assessment methods to estimate occupational lead exposure. This approach should have decreased misclassification and increased the sensitivity of the exposure estimate compared to the earlier analyses, which relied only on self-reported exposures; however, it likely resulted in a loss of specificity. As expected, the prevalence of occupational lead exposure increased for both mothers and fathers when using all three methods combined (mothers: 7.8% and fathers: 37.0%) compared to self-reports alone (mothers: 1.0% and fathers: 12.0%), suggesting an increase in sensitivity.

We were unable to determine the validity of these estimates, as no exposure measures or biological markers of exposure were available for comparison. However, given the high prevalence of exposure among fathers (>46%), nondifferential misclassification would not have substantially affected the power of the study or the sensitivity and specificity of the exposure measure (Hemminki et al., 1995). When we used a more specific exposure estimate

Table 6
Unadjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for Total Anomalous Pulmonary Venous Return and the Joint Effects of Maternal and Paternal Lead Exposure during Their Relevant Critical Periods*

Parental exposure ^a	Cases		Controls		OR	95% CI ^b
	<i>n</i>	%	<i>n</i>	%		
Neither parent exposed during their relevant critical period	20	37.0	257	49.2	1.00	
Mother exposed during MCP and father not exposed during PCP	1	1.9	24	4.6	0.54	0.01–3.66
Father exposed during PCP and mother not exposed during MCP	25	46.3	206	39.5	1.56	0.81–3.05
Both parents exposed during their relevant critical periods	8	14.8	35	6.7	2.94	1.03–7.60

*Lead exposure as determined by industrial hygiene assessment, job exposure matrix, or self-report (occupational and nonoccupational).

^aMaternal critical period (MCP) is defined as the three months prior to conception through first trimester. Paternal critical period (PCP) is defined as the six months prior to conception.

^b95% exact confidence intervals.

(father categorized as exposed by all three methods independently), the OR did not change greatly (OR, 1.91; 95% CI, 0.46–5.97). Among mothers, however, even a low level of misclassification (10%) would have resulted in a substantial drop in the sensitivity of the exposure estimate due to the low prevalence of exposure, thereby decreasing the power to detect a true association if it existed (Hemminki et al., 1995). It is believed that any misclassification of exposure by the industrial hygiene assessment or the JEM would have been nondifferential, as the hygienist and JEM were blinded to case-control status; however, if case parents provided more detail in their work histories than control parents, misclassification could be differential. Self-reported exposures may have been more susceptible to differential reporting by case and control parents; however, within the BWIS, we were able to evaluate the potential for reporting bias in relation to self-reported exposures by comparing self-reported lead exposures for mothers and fathers of TAPVR cases ($n = 54$) with self-reported lead exposures of mothers and fathers of cases having cardiovascular malformations other than TAPVR ($n = 3220$). This method is based upon the assumption that the case groups would not recall exposures differentially, as there were no hypotheses regarding the association between lead and TAPVR or other cardiovascular malformations at the time of the BWIS study. We found TAPVR mothers and fathers were more likely to report lead-related exposures compared to other case mothers and fathers (mothers: OR, 2.00; 95% CI, 0.89–4.48; fathers: OR, 1.60; 95% CI, 0.93–2.74), suggesting that recall bias does not explain differences in lead exposure among case and control parents. Recall bias within the BWIS may have been diminished, as study personnel with environmental or toxicological expertise reviewed all self-reported exposures in relation to verbatim activity descriptions, and any false-positives were reassigned ($\approx 5\%$ of all reported exposures) (C. Loffredo, personal communication, 2003).

The lack of recall bias in the current study is consistent with other studies investigating environmental and occupational exposures and reproductive outcomes (Roeleveld et al., 1990; Teschke et al., 2000). In a study of childhood cancers, Teschke et al. (2000) found no evidence of recall bias for prompted exposures and activities. In addition, Roeleveld et al. (1990) found little evidence of recall bias in a case-control study of parental occupation and mental retardation in children when comparing parental reports of exposures to colleagues' reports of exposures. In contrast to these two reports and the current study, Schuz et al. (2003) recently found evidence of potential overreporting of paternal occupational exposures among cases in a study of childhood cancers. While Schuz et al. (2003) found similar results across cancer diagnostic groups, we were able to compare results of TAPVR cases and other case groups and, as shown above, we found that TAPVR parents were more likely to report lead exposure than parents of other cases, suggesting recall bias does not explain the reported results.

Another potential limitation of the study is the selection of controls. Within the current study, controls were selected to be a random sample of all BWIS controls that were singletons, were of "white" or "black" race, had no congenital malformations and were of normal birthweight. This control group was originally selected for a case-control study of low birthweight (Min et al., 1996), and there-

fore was not optimal for the current study; however it was not possible to select a new control group. As the cases included low birthweight infants and the controls did not, our risk estimates may have been biased upwards, since lead exposure has been associated with low birthweight in other studies (Min et al., 1996; Lin et al., 1998). Furthermore, sociodemographic differences between cases and controls may have been exaggerated, as low birthweight and birth defects have been associated with lower socioeconomic status, being African-American, single marital status, low level of education, and/or maternal age (Institutes of Medicine, 1985; Gould and LeRoy, 1988; Hessel et al., 1998; Martin et al., 2002). As a result, it is difficult to generalize the study findings to a wider population. In order to determine the effect this selection procedure had on the results, a sensitivity analysis was performed by limiting cases to infants who were of normal birthweight, of "white" or "black" race, and were free of noncardiac defects. While there was little change in the estimate for maternal lead exposure (unadjusted OR, 1.35; 95% CI, 0.50–3.63), the risk estimate for paternal exposure actually increased, and was statistically significant after adjusting for infant race, maternal residence at delivery, maternal employment during the critical period, and maternal pesticide exposure during the critical period (adjusted OR, 2.62; 95% CI, 1.21–5.71).

Finally, the current study included only live-born infants with TAPVR, and did not take into consideration those cases that might have ended in embryonic or fetal death. While TAPVR by itself is unlikely to result in a spontaneous abortion or stillbirth (because the fetus has other means for oxygen exchange and distribution in the womb), other congenital anomalies coexisting with TAPVR could result in fetal death. In a study of 400 spontaneously aborted or stillborn fetuses, congenital heart disease was identified in 13% of the fetuses, including one case of anomalous pulmonary return that was also diagnosed as having Turner syndrome, coarctation of the aorta, a single ventricle, horseshoe kidney, and hydrops (Chinn et al., 1989). If lead exposure results in TAPVR and other congenital anomalies that might be related to fetal survival, the overall effect of lead on TAPVR might have been underestimated, because only live-born infants were selected for the BWIS.

The strong association between TAPVR and maternal self-reported lead exposure found in the earlier BWIS analysis was not found in the current study when using a more sensitive exposure measure for occupational exposures. In the earlier analysis, TAPVR was significantly associated with maternal self-reported "paint stripping" (OR, 3.2; 95% CI, 1.1–8.9) and "soldering with lead" (OR, 7.7; 95% CI, 1.7–34.4) (Ferencz et al., 1997). While these associations remained elevated in the current analyses (paint stripping: OR, 2.70; 95% CI, 0.63–8.91; and soldering: OR, 10.00; 95% CI, 0.71–139.41), the OR decreased when additional sources of occupational lead exposure were considered (OR, 1.57; 95% CI, 0.64–3.47). Given the limited power of the current study to investigate maternal lead exposure, it would be worthwhile to investigate this association in a larger population.

If there is truly an association between TAPVR and paternal lead exposure during the six months prior to pregnancy, as suggested by this study, it would imply that the critical period of exposure is during spermatogenesis

and that lead could cause chromosomal damage or an epigenetic change in gene expression. Alternatively, lead in semen could result in chromosomal damage or epigenetic changes in the ovum or zygote. Given that previous studies have found significant levels of lead in semen and sperm among lead-exposed men (Plechaty et al., 1977; Chowdhury et al., 1986; Assennato et al., 1987; Kuo et al., 1997; Robins et al., 1997; Apostoli et al., 1999; Kumar et al., 2000; Bonde et al., 2002), a paternal mechanism is not implausible.

While very little is understood about the development of the pulmonary vein, Bleyl et al. (1995) described TAPVR as an autosomal dominant, single-gene defect with low penetrance, and localized the gene to the centromeric region of chromosome 4 in a large Utah-Idaho family with familial TAPVR. A vascular endothelial growth factor receptor (VEGF, kinase insert domain receptor), which is expressed early in development and is potentially involved with vasculogenesis, maps to the same region of the chromosome (Bleyl et al., 1995). It may be that lead exposure causes a single gene defect or epigenetic change, resulting in impaired vasculogenesis and TAPVR; however, this is only theoretical.

The evidence that paternal lead exposure is associated with birth defects has been weak due to the lack of studies and the quality of the studies. Two Norwegian studies found an increased risk of cleft lip (standardized morbidity ratio, 4.1; 95% CI, 1.8–8.1) (Kristensen et al., 1993) and isolated cleft palate (OR, 1.73; 95% CI, 0.97–2.89) (Irgens et al., 1998) among male offspring of lead-exposed fathers; however, both of these studies were limited, as exposure was based upon job title only. Using blood lead levels from workplace monitoring programs, two studies found an increased OR for birth defects (OR, 2.4; 95% CI, 0.9–6.5) (Sallmén et al., 1992) and stillbirths and birth defects combined (OR, 2.9; 95% CI: 0.8–13.1) (Alexander et al., 1996a) associated with blood lead levels greater than 20 and 25 $\mu\text{g}/\text{dl}$, respectively. Both of these studies were limited by small sample sizes, heterogeneous case groups, and the use of blood lead measurements that were collected for monitoring purposes and were not always collected at the optimal time nor collected on the entire study population. While the above studies do have their weaknesses, they do provide some consistent results linking paternal lead exposure with birth defects, as does the current study.

Given the morbidity and mortality associated with TAPVR, it is important to better understand the epidemiology of this anomaly. Lead exposures in the BWIS represent those present during the 1980s, and therefore might not be similar to lead exposures today. However, permissible exposure limits (PELs) for lead ($0.05 \text{ mg}/\text{m}^3$ in air as a time-weighted concentration over an 8-hr work shift) have not changed since the Occupational Safety and Health Administration set them in 1978, and at some workplaces they likely remain above those currently thought to cause adverse reproductive outcomes. In addition, nonoccupational exposures are a concern, as these activities could result in very high intensities of lead exposure if individuals are unaware of the associated risks and do not take adequate precautions. For example, over 80% of privately-owned occupied houses built before 1980 still contain some lead-based paint, which could potentially expose owners to high lead levels if they were to engage in paint stripping or paint sanding without proper protection

(OPPT, 1995). This is consistent with our finding that for both mothers and fathers, nonoccupational exposure to "paint stripping and sanding paint which might have lead in it" resulted in increased odds of TAPVR. In addition, many developing nations continue to use leaded gasoline and lead paint, and continue to have high occupational lead exposures. If an association between parental lead exposure and TAPVR exists at the lower exposure levels found in the U.S., parents in developing countries could be at an even greater risk of having children with TAPVR, as well as other adverse outcomes. These countries may not have the means to diagnose and care for an infant with TAPVR, as we are now able to do in the United States, resulting in high infant mortality associated with TAPVR.

Finally, we need to continue to improve retrospective exposure assessment methods and validate the methods currently in practice. The majority of the research in this area has focused on occupational exposures; however, given the importance of nonoccupational exposures shown here, it may be worthwhile in future studies to develop more in-depth questions regarding these exposures, which could then be reviewed by industrial hygienists, in a similar manner as occupational histories, to provide a more complete and valid exposure profile.

CONCLUSION

This study suggests a possible association between paternal lead exposure and TAPVR. Further studies are warranted using validated exposure assessment methods for occupational and nonoccupational lead exposures to corroborate this association and to determine the possible biological mechanism. Given the widespread use of lead in industry and the environment, it is important to elucidate the association between lead exposure and TAPVR, as well as with other adverse reproductive outcomes.

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