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BRIEF REPORT

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Maternal occupational cadmium exposure and nonsyndromic orofacial clefts

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Background: Cigarette smoking is a well-studied risk factor for orofacial clefts (OFCs). Little is known about which constituents in cigarette smoke contribute to this teratogenicity in humans. One constituent, cadmium, has been associated with OFCs in animal studies; in humans, the role of maternal cadmium exposure on OFCs, independent of cigarette smoke, is unclear. In particular, the relation between maternal occupational cadmium exposure and OFCs is largely unexplored.

Methods: Using data from a large, population-based case-control study, we compared expert rater assessed maternal occupational cadmium exposure from self-reported occupational histories during the period 1 month before through 3 months after conception between OFC cases ($n = 1{,}185$) and unaffected controls ($n = 2{,}832$). Multivariable logistic regression analyses were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals for any (yes/no) and cumulative (no, low, high exposure) occupational cadmium exposures and all OFCs, cleft lip ± cleft palate (CL/P) and cleft palate (CP).

Results: Overall, 45 mothers (cases = 13, controls = 32) were rated as having occupational cadmium exposure. Comparing all OFCs to controls, we observed inverse, nonsignificant aORs for any or low exposure, and positive, nonsignificant aORs for high exposure. Where data were available, aORs for CL/P and CP tended to parallel those for all OFCs.

Conclusion: To our knowledge, this is the first study to specifically examine maternal occupational cadmium exposure and OFCs, using expert rater exposure assessment. The small numbers of exposed mothers observed, however, led to imprecise estimates. Continued research using more detailed occupational exposure assessment and increased sample sizes is recommended.

KEYWORDS
cadmium, cleft lip, cleft palate, metal, occupation, pregnancy

1 | INTRODUCTION

Nonsyndromic orofacial clefts (OFCs), which include clefts of the lip (CL) and palate (CP), are common birth defects (Mossey & Castillia, 2003). Lip and palate development occurs in the first trimester of pregnancy, and is sensitive to various environmental exposures (Mossey, Little, Munger, Dixon, & Shaw, 2009). To date, associations between several maternal exposures and OFCs have been reported. Except for cigarette smoke exposure (Little, Cardy, & Munger,

2004; Sabbagh et al., 2015), findings for many exposures are inconclusive.

Cadmium is a constituent in cigarette smoke (Järup & Akesson, 2009), yet most knowledge regarding the teratogenicity of cadmium to induce OFCs (Chernoff, 1973; Holt & Webb, 1987; Hovland, Machado, Scott, & Collins, 1999; Salvatori, Talassi, Salzgeber, Spinosa, & Bernardi, 2004) has been derived from animal studies. Little is known in humans about the impact of maternal cadmium exposure on OFC development in offspring, independent of cigarette smoke. In particular, workers in several industries may be exposed to cadmium (reviewed in ATSDR, 2012), yet little is known about this exposure and development of OFCs.

We identified one study that examined the relation between maternal occupational exposure to cadmium and birth defects (Nordstrom, Beckman, & Nordenson, 1979). The investigators reported a positive, statistically significant association for diagnosis of any birth defect among offspring of pregnant smelter workers exposed to a combination of metals, including cadmium, compared to those of nonworking pregnant women; cleft lip with or without cleft palate (CL/P) were among the most commonly reported defects among the exposed women (Nordstrom et al., 1979). The relevance of these findings regarding cadmium for OFCs were limited largely by using smelter employment as a proxy for cadmium exposure and not restricting exposures to the first trimester of pregnancy, the critical period for lip and palate development (Mossey et al., 2009). To better elucidate the potential teratogenicity of occupational cadmium exposure, we used detailed occupational data from the National Birth Defects Prevention Study (NBDPS) to examine associations between maternal occupational cadmium exposure and nonsyndromic OFCs in offspring.

2 | MATERIALS AND METHODS

2.1 | Study sample

The NBDPS was a population-based case-control study of major birth defects among pregnancies with expected dates of delivery (EDDs) from October 1997 through December 2011. NBDPS methods were published elsewhere (Cogswell et al., 2009; Rasmussen et al., 2003; Reefhuis et al., 2015). Briefly, study sites in Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah identified CL/P and CP cases through medical record abstraction. Data abstracted were reviewed by clinical geneticists to classify cases as isolated (no other major defect) or multiple (one or more additional major, unrelated defects); cases with monogenic disorders, chromosome abnormalities, or OFC secondary to another defect were excluded. Controls were a random sample of live births without major defects identified through hospital delivery logs or birth certificates and delivered in the same time frame and geographic area as cases.

Case and control mothers completed a telephone interview 6 weeks to 24 months after their EDDs; 71% of case and 64% of control mothers participated. As part of the interview, mothers were asked to report employer name and description of the product/service; job title, activities/tasks, and associated exposures; hours and days worked/week; and month and year employment began and ended (if applicable) for jobs held for at least 1 month during the 3 months before conception through the end of pregnancy (full-term birth or earlier due to fetal loss or termination).

2.2 | Occupational exposure assessment

Funding to date has permitted occupational exposure assessment of cadmium through be completed for mothers with EDDs from October 1997 through December 2002; data from North Carolina and Utah were not available for this time period. Exposure assessment was conducted by the National Institute for Occupational Safety and Health and Battelle Center for Public Health Research and Evaluation. Reported jobs were assigned 2007 North American Industrial Classification System codes and 2000 Standard Occupational Classification codes. Total hours worked/week were calculated for each job as hours worked/day × days worked/week. Reports of working ≥12 hr/day were reviewed; these were generally 24-hr on-call jobs and were truncated to 16 hr/day. Interviews with missing hours or days worked (<1% of reported jobs) were assigned an 8-hr/day, 5-day/week schedule.

Exposure assessment was based on methods used in the Baltimore-Washington Infant Study (Jackson et al., 2004). Reported jobs were reviewed by an industrial hygienist (IH) and assigned a yes/no exposure rating for cadmium. Exposed jobs were assigned to categories of direct and indirect intensity levels (<1.25, 1.25–3.74, 3.75–4.99, ≥5 μg/m^3) and exposure fractions (0%–90%) to reflect the fraction of time a job was likely exposed. Intensity levels were computationally mapped to the midpoint of their range, and a weighted intensity was calculated as: (direct exposure intensity × direct exposure fraction) + (indirect exposure intensity × indirect exposure fraction).

Cumulative exposures estimated for jobs that overlapped all or part of the critical exposure period (Mossey et al., 2009)—1 month before conception through the 3rd month of pregnancy—were analyzed. Cumulative exposure, in intensity-hours (μg/m^3-hr), was calculated as: (weighted intensity) × (hours worked/week/ 7 days/week) × (number of days worked in the relevant period). Total cumulative exposure was estimated by summing across relevant jobs. To account for imprecision, cumulative exposure was categorized as unexposed, low (<median exposure level in controls), or high (≥median exposure

level in controls); mothers with no exposure in all jobs were considered unexposed and used as the referent group. Jobs also were assigned an IH exposure confidence score (very low, low, moderate, high).

2.3 | Statistical analysis

We compared cases and controls on sex, gestational age, plurality, first-degree family history of OFCs, and NBDPS site using chi-square or Fisher's exact tests. Case and control mothers were compared on race/ethnicity, age and education at delivery, parity, and prepregnancy body mass index (BMI), along with alcohol consumption, cigarette smoking, use of folic acid-containing supplements, and use of vitamin A-containing supplements during the critical exposure period. Mothers (cases = 16, controls = 14) who reported prepregnancy Type 1 or Type 2 diabetes were excluded.

Analyses were conducted using SAS 9.4 (SAS Institute Inc., 2012). We used unconditional logistic regression analyses to estimate adjusted odds ratios (aORs), and 95% Wald confidence intervals (CIs) between any (yes/no) and cumulative (unexposed, low, high) maternal occupational cadmium exposure during the critical exposure period and all cases, CL/P, and CP. Covariables examined were NBDPS site, along with maternal race/ethnicity, age and education at delivery, prepregnancy BMI, and cigarette smoking during the critical exposure period based on previously reported associations with OFCs.

Subanalyses examined possible etiologic differences between CL with CP and CL without CP by analyzing each separately with controls, risk independent of other defects by analyzing isolated cases and controls, and risk independent of potential increased hereditary risk by analyzing only cases and controls without a family history of OFCs. To examine possible exposure misclassification, we repeated our main analyses among mothers with high confidence rated jobs (moderate, high). We had intended to compare unexposed mothers to those with jobs rated with high direct exposure intensity ($\geq$5 μg/m^3), regardless of cumulative exposure, and to those in the top 25% with high cumulative exposure; however, sample sizes precluded these analyses.

3 | RESULTS

Of the 5,880 mothers (cases = 1,763, controls = 4,117) interviewed, 4,220 mothers (cases = 1,236, controls = 2,984) reported employment. Of these, 183 (cases = 45, controls = 138) did not report dates of employment that overlapped with the critical exposure period, and 20 (cases = 6, controls = 14) did not provide sufficient information to complete exposure assessment; thus, reports from 4,017 mothers (cases = 1,185, controls = 2,832) were analyzed.

We observed statistical differences ($p < .05$) between controls and all cases and CL/P cases for each child and maternal characteristic examined, except maternal alcohol use or use of either folic acid- or vitamin A-containing supplements during the critical exposure period (Table 1). CP cases and controls differed statistically for family history of OFCs, gestational age, NBDPS site, maternal race/ethnicity, and cigarette smoke exposure during the critical exposure period.

Similar proportions of case and control mothers were rated with any occupational cadmium exposure, although the estimated median cumulative exposures (in intensity-hours) were higher for case than control mothers (Table 2). Exposures were most often rated as infrequent (exposure fraction < 50%), low intensity (<3.75 μg/m^3) direct exposures and infrequent, low-intensity indirect exposures. The most prevalent exposed jobs were farmworker (15.4%) or welding/soldering worker (15.4%) among cases and dentist/dental assistant (31.0%) among controls (data not shown).

Compared to controls, we observed inverse, nonsignificant aORs between any maternal occupational cadmium exposure and all cases and each subtype (Table 2). We observed positive, nonsignificant aORs between high cumulative exposure and all cases and each subtype; estimates for CP were based on less than five exposed cases. Additionally, inverse, nonsignificant aORs with low cumulative exposure were observed for all cases and CL/P cases. Subanalyses reflected the main analyses (data not shown).

4 | DISCUSSION

To our knowledge, our study is the first to specifically examine maternal occupational cadmium exposure and OFCs, using expert rater exposure assessment. Compared to controls, aORs for any cadmium exposure during the critical exposure period were below unity for all OFCs and OFC subtypes. The aORs exceeded unity for high cumulative cadmium exposure for all OFCs and each subtype, but were below unity for low exposures for all OFCs and CL/P. Our small number of exposed cases produced imprecise odds ratios as reflected by wide CIs.

The single previous study identified used only place of employment as a proxy for a combination of metals exposure, including cadmium; this precluded direct comparison with our findings (Nordstrom et al., 1979). Several animal studies, however, reported OFCs associated with prenatal cadmium exposure (Chernoff, 1973; Holt & Webb, 1987; Hovland et al., 1999; Salvatori et al., 2004), although the mechanisms to explain this teratogenicity are unclear. Proposed mechanisms from animal (Cui & Freedman, 2009;

TABLE 1 Selected child and maternal characteristics of controls and OFC cases, NBDPS, 1997–2002

Characteristic	Controls (n = 2,832) N^a (%)[b]	All cases (n = 1,185) N^a (%)[b]	CL/P cases[c] (n = 765) N^a (%)[b]	CP cases (n = 420) N^a (%)[b]
Child				
Phenotype				
Isolated	NA	1,018 (85.9)	672 (87.8)	346 (82.4)
Multiple	NA	167 (14.1)	93 (12.2)	74 (17.6)
Sex[d,e]				
Male	1,407 (49.7)	709 (59.8)	520 (68.0)	189 (45.0)
Female	1,423 (50.2)	472 (39.8)	242 (31.6)	230 (54.8)
Plurality[d,e]				
Singleton	2,736 (96.6)	1,123 (94.8)	721 (94.3)	402 (95.7)
Multiple	94 (3.3)	61 (5.2)	43 (5.6)	18 (4.3)
First-degree family history of OFCs[d,e,f]				
Yes	7 (0.2)	68 (5.7)	48 (6.3)	20 (4.8)
No	2,825 (99.8)	1,117 (94.3)	717 (93.7)	400 (95.2)
Gestational age (weeks)[d,e,f]				
Preterm: ≤36 weeks	247 (8.7)	203 (17.1)	119 (15.6)	84 (20.0)
Term: >36 weeks	2,585 (91.3)	982 (82.9)	646 (84.4)	336 (80.0)
NBDPS site[d,e,f]				
Arkansas	353 (12.5)	123 (10.6)	80 (10.5)	43 (10.2)
California	323 (11.4)	137 (12.2)	99 (12.9)	38 (9.1)
Georgia	332 (11.7)	147 (9.7)	86 (11.2)	61 (14.5)
Iowa	398 (14.1)	158 (13.7)	111 (14.5)	47 (11.2)
Massachusetts	422 (14.9)	198 (16.7)	112 (14.6)	86 (20.5)
New Jersey	391 (13.7)	126 (10.7)	79 (10.3)	47 (11.2)
New York	318 (11.3)	135 (11.3)	85 (11.1)	50 (11.9)
Texas	295 (10.5)	161 (13.7)	113 (14.8)	48 (11.4)
Maternal				
Race/ethnicity[d,e,f]				
Non-Hispanic White	1,872 (66.1)	831 (70.1)	519 (67.8)	312 (74.3)
Non-Hispanic Black	358 (12.6)	71 (6.0)	44 (5.8)	27 (6.4)
Hispanic	476 (16.8)	216 (18.2)	156 (20.4)	60 (14.3)
Other	126 (4.5)	67 (5.7)	46 (6.0)	21 (5.0)
Age at delivery (years)[d,e]				
<20	204 (7.2)	107 (9.0)	75 (9.8)	32 (7.6)
20–24	605 (21.4)	285 (24.1)	198 (25.9)	87 (20.7)
25–29	768 (27.1)	316 (26.7)	203 (26.5)	113 (26.9)
30–34	825 (29.1)	290 (24.5)	181 (23.7)	109 (26.0)
35–39	365 (12.9)	151 (12.7)	88 (11.5)	63 (15.0)
≥40	65 (2.3)	36 (3.0)	20 (2.6)	16 (3.8)
Education at delivery (years)[d,e]				
0–8	65 (2.3)	38 (3.2)	29 (3.8)	9 (2.1)
9–11	198 (7.0)	110 (9.3)	78 (10.2)	32 (7.6)
12	685 (24.2)	312 (26.4)	209 (27.3)	103 (24.5)
13–15	861 (30.5)	366 (30.9)	220 (28.8)	146 (34.8)
≥16	1,018 (36.0)	358 (30.2)	228 (29.8)	130 (31.0)
Prepregnancy BMI (kg/m^2)[d,e]				
Underweight (<18.5)	144 (5.1)	83 (7.0)	60 (7.8)	23 (5.5)
Normal weight (18.5–24.9)	1,595 (56.3)	629 (53.1)	403 (52.7)	226 (53.8)
Overweight (25–<30.0)	622 (22.0)	243 (20.5)	151 (19.7)	92 (21.9)
Obese (≥30.0)	419 (14.8)	204 (17.2)	131 (17.1)	73 (17.4)

(Continues)

TABLE 1 (Continued)

Characteristic	Controls (n = 2,832) N^a (%)[b]	All cases (n = 1,185) N^a (%)[b]	CL/P cases[c] (n = 765) N^a (%)[b]	CP cases (n = 420) N^a (%)[b]
Parity[d,e]				
Nullliparous	1,233 (43.5)	567 (47.9)	370 (48.4)	197 (46.9)
Primiparous	988 (34.9)	382 (32.3)	241 (31.5)	141 (33.6)
Multiparous	610 (21.5)	236 (19.9)	154 (20.1)	82 (19.5)
Use of folic acid-containing supplements[g]				
Yes	2,508 (88.6)	1,044 (88.1)	671 (87.7)	373 (88.9)
No	283 (10.0)	128 (10.8)	87 (11.4)	41 (9.8)
Alcohol w/ binge events[g]				
No drinking	1,566 (55.3)	651 (54.9)	425 (55.6)	226 (53.8)
Drinking and binge event (≥4 drinks on one occasion)	432 (15.3)	166 (14.0)	110 (14.4)	56 (13.3)
Drinking but no binge events	808 (28.5)	354 (29.9)	222 (29.0)	132 (31.4)
Cigarette smoking[d,e,f,g]				
No active or passive smoking	1,762 (62.2)	678 (57.2)	439 (57.4)	239 (56.9)
Active smoking only	188 (6.6)	103 (8.7)	60 (7.8)	43 (10.2)
Passive smoking only	491 (17.3)	196 (16.5)	126 (16.5)	70 (16.7)
Active and passive smoking	384 (13.6)	203 (17.1)	136 (17.8)	67 (16.0)
Use of vitamin A-containing supplements[g]				
Yes	1,464 (51.7)	581 (49.0)	371 (48.5)	210 (50.0)
No	1,348 (47.6)	600 (50.6)	391 (51.1)	209 (49.8)

Note. OFC, orofacial cleft; CL/P, cleft lip with or without palate; CP, cleft palate; NA, not applicable; BMI, body mass index.
[a]Numbers may vary due to incomplete or missing data.
[b]Due to rounding, percentages may not total 100.
[c]CL/P: 499 CL with CP cases; 266 CL without CP cases.
[d]$p < .05$ for all OFCs versus controls.
[e]$p < .05$ for CL/P versus controls.
[f]$p < .05$ for CP versus controls.
[g]During the maternal critical exposure period (1 month before conception through the first 3 months of pregnancy).

Salvatori et al., 2004; reviewed in Thévenod, 2009) and human (Kippler et al., 2010) studies include alterations to retinoic acid signaling (Cui & Freedman, 2009; reviewed in Thévenod, 2009) or restricted maternal-fetal nutrient transfer from cadmium accumulation in the placenta (Kippler et al., 2010; Salvatori et al., 2004).

TABLE 2 Adjusted OR estimates for all OFC cases and for OFC subtypes associated with maternal occupational cadmium exposure, NBDPS, 1997–2002

Cadmium exposure	Controls (n = 2,832) N (%)	All cases (n = 1,185) N (%)	All cases (n = 1,185) aOR[a] (95% CI)	CL/P cases (n = 765) N (%)	CL/P cases (n = 765) aOR[a] (95% CI)	CP cases (n = 420) N (%)	CP cases (n = 420) aOR[a] (95% CI)
No	2,800 (98.8)	1,172 (98.9)	Ref	755 (98.7)	Ref	417 (99.3)	Ref
Any	32 (1.1)	13 (1.1)	0.8 (0.4, 1.6)	10 (1.3)	0.9 (0.4, 2.0)	3 (0.7)	0.6 (0.2, 2.0)
Cumulative exposure	**Median ($\mu g/m^3$-hr)**		**Median ($\mu g/m^3$-hr)**		**Median ($\mu g/m^3$-hr)**		**Median ($\mu g/m^3$-hr)**
	(190)		(540)		(435)		(1,000)
Low	16 (0.6)	3 (0.3)	0.3 (0.1, 1.2)	3 (0.4)	0.4 (0.1, 2.0)	0 (0.0)	NC
High	16 (0.6)	10 (0.8)	1.4 (0.6, 3.2)	7 (0.9)	1.4 (0.5, 3.7)	3 (0.7)	1.3 (0.4, 4.6)

Note. OFCs, orofacial clefts; CL/P, cleft lip with or without palate; CP, cleft palate; aOR, adjusted odds ratio; Ref, reference; NC, not calculated.
[a]aORs adjusted for NBDPS site, maternal race/ethnicity, age at delivery, education at delivery, prepregnancy BMI, and cigarette smoking during the critical exposure period.

A strength of using NBDPS data was the reduced potential for case misclassification and selection bias. Cases were reviewed by clinical geneticists using predefined case definitions and inclusion criteria for classification, allowing for examination of OFC subtypes. NBDPS control participants were observed to be representative of all live births in the corresponding areas on several maternal characteristics (Cogswell et al., 2009). Another strength of the NBDPS was the ability to examine exposure during the critical period of lip and palate development, rather than at any time during pregnancy. Unlike the previous study that examined one occupational workplace with exposure to a combination of metals compared to nonworking mothers, our analyses included only working mothers across multiple workplaces with varying opportunities for cadmium exposure. Even with this heterogeneity in workplaces, exclusion of nonworking mothers from our analysis reduced the potential for confounding through factors related to employment (Rocheleau et al., 2017). Additionally, use of IH review of maternal occupational histories to assign cadmium exposures may have decreased the potential for exposure misclassification and improved the precision of exposure estimates compared to other retrospective methods (Rybicki et al., 1997). Furthermore, our approach allowed for assignment of cadmium exposure, specifically, rather than using a summary measure of metal exposure, which may dilute cadmium-specific effects (Friesen et al., 2007).

Our results must be interpreted cautiously. Our exposure assessment was based on self-reported occupational histories, possibly introducing exposure misclassification; subanalyses examining jobs rated with high exposure intensity and those with the highest cumulative exposure were limited by small sample sizes. Another limitation was that information regarding other occupational exposures or factors (e.g., personal protective equipment) that modify exposure was unavailable for most reported jobs and not considered in our analyses. Similarly, other than cigarette smoke, we did not have data on nonoccupational cadmium exposures. Furthermore, a previous study suggested there may be sex-specific differences between cadmium exposure and adverse birth outcomes (Taylor, Golding, & Emond, 2016); our sample size precluded examination of sex-specific differences.

In summary, using NBDPS data, we observed inverse, nonsignificant aORs between any maternal occupational cadmium exposure and all OFC cases and subtypes, although the estimates were imprecise. Positive, nonsignificant aORs between high cumulative exposures and all cases, CL/P, and CP were observed, although the estimates also were imprecise. Use of IH exposure assessment allowed us to estimate levels of cadmium exposure, rather than relying on place of employment as a proxy for exposure. Future studies should continue to improve exposure assessment. Additionally, future studies should increase sample sizes to facilitate examination of subtype-specific and sex-specific risk differences. Last, future studies should more completely characterize occupational cadmium exposure and incorporate nonoccupational sources of exposure.

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