

Risk of non-syndromic orofacial clefts by maternal rural-urban residence and race/ethnicity: A population-based case-control study in Washington State 1989-2014

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Funding information

Research reported in this publication was supported by the National Institute of Dental and Craniofacial Research and the National Cancer Institute of the National Institutes of Health under award numbers R90DE023059 (FPK) and T32CA094880 (KAS), and the Patrick-Beresford Fellowship in Social Epidemiology (FPK). The content is solely the responsibility of the authors and does not necessarily represent the views of the National Institutes of Health.

Abstract

Background: Orofacial clefts (OFC) have multifactorial aetiology. Established risk factors explain a small proportion of cases.

Objectives: To evaluate OFC risk by maternal rural residence and race/ethnicity, and test whether these associations changed after US-mandated folic acid fortification.

Methods: This population-based case-control study included all non-syndromic OFC cases among Washington State singleton livebirths between 1989-2014 and birth year-matched controls. Data sources included birth certificates and hospital records. Logistic regression estimated odds ratios (OR) and 95% confidence intervals (CI) for OFC by maternal rural-urban residence (adjusted for maternal race/ethnicity) and by maternal race/ethnicity. We evaluated additive and multiplicative effect measure modification by time of folic acid fortification (before vs. after). Probabilistic quantitative bias analysis accounted for potential differential case ascertainment for infants born to Black mothers.

Results: The overall non-syndromic OFC birth prevalence was 1.0 per 1000 livebirths ($n = 2136$ cases). Among controls ($n = 25\ 826$), 76% of mothers were urban residents and 72% were of White race/ethnicity. OFC risk was slightly higher for infants born to rural than to urban mothers, adjusting for race/ethnicity (OR 1.12, 95% CI 1.01, 1.25). The association was similar before and after US-mandated folic acid fortification. Compared with infants born to White mothers, OFC risk was higher for American Indian mothers (OR 1.73, 95% CI 1.35, 2.23) and lower for Black (OR 0.62, 95% CI 0.48, 0.81), Hispanic (OR 0.75, 95% CI 0.64, 0.87), and Asian/Pacific Islander (API) mothers (OR 0.87, 95% CI 0.74, 1.02). Bias analysis suggests the observed difference for Black mothers may be explained by selection bias. Post-fortification, the association of OFC with maternal API race/ethnicity decreased and with maternal Black race/ethnicity increased relative to maternal White race/ethnicity.

Conclusions: Infants born to rural mothers and to American Indian mothers in Washington State during 1989-2014 were at higher OFC risk before and after US-mandated folic acid fortification.

KEYWORDS

orofacial cleft, non-syndromic, cleft lip-palate, non-syndromic, rural health, American Indians, ethnic groups, congenital abnormalities

1 | BACKGROUND

Orofacial clefts (OFC) result from improper fusion of the tissues of the lip and/or palate during embryonic development.¹ They are among the most prevalent birth defects, affecting approximately 1.4 per 1000 livebirths globally.² Families of children with OFC are burdened by financial and psychosocial costs, including those associated with multiple craniofacial and dental surgeries, speech and hearing interventions, and psychological and social work support.^{3,4}

The pathogenesis of OFC is multifactorial, with both genetic and non-genetic contributing factors. Familial aggregation studies have suggested some degree of genetic heritability of non-syndromic clefts.⁵ Non-genetic risk factors for non-syndromic OFC include maternal exposures during pregnancy to cigarette smoking, low folate levels, obesity, diabetes, and anticonvulsants.⁶

Maternal residence, whether rural or urban, and race/ethnicity may also affect OFC risk through patterns of social and environmental exposures (eg racism, targeted tobacco advertisement, and occupational closure) leading to inequitable access to resources (eg prenatal care and food quality and diversity), teratogen exposure, psychosocial stress, smoking, and poor health during pregnancy.

Rural-urban differences have been reported for many health and birth outcomes,⁷ but few studies have investigated the relationship between rural maternal residence and OFC risk.⁸⁻¹³ In all but one of these studies, infant OFC risk was higher for rural than for urban resident mothers.¹²

Orofacial clefts risk has been reported to vary by race/ethnicity strongly enough to garner recommendations for studying aetiology separately for different racial/ethnic groups.¹⁴ However, estimates of these associations across the literature are highly variable.¹⁵ This may be partially attributed to variation in measurement and classification of racial/ethnic groups, time periods, geography, and OFC case classifications.¹⁶ Furthermore, different operationalisations may reflect changes in the scientific conceptualisation of race/ethnicity as a construct.^{17,18} In a 2014 study in the state of California,¹⁹ OFC birth prevalence for infants born to non-Hispanic White mothers was 1.6 per 1000 livebirths, higher than for infants born to African American (0.9 per 1000 livebirths) or Hispanic (1.2 per 1000 livebirths) mothers. Infants born to Asian/Pacific Islander mothers experienced an OFC birth prevalence of 1.2 per 1000 livebirths,¹⁹ which contrasted with other studies reporting Asians and Pacific Islanders to be among racial/ethnic groups with highest OFC birth prevalence.^{15,20} The highest OFC birth prevalence by race/ethnicity was for infants born to American Indian mothers: 8.0 per 1000 livebirths, which was consistent with other studies that included American Indian populations.^{15,19,20} There is a dearth of research focused on changes

Synopsis**Study question**

Is risk of non-syndromic orofacial clefts (OFC) associated with maternal rural residence or with maternal race/ethnicity? Did these relationships change after US-mandated folic acid fortification of cereal grains?

What's already known

OFC affect ~1.4 per 1000 livebirths globally and have multifactorial aetiology. Known risk factors explain a small proportion of cases. There is mixed evidence for the effectiveness of folic acid fortification for OFC prevention.

What this study adds

Infants born to mothers of rural residence (vs urban) or American Indian race/ethnicity (vs White) were at higher risk of OFC before and after folic acid fortification.

in associations between race/ethnicity and OFC over time, which may contribute to the wide variation among reported study results.¹⁹

A policy mandating folic acid fortification of cereal grains in the United States (US) passed in 1996 and was fully implemented in 1998.²¹ A meta-analysis of the United States and Canadian studies suggests a small reduction in birth prevalence of both OFC subtypes—cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO)—after mandatory folic acid fortification (Prevalence ratio [PR] CL/P: 0.93, 95% CI 0.90, 0.98 and PR CPO: 0.92, 95% CI 0.85, 0.99).²² However, accounting for pre-fortification trends, there was no evidence of changes in CL/P or CPO risk in the state of California after the fortification policy implementation.²³ It is possible that mothers with lower baseline levels of folate could benefit more from folic acid fortification than mothers whose folate levels already provide maximum protection against OFC. Thus, it is important to evaluate the effect of the policy for folic acid fortification in subpopulations with potential differences in access to foods and supplements containing folic acid. To our knowledge, previous studies comparing OFC risk before and after mandated folic acid fortification by race/ethnicity were limited to White, Black and Hispanic groups and none investigated urban-rural differences.

This study aimed to: (1) Evaluate associations of maternal rural residence and race/ethnicity with risk of OFC and its subtypes (CL/P



and CPO); and (2) Assess whether these relationships differed over time, relative to the full implementation of the US policy mandating folic acid fortification that occurred in 1998.²⁴

2 | METHODS

2.1 | Data sources and linkage

Data sources for this population-based case-control study included Washington State Department of Health birth certificates from 1989 to 2014, which were probabilistically linked to the Washington Comprehensive Hospital Abstract Reporting System (CHARS) database based on mother's name, date of birth, and birth hospital. Details of the linkage approach are published elsewhere.²⁵ CHARS contains hospital inpatient discharge data on mother and child, derived from hospital billing systems. It captures all births in Washington State except home-births and those in federal hospitals. For this study, we used only birth certificate and CHARS records for birth hospitalisation. Subsequent CHARS data (eg well-baby visits or follow-ups after birth) were excluded.

2.2 | Study population

Washington-born singleton livebirths occurring between 1989 and 2014 with a successful linkage between birth certificate and CHARS data were eligible for inclusion. Approximately 94-97% of birth certificates from non-federal hospital births are successfully linked to hospital records.²⁵ To ensure independence of observations, siblings of infants with OFC or controls were excluded.

2.3 | Orofacial cleft cases

Cases were infants with non-syndromic orofacial cleft (OFC) diagnosed during the birth hospitalisation ascertained in either of two ways: (1) International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes for Cleft Palate (749.0), Cleft Lip (749.1), or Cleft Palate with Cleft Lip (749.2) listed in CHARS, and/or (2) the appropriate box being checked off on the birth certificate indicating CL/P or CPO. Among 2661 infants identified with orofacial clefts, 525 infants were excluded because they had a second major malformation identified on the birth certificate or through ICD-9 codes listed in CHARS: 740-748 and 750-759, except any codes for minor malformations as defined by the New York Birth Defects Registry Criteria.²² This yielded a total of 2136 non-syndromic OFC cases, including 1412 infants with CL/P and 652 infants with CPO. Cases born prior to 2003 identified through birth certificate only (n = 72) could not be disaggregated into CL/P and CPO categories due to birth certificate coding of orofacial clefts during this period including a single "cleft lip/palate" item.

2.4 | Controls

Controls were selected randomly from all remaining singleton livebirths in Washington State between 1989 and 2014, frequency matched to cases by birth year at a ratio of 10:1 controls per case before exclusion of syndromic cases. There were 26 610 potential controls. As with cases, we excluded infants with major malformation²⁶, yielding 25 826 controls.

2.5 | Maternal rural-urban residence and race/ethnicity

The locations of maternal residences reported on infants' birth certificates were classified as rural or urban based on 2000 Census definitions of urbanicity levels. Residence was defined as urban if in a "densely settled territory containing at least 2500 people" and rural otherwise.²⁷

Maternal White, Black, Hispanic and American Indian race/ethnicity was classified as reported on infant's birth certificate. The categories Chinese, Japanese, Filipino, Hawaiian, Other Asian, Asian Indian, Korean, Samoan, Vietnamese, and Guamanian were consolidated into one category: Asian/Pacific Islander. The Hispanic race/ethnicity category consists of infants born to mothers of any race who reported Hispanic ethnicity. Only infants born to mothers of non-Hispanic ethnicity are included in the White, Black, Asian/Pacific Islanders and American Indian race/ethnicity categories. We excluded seven mothers who reported "Other Non-White" race/ethnicity.

2.6 | Assessment for changes of associations over time

The aetiologically relevant period for OFC development is early in gestation, during weeks 4-9.²⁸ Therefore, we used the conception year (infant date of birth minus gestational age at delivery) to assign infants to one of two time periods; infants conceived in 1998-2014 were considered exposed to the folic acid fortification policy and infants conceived in 1989-1995, unexposed. Infants conceived in 1996-1997 (153 cases and 1755 controls) were excluded from this analysis because many, but not all, grain products were fortified prior to the requirement date. Similar cut-offs have been used by others.²⁹

2.7 | Assessment of confounding

Potential confounders were determined *a priori* based on literature review and the study's conceptual framework (Figure 1). We considered putative risk factors for the outcome that were plausibly associated with maternal rural-urban residence or maternal race/ethnicity and were not intermediate on the causal pathway.

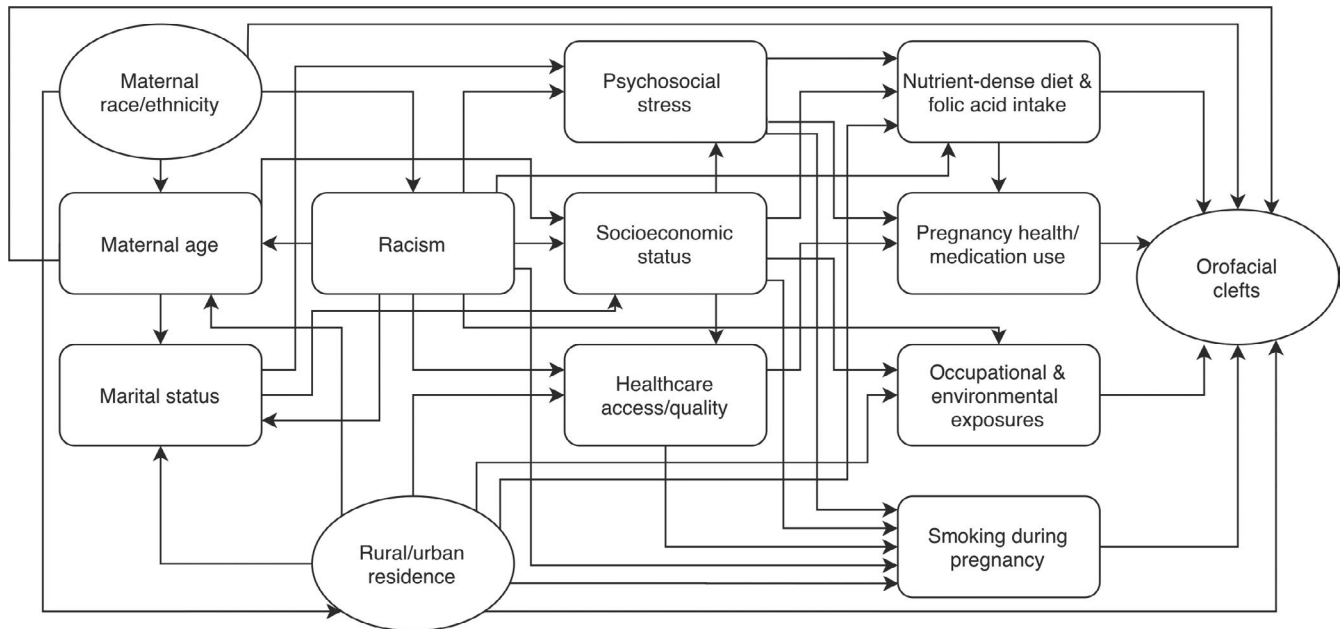


FIGURE 1 Directed acyclic graph (DAG) for maternal rural-urban residence and race/ethnicity as social and environmental risk factors for nonsyndromic orofacial clefts.

In the rural-urban models, the only potential confounder identified and adjusted for was maternal race/ethnicity.

In the maternal race/ethnicity models, other maternal characteristics were not considered confounders because they could not be thought of as influencing race/ethnicity though they may be strongly associated with race/ethnicity (eg rural-urban residence). Such putative OFC risk factors were not adjusted for since they could be on the causal pathways of interest according to the study's conceptual framework.

2.8 | Statistical analysis

We estimated the distributions of maternal characteristics (age, marital status, race, income, education, reported average number of cigarettes smoked per day during pregnancy, diabetes status, adequacy of prenatal care utilisation [Kotelchuck index]³⁰ and rural-urban residence) by infant case status.

We fit logistic regression models to estimate odds ratios (OR) for the associations of OFC with maternal rural residence (vs urban, adjusted for race/ethnicity) and maternal race/ethnicity (vs White, crude), and 95% confidence intervals (95% CI). We then repeated these analyses for OFC subtypes, CL/P and CPO.

To the logistic regression models, we added multiplicative interaction terms to evaluate how associations differed before and after folic acid fortification. We estimated ORs and 95% CI before and after folic acid fortification for each category of maternal characteristics relative to the reference category (ie urban residence before folic acid policy for the urban-rural model, and White race/ethnicity before folic acid policy for the race/ethnicity model). We calculated

measures of effect measure modification in the additive scale (RERI: relative excess risk due to interaction) and the relative scale (ROR: ratio of odds ratios).^{31,32} We obtained the RERI and 95% CI using the "ic" package in Stata, and the RORs and 95% CI from the exponentiated coefficient and 95% CI for interaction terms in the logistic models. A value of RERI different than 0 indicates the presence of additive interaction, while a value of ROR different than 1 indicates the presence of relative interaction.³² All logistic models were adjusted for birth year.

2.9 | Sensitivity analysis

We estimated the completeness of case ascertainment strategy by comparing the observed OFC birth prevalence to previous studies,³³ including an estimate from a study of 12 US population-based birth defect surveillance systems,³⁴ standardised to the racial distribution of livebirths in this study period in WA State.

Others have reported lower ascertainment of OFC in birth records of infants born to non-Hispanic Black mothers relative to non-Hispanic White mothers.^{35,36} Therefore, we conducted probabilistic quantitative bias analysis with 20 000 repetitions to estimate a range of bias-adjusted ORs and 95% simulation limits for OFC, CL/P and CPO, using reference values from those two studies to specify prior distributions of the magnitude of selection bias and two possible bias patterns (systematic error, systematic and random error).³⁷

We also evaluated whether our findings were robust to using conditional logistic regression stratified by infant birth year.

All analyses were conducted by using Stata statistical software (version 14.0 Stata Corp).



2.10 | Missing data

The proportion of missingness for variables included in logistic models was at most 5.0%. Therefore, we conducted complete case analyses and presented the number of observations for each variable and model.

To assess potential for bias due to missing data in maternal urban-rural residence and race/ethnicity, we evaluated whether multiple imputation by chained equations meaningfully changed our results. Variables included in the imputation model were maternal rural-urban residence, race/ethnicity, age, education, marital status, income, pre-pregnancy diabetes, smoking, Kotelchuck Index, infant birth year and OFC status. We imputed values for binary and categorical variables using logistic and multinomial logistic regression, respectively, to obtain 50 complete data sets. Regression augmentation ("augment" option in Stata 14 multiple imputation suite) was used to avoid perfect prediction during the imputation based on multiple categorical covariates.

2.11 | Ethics approval

Use of data for this study was reviewed and approved by the Washington State Department of Health Institutional Review Board.

3 | RESULTS

The study population was mostly urban dwelling, married, White, and between 20-34 years old (Table 1). Birth prevalence of non-syndromic OFC in WA State 1989-2014 was 1.0 per 1000 livebirths, and remained stable before and after mandated folic acid fortification (from 0.9 to 1.0 per 1000 livebirths).

Proportion of missingness was 5.0% for maternal rural-urban residence and 2.3% for race/ethnicity. The pooled analysis using 50 complete data sets obtained by multiple imputation and conditional logistic regression (Table S1) had nearly identical results to the unimputed logistic regression analysis. Thus, we report results from the latter, simpler approach below.

Infants born to rural-dwelling mothers were slightly more likely to be born with OFC than infants born to urban-dwelling mothers of the same race/ethnicity (OR 1.12, 95% CI 1.01, 1.25) (Table 2). There was negligible difference in the associations between rural-urban maternal residence and OFC (adjusting for race/ethnicity) before and after folic acid fortification in the additive or multiplicative scales (Table 3).

Infants born to American Indian mothers were more likely to be born with OFC than infants born to White mothers (OR 1.73, 95% CI 1.35, 2.23) (Table 2). This difference was confined to infants with CL/P and was not observed in relation to risk of CPO. Infants born to Hispanic mothers and Black mothers were less likely to be born with OFC than infants born to White mothers (Table 2). These associations were stronger for CPO risk than for CL/P risk. Infants born

to Asian/Pacific Islander mothers had a slightly lower risk of OFC compared with those born to White mothers, with little difference by OFC subtypes (Table 2).

Associations of OFC risk with various maternal racial/ethnic groups changed over time, while the birth prevalence of OFC in the referent group of infants born to White mothers remained stable (Table 3, Figure 2). Post-fortification, on both the additive and multiplicative scales, the association of OFC with maternal Asian/Pacific Islander race/ethnicity decreased and with maternal Black race/ethnicity increased, relative to White race/ethnicity. Maternal American Indian race/ethnicity maintained the highest OFC risk relative to White across the study period (Table 3, Figure 2).

Probabilistic quantitative bias analysis suggests that selection bias of the magnitude reported in the literature could have explained the observed difference in OFC risk between infants born to Black mothers relative to White mothers. The median bias-adjusted ORs for OFC ranged from 0.90 (95% CI 0.67, 1.22) to 1.21 (95% CI 0.81, 1.84) under different specifications. A similar pattern was observed for CL/P and CPO with the 95% simulation limits containing the null value of 1 in all but one of the tested scenarios.

When standardising the birth prevalence of OFC reported by Kirby et al³⁴ to the racial distribution of livebirths in this study period in WA State, the overall expected birth prevalence would be 1.6 per 1000 livebirths, including syndromic cases. The observed birth prevalence of 1.3 per 1000 livebirths (including syndromic cases) in the present study would represent 81% of all true OFC cases. The observed non-syndromic OFC birth prevalence of 1.0 per 1000 livebirths in the present study would represent 83% completeness when comparing to the prevalence of 1.2 per 1000 livebirths in the National Birth Defects Prevention Study.³³

4 | COMMENT

4.1 | Principal findings

This study, in agreement with the scarce existing literature,⁸⁻¹³ provides additional evidence indicating that infants born to mothers living in rural areas are at higher risk of non-syndromic OFC than infants born to mothers living in urban areas. Risk of non-syndromic OFC also differed by maternal race/ethnicity, with the highest risk for infants born to American Indian mothers relative to White mothers, before and after US-mandated folic acid fortification. The lower OFC risk observed for infants born to Black mothers relative to White mothers may be due to disparities in OFC ascertainment in birth records.

4.2 | Strengths of study

We report a novel investigation of changes in the association of OFC with maternal rural residence, relative to US-mandated folic acid fortification of cereal grains. To our knowledge, there

TABLE 1 Demographic and clinical characteristics of mothers delivering singleton infants in Washington State, 1989-2014

	Orofacial cleft (n = 2136)	No orofacial cleft (n = 25 826)
	n (%)	n (%)
Age, (years)	2134 (100)	25 808 (100)
<20	219 (10.3)	3371 (13.1)
20-34	1630 (76.4)	19 298 (74.8)
35+	285 (13.4)	3139 (12.2)
Missing	2	18
Race/Ethnicity	2085 (100)	25 227 (100)
White	1573 (75.4)	18 197 (72.1)
Black	60 (2.9)	1112 (4.4)
Hispanic	198 (9.5)	3049 (12.1)
Asian/Pacific Islander	180 (8.6)	2376 (9.4)
American Indian	74 (3.6)	493 (2.0)
Missing	51	599
Education	1826 (100)	21 929 (100)
Less than High School	359 (19.7)	4324 (19.7)
High School Degree	508 (27.8)	5806 (26.5)
1-3 Years of College	520 (28.5)	5863 (26.7)
4 + Years of College	439 (24.0)	5936 (27.1)
Missing	310	3897
Marital Status	2132 (100)	25 774 (100)
Married	1420 (66.6)	16 893 (65.5)
Not Married	712 (33.4)	8881 (34.5)
Missing	4	52
Median Annual Family Income at Census Tract of Residence, (USD) ^a	2024 (100)	24 655 (100)
<30 000	385 (19.0)	4664 (18.9)
30 000-55 000	1257 (62.1)	14 817 (60.1)
>55 000	382 (18.9)	5174 (21.0)
Missing	112	1171
Rural-Urban Residence	2017 (100)	24 535 (100)
Rural	537 (26.6)	5812 (23.7)
Urban	1480 (73.4)	18 723 (76.3)
Missing	119	1291
Pre-pregnancy Diabetes	2044 (100)	25 419 (100)
Yes	14 (0.7)	154 (0.6)
No	2030 (99.3)	25265 (99.4)
Missing	92	407
Average Number of Cigarettes Smoked per Day During Pregnancy	2136 (100)	25 826 (100)
0	1734 (84.1)	22 252 (86.8)
1-9	155 (7.5)	1269 (5.1)
10-19	115 (5.6)	1046 (4.2)

(Continues)

TABLE 1 (Continued)

	Orofacial cleft (n = 2136)	No orofacial cleft (n = 25 826)
	n (%)	n (%)
20-29	52 (2.5)	434 (1.7)
30+	5 (0.2)	59 (0.2)
Missing	75	766
Kotelchuck Prenatal Care Index	1869 (100)	22 921 (100)
Inadequate	278 (15.1)	3352 (14.6)
Intermediate	389 (20.4)	4667 (20.4)
Adequate	843 (44.3)	10 681 (46.6)
Intensive	359 (20.3)	4221 (18.4)
Missing	267	2905

^aMedian annual family income of census tract of maternal residence in the 2000 Census.

has been only one other investigation of changes in OFC risk over time with the same level of detail of race/ethnicity categories.¹⁹ However, that study included only a limited pre-fortification period (1995-1997). We included all OFC cases captured by birth certificate and/or ICD codes in the birth hospitalisation records during a 25-year period in WA State and used a large random sample of matched controls in this well-defined source population. Additionally, we used a separate American Indian category for maternal race/ethnicity, which is often excluded due to small numbers. Yet, it is important to report because of their higher OFC risk.¹⁹

4.3 | Limitations of the data

Birth certificates reportedly have low sensitivity for birth defects, which could present a risk of selection bias to our study, to the extent that incomplete case finding was associated with our exposures of interest. To improve case ascertainment completeness, we used a combination of two data sources: birth certificates and hospital discharge data for birth hospitalisations. Hospital records have much more robust sensitivity, with reports of approximately 93% completeness for major birth defects relative to a population-based surveillance congenital malformation registry.³⁸

Relative to birth prevalence estimates from rigorously conducted, large, national studies, the birth prevalence in this study would be estimated to have captured 81-83% of OFC cases. This calculation assumes determinants of OFC are on average similar in WA State compared with the United States as a whole. However, WA State has lower than the national average prevalence of smoking during pregnancy, one of the strongest known risk factors for OFC.³⁹ This may lead to a true OFC birth prevalence that is lower, so the proportion of all true cases captured by this study would be greater.

**TABLE 2** Association of maternal characteristics with birth prevalence of non-syndromic orofacial clefts in Washington State, 1989-2014

Maternal characteristics	All orofacial clefts (OFC)	Cleft lip with or without cleft palate (CL/P)	Cleft palate only (CPO)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Rural-Urban ^a (n = 25 921)			
Urban	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Rural	1.12 (1.01, 1.25)	1.14 (1.01, 1.30)	1.07 (0.89, 1.29)
Race/Ethnicity (n = 27 312)			
White	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Black	0.62 (0.48, 0.81)	0.71 (0.52, 0.97)	0.48 (0.29, 0.81)
Hispanic	0.75 (0.64, 0.87)	0.91 (0.76, 1.08)	0.46 (0.33, 0.64)
Asian/Pacific Islander	0.87 (0.74, 1.02)	0.82 (0.67, 1.00)	0.97 (0.75, 1.26)
American Indian	1.73 (1.35, 2.23)	2.36 (1.80, 3.08)	0.61 (0.31, 1.18)

Note: Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression adjusted for birth year.

^aRural-urban models were also adjusted for maternal race/ethnicity.

We addressed possible bias due to differential incomplete case ascertainment by maternal race/ethnicity by conducting probabilistic quantitative bias analysis. The range of bias-adjusted estimates and 95% simulation limits under various scenarios indicate that selection bias could account for the lower OFC risk for infants born to Black mothers relative to White mothers observed in the unadjusted estimates. Without a more complete birth defects registry, it is not possible to determine whether differential reporting of OFC in WA State was as severe as reported by others.

4.4 | Interpretation

There are multiple potential pathways that could contribute to the observed increased risk of OFC for infants born to mothers of rural residence compared to mothers living in urban areas. Decreased access to nutrient-dense foods has been implicated as one potential mechanism linking rural living to increased risk of adverse birth outcomes.⁴⁰ Parental contact with various teratogens used in agricultural work via environmental or occupational exposure has also

TABLE 3 Association of maternal characteristics with birth prevalence of non-syndromic orofacial clefts in Washington State, before and after US-mandated folic acid fortification of cereal grains

Maternal characteristics	Infants conceived 1989-1995	Infants conceived 1998-2014 ^b	Effect measure modification	
			Additive Scale	Multiplicative Scale
	OR (95% CI)	OR (95% CI)	RERI ^c (95% CI)	ROR ^d (95%CI)
Rural-Urban ^a (n = 24 195)				
Urban	1.00 (Reference)	1.07 (0.87, 1.31)	<-0.01 (-0.28, 0.27)	0.99 (0.77, 1.27)
Rural	1.12 (0.90, 1.38)	1.19 (0.95, 1.49)		
Race/Ethnicity (n = 25 455)				
White (Reference)	1.00 (Reference)	1.10 (0.98, 1.23)		
Black	0.30 (0.13, 0.69)	0.77 (0.57, 1.04)	0.37 (0.02, 0.71)	2.30 (0.97, 5.47)
Hispanic	0.69 (0.49, 0.98)	0.86 (0.71, 1.04)	0.07 (-0.23, 0.36)	1.12 (0.76, 1.66)
Asian/Pacific Islander	1.24 (0.90, 1.72)	0.87 (0.71, 1.07)	-0.47 (-0.91, -0.02)	0.64 (0.44, 0.94)
American Indian	1.54 (0.93, 2.53)	1.89 (1.38, 2.59)	0.26 (-0.69, 1.20)	1.12 (0.62, 2.01)

Note: Odds ratios (OR) and 95% confidence intervals (CI) from logistic regression adjusted for birth year.

^aRural-urban models were also adjusted for race/ethnicity.

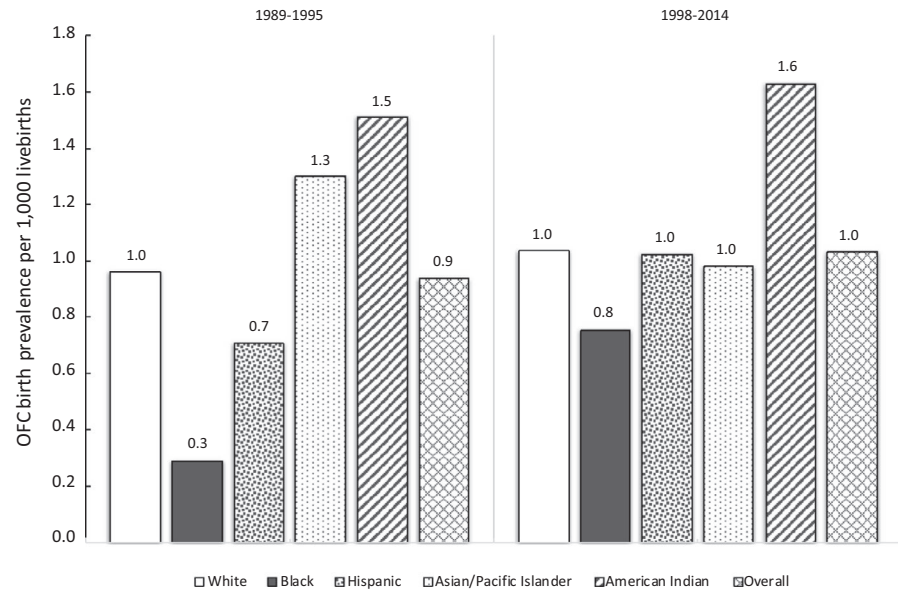
^bYears 1996 and 1997 were omitted due to partial implementation of the folic acid fortification policy.

^cRERI = Relative excess risk due to interaction. Values different than zero indicate the presence of effect measure modification in the absolute scale.

^dROR = Ratio of odds ratios. Values different than one indicate the presence of effects measure modification in the relative scale.



FIGURE 2 Birth prevalence of non-syndromic orofacial clefts (OFC) per 1,000 livebirths in Washington State by maternal race/ethnicity and infant conception period, before and after US-mandated folic acid fortification of cereal grains.



been identified as a risk factor for congenital anomalies.^{41,42} Other possible pathways include: differences in maternal smoking during pregnancy,⁴³ socioeconomic factors,⁴⁴ maternal age⁴⁵ and access to or quality of prenatal health care.⁴⁶

Infant OFC risk differed by maternal racial/ethnicity. Potential explanations for these results include differences in maternal smoking, rural-urban residence and prenatal care. The distribution of maternal smoking during pregnancy somewhat mirrored the direction and magnitude of OFC risk by maternal race/ethnicity (data not shown). Additionally, there was a higher proportion of mothers with rural residence and with inadequate prenatal care among American Indian mothers (data not shown), consistent with reports of insufficient access to care, poor healthcare environment, negative provider interactions,⁴⁷ and targeted cigarette marketing⁴⁸ in this group. Future studies should investigate these potential pathways using robust mediation analysis methods.^{49,50}

In secondary analyses, there was little difference in the association between rural residence and risk of CL/P or CPO. Infants born to Black, Hispanic, and American Indian mothers had a lower CPO risk compared with infants born to White mothers, which is consistent with other reports.⁶ The difference for infants born to Black mothers may be fully explained by selection bias due to poorer OFC ascertainment relative to White mothers. However, we are unaware of previous studies comparing relative OFC sensitivity of birth records for infants born to American Indian mothers, or studies evaluating disparities in reporting for CL/P and CPO separately. The less obvious diagnosis of CPO could be associated with more severe under-reporting among Black mothers than assumed by our bias analysis, which was based on parameters derived for non-syndromic OFC in general. The interpretation of strongly protective ORs for CPO should be cautious, since under-reporting patterns could also extend to infants born to Hispanic and American Indian mothers, consistent with between and within-hospital disparities found across several other delivery-related indicators.⁵¹ Distribution of other aetiologic factors

such as genetic mutations may also explain the CL/P and CPO differences.

While there is mixed evidence regarding the effect of US-mandated folic acid fortification on OFC risk,^{22,23,52-57} differences by race/ethnicity (limited to White, Black, Hispanic, and Other) have been reported.^{52,58} Relative to White mothers, we observed a post-fortification decrease in OFC risk among infants born to Asian/Pacific Islander mothers. This apparent benefit may reflect a lower average folate level prior to the policy implementation, therefore, allowing them to benefit more from the policy mandating supplementation. However, direct measures of folate by race/ethnicity prior to 2011 have typically been limited to White, Black, and Hispanic adults.⁵⁹ Consistent with our results, an international meta-analysis of randomised controlled trials reported that studies conducted in Asian populations showed greater risk reduction in stroke and cardiovascular disease with folic acid supplementation than studies conducted in European and North American populations.⁶⁰ Lower smoking rates in Asian/Pacific Islander mothers may also contribute to their relative reduction in OFC post-fortification.⁵²

5 | CONCLUSIONS

Investigation of social determinants of health can contribute to the understanding of the aetiology of OFC and inform future policy and prevention strategies. Further research should investigate specific pathways in rural environments and in American Indian populations contributing to higher relative risks observed across the study period. Potential research avenues to be considered include spatial investigation of agricultural chemicals, smoking, and access to appropriate prenatal care.

ACKNOWLEDGEMENTS

The authors thank Dr Alyson Littman for early guidance in the project, Seth Rowley for dataset preparation and the State of Washington



Department of Health for the partnership with the University of Washington Department of Epidemiology for data access.

CONFLICTS OF INTEREST

The authors report no conflicts of interest related to this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kapos FP, White LA, Schmidt KA, Hawes SE, Starr JR. Risk of non-syndromic orofacial clefts by maternal rural-urban residence and race/ethnicity: A population-based case-control study in Washington state 1989–2014. *Paediatr Perinat Epidemiol.* 2021;35:292–301. <https://doi.org/10.1111/ppe.12727>