Published in final edited form as:

Cleft Palate Craniofac J. 2019 February ; 56(2): 151–158. doi:10.1177/1055665618774019.

Proportion of Orofacial Clefts Attributable to Recognized Risk Factors

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Abstract

Objective: Estimate the population attributable fraction (PAF) for a set of recognized risk factors for orofacial clefts.

Design: We used data from the National Birth Defects Prevention Study. For recognized risk factors for which data were available, we estimated crude population attributable fractions (cPAFs) to account for potential confounding, average-adjusted population attributable fractions (aaPAFs). We assessed 11 modifiable and 3 nonmodifiable parental/maternal risk factors. The aaPAF for individual risk factors and the total aaPAF for the set of risk factors were calculated using a method described by Eide and Geffler.

Setting: Population-based case–control study in 10 US states.

Participants: Two thousand seven hundred seventy-nine cases with isolated cleft lip with or without cleft palate (CL±P), 1310 cases with isolated cleft palate (CP), and 11 692 controls with estimated dates of delivery between October 1, 1997, and December 31, 2011.

Main Outcome Measures: Crude population attributable fraction and aaPAF.

Results: The proportion of CL±P and CP cases attributable to the full set of examined risk factors was 50% and 43%, respectively. The modifiable factor with the largest aaPAF was smoking

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Authors' Note

The manuscript was presented orally at The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) 43rd Annual Meeting; September 18-21, 2016; Herrenkrug Parkhotel, Magdeburg, Germany. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

during the month before pregnancy or the first month of pregnancy (4.0% for CL±P and 3.4% for CP). Among nonmodifiable factors, the factor with the largest aaPAF for CL±P was male sex (27%) and for CP it was female sex (16%).

Conclusions: Our results may inform research and prevention efforts. A large proportion of orofacial cleft risk is attributable to nonmodifiable factors; it is important to better understand the mechanisms involved for these factors.

Keywords

cleft lip/palate; population attributable fraction

Orofacial clefts are congenital malformations with a worldwide prevalence of 17 per 10 000 live births (Mossey et al., 2009; Dixon et al., 2011). Cleft lip with or without cleft palate (CL ±P) and cleft palate only (CP) have a complex etiology, and the cause is unknown in most nonsyndromic cases. Several modifiable and nonmodifiable risk factors are recognized as potentially causal, but it is unclear what proportion of total risk is explained by these factors in combination, and what proportion of risk remains unexplained.

The population attributable fraction (PAF) is a measure that is useful for assessing how risk factors contribute to health outcomes at a population level (Spiegelman et al., 2007; Rämsch et al., 2009; Laaksonen et al., 2010). The PAF estimates the proportion of cases in the population ascribed to a particular risk factor. In other words, the PAF represents the proportion of disease that would be reduced by eliminating exposure to a given risk factor in the population, assuming that risk factor is causal. Computing PAF estimates requires the assumption that the probability of disease among the exposed individuals if they were theoretically not exposed would be the same as the probability of disease among the nonexposed individuals. However, this assumption does not hold true for complex traits like orofacial clefts because of the influence of confounding factors and multifactorial etiology (Laaksonen et al., 2010; Bezerra et al., 2015). The crude PAF (cPAF) does not account for confounding or other risk factors and can provide a biased or inflated estimate.

In order to estimate an unbiased PAF, a method has been proposed based on calculating the average-adjusted population attributable fraction (aaPAF) (Eide, 2008). Briefly, the adjusted population attributable fraction (aPAF) for a risk factor is calculated, adjusting for other known risk factors, based on extensions of the cPAF formula. This is repeated iteratively to separately account for effects of eliminating both single risk factors and combinations of risk factors (eg, smoking and drinking) from the population (Eide, 2008; Ruckinger et al., 2009).

Although methods for quantifying aaPAFs are available (Eide, 2008; Ruckinger et al., 2009), researchers have rarely applied this measure in birth defects research (Simeone et al., 2016). Therefore, we estimated the aaPAF for a set of recognized risk factors for orofacial clefts. Specifically, 2 orofacial cleft phenotypes were separately considered: (1) CL±P and (2) CP. We estimated the extent to which each of several individual recognized risk factors accounts for the PAF of CL±P and CP. Further, we estimated the extent to which the set of recognized risk factors combined accounts for the PAF of each of these phenotypes.

Methods

Study Subjects

Our study was based on data from the National Birth Defects Prevention Study (NBDPS). A review of the methods for subject recruitment and data collection has been described (Reefhuis et al., 2015). The NBDPS data were collected from subjects identified through population-based surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Cases were ascertained as live births, stillbirths, or induced abortions. Medical records of cases were reviewed by board-certified clinical geneticists to confirm study eligibility. Controls were live born infants without major birth defects randomly selected from birth certificates or hospital birth logs in the same time periods and geographical regions as the cases. Cases with recognized syndromes (single gene conditions or chromosome abnormalities) were excluded from the NBDPS. Cases and controls with estimated dates of delivery between October 1, 1997, and December 31, 2011, were included. Our analyses included cases with CL±P and CP. For our analyses, cases with additional major malformations nonsecondary to the cleft (eg, spina bifida) were excluded to reduce heterogeneity (ie, cases had isolated clefts). The study was approved by the institutional review board at each study site.

Risk Factors

Participating mothers completed computer-assisted telephone interviews on exposures before and during pregnancy. These interviews included information on 11 recognized modifiable orofacial cleft risk factors: low maternal education (maternal education < high school) (Yang et al., 2008; Carmichael et al., 2009; Acuña-González et al., 2011), maternal age >35 years (Bille et al., 2005; de Queiroz Herkrath et al., 2012; Luo et al., 2013; Mai et al., 2014; Salihu et al., 2014), obesity (body mass index ≥30.0 kg/m^2) (Blomberg and Källén, 2010; Marengo et al., 2013), pregestational diabetes (preexisting diabetes type I or II) (Krapels et al., 2006; Correa et al., 2008; Lebby et al., 2010; Figueiredo et al., 2015), gestational diabetes (diagnosed during pregnancy) (Krapels et al., 2006; Correa et al., 2008; Lebby et al., 2010; Figueiredo et al., 2015), ≥2 previous pregnancies including pregnancies that may have ended in miscarriages, still births, abortion, or a tubal or molar pregnancy (Harville et al., 2007; Golalipour et al., 2012; Lei et al., 2013), dietary folate deficiency during the year before pregnancy (based on the lowest quartile of dietary folate equivalent level in controls), lack of any folic acid supplementation (folic acid, multivitamin, or prenatal vitamin supplement) during the month before pregnancy or the first month of pregnancy (B1-P1) (Krapels et al., 2006; Kelly et al., 2012; Lin et al., 2014; Xu et al., 2015), any smoking during B1-P1 (Grewal et al., 2008; Leite and Koifman, 2009; Gunnerbeck et al., 2014), any alcohol consumption during B1-P1 (Romitti et al., 2007; Grewal et al., 2008; Leite and Koifman, 2009), and fever during B1-P1 (Shahrukh Hashmi et al., 2010).

Nonmodifiable factors (eg, race/ethnicity) may serve as effect modifiers and/or markers for underlying modifiable factors (eg, diet) or genetic factors. Thus, we also assessed 3 nonmodifiable factors: infant sex (male for CL±P and female for CP only) (Harville et al., 2007; Mossey et al., 2009; Dixon et al., 2011; Martelli et al., 2012; Lei et al., 2013; Mai et al., 2014; Burg et al., 2016; Scheller et al., 2016), family history of clefts in a first- or

second-degree relative (Kot and Kruk-Jeromini, 2007; Sivertsen et al., 2008) and maternal non-Hispanic white ethnicity (Genisca et al., 2009; Lebby et al., 2010; Saad et al., 2014).

Statistical Methods

We conducted separate analyses for cases with CL±P and CP. The crude PAF formula can be rearranged in 2 ways:

$$\mathrm{PAF} = \frac{P - P_{\text{expected}}}{P} = 1 - \frac{N_{\text{expected}}}{N} = P(E \,/\, D) \times \left(1 - \frac{1}{\mathrm{OR}}\right). \quad (1)$$

where P is the observed prevalence, P_{expected} is the expected prevalence under the absence of the exposure, N is the observed number of cases in the population and N_{expected} is the expected number of cases under the absence of exposure, P(E/D) is the prevalence of exposure in cases, and OR is the odds ratio (Cox, 2006; Mason and Tu, 2008). In our analyses, we used equation (1) to calculate cPAFs for each individual risk factor (for comparison to aaPAFs). Because 10% of participants were missing data on maternal report of fever, we repeated the main analyses for CL±P, excluding fever, to see whether the aaPAFs changed for other variables.

We calculated the aaPAFs for risk factors using the approach described by Eide and Gefeller (1995), modified for case–control studies. Eide and Gefeller's approach is the preferred method for valid PAF estimation and involves calculating the average of several estimated PAFs for each variable in the multivariable model, after sequential removal of other variables in every possible ordering (further described below). This was implemented using the SAS macro code provided by Ruckinger and colleagues (2009), modified for use with case–control studies, which constructs 95% confidence intervals for each aaPAF using a bootstrapping technique.

Initially, a univariate model was fitted with each risk factor. In order to build a parsimonious predictive model, only variables suggestive of a crude association ($P < .2$ in the univariate model) were included in an initial multivariable model. An assumption of estimating PAFs is that the exposure is a true risk factor. Therefore, in the multivariable model, if any of the risk factors had an association that was not in the expected direction (ie, result inconsistent with previous reports), the risk factor was excluded from the model (regardless of statistical significance). The macro code was then applied to calculate the aaPAFs for each given risk factor using the steps below:

1. The dichotomous risk factor was first "eliminated" from the population by recoding all participants as unexposed, irrespective of their real exposure status.
2. A logistic model was fitted to this modified data set to estimate predicted probabilities for each participant.
3. All predicted probabilities were summed to estimate the adjusted number of cases of the disease that would be expected if exposure to the risk factor was eliminated in the population.

4. These expected cases were then substituted in equation (1) to calculate the aPAF for the given risk factor.

This process was repeated iteratively to account for effects of removing both single risk factors and combinations of risk factors (eg, smoking and drinking). After sequentially "removing" the adjusted effect of each risk factor combination, we averaged the sequential PAFs over all possible removal sequences of the risk factors in the set to calculate the aaPAF for each risk factor. The total aaPAF for all recognized risk factors in combination was calculated by removing all risk factors from the population at the same time. This was repeated over all possible removal sequences of the risk factors in the set. The sequential PAFs over all possible removal sequences were averaged to calculate the total aaPAF. The total aaPAF thus calculated was also equal to the sum of the aaPAFs for all individual risk factors.

Receiver operating characteristic (ROC) curves were generated to assess the predictive ability of the logistic regression models. For each phenotype, the ROC curve was constructed by plotting the model's true-positive rate (sensitivity) against its false-positive rate (1-specificity). The area under the curve (AUC) and 95% confidence intervals were calculated to evaluate the ability of the models to discriminate between cases and controls. A value of AUC = 1 indicates perfect predictive ability, while AUC = 0.5 indicates prediction only by chance (Chambless and Diao, 2006). All statistical analyses were performed using SAS (version 9.3 copyright 2002-2010; SAS, Cary, North Carolina) and STATA version 14 (StatCorp, College Station, Texas).

Results

After excluding cases with additional birth defects nonsecondary to the cleft (eg, spina bifida), there were 2779 cases with CL±P and 1310 cases with CP included in the analysis. There were data for 11 692 controls. We tabulated the distribution of risk factors among cases and controls (Table 1). As expected, most of the recognized risk factors were more prevalent in cases than in controls. Information on maternal fever was missing for 10% of controls.

The following variables were not suggestive of an association with CL±P in the univariate logistic regression (*P* value > .2) and were therefore excluded from the final multivariable model: maternal age >35 years, ≥2 previous pregnancies, obesity, gestational diabetes, and any alcohol consumption during B1-P1. For CP, the following variables were excluded for the same reason: ≥2 previous pregnancies, obesity, lack of any folic acid supplementation during B1-P1, and fever during B1-P1. For CP, the direction of the effect estimate for maternal education <high school was not in the expected direction (ie, protective effect), so this variable was excluded from the final multivariable model before crude and adjusted PAFs were calculated (Table 2). No other variable was excluded for this reason.

For CL±P, the modifiable factors with the largest aaPAFs were maternal smoking (3.99%), lack of folic acid supplementation (3.34%), and maternal education <high school (3.23%; Table 2). Among nonmodifiable factors, the factors with the largest aaPAFs for CL±P were male infant sex (aaPAF, 26.53%) and maternal non-Hispanic white ethnicity (aaPAF,

7.32%). The aaPAF for each of the remaining risk factors was less than 3%. The total aaPAF for the combined set of all risk factors was 50.40%. The area under the ROC curve for the logistic model was 0.62. To assess the potential impact of missing data for maternal fever, our aaPAF analyses were repeated without fever in the model, and the results were similar to those from the main analyses (data not shown).

For CP, the modifiable factor with the largest aaPAF was maternal smoking (3.38%). Among nonmodifiable factors, the factors with the largest aaPAFs for CP were female infant sex (aaPAF, 16.43%) and maternal non-Hispanic white ethnicity (aaPAF, 13.49%). The aaPAF for each of the remaining risk factors was less than 3%. The total aaPAF for the combined set of all risk factors was 42.97%. The area under the ROC curve for the logistic model was 0.60.

Discussion

We report the application of a multidimensional approach to estimate aaPAFs for recognized orofacial cleft risk factors on which data are available in the NBDPS. This approach is expected to produce a more valid estimate of the proportion of risk due to selected recognized risk factors than the crude estimate. For most of the individual risk factors, the cPAF was higher than the aaPAF, which may suggest the cPAFs were inflated. For example, for CP, the cPAF and aaPAF for maternal non-Hispanic white ethnicity was 19.6% and 13.5%, respectively. Further, the total of the cPAFs for the set of risk factors was much higher than the total of the aaPAFs for the set (CL±P, 61.6% vs 50.4%; CP, 59.7% vs 43.0%, respectively), potentially overestimating the proportion of cases attributable to the set of risk factors. Similar trends have been observed for cPAFs versus aaPAFs for neural tube defect risk factors (Agopian et al., 2013) and for congenital heart defect risk factors (Simeone et al., 2016).

Among the modifiable factors assessed, the factor accounting for the largest risk was maternal smoking (aaPAF 4.0% for CL±P and 3.4% for CP). Previously reported cPAF for smoking in early pregnancy and orofacial clefts (phenotypes combined) range from 4% to 6% (Honein et al., 2007; Honein et al., 2014). Thus, strategies for smoking prevention and cessation among reproductive age women should be considered as a priority area for orofacial cleft prevention, as removing the risk related to smoking would likely have the largest effect on reducing the population prevalence of these defects, among modifiable factors examined in this analysis. Among nonmodifiable factors, the factor with the largest aaPAF for CL±P was male infant sex (27%), whereas it was female infant sex for CP (16%). Given the large proportion of risk related to sex, the mechanisms that underlie this association should be explored to determine if there are genetic (eg, sex chromosome genes) or modifiable factors (eg, pathways related to hormones) involved. For example, it has been suggested that estradiol levels may be related to the etiology of cleft lip and/or palate in mice (Miura et al., 1989).

After infant sex, the factor with the largest aaPAF was maternal non-Hispanic white race/ethnicity (aaPAF 7.3% for CL±P and 13.5% for CP). Numerous studies have reported a higher prevalence of CL±P and CP among infants of white race/ethnicity (Genisca et al.,

2009; Lebby et al., 2010; Saad et al., 2014). It is not clear whether this association is related to genetic differences; nongenetic factors related to race/ethnicity (eg, diet, healthcare access) might also play a role. A better understanding of the mechanisms that underlie this association might help identify modifiable factors that could be useful targets for orofacial cleft prevention approaches. Several genetic associations with CL±P have been reported (Mostowska et al., 2010; Murray et al., 2012; Figueiredo et al., 2014), and differences in genetic associations have been reported between racial/ethnic populations for multiple loci (Beaty et al., 2010; Figueiredo et al., 2014; Leslie et al., 2016).

In our analysis, other than infant sex, maternal non-Hispanic white ethnicity, and smoking, all other factors individually accounted for a relatively small proportion of the risk (individual aaPAFs <4%). Furthermore, the observed AUC scores from our final predictive models were less than 0.7 for both CL±P and CP. These scores indicate the recognized risk factors analyzed were not sufficient for prediction of case status. At least half of the risk of orofacial clefts could not be accounted for by recognized risk factors. These findings highlight the need to identify novel risk factors (eg, hypothesis generating approaches, large-scale genomics approaches) in order to account for a greater proportion of risk and subsequently develop prevention strategies for novel targets identified, as well as more accurately identify high-risk women.

Our findings are subject to potential limitations. Several genetic loci have been associated with nonsyndromic CL±P (eg, *IRF6*, 8q24 locus, and Ventral Anterior Homeobox 1 [*VAX1*]) (Birnbaum et al., 2009; Beaty et al., 2010), and it has been suggested that Interferon Regulatory Factor 6 (IRF6) could contribute to as much as 12% of all cleft cases (Zucchero et al., 2004). However, we assessed the aaPAFs of recognized nongenetic factors only, as data on genetic risk factors were not available. Because our models were built to only include recognized risk factors, there is a possibility that we did not account for important confounders that are not recognized risk factors, and our approach did not account for effect modification. Similar to many other studies of birth defects, we used self-reported data for exposure ascertainment, and some of the variables of interest (eg, smoking) may have been subject to recall bias. Our modeling of these variables may not have fully accounted for their effects (eg, intensity, duration and dose of smoking; racial ethnic heterogeneity). Further, PAF is strongly influenced by the magnitude of association and the prevalence of the exposure in the population. For our study, these factors may be specific to the NBDPS and hence the PAF estimates may not be generalizable to other populations.

We recognize that there are certain inherent limitations of PAFs. Population attributable fraction calculations are based on the assumption that all risk factors are causal, and it is possible that some of the factors we assessed are not true causal factors. Population attributable fraction calculations are also based on the assumption that if a given causal factor was eliminated, 100% of the risk related to that risk factor would be removed. It is unclear if this assumption would hold for all of the variables we analyzed. For example, it seems doubtful that all of the risk related to unmodifiable factors (eg, infant sex) could be "removed" from the population. Similarly, interpretation of PAFs is based on the exposure categories specified, and it may be that the unexposed level for some CLP risk factors cannot be practically attained by those in the exposed group. This study also has several strengths. It

benefited from the use of a large, multisite, population-based data set with data representative of diverse populations across the United States. Standardized methods were used for recruitment and ascertainment procedures, reducing the likelihood of selection bias. The estimated aaPAFs account for potential confounding and are expected to represent a more valid estimate than the crude estimate. In summary, this study thus provides a comprehensive investigation of the proportion of orofacial clefts attributable to a set of recognized nongenetic risk factors.

Conclusion

Our results may be helpful for prioritizing future research and prevention efforts. Since half or more of the risk is not explained by the examined risk factors, efforts are needed to identify additional risk factors, or interactions between known risk factors, including gene–environment interaction. As the modifiable risk factor responsible for the largest proportion of risk was smoking, strategies for smoking prevention and cessation among reproductive age women should be considered as a priority area for orofacial cleft prevention. Furthermore, since the majority of risk due to recognized factors is attributable to nonmodifiable factors (ie, infant sex and maternal non-Hispanic white ethnicity), it is also important to better understand the mechanisms involved in the contribution of risk by these factors.

Acknowledgments

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported through cooperative agreements under PA 96043, PA 02081, and FOA DD09–001 from the Centers for Disease Control and Prevention to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study. More specifically, this project was partially supported by the Texas Center for Birth Defects Research and Prevention, under cooperative agreement U01DD000494 from the Centers for Disease Control and Prevention with the Texas Department of State Health Services.

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Table 1.

Distribution of Selected Recognized Risk Factors for Orofacial Clefts Among Controls and Cases With Isolated Cleft Lip (With or Without Cleft Palate) or Cleft Palate Only, National Birth Defects Prevention Study, 1997-2011.

Risk Factor	Controls (N = 11 692), n (%)[a]	CL±P (N = 2779), n (%)[a]	CP (N = 1310), n (%)[a]
Infant factors			
Sex			
Male	5959 (51)	1838 (66.2)	543 (41.5)
Female	5721 (49)	937 (33.8)	766 (58.5)
Missing	12	4	1
Family history of clefts[b]			
Yes	41 (0.4)	99 (3.6)	48 (3.7)
No	11651 (99.6)	2680 (96.4)	1262 (96.3)
Maternal factors			
Education < high school			
Yes	1895 (16.7)	538 (19.8)	186 (14.6)
No	9455 (83.3)	2181 (80.2)	1088 (85.4)
Missing	342	60	36
Age at delivery (years)			
≤35	10 040 (85.9)	2392 (86.1)	1082 (82.6)
>35	1652 (14.1)	387 (13.9)	228 (17.4)
Race/ethnicity			
Non-Hispanic white	6718 (57.5)	1697 (61.1)	862 (65.8)
Other	4967 (42.5)	1081 (38.9)	448 (34.2)
Missing	7	1	-
Number of previous pregnancies			
<2	6739 (57.9)	1610 (58.1)	748 (57.3)
≥2	4903 (42.1)	1159 (41.9)	558 (42.7)
Missing	50	10	4
BMI (kg/m^2)			
≥ 30 (obese)	2051 (18.4)	513 (19.5)	243 (19.2)
<30 (nonobese)	9089 (81.6)	2121 (80.5)	1022 (80.8)
Missing	552	145	45
Lack of folic acid supplementation[c,d]			
Yes	5454 (47.3)	1382 (50.2)	601 (46.5)
No	6082 (52.7)	1368 (49.8)	690 (53.5)
Missing	156	29	19
Dietary folate intake (daily μg)[e,f]			
≤295.6	2887 (25.1)	751 (27.4)	351 (27.3)
>295.6	8614 (74.9)	1991 (72.6)	936 (72.7)
Missing	191	37	23

Risk Factor	Controls (N = 11 692), n (%)[a]	CL±P (N = 2779), n (%)[a]	CP (N = 1310), n (%)[a]
Pregestational diabetes (type I or II)			
Yes	71 (0.6)	37 (1.3)	19 (1.5)
No	11 542 (99.4)	2730 (98.7)	1285 (98.5)
Missing	79	12	6
Gestational diabetes			
Yes	535 (4.6)	143 (5.2)	79 (6.1)
No	11 078 (95.4)	2624 (94.8)	1225 (93.9)
Missing	79	12	6
Any smoking [d]			
Yes	2047 (18)	641 (23.5)	279 (21.8)
No	9348 (82)	2084 (76.5)	999 (78.2)
Missing	297	54	32
Any alcohol consumption[d]			
Yes	4103 (36.1)	947 (34.8)	496 (38.9)
No	7259 (63.9)	1771 (65.2)	779 (61.1)
Missing	330	61	35
Fever[d]			
Yes	1155 (11)	296 (11.9)	126 (11.1)
No	9365 (89)	2194 (88.1)	1011 (88.9)
Missing	1172	289	173

Abbreviations: BMI, body mass index; CL±P, cleft lip with or without cleft palate; CP, cleft palate only.

[a] Characteristic totals may not equal group totals due to missing data.

[b] In first- or second-degree relative.

[c] Any use of folic acid, multivitamin, or prenatal vitamin supplementation.

[d] During the month before pregnancy or the first month of pregnancy.

[e] Based on the lowest quartile of dietary folate equivalent level in controls.

[f] During the year before pregnancy.

Table 2.

Average Adjusted Population Attributable Fraction Estimates for Selected Recognized Orofacial Cleft Risk Factors Among Cases With Isolated Orofacial Clefts, National Birth Defects Prevention Study, 1997-2011.

		Cleft Lip (With or Without Cleft Palate), N = 2779				Cleft Palate Without Cleft Lip, N = 1310			
Variable	**Exposure Rate in Controls**	**aOR**	**95% CI**	**cPAF, %**	**aaPAF, %**	**aOR**	**95% CI**	**cPAF, %**	**aaPAF, %**
Non-Hispanic white ethnicity	57.5%	1.19	1.07-1.32	8.46	7.32	1.33	1.17-1.51	19.55	13.49
Any smoking[a]	18.0%	1.31	1.17-1.46	6.78	3.99	1.25	1.08-1.45	4.71	3.38
Family history of clefts[b]	0.4%	9.97	6.76-14.72	3.22	2.40	10.92	7.11-16.75	3.33	2.68
Low dietary folate intake[c,d]	25.1%	1.12	1.01-1.24	3.05	2.22	1.08	0.95-1.24	2.90	1.60
Pregestational diabetes	0.6%	2.33	1.52-3.57	0.73	0.60	2.46	1.45-4.16	0.85	0.69
Male infant sex	51.0%	1.88	1.71-2.07	31.06	26.53	-	-	-	-
Lack of folic acid supplementation[a,e]	47.3%	1.10	1.00-1.21	5.65	3.34	_[f]	_[f]	_[f]	_[f]
Maternal education <high school	16.7%	1.26	1.12-1.43	1.23	3.23	_[f]	_[f]	_[f]	_[f]
Fever[a]	11.0%	1.10	0.95-1.26	1.02	0.77	_[f]	_[f]	_[f]	_[f]
Female infant sex	49.0%	–	–	–	–	1.49	1.32-1.68	18.69	16.43
Maternal age >35 years	14.1%	_[f]	_[f]	_[f]	_[f]	1.25	1.07-1.46	3.81	2.70
Gestational diabetes	4.6%	_[f]	_[f]	_[f]	_[f]	1.35	1.05-1.74	1.52	1.22
Any alcohol consumption[a]	36.1%	_[f]	_[f]	_[f]	_[f]	1.03	0.91-1.16	4.37	0.78
Number of previous pregnancies ≥2	42.1%	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]
Obesity	18.4%	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]	_[f]
Combined				61.55[g]	50.40			59.73[g]	42.97

Abbreviations: aPAF, adjusted PAF; aaPAF, average adjusted PAF; CI, confidence interval; cPAF, crude PAF; aOR, adjusted odds ratio; PAF, population attributable fraction

[a] During the month before pregnancy or the first month of pregnancy (B1-P1).

[b] In first- or second-degree relative.

[c] Based on the lowest quartile of dietary folate equivalent level in controls.

[d] During the year before pregnancy.

[e] Any use of folic acid, multivitamin, or prenatal vitamin supplementation.

[f] Variable was excluded from the final regression model (*P* value >.2 in univariate logistic regression).

[g] The sum of individual crude population attributable fractions are presented.