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A population-based case–control study of the association between weather-related extreme heat events and orofacial clefts

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Abstract

Background—Limited epidemiologic research exists on the association between weather-related extreme heat events (EHEs) and orofacial clefts (OFCs). We estimated the associations between maternal exposure to EHEs in the summer season and OFCs in offspring and investigated the potential modifying effect of body mass index on these associations.

Methods—We conducted a population-based case-control study among mothers who participated in the National Birth Defects Prevention Study for whom at least 1 day of their first two post-conception months occurred during summer. Cases were live-born infants, stillbirths, and induced terminations with OFCs; controls were live-born infants without major birth defects. We defined EHEs using the 95th and the 90th percentiles of the daily maximum universal apparent temperature distribution. We used unconditional logistic regression with Firth's penalized

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

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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, or the views of the California Department of Public Health.

SUPPORTING INFORMATION
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likelihood method to estimate adjusted odds ratios and 95% confidence intervals, controlling for maternal sociodemographic and anthropometric variables.

Results—We observed no association between maternal exposure to EHEs and OFCs overall, although prolonged duration of EHEs may increase the risk of OFCs in some study sites located in the Southeast climate region. Analyses by subtypes of OFCs revealed no associations with EHEs. Modifying effect by BMI was not observed.

Conclusions—We did not find a significantly increased risk of OFCs associated with maternal exposure to EHEs during the relevant window of embryogenesis. Future studies should account for maternal indoor and outdoor activities and for characteristics such as hydration and use of air conditioning that could modify the effect of EHEs on pregnant women.

Keywords

congenital malformations; cleft lip; cleft palate; weather-related extreme heat; NBDPS

1 | INTRODUCTION

Orofacial clefts (OFCs) are among the most prevalent birth defects. Each year in the United States, an estimated 2,651 babies are born with cleft palate (CP) only (prevalence of 6.35/10,000 live births) and 4,437 babies are born with cleft lip with or without cleft palate (CL ±P) (prevalence of 10.63/10,000 live births) (Parker et al., 2010). OFCs can impair the development of teeth, speech, and feeding capabilities and can result in emotional stress for affected children and their families (DeRoo, Gaudino, & Edmonds, 2003). The causes of OFCs are largely unknown; however, it has been hypothesized that both genetic and environmental factors are important contributors (Wyszynski, 2002).

Hyperthermia during pregnancy, a condition that could be the result of febrile illnesses, hot/humid environment, use of heat devices, hot tub, sauna, and heavy exercise, has been identified as a teratogen in various animal species (Graham, Edwards, & Edwards, 1998). Because of hormonal changes during pregnancy and because of high environmental temperature interferes with the ability of the human body to thermoregulate, pregnant women are at risk of experiencing higher than normal core body temperature (Kuehn & McCormick, 2017; Rylander, Odland, & Sandanger, 2013).

Human studies have evaluated the association between OFCs and various indicators of elevated body temperature during pregnancy, including fever (Acs, Banhidy, Puho, & Czeizel, 2005; Shahrukh, Gallaway, Waller, Langlois, & Hecht, 2010; Wang, Guan, Xu, & Zhou, 2009), hot tub use (Duong et al., 2011), bathing habits (Agopian, Waller, Lupo, Canfield, & Mitchell, 2013), and use of electric bed-heating devices (Shaw, Nelson, Todoroff, Wasserman, & Neutra, 1999). In some of these studies, the authors reported no association (Duong et al., 2011), or only modestly elevated risks (Agopian et al., 2013; Shahrukh et al., 2010; Shaw et al., 1999), whereas others (Acs et al., 2005 and Wang et al., 2009) reported odds ratios (ORs) that ranged from 2.3 to 3.2. There is very limited research on the potential association between weather-related extreme heat events (EHEs) and OFCs, even though pregnant women seem to be vulnerable to environmental temperature extremes (Rylander et al., 2013; Strand, Barnett, & Tong, 2011).

To the best of our knowledge, only one study evaluated the impact of weather-related extreme heat in the summer on various birth defects, including OFCs (Van Zutphen, Lin, Fletcher, & Hwang, 2012). Therefore, the objectives of the current study were (a) to estimate the associations between maternal exposure to weather-related EHEs in the summer season and OFCs in offspring and (2) to assess the potential modifying effect of elevated maternal body mass index (BMI) on these associations.

2 | METHODS

2.1 | Study design and population

We used data from the National Birth Defects Prevention Study (NBDPS) to assess the association between maternal exposure to EHEs during the critical period of embryogenesis (first 8 weeks postconception) and OFCs (Shahrukh et al., 2010; Wyszynski, 2002). The NBDPS is a population-based case–control study designed to investigate genetic and environmental risk factors for more than 30 major structural birth defects. The methods of data collection have been described in detail elsewhere (Reefhuis et al., 2015). In our study, we included singleton OFC cases and nonmalformed controls with estimated dates of delivery (EDD) during October 1, 1997 through December 31, 2007, whose mothers participated in the NBDPS and whose residence was geocoded (83%). We included participants from eight NBDPS study sites: Arkansas (AR), California (CA), Georgia (GA), Iowa (IA), New York State (NY), North Carolina (NC), Texas (TX), and Utah (UT). Sites in New Jersey and Massachusetts also participated in NBDPS, but they were excluded from this study because they did not provide geocoded residential data.

Eligible cases were singleton live-born babies, stillbirths, and induced terminations diagnosed with nonsyndromic CP or CL ±P. To ensure consistency in case definition and ascertainment, clinical geneticists reviewed medical records of cases identified through birth defect surveillance systems (Rasmussen et al., 2003). Eligible controls were nonmalformed, singleton live-born infants randomly selected from hospital records or birth certificates. We excluded participants whose residential address was not geocoded or was incorrectly geocoded, those whose first 8 weeks postconception did not overlap with the summer months (June, July, and August), as well as those with pregestational diabetes due to increased risk of OFCs (Spilson, Kim, & Chung, 2001; Stott-Miller, Heike, Kratz, & Starr, 2010). Figure 1 displays the exclusion criteria for this study.

Trained interviewers conducted an approximately 1-hr computer assisted telephone interview in English or Spanish and collected information on maternal and infant sociodemographic characteristics, maternal medical history, and a variety of exposures, including residential history, which occurred from 3 months before conception through birth. The interview took place between 6 weeks and 24 months after the infant’s EDD to minimize recall bias (Tinker et al., 2013). All participants provided informed consent and each study site and the Centers for Disease Control and Prevention (CDC) obtained institutional review board (IRB) approval for data collection.

2.2 | Exposure assessment and definition

All maternal residential addresses from 3 months before conception through the end of pregnancy were geocoded centrally by the Agency for Toxic Substances and Disease Registry's Geographic Research, Analysis and Services Program. Each geocoded residence was linked with the closest weather monitoring station. If residential history dates were missing, we used the mean length-of-stay in one residence of mothers who reported complete residential history to impute dates (12.4% of the study population).

Daily maximum temperature in degrees Fahrenheit (°F), dew point (in °F), wind speed (in knots), and atmospheric pressure (in millibars) data obtained from the National Centers for Environmental Information for each station (National Centers for Environmental Information, Climate Data Online) were used to compute universal apparent maximum temperature (UATmax) using Steadman's formula (Steadman, 1984). UATmax is a better proxy for heat exposure, because it captures thermal stress more accurately than maximum temperature alone (Madrigano et al., 2013; Steadman, 1984; Van Zutphen et al., 2012).

We defined the vulnerable window based on the infant's estimated date of conception (EDC) and then assigned the daily UATmax to the corresponding dates for the first 8 weeks of each pregnancy. Per NBDPS protocol, the EDC was calculated by subtracting 226 days (38 weeks) from the due date. If due date was missing, then the date of the last menstrual period was used by adding 14 days to the date of last menses. We included only women for whom at least 1 day of the first 8 weeks postconception occurred during the summer season. We focused on summer exposures to avoid bias due to seasonal variation in OFC occurrence and because summer is the time of year when absolute temperatures are high enough to potentially result in hyperthermia. We defined the summer season as the months of June, July, and August of each year and used two definitions of EHEs as follows: (a) at least two consecutive days with daily UATmax above the 95th percentile of the UATmax distribution for the season and the year (EHE95) (Anderson & Bell, 2011) and (b) at least three consecutive days with daily UATmax above the 90th percentile of the UATmax distribution for the season and the year (EHE90) (Van Zutphen et al., 2012).

For each EHE definition, we further defined three exposure indices: any EHE95/EHE90, EHE95/EHE90 frequency (number of distinct EHE95/EHE90 episodes), and EHE95/EHE90 duration (number of days within each extreme heat event). As the absolute values of the 90th and 95th percentile vary by geographic region and people in different parts of the country have different adaptive capacity to extreme weather, this study evaluated the impact of EHEs on OFCs using thresholds that were aggregated to the following six climate regions: South (AR, TX), Southeast (NC, GA), Northeast (NY), Southwest (UT), West (CA), and Upper Midwest (IA) (National Centers for Environmental Information, U. S. Climate Regions).

2.3 | Confounders and effect modifiers

We evaluated the variables in Table 1 for their potential confounding effect on the association between maternal exposure to weather-related EHEs and OFCs. We also obtained the 2000 Standard Occupational Classification (SOC) System codes for occupations reported during the interview by a subset of mothers (n = 2,204) and classified them based on whether their reported occupations involved outdoor work. In addition, we evaluated BMI as an effect modifier. Obesity also plays a role in thermoregulation; in obese individuals, the subcutaneous adipose tissue prevents heat loss and limits the body's response to changes in core temperature (Savastano et al., 2009).

2.4 | Statistical analysis

We used unconditional logistic regression models with Firth's penalized likelihood method to compute adjusted prevalence odds ratios (aORs) and 95% confidence intervals (CI). The penalized likelihood method addressed issues of small sample size or quasi-complete separation of data. We used Directed Acyclic Graphs (DAGs) and the 10% change-in-estimate criterion to build the final model, which included maternal age at delivery (≤19, 20–34, ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), exposure to first trimester cigarette smoke (both maternal and secondhand smoke, maternal smoking only, secondhand smoke only, none), and pre-gestational BMI (<18.5, $18.5 \le$ BMI < 25, $25 \le$ BMI < 30, ≥ 30). To evaluate effect modification by maternal pregestational BMI, we dichotomized BMI as <25 kg/m^2 and ≥ 25 kg/m^2. For effect modification on the multiplicative scale, we calculated stratum-specific aORs and performed the Likelihood Ratio test using an alpha of 0.05. For effect modification on the additive scale, we computed the relative excess risk due to interaction (RERI) (Hosmer & Lemeshow, 1992).

To evaluate the potential impact of exposure misclassification on the association between EHE95/EHE90 (Yes, No), we conducted probabilistic sensitivity analysis to correct for misclassification of exposure. Using this method, we reconstructed the data that would have been observed accounting for plausible degrees of exposure misclassification and obtained simulation intervals that incorporate both systematic and random error (Fox, Lash, & Greenland, 2005).

We also conducted analyses to estimate the associations between maternal exposure to EHEs and OFCs in various data subsets. Embryologic and epidemiologic data support the hypothesis that cleft lip (CL) and cleft lip with cleft palate (CLP) are pathogenically similar; therefore, these defects were grouped together in CL ±P (Mitchell et al., 2002). We assessed the association between maternal exposure to EHEs and CP and CL ±P separately (Hobbs, Cleves, & Simmons, 2002; Kerrigan, Mansell, Sengupta, Brown, & Sandy, 2000). To assess the impact of residential history imputation, we estimated the association among mothers who reported complete residence history. We evaluated the potential impact of the distance between the weather monitoring station and maternal residence on the aOR estimates by calculating logistic regression estimates among mothers residing within geographical radii around the nearest weather station of 10 miles, 20 miles, and 30 miles. To assess the potential of confounding due to incomplete adjustment for occupational exposure to extreme heat, diuretic/laxative medication use, or fever during the first trimester, we analyzed subsets of mothers with complete information on their occupation, no diuretic/laxative medication use, and no fever, respectively.

Finally, to evaluate the potential of selection bias due to exclusion of study participants with incorrect geocodes, we compared the distribution of the major demographic characteristics between all eligible participants from the included study sites (N = 9,304) and those with correctly geocoded addresses (N = 7,708). The significance level for all statistical tests was set to α = 0.05. We used SAS 9.3 software for data management and logistic regression analysis.

3 | RESULTS

Our analytic dataset consisted of 907 OFC cases (294 CP cases and 613 CL ±P cases) and 2,206 controls. Table 1 shows the distribution of selected maternal characteristics by case status. Compared to control mothers, a higher percentage of case mothers were Hispanic and a lower percentage of case mothers were non-Hispanic black. A higher percentage of case mothers had <12 years of education at delivery, reported family history of OFCs, and reported smoking or exposure to secondhand smoke during first trimester. There were also slight differences in the case distribution by climate region. The other characteristics analyzed were similar between case and control mothers.

Supporting Information Table S1 shows the mean values of the UATmax in the summer season for the 95th (UATmax95%) and 90t^{h} (UATmax90%) percentiles by climate region and by case status. Overall and at most of the sites, the mean UATmax was slightly higher among cases than controls, although generally by < 1 °F. The exception is UT (Southwest), where the mean UATmax95% and UATmax90% were statistically significantly higher among controls than among cases.

Table 2 displays the adjusted estimates of the association between maternal exposure to EHE95 (Yes, No) and EHE90 (Yes, No) and OFCs, overall and by climate region. The estimates ranged from 0.45 to 1.43; therefore, results were not statistically significant and most were close to null. There also were no discernable patterns of OFCs associated with EHE frequency (Table 3). Estimates were generally similar in magnitude and direction for mothers exposed to one or two EHE95 and not statistically significant. The results were also similar for EHE90, except that the inverse association observed among mothers who experienced two EHE90 in IA (Upper Midwest) was statistically significant.

With respect to EHE duration (Table 4), we did not observe any significant associations overall, but we did observe significant associations within the Southeast and Upper Midwest climate regions. Mothers who resided in NC and GA (Southeast) and experienced a 3-day long EHE95, but not those who experienced a 2- or 4-day EHE95, had a significantly increased risk of OFCs compared to those who experienced no EHE95. Similarly, NC and GA mothers who experienced a 4-day EHE90, but not those who experienced a 3or 5-day EHE90, had a significantly increased risk of OFCs. Three-day long EHE90 exposure was inversely associated with OFCs in IA (Upper Midwest). Inverse associations were observed in UT (Southwest) for both EHE95 and EHE90, although they were not statistically significant. All remaining estimates were relatively close to null, nonsignificant, and with no clear exposure-response pattern.

Figure 2 displays the BMI-specific aOR for the associations between maternal exposure to EHE95 and EHE90 and OFCs in offspring. The estimates were not statistically different between the two levels of BMI for either EHE, nor did the RERI values show any evidence of effect modification on the additive scale: 0.11 (−0.58, 0.36) for EHE95 and − 0.18 (−0.67, 0.30) for EHE90.

We evaluated the impact of the misclassification of EHE95/EHE90 (Yes, No) on the aOR estimates and observed no bias. The probabilistic sensitivity analyses yielded aOR = 1.00, 95% CI 0.72, 1.43 for EHE95 (Yes, No), and aOR = 0.95, 95% CI 0.60, 1.27 for EHE90 (Yes, No). In addition, we also estimated associations between maternal exposure to EHE95/EHE90 and OFCs in offspring among selected subsets of the study sample. We observed similar estimates in magnitude and direction to those in the main analysis among participants with complete residence history, with varying levels of geographic proximity to a weather station, with outdoor occupations, and who did not report diuretic/laxative use or fever in the first trimester (Supporting Information Table S2). We did not observe any overall association between EHE95 (Yes, No) and EHE90 (Yes, No) and CP or CL ±P; however, we observed a significantly inverse association between EHE90 and CL ±P in IA (Upper Midwest).

4 | DISCUSSION

We observed no statistically significant associations between maternal exposure to EHEs (Yes, No) and OFCs, either overall or within each climate region. Overall, we estimated almost exactly null associations between both EHE95 and EHE90 and OFCs. Our findings are consistent with those observed by Van Zutphen et al., who evaluated the association between maternal exposure to EHE90 and occurrence of various birth defects in NY, including CP (aOR = 1.14, 95% CI 0.88, 1.48) and CL ±P (aOR = 0.94, 95% CI 0.76, 1.17) (Van Zutphen et al., 2012). Three other studies assessed the association between maternal exposure to external heat and OFCs (Agopian et al., 2013; Duong et al., 2011; Shaw et al., 1999). Duong et al. reported no association between maternal hot tub use in the first trimester and CL or CL ±P regardless of the duration and frequency of use (Duong et al., 2011). Agopian et al. observed modest elevated estimates for the association between bathing/shower habits and CL ±P (aOR = 1.14, 95% CI: 1.01, 1.28) (Agopian et al., 2013). Similarly, Shaw et al. reported elevated risks of CP (aOR range: 2.7–4.2) and CL ±P (aOR range: 1.6–1.8) associated with exposure to electric bed-heating devices; however, risk estimates were imprecise (Shaw et al., 1999). Due to the differences in the sources of exposure, our findings cannot be directly compared with findings from these three aforementioned studies.

Our primarily null—and, in some cases, protective—findings may be partly explained by our inability to control for adaptive behaviors to EHEs. Sensitivity to weather extremes is influenced by demographic and socioeconomic factors, including age, material constraints, and health conditions (Hayden, Brenkert-Smith, & Wilhelmi, 2011). Adaptive capacity to extreme weather events is a key factor in reducing the likelihood and magnitude of harmful outcomes. In a study on adaptive capacity to extreme heat by Hayden et al., the authors conducted door-to-door household surveys in Phoenix during first 2 weeks in August 2009. The most common strategies of coping with extreme heat reported were staying indoors (62.1%) and hydration (66.9%). Participants reported altering daily outdoor activities by limiting the time spent outdoors, engaging in outdoor activities early in the morning or late in the evening, and staying inside. However, with respect to adaptive capacity, while 89% reported having air conditioning in their homes, a little over one-third of participants reported not using it due to high electricity costs, while 6% had a nonfunctional air conditioner (Hayden et al., 2011). Semenza et al. explored the behavior change in relationship to hot weather and observed significant relationships between age, sex, race, and income and change in response to extreme heat (Semenza et al., 2008). It is therefore plausible that the pregnant women in our study restricted their outdoor activities during extreme weather-related heat events.

Next, we evaluated the relationship between frequency and duration of EHE95/EHE90 and OFCs. We observed no association overall between EHE95/EHE90 frequency and OFCs, and most regional estimates were close to null and not statistically significant. The one exception was IA (Upper Midwest), where we detected a significant inverse relationship among study participants who experienced two EHE90 vs no EHE90.

With respect to duration of EHEs, compared to no maternal exposure to EHEs, we observed no association overall or generally within the climate regions. However, we found significantly increased aORs in NC and GA (Southeast) among mothers who experienced 3-day long EHE95 but not 2- or 4-day long EHE95. Also, compared to no exposure to EHE90, we observed significantly increased aORs among mothers who experienced 4-day long EHE90, but not 3 or 5-day long EHE90, suggesting no pattern of association. Although the increased risk of OFCs among babies of mothers residing in warm climate regions located in the Southeast could be possibly explained in part by the increases in relative humidity in this part of the United States, we observed no association at other sites with humid climate (AR, TX in the South climate region). One potential explanation for the inverse associations could be that exposure to multiple or longer duration EHEs during the vulnerable period may result in early fetal loss, and thus a lower probability of OFCs to be included in NBDPS (Edwards, Saunders, & Shiota, 2003). However, given the high number of statistical tests we performed, our significant findings could be due to chance.

We identified one study that evaluated the relationship between the frequency of EHE90 and CP and CL ±P in NY and observed similar aOR estimates to those we observed in NY (Northeast) (Van Zutphen et al., 2012). However, although Van Zutphen et al. used the daily average value of the temperature in the 14 weather regions in NY to assess EHE, there is overlap between the participants in these two studies. We are not aware of any literature to date that has explored the relationship between the duration of EHEs and OFCs.

We did not observe any effect modification on the additive or multiplicative scale by maternal pregestational BMI and there is no literature to date to compare our findings. We explored the relationship between EHE95 (Yes, No) and EHE90 (Yes, No) separately for CP and CL ±P. We found no overall significant association; however, we observed a significant inverse association for EHE90 and CL ±P in IA (Upper Midwest). Finally, the aOR estimates of the association between EHE95 (Yes, No)/EHE90 (Yes, No) and OFCs among selected subgroups of participants were similar in magnitude and direction to those observed in the main analysis.

The hypothesized teratogenic mechanism of maternal hyperthermia involves exposures that could result in elevated body core temperature, which in turn may result in inhibition and delay in cellular proliferation, protein denaturation and cell death, alteration in cell membrane and intracellular structures, microvascular disruptions and placental infarction, and enzyme inhibition (Edwards, 2006; Graham et al., 1998). Although we used EHE occurrence as a surrogate for elevated body core temperature, it is possible that mothers who experienced EHE did not actually experience elevated body core temperature and therefore the pathogenic mechanism did not initiate.

4.1 | Study strengths

Our study is among the first to evaluate the potential association between maternal exposure to weather-related EHEs and OFCs among a geographically and racially diverse population more than a 10-year time period. We assessed exposure during the vulnerable time window of orofacial development and used UATmax to define multiple exposure indicators, as universal apparent temperature is a better indicator of thermal stress on the human body than temperature alone. Temperature measurement was not based on maternal recall and centralized geocoding ensured consistency of the data across participating sites. In addition, to account for acclimatization, we created the exposure indicators using the regional distribution of UATmax. Case ascertainment and classification of various subtypes of OFCs was performed systematically by trained clinical geneticists, using standardized criteria for diagnosis. Selection bias was minimized using a standard procedure (population based) for recruitment of cases and controls. NBDPS controls were randomly selected and participants have been shown to be representative of their source population on several maternal characteristics (Cogswell et al., 2009).

4.2 | Study limitations

Selection bias is often a concern with case–control studies; however, the similar response rate between cases and controls for the time period from October 1, 1997 through December 31, 2007 (68.5% for cases and 64.9% for controls) limited the selection bias in our study to some extent. In addition, in our study, we compared the distribution of demographic characteristics between eligible participants and those with correct maternal residence geocoded who were ultimately included and observed no significant difference. We assessed exposure by linking maternal residence to the closest weather monitoring station and did not have individual-level temperature measurements. We cannot know whether an individual was actually present at her residence during the time of a given EHE, or her use of adaptive behaviors to avoid extreme heat exposure (e.g., avoiding outdoor activities, utilizing air conditioning). However, our sensitivity analysis to correct for misclassification of exposure yielded estimates similar to those observed in the overall analysis. We calculated the mean distance between maternal residence and weather monitoring stations for each climate region and found that, although participants from NY (Northeast) resided the closest (11.2 miles) and participants from NC and GA (Southeast) resided the farthest (36.7 miles), these mean distances were not statistically different between cases and controls. Also, to assess the impact of distance from the monitoring station on the aOR, we conducted analyses restricted to study participants who resided within geographical radii of 10 miles, 20 miles, and 30 miles around the weather monitoring stations, compared the estimates to the overall aORs and observed no statistically significant differences. In addition, although errors in estimated date of conception and therefore in assignment of the vulnerability window are possible, we have no reason to believe that these errors are differential by case and control status.

Because we could not adjust for occupational exposure to heat in the main analysis, we calculated aORs on a subset of mothers for whom occupational data were coded (644 OFC cases and 1,579 controls) and observed that they were of similar magnitude and direction to those in the primary analysis. Our estimates may be biased due to residual confounding, as we could not adjust for other potential confounding variables such as indoor temperature, hydration, air conditioner use, urban/rural housing location, and time spent outdoors/ outdoors activities. Finally, our findings may also be due to chance. For our main analysis, we performed 112 statistical tests and would expect approximately six statistically significant estimates at an $\alpha = 0.05$; we observed five statistically significant estimates.

5 | CONCLUSIONS

Overall, we did not observe a generalized pattern of increased risk between maternal exposure to EHEs occurring during orofacial embryogenesis and OFCs in offspring. Increase in frequency or longer duration of EHEs may be associated with OFCs in certain climate regions. The protective results that we observed for some climate regions may suggest adaptive behaviors of pregnant women during weather-related EHEs. We did not observe any overall significant association for CP or CL ±P, specifically, nor any effect modification by pregestational BMI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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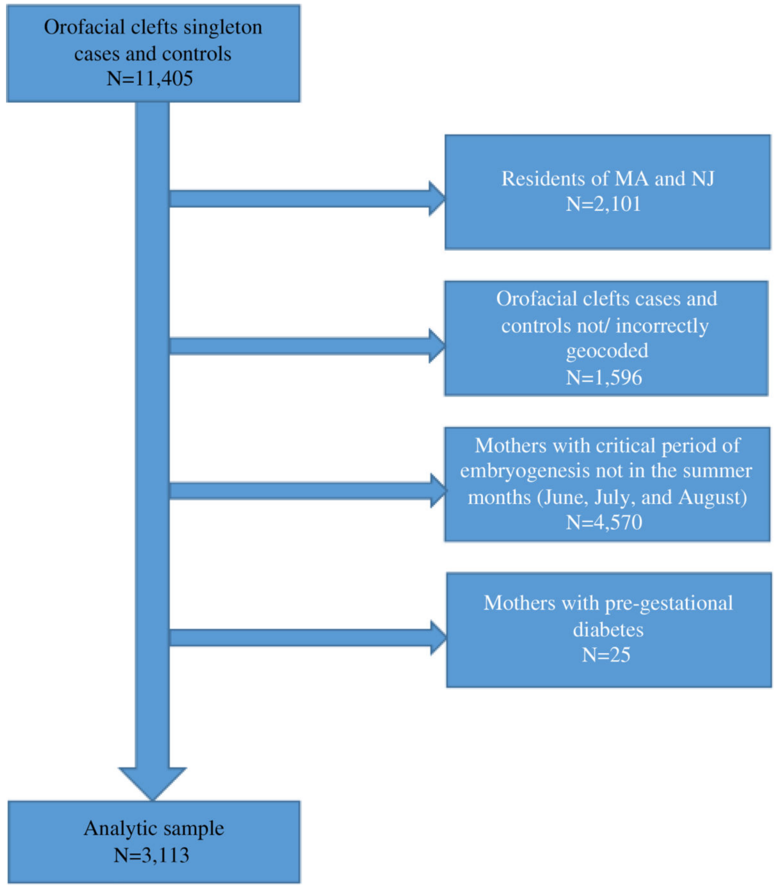

FIGURE 1.

Exclusion criteria for orofacial cleft cases and controls sample, National Birth Defects Prevention Study, 1997–2007. MA = Massachusetts; NJ = New Jersey

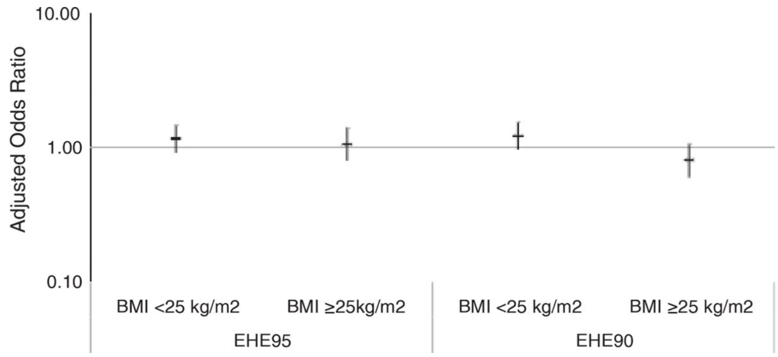

FIGURE 2.

Adjusted odds ratios of the association between EHEs and OFCs stratified by BMI, National Birth Defects Prevention Study, 1997–2007. EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least 3 consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region

TABLE 1

Distribution of sociodemographic characteristics between OFC cases and controls, NBDPS, 1997–2007

Maternal characteristics	Cases (N = 907)		Controls (N = 2,206)		
	N	%	N	%	$\chi^{2\,a}$
Maternal age					
≤19 years	100	11.03	257	11.65	0.76
20–34 years	697	76.85	1668	75.61	
≥35 years	110	12.13	281	12.74	
Maternal race					
White non-Hispanic	529	58.32	1249	56.62	<0.0001
Black non-Hispanic	54	5.95	278	12.60	
Hispanic	257	28.34	531	24.07	
Other/mixed	67	7.39	147	6.66	
Maternal education					
≤12 years	447	49.28	933	42.29	0.001
>12 years	456	50.28	1245	56.44	
Parity					
0	345	38.04	849	38.49	0.35
1	298	32.86	768	34.81	
≥2	264	29.11	589	26.70	
Prenatal care					
Yes	896	98.79	2183	98.96	0.59
No	11	1.21	22	1.00	
Folic acid use first trimester					
Yes	748	82.47	1827	82.82	0.81
No	159	17.53	379	17.18	
Body mass index					
Underweight (BMI < 18.5)	59	6.50	112	5.08	0.06
Normal (18.5 ≤ BMI < 25)	424	46.75	1129	51.18	
Overweight (25 ≤ BMI < 30)	193	21.28	486	22.03	
Obese (BMI ≥ 30)	181	19.96	385	17.45	

Maternal characteristics	Cases (N = 907)		Controls (N = 2,206)		$\chi^{2\,a}$
	N	%	N	%	
Fever first trimester					
Yes	74	8.16	139	6.30	0.06
No	833	91.94	2067	93.70	
Family history of OFCs					
Yes	62	6.84	8	0.36	<0.0001
No	845	93.16	2198	99.64	
Diuretics/laxatives first trimester					
Yes	107	11.80	284	12.87	0.40
No	800	88.20	1919	86.99	
Caffeine consumption first trimester					
>100 mg	419	46.20	939	42.57	0.06
≤100 mg	488	53.80	1267	57.43	
Alcohol consumption first trimester					
Yes	314	34.62	753	34.13	0.92
No	588	64.83	1422	64.46	
Maternal smoking first trimester					
Yes	222	24.48	396	17.95	<0.0001
No	682	75.19	1790	81.14	
Secondhand smoke first trimester					
Yes	270	29.77	525	23.80	0.0006
No	631	69.57	1658	75.16	
Antifolate medication					
Yes	7	0.77	26	1.18	0.31
No	896	98.79	2172	98.46	
Climate region					
South (AR, TX)	205	22.60	562	25.48	0.009
Southeast (NC, GA)	183	20.18	499	22.62	
Northeast (NY)	105	11.58	277	12.56	
Southwest (UT)	78	8.60	171	7.75	
West (CA)	194	21.39	354	16.05	

Maternal characteristics	Cases (N = 907)		Controls (N = 2,206)		
	N	%	N	%	χ^{2} [a]
Upper Midwest (IA)	142	15.66	343	15.55	
Imputed maternal residence dates					
Yes	124	13.67	264	11.97	0.19
No	783	86.33	1942	88.03	

NBDPS = National Birth Defects Prevention Study; BMI = body mass index; OFCs = orofacial clefts; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa;

The total percentage may not add to 100 because the counts on variables with missing values are not shown.

[a] χ^2 test of equal proportions.

TABLE 2

Adjusted odds ratio estimates of the association between EHE95 (Yes/No) /EHE90 (Yes/No) and OFCs by climate region, NBDPS, 1997–2007

Climate region	Mothers of cases/controls who experienced EHE95 n	EHE95 aOR (95% CI)[a]	Mothers of cases/controls who experienced EHE90 n	EHE90 aOR (95% CI)[a]
South (AR, TX)	155/433	0.87 (0.58, 1.29)	158/452	0.80 (0.53, 1.21)
Southeast (NC, GA)	145/368	1.43 (0.92, 2.20)	133/363	1.04 (0.70, 1.56)
Northeast (NY)	71/187	1.04 (0.63, 1.72)	69/174	1.08 (0.66, 1.77)
Southwest (UT)	73/166	0.45 (0.11, 1.80)	73/163	0.55 (0.17, 1.85)
West (CA)	166/315	0.80 (0.46, 1.40)	177/322	1.21 (0.62, 2.37)
Upper Midwest (IA)	109/280	0.74 (0.45, 1.20)	109/283	0.65 (0.40, 1.07)
Overall NBDPS	719/1749	1.01 (0.83, 1.23)	719/1757	0.96 (0.78, 1.17)

Note. EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study.

[a]Adjusted for maternal age, maternal race/ethnicity, body mass index, and smoking (maternal and secondhand smoking)

TABLE 3

Adjusted odds ratio estimates of the association between frequency of EHE95/EHE90 and OFCs by climate region, NBDPS, 1997–2007

	South (AR, TX) aOR (95% CI)[a]	Southeast (NC, GA) aOR (95% CI)[a]	Northeast (NY) aOR (95% CI)[a]	Southwest (UT) aOR (95% CI)[a]	West (CA) aOR (95% CI)[a]	Upper Midwest (IA) aOR (95% CI)[a]	Overall NBDPS aOR (95% CI)[a]
EHE95							
1 EHE vs 0	0.92 (0.61, 1.39)	1.34 (0.85, 2.12)	0.95 (0.56, 1.60)	0.43 (0.11, 1.73)	0.79 (0.45, 1.40)	0.70 (0.42, 1.16)	0.98 (0.79, 1.20)
2 EHEs vs 0	0.73 (0.43, 1.24)	1.63 (0.97, 2.74)	1.52 (0.73, 3.20)	0.54 (0.12, 2.35)	0.84 (0.44, 1.60)	0.86 (0.46, 1.59)	1.11 (0.86, 1.42)
EHE90							
1 EHE vs 0	0.81 (0.52, 1.25)	0.97 (0.63, 1.49)	1.02 (0.60, 1.72)	0.65 (0.19, 2.25)	1.34 (0.67, 2.70)	0.81 (0.48, 1.37)	0.99 (0.80, 1.22)
2 EHEs vs 0	0.80 (0.49, 1.30)	1.22 (0.74, 2.01)	1.28 (0.66, 2.50)	0.49 (0.14, 1.69)	1.10 (0.55, 2.21)	**0.49 (0.28, 0.86)**	0.91 (0.72, 1.14)

Note. EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study. The data given in boldface represent statistically significant estimates.

[a] Adjusted for maternal age, maternal race/ethnicity, body mass index, and smoking (maternal and secondhand smoking).

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TABLE 4

Adjusted odds ratio estimates of the association between duration of EHE95/EHE90 and OFCs by climate region, NBDPS, 1997–2007

	South (AR, TX) aOR (95% CI)[a]	Southeast (NC, GA) aOR (95% CI)[a]	Northeast (NY) aOR (95% CI)[a]	Southwest (UT) aOR (95% CI)[a]	West (CA) aOR (95% CI)[a]	Upper Midwest (IA) aOR (95% CI)[a]	Overall NBDPS aOR (95% CI)[a]
EHE95							
2 days vs 0	0.96 (0.63, 1.47)	1.22 (0.76, 1.94)	1.09 (0.63, 1.90)	0.49 (0.12, 2.01)	0.94 (0.51, 1.75)	0.61 (0.36, 1.05)	0.99 (0.80, 1.23)
3 days vs 0	0.69 (0.41, 1.13)	**1.89 (1.11, 3.23)**	0.81 (0.38, 1.75)	0.44 (0.10, 1.90)	0.76 (0.41, 1.41)	0.93 (0.51, 1.69)	1.01 (0.79, 1.29)
4 days vs 0	1.02 (0.52, 1.98)	1.63 (0.82, 3.23)	1.22 (0.56, 2.63)	0.40 (0.09, 1.79)	0.72 (0.38, 1.37)	0.88 (0.45, 1.72)	1.07 (0.81, 1.41)
EHE90							
3 days vs 0	0.80 (0.49, 1.30)	0.86 (0.53, 1.39)	0.78 (0.42, 1.44)	0.28 (0.05, 1.32)	1.53 (0.69, 3.40)	**0.42 (0.22, 0.82)**	0.78 (0.60, 1.00)
4 days vs 0	0.72 (0.42, 1.23)	**1.70 (1.02, 2.81)**	1.27 (0.63, 2.56)	0.67 (0.17, 2.61)	0.83 (0.39, 1.75)	0.76 (0.43, 1.34)	0.99 (0.78, 1.27)
5 days vs 0	0.87 (0.54, 1.38)	0.85 (0.51, 1.43)	1.48 (0.79, 2.77)	0.59 (0.17, 1.98)	1.36 (0.68, 2.71)	0.74 (0.43, 1.30)	1.07 (0.85, 1.33)

Note. EHE95 = extreme heat event defined as at least two consecutive days with daily universal apparent maximum temperature above the 95th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; EHE90 = extreme heat event defined as at least three consecutive days with daily universal apparent maximum temperature above the 90th percentile of the universal apparent maximum temperature distribution for the summer season and for climate region; aOR = adjusted odds ratio; CI = confidence interval; AR = Arkansas; TX = Texas; NC = North Carolina; GA = Georgia; NY = New York; UT = Utah; CA = California; IA = Iowa; NBDPS = National Birth Defects Prevention Study. The data given in boldface represent statistically significant estimates.

[a] Adjusted for maternal age, maternal race/ethnicity, body mass index, and smoking (maternal and secondhand smoking).