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Maternal ambient heat exposure during early pregnancy in summer and spring and congenital heart defects – A large US population-based, case-control study

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ABSTRACT

Background/objective: Few studies have assessed the effect of ambient heat during the fetal development period on congenital heart defects (CHDs), especially in transitional seasons. We examined and compared the associations between extreme heat and CHD phenotypes in summer and spring, assessed their geographical differences, and compared different heat indicators.

Methods: We identified 5848 CHD cases and 5742 controls (without major structural defects) from the National Birth Defects Prevention Study, a US multicenter, population-based case-control study. Extreme heat events (EHEs) were defined by using the 95th (EHE95) or 90th (EHE90) percentile of daily maximum temperature and its frequency and duration during postconceptional weeks 3–8. We used a two-stage Bayesian hierarchical model to examine both regional and study-wide associations. Exposure odds ratios (ORs) were calculated using multivariate logistic regression analyses, while controlling for potential confounding factors.

Results: Overall, we observed no significant relationships between maternal EHE exposure and CHDs in most regions during summer. However, we found that 3–11 days of EHE90 during summer and spring was significantly associated with ventricular septal defects (VSDs) study-wide (ORs ranged: 2.17–3.24). EHE95 in spring was significantly associated with conotruncal defects and VSDs in the South (ORs: 1.23–1.78). Most EHE indicators in spring were significantly associated with increased septal defects (both VSDs and atrial septal defects (ASDs)) in the Northeast.

Conclusion: While generally null results were found, long duration of unseasonable heat was associated with the increased risks for VSDs and ASDs, mainly in South and Northeast of the US. Further research to confirm our findings is needed.

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1. Introduction

Congenital heart defects (CHDs) are the most prevalent birth defect category and are associated with the highest mortality during the infant period (Gilboa et al., 2016). In the United States, CHDs occur in 8 of every 1000 live births and account for > 24% of birth defect-related infant deaths (Go et al., 2013). CHDs greatly impair the quality of life among affected individuals and involve substantial medical expenditures for the family and society (Waitzman et al., 1996). CHDs are a broad grouping of a variety of phenotypes that may involve heterogeneous pathogenic mechanisms, and therefore likely heterogeneous underlying etiologies, many of which remain unknown.

Limited studies have found that some phenotypes within the broader classification of CHDs may be associated with maternal exposure to environmental hazards, including air pollution (Van Der Bom et al., 2011; Stingone et al., 2014), residential or occupational exposure to cleaning products or chemicals (Lin et al., 2013; Ou et al., 2015), and extreme heat (Agay-Shay et al., 2013; Auger et al., 2017). Extreme weather events are expected to become more frequent and longer in duration and will differ both geographically and seasonally (Pachauri et al., 2014). Some weather-health studies to date have assessed mortality rates among elderly and minority populations (Anderson and Bell, 2009; Berko, 2017). Pregnant women, have not been considered a vulnerable group to extreme heat events (EHEs); this is in spite of biological plausibility and evidence from multiple animal (Vitali et al., 2015; Germain et al., 1985; Edwards et al., 1995) and human studies (Lynberg et al., 1994; Shi et al., 2014; Dreier et al., 2014), in which increased core body temperature resulting from fever, hot tub or sauna use, and/or exercise were found to be related to adverse birth outcomes including preterm delivery, intrauterine growth restriction, and birth defects.

While several studies found inconsistent patterns between extreme heat and gestational length and birthweight (Carolan-Olah and Frankowska, 2014; Poursafa et al., 2015; Strand et al., 2011; Zhang et al., 2017), there are only three studies examining the effects of extreme heat on CHDs (Agay-Shay et al., 2013; Auger et al., 2017; Van Zutphen et al., 2012). Using surveillance data from Congenital Malformations Registry in New York State (NYS), we previously reported that maternal exposure to extreme heat in summer was positively associated with congenital cataracts, but not with CHDs (Van Zutphen et al., 2012). Agay-Shay et al. (2013) in Israel reported that for birth conceived during the cold season, when maximum variance in temperature was observed, a 1-day EHE in the cold season was associated with an increased risk of multiple CHDs and isolated atrial septal defects (ASDs). In a study in Quebec, Auger et al. (2017) found that fetuses exposed to 15 days of temperature ≥ 30 °C during the summer, especially starting with the 3rd week post-conception, had significantly increased risks of CHDs, especially ASDs. Given the rarity of individual birth defects and only using a few temperature monitor sites, the prior studies may have been limited by statistical power or by exposure misclassification. Additionally, seasonal effects and regional differences of heat on CHD have rarely been evaluated. Pregnant women may be more susceptible to extreme heat in a transitional season due to lack of physical and behavioral adaptation (i.e. fans and air conditioners in use). By using the U.S. National Birth Defect Prevention Study (NBDPS) data, the current study intended to: 1) examine the associations between extreme heat and CHDs in summer; 2) evaluate if the heat-CHDs associations are stronger in spring than in summer; 3) assess heat-CHDs associations by CHD phenotypes and geographic region; and 4) compare heat-CHD associations using different heat indicators.

2. Methods

2.1. Study design and population

We used data from the NBDPS, a multicenter, population-based, case-control study in the United States that investigated genetic and environmental risk factors for > 30 major birth defects. The methods used by NBDPS have been described previously (Reefhuis et al., 2015).

Our study included CHD cases and control births from eight (of ten) participating centers (Arkansas, Texas, North Carolina, Georgia, New York, Utah, California, and Iowa) with estimated dates of delivery from October 1, 1997 through December 31, 2007, except for Utah and North Carolina, which started in 2003. ***Cases*** included livebirths, stillbirths of 20 or more weeks' gestation or > 500 g, and elective terminations, which ensure complete ascertainment of cases. To reduce etiologic heterogeneity among CHD cases, separate analyses for the larger CHD grouping, such as conotruncal heart defects, left or right outflow tract obstruction defects, and septal defects, as well as further sub-grouping for perimembranous ventricular septal defects (VSDs) and ASDs were performed as permitted by sample size. CHD cases were identified from each state's birth defects surveillance system and abstracted medical information was reviewed by clinical geneticists using specific case criteria, including standardized definitions of defects and required confirmatory diagnostic procedures (Rasmussen et al., 2003). ***Controls*** consisted of non-malformed live-born infants, randomly selected either from birth certificates or from birth hospitals in the same catchment areas and the same month of birth as the cases. Cases and controls who were adopted, in foster care, whose mothers did not speak English or Spanish, or who had a known chromosomal or single-gene abnormality were excluded from this study. This study received approval from NYS Department of Health Institutional Review Board (IRB), and each of the eight NBDPS site's IRB for access to the NBDPS data and geocoded data.

2.2. Data collection

Mothers of cases and controls completed a computer-assisted telephone interview between six weeks and two years after their estimated date of delivery. The information collected included maternal health status, medication use, pregnancy history and complications, vitamin use, caffeine, tobacco, alcohol use, home and work exposures, and demographics. Mothers were asked for their home addresses from three months before conception through the end of pregnancy. To aid mothers in their recall of exposures, a pregnancy calendar was used so that the mother could specify timing by date, month of pregnancy, or trimester.

2.3. Exposure assessment

Meteorological data including daily temperature, dew point, wind speed, and atmospheric pressure were obtained from the National Center for Atmospheric Research (NCAR) for each included center (National Centers for Environmental Information, 2017a). To assess the geographic differences of the heat-CHD relationships and population adaptability to extreme weather in different parts of the nation, we regrouped the eight NBDPS centers into six weather regions based on the NCAR guideline, including South (AR, TX), Southeast (NC, GA), Northeast (NY), Southwest (UT), West (CA), and Midwest (IA) (National Centers For Environmental Information, 2017b). There were 142 meteorological monitor sites throughout the study locations. All maternal self-reported residences were geocoded by a CDC contractor and then linked to the closest weather monitoring stations to assign the daily temperature value for each day of pregnancy. If a mother reported multiple residences but had missing values on dates she moved, we conducted data imputation under the assumption the mechanism leading to missing values were random by using the mean length-of-stay in one residence of mothers who reported complete residential history.

Experiencing extreme heat events (EHE) required that a case or control mother had at least one day of the critical period of CHD embryogenesis (postconceptional weeks 3–8) in the summer (June, July,

and August) or spring (March, April, May) season as a screening criterion for excluding the pregnancies with completed weeks only in the fall and winter seasons. We further restricted our analyses to summer and spring months respectively (Van Zutphen et al., 2012; Soim et al., 2017). Daily maximum temperature (Tmax) was used to define two EHEs: 1) at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the specific season and specific year (EHE95) when the mother was pregnant by weather station; 2) at least three consecutive days with daily Tmax above the 90th percentile of the Tmax distribution for the specific season and specific year (EHE90) when the mother was pregnant by weather station. We further examined heat exposure frequency (number of EHE90 or EHE95, continuous variable), and duration (longest consecutive days of EHE90 or EHE95, continuous variable). We also used a cumulative exposure index, i.e., number of days with daily Tmax above 90th or 95th percentiles (cumulative but not necessarily consecutive, continuous variable) during the 6-week critical period.

2.4. Potential confounders and assessment

The risk factors of CHD (based on previous literature Ou et al., 2015) and our data in Table 1) include sociodemographic factors, such as race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); maternal education level (< 12, ≥ 12 years), maternal age (≤ 19, 20–34, ≥ 35 years), infant gender, and residential weather region. Other maternal variables evaluated as potential confounders during the year before pregnancy to infant birth included parity (0, 1, ≥ 2); family history of CHDs (Yes/No); average dietary caffeine consumption (Yes/No); and pre-pregnancy body mass index (BMI) (underweight, normal weight, overweight, obese) as well as risk factors occurring 3 months before pregnancy to infant birth, including maternal fever during pregnancy (Yes/No); folic acid intake (Yes/No), alcohol consumption and smoking (Yes/No).

We then used Directed Acyclic Graphs (DAGs) (Appendix 2) to determine whether these CHD risk factors theoretically confounded the relationship between EHE and CHDs. To assess if these factors are also associated with heat exposure, we also examined the relationships between these CHD risk factors and EHE95 because a typical confounder should be associated with both health outcomes (CHDs) and the exposure variables (extreme heat here). In addition, dew point, a better indicator of moisture in the air than relative humidity, and air pollution were also examined as potential confounders. We finally identified maternal age, maternal education, race/ethnicity, mother's BMI, and dew point as potential confounders among all the possible factors through a DAG. Mother's BMI was then excluded as it was missing in > 500 cases and controls (approximately 5%). Air pollutants were not confounders based on DAGs, but their potential interactions with heat on CHDs will be examined in a separate paper.

Table 1
Maternal Characteristics of the Congenital Heart Defect Cases and Controls, National Birth Defects Prevention Study, 1997–2007.

Characteristic		Controls (n = 5742)	Cases (n = 5848)	ORs (95% CI)
Maternal age (years)*	< 19	626 (10.90)	549 (9.39)	0.86 (0.76, 0.97)
	20–34	4393 (76.51)	4486 (76.71)	1.00
	≥35	723 (12.59)	813 (13.90)	1.10 (0.99, 1.23)
Maternal education (years)	< 12	2437 (42.81)	2614 (44.89)	1.09 (1.01, 1.17)
	≥12	3256 (57.19)	3209 (55.11)	1.00
Maternal race/ethnicity[a]	B-NH	663 (11.55)	703 (12.02)	1.08 (0.96, 1.21)
	Hispanic	1400 (24.39)	1480 (25.31)	1.07 (0.98, 1.17)
	Other race	374 (6.52)	415 (7.10)	1.13 (0.97, 1.31)
	W-NH	3302 (57.54)	3249 (55.57)	1.00
Maternal BMI (kg/m^2)[a]	< 18.5	289 (5.27)	304 (5.47)	1.13 (0.95, 1.34)
	18.5– < 25	2907 (52.96)	2711 (48.77)	1
	25– < 30	1294 (23.57)	1296 (23.31)	1.07 (0.98, 1.18)
	≥30	999 (18.20)	1248 (22.45)	1.34 (1.21, 1.48)
Maternal smoking[b,*]	Yes	914 (16.01)	1001 (17.16)	1.09 (0.99, 1.20)
	No	4796 (83.99)	4831 (82.84)	1.00
Maternal alcohol use[b]	Binge drinking	702 (12.39)	715 (12.37)	0.96 (0.86, 1.08)
	Drinking but not binge	1215 (21.45)	1098 (19.00)	0.85 (0.78, 0.94)
	No drinking	3748 (66.16)	3967 (68.63)	1.00
Maternal caffeine use[a,*]	Yes	2488 (43.33)	2661 (45.50)	1.09 (1.02, 1.18)
	No	3254 (56.67)	3187 (54.50)	1.00
Family history of heart defect*	Yes	68 (1.18)	218 (3.73)	3.23 (2.46, 4.25)
	No	5674 (98.82)	5630 (96.27)	1.00
Maternal fever[b]	Yes	1251 (21.79)	1241 (21.22)	0.97 (0.89, 1.06)
	No	4491 (78.21)	4607 (78.78)	1.00
Infant sex*	Female	2802 (48.84)	2695 (46.12)	0.90 (0.83, 0.96)
	Male	2935 (51.16)	3149 (53.88)	1.00
Weather region	South (AR, TX)	1397 (24.33)	1706 (29.17)	–
	Southeast (NC, GA)	1271 (22.14)	1341 (22.93)	–
	Northeast (NY)	684 (11.91)	593 (10.14)	–
	Southwest (UT)	572 (9.96)	673 (11.51)	–
	West (CA)	902 (15.71)	896 (15.32)	–
	Midwest (IA)	916 (15.95)	639 (10.93)	–
Folic acid use[b]	Yes	2937 (51.88)	2923 (50.83)	1.00
	No	2724 (48.12)	2828 (49.17)	1.04 (0.97, 1.12)
Parity	≥2	1632 (28.43)	1742 (29.80)	1.03 (0.94, 1.13)
	1	1903 (33.15)	1818 (31.10)	0.92 (0.85, 1.01)
	0	2206 (38.43)	2285 (39.09)	1.00

* Significant difference between cases and controls ($P \leq 0.05$).

[a] Maternal body mass index (BMI) was calculated based on pre-pregnancy weight and height; Maternal caffeine use was defined as maternal average dietary caffeine consumption during the year before pregnancy to infant birth; B-NH: Black Non-Hispanic; W-NH: White Non-Hispanic.

[b] Maternal Smoking, alcohol intake, fever, and folic acid use were defined as maternal smoking, alcohol intake, fever, and folic acid use 3 months before pregnancy to the date of infant birth.

2.5. Statistical analysis

We used a two-stage Bayesian hierarchical model to examine both regional and nationwide effects. CHD outcomes were treated as dummy dependent variables in logistic regression models. In the first stage, we examined the CHDs in relation to EHEs by geographic regions. Exposure odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated using multivariate unconditional logistic regression, while controlling for potential confounding factors, separately for spring and summer to assess season-specific associations. While a pregnancy spanned from spring to summer, EHE exposures were defined based on the days falling within the critical window (3–8 weeks) for both seasons respectively. The relationship between a CHD and number of days, frequency, and duration of EHEs was also examined to assess the effect-response relationship. In the second stage, we pulled the point estimates from each region-specific model from stage 1 as the outcome, and region-specific variables as predictors. The regression model was weighted by inverse variances of the stage 1 risks estimated across regions to get an overall study-wide estimate while controlling for population density in each region by using a Bayesian hierarchical model (Feng et al., 2014). All analyses were performed using SAS 9.3 and the final model was assessed for fitness.

To evaluate the impacts of residual confounding or uncontrolled confounders on our findings, we reran the final models for sensitivity analyses by: 1) excluding mothers with pre-gestational diabetes or family history of CHDs, which are known risk factors of CHDs; 2) excluding multiple births; 3) excluding preterm births given that CHD infants are more likely to be delivered early; 4) evaluating if residential distance from the monitoring site had any substantial impact on the adjusted ORs using the buffers of 10 miles, 20 miles, and 30 miles for stratified analyses; 5) assessing if combining isolated and multiple CHDs could affect the associations tested; 6) addressing multiple-testing concerns by using Bayesian analysis approach by Greenland (2006, 2007), in which Jeffreys' prior is based on the observed Fisher information matrix, that provides an automated way of finding a non-informative prior for any parametric model; and 7) an augmented dataset was created by incorporating prior specifications and actual data in the logistic regression analysis. (Stokes et al., 2014)

3. Results

We found that the increased crude odds of CHDs were significantly associated with older maternal age, maternal education less than high school, pre-pregnancy BMI > 30 kg/m^2, smoking, alcohol drinking, maternal caffeine use, pre-gestational and gestation diabetes, family history of CHDs, and infant male sex (Table 1: positive ORs ranged from 1.09–3.23). The exposed and unexposed numbers (EHE95) of CHD cases (by phenotype) and controls in each region in spring and summer are described in Appendix 1. In terms of temperature by United States region (Table 2), as expected, we observed large variations in temperature distribution among different states/regions, especially in the spring season. Texas had larger temperature variabilities of EHE95 thresholds during the summer (Tmax–Tmin = 50.4 °F, Table 2) and spring (37.8 °F) respectively, but New York had the highest numbers of cumulative EHE days among all eight regions in both seasons. The adjusted ORs of the association between EHEs during the critical period (gestational age 3–8 weeks) and total (first row)/major phenotypes of CHDs in summer and spring are presented in Table 3 using EHE95 as the extreme heat indicator. Most of the results were null. However, in summer, we observed significant associations between EHE95 frequency and left ventricular outflow tract obstruction in the Southwest region (OR: 1.53, 95% CI: 1.00–2.35), and septal heart defects in the Midwest region (OR: 1.71, 95% CI: 1.09–2.69). In regards to the effect of EHE during spring (Table 3), we found consistently positive relationships between three EHE95 indicators (EHE95, EHE95 frequency and EHE95 duration) and conotruncal heart defects in South areas (AR and TX) with ORs ranging from 1.23–1.78. We also found that EHE95 duration was significantly associated with conotruncal defects in Utah (OR: 1.34, 95% CI: 1.00–1.81) and septal defects in NY (OR: 1.30, 95% CI: 1.05–1.62).

We further examined the relationships between EHE95 and two subtypes of septal defects, VSDs and ASDs, in summer and spring, and the results are presented in Table 4. We observed generally positive, though not statistically significant, associations between EHE95 and both VSDs and ASDs across climate regions during summer; these associations were stronger and significantly positive with a tighter 95% CI during spring. For example, we observed positive associations between VSDs and EHE95 (OR: 1.64, 95% CI: 1.00–2.71), EHE95 frequency (OR: 1.67, 95% CI: 1.07–2.62), and EHE95 duration (OR: 1.24, 95% CI: 1.01–1.52) in the South region (AR, TX) during spring. Compared to controls, the VSD cases had the highest exposure OR of 2.28 (95% CI: 1.00–5.21) to EHE95 in spring. We also found that EHE95 duration in spring was positively associated with VSDs (OR: 1.44, 95% CI: 1.11–1.88) and ASDs (OR: 1.87, 95% CI: 1.11, 3.16) in the Northeast region (NY) (Table 4).

Since we observed the duration of EHE exposure (continuous EHE days) appeared to be more persistently associated with CHD phenotypes than other indicators (Tables 3 and 4), we examined the relationships between VSDs (which had more significant findings) and cumulative days of EHE (EHE90 and EHE95 respectively) during the critical period by combining all regions in summer and in spring, respectively (Fig. 1a–d). The significantly increased odds for VSDs was observed for cumulative EHE90 durations of 3–5 days (ORs ranged: 2.17–2.57, all $P < 0.05$) and 11 days (OR: 3.24, 95% CI: 1.01–10.40) in summer (Fig. 1a). In addition, VSD was also significantly associated with cumulative EHE95 exposure for 6 days in summer (OR: 2.49, 95% CI: 1.02–6.09, Fig. 1b). Spring cumulative heat significantly increased VSD risk after 10 days of EHE90 with an OR of 9.62 (95% CI: 2.95–31.39,

Table 2
Extreme Heat Event (EHE) 90th and 95th percentile thresholds of daily maximum temperature (°F) in Summer and Spring, Eight States of the National Birth Defects Prevention Study, 1997–2007.

	Summer				Spring			
	90% EHE threshold		95% EHE threshold		90% EHE threshold		95% EHE threshold	
	Mean	(Min, max)	Mean	(Min, max)	Mean	(Min, max)	Mean	(Min, max)
Arkansas	97.16	(89.10, 104.70)	98.78	(89.60, 105.80)	86.41	(75.20, 95.00)	87.92	(75.20, 96.80)
California	92.54	(53.60, 117.00)	94.64	(53.60, 120.90)	84.10	(62.60, 109.90)	87.32	(62.60, 111.20)
Georgia	95.85	(73.40, 101.70)	97.14	(75.20, 104.00)	89.80	(55.40, 100.40)	91.17	(58.30, 100.40)
Iowa	91.01	(82.40, 98.60)	92.84	(86.00, 100.40)	83.03	(73.40, 93.20)	85.75	(77.00, 96.80)
North Carolina	93.38	(78.80, 102.20)	94.95	(80.60, 113.00)	85.78	(68.00, 98.60)	87.42	(68.00, 100.40)
New York	87.00	(66.20, 97.00)	88.90	(66.20, 100.00)	76.50	(55.40, 88.00)	79.64	(55.40, 91.00)
Texas	98.91	(60.80, 109.40)	100.20	(60.80, 111.20)	90.90	(77.00, 106.00)	92.47	(77.00, 107.60)
Utah	97.99	(80.60, 109.40)	99.76	(82.40, 111.20)	85.14	(68.00, 100.40)	87.52	(68.00, 105.80)

Table 3
Adjusted Odds Ratio* Estimates of the Association between Extreme Heat Events in Summer and Spring during Pregnancy Critical Period (Weeks 3–8) and Congenital Heart Defects Phenotypes, National Birth Defects Prevention Study 1997–2007.

	Adjusted ORs* for EHE95 Summer			Adjusted ORs* for EHE95 Spring		
	Having EHE95[a] or not	EHE95 frequency[b]	EHE95 duration[c]	Having EHE95[a] or not	EHE95 frequency[b]	EHE95 duration[c]
All CHD defects	1.09 (0.93, 1.29)	1.06 (0.93, 1.21)	1.02 (0.96, 1.08)	1.08 (0.88, 1.32)	1.03 (0.86, 1.24)	1.03 (0.95, 1.11)
Conotruncal defects	1.03 (0.76, 1.40)	0.96 (0.76, 1.22)	0.99 (0.89, 1.11)	1.39 (0.46, 4.23)	1.16 (0.31, 4.16)	1.12 (1.14, 8.94)
South (AR, TX)	0.74 (0.44, 1.23)	0.93 (0.60, 1.44)	0.87 (0.72, 1.06)	**1.78 (1.10, 2.90)**	**1.72 (1.10, 2.69)**	**1.23 (1.00, 1.51)**
Southeast (NC, GA)	1.14 (0.72, 1.80)	1.01 (0.73, 1.40)	1.03 (0.86, 1.22)	0.71 (0.41, 1.24)	0.74 (0.46, 1.19)	0.90 (072, 1.11)
Northeast (NY)	1.39 (0.75, 2.59)	1.11 (0.70, 1.75)	1.14 (0.91, 1.43)	1.51 (0.79, 2.89)	1.10 (0.66, 1.84)	1.12 (0.89, 1.41)
Southwest (UT)	0.60 (0.26, 1.40)	0.53 (0.28, 1.00)	0.87 (0.64, 1.17)	1.97 (0.74, 5.22)	1.11 (0.55, 2.25)	**1.34 (1.00, 1.81)**
West (CA)	1.14 (0.64, 2.02)	0.92 (0.58, 1.47)	0.99 (0.83, 1.17)	1.27 (0.76, 2.12)	1.12 (0.73, 1.71)	1.08 (0.90, 1.29)
Midwest (IA)	1.38 (0.72, 2.66)	1.36 (0.7, 2.34)	1.08 (0.84, 1.40)	1.33 (0.65, 2.72)	1.25 (0.67, 2.34)	1.08 (0.79, 1.48)
Left outflow tract defects	1.02 (0.73, 1.44)	1.00 (0.76, 1.32)	1.01 (0.89, 1.14)	0.84 (2.91, 2.41)	0.91 (0.27, 3.07)	0.97 (0.14, 6.91)
South (AR, TX)	0.89 (0.52, 1.51)	0.89 (0.55, 1.43)	0.95 (0.78, 1.15)	1.34 (0.77, 2.34)	1.39 (0.84, 2.31)	1.09 (0.86, 1.39)
Southeast (NC, GA)	1.08 (0.59, 1.97)	0.95 (0.60, 1.49)	1.01 (0.80, 1.27)	0.65 (0.32, 1.35)	0.62 (0.32, 1.20)	0.81 (0.60, 1.10)
Northeast (NY)	1.02 (0.49, 2.13)	1.24 (0.74, 2.0)	1.13 (0.86, 1.49)	0.42 (0.15, 1.22)	0.64 (0.28, 1.46)	0.83 (0.57, 1.20)
Southwest (UT)	2.00 (0.96, 4.19)	**1.53 (1.00, 2.35)**	1.24 (0.98, 1.58)	1.28 (0.71, 2.30)	1.16 (0.75, 1.79)	1.09 (0.90, 1.33)
West (CA)	0.80 (0.41, 1.58)	0.80 (0.45, 1.42)	0.89 (0.72, 1.10)	1.15 (0.65, 2.06)	1.12 (0.70, 1.79)	0.97 (0.78, 1.20)
Midwest (IA)	0.89 (0.47, 1.67)	0.79 (0.44, 1.40)	0.95 (0.74, 1.22)	1.36 (0.73, 2.53)	1.18 (0.68, 2.07)	1.15 (0.88, 1.49)
Right outflow tract defects	0.92 (0.63, 1.36)	0.94 (0.70, 1.25)	0.98 (0.85, 1.12)	1.11 (0.45, 2.77)	1.08 (0.35, 3.31)	1.02 (0.16, 6.65)
South (AR, TX)	0.83 (0.49, 1.40)	0.90 (0.57, 1.44)	0.96 (0.79, 1.16)	1.27 (0.72, 2.27)	1.43 (0.87, 2.35)	1.08 (0.85, 1.38)
Southeast (NC, GA)	0.87 (0.48, 1.55)	0.82 (0.52, 1.27)	0.92 (0.73, 1.16)	0.69 (0.33, 1.45)	0.78 (0.42, 1.45)	0.88 (0.66, 1.18)
Northeast (NY)	1.06 (0.48, 2.31)	0.93 (0.52, 1.70)	1.06 (0.79, 1.43)	1.20 (0.46, 3.11)	1.03 (0.49, 2.17)	1.12 (0.80, 1.57)
Southwest (UT)	0.60 (0.27, 1.37)	0.84 (0.48, 1.47)	0.87 (0.65, 1.16)	1.29 (0.58, 2.88)	1.11 (0.61, 2.02)	1.10 (0.85, 1.42)
West (CA)	1.89 (0.71, 5.07)	1.41 (0.70, 2.86)	1.15 (0.87, 1.50)	1.62 (0.71, 3.67)	1.44 (0.76, 2.73)	1.11 (0.84, 1.48)
Midwest (IA)	0.88 (0.43, 1.80)	0.95 (0.51, 1.77)	0.94(0.71,1.23)	0.79 (0.37, 1.69)	0.93 (0.48, 1.81)	0.89 (0.64, 1.25)
Septal defects	1.08 (0.80, 1.44)	1.06 (0.81, 1.37)	1.00 (0.90, 1.12)	0.95 (0.26, 3.48)	0.90 (0.21, 3.80)	0.98 (0.10, 9.42)
South (AR, TX)	1.03 (0.75, 1.41)	1.05 (0.79, 1.38)	1.00 (0.89, 1.12)	1.08 (0.77, 1.51)	1.11 (0.82, 1.52)	1.03 (0.90, 1.19)
Southeast (NC, GA)	1.13 (0.76, 1.69)	1.04 (0.78, 1.39)	1.02 (0.87, 1.20)	0.79 (0.51, 1.23)	0.77 (0.52, 1.14)	0.90 (0.76, 1.08)
Northeast (NY)	0.67 (0.36, 1.24)	0.69 (0.43, 1.13)	0.78 (0.60, 1.01)	1.72 (0.89, 3.34)	1.34 (0.81, 2.21)	**1.30 (1.05, 1.62)**
Southwest (UT)	1.07 (0.50, 2.28)	0.97 (0.60, 1.59)	1.09 (0.84, 1.41)	0.72 (0.40, 1.29)	0.72 (0.45, 1.16)	0.93 (0.77, 1.13)
West (CA)	1.37 (0.71, 2.66)	1.01 (0.60, 1.71)	1.05 (0.86, 1.27)	0.92 (0.51, 1.65)	0.85 (0.51, 1.40)	0.92 (0.74, 1.15)
Midwest (IA)	1.35 (0.77, 2.39)	**1.71 (1.09, 2.69)**	1.09 (0.88, 1.36)	0.72 (0.40, 1.30)	0.78 (0.46, 1.34)	0.85 (0.65, 1.11)

* Adjusted for age, race, education, dew point and all numbers in bold indicated statistically significant with $P < 0.05$.
[a] EHE95: at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the season and the year.
[b] EHE95 frequency: number of EHE95.
[c] EHE95 duration: longest consecutive days of EHE95.

Fig. 1c). No significant finding was observed for cumulative EHE95 and VSD in spring (Fig. 1d).

As demonstrated in Fig. 2, many heat indicators for both EHE90 and EHE95, especially EHE duration for all indicators, showed significantly positive associations with septal defects, VSD and ASD during spring time in NY. By comparing the hottest region (AR, TX) with the coldest region (NY) during spring (Fig. 3), we found that the risks for VSDs were significantly associated with most heat indicators in NY, and the increased VSDs risks were significantly associated with all three 95EHE indicators, but not 90EHE indicators during spring in the South region (AR, TX).

In the multiple sensitivity analyses (data not shown), we first

Table 4
Adjusted Odds Ratio* Estimates of the Association between Extreme Heat Events in Summer and Spring during Pregnancy Critical Period (Weeks 3–8) and Ventricular Septal Defects and Atrial Septal Defects, National Birth Defects Prevention Study 1997–2007.

	Adjusted ORs* for EHE95 Summer			Adjusted ORs* for EHE95 Spring		
	Having EHE95[a] or not	EHE95 frequency[b]	EHE95 duration[c]	Having EHE95[a] or not	EHE95 frequency[b]	EHE95 duration[c]
Ventricular septal defects	1.18 (0.81, 1.72)	1.14 (0.83, 1.57)	1.04 (0.90, 1.19)	1.06 (0.41, 2.74)	0.97 (0.32, 2.93)	1.03 (0.15, 6.70)
South (AR, TX)	1.38 (0.81, 2.35)	1.34 (0.84, 2.12)	1.12 (0.94, 1.35)	**1.64 (1.00, 2.71)**	**1.67 (1.07, 2.62)**	**1.24 (1.01, 1.52)**
Southeast (NC, GA)	1.30 (0.77, 2.18)	1.12 (0.78, 1.60)	1.05 (0.86, 1.29)	0.76 (0.41, 1.39)	0.75 (0.44, 1.27)	0.91 (0.71, 1.16)
Northeast (NY)	0.78 (0.34, 1.79)	0.81 (0.42, 1.55)	0.80 (0.56, 1.14)	**2.28 (1.00, 5.21)**	1.58 (0.86, 2.88)	**1.44 (1.11, 1.88)**
Southwest (UT)	1.27 (0.38, 4.23)	1.07 (0.50, 2.26)	1.13 (0.76, 1.69)	0.63 (0.24, 1.64)	0.67 (0.30, 1.49)	0.92 (0.67, 1.25)
West (CA)	1.01 (0.40, 2.54)	0.81 (0.38, 1.74)	1.04 (0.79, 1.37)	0.91 (0.33, 2.47)	0.77 (0.32, 1.86)	0.91 (0.63, 1.31)
Midwest (IA)	1.19 (0.58, 2.42)	1.70 (0.96, 3.00)	1.02 (0.77, 1.36)	0.98 (0.49, 1.98)	1.07 (0.58, 1.99)	0.97 (0.71, 1.32)
Atrial septal defects	1.32 (0.88, 1.99)	1.20 (0.90, 1.62)	1.07 (0.93, 1.24)	1.15 (0.33, 4.04)	0.92 (0.30, 2.90)	1.03 (0.16, 6.75)
South (AR, TX)	0.97 (0.68, 1.40)	1.00 (0.73, 1.38)	0.97 (0.85, 1.11)	0.87 (0.58, 1.31)	0.89(0.61,1.30)	0.95 (0.80, 1.12)
Southeast (NC, GA)	1.19 (0.64, 2.21)	1.09 (0.71, 1.68)	1.08 (0.86, 1.37)	0.83 (0.45, 1.52)	0.81 (0.47, 1.38)	0.91 (0.71, 1.16)
Northeast (NY)	2.79 (0.69, 11.31)	1.70 (0.67, 4.30)	1.24 (0.79, 1.95)	4.15 (0.73, 23.71)	1.88 (0.55, 6.47)	**1.87 (1.11, 3.16)**
Southwest (UT)	0.90 (0.36, 2.24)	0.84 (0.46, 1.55)	1.06 (0.77, 1.45)	0.83 (0.42, 1.65)	0.80 (0.46, 1.38)	0.97 (0.77, 1.21)
West (CA)	1.72 (0.69, 4.29)	1.16 (0.60, 2.27)	1.04 (0.81, 1.34)	0.94 (0.47, 1.87)	0.89 (0.49, 1.61)	0.93 (0.72, 1.21)
Midwest (IA)	1.72 (0.73, 4.06)	1.84 (0.91, 3.68)	1.22 (0.88, 1.70)	0.40 (0.14, 1.14)	0.41 (0.15, 1.11)	0.67 (0.42, 1.08)

* Adjusted for age, race, education, dewpoint and all numbers in bold indicated statistically significant with $P < 0.05$.
[a] EHE95: at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the season and the year.
[b] EHE95 frequency: number of EHE95.
[c] EHE95 duration: longest consecutive days of EHE95.

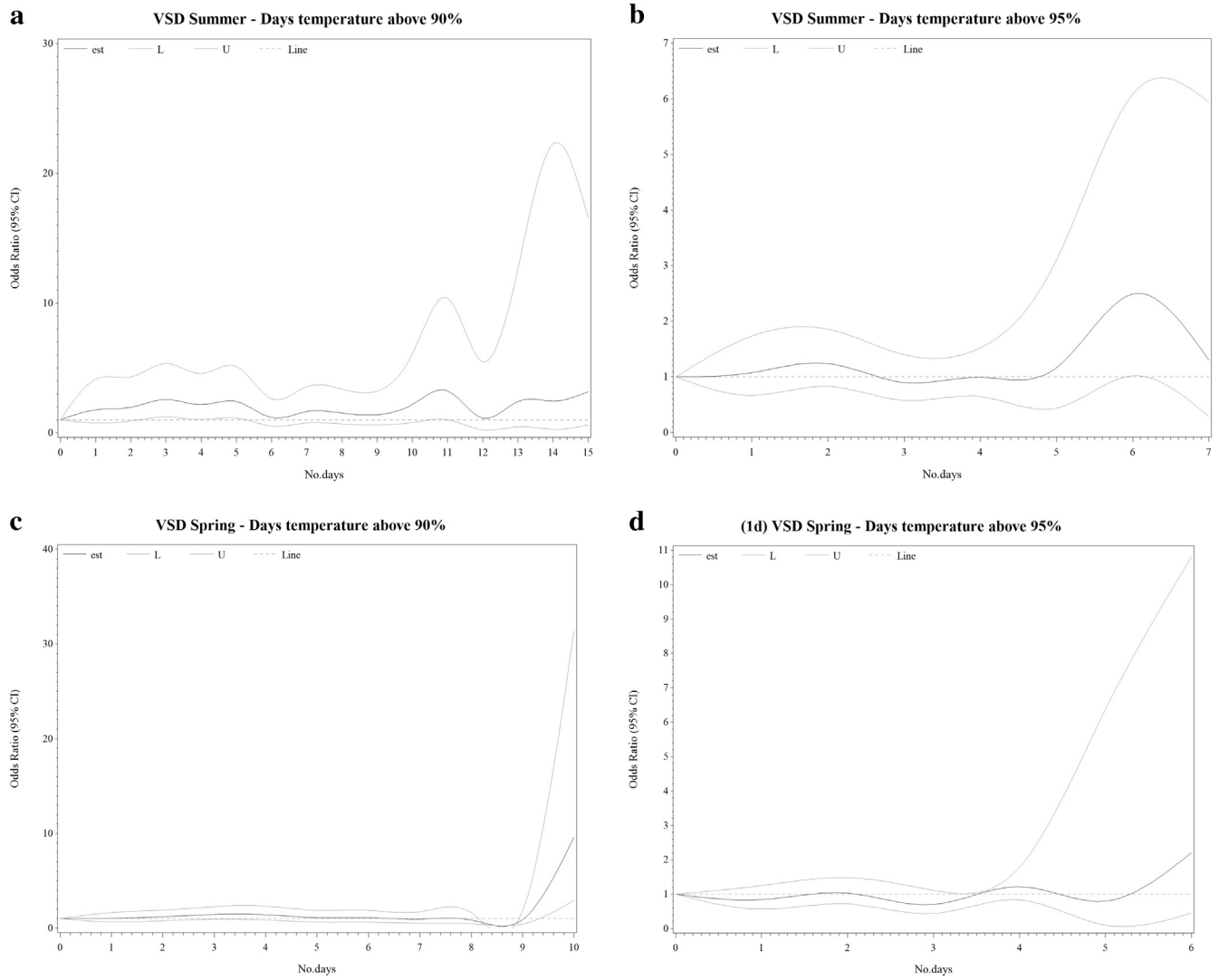

Fig. 1. a. Adjusted Odds Ratio* Estimates of the Association between Total Days of EHE90 during Pregnancy Critical Period (weeks 3–8) in summer (June–August) and Ventricular septal defect, NBDPS 1997–2007. Number of days with daily Tmax above 90th percentiles (cumulative but not necessarily consecutive) during the 6-week critical period (case = 236).

b. Adjusted Odds Ratio* Estimates of the Association between Total Days of EHE95 during Pregnancy Critical Period (weeks 3–8) in summer (June–August) and Ventricular septal defect, NBDPS 1997–2007. Number of days with daily Tmax above 95th percentiles (cumulative but not necessarily consecutive) during the 6-week critical period (case = 236).

c. Adjusted Odds Ratio* Estimates of the Association between Total Days of EHE90 during Pregnancy Critical Period (weeks 3–8) in spring (March–May) and Ventricular septal defect, NBDPS 1997–2007. Number of days with daily Tmax above 90th percentiles (cumulative but not necessarily consecutive) during the 6-week critical period (case = 276).

d. Adjusted Odds Ratio* Estimates of the Association between Total Days of EHE95 during Pregnancy Critical Period (weeks 3–8) in spring (March–May) and Ventricular septal defect, NBDPS 1997–2007. Number of days with daily Tmax above 95th percentiles (cumulative but not necessarily consecutive) during the 6-week critical period (case = 276).

*Adjusted for age, race, education, dewpoint.

excluded mothers with pre-gestational diabetes or family history of CHD, and reran the models; all estimates from the sensitivity analyses showed similar direction, and most positive results remained statistically significant (about 20% of the original estimates were non- or borderline-significant in the sensitivity analysis). Additionally, the results of excluding multiple and preterm births did not change significantly compared to the original results. Compared to the stratified distance, the adjusted ORs obtained in our original analysis were slightly lower and closer to the null for most weather regions. After excluding those with multiple CHDs from the analysis, we found that the original results' magnitudes and statistical significances remain similar. Finally, to estimate the potential impact of multiple testing, we used Bayesian analysis and observed similar findings, i.e., twelve (92.3%) out of the 13 originally positive findings remained the same (very similar ORs and still statistically significant or borderline significant) with only one non-significant. The ranges of ORs before the multi-test correction (ORs range: 1.23–2.28) and after the correction (ORs: 1.22–2.28) are basically the same.

4. Discussion

4.1. Summer heat's association with CHDs

Overall, we did not observe significant associations between EHEs during the critical development period and CHDs in most regions during the summer. This null finding agrees with the findings from a

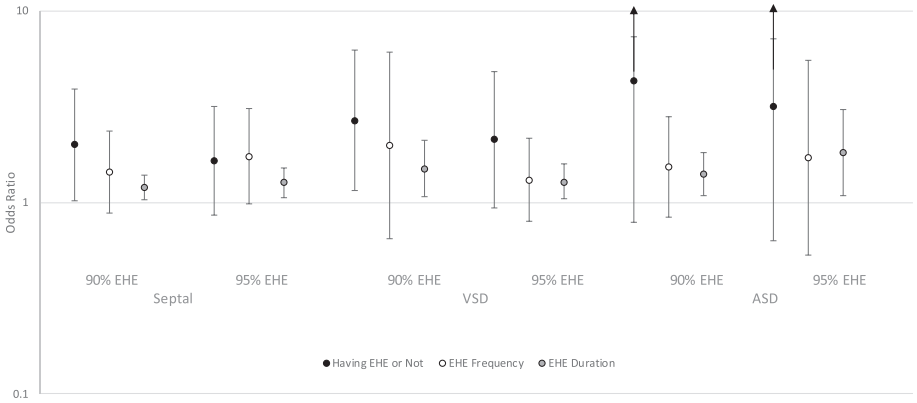

Fig. 2. Odds ratios and 95% confidence intervals for septal defects, ventricular septal defects (VSD) and atrial septal defects (ASD) and exposure to extreme heat events (EHEs) in the Northeast during the spring. EHEs were evaluated as either having an EHE or not during postconceptional weeks 3–8 (black circles), the frequency of EHE events (white circles) and the duration of EHE events (grey circles). Daily maximum temperature (Tmax) was used to define EHE indicators as: 1) at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the season and the year (EHE95); or 2) at least three consecutive days with daily Tmax above the 90th percentile of the Tmax distribution for the season and the year (EHE90).

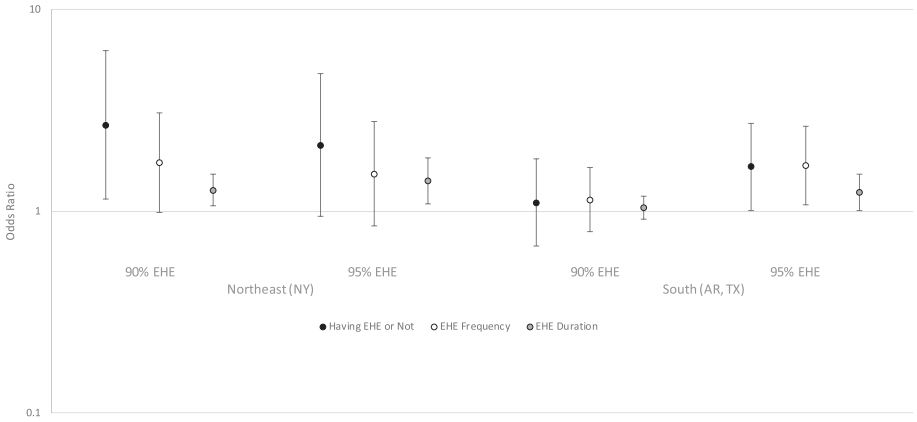

Fig. 3. Odds ratios and 95% confidence intervals for ventricular septal defects (VSD) and exposure to extreme heat events (EHEs) in the Northeast and South during the spring. EHEs were evaluated as either having an EHE or not during postconceptional weeks 3–8 (black circles), the frequency of EHE events (white circles) and the duration of EHE events (grey circles). Daily maximum temperature (Tmax) was used to define EHE indicators as: 1) at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the season and the year (EHE95); or 2) at least three consecutive days with daily Tmax above the 90th percentile of the Tmax distribution for the season and the year (EHE90).

retrospective cohort study conducted by Agay-Shay et al. (2013) in Israel, which found no significant associations between high ambient temperature and isolated CHDs during summer season (May 31–September 22). In addition, the findings from the current study agree with our previous study (Van Zutphen et al., 2012) that used 15 years of NYS Congenital Malformation Registry data, in which CHD phenotypes did not show significant associations with heat indicators, including a 5 °F increase in daily universal apparent temperature (UAT), as well as the presence of a heat wave, frequency and duration of heat waves (EHE90). On the other hand, our findings of 2.17–3.24 fold increased risk for VSD (combining regions) after maternal cumulative exposure to EHE (3–5 and 11 days) during the summer suggest the importance of summer EHE cumulative exposure in pregnant women, which is consistent with the results of a study conducted in Quebec, Canada (Auger et al., 2017). Auger et al. (2017) found that fetuses that were exposed to 15 days of temperature ≥ 30 °C between 2 and 8 weeks post-conception had 1.06 times the risk of critical CHD defects and 1.12 times the risk of noncritical defects compared to 0 days for heat exposure. The threshold we used to define EHE90 (87 °F or 31 °C) during summer months in the Northeast region is comparable with the threshold used by Auger et al. (2017) (30 °C), which may explain the higher health risks we found in the North American region. These findings also suggest that both the magnitude and duration of high temperature exposure play important roles in the positive associations between heat exposure and VSD.

4.2. Unseasonably warm weather in spring and CHDs

While we did not find a consistently positive association between EHEs in summer and CHDs, we did identify associations between EHE and CHDs in the spring, a transitional season to summer. We found positive associations between exposure to EHEs in spring and CHDs in multiple regions with the ORs ranging from 1.23 to 9.62 (10 days of cumulative EHE90 for VSD). These positive associations were consistently shown in NBDPS sites in the South region and in Northeast region and for multiple EHE indicators. It is unclear why adverse effects would have been observed in spring but not in summer. There is no available literature or prior studies assessing the effects of high temperature on birth defects in spring that could be directly compared to our findings. However, Loughnan et al. (2014) found that an increase in "unseasonably" warm weather during the cooler months of spring may result in increased acute myocardial infarction (AMI) in Melbourne, Australia, and indicated that an alert system based on summer thresholds may not be appropriate for heat warnings in the early summer or spring. Saez et al. (1995) reported that unusual periods of weather, demonstrated by increased temperature and humidity for 3 consecutive days increased total daily mortality by 2% on average and 2.6% in people aged 65 years old in summer in Barcelona, Spain. Another study led by Fitzgerald et al. (2014) found that unseasonably cold weather in November was associated with an increase in asthma admission rates in NYS, but not in typical winter seasons. The possible explanation for a positive association between extreme temperature and CHDs only found in the transition season (spring) may be due to the lack of acclimatization to large weather changes physically and behaviorally (e.g., without appropriate clothing or hat, participation in more outdoor activities, no use of air conditioner, and no early heat warning systems operated) in the transitional season (Loughnan et al., 2014; Schifano et al., 2012).

4.3. CHD subtypes and regional differences

We found that certain CHD phenotypes, such as conotruncal heart defects and septal defects (VSDs and ASDs), were more likely to be associated with EHEs than other phenotypes. One possibility is since VSDs and ASDs have larger sample sizes compared with other CHD

phenotypes, the power to detect a difference is larger for these defects. However, our findings concurred with the positive findings in ASDs and VSDs by Agay-Shay et al. (2013) and a positive association with ASDs found by Auger et al. (2017). The similarity of the findings pertaining to these phenotypes in these three studies is quite compelling. Congenital septal defects have been linked with other environmental exposures such as NO_2 (Chen et al., 2014).

We observed substantial variability in findings by geographic areas, i.e., the positive associations between EHEs in spring and certain CHDs were limited to the South (AR, TX) and Northeast regions (NY). The most plausible explanation is that there are large differences in temperature and temperature ranges (> 10 °F) among different states. For instance, Texas has larger variation in temperature, 50.4 °F for EHE95 in summer and 37.8 °F in spring for daily maximum temperature. Large daily temperature variation has been found to be associated with increased risk of respiratory diseases (Lin et al., 2012). Additionally, pregnant women living in NY had the highest cumulative days with EHE90 or EHE95 during the critical period of development, which implies that duration of heat exposure may be a key factor for women in northeast. As extreme weather and large weather changes occur more often, people living in the Northeast or cold areas may have increased susceptibility to EHEs and related health risks due to lack of physical or behavioral acclimatization or coping with large weather changes in spring, as suggested by Loughnan et al. (2014). In addition, it is possible that the differences in socio-demographic compositions among different areas could explain the observed variability in associations. For instance, some risk factors for CHDs in the unexposed group, such as maternal age < 19 years old at delivery, maternal education (< 12 years), maternal Hispanic ethnicity, and maternal smoking rates were significantly higher in pregnant women in the South region. The Northeast region had a higher percentage of ≥ 35 years old mothers and more smokers than those in other regions. However, these factors were either controlled for in the multivariate analysis or not related to extreme heat, which made it difficult to explain the findings due to the potential confounding effects of these factors. Additionally, results were largely similar while the specific ratios of phenotype vs. total CHDs per center were computed and controlled in the final analyses models for sensitivity analysis.

4.4. Heat indicators comparison

As there is no gold standard to define extreme heat exposure, this study used two relative standards, EHE90 and EHE95, in which three further EHE definitions were used, including Yes/No for EHE, EHE frequency, and EHE duration (consecutive heatwave period). Additionally, cumulative days of exceeding EHE90 or EHE95 were also used to estimate effect-response relationship. Among all these indicators, we found that EHE frequency during the summer and EHE duration during the spring were more consistently associated with CHDs. In addition, we also found that total or cumulative numbers of extreme heat days (3–11 days) occurring during the critical period were significantly associated with increased odds of VSDs and ASDs in both seasons. Our findings suggest that the number of days or duration of EHEs may be the indicator most consistently associated with CHDs risk, which agrees with Auger's findings that found that maternal exposure to more days with temperature ≥ 30 °C had an increased risk of CHDs (Auger et al., 2017). Unfortunately, no prior studies have examined the effect of these heat indicators on CHDs with which we can compare our findings to.

4.5. Potential teratogenic mechanism of hyperthermia

The potential mechanism of how EHEs might cause CHDs is not clear. An experimental study suggested that extremely high temperatures could directly cause fetal cell death (Bennett, 2010), leading to placental insufficiency, or trigger a heat-shock response that blocks transcription and translation of normal protein, thus interrupting the normal biochemical/molecular sequence or causing vascular disruption during the organogenesis period (Auger et al., 2017). A new animal study by Hutson et al. (2017) identified a molecular mechanism for hyperthermia-induced teratogenicity mediated through temperature activated ion channels, TRPV1 and TRPV4, in neural crest cells during critical windows of fetal development. High ambient temperature in summer may not lead to a severe heat-shock response or adverse reproductive outcomes in pregnancy due to mother's gradual adaptation to the hot weather in the summer. However, high temperatures may trigger a stronger response during transitional seasons with a plausible effect on ASDs or VSDs due to the lack of human physical system preparation or adaptation (Auger et al., 2017). In addition, other factors such as maternal medication use, chronic diseases, alcohol drinking/smoking/caffeine consumption, or maternal occupation may interact with or mediate the heat-CHDs relationship (Ou et al., 2015).

4.6. Strengths and limitations

To our knowledge, this may be the first study assessing the effect of high ambient temperatures in transitional seasons or unseasonable heat on CHDs. In contrast to many prior studies that use the data from only one geographic area, we used data from the NBDPS that covered diverse populations from eight U.S. states with substantial geographic variations over a 10-year period, one of the largest and most comprehensive birth defect studies in the United States. Since most teratogenic agents affect the development of specific phenotypes rather than all birth defects (Lin et al., 2008), this national study has a large sample size to allow evaluating extreme heat effect on specific CHD phenotypes defects, another special strength comparing to prior studies that examined all birth defects combined. We were also able to control for multiple potential confounders by using the rich and detailed NBDPS questionnaire. This is also one of the few studies evaluating different EHE indicators and geographic differences in maternal heat exposure and associations with CHDs.

On the other hand, potential selection bias is always a concern for a population-based study. To reduce selection bias, a systematic procedure was used for recruiting both cases and controls into the NBDPS through the birth defects surveillance systems in each state. To estimate such bias, we checked the maternal characteristics between the controls and all live births at each state and they were similar. In addition, the participation rate of cases was similar to that of controls, indicating similar recruitment possibility and smaller likelihood of selection bias. To ensure a complete ascertainment, all CHDs, including live births and fetal losses were included. Clinical geneticists reviewed medical records using standardized definitions and confirmatory diagnostic procedures to reduce misclassification and to ensure the validity of case diagnoses.

Recall bias resulting from differential recall between cases and controls is always a concern in a case-control study as mothers of the cases may be more likely to recall their exposures than the mothers of controls. As the primary exposure (extreme heat) and outcome (CHDs) in this study were obtained from existing and objective datasets, recall bias may not be a major issue in this study. For other potential confounding variables from the interview data, several strategies were used to minimize recall bias, including asking about specific diseases and names of medications, as well as the timing and dosage/amount (for alcohol, caffeine, and smoking) by using a pregnancy calendar to promote mothers' recall. Most interview questions were pre-coded and specific responses were listed. We also found that the interview timing between the cases and the controls were similar.

Since no individual measurement data were available to define each mother's residential heat exposure, we used the data from the closest weather station, which is similar to the methods used by most of the prior weather-maternal health studies. To estimate the potential misclassification bias we checked the mean distance between maternal residence and the closest weather station, which varied by region. We

found that mothers in the Northeast region had the shortest distance (9.79 miles for cases and 10.36 miles for controls), but those in the Southeast region lived the farthest from a weather station (37.66 miles for cases and 36.11 miles for controls). For potential cross-seasonal misclassification during the weeks 3–8 post-conception, we estimated that such misclassification of the season will be non-differential and the bias would be towards the null as this is a case-control study rather than a case-crossover or case only study. In addition, the extreme heat definitions are seasonally specific and relied on frequency and duration of heat exposure rather than season only. We conducted a sensitivity analysis by using ≥ 7 and ≥ 21 summer or spring days during weeks 3–8 post-conception and reran all analyses. We found that all original positive ORs remained in the same direction and with similar magnitudes although some were no longer significant (especially when we used ≥ 21 days) due to smaller sample size. Although our use of two binary variables, EHE90 and EHE95, in this study may lose information compared to continuous variables, it may be appropriate as the first step since the relationship between ambient heat and health is not linear. We also further examined the health impacts of heat exposure frequency, duration, and cumulative heat exposure as continuous variables by fully using the data. Additionally, the effects of other potential confounders such as occupational exposure, air conditioner use, activity patterns and water consumption were not evaluated in this study, but the modifying effects of maternal occupation and caffeine consumption with heat on CHDs will be examined in separate papers.

To rule out potential detection bias associated with preterm delivery on the heat-VSDs relationship, we performed a sensitivity analysis by rerunning the final model after excluding preterm infants, and results remained similar. To assess the potential confounding or mediating effects of maternal diabetes, family history of CHD, multiple births and preterm births, we excluded infants whose mothers had such conditions and reran the original models respectively, and found no significant changes. Another concern is that our positive results may be due to chance through multiple testing. We rechecked all results using Bayesian analysis, and found most estimates (92%) that were previously positive remained significant.

5. Conclusion

We did not observe consistently increased risks of CHD phenotypes related to maternal exposure to EHEs in summer. However, increased risks for certain CHDs, including conotruncal heart defects, and septal defects were observed with maternal exposure to EHEs and multiple days (3–11 days) of extreme heat in spring. These adverse effects with unseasonable heat were mainly found in the South (AR, TX) and Northeast regions (NY), and were steadily significant when using multiple heat indicators. The cumulative number of EHE days was the indicator most constantly associated with CHDs. Our findings highlight the importance of possible early warnings against heat in transitional seasons, although additional research and validation of our findings are needed in further characterizing the associations observed.

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Disclosures

None.

Disclaimer

The views expressed in this manuscript are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the California Department of Public Health. 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.

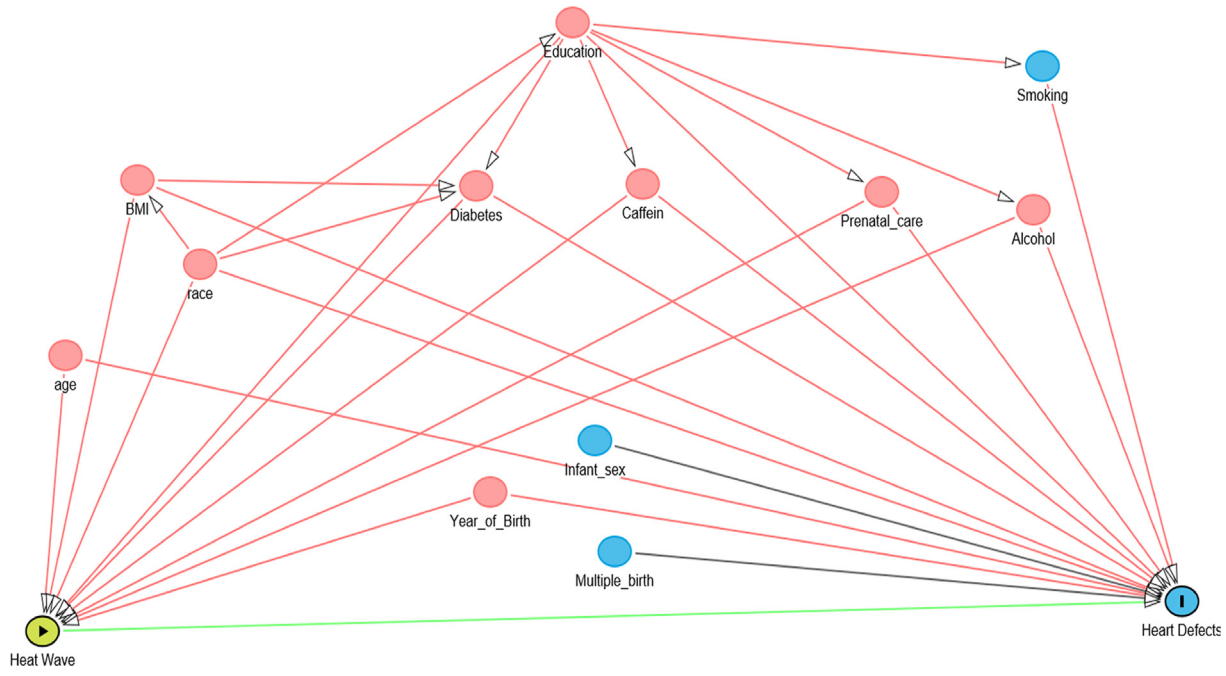
Appendix 1. Cases and Controls in Spring and Summer during Pregnancy Critical Period (Weeks 3–8) by Exposure Status and Heart Defects Phenotypes, National Birth Defects Prevention Study 1997–2007

	Spring		Summer	
	Case	Control	Case	Control
	Exposed[a]/unexposed	Exposed[a]/unexposed	Exposed[a]/unexposed	Exposed[a]/unexposed
Conotruncal heart defects				
South (AR, TX)	32/61	128/405	32/45	236/282
Southeast (NC, GA)	19/75	129/356	49/42	238/233
Northeast (NY)	24/34	85/159	30/21	139/131
Southwest (UT)	13/8	90/114	17/12	141/61
West (CA)	33/50	128/219	51/22	216/112
Midwest (IA)	16/18	129/198	26/17	169/150
Left outflow tract heart defects				
South (AR, TX)	21/50	128/405	31/36	236/282
Southeast (NC, GA)	10/46	129/356	25/23	238/233
Northeast (NY)	5/27	85/159	17/16	139/131
Southwest (UT)	33/33	90/114	51/11	141/61
West (CA)	26/40	128/219	28/17	216/112
Midwest (IA)	23/25	129/198	23/22	169/150

Right outflow tract heart defects				
South (AR, TX)	21/45	128/405	30/40	236/282
Southeast (NC, GA)	10/39	129/356	24/27	238/233
Northeast (NY)	9/16	85/159	16/14	139/131
Southwest (UT)	15/17	90/114	19/12	141/61
West (CA)	14/14	128/219	21/6	216/112
Midwest (IA)	12/21	129/198	18/17	169/150
Septal heart defects				
South (AR, TX)	75/217	128/405	114/132	236/282
Southeast (NC, GA)	34/123	129/356	67/58	238/233
Northeast (NY)	23/28	85/159	21/29	139/131
Southwest (UT)	26/45	90/114	34/12	141/61
West (CA)	22/43	128/219	39/15	216/112
Midwest (IA)	20/42	129/198	37/24	169/150
VSD heart defects				
South (AR, TX)	29/60	128/405	36/29	236/282
Southeast (NC, GA)	16/58	129/356	39/31	238/233
Northeast (NY)	16/15	85/159	11/14	139/131
Southwest (UT)	8/16	90/114	14/4	141/61
West (CA)	7/13	128/219	15/8	216/112
Midwest (IA)	15/23	129/198	20/15	169/150
ASD heart defects				
South (AR, TX)	45/154	128/405	74/95	236/282
Southeast (NC, GA)	16/57	129/356	26/20	238/233
Northeast (NY)	4/3	85/159	8/3	139/131
Southwest (UT)	18/27	90/114	19/8	141/61
West (CA)	15/29	128/219	24/7	216/112
Midwest (IA)	5/19	129/198	17/9	169/150

[a] 95% EHE exposure: at least two consecutive days with daily Tmax above 95th percentile of the Tmax distribution for the season and the year.

Appendix 2. Directed Acyclic Graphs (DAGs) for determining potential confounders, NBDPS, 1997–2007



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