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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,