Science of the Total Environment 882 (2023) 163613

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Ambient temperature and major structural anomalies: A retrospective study of over 2 million newborns

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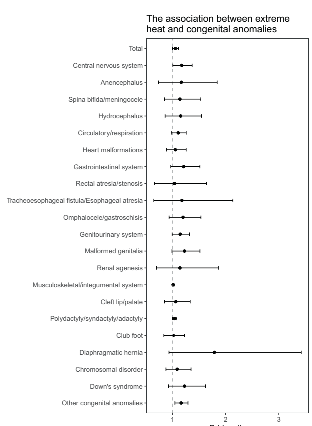
HIGHLIGHTS

- We estimated the association of heat with total and diagnostic categories of congenital anomalies.
- Heat was associated with higher risk of total, nervous system, and uncategorized anomalies.
- The associations were more pronounced among births with multiple anomalies.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Scott Sheridan

Keywords:
Ambient heat
Congenital anomalies
United States

ABSTRACT

Background: Maternal exposure to ambient heat may be associated with congenital anomalies, but evidence is still limited.
Objectives: We aimed to estimate the association between maternal exposure to ambient heat during the 3–12 weeks post-conception (critical window of organogenesis) and risk of total and various diagnostic categories of major structural anomalies among live singleton births in the contiguous United States (US).
Methods: We included data on 2,352,529 births with the first day of critical developmental windows falling within months of May through August from 2000 to 2004 across 525 US counties. We used a validated spatial-temporal model to estimate daily county-level population-weighted temperature. We used logistic regression to estimate the

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http://dx.doi.org/10.1016/j.scitotenv.2023.163613
Received 17 December 2022; Received in revised form 16 April 2023; Accepted 16 April 2023
Available online 21 April 2023
0048-9697/

association between ambient temperature and risk of diagnostic categories of anomalies during the critical window after adjusting for individual and county-level factors. We conducted subgroup analysis to identify potential susceptible subpopulations.

Results: A total of 29,188 anomalies (12.4 per 1000 births) were recorded during the study period. Maternal exposure to extreme heat (> 95th percentile) was associated with higher risk of total anomalies, central nervous system anomalies, and other uncategorized anomalies with an odds ratio (OR) of 1.05 (95 % CI: 1.00, 1.11), 1.17 (95 % CI: 1.01, 1.37), and 1.16 (95 % CI: 1.04, 1.29) compared with minimum morbidity temperature, respectively. The associations were homogeneous across subgroups defined by maternal age, maternal race/ethnicity, marital status, educational attainment, and parity, but were more pronounced among mothers residing in more socially vulnerable counties and births with multiple anomalies.

Conclusions: Among US live singleton births, maternal exposure to ambient heat may be associated with higher risk of total anomalies, central nervous system anomalies, and other uncategorized anomalies. We suggest additional research is carried out to better understand the relations between maternal heat exposure and congenital anomalies in the presence of global warming.

1. Introduction

Congenital anomalies, also known as birth defects or congenital malformations, comprise a wide range of structural or functional abnormalities that occur during intrauterine life. Congenital anomalies are leading causes of infant deaths and important contributors to childhood and adult morbidity (Aguilera et al., 2020; Zimmerman et al., 2020). It is estimated that congenital anomalies affect ~6 % of babies worldwide, resulting in 270,000 associated deaths during the first 28 days of life in 2010 (Kancherla et al., 2022). Among congenital anomalies, major structural anomalies are due to abnormal formation of organs or body structures in the first trimester of pregnancy, especially 3–12 weeks post-conceptional age, which are the conditions that account for most of the deaths, morbidity, and disability (Organization of Teratology Information Specialists OTIS, 2021).

Most major structural anomalies showed multifactorial etiologies, and both genetic and environmental factors play an important role in developing these anomalies, such as cleft lip and palate (Lace et al., 2022), dislocation of the hip joint (Harsanyi et al., 2020), and heart defect and spina bifida (Petronic et al., 2020). Only a few risk factors have been identified for major structural anomalies, including folic acid deficiency, alcohol use during pregnancy, uncontrolled maternal diabetes and phenylketonuria, and obesity (Harris et al., 2017). However, the etiology of most major structural anomalies remains largely unknown.

Environmental risk factors might be important contributors to major structural anomalies, including particulate matter and gaseous pollutants (Hu et al., 2020; Ma et al., 2021; Vrijheid et al., 2011; Yu et al., 2021; Zhang et al., 2018), and chemical hazardous materials (Janitz et al., 2019; Ou et al., 2021; Richter et al., 2022). Maternal exposure to ambient heat has been associated with preterm birth and low fetal growth (Chersich et al., 2020), and stillbirths (McElroy et al., 2022), and may also affect congenital anomalies (Haghighi et al., 2021). Emerging studies started to examine the association between maternal exposure to ambient heat and major structural anomalies (Agay-Shay et al., 2013; Aminzadeh et al., 2010; Auger et al., 2017a; Auger et al., 2017b; Cil and Cameron, 2017; Kilinc et al., 2016; Lin et al., 2018; Soim et al., 2018; Van Zutphen et al., 2012; Wang et al., 2019; Zhang et al., 2019), but findings have been mixed (Agay-Shay et al., 2013; Lin et al., 2018), with studies reported positive associations (Auger et al., 2017a; Auger et al., 2017b; Cil and Cameron, 2017; Kilinc et al., 2016; Soim et al., 2018) or no evidence of any association (Soim et al., 2018; Zhang et al., 2019). For example, in an analysis of 887,710 births, Auger et al. (2017a) reported that exposure to heat was associated with increased risk of neural tube defects in Canada, but the association was not observed in the US (Soim et al., 2018). In addition, previous studies of the health effects of ambient heat have examined a few major structural anomalies, such as cardiac defects (Auger et al., 2017b; Judge et al., 2004; Stingone et al., 2019) or neural tube defects (Auger et al., 2017a; Soim et al., 2018), or limited to a few cities, evidence from a large-scale study with comprehensive analysis of the effects of ambient heat on various diagnostic categories of major structural anomalies is still limited.

Considering the continued climate change and the health consequences of major structural anomalies, we aimed to examine the association of maternal exposure to heat with total and various diagnostic categories of major structural anomalies among over 2 million live singleton births during the four warmest months from 2000 to 2004 in the contiguous United States (US). We also conducted secondary analysis to identify potential susceptible subpopulations.

2. Methods

2.1. Study population

We obtained data on US live births ranging from 2000 to 2004 (5 years in total) from the CDC's National Center for Health Statistics. Data were available only for US resident mothers living in counties with a population of >100,000. We restricted our analysis to births born to mothers aged from 20 to 50 years old (n = 15,936,611). We excluded births with the following conditions: (1) births occurring in counties with populations of below 100,000 or mothers' residences being outside of the US (n = 3,954,850); (2) births with missing values of last menstrual period (LMP), race/ethnicity, educational attainment, parity, and beginning month of prenatal care (n = 1,034,886); (3) births with the start date of the critical developmental windows (i.e., 3–12 weeks post-conception) falling outside months of May through August (n = 8,477,140); (4) multiple births (n = 88,701) and (5) births with missing values for congenital anomalies (n = 28,505), resulting in 2,352,529 births in the final analytic dataset (Fig. 1). We defined the first day of conception as two weeks after the LMP (Toh et al., 2008). We selected 3–12 weeks post-conception as the critical developmental window based on evidence that major defects of the body and internal organs are more likely to occur during this time (Organization of Teratology Information Specialists OTIS, 2021). To estimate the association between ambient heat exposure and risk of major structural anomalies, we restricted our analysis to births with the first day of the critical developmental window of organogenesis falling within the months of May through August, which are the four warmest months for the critical windows among the study population. Note that for those included in late August, the embryonic period will be in late September or October.

2.2. Major structural anomalies assessment

Infants born with identifiable major structural anomalies were reported on the birth certificate, each with a checkbox (Center for Disease Control and Prevention CDC, 2002). We included six broad systems and fifteen diagnostic categories of major structural anomalies, including any type, central nervous system, anencephalus, spina

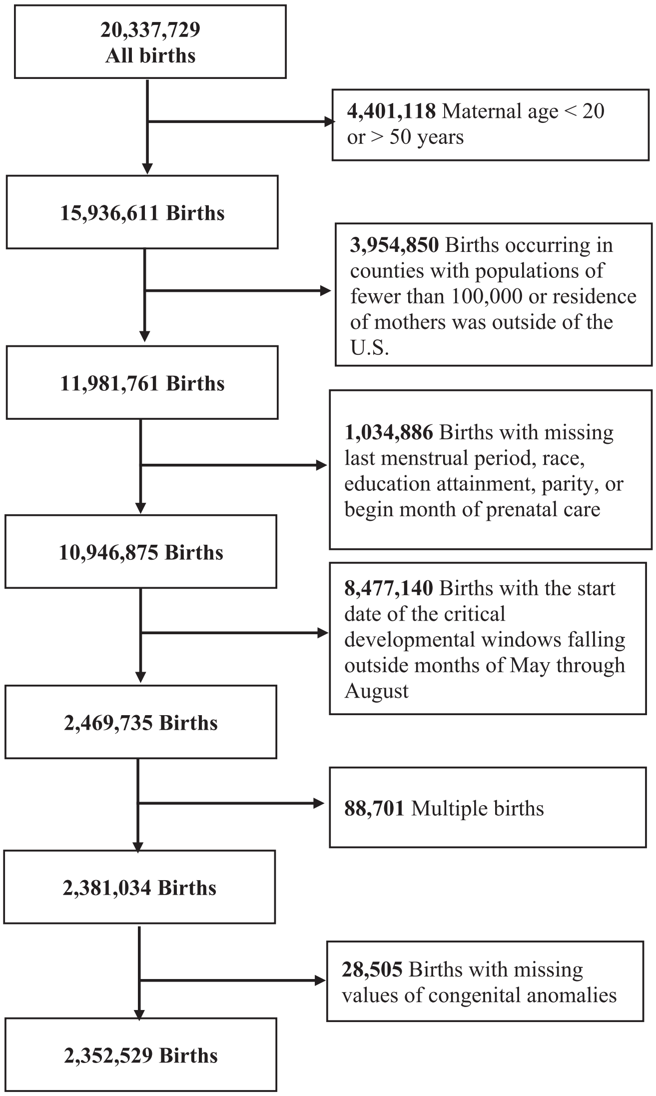

Fig. 1. Flow diagram of birth exclusion in this study.

bifida/meningocele, hydrocephalus, circulatory/respiration, heart malformations, gastrointestinal system, rectal atresia/stenosis, tracheo-esophageal fistula/esophageal atresia, omphalocele/gastroschisis, genitourinary system, malformed genitalia, renal agenesis, musculoskeletal/integumental system, cleft lip/palate, polydactyly/syndactyly/adactyly, club foot, diaphragmatic hernia, and other uncategorized major structural anomalies. We included anomalies due to chromosomal disorder and Down's syndrome as negative outcome controls because these diagnostic categories of anomalies were driven by gene mutation instead of environmental factors.

2.3. Ambient temperature assessment

We estimated daily ambient temperature using the Parameter-elevation Relationships on Independent Slopes (PRISM) model, a gridded climate dataset on a 4-km grid (Daly et al., 2008). Temperature data from PRISM model has been widely used to estimate the health effects of extreme temperatures (Nori-Sarma et al., 2022; Spangler et al., 2019; Sun et al., 2019). We calculated the daily county-level population-weighted average of temperatures to represent population temperature exposure (eMethod). We calculated the average ambient temperature during the 3–12 weeks post-conception for each birth and then calculated temperature percentiles by day in each county to reflect county-specific temperature distribution.

2.4. Air pollution assessment

Daily concentrations of fine particulate matter ($PM_{2.5}$) were obtained from the US Environmental Protection Agency for the Tracking Network and were estimated by hierarchical Bayesian space-time downscaling fusion models combining data from multiple sources, including the Community Multi-scale Air Quality model and air monitoring stations (Berrocal et al., 2012; Sun et al., 2022). We calculated a population-weighted average of $PM_{2.5}$ on each day in each county, and then calculated the average concentration of $PM_{2.5}$ during the 3–12 weeks post-conception for each birth.

2.5. Statistical analysis

We used logistic regression models to estimate the association between county-specific maternal exposure to ambient temperature percentile and risk of total and diagnostic categories of major structural anomalies from May to August 2000–2004. We used the directed acyclic graph analysis to guide the selection of potential confounders (Fig. S1). In the main models, we adjusted for maternal age (18–24, 25–29, 30–34, 35–39, 40–50 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, or other), marital status (married or not married), educational level (lower than high school, high school, or higher than high school), beginning months of prenatal care (no prenatal care, 1st-3rd month, 4th–6th month, or 7th-final month), smoking during pregnancy (yes, no, or unknown), alcohol drinking during pregnancy (yes, no, or unknown), medical risk factors (yes or no), parity (0,1, and ≥ 2), county poverty rate (<10 %, 10 %–14.9 %, 15 %–19.9 %, or ≥ 20 %), and census regions (Northeast, Midwest, South, West). Medical risk factors were defined as the presence of any risk factors, including anemia, cardiac disease, acute or chronic lung disease, diabetes, genital herpes, hydramnios/oligohydramnios, hemoglobinopathy, chronic hypertension, pregnancy-associated hypertension, eclampsia, incompetent cervix, previous infant 4000 + grams, previous preterm or small for gestation age infant, renal disease, Rh sensitization, and uterine bleeding. The relationships between ambient temperature, ambient air pollution, and health outcomes are complex (Buckley et al., 2014), and thus we did not adjust for air pollution in the main models. However, we conducted sensitivity analyses by additionally adjusting for $PM_{2.5}$ to assess potential confounding by air pollution. To assess whether there is a synergistic effect between ambient heat and $PM_{2.5}$, we performed a stratified analysis by $PM_{2.5}$ and used median $PM_{2.5}$ as the cutoff.

We modeled the average ambient temperature during the critical developmental window as a natural cubic spline to allow a nonlinear relationship with anomalies. We defined extreme and moderate temperature as the percentile of temperature distribution equals to the 95th and 85th percentile of the critical developmental window temperature distribution in that county, respectively. We reported odds ratio (OR) for extreme and moderate temperature relative to the county-specific minimum morbidity temperature. We identified minimum morbidity temperature based on the exposure-response relationship between ambient temperature and anomalies and corresponds to a minimum morbidity temperature percentile associated with the minimum risk of anomalies between the 1st and 99th percentiles (Gasparrini et al., 2015).

To identify potential susceptible sub-population, we performed secondary analysis to assess whether the associations were varied by maternal age, maternal race/ethnicity, marital status, education level, poverty level, and parity.

The etiology of single versus multiple anomalies may be different. To explore whether the effects of heat were varied by the number of anomalies, we separately fitted logistic regression for single and multiple anomalies and adjusted the same covariates as in the above main models. All statistical analyses were performed in R software.

3. Results

We identified 29,188 (12.4 per 1000 births) newborns with congenital anomalies among 2,352,529 live singleton births across 525 counties between 2000 and 2004. Newborns with anomalies were more likely to be males, born to mothers aged 40–50 years old, born to mothers who smoked, consumed alcohol, or received no prenatal care during pregnancy or presented any medical risk factor (Table 1). Among structural anomalies due to broad systems, musculoskeletal/integumental system contributed to the highest proportion of total congenital anomalies (33.2 %), followed by circulatory/respiration (19.2 %), and genitourinary system (14.6 %) (Table 2). The 95th percentiles of average ambient temperatures during the critical windows by US county were presented in Fig. S2.

Table 1
Demographic characteristics of singleton live births across 525 counties in the United States, May to August from 2000 to 2004.

Characteristics	Total births No. (%)	Congenital anomalies[a] No. (No. per 1000 births)
Total population	2,352,529 (100.0)	29,188 (12.4)
Infant sex		
Male	1,205,161 (51.2)	16,895 (14.0)
Female	1,147,368 (48.8)	12,293 (10.7)
Parity		
0	929,991 (39.5)	12,100 (13.0)
1	780,193 (33.2)	9146 (11.7)
≥2	642,345 (27.3)	7942 (12.4)
Maternal age (years)		
18–24	724,642 (30.8)	9069 (12.5)
25–29	647,772 (27.5)	7605 (11.7)
30–34	615,454 (26.2)	7427 (12.1)
35–40	298,947 (12.7)	3916 (13.1)
40–50	65,714 (2.8)	1171 (17.8)
Maternal race/ethnicity		
Non-Hispanic White	1,238,794 (52.7)	16,100 (13.0)
Non-Hispanic Black	349,615 (14.9)	5157 (14.8)
Hispanic	589,059 (25.0)	5725 (9.7)
Other	175,061 (7.4)	2206 (12.6)
Marital status		
Married	1,617,389 (68.8)	19,321 (11.9)
Not married	735,140 (31.2)	9867 (13.4)
Education level		
Lower than high school	143,571 (6.1)	1478 (10.3)
High school	992,413 (42.2)	12,604 (12.7)
Higher than high school	1,216,545 (51.7)	15,106 (12.4)
Timing of initiation of prenatal care		
No prenatal care	19,468 (0.8)	305 (15.7)
1st-3rd month	1,999,981 (85.0)	24,206 (12.1)
4th–6th month	273,236 (11.6)	3781 (13.8)
7th-final month	59,844 (2.5)	896 (15.0)
Smoking during pregnancy		
Yes	170,127 (7.2)	2900 (17.0)
No	1,773,483 (75.4)	23,927 (13.5)
Unknown	408,919 (17.4)	2361 (5.8)
Alcohol drinking during pregnancy		
Yes	15,921 (0.7)	314 (19.7)
No	1,927,235 (81.9)	26,514 (13.8)
Unknown	409,373 (17.4)	2360 (5.8)
Medical risk factors[b]		
Yes	260,254 (11.1)	5952 (22.9)
No	1,948,017 (82.8)	22,165 (11.4)
Unknown	144,258 (6.1)	1071 (7.4)
County poverty rate[c]		
<10 %	861,074 (36.6)	12,949 (15)
10 %–14.9 %	947,647 (40.3)	10,917 (11.5)
15 %–19.9 %	391,617 (16.6)	4088 (10.4)
≥20 %	152,191 (6.5)	1234 (8.1)

[a] Congenital anomalies include newborns with anomalies of central nervous system, circulatory/respiration, gastrointestinal system, genitourinary system, musculoskeletal/integumental system, chromosomal disorder, or other uncategorized anomalies.

[b] Medical risk factors include pregnant women with anemia, cardiac, acute or chronic lung disease, diabetes, genital herpes, hydramnios/oligohydramnios, hemoglobinopathy, incompetent cervix, previous infant 4000+ grams, previous preterm small for gestation, or renal disease.

[c] The percentage of people in a county below the federal poverty line.

The exposure-response relationships between ambient temperature and anomalies were approximately linear, except for total, circulatory/respiration, heart malformations, and other uncategorized anomalies (Fig. 2 and Fig. S3). For illustration, we presented OR for extreme heat defined by temperatures at the 95th percentile of the county-specific critical developmental window average temperature distribution and moderate heat defined by temperatures at the 85th percentiles of the county-specific critical developmental window average temperature distribution, relative to county-specific minimum morbidity temperature. We found that extreme heat was associated with higher risk of total anomalies (OR: 1.05, 95 % CI: 1.00, 1.11), central nervous system anomalies (OR: 1.17, 95 % CI: 1.01, 1.37), and other uncategorized anomalies (OR: 1.16, 95 % CI: 1.04, 1.29) compared with minimum morbidity temperature (Table 3). We also found that the association was marginally significant for genitourinary system anomalies and malformed genitalia with an OR of 1.14 (95 % CI: 0.99, 1.32) and 1.22 (95 % CI: 0.99, 1.52) for extreme heat, respectively. Results were generally stronger when additionally adjusted for $PM_{2.5}$ (Table S1). To assess whether there is a synergistic effect between ambient heat and $PM_{2.5}$, we performed a stratified analysis by $PM_{2.5}$ and used median $PM_{2.5}$ as the cutoff. We found the effects of heat were generally more pronounced when pregnant women were exposed to higher levels of $PM_{2.5}$ for total congenital anomalies, genitourinary system anomalies, musculoskeletal/integumental system anomalies, and other uncategorized anomalies (Table S2).

In the secondary analysis, we conducted subgroup analysis to identify potentially vulnerable subgroups. We found that the associations were homogenous across subgroups defined by maternal age, race/ethnicity, marital status, educational attainment, and parity (Table 4). For example, extreme heat was associated with an OR of 1.02 (95 % CI: 0.95, 1.10) for non-Hispanic White vs. 1.07 (95 % CI: 0.94, 1.21) for non-Hispanic Black.

To explore whether the effects of heat were varied by the number of anomalies, we fitted logistic regression separately for single and multiple anomalies. We found the associations were more pronounced among births with multiple anomalies (Table S3). For example, exposure to extreme heat was associated with an OR of 1.24 (95 % CI: 1.03, 1.49) for multiple anomalies vs. 1.04 (95 % CI: 0.98, 1.10) for single anomalies.

Table 2
Type of newborns with major structural anomalies among 2,352,529 singleton live births in the United States, May to August from 2000 to 2004.

Congenital anomalies	No.	% of congenital anomalies	No. per 1000 births
Total[a]	29,188	100	12.4
Central nervous system	1580	5.4	0.7
Anencephalus	211	0.7	0.1
Spina bifida/meningocele	435	1.5	0.2
Hydrocephalus	479	1.6	0.2
Circulatory/respiration	5603	19.2	2.4
Heart malformations	2873	9.8	1.2
Gastrointestinal system	1699	5.8	0.7
Rectal atresia/stenosis	188	0.6	0.1
Tracheoesophageal fistula/esophageal atresia	252	0.9	0.1
Omphalocele/gastroschisis	606	2.1	0.3
Genitourinary system	4266	14.6	1.8
Malformed genitalia	1799	6.2	0.8
Renal agenesis	339	1.2	0.1
Musculoskeletal/integumental system	9699	33.2	4.1
Cleft lip/Palate	1605	5.5	0.7
Polydactyly/Syndactyly/Adactyly	1705	5.8	0.7
Club foot	1183	4.1	0.5
Diaphragmatic hernia	243	0.8	0.1
Chromosomal disorder	1805	6.2	0.8
Down's syndrome	1086	3.7	0.5
Other congenital anomalies	8071	27.7	3.4

[a] Total includes newborns with anomalies of central nervous system, circulatory/respiration, gastrointestinal system, genitourinary system, musculoskeletafl/integumental system, chromosomal disorder, or other uncategorized anomalies.

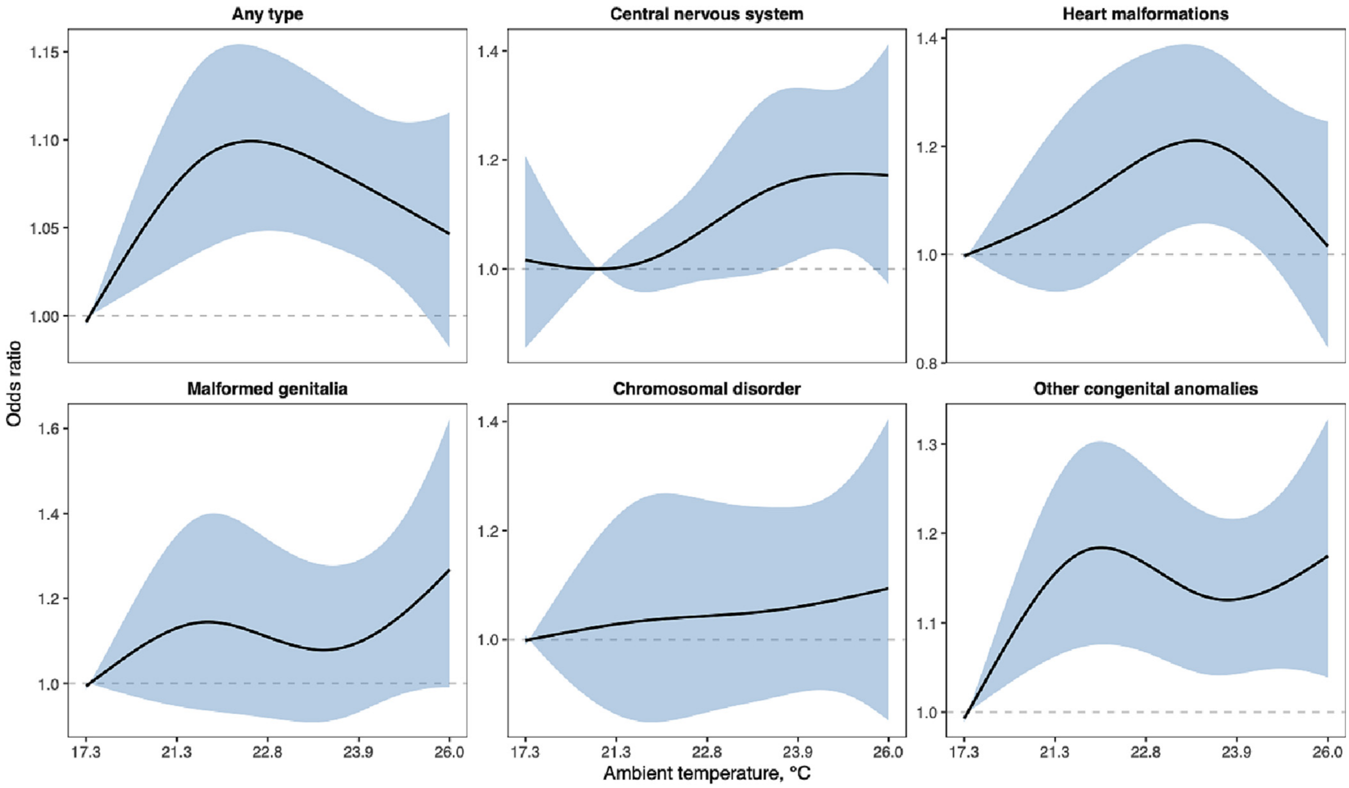

Fig. 2. The exposure-response curves for association between ambient temperature during 3–12 weeks post-conception and any type of major structural anomalies in the United States, May to August from 2000 to 2004.

4. Discussion

In this nationwide study of over 2 million live singleton births across 525 populous US counties, we found that maternal exposure to ambient heat was associated with higher risk of total anomalies, central nervous system anomalies, and other uncategorized anomalies. The associations were homogeneous across subgroups defined by maternal age, maternal race/ethnicity, marital status, educational attainment, and parity but were more pronounced among mothers residing in more socially vulnerable counties and births with multiple anomalies.

The evidence for the association between maternal exposure to heat and risk of congenital anomalies is limited and inconclusive. A recent systematic review only identified thirteen studies that examined ambient heat during pregnancy and congenital anomalies (Haghighi et al., 2021). We found

Table 3
Odds ratios of any type of congenital anomalies associated with ambient heat in the United States, May to August from 2000 to 2004.

Congenital anomalies	Minimum morbidity centile	Minimum morbidity temperature (°C)	Odds ratio (95 % CI)	
			Moderate heat[b]	Extreme heat[b]
Total[a]	1	16.7	1.06 (1.02, 1.11)	1.05 (1.00, 1.11)
Central nervous system	20	20.3	1.17 (1.04, 1.33)	1.17 (1.01, 1.37)
Anencephalus	35	21.6	1.20 (0.83, 1.73)	1.17 (0.74, 1.84)
Spina bifida/meningocele	26	20.9	1.20 (0.93, 1.54)	1.14 (0.85, 1.53)
Hydrocephalus	29	21.1	1.19 (0.93, 1.52)	1.15 (0.86, 1.54)
Circulatory/respiration	1	16.7	1.15 (1.04, 1.28)	1.11 (0.98, 1.26)
Heart malformations	1	16.7	1.13 (0.98, 1.29)	1.05 (0.88, 1.26)
Gastrointestinal system	1	16.7	1.19 (0.99, 1.42)	1.21 (0.97, 1.52)
Rectal atresia/stenosis	76	23.6	1.01 (0.84, 1.22)	1.04 (0.66, 1.64)
Tracheoesophageal fistula	1	16.7	1.25 (0.77, 2.02)	1.18 (0.65, 2.14)
Omphalocele/gastroschisis	24	20.7	1.23 (1.00, 1.51)	1.20 (0.93, 1.53)
Genitourinary system	1	16.7	1.12 (1.01, 1.26)	1.14 (0.99, 1.32)
Malformed genitalia	1	16.7	1.15 (0.97, 1.36)	1.22 (0.99, 1.52)
Renal agenesis	1	16.7	1.07 (0.73, 1.57)	1.14 (0.70, 1.86)
Musculoskeletal/integumental system	99	25.2	1.04 (0.98, 1.10)	1.01 (0.99, 1.03)
Cleft lip/Palate	1	16.7	1.04 (0.87, 1.24)	1.06 (0.85, 1.33)
Polydactyly/Syndactyly/Adactyly	99	25.2	1.13 (0.99, 1.29)	1.04 (1.00, 1.08)
Club foot	75	23.5	1.00 (0.92, 1.09)	1.01 (0.84, 1.23)
Diaphragmatic hernia	1	16.7	1.65 (0.98, 2.78)	1.79 (0.93, 3.42)
Chromosomal disorder	1	16.7	1.07 (0.91, 1.27)	1.09 (0.88, 1.35)
Down's syndrome	1	16.7	1.17 (0.94, 1.46)	1.23 (0.93, 1.62)
Other congenital anomalies	1	16.7	1.14 (1.05, 1.24)	1.16 (1.04, 1.29)

[a] Total includes newborns with anomalies of central nervous system, circulatory/respiration, gastrointestinal system, genitourinary system, musculoskeletal/integumental system, chromosomal disorder, or other uncategorized anomalies.
[b] Moderate heat = 85th percentile of temperature distribution (24.4 °C on average); extreme heat = 95th percentile of temperature distribution (25.3 °C on average).

Table 4
Odds ratios of any type of congenital anomalies associated with extreme heat in the United States, May to August from 2000 to 2004.

Characteristics	Odds ratio (95 % CI)	P for heterogeneity
Maternal age (years)		
18–24	1.08 (0.98, 1.19)	0.13
25–29	1.00 (0.98, 1.02)	[Reference]
30–34	1.11 (1.00, 1.24)	0.06
35–39	1.02 (0.99, 1.04)	0.22
40–50	1.13 (0.86, 1.49)	0.39
Race/ethnicity		
Non-Hispanic White	1.03 (0.96, 1.11)	[Reference]
Non-Hispanic Black	1.11 (0.97, 1.27)	0.34
Hispanic	1.08 (0.98, 1.19)	0.44
Other	1.01 (0.81, 1.26)	0.87
Marital status		
Married	1.07 (1.00, 1.14)	[Reference]
Not married	1.02 (0.93, 1.12)	0.41
Educational attainment		
Lower than high school	1.17 (1.00, 1.38)	[Reference]
High school	1.04 (0.95, 1.13)	0.21
Higher than high school	1.06 (0.98, 1.14)	0.28
Parity		
0	1.04 (0.95, 1.13)	[Reference]
1	1.02 (1.00, 1.04)	0.67
≥2	1.16 (1.04, 1.29)	0.12
County poverty rate		
<10 %	1.02 (1.00, 1.04)	[Reference]
10 %–14.9 %	1.15 (1.05, 1.25)	0.01
15 %–19.9 %	1.07 (0.93, 1.23)	0.51
≥20 %	1.10 (0.84, 1.44)	0.58

Extreme heat = 95th percentile of temperature distribution (25.3 °C on average).

that maternal exposure to heat was associated with higher risk of central nervous system anomalies, and the effect size of the association for cause-specific central nervous system anomalies was in the direction of effect, but it did not reach statistically significant, which was generally in line with previous studies. For example, exposure to heat waves (≥3 consecutive days with daily ambient temperature above the 90th percentile) was associated with an OR of 1.30 (95 % CI: 0.82, 2.05) for spina bifida without anencephalus in a case-control study in New York state among 6422 cases and 59,328 controls. In a case-control study in Mexico, Davies (2000) reported a two-fold increase in anencephalus associated with the ambient temperature above 18 °C compared with ambient temperatures below 18 °C.

We found that maternal exposure to heat was marginally associated with higher risk of malformed genitalia. These findings were consistent with a study conducted in Turkey, which found that maternal exposure to a higher temperature during 8 to 14 weeks increased the risk of hypospadias by 1.32-fold compared with the cooler periods (Kilinc et al., 2016). Note that malformed genitalia include several subtypes, such as anomalies of ovaries, cervix, vagina, and external female genitalia. Future studies with more detailed information on subtypes of malformed genitalia are warranted to conduct to examine the association between heat and subtypes of malformed genitalia.

Our findings of no evidence of a positive association between heat and congenital heart anomalies are in contrast with most previous studies. Six studies that examined the impact of heat on cardiac defects were documented in the recent systematic review, and three of them reported a positive association (Haghighi et al., 2021). For example, in an analysis of over 700,000 births in Quebec, Canada, exposure to heat during the critical developmental window was associated with higher risk of critical cardiac defects (Auger et al., 2017b). The inconsistency among studies might be due to differences in the assessment of congenital anomalies and critical developmental window definition. In our study, we collected information on congenital anomalies from birth certificates, which only captured congenital anomalies that are identifiable at birth.

Although the biological mechanisms for the association between ambient heat and anomalies are largely unknown, oxidative stress, systemic inflammation, and protein synthesis disturbance may play a role (Bennett, 2010; Halonen et al., 2010; Wu et al., 2017). The animal study suggested that exposure to heat during early pregnancy could disturb protein synthesis by generating heat shock protein (Bennett, 2010). Besides, maternal fevers were linked with congenital anomalies via triggering the release of heat shock protein interfering with protein synthesis (Edwards, 2006). In addition, exposure to heat may increase the circulating levels of oxidative stress and inflammation markers (Halonen et al., 2010; Wu et al., 2017). The formation of reactive oxygen species during pregnancy, such as hydroxyl radicals, may interfere with the development of the embryo and fetus by causing cellular lipids, protein, and DNA damage, thus altering signal transduction (Wells et al., 2009).

We found that the association was more pronounced among multiple anomalies. Although it is not directly comparable, our finding was consistent with a study conducted in Israel, which examined the association between exposure to heat and congenital heart defects. The Israel study reported that a 1-day increase in extreme heat events was associated with an 13 % (95 % CI: 6 %, 21 %) increase in the risk of multiple congenital heart defects (Agay-Shay et al., 2013).

Our study has several limitations. First, we obtained information on major structural anomalies from birth certificates, and those most serious and/or apparent anomalies at birth were easily captured. We might miss types of anomalies that were not identifiable at birth or identified in children and adults, such as spina bifida and heart malformations, and thus our findings should be interpreted with caution, especially for types of congenital anomalies that cannot be easily identified at birth. This information bias from various completeness of identified anomalies might bias our results toward the null association (Kesmodel, 2018). Second, we restricted our analyses to live births. Early miscarriages and stillbirths at viable gestations have higher rates of congenital anomalies, and they were excluded from the analysis. Thus, findings of our study could not be generalizable to all births. In addition, we excluded termination of pregnancy, which is more likely to occur among specific anomalies or among some groups of women. For example, central nervous system anomalies or women with basic education are more likely to have an abortion (Schechtman et al., 2002; Väisänen, 2015). Thus, findings of our study should be interpreted with caution. Third, we relied on outdoor ambient temperature instead of personal ambient temperature exposure, which might result in exposure misclassification. Another source of exposure misclassification might be from a lack of information on residential relocation. However, prior studies suggested that most pregnant women resided in local counties, with only a small proportion of them relocating to other counties during pregnancy (Bell and Belanger, 2012). These two sources of potential exposure misclassification would be nondifferential and tend to bias estimates toward the non-association (Kioumourtzoglou et al., 2014). Fourth, although we adjusted for a wide range of potential confounders, some confounders might be missed, such as folic acid. However, folate deficiency may not be an issue in the US as the US has implemented mandatory folic acid fortification since 1998 (Honein et al., 2001). Fifth, we selected 3–12 weeks post-conception as the critical developmental window as most major defects of the body and internal organs are more likely to occur during this period (Organization of Teratology Information Specialists OTIS, 2021). However, some malformations occur later in development. For example, the critical development window for nervous system is 3–16 weeks post-conception. Sixth, we restricted our analysis to women who were pregnant during the four warmest months. Findings from our study might not be generalizable to women who are pregnant in other months as women pregnant on very hot days tend to adapt biologically or use cooling strategies like air conditioning. Seventh, findings of our study might also not be generalizable to counties with a population of <100,000. Nevertheless, to our knowledge, our study is one of the first nationwide studies to examine the association between maternal exposure to heat and diagnostic categories of congenital anomalies.

5. Conclusions

In summary, among 2,352,529 live singleton births with 12.4 per 1000 births with major structural anomalies across 525 US counties, maternal exposure to ambient heat may be associated with higher risk of total anomalies, central nervous system anomalies, and other uncategorized anomalies. Our findings suggest pressing concerns should be addressed to continued global warming for congenital anomalies.

CRediT authorship contribution statement

Yangchang Zhang: Writing – original draft, Methodology, Data curation, Investigation.

Feng Sun: Writing – review & editing,

Kun Yuan: Writing – review & editing,

Ying Du: Writing – review & editing,

Lizhi Wu: Writing – review & editing,

Yang Ge: Writing – review & editing,

Zhenyu Zhang: Writing – review & editing,

Wangnan Cao: Conceptualization, Writing – review & editing, Data curation, Investigation.

Shengzhi Sun: Conceptualization, Writing – original draft, Formal analysis, Resources, review & editing.

Funding

None.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163613.

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