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Extreme winter temperature and birth defects: A population-based case-control study

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ABSTRACT

Background/objective: We examined the relationship between extreme winter temperatures and birth defects to determine whether pregnant women might be vulnerable to the weather extremes expected with climate change.
Methods: In this population-based, case-control study, we linked the New York State Congenital Malformations Registry to birth certificates (1992–2006). Cases were defined as live births with birth defects, and controls were selected from a 10% random sample of live births. We assigned meteorological data based on maternal birth residence and summarized universal apparent temperature across gestational weeks 3–8 (embryogenesis). We defined an extreme cold day as a day with mean temperature below the 10th percentile of the regional winter temperature distribution and a cold spell as 3 consecutive extreme cold days. We averaged temperature for each week of the first trimester to identify susceptible periods. We estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) with multivariable logistic regression for 30 birth defects groups.
Results: Among 13,044 cases and 59,884 controls with at least 1 week of embryogenesis in winter, coarctation of the aorta was associated with a 1 °C decrease in mean universal apparent temperature (OR 1.06, 95% CI 1.02-1.11), cold spell (OR 1.61, 95% CI 1.11-2.34), and number of extreme cold days. We observed reduced odds of hypoplastic left heart syndrome and dislocated hip for some cold indicators.
Conclusions: Most birth defects were not associated with cold indicators; however, we found positive associations between cold indicators and coarctation of the aorta in the biologically-relevant developmental window which warrants replication.

1. Introduction

Climate change may increase the frequency and severity of weather extremes, including heat waves and cold spells (Intergovernmental Panel on Climate Change, 2007). At present, pregnant women are not considered to be particularly vulnerable to climate change. However, in a review of studies of seasonality and ambient temperature in relation to preterm, low birth weight, and stillbirth, Strand et al. (2011) suggested that the observed peaks in winter, summer, or both seasons might indicate that extremes of temperature are an important determinant of poor birth outcomes. We previously reported on the association between extreme heat in summer and congenital cataracts in New York State (Van Zutphen et al., 2012). In a study of the seasonality of birth defects using the New York State Congenital Malformations Registry, conceptions in winter months were associated with ventricular septal defect and coarctation of the aorta, suggesting that cold ambient temperatures might play a role in the etiology of congenital heart defects (Caton, 2012).

Though peripheral vasoconstriction, a physiologic response to cold (Borkenhagen, 1988), plausibly could alter uteroplacental perfusion and adversely affect the developing fetus, there are few studies on the relationship between maternal exposure to cold ambient temperatures and adverse birth outcomes. Hypertensive disorders of pregnancy were associated with winter delivery in a systematic review of the literature (TePoel et al., 2011). Low birth weight has been associated with low temperatures in the first (Chodick et al., 2007), second (Elter et al., 2004; Murray et al., 2000), and third trimesters (Chodick et al., 2007; Lawlor et al., 2005). Exposure to "too cold" environmental conditions at work was associated with spontaneous abortion in one study (McDonald et al., 1988). An occupational study in New York State showed no relationship between congenital heart defects and time

Abbreviations: OR, odds ratio; CI, confidence interval
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spent in environments with temperatures less than 0 °F (−18 °C) (Judge et al., 2004). In a study of congenital heart defects in Tel-Aviv Israel, a 1-day increase in extreme heat events in the cold season was associated with multiple congenital heart defects and isolated atrial septal defects (Agay-Shay et al., 2013).

To determine whether pregnant women and their infants in New York might be vulnerable to cold weather extremes, we explored the relationship between ambient winter temperatures, extreme cold days, cold spells, and the occurrence of selected birth defects using the population-based, New York State Congenital Malformations Registry.

2. Methods

2.1. Study population and data sources

The source population was all live births to residents of New York State (excluding New York City) from 1992 through 2006. Appropriate institutional review board approvals were granted to access New York State birth certificate data from Vital Records and birth defects data from the Congenital Malformations Registry. The birth certificate contains data on maternal and infant characteristics, such as maternal age, race, ethnicity, education, date of last menses, prenatal care (e.g., timing and number of visits), residential address, and maternal behavioral characteristics (e.g., smoking), infant date of birth, sex, birth weight, and gestational age. The Congenital Malformations Registry is a population-based registry that receives mandated reports on children who were born in New York State and were diagnosed with birth defects, metabolic defects, or chromosomal anomalies up until 2 years of age from hospitals and physicians. The registry routinely matches reports to the New York State birth certificate files and has a 95% match rate. Roohan et al. (2003) assessed the validity of information reported on the New York State birth certificate by checking medical records and found high specificity (91–100%) for most data elements and high sensitivity for infant information such as birth weight (100%) and maternal lifestyle (86–100%). Hospital audits are conducted to capture the unreported Congenital Malformations Registry cases. On site hospital medical record audits documented that the Congenital Malformations Registry reports were >90% correct (Wang et al., 2010), which is comparable to that of Metropolitan Atlanta Congenital Defects Program, an active surveillance system which is regarded as the "gold standard" (Honein and Paulozzi, 1999).

2.2. Study design

We used the case-control study design to determine the association between cold ambient temperature during the critical period of embryogenesis and the risk of birth defects. Cases were defined as New York State (excluding New York City) live births with birth defects delivered in the 1992–2006 study period. A 10% random sample of live births without birth defects selected from the same period and geographic region was used as the control group.

2.3. Outcome assessment

Using ICD-9-CM diagnoses codes from the Congenital Malformations Registry records, birth defect cases were classified into the 45 birth defects categories that meet the reporting standards of the National Birth Defects Prevention Network (2010). Of these, chromosomal anomalies (Trisomies 13, 18, and 21), fetal alcohol syndrome, and case groups with fewer than 50 cases (anencephalus, encephalocele, anophthalmia/microphthalmia, aniridia, tricuspid atresia/stenosis, Ebstein's anomaly, biliary atresia, bladder exstrophy, and amniotic bands) were excluded from analyses.

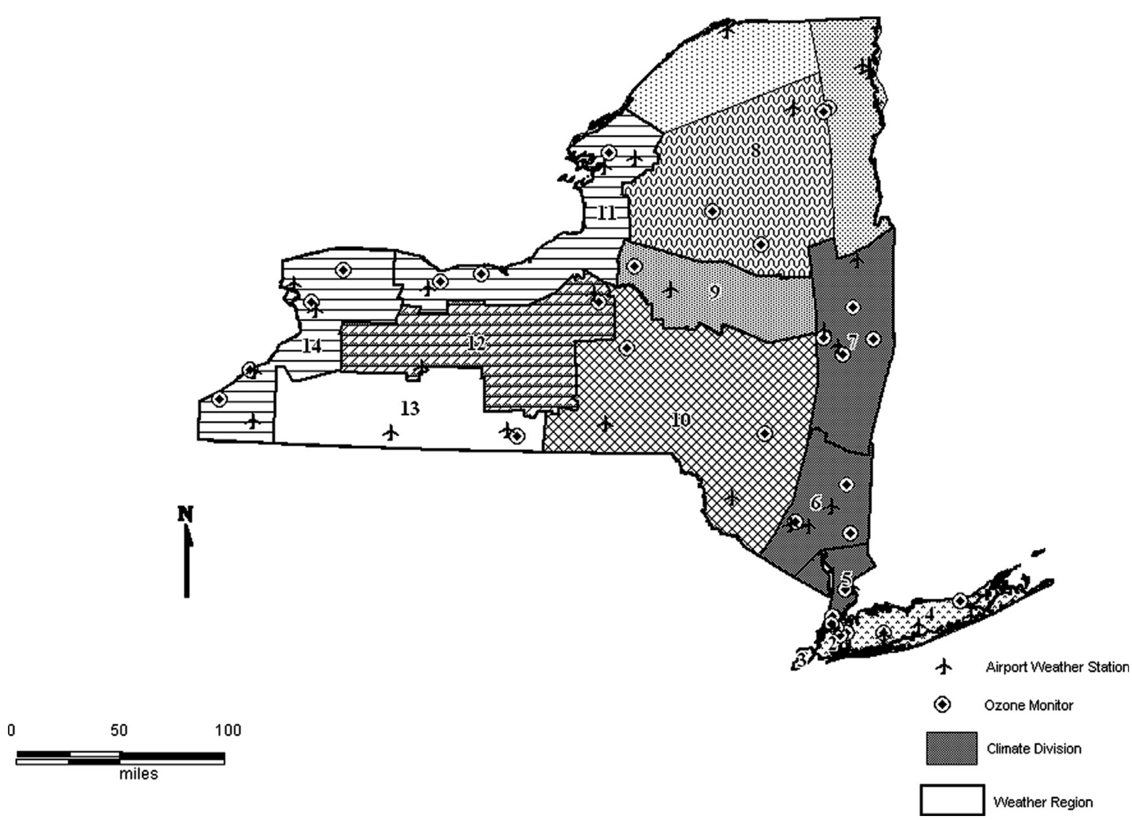

Fig. 1. Weather regions, climate divisions, airport weather stations, and ozone monitors in New York State.

2.4. Weather and ozone exposure assessment

For consistency across our public health surveillance studies related to climate change and air pollution in New York State, we divided the state into the 14 weather regions depicted in Fig. 1. To allow for adjustment of the effect of ozone in our studies, 14 regions of relatively homogeneous weather and ozone exposures were developed by overlaying and merging the 10 New York State climate divisions of the National Climate Data Center with the 11 ozone regions developed for New York State by Chinery and Walker (2009). Hourly meteorological observations were obtained from the National Center for Atmosphere Research for 18 first-order airport weather stations. These stations are professionally maintained by the National Weather Service or the Federal Aviation Administration. If more than one weather station was located in one weather-ozone region, we used the average value across stations to represent the region.

Each weather region was assigned a daily average value of temperature (minimum, mean, and maximum in °C), barometric pressure, dew point, and wind speed by using all available airport data for that region. Universal apparent temperature was calculated using temperature, vapor pressure, and wind speed (Steadman, 1984):

$UAT = -2.7 + 1.04\,T + 2.0\,VP - 0.65\,W$, where
Temperature (T) in °C
Vapor pressure (VP) in kPa
Wind speed (W) in m s^{-1}

$VP = 0.6108^{(17.27DP/(237.3+DP))}$, where
Dew Point (DP) in °C

About 94% of the maternal residential addresses from the birth certificate were successfully geocoded to ZIP code using Map Marker Plus and MapInfo Professional (Pitney Bowes Business Insight, Troy, NY) and assigned to one of the New York State weather regions. Less than 6% of records were excluded from the analysis due to inadequate address information.

We estimated date of conception by adding 14 days to the maternal date of last menses, and we estimated day of pregnancy based on this reference point. Daily average values of meteorological variables were merged with the birth record based on estimated day of pregnancy and maternal residence within the weather region (at time of infant's birth). To examine the effects of extreme cold in winter, we restricted the analyses to winter months (December, January, and February). We focused on the critical period of organogenesis which occurs during weeks 3–8 post-conception (Sadler, 2004). Because universal apparent temperature incorporates the combined effects of heat, humidity, and wind chill, it is a better indicator of thermal stress on the human body (Steadman, 1984). Thus, we averaged the daily minimum, mean, and maximum universal apparent temperature across the critical period for each case and control birth. We constructed exposure indices to capture frequency and duration of extreme cold events using the mean universal apparent temperature distributions within each weather region during winter to account for potential differential acclimatization by region. There is no standard definition of cold spell. Because we used an average universal apparent temperature above the 90th percentile as our definition of an extreme heat day and 3 consecutive extreme heat days as our definition of heat wave in a previous study of extreme summer temperature and birth defects (Van Zutphen et al., 2012), we selected the 10th percentile as our cut point to define an extreme cold day in winter and 3 consecutive extreme cold days as our definition of a cold spell. We counted the number of days below the 10th percentile. To examine narrower exposure windows, we also averaged the daily minimum, mean, and maximum universal apparent temperature for each week of the first trimester for each birth.

We obtained hourly ambient ozone data (in parts per billion) from 32 ozone monitoring sites from the New York State Department of Environmental Conservation and used the 8-h maximum hourly value during the peak outdoor exposure time (1000–1800 h) to represent the daily ozone level (Lin et al., 2008). If more than one monitoring site was located in one weather region, we used the average value of the 8-h maximum to represent the region. We merged daily ozone levels to the birth record based on the estimated day of pregnancy and maternal residential address within the weather region. Next, we averaged the daily ozone level across the critical period for each birth and constructed quartiles based on the distribution in winter months within the control group.

2.5. Confounders and effect modifiers

Maternal age (< 20, 20–34, 35+ years), maternal education level (< 12, 12–15, 16+ years), maternal race (white, black, other), maternal ethnicity (Hispanic, non-Hispanic), total previous live births (0, 1, 2+), prenatal care (modified Kessner Index: adequate, intermediate, inadequate), tobacco use during pregnancy (yes, no), alcohol use during pregnancy (yes, no), multiple birth (yes, no), and infant sex (male, female) were available across all years on the birth certificates and were considered as potential confounders and effect modifiers based on their associations with certain birth defects in the literature. In addition, average daily ozone level during the critical period (as a continuous variable and in quartiles as described in Section 2.4) was evaluated as a potential confounder based on prior studies suggesting a possible relationship with certain birth defects (Gilboa et al., 2005; Strickland et al., 2009).

2.6. Statistical analysis

To study temperature and temperature extremes in winter, we restricted our subset of births to those with at least 1 week of the critical period of embryogenesis within winter. We used unconditional logistic regression to estimate the association between 30 selected birth defects groups and seven cold exposure indicators: average daily minimum, mean, and maximum universal apparent temperature, occurrence of a cold spell, and number of extreme cold days in the critical period. Crude prevalence odds ratios (OR) and 95% confidence intervals (CI) were calculated, and confounding and interaction were assessed using bivariate and stratified analyses. Multivariable unconditional logistic regression was used to calculate adjusted OR and 95% CI. The final models were adjusted for covariates that were associated with cold indicators among the control group and at least one birth defect: maternal race, ethnicity, education, weather region, average daily ozone level, and year of birth. We examined average daily mean universal apparent temperature for each of the first 12 weeks of pregnancy to identify narrower windows of susceptibility. To verify our assumption of linearity between temperature and the risk of birth defects, we modeled the log odds of each birth defect as a function of average daily mean universal apparent temperature using a b-spline with 3 degrees of freedom. We plotted the smoothing functions with 95% confidence bands to verify that the horizontal reference line at zero was entirely within the band. For the associations between cold spell and each birth defects group, we performed stratified analyses by weather region, maternal age, race, ethnicity, education, adequacy of prenatal care, smoking status, and quartile of average daily ozone level. Because certain mild defects (e.g., cataracts, patent ductus arteriousus) are more likely to be

Table 1
Characteristics of resident live births with at least 1 week of the critical period within winter (December–February), New York (excluding New York City), 1992–2006.

Characteristic	By case-control status		Exposure to a cold spell during the critical period among controls	
	Cases (n=13,044), n (%)	Controls (n=59,884), n (%)	Yes (n=15,653), n (%)	No (n=44,231), n (%)
Maternal age (years)				
< 20	1065 (8.2)	4632 (7.7)	1183 (7.6)	3449 (7.8)
20–24	9672 (74.2)	44,868 (75.0)	11,723 (74.9)	33,145 (75.0)
35+	2302 (17.7)	10,363 (17.3)	2745 (17.5)	7618 (17.2)
Maternal education (years)[a]				
< 12 years	2022 (15.8)	8507 (14.5)	2292 (14.9)	6215 (14.3)
12–15 years	7138 (55.8)	32,618 (55.5)	8555 (55.5)	24,063 (55.4)
16+ years	3623 (28.3)	17,680 (30.1)	4556 (29.6)	13,124 (30.2)
Maternal Race				
White	11,063 (85.3)	50,780 (85.2)	13,242 (84.9)	37,538 (85.3)
Black	1323 (10.2)	5932 (10.0)	1582 (10.1)	4350 (9.9)
Other Race	591 (4.6)	2905 (4.9)	779 (5.0)	2126 (4.8)
Maternal ethnicity[a]				
Hispanic	1149 (8.8)	6040 (10.1)	1624 (10.4)	4416 (10.1)
Non-hispanic	11,895 (91.2)	53,844 (89.9)	14,029 (89.6)	39,815 (90.2)
Total previous live births[a]				
0	5596 (42.9)	23,924 (40.0)	6273 (40.1)	17,651 (39.9)
1	4177 (32.0)	20,203 (33.7)	5246 (32.0)	14,957 (33.8)
2+	3270 (25.1)	15,757 (26.3)	4134 (26.4)	11,623 (26.3)
Modified Kessner Prenatal Care Index				
Adequate care	8767 (67.2)	40,216 (67.2)	10,474 (66.9)	40,216 (67.2)
Intermediate care	3017 (23.1)	14,146 (23.6)	3709 (23.7)	14,146 (23.6)
Inadequate care	1260 (9.7)	5522 (9.2)	1470 (9.4)	5522 (9.2)
Maternal smoking during pregnancy[a]				
Yes	2211 (17.1)	9225 (15.6)	2362 (15.4)	6863 (15.7)
No	10,691 (82.9)	49,825 (84.4)	13,002 (84.6)	36,823 (84.3)
Maternal alcohol use during pregnancy				
Yes	140 (1.1)	544 (0.9)	142 (0.9)	4024 (0.9)
No	12,729 (98.9)	58,429 (99.1)	15,198 (99.0)	43,231 (99.1)
Multiple birth[a]				
Yes	663 (5.1)	2005 (3.4)	506 (3.2)	1499 (3.4)
No	12,381 (94.9)	57,879 (96.7)	15,147 (96.8)	42,732 (96.6)
Infant sex[a]				
Male	8463 (64.9)	30,613 (51.1)	8019 (51.2)	22,594 (51.1)
Female	4578 (35.1)	29,269 (48.9)	7632 (48.8)	21,637 (48.9)
Low birth weight (g)[a]				
< 2500	2191 (16.8)	3711 (6.2)	934 (6.0)	2777 (6.3)
2500+	10,841 (83.2)	56,130 (93.8)	14,714 (94.0)	41,416 (93.7)
Preterm birth (weeks)[a]				
< 37	2721 (20.9)	6121 (10.2)	1563 (10.0)	4558 (10.3)
37+	10,323 (79.1)	53,763 (89.8)	14,090 (90.0)	39,673 (89.7)
Quartile of average daily ozone level (ppb)[a,b]				
Q1: 14.1–22.2	3105 (24.3)	14,679 (25.0)	2057 (13.4)	12,622 (29.1)
Q2: 22.2–25.9	3187 (25.0)	14,678 (25.0)	4347 (28.4)	10,331 (23.8)
Q3: 25.9–31.2	3300 (25.8)	14,700 (25.0)	5355 (35.0)	9345 (21.5)
Q4: 31.2–48.6	3178 (24.9)	14,689 (25.0)	3555 (23.2)	11,134 (25.6)
Maternal residence within weather region (at birth)[a,b]				
4-Long Island	3516 (27.0)	15,233 (25.4)	4182 (26.7)	11,051 (25.0)
5-Westchester/Rockland	1283 (9.8)	6672 (11.1)	1776 (11.4)	4896 (11.1)
6-Hudson Valley-South	805 (6.2)	4218 (7.0)	1276 (8.2)	2942 (6.7)
7-Hudson Valley-North	1003 (7.7)	5010 (8.4)	1346 (8.6)	3664 (8.3)
8-Adirondack & North	377 (2.9)	1802 (3.0)	505 (3.2)	1297 (2.9)
9-Mohawk Valley	501 (3.8)	2099 (3.5)	510 (3.3)	1589 (3.6)
10-Binghamton	862 (6.6)	4270 (7.1)	993 (6.3)	3277 (7.4)
11-Great Lakes-Rochester	1340 (10.3)	6145 (10.3)	1377 (8.8)	4768 (10.8)
12-Central Lakes	1085 (8.3)	5164 (8.6)	1218 (7.8)	3946 (8.9)
13-Western Plateau	428 (3.3)	1700 (2.8)	483 (3.1)	1217 (2.8)
14-Great Lakes-Buffalo	1844 (14.1)	7571 (12.6)	1987 (12.7)	5584 (12.6)

[a] Differences in the distributions between cases and controls were statistically significant ($p \leq 0.05$).
[b] Differences in the distributions between controls with and without a cold spell during the critical period were statistically significant ($p \leq 0.05$).

ascertained in preterm infants, we performed subanalyses among term infants to evaluate detection bias (Prakalapakorn et al., 2010; Tanner et al., 2005). Lastly, we did an analysis of the subgroup of cases with isolated coarctation of the aorta because the etiology might be different for cases with multiple birth defects (Khoury et al., 1992).

Table 2
Regional distributions of daily mean universal apparent temperature (°C) in winter (December–February), New York (excluding New York City), 1991–2006.

Weather region	Daily minimum UAT					Daily mean UAT					Daily maximum UAT				
	Mean	±SD	Min	P10	Max	Mean	±SD	Min	P10	Max	Mean	±SD	Min	P10	Max
4-Long Island	−7.2	−11.0	−30.2	−16.1	15.0	−2.3	−11.2	−23.7	−10.9	16.0	2.6	−10.8	−19.6	−6.3	31.7
5-Westchester/Rockland	−8.5	−10.6	−34.5	−18.1	13.9	−3.4	−10.9	−26.7	−12.5	16.4	1.7	−10.6	−20.4	−7.2	22.5
6-Hudson Valley – South	−10.0	−10.6	−35.2	−20.1	13.1	−4.5	−11.0	−26.7	−13.5	17.7	1.0	−10.9	−21.5	−7.5	21.2
7-Hudson Valley – North	−12.9	−9.7	−42.0	−24.2	11.9	−7.4	−10.5	−30.8	−17.2	15.5	−2.0	−10.9	−25.0	−11.0	18.6
8-Adirondack & North	−17.5	−8.3	−47.2	−30.1	10.0	−11.7	−9.2	−39.3	−22.9	12.4	−5.7	−9.7	−32.4	−16.7	20.0
9-Mohawk Valley	−13.7	−9.4	−41.5	−25.2	12.2	−8.7	−10.2	−33.4	−18.9	14.5	−3.3	−10.2	−29.4	−12.8	20.0
10-Binghamton	−13.2	−9.9	−38.8	−23.9	13.9	−8.6	−10.2	−33.9	−18.4	14.6	−3.6	−10.1	−30.1	−13.6	17.8
11-Great Lakes – Rochester	−14.8	−8.8	−43.4	−27.0	10.9	−9.1	−9.7	−33.5	−19.9	15.1	−3.6	−10.0	−27.1	−13.7	19.8
12-Central Lakes	−12.3	−9.7	−37.7	−22.9	13.9	−7.1	−10.3	−30.8	−17.2	17.5	−1.8	−10.1	−25.0	−11.7	20.6
13-Western Plateau	−11.7	−10.0	−38.6	−22.1	15.6	−5.9	−10.7	−33.0	−15.4	17.0	−0.4	−10.5	−26.8	−9.5	20.6
14-Great Lakes-Buffalo	−11.8	−10.3	−36.6	−22.0	11.7	−7.4	−10.5	−33.5	−17.2	16.3	−2.7	−10.1	−30.9	−12.3	20.3
Overall-Upstate New York	−12.2	−9.4	−47.2	−23.8	15.6	−6.9	−9.9	−39.3	−17.5	17.7	−1.6	−10.0	−32.4	−11.7	31.7

UAT = universal apparent temperature; SD = standard deviation; Min = minimum; P10 = 10th percentile; and Max = maximum.

Table 3
Associations between daily mean universal apparent temperature, cold spells, and number of extreme cold days during the critical period and the occurrence of selected birth defects, New York (excluding New York City), 1992–2006.

Birth outcome group	*n*	1 °C decrease in daily mean universal apparent temperature			Cold spell[a]			# Extreme cold days[b]		
		Mean (±SD)	OR[b]	95% CI	*n* (%)	OR[c]	95% CI	Mean (±SD)	OR[c]	95% CI
Controls	59,844	−4.6 (4.8)			15,653 (26.1)			3.3 (4.2)		
Central nervous system										
Spina bifida without anencephalus	115	−4.9 (4.3)	0.98	0.93–1.04	34 (29.6)	1.13	0.82–1.55	3.3 (4.3)	0.98	0.94–1.04
Hydrocephalus without spina bifida	335	−5.0 (4.8)	1.03	1.00–1.06	96 (28.7)	1.15	0.48–2.76	3.7 (4.5)	1.02	0.98–1.05
Microcephalus	214	−4.5 (5.0)	0.98	0.94–1.02	51 (23.8)	0.78	0.53–1.15	3.2 (4.2)	0.98	0.94–1.02
Eye										
Congenital cataract	77	−4.7 (4.2)	1.01	0.94–1.08	23 (29.9)	1.21	0.63–2.32	3.2 (3.7)	0.99	0.93–1.07
Cardiovascular										
Transposition of great arteries	86	−4.5 (4.6)	0.98	0.92–1.04	24 (27.9)	1.18	0.66–2.11	3.1 (4.1)	1.00	0.94–1.06
Tetralogy of Fallot	123	−5.1 (5.4)	1.03	0.97–1.08	37 (30.1)	1.4	0.84–2.31	3.6 (4.8)	1.03	0.98–1.08
Ventricular septal defect	1586	−4.7 (4.6)	1.01	0.99–1.02	426 (26.9)	1.05	0.91–1.21	3.4 (4.3)	1.00	0.99–1.02
Atrial septal defect	873	−4.1 (4.7)	1.00	0.97–1.01	232 (26.6)	1.08	0.89–1.31	3.1 (4.0)	0.99	0.97–1.01
Endocardial cushion defect	52	−5.3 (5.4)	1.01	0.93–1.10	16 (30.8)	1.48	0.63–3.47	4.3 (5.0)	1.06	0.98–1.14
Pulmonary valve atresia/stenosis	426	−4.6 (4.7)	0.99	0.96–1.02	111 (26.1)	1.03	0.79–1.35	3.1 (4.1)	0.98	0.96–1.01
Aortic valve stenosis	91	−4.3 (4.4)	0.99	0.93–1.06	24 (26.4)	0.94	0.51–1.70	3.1 (4.1)	1.01	0.94–1.08
Hypoplastic left heart syndrome	85	−4.4 (4.7)	**0.92**[d]	**0.86–0.98**	18 (21.2)	0.6	0.31–1.18	2.5 (3.2)	0.93	0.86–1.00
Patent ductus arteriosus (≥2500 g)	542	−4.4 (4.5)	0.99	0.96–1.01	131 (24.2)	0.87	0.69–1.10	3.3 (4.2)	0.99	0.97–1.01
Coarctation of aorta	220	−5.6 (4.5)	**1.06**[d]	**1.02–1.11**	71 (32.3)	**1.61**[d]	**1.11–2.34**	3.8 (4.4)	**1.04**[d]	**1.01–1.08**
Orofacial										
Choanal atresia	95	−5.0 (4.7)	1.01	0.95–1.07	24 (25.3)	0.88	0.47–1.64	3.0 (3.9)	0.97	0.91–1.04
Cleft palate without cleft lip	350	−5.2 (4.9)	1.01	0.98–1.04	102 (29.1)	1.2	0.90–1.60	3.6 (4.6)	1.01	0.99–1.04
Cleft lip ± cleft palate	490	−4.8 (4.8)	1.00	0.97–1.02	126 (25.7)	1.08	0.84–1.40	3.2 (4.2)	1.01	0.98–1.03
Gastrointestinal										
Esophageal/tracheoesophageal fistula	118	−4.5 (4.5)	1.01	0.94–1.05	37 (31.4)	1.32	0.81–2.15	3.3 (4.2)	1.01	0.96–1.06
Rectal/large intestinal atresia/stenosis	168	−4.2 (4.8)	0.97	0.93–1.01	31 (18.5)	0.64	0.40–1.02	3.1 (4.5)	0.98	0.94–1.03
Pyloric stenosis	1315	−4.8 (4.5)	1.00	0.98–1.02	350 (26.6)	0.92	0.79–1.07	3.3 (4.2)	0.99	0.98–1.01
Congenital megacolon	126	−4.7 (4.6)	0.99	0.94–1.04	35 (27.8)	0.93	0.58–1.51	3.4 (4.8)	0.99	0.95–1.04
Genitourinary										
Renal agenesis/hypoplasia	183	−5.0 (5.1)	1.01	0.96–1.05	50 (27.3)	0.97	0.64–1.46	3.6 (5.0)	1.01	0.97–1.05
Obstructive genitourinary	1659	−4.2 (4.9)	0.99	0.98–1.01	442 (26.6)	0.95	0.32–1.08	3.3 (4.3)	1.00	0.98–1.01
Hypospadias/epispadias	2438	−4.5 (4.7)	1.00	0.98–1.01	644 (26.4)	1.01	0.90–1.14	3.2 (4.2)	1.00	0.99–1.01
Musculoskeletal										
Upper limb reduction	144	−4.8 (4.7)	0.97	0.93–1.02	45 (31.3)	1.04	0.67–1.61	3.4 (4.3)	0.99	0.94–1.03
Lower limb reduction	73	−5.2 (4.0)	1.02	0.95–1.09	14 (19.2)	0.74	0.37–1.51	3.4 (4.4)	1.01	0.95–1.08
Gastroschisis	116	−5.8 (4.1)	1.03	0.97–1.09	36 (31.0)	1.14	0.69–1.91	3.4 (3.9)	1.01	0.96–1.07
Omphalocele	82	−5.1 (4.4)	0.98	0.92–1.05	20 (24.4)	0.78	0.41–1.51	3.1 (3.8)	0.98	0.91–1.04
Congenital hip dislocation	744	−4.1 (4.8)	0.98	0.96–1.00	166 (22.3)	**0.74**[d]	**0.60–0.92**	2.9 (4.0)	0.98	0.95–1.00
Diaphragmatic hernia	104	−5.7 (4.9)	1.03	0.97–1.09	29 (27.9)	1.00	0.57–1.73	3.8 (4.5)	1.01	0.96–1.07

[a] Cold spell (≥3 consecutive days with regional daily mean universal apparent temperature below the 10th percentile).
[b] Extreme cold day (day with regional daily mean universal apparent temperature below the 10th percentile).
[c] ORs were adjusted for maternal race, ethnicity, education, weather region, average daily ozone level, and year of birth.
[d] Statistically significant ($p \leq 0.05$).

3. Results

A total of 13,044 selected birth defects cases and 59,884 controls with at least 1 week of the critical period of embryogenesis in winter were included in the analyses of New York State (excluding New York City) resident live births in the 1992–2006 study period. Distributions of maternal education, ethnicity, total previous live births, smoking, multiple birth, infant sex, low birth weight, preterm birth, maternal residence within a weather region, and year of birth were significantly different among cases and controls (Table 1). In a comparison of characteristics among controls with and without an exposure to a cold spell during the critical period, there were significant variations in maternal residence within weather region at birth, year of birth, and quartile of ozone concentration. Distributions of daily universal apparent temperature (minimum, mean, maximum) in winter by weather region are displayed in Table 2.

In analyses of universal apparent temperature as a continuous variable (Table 3), a 1 °C decrease in the average daily mean universal apparent temperature in the critical period was significantly associated with an increased odds of coarctation of the aorta (OR 1.06, 95% CI 1.02-1.11) and a reduced odds of hypoplastic left heart syndrome (OR 0.92, 95% CI 0.86-0.98). Similar relationships as displayed in Table 3 were found in analyses of the minimum and maximum universal apparent temperature (data not shown). In the analyses of indicators of extreme cold (Table 3), an increased odds of coarctation of the aorta was associated with cold spell (OR 1.61, 95% CI 1.11-2.34) and number of extreme cold days (OR 1.04, 95% CI 1.01-1.08). A decreased odds of congenital hip dislocation was associated with cold spell (OR 0.746, 95% CI 0.60-0.92). In stratified analyses of cold spells by weather region, maternal race, ethnicity, age, education, prenatal care adequacy, and smoking status, the CI were imprecise and overlapping due to small sample sizes within strata. In a subanalysis among term infants to minimize detection bias (data not shown), the estimates for congenital cataracts and mild heart defects were similar to the full analyses with no statistically significant associations. In a subanalysis of isolated coarctation of the aorta cases ($n=178$), the findings were similar for a 1 °C decrease in the average daily mean universal apparent temperature in the critical period (OR 1.06, 95% CI 1.01-1.11), cold spell (OR 1.69, 95% CI 1.12-2.56), and number of extreme cold days (OR 1.05, 95% CI 1.01-1.10).

To identify the period of highest susceptibility for the development of coarctation of the aorta, the birth defects group that showed consistent and significantly positive associations with cold exposures, we examined the associations by gestational week in the first trimester. Fig. 2 shows statistically significant elevations in the ORs for mean daily mean universal apparent temperature and coarcation of the aorta for weeks 1 through 5. The shape of the plot suggests a susceptibility to cold between weeks 1 and 5 with an attenuation of risk beyond week 5.

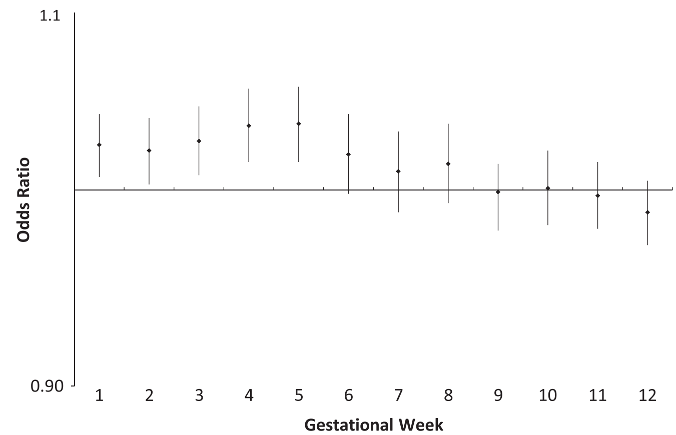

Fig. 2. Associations between a 1 °C decrease in mean universal apparent temperature and coarctation of the aorta by gestational week.

4. Discussion

In our population-based study of 15 years of birth defects data in New York State (excluding New York City), we found elevated ORs for associations between multiple indicators of decreasing winter temperature and extreme cold during the critical period of embryogenesis and coarctation of the aorta. On the other hand, some cold indicators were associated with decreased odds of hypoplastic left heart syndrome and congenital hip dislocation. We did not identify statistical associations for the other 27 birth defects groups. Few studies have reported on the associations between cold temperatures and the occurrence of birth defects, although some have reported on the seasonality of birth defects. In a descriptive study of the seasonality of birth defects in New York State (excluding New York City), conceptions occurring in winter months were associated with ventricular septal defect and coarctation of the aorta which suggested that cold ambient temperatures or that other factors in winter might play a role in the etiology of these birth defects (Caton, 2012). In the current analysis, we examined ambient temperatures within the winter season to control for confounding by other seasonal factors and thus determine whether temperature itself was associated with the occurrence of birth defects. Since we found consistent positive associations between cold temperature indicators and coarctation of the aorta, coarctation of the aorta might be due to extremes in cold temperatures, whereas the seasonality of ventricular septal defect might be explained by seasonal factors other than temperature. In contrast, studies in Flyde of Lancashire (Bound et al., 1989) and Finland (Tikkanen and Heinonen, 1993) found no evidence of seasonal variation in coarctation of the aorta, which could be due to geographical differences in associations. An occupational study in New York State showed no relationship between congenital heart defects and maternal self-reported number of hours per week spent in temperatures less than 0° F (−18 °C) (Judge et al., 2004); however, all congenital heart defects were grouped together and coarctation of the aorta represents less than 10% of heart defects (O'Brien, 2010).

More recently, a 1-day increase in extreme heat events in the cold season was associated with multiple congenital heart defects and isolated atrial septal defects in Tel-Aviv, Israel, suggesting that unusually warm temperatures in the cold season increase the risk of certain heart defects (Agay-Shay et al., 2013). Because the study only analyzed three groupings of congenital heart defects (multiple congenital heart defects, isolated atrial septal defects, and isolated ventricular septal defects), we are unable to directly compare our results for hypoplastic left heart syndrome for which we found a decreased odds with colder temperatures in winter. We did not detect any relationships between ambient temperature and the septal defect groups in our study.

4.1. Coarctation of the aorta

Our most consistent findings were for coarctation of the aorta, a left ventricular outflow tract obstruction which occurs in 5.01 per 10,000 live births in New York State (National Center on Birth Defects and Developmental Disabilities, 2011) and is hypothesized to be caused by altered embryonic blood flow through the left side of the heart during cardiac development (Clark, 1996). However, other left ventricular outflow tract obstructions (e.g., aortic valve stenosis, hypoplastic left heart syndrome) did not show associations with decreasing temperatures in our study. Furthermore, the odds of hypoplastic left heart syndrome decreased with decreasing temperatures. In our analysis by gestational week, we detected statistical elevations in the ORs for coarctation of the aorta during weeks 1–5 with attenuation of the ORs after week 5 which supports biologic plausibility since this period is just prior to the development of the aortic arch which occurs during 6th–8th week of gestation (O'Brien, 2010).

4.2. Maternal thermoregulation and potential mechanisms of cold teratogenesis

Peripheral vasoconstriction and increased heat production from shivering are the two physiologic responses to cold ambient temperature (Borkenhagen, 1988). These changes in maternal circulation might alter uteroplacental perfusion and adversely affect the developing fetus (Chodick et al., 2009; Lawlor et al., 2005; Murray et al., 2000). In sheep, fetal blood flow is redistributed from peripheral tissues to the placenta and thermogenic tissues during cooling (Gunn et al., 1985). In our study, we did not see increased occurrences of birth defects that have been previously reported to be associated with vascular disruption, such as limb reductions, small intestinal atresia, and gastroschisis (van Gelder et al., 2010); however, humans have a greater ability to protect themselves from environmental cold stress via housing, indoor heating, clothing, and blankets (Lawlor et al., 2005).

4.3. Study strengths

In one of the first studies to address the associations between extreme cold environmental temperatures and the occurrence of birth defects, we were able to analyze 15 years of Congenital Malformations Registry and birth certificate data for a large geographically and demographically diverse population and adjust for individual-level confounders available on the birth certificate. We examined etiologically homogeneous groups of birth defects based on surveillance definitions proposed by the National Birth Defects Prevention Network (2010) which will enable comparisons and collaborations with other participating surveillance programs. For the exposure assessment, we used objective daily meteorological data during the relevant developmental window of organogenesis. We used universal apparent temperature, a better indicator of cold stress on the human body than temperature alone (Steadman, 1984), and examined multiple cold indicators to capture intensity and duration. We used a relative measure of extreme cold by using regional distributions of universal apparent temperature to adjust for acclimatization. We performed a subanalysis among term births to address the potential for detection bias of milder defects in preterm infants (Prakalapakorn et al., 2010; Tanner et al., 2005) and a subanalysis of isolated cases of coarctation of the aorta to create a more etiologically homogeneous case group. We also analyzed ambient temperature by week of gestation to identify susceptible windows during organogenesis.

4.4. Study limitations

Exposure was estimated using regional ambient temperatures measured at airport weather stations and maternal residence at the time of the infant's birth as a surrogate measure of individual exposure during early pregnancy. Thus, heterogeneity of outdoor and indoor temperatures, time-activity patterns (e.g., time spent inside and outside at home, work), and thermoregulating behaviors (e.g., indoor heater use, choice of clothing) were not taken into account (Lawlor et al., 2005; Nethery et al., 2009). In a previous study to evaluate residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification in upstate New York, 16.5% of mothers moved during pregnancy and most moved a short distance within the same exposure region (Chen et al., 2010). Confounding may be present due to unmeasured nutritional factors, infection, indoor air pollution, and other factors which vary by season (Chodick et al., 2009; Elter et al., 2004; Murray et al., 2000; Strand et al., 2011). Bias due to these unmeasured factors is likely non-differential by case-control status. In addition, risk estimates for major birth defects that are more likely to be detected and terminated or result in fetal death may be biased because the Congenital Malformations Registry does not collect data on elective terminations or stillbirths (Parker et al., 2010). Lastly, because we performed multiple tests to examine the relationships between 30 birth defects groups and various cold exposure indicators in this hypothesis generating study, statistically significant findings may be due to chance.

5. Conclusions

We did not identify consistent elevations in the odds ratios for the relationship between ambient cold temperature in winter and most major structural birth defects in this study. However, we found positive and consistent associations between cold exposure indicators, including a 1 °C decrease in the average daily mean universal apparent temperature, the occurrence of a cold spell, and the number of extreme cold days within a biologically-plausible developmental window and coarctation of the aorta. Due to limitations of live birth only surveillance, potentially uncontrolled confounding, and multiple testing concerns, the findings of this hypothesis-generating study warrant confirmation.

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Disclaimers

The authors declare they have no actual or potential competing financial interests.

Evidence of human subjects review and approval

The study protocol (#08-087 Environmental Exposures and Adverse Reproductive Outcomes) was reviewed and approved by the New York State Department of Health Institutional Review Board (FWA00003700/IRB 00000299), Empire State Plaza, Corning Tower, Room 474, Albany, NY 12237. Tel. +1 518 474 8539.

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