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Ambient Temperature and Stillbirth: A Multi-Center Retrospective Cohort Study

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BACKGROUND: Climate change is expected to have adverse health effects, but the association between extreme ambient temperatures and stillbirth is unclear.

OBJECTIVES: We investigated acute and chronic associations between extreme ambient temperatures and stillbirth risk, and estimated the attributable risk associated with local temperature extremes in the United States.

METHODS: We linked 223,375 singleton births $\geq$23 weeks of gestation (2002–2008) from 12 U.S. sites to local temperature. Chronic exposure to hot ($>$90th percentile), cold ($<$10th percentile), or mild (10th–90th percentile) temperatures was defined using window- and site-specific temperature distributions for three-months preconception, first and second trimester, and whole-pregnancy averages. For acute exposure, average temperature for the week preceding delivery was compared to two alternative control weeks in a case-crossover analysis.

RESULTS: In comparison with mild, whole-pregnancy exposure to cold [adjusted odds ratio (aOR) = 4.75; 95% confidence interval (CI): 3.95, 5.71] and hot (aOR = 3.71; 95% CI: 3.07, 4.47) were associated with stillbirth risk, and preconception and first and second trimester exposures were not. Approximately 17–19% of stillbirth cases were potentially attributable to chronic whole-pregnancy exposures to local temperature extremes. This is equivalent to ~1,116 cold-related and ~1,019 hot-related excess cases in the United States annually. In the case-crossover analysis, a 1°C increase during the week preceding delivery was associated with a 6% (3–9%) increase in stillbirth risk during the warm season (May–September). This incidence translates to ~4 (2–6) additional stillbirths per 10,000 births for each 1°C increase.

CONCLUSIONS: Extremes of local ambient temperature may have chronic and acute effects on stillbirth risk, even in temperate zones. Temperature-related effects on pregnancy outcomes merit additional investigation. https://doi.org/10.1289/EHP945

Background

Climate change is considered the biggest global health threat of the 21st century by the World Health Organization (Godlee 2014). However, research on climate change and public health is still limited. With global warming, not only is ambient temperature expected to increase, but the frequency and severity of extreme hot weather events is also predicted to increase (IPCC 2013). Extreme ambient temperatures may affect health through several potential mechanisms. When ambient temperature reaches a critical level, thermoregulation may become compromised, and body temperature slowly increases or decreases. At the molecular level, extreme temperatures may lead to increased systemic inflammatory responses, cell permeability, and release of endotoxins (Becker and Stewart 2011). These responses may ultimately affect cell function and survival (Pease et al. 2009). At the population level, extreme ambient temperatures have been linked to adverse health outcomes, including mortality (Guo et al. 2014), cardiovascular events (Lian et al. 2015), and many other adverse health outcomes (Sarofim et al. 2016), such as birth defects (Van Zutphen et al. 2012) and pneumonia (Qiu et al. 2016). Although maternal hot-tub use during pregnancy has been associated with birth defects and miscarriage risk (Chambers 2006), evidence for adverse pregnancy outcomes associated with extreme ambient temperature exposure during pregnancy is limited (Gamble et al. 2016).

Stillbirth is an important and preventable global concern (Chou et al. 2015) with a prevalence of up to 3% in some regions of the world (Stanton et al. 2006), yet this research area receives low priority on the global health agenda (Qureshi et al. 2015). Some known contributors to stillbirth risk include genetics, childbirth complications, pregnancy complications (e.g., preeclampsia), fetal growth restriction, and congenital abnormalities (Flenady et al. 2011; Gardosi et al. 2013). Environmental factors such as ambient temperature have been rarely studied, although increased stillbirth risk reported for colder temperatures in Sweden has been investigated (Bruckner et al. 2014); higher temperatures in Australia (Strand et al. 2012), the United States (U.S.) (Basu et al. 2016), and Canada (Auger et al. 2016) also have been studied.

We had two purposes for this study. First, we aimed to determine the associations between acute and chronic exposures to temperature extremes (e.g., cold and hot relative to usual environment) and stillbirth risk in a large contemporary U.S. cohort of pregnant women. Second, we estimated the excess number of stillbirths potentially attributable to extreme temperatures in the United States.

Methods

Data and Study Population

We used data from the Air Quality and Reproductive Health study, which linked meteorological data from the Weather Research and Forecasting (WRF) model to the Consortium on Safe Labor Study (CSL) in 2013. As described elsewhere (Zhang et al. 2010), CSL was an observational cohort study which aimed to study labor management. CSL included 228,438 deliveries at $\geq$23 weeks of gestation from 12 clinical centers (15 hospital referral regions) across the U.S. from 2002 to 2008 (Figure 1). Data on maternal demographicsand medical history, as well as labor and delivery, obstetric, and neonatal outcomes were extracted from electronic delivery records and supplemented with

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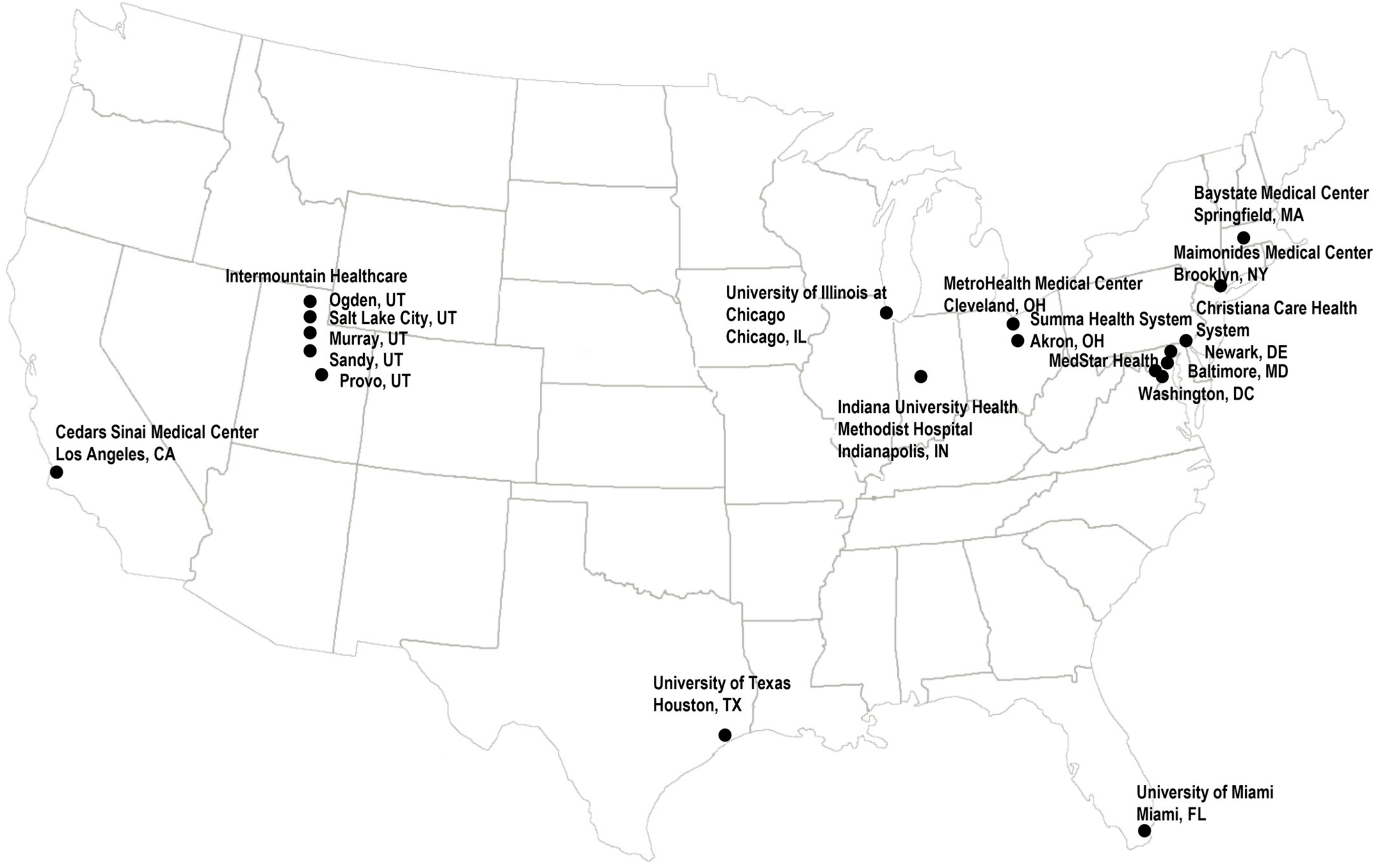

Figure 1. Locations of study sites. Adapted from Mendola P, Wallace M, Hwang SH, Liu D, Robledo C, Männistö T, et al. Preterm birth and air pollution: Critical windows of exposure for women with asthma, *J Aller Clin Immunol* 138:432–440e5.

International Classification of Diseases, 9th Revision (ICD-9) codes in the hospital discharge summaries (WHO 1998). After excluding multifetal pregnancies ($n = 5,053$) and those pregnancies without exposure information ($n = 10$), a total of 223,375 singleton births were available for analysis. The study was approved by institutional review boards from all participating centers. Informed consent was not required because data were rendered anonymous.

Exposure Assessment

Due to the anonymity of the CSL data, 15 distinct hospital-referral regions (415–312,644 km^2) were used as a proxy for maternal residence and local mobility. Hourly temperature data were obtained from the WRF model v3.2.1 at a (12×12)-km resolution, and averaged across each hospital referral region. WRF is a next-generation weather prediction system used by many governmental, research, and weather-forecasting entities to predict metrological parameters at any given place or time while accounting for small spatial variability. A description of the WRF modeling approach and its performance has been reported elsewhere (Zhang H et al. 2014).

For chronic exposure, we obtained average ambient temperature over three-month preconception [91 d prior to estimated last menstrual period (eLMP)], first trimester (eLMP to 13 weeks), second trimester (14–28 wk), and the whole pregnancy (eLMP to date of delivery) for each woman. Third trimester was not assessed because most of the stillbirths ($n = 756$ of 992) were delivered before 37 wk. Because deviation from the normal environment is what likely drives temperature-related risk (Watts et al. 2015), we categorized our temperature exposure using local temperature distributions at each study site for each pregnancy window. This categorization allows us to account for regional acclimation, by varying the cut points for hot and cold extremes to specific geographic areas. For each of the 12 sites, we defined cut points based on the temperature distribution among participants for each exposure window: cold (<10th percentile), hot (>90th percentile), and mild (10th–90th percentile). In other words, a woman's exposure (cold, hot, or mild) during a specific exposure window was determined by the window-specific temperature distribution among all women from her site.

To assess acute exposure, average temperature in the week preceding a stillbirth delivery was compared to two control periods for the same subject in a case-crossover analysis. To control for time-trend bias, we used a symmetric bidirectional method to select the control periods: the second week after delivery and the period two weeks before delivery (Bateson and Schwartz 1999). The week preceding delivery was designated as the hazard period because the literature on acute perinatal health effects of ambient temperature shows meaningful associations within this time window (Basu et al. 2010).

Outcome and Covariate Assessment

Stillbirth was defined as any fetal death ≥ 23 wk of gestation reported in electronic medical records supplemented with ICD-9 codes in discharge summaries. The date of delivery was used as a proxy for event time. Due to potential differences in etiology between antepartum and intrapartum stillbirth, we also stratified our analyses by type of stillbirth.

In addition to temperature, we also obtained relative humidity predicted from WRF; and particulate matter with diameter

<2.5 microns ($PM_{2.5}$) and ozone predicted from modified Community Multiscale Air Quality models (CMAQ) (Chen et al. 2014). In brief, estimates from CMAQ were based on inputs from emissions, meteorology, photochemical properties of pollutants, and population density; estimates were fused to observed monitor data using inverse distance weighting. These variables were aggregated over the same windows as temperature. Other covariates included infant sex, maternal age, race, marital status, parity, prepregnancy body mass index (BMI), insurance, hypertensive disorders of pregnancy, season of conception, and clinical site—all of which were obtained from medical records.

Statistical Analysis

We determined chronic and acute associations between ambient temperature and stillbirth using two approaches. For chronic exposure, separate logistic regression models were used to determine the odds of stillbirth associated with relative cold or hot exposure in comparison with mild exposure during the preconception period, first trimester, second trimester, and the whole pregnancy for the entire cohort. For the second trimester exposure, we restricted our analyses to 664 stillbirths and 220,345 live births with a completed second trimester. Models were adjusted for infant sex, maternal age, race, marital status, parity, prepregnancy BMI, insurance, hypertensive disorders of pregnancy, site, humidity, $PM_{2.5}$, and ozone. All covariates except environmental exposures were treated as categorical variables. We also adjusted for season of conception (spring, summer, fall, winter) to account for seasonal effects. A total of 19,210 (8.6%) women had more than one singleton delivery during the study period, so we used robust standard errors from generalized estimating equations to adjust for the clustering effects from repeated pregnancies among the same woman. Missing data for BMI (41% among stillbirths), infant sex (19%), and insurance (21%) were imputed using multiple imputations with 10 iterations that used variables hypothesized to be related to lack of data, including maternal age, race, marital status, insurance, site, parity, hypertensive disorders of pregnancy, gestational age, and season of conception. Missing data for other variables were retained in analyses as their own category.

The case-crossover analyses for acute exposures were separated for stillbirths delivered during the warm (May–September) and cold (October–April) season. Because the temperature difference between a hazard period and control period is likely to be small, and a quadratic term was not statistically significant, we included temperature as a continuous exposure to preserve more information on the temperature change. Conditional logistic regression estimated the odds of stillbirth associated with each °C increase in temperature during the week preceding delivery after adjustment for relative humidity, $PM_{2.5}$, and ozone. We restricted this analysis to only the first stillbirth case for each woman in the cohort.

We also calculated the population attributable fraction (PAF) associated with exposures to relative cold or hot temperature in our chronic exposure (cohort) analysis using the following formula (Rockhill et al. 1998):

$$PAF = pd_i\left(\frac{OR_i - 1}{OR_i}\right)$$

where pd_i is the proportion of exposed case (to hot or cold), OR_i is the adjusted OR of the association between exposure and stillbirth, and i is the level of exposure (hot or cold). PAF can be interpreted as the proportion of cases that could have been averted if women from the cold or hot group in our cohort were in the mild group. For our acute exposure (case-crossover) analysis, we calculated the attributable risk (AR) to estimate the number of excess cases per 10,000 births associated with 1°C increase in temperature using the following formula:

$$AR = I_e - I_u$$

where I_e stands for the incidence among the exposed, and I_u stands for background incidence. I_e was calculated as the background incidence I_u times the OR (which approximates the relative risk since stillbirth is rare) for 1°C increase in temperature. We used two measures for I_u: our study-specific background incidence (0.44%), and the U.S. background incidence of stillbirths from 2002–2008 (0.62%), based on the National Vital Statistics Report (MacDorman and Gregory 2015).

Additional Analysis

To ensure that length of pregnancy did not impact our chronic exposures (i.e., stillbirths generally have a shorter gestation period than do their counterparts), we did an additional analysis using a case–control analysis matched on gestational age and study site. Specifically, for each stillbirth at gestational week x, we randomly selected four live births at gestational week $\geq x$ from the same site, and repeated the same method using conditional logistic regression adjusting for all covariates except site (matched variable) and air pollutants given no evidence of effects in main analyses. For this analysis, whole-pregnancy length for controls was truncated to the same length as cases. For example, a stillbirth case at wk 32 was compared to four ongoing pregnancies during this week truncated to 32 wk of exposure.

All data analyses were performed using PROC GENMOD and PROC PHREG in SAS 9.4 (Cary, NC). p-Values <0.05 were considered statistically significant.

Results

The data included a total of 992 stillbirths (0.44%). Stillbirths were more common among women at the extremes of maternal age (<20 or ≥ 35 years old), and among women who were black, not married, had hypertensive disorders of pregnancy, or were nulliparous (Table 1). Stillbirths were less common among women with normal BMI and among those women who had private insurance.

Table S1 presents the distribution of extreme ambient temperature by stillbirth outcome. In general, no differences in risk were found for cold/hot exposure during the preconception period or first trimester. However, prevalence of exposure to extreme cold (24.9% vs. 9.9%) or hot (24.0% vs. 9.9%) temperature during the whole pregnancy was significantly higher among stillbirths compared to nonstillbirths. The temperature during the week preceding delivery for cases included in this cohort was slightly higher (21.2 vs. 20.8°C) than two weeks before and after during the warm season (Table S1). The distribution of absolute temperature (e.g., 10th and 90th percentiles) by site that was used to define extreme hot and cold exposure in the cohort analysis is presented in Table S2. Temperature varied greatly by site. Note that the definition of hot and cold were different across sites. For example, cold was defined as <5.0°C for women from Chicago, IL, but <19.2°C for women in Texas (Table S2).

Chronic Exposure Analysis

In comparison with women in the mild local temperature range (10th–90th percentile), those exposed to site-specific relative cold and hot temperatures during the whole pregnancy had an increased risk of stillbirth after adjustment for potential confounders and air pollutants (cold adjusted OR = 4.75; 95% CI: 3.95, 5.75; hot adjusted OR = 3.71; 95% CI: 3.07, 4.47 (Table 2). Exposures

Table 1. Characteristics of singleton births in the consortium on safe labor, 2002–2008 ($n = 223{,}375$).

	Stillbirth		No stillbirth		
Characteristics	*n*	%	*n*	%	*p*-value[c]
Total	992	100	222,383	100	
Infant sex[a]					
Female	453	45.7	108,666	48.9	<.0001
Male	469	47.3	113,689	51.1	
Ambiguous	70	7.1	28	0.01	
Maternal age					
<20	121	12.2	20,574	9.3	0.8437
20–24	248	25.0	56,333	25.3	
25–29	230	23.2	61,982	27.9	
30–34	198	20.0	49,947	22.5	
≥35	193	19.5	33,242	15.0	
Unknown	2	0.2	305	0.1	
Race/ethnicity					
NH-white	325	32.8	110,216	49.6	<.0001
NH-black	338	34.1	49,917	22.5	
Hispanic	183	18.5	38,628	17.4	
Other	58	5.9	14,347	6.5	
Unknown	88	8.9	9,275	4.2	
Marital status					
Married	447	45.1	130,728	58.8	<.0001
Not married	464	46.8	84,530	38.0	
Unknown	81	8.2	7,125	3.2	
Parity					
0	444	44.8	88,580	39.8	0.1567
1	238	24.0	68,151	30.7	
≥2	310	31.3	65,652	29.5	
Prepregnancy BMI[a]					
<18.5	26	2.6	8,950	4.0	<.0001
18.5–24.9	376	37.9	109,598	49.3	
25–29.9	363	36.6	68,053	30.6	
≥30	227	22.9	35,782	16.1	
Hypertensive disorders of pregnancy[b]					
Yes	67	6.8	12,977	5.8	0.2246
No	925	93.3	209,406	94.2	
Insurance type[a]					
Private	501	50.5	136,472	61.4	<.0001
Public	468	47.2	82,664	37.2	
Other	23	2.3	3,247	1.5	
Season of conception					
Spring (March to May)	253	25.5	52,615	23.7	0.0245
Summer (June to August)	214	21.6	57,450	25.8	
Fall (September–November)	257	25.9	61,002	27.4	
Winter (December–February)	268	27.0	51,316	23.1	

Note: BMI, body mass index; NH, non-Hispanic.

[a] Tabulated based on 1 of 10 iterations of multiple imputation.

[b] Defined as at least one of the following: gestational hypertension, preeclampsia, eclampsia, or preeclampsia superimposed on chronic hypertension.

[c] *p*-Values were obtained by generalized estimating equations, accounting for multiple pregnancies of the same woman during the study period.

Table 2. Chronic associations between extreme ambient temperatures and stillbirth among singleton births in the consortium on safe labor, 2002–2008 (cohort analysis).

	Unadjusted		Adjusted[a]		Adjusted[b]	
Exposure windows	OR	95% CI	OR	95% CI	OR	95% CI
Hot						
Preconception	0.91	0.73, 1.13	0.98	0.77, 1.24	1.02	0.80, 1.30
Trimester 1	**0.73**	**0.58, 0.93**	0.83	0.64, 1.07	0.83	0.63, 1.08
Trimester 2[c]	1.13	0.89, 1.44	1.06	0.82, 1.37	1.03	0.78, 1.34
Whole Pregnancy	**3.79**	**3.24, 4.42**	**3.80**	**3.16, 4.56**	**3.71**	**3.07, 4.47**
Cold						
Preconception	**1.25**	**1.03, 1.51**	1.23	0.99, 1.53	1.21	0.97, 1.50
Trimester 1	0.94	0.76, 1.16	0.92	0.72, 1.17	0.91	0.71, 1.16
Trimester 2[c]	0.83	0.63, 1.09	0.90	0.67, 1.20	0.90	0.68, 1.22
Whole Pregnancy	**3.93**	**3.37, 4.58**	**4.54**	**3.78, 5.45**	**4.75**	**3.95, 5.71**

Note: Bold face indicates statistical significance at $p < 0.05$. CI, confidence interval; OR, odds ratio.

[a] Adjusted for clustering resulting from multiple singleton deliveries for the same mother and potential confounders including study site, infant sex, maternal age, race, marital status, parity, prepregnancy BMI, hypertensive disorders of pregnancy, insurance status, humidity, and season of conception.

[b] Additionally adjusted for exposures to particulate matter with diameter <2.5 μm and ozone.

[c] Analyses were based on pregnancies with a completed second trimester (664 stillbirths and 220,345 live births).

during preconception, first trimester, and second trimester were not associated with stillbirth. Similar findings were observed for intrapartum and antepartum stillbirths, but the second trimester analyses for intrapartum stillbirths did not converge due to small sample size (Table S3). Additional analysis using a case-control analysis matched on gestational age and site also produced similar results although the cold temperature results were somewhat attenuated (Table S4). For example, in comparison with mild temperature, exposure to relative cold and hot extremes during the whole-pregnancy was associated with a 2.96, and 4.29-fold increase in odds of stillbirth, respectively (cold: 95% CI: 2.21, 3.96; hot: 95% CI: 3.22, 5.72).

Acute Exposure Analysis

Among the 992 stillbirth cases, 987 were included in the acute exposure analysis after exclusion of a second stillbirth delivery for five women. Of these, 540 stillborn babies were delivered in a cold season, and 447 were delivered in a warm season. Ambient temperature during the week preceding delivery was significantly associated with the risk of stillbirth during a warm season (adjusted OR (aOR) = 1.06; 95% CI: 1.03, 1.09 for 1°C increase) but not during a cold season (aOR = 1.00; 95% CI: 0.98, 1.02 with no protective effect observed for 1°C increase) (Table 3). Restricting the cold season to November–February to ensure consistency during even colder months did not change the results (aOR = 0.99; 95% CI: 0.97, 1.02). When stratified by type of stillbirth, the results were generally consistent, but the confidence intervals were wide for intrapartum stillbirth due to low sample size (Table S5). Additional adjustment for $PM_{2.5}$ and ozone did not change the estimates (not shown).

Attributable Risk

In our cohort, approximately 19% and 17% of the stillbirth cases were potentially attributable to chronic exposures to both cold and hot temperature, respectively. This percentage is equivalent to about 48 excess cases due to chronic exposure to cold and 42 excess cases due to hot temperature in our data (Table 4). When the annual number of stillbirths in the United States is 23,595 (MacDorman and Gregory 2015), this translates to approximately 1,116 (95% CI: 1,057, 1,175) excess cases due to chronic cold exposure, and 1,019 (95% CI: 906, 1,076) excess cases due to chronic hot exposure each year. Stratified analyses by type of stillbirth showed consistent results (Table S6). Using the case-control analysis estimates, the number of excess cases due to chronic exposures to relative extreme cold and hot was approximately 38 and 47, respectively.

In the acute exposure analysis, a 1°C increase in temperature during the week preceding delivery was associated with approximately four excess cases (95% CI: 2.0, 6.0) per 10,000 births during a warm season using the U.S. background incidence as a reference (Table 3). Results by type of stillbirth were consistent (Table S5).

Discussion

In this large, nationwide cohort of U.S. women, we observed strong evidence suggesting that prolonged exposures to both relative cold and hot local temperature extremes that account for regional acclimation were independently associated with a higher

Table 3. Acute association between ambient temperature during the week prior and stillbirth among cases in the consortium on safe labor, 2002–2008 (case-crossover analysis, $n = 987$).

		OR[a]		AR[b]		AR[c]	
Season of delivery	n	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Cold (Oct–Apr)	540	1.00	0.98, 1.02	0	− 1.2, 1.2	0	− 0.9, 0.9
Warm (May–Sept)	447	**1.06**	**1.03, 1.09**	**3.8**	**1.8, 5.8**	**2.7**	**1.3, 4.1**

Note: Bold face indicates statistical significance established at $p < 0.05$; AR, attributable risk; CI, confidence interval; OR, odds ratio.

[a] The ORs for case-crossover models were obtained from conditional logistic regression with robust standard errors where only cases were selected and they act as their own controls. Estimates are for 1°C (2.8°F) increase in ambient temperature adjusted for relative humidity and time invariant confounders.

[b] Calculated using U.S. background rate as I_u; risk is expressed as per 10,000 births.

[c] Calculated using study specific background rate during specific season as I_u; risk is expressed as per 10,000 births.

risk of stillbirth. These associations were consistent after controlling for gestational length using a matched case–control analysis, but we did not observe significantly elevated risks for shorter chronic exposures preconception or in the first or second trimester. In our acute exposure analysis using a case-crossover design, we also found acute associations with higher absolute temperature during the week preceding delivery during the warm season. However, no evidence of an acute association during the cold season was found. Taken together, these findings suggest that both relative extremes of temperature are associated with stillbirth, but only hot temperature appears to have an observable acute association with stillbirth risk.

In this first multi-city study of stillbirth and temperature, we find results similar to the four existing studies that focus specifically on the association between ambient temperature and stillbirth in a single location. Using data from Brisbane, Australia, from 2005–2009, Strand et al. (2012) found temperature increases during the previous 4 weeks and last week of pregnancy were associated with stillbirth, especially at early gestational ages. Bruckner et al. (2014) with historic data from Uppsala, Sweden, from 1915–1929, found that a 1°C increase in average temperature during the whole pregnancy was associated with an 8% decrease in risk, suggesting an adverse chronic effect for cold exposure. This finding is consistent with our cohort analysis, which also suggested a strong association between whole-pregnancy exposure to cold temperature and stillbirth. Although the study in Sweden also implied that hot temperature is protective, which is contradictory to our findings, our U.S. data has a broader range of temperature and more spatial variation in comparison with the city of Uppsala. Our acute effect results are also consistent with a recent California-based case-crossover report by Basu et al. (2016) that found that while there was no association between temperature and stillbirth during the cold season, a 10.4% increase in stillbirth risk was associated with each 10°F increase in apparent temperature during the week preceding delivery (lags 2–6). Similar findings were also observed in Quebec, Canada, in a case-crossover analysis in which outdoor temperature of 28°C during the day before death was associated with a 16% increase in risk of term stillbirth in comparison with 20°C (Auger et al. 2016).

Table 4. PAF associated with chronic exposure to extreme ambient temperature among singleton births in the consortium on safe labor, 2002–2008.

Whole-pregnancy temperature	PAF[a]	95% CI	Total cases	Excess cases	95% CI
Cold	**0.19**	**0.18, 0.20**	247	**48.0**	**45.2, 50.2**
Hot	**0.17**	**0.16, 0.19**	238	**42.1**	**39.0, 44.6**

Note: Bold face indicates statistical significance established at $p < 0.05$; CI, confidence interval; PAF, population attributable fraction.

[a] PAF was calculated using the following formula: $\text{PAF} = \text{pd}[(\text{OR} - 1)/\text{OR}]$, expressed as a proportion.

Despite the strong chronic association, we did not observe an acute association with cold temperature during cold season in our acute exposure analysis. This lack of acute association is consistent with the literature pertaining to respiratory and cardiovascular outcomes, which generally suggests that people are more likely to intervene when it is cold than when it is hot (Braga et al. 2002). It can also be explained by the fact that people may be more likely to intervene behaviorally during cold temperatures in comparison with warm temperatures. In a survey of public perception and response to heat warnings across four large U.S. cities, despite heat-warning coverage of 90%, most participants reported that they merely avoided the outdoors, and over a third of participants reported that air conditioning (AC)-related energy cost was an issue (Sheridan 2007). In addition, the Residential Energy Consumption Survey estimated that during 2009, about 15% of all households did not have AC (U.S. Energy Information Administration 2011a) vs. 3.5% (U.S. Energy Information Administration 2011b) who lacked heating equipment. These findings may suggest that pregnant women may be more likely to use a heater during cold season than to use AC during warm seasons in a temperate zone, which may explain the consistent acute association between temperatures during warm season and the lack thereof during cold seasons.

Existing studies of temperature-related health effects generally assess acute risk after an extreme event (e.g., heat wave) or recent exposure, leaving the chronic effects relatively to be researched less often (McGeehin and Mirabelli 2001). In addition, animal experiments and human observational studies do not converge on a critical window for temperature-related risk during pregnancy. We found an association between exposure to whole-pregnancy temperature extremes and stillbirth, but not for preconception, first trimester, or second trimester exposures. These novel findings suggest that chronic exposure to extreme temperature throughout pregnancy maybe more important than previously thought, but the existence of a critical window of chronic exposure is not clear, and we encourage further investigation of this topic.

Global temperature has been reported to be increasing since the beginning of the 20th century; the rate of increase has been faster during the last 50 years (NOAA 2011). In addition, U.S. temperature has risen more than 1°C (2°F) over the past 50 years and is projected to continue to increase (Karl et al. 2009). This increase means that the frequency, duration, and severity of extreme heat events will become less favorable for health. If a 1°C increase is associated with an excess of 2–6 stillbirths per 10,000 births in the United States, this increase could translate to a large number of temperature-related stillbirths (362–1,087) during the warm season each year, given the current annual number of births of about 4 million (Martin et al. 2015) with 45.3% born during warm season. Similarly, the 17% of cases of stillbirth attributed to chronic exposure to hot temperature may increase as the temperature distribution shifts to the right. In the context of global warming, it is still important to recognize the importance of exposure to cold temperatures, given the strong association suggested by our findings.

Our findings are biologically plausible. Extreme temperatures can lead to compromised endothelial functions as well as rheological changes, both of which may affect blood pressure and blood viscosity (Garcia-Trabanino et al. 2015; Zhang X et al. 2014). These responses may ultimately alter the maternal–fetal exchange and disturb fetal growth and survival (Slama et al. 2008), leading to an increased risk of stillbirth, specifically antepartum. Some studies also suggest that hyperthermia may also disrupt the normal sequence of gene activity during organogenesis (Edwards et al. 1995; Edwards 2006), leading to fetal death or stillbirth. We recognize that the etiologies for intrapartum and antepartum stillbirths are different. Specifically, the causes of intrapartum death are likely related to complications of delivery (Walsh et al. 2008). Thus, our similar effect estimates for intrapartum and antepartum deaths suggest that some risks may be related to upstream complications, although further studies are needed to confirm this possibility because we lack statistical power to examine intrapartum deaths in more detail, and the cause of death is unavailable in our anonymous data.

Several limitations should be noted. Approximately 30% of women move during the course of pregnancy (Bell and Belanger 2012), but our analyses assumed that there was no residential mobility during the exposure periods, which may have caused some degree of exposure misclassification. However, it is unlikely that many women moved during the few weeks covered in the case-crossover analysis period, and even when women do move during pregnancy, most move within a short distance, often <10 km (Bell and Belanger 2012), so our use of hospital referral region as a proxy for residence and local mobility may have helped mitigate this potential misclassification; however the varying region sizes may still be a limitation. The lack of daily-activity pattern data (e.g., indoor or outdoor activities and/or AC/heater use) may also be another source of potential misclassification. However, we do not expect this factor to be differential based on outcome status, which may have biased our estimates towards the null. Due to the large sample size and geographic coverage, we used model-based estimates instead of observed values at sparsely located monitoring stations. Model evaluation showed mean bias within recommended performance criteria (Zhang H et al. 2014). In addition, we intentionally chose our control periods close to the case period to account for potential seasonal effects, but this choice may have biased our results towards the null due to potential overmatching.

For antepartum stillbirths, the actual event time before the date of delivery was unknown and we used the delivery date as proxy for time of event. This may have caused some error in the determination of acute exposure window. Given most antepartum stillbirths are delivered within 48 h after diagnosis (Gardosi et al. 1998), the use of average temperature during week preceding delivery is a reasonable proxy in the acute exposure case-crossover analysis. For the chronic exposure models, the difference in average temperature exposure for the whole pregnancy (i.e., to event time or proxy delivery) is likely to be negligible. In addition, we found consistent results when we conducted a case-control analysis that matched the length of gestation in a subgroup of the cohort. Nevertheless, we caution readers that the magnitude of associations observed for our whole-pregnancy exposure is larger than expected given the limited literature on this topic and we encourage further investigation of these associations. Missing data and potential unmeasured factors such as changes in the prevalence of infection and availability of local food sources have affected our chronic exposure findings, but we are reassured that our acute exposure findings were not due to confounding by either measured or unmeasured factors since the case-crossover design addresses these issues. However, it is possible that potential lag effects longer than one week may have been missed. In addition, due to the small number of stillbirths each month, we were only able to adjust for season. Since a large proportion of our stillbirths did not have a third trimester, we were not able to reasonably assess the effects for this window separately in the cohort analyses; however we considered the acute exposure case-crossover analysis as a way to assess acute effects. Furthermore, we were only able to address stillbirths at or after 23 wk of gestation because data abstraction for the CSL, designed to study labor management, was limited to those deliveries. Stillbirths prior to 23 wk might have similar etiologic patterns as other early deaths, but this avenue remains to be explored. Lastly, the literature on population-level measures of morbidity and mortality suggests that the association between temperature and health outcomes may vary by location. This association may or may not hold true for stillbirth, but our site-specific number of stillbirth cases was too low to allow investigation of such hypothesis, although we have adjusted for site in our analyses.

This is the first study to report both chronic and acute associations between ambient temperature and stillbirth in a contemporary nationwide U.S. obstetric cohort. Detailed medical records allowed us to adjust for important clinical confounders. The study also includes a large sample of women across the United States, which contributes to the generalizability of our findings. The acute exposure case-crossover analysis also, by design, allowed us to adjust for potential time-invariant confounders including unmeasured factors that might predispose women to have a stillbirth. Lastly, the use of site-specific temperature distributions to define relative high and low extreme temperatures allowed us to account for regional acclimation while the acute specific temperature differences in risk were evaluated using a case-crossover model.

Conclusions

We found evidence of association between acute and chronic exposures to relative extreme ambient temperature and stillbirth risk. Whole-pregnancy exposures to extreme hot and cold relative to usual environment appears to increase the stillbirth risk substantially with adjusted odds three to five times higher for temperature extremes in comparison with mild temperature. A 1°C increase during the week preceding delivery during the warm season was associated with 6% increase in risk that translates to about four additional stillbirths per 10,000 births. Given the concerns related to global warming and the shift in population-level risk factors, these potential risks highlight the need for awareness among health professionals, policy makers, and women of reproductive age; effective intervention to minimize exposure of pregnant women to extreme temperature; and more research effort on the potential effects of extreme temperatures on stillbirth and other adverse birth outcomes.

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