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# Ambient temperature and air quality in relation to small for gestational age and term low birthweight

Sandie Ha[a], Yeyi Zhu[a], Danping Liu[b], Seth Sherman[c], Pauline Mendola[a,*]

[a] Epidemiology Branch, Division of Intramural Population Health Research, NICHD, Bethesda, MD, USA
[b] Biostatistics and Bioinformatics Branch, Division of Intramural Population Health Research, NICHD, Bethesda, MD, USA
[c] The Emmes Corporation, Rockville, MD, 20850 USA

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ABSTRACT

*Background:* Exposures to extreme ambient temperature and air pollution are linked to adverse birth outcomes, but the associations with small for gestational age (SGA) and term low birthweight (tLBW) are unclear. We aimed to investigate exposures to site-specific temperature extremes and selected criteria air pollutants in relation to SGA and tLBW.

*Methods:* We linked medical records of 220,572 singleton births (2002–2008) from 12 US sites to local temperature estimated by the Weather Research and Forecasting model, and air pollution estimated by modified Community Multiscale Air Quality models. Exposures to hot ( > 95th percentile) and cold ( < 5th percentile) were defined using site-specific distributions of daily temperature over three-month preconception, each trimester, and whole-pregnancy. Average concentrations of five criteria air pollutants and six fine particulate matter constituents were also calculated for these pregnancy windows. Poisson regression with generalized estimating equations calculated the relative risks (RR) and 95% confidence intervals for SGA (weight < 10th percentile conditional on gestational age and sex) and tLBW (≥37 weeks and < 2500 g) associated with an interquartile range increment of air pollutants, and cold or hot compared to mild (5–95th percentile) temperature. Models were adjusted for maternal demographics, lifestyle, and clinical factors, season, and site.

*Results:* Compared to mild temperature, cold exposure during trimester 2 [RR: 1.21 (1.05–1.38)], trimester 3 [RR: 1.18 (1.03–1.36)], and whole-pregnancy [RR: 2.57 (2.27–2.91)]; and hot exposure during trimester 3 [RR: 1.31 (1.15–1.50)] and whole-pregnancy [RR: 2.49 (2.20–2.83)] increased tLBW risk. No consistent association was observed between temperature and SGA. Air pollutant analyses were generally null but preconception elemental carbon was associated with a 4% increase in SGA while dust particles increased tLBW by 10%. Particulate matter ≤10 µm in the second trimester and whole pregnancy also appeared related to tLBW.

*Conclusions:* Our findings suggest prenatal exposures to extreme ambient temperature relative to usual environment may increase tLBW risk. Given concerns related to climate change, these findings merit further investigation.

## 1. Introduction

Fetal growth restriction is a relatively common birth outcome that is due to a variety of conditions resulting in a fetus being unable to achieve its potential size (Stan et al., 2013). Small for gestational age (SGA), and term low birthweight (tLBW), two common indicators of fetal growth restriction, affects about 10% and 2% of live births in the US, respectively (ACOG, 2013; CDC, 2016). Fetal growth restriction is responsible for many adverse perinatal and childhood outcomes including perinatal mortality; complications related to immunologic, respiratory, and metabolic function; and impaired motor and neurobehavioral development during childhood (Arcangeli et al., 2012; Pallotto and Kilbride, 2006). The etiology of growth restriction may be influenced by many factors including exposure to environmental risk factors (Stan et al., 2013).

Environmental risk factors, such as prenatal exposure to tobacco smoke, have received considerable attention in the literature, and have been shown to have a deleterious impact on fetal growth (Janisse et al., 2014; Prabhu et al., 2010; Reeves and Bernstein, 2008). However, other potentially harmful and ubiquitous prenatal exposures, such as

* Correspondence to: Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, 6710B Rockledge Drive Room 3119, Bethesda, MD 20817, USA.
*E-mail address:* pauline.mendola@nih.gov (P. Mendola).

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extreme ambient temperature have been relatively understudied with respect to their potential effects on fetal outcomes. Prenatal exposures to air pollution in relation to fetal growth have received more attention, but findings are generally inconsistent across pollutants and studies partially due to heterogeneity in study design and exposure distribution (Jacobs et al., 2016; Stieb et al., 2012). Previous research suggests that exposures to extreme temperature as well as high air pollution may increase oxidative stress and systemic inflammation in the general population (Ghio et al., 2012; Kahle et al., 2015; Moller et al., 2014). Although mechanistic studies in pregnant women are still scarce in relation to these environmental risk factors, exposures during pregnancy may decrease uterine blood flow, placental fetal exchange and ultimately slow fetal growth (Biberoglu et al., 2016; Browne et al., 2015; Prada and Tsang, 1998; Slama et al., 2008). Consistent with this potential biologic mechanism, extreme ambient temperature and air pollution exposure have been linked to adverse birth outcomes such as low birthweight and preterm birth, but their association with SGA and tLBW— is still unclear given the scarcity of literature on this topic and the inconsistent findings across pollutants and studies (Auger et al., 2014; Shah and Balkhair, 2011; Strand et al., 2011). This is an important knowledge gap given the expected increase in ambient temperature associated with global warming (Karl et al., 2015), and the increasing concerns due to air pollution emission from anthropogenic sources including transportation and industrial activities (EPA, 2016). We sought to investigate the potential association of extreme ambient temperature, five criteria air pollutants, and six particulate matter constituents with fetal growth restriction, indicated by SGA and tLBW, in a large nationwide US obstetric cohort.

## 2. Methods

### 2.1. Participants

We used data from the Air Quality and Reproductive Health Study, which linked local air pollution and meteorological data to participants in the Consortium on Safe Labor (CSL) in 2013. A detailed description of the CSL study design has been published elsewhere (Zhang et al., 2010). Briefly, CSL was an observational cohort study that collected detailed medical records from 228,438 deliveries at ≥23 weeks of gestation (2002–2008) from 12 clinical sites (15 hospital referral regions, 19 hospitals) across the US (eFig. 1). Maternal and infant data were abstracted from electronic delivery records and/or discharge summaries. After excluding multiple births (n=5053) and those missing exposure information (n=10), birthweight (n=2485), or infant sex (n=318), 220,572 births remained in the analyses. The CSL was approved by Institutional Review Boards from all participating clinical centers. Since data were de-identified, informed consent was not required.

### 2.2. Exposure assessment

#### 2.2.1. Temperature

Due to the anonymity of CSL data, we did not have residential address to perform detailed interpolation of exposures. Alternatively, we estimated exposures for each woman based on the average concentrations in the 15 non-overlapping delivery hospital referral regions (area range: 415–312,644 $km^2$) as a proxy for maternal residence and local mobility (i.e. short range spatial movements associated with daily activities such as work and errands). In other words, a woman's exposure percentile during pregnancy was assigned based on the average temperature distribution within her hospital referral region. Hourly ambient temperature and relative humidity were obtained using the Weather Research and Forecasting Model (WRF). Modeling approach of the WRF and model evaluation has been described elsewhere (Chen et al., 2014; Zhang et al., 2014). Briefly, WRF is a next-generation weather prediction system designed for atmospheric research and forecasting, developed by research, governmental, and academic entities. Performance statistics comparing with observed records suggested that temperature estimates were acceptable and in agreement with other WRF modeling studies (Chen et al., 2014; Zhang et al., 2014). For each pregnancy, daily data for temperature and relative humidity were averaged across several potentially critical windows before and during pregnancy: three months preconception (91 days before last estimated menstrual period (eLMP)), first trimester (eLMP through 13 weeks), second trimester (weeks 14–28), third trimester (weeks 29 to delivery), and whole pregnancy (eLMP through delivery). eLMP was back calculated from date of delivery using best clinical estimate of gestational age recorded in delivery records. In obstetrical practice in the U.S., the best clinical estimate of gestational age is typically derived from either last menstrual period (LMP) or ultrasound measurements if they differ from the LMP based on specific criteria. Since temperature-related health risk is likely driven by temperature deviation from the usual environment, we accounted for regional acclimatization by categorizing our temperature exposure based on the local area temperature distributions for each of the perinatal time windows. Specifically, for each clinical site, we evaluated the temperature distributions for all perinatal time windows (preconception, trimesters and whole pregnancy) among all women from that site. For each site and time window, we defined cold exposure as the bottom ( < 5th percentile), hot exposure as the top ( > 95th percentile), and mild exposure as the middle (5–95th percentile) of that site- and window-specific temperature distribution (three-level exposure variable). In other words, cold/hot cut-offs varied for women from different sites to account for acclimatization.

#### 2.2.2. Selected criteria air pollutants

Hourly concentrations were calculated for five criteria air pollutants including carbon monoxide (CO), nitrogen oxides ($NO_x$), ozone ($O_3$), particulate matter with diameter $< 2.5$ or $< 10$ µm ($PM_{2.5}$ or $PM_{10}$), and sulfur dioxide ($SO_2$); and six $PM_{2.5}$ constituents including elemental carbon, organic compound, ammonium ions, sulfate particles, nitrate particles, and dust particles. These pollutants were assessed using a modified Community Multiscale Air Quality (CMAQ) model (v4.7.1), which is a three-dimensional multipollutant air quality model developed by the US Environmental Protection Agency (Foley et al., 2010). A detailed description and model evaluation have been published (Chen et al., 2014). Briefly, CMAQ predicts air pollution concentrations at any location/ time using inputs from several sources including local emission from the National Emission Inventory, local weather from the WRF, and photochemical properties of the pollutants. Outputs for criteria air pollutant concentrations were corrected for measurement errors between modelled and observed levels at local air monitors using inverse distance weighting (IDW). IDW is a commonly used technique to interpolate to unknown points based on measured data at known points. We corrected our model estimates to match the monitor at the point of measurement and then reduce the correction coefficient as the distance gets further away. Data were also weighted by population density to improve accuracy. Model evaluation showed that these methods significantly improved model performance for all pollutants (Chen et al., 2014; Zhang et al., 2014). Since $PM_{2.5}$ constituents were rarely monitored by air quality monitors, only modelled concentrations were used. The concentration of each pollutant was averaged over the same exposure windows as previously described for temperature.

#### 2.2.3. Outcome and covariates

Variables related to the main outcomes and a set of *a priori* covariates were obtained from electronic delivery records or discharge summaries for each participant. SGA was defined as any infant who weighed < 10th percentile of infants with the same gestational age and sex using an internal reference (Mannisto et al., 2013). tLBW was defined as any infant born ≥37 weeks with a birthweight < 2500 g. The