Cold ambient temperature *in utero* and birth outcomes in Uppsala, Sweden, 1915 to 1929

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Abstract

The literature reports adverse birth outcomes following ambient heat. Less work focuses on birth outcomes following cold, and we know of no studies of cold that examine stillbirth. We test the relation between cold ambient temperature during pregnancy in Sweden and four outcomes: stillbirth, preterm, birthweight for gestational age, and birth length for gestational age (a measure of leanness). We examine births from 1915 to 1929 in Uppsala, Sweden which—unlike most societies today—experienced sub-standard indoor-heating and fewer amenities to provide shelter from cold. We retrieved data on almost 14,000 deliveries from the Uppsala Birth Cohort Study. We linked a validated, daily ambient temperature series to all pregnancies. We applied Cox proportional hazards for time-to-event outcomes (stillbirth and preterm) and linear regression for birthweight and birth length. Month indicator variables controlled for confounding by season of conception. The risk of stillbirth (but not preterm) rises as ambient temperature during pregnancy falls. Infant birth length for gestational age declines with lower temperatures. We observe no relation between cold and birthweight for gestational age. In historical Sweden, cold temperatures during pregnancy increase the risk of stillbirth and infant leanness. Our work holds relevance to maternal-fetal biology as well as to contemporary societies (e.g., indigenous Arctic populations) with limited resources to mitigate the adverse consequences of cold.

Forecasts of rising temperatures as well as more frequent and severe temperature oscillations have raised interest in identifying whether, and to what extent, human health responds to climate change.[1,2] A recent review by Strand[3] summarized health research concerned with temperature during the sensitive period of pregnancy. Strand's review and other reports[4,5,6] provide suggestive evidence that maternal sensitivity to temperatures may perturb fetal development and increase the risk of adverse birth outcomes.

Whereas most work in this field examines birth outcomes following heat stress or warm temperatures in tropical and temperate climates[3], scant work studies extreme cold despite mammalian research that indicates a physiological reactivity to cold.[7,8] We address this gap in the literature and employ rigorous methodology to test the relation between cold ambient temperature *in utero* and perinatal outcomes in Sweden—one of the most populous societies ever forced to adapt to extreme cold.

Ambient cold may perturb fetal development via direct and indirect mechanisms. Although fetal temperature remains relatively constant despite fluctuations in ambient temperature, thermoregulatory responses to cold may include increased blood viscosity and vascular constriction.[9,10] Maternal responses such as these may limit blood flow to the placenta, thereby reducing fetal growth.[11] Experimental mammalian research, moreover, indicates elevated stress hormone levels following cold challenge.[7,8] Maternal-fetal transmission of these hormones may hasten the timing of parturition.[12,13]

We suspect that less research focuses on cold temperatures during pregnancy based on the belief, articulated by Wells, that ". . . cold stress is generally avoidable by cultural means.[14]" This assertion assumes that efficient indoor-heating systems, modern housing insulation, and weather forecasts that warn of cold spells all serve to shelter societies from ambient cold. An "ideal" test, therefore, of biological cold sensitivity during pregnancy would involve a population that routinely encounters cold but enjoys fewer of the modern-day amenities to shelter themselves from cold. Consistent with the logic above, we examine births from 1915 to 1929 in an academic hospital in Uppsala, Sweden. The dataset, which serves as the basis for over 40 peer-reviewed publications,[15] includes high-quality information on four birth outcomes: stillbirth, gestational age at birth, birth weight, and birth length. Using ambient daily temperature measurements that are linked to this dataset, we test the whether exposure to cold *in utero* precedes an increased risk of still and preterm birth but reduces birth weight and length.

We contribute to the literature in three ways. First, we provide the first test, to our knowledge, of the relation between cold temperature and stillbirth in a society that routinely confronts cold. Second, our approach improves upon earlier work in that we remove confounding by factors related to month of conception (e.g., fertility timing, respiratory infections) and employ rigorous hazard analyses for time-to-event outcomes (e.g., preterm birth, stillbirth). Third, we examine birth outcomes in an early 20th century population with relatively fewer amenities to provide shelter from cold.

Methods

Data and Variables

We examined birth outcomes among approximately 14,000 births registered at Uppsala Hospital in Sweden from January 1, 1915 to December 31, 1929. These births, referred to as the first generation of the Uppsala Birth Cohort Study (UBCoS), include births (stillbirth and live) registered at Uppsala hospital over the time period. Mothers that delivered in Uppsala hospital appear representative of the city's population of gravid mothers with respect to age, social, and economic characteristics.[16] We refer the reader to the UBCOS website[15] for a detailed description the quality and provenance of UBCoS.

UBCoS contains information on social and demographic variables of the mother as well as several birth characteristics. We identified four perinatal outcomes in the dataset that, consistent with the literature,[3,17,18] may respond to ambient temperatures *in utero*: stillbirth, live birth gestational age, birth weight, and infant length.

A stillbirth was defined as a fetal death irrespective of the duration of pregnancy. The death is indicated by the fact that after expulsion or extraction, the fetus does not breathe or show any other evidence of life. The dataset includes only stillbirths at or beyond 24 weeks of gestation. We also retrieved gestational age data on still and live births. Uppsala hospital relied on maternal recall of last menstrual period to derive a clinical estimate of gestational age. We removed implausible values of gestational age using the Alexander correction method[19] which flags subjects that fall outside of the plausible range of birth weight distribution for that gestational age.

Given the distinct etiologies of intrauterine growth restriction and preterm delivery, epidemiologists recommend separate analyses of these outcomes.[20] We derived a birth weight percentile measure that captures intrauterine growth for the infant's particular gestational age at birth. We used standardized, sex-specific birth weight for gestational age tables[21] to assign birth weight percentiles; as a result, we excluded from this analysis records with missing gestational age information. We also restricted the population to pregnancies with an estimated conception date between 24 weeks before the cohort started and 45 weeks before the cohort ended. This restriction removes potential "fixed cohort bias" in birth outcome studies in which pregnancies close to the start date (January 1, 1915) tend to have a longer duration, whereas the pregnancies close to the end date (December 31, 1929) tend to have a shorter duration.[22,23] This process left us with 13,839 births for the preterm analysis.

Previous research indicates that length at birth may respond to environmental stressors *in utero*.[17] We, therefore, explored the relation between cold temperatures and length at birth. UBCoS data include length at birth, measured from crown to heel (rounded to the nearest centimeter).

We retrieved daily instrument-based measurements of surface temperature in Uppsala, Sweden (59°52' N, 17°38' E) from the widely used and publicly available Moberg and Bergstrom dataset.[24,25] These authors calculated daily temperature as the mean of hourly temperatures taken at least four times over each 24 hour period. Researchers have homogenized the data to permit valid comparisons of temperature exposure across time periods. [24,25] We calculated weekly mean temperatures for each pregnancy over the entire gestation. As described below, we used gestational age information to take into account different durations of temperature exposure *in utero*.

Analysis

Researchers note several limitations of using logistic or linear regression models for time-to-event pregnancy outcomes.[4,26] For our tests, preterm delivery and stillbirth represent time-to-event outcomes in which pregnancies of longer duration experience more “opportunities” for preterm or stillbirth delivery. To address the inherent temporal nature of the risk of preterm and stillbirth delivery, for these outcomes we applied a Cox proportional hazards model with gestational age (in weeks) as the time axis. A gestation can pass through each week still *in utero*, born live, or born dead. In this context, stillbirth and live birth represent competing risks. We used weekly temperature as a time-dependent variable by assigning the average temperature over the gestation—from date of conception up to, and including, that current gestational week—to that particular gestational week. For instance, a birth that occurred at week 36 would receive 13 time-varying temperature exposures, one per week of gestation with an “opportunity” of being delivered, beginning at week 24 (i.e., earliest week of delivery in UBCoS data) and ending at the week of parturition (in this example, week 36).

The literature does not converge on a well-defined critical period *in utero* in which gravid mothers may respond to cold.[3] For the non time-to-event outcomes (i.e., birth weight percentile and birth length), we classified exposure to temperature *in utero* as the weekly average temperature over the entire gestation. Temperatures in Uppsala fell below 17° C (the nadir on the J-shaped temperature / mortality relation in Scandinavia[27]) in over 95 percent of all weeks in our test period. We, therefore, posited no heat-related risk of adverse perinatal outcomes and tested a linear relation between cold temperature and our dependent variables. To examine a potential non-linear relation at extreme cold, we further specified the fraction of weeks in gestation spent in the coldest quintile of Uppsala temperatures from 1915 to 1929 (< -.2.24° C). Previous research also employs this quintile approach.[28]

Strong documented seasonal patterns in coital frequency and fertility,[29] especially in Sweden,[30] may affect preterm and stillbirth risk and confound our tests. We, therefore, controlled for seasonal confounding by including a calendar month of conception variable, which we estimate by subtracting gestational age (in days) from the date of birth. Consistent with previous work, we also specified as covariates infant sex, maternal age (<18, 18 to 34yrs , 35+), parity (1^{st}, 2^{nd}, 3^{rd}, 4^{th}, and 5^{th} or higher birth), father's occupation (an measure of social class), and marital status (married vs. non).[31] In the preterm analysis, we right-censored all gestations at the end of the preterm risk period (i.e., 37 completed weeks).

For the non- time-to-event outcomes (i.e., birth weight percentile and length), we specified a linear regression model and similarly controlled for all confounders specified above. In the analysis of birth length, we further adjusted for gestational age and birth weight percentile. Such adjustment yields a measure of leanness in that greater birth length would indicate relative leanness compared to other births at the same gestational age and weight. We chose birth length, rather than the often used ponderal index (kg / m^3) as a measure of leanness, since we specified the numerator of the ponderal index as the dependent variable in a separate analysis.

Results

The analytic sample comprised 13,839 birth records that contained plausible gestational age information. Table 1 describes characteristics of these births. Mean gestational age is 280.1 days, and the prevalence of stillbirth after 24 weeks of gestation is 2.6%. Births at Uppsala hospital include mothers from a broad range of social classes. Figure 1 plots the average temperature for all pregnancies by calendar month of conception. The mean daily temperature during gestation was 5.0°C. As expected, temperature during gestation exhibits strong seasonality. Within each month of conception, moreover, gestational temperature shows variation around its mean. Additional plots of temperature exposure for births of equal gestational duration by conception month indicate much variability, which underscores substantial year-to-year fluctuations in temperature from 1915 to 1929.

Tables 2 through 5 display the main results of our four tests. Maternal characteristics (e.g., age, parity, and marital status) vary with a subset of adverse birth outcomes. In addition, several summer and fall months of conception also predict stillbirth risk as well as birth length.

In the time-to-event analyses, we observe an inverse relation between temperature over gestation and the risk of stillbirth (Table 2: temperature coef: -.080, SE= .039, p=.04). The negatively signed coefficient indicates that colder temperatures during gestation accelerate the risk of stillbirth. To assist the reader with interpreting the coefficient, we estimated the increased hazard ratio associated with a one standard-deviation fall (i.e., 2.38°C) in gestational temperature. Taking the antilog of the coefficient implies a 1.21 fold increased risk of stillbirth statistically attributable to a one standard deviation drop in temperatures. We, however, find no relation between temperature over gestation and preterm birth (Table 3: temperature coef: -.006, SE= .022, p=.77).

As shown in Table 4, birth weight for gestational age does not vary with temperature during gestation (Table 4: temperature coef: -.239, SE= .215, p=.27). By contrast, birth length varies positively with temperature (Table 5 temperature coef: .070, SE=.013, p<.0001). These findings indicate that cold temperatures during gestation may influence fetal growth via length but not weight. For example, the temperature coefficient for birth length implies that a one standard deviation fall in gestational temperature yields a 0.1 cm decrease in birth length.

We then investigated the potential non-linear relation between temperature and our four birth outcomes. We repeated all tests but replaced the key temperature variable with the percent of weeks in gestation exposed to the coldest temperature quintile (< -.2.24° C). The risk of stillbirth varies positively with gestational exposure to the coldest quintile (cold quintile coef: 1.38, SE=.69, p=.04), whereas birth length varies inversely with the coldest quintile (cold quintile coef: -.919, SE=.21, p<.0001). We, however, observe no relation with preterm birth or birth weight for gestational age. The magnitudes of the associations that reach conventional levels of statistical significance (i.e., stillbirth and birth length) appear similar to earlier results which retain temperature in its original form (full results available upon request).

Exploration

Previous research indicates sex-specific responses to cold temperatures *in utero*.[32-34] We, therefore, explored whether our main findings differed by infant sex. For the preterm, stillbirth, birth weight for gestational age and birth length analyses, we detected no effect modification of temperature by infant sex (full results available upon request).

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Discussion

Using a historical population with relatively fewer resources than contemporary societies to offer shelter from cold, we test whether cold ambient temperature *in utero* precedes an increased risk of adverse birth outcomes. Findings from almost 14,000 births in Uppsala, Sweden support that the risk of stillbirth rises as ambient temperature over gestation falls. In addition, infant birth length varies positively with temperature, whereas we find no relation between temperature and preterm or birth weight for gestational age. Taken together, results in Sweden indicate that maternal adaptations to cold adversely affect the course of their gestations.

To our knowledge, we provide the first evidence of an elevated risk of stillbirth following exposure to ambient cold. Strand and colleagues report a positive relation between temperatures in excess of 20°C and the risk of stillbirth and preterm delivery in Australia.[4] Young and Makinen,[35] moreover, examine infant mortality rates in an ecological analysis of Arctic populations. We build on this work by focusing on exposure to cold temperatures during gestation and employing survival analytic methods, which overcome confounding induced by comparing fetuses of different gestational age. In addition, time-to-event methods (for the preterm and stillbirth tests) account for the time-varying nature of exposure to ambient cold *in utero*.

Key strengths of our approach involve assignment of instrument-based daily ambient temperature to individual gestations as well as the removal of potential confounding by month of conception. The literature documents strong seasonality in fertility timing, especially in Sweden.[30] This variation in timing of conception, in conjunction with social differences in fertility timing within region, may confound perinatal studies that use season of birth as a proxy for temperature exposure *in utero*.[29,36] Another strength involves investigation of births in Sweden from 1915 to 1929. This historical dataset allows for assessment of maternal physiological responses to cold stress that may be less common in contemporary societies that enjoy modern amenities (e.g., gas furnaces for central heating). We, moreover, applied methods recommended by Strand and colleagues to eliminate the "fixed cohort bias" that occurs when cohort studies include pregnancies based on a fixed calendar date of birth rather than on an estimated date of conception.[23]

Limitations include the inability to examine exposure to other meteorological factors (e.g., humidity, wind, rainfall) given the absence of instrument-based measures over the test period. We also did not have information on ambient air pollutants. We view this potential confounding as minimal given the absence of heavy industry, as well as limited automobile travel, in the larger Uppsala region from 1915 to 1929. Our adjustment for month of conception also minimizes confounding by seasonal variation in ambient air quality levels. Data limitations also preclude the assessment of other adverse conditions that may be caused by cold temperatures and perturb birth outcomes. For instance, maternal inhalation of smoke or particulate matter from using wood and/or coal-burning stoves may appear elevated following a cold wave. We await research on modern-day populations (e.g., indigenous Arctic populations) to identify intervening behavioral and biological mechanisms. In addition, lack of modern-day technology (e.g., ultrasound) implies measurement error in estimating gestational age at delivery.

Hans Selye's widely cited 1936 paper, in which challenge to various "stressors" in rats produced the same "non-specific general adaption syndrome," included a cold challenge.[37] Following that tradition, our work supports the notion that ambient stressors perturb the trajectory of gestations. We, however, observe that maternal responses to cold appear rather specific in that they vary with, for instance, stillbirth but not birthweight for gestational age.

Extensions of our work could explore time periods during gestation that may appear especially sensitive to cold. Previous research has specified each of the three trimesters, ten days in the middle of each trimester, the last month, week, and day of gestation, and the days around conception.[3] The experimental and observational literatures, however, do not converge on a specific period *in utero* when mothers respond sensitively to ambient temperature. Absent a clear time window *a priori*, analyses of suspected critical periods would necessarily take the form of an exploration.

Climate forecasts of rising temperatures have understandably generated research interest in quantifying the health sequelae of ambient heat. Less work, especially in infant health, focuses on the "left-end" of the J-shaped temperature / health relation. Given that long-term climate forecasts predict increasing temperature oscillations—including cold waves— additional investigations of cold reactivity during gestation appears warranted.[38] Our findings indicate that, for a historical Swedish population, cold ambient temperature *in utero* precedes an increased risk of stillbirth but a relatively shorter birth length. Although we await replication of our findings in other places and times, our work holds relevance to the understanding of maternal-fetal reactivity as well as to the health of contemporary societies (e.g., indigenous Arctic populations) with limited resources to mitigate the adverse consequences of cold. [35] In addition, given the somatic and psychological pain of stillbirth and the sequelae of birth length[39] into adulthood, we encourage further investigation on the physiological processes that may connect cold temperatures to fetal reactivity.

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Table 1. Characteristics of births (live and stillborn) at Uppsala Hospital, Sweden, 1915-1929 (n=13,839 births with gestational age information).

	n	%	Mean (SD)
Temperature during gestation (in °C)			5.0 (2.4)
Gestational Age (in weeks)			39.6 (2.5)
Birth weight-for-gestational age percentile			48.5 (29.3)
Birth length (cm)			50.5 (2.9)
Stillbirth	359	2.6	
Female birth	6,587	47.6	
Mother is married	10,933	79.0	
Maternal Age (yrs)			
< 18 years	152	1.1	
18-34 years	10,947	79.1	
≥ 35 years	2,740	19.8	
Parity			
1st birth	5,466	39.5	
2nd birth	3,211	23.2	
3rd birth	1,813	13.1	
4th birth	1,190	8.6	
5th birth or higher	2,159	15.6	
Father's occupation			
Non-manual laborer	2,090	15.1	
Manual laborer	8,179	59.1	
Entrepreneur or farmer	2,408	17.4	
Not classified	1,162	8.4	

Note: column percents may not sum to 100% due to rounding and non-exhaustive nature of categories.

Figure 1. Scatterplot of average temperature (in ℃) during gestation for 13,839 births in Uppsala hospital, 1915-1929, by calendar month of conception.

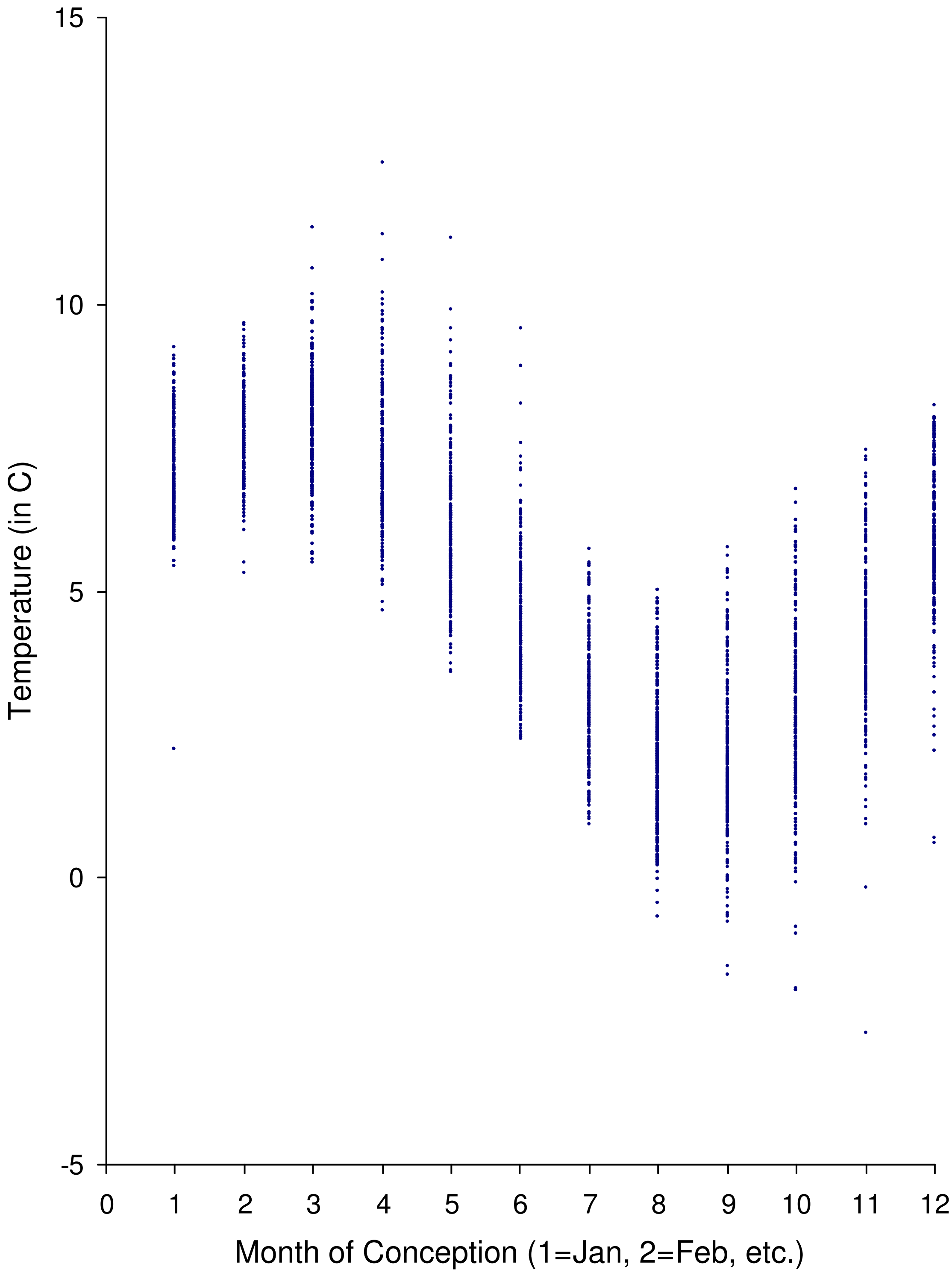

Table 2. Cox proportional hazards model of **stillbirths** as a function of temperature during gestation, month of conception, and other covariates, Uppsala, Sweden, 1915-1929 (232,650 weeks of observation).

Variable	**Coef.**	**(SE)**
Temperature during gestation	-.080	(.039)*
Calendar month of conception (referent: December)		
January	-.231	(.255)
February	-.400	(.304)
March	-.200	(.275)
April	-.069	(.252)
May	-.374	(.259)
June	-.330	(.240)
July	-.600	(.267)*
August	-.553	(.275)*
September	-.743	(.282)**
October	-.354	(.258)
November	-.182	(.240)
Conception year (continuous)	-.020	(.012)
Male infant (referent: Female)	.038	(.106)
Maternal Age (referent: 18-34yrs)		
< 18 years	-1.45	(1.01)
≥ 35 years	.757	(.139)***
Mother is married (referent: not married)	-.134	(.156)
Father's occupation (referent: non-manual laborers)		
Manual laborers	-.045	(.160)
Entrepreneurs or farmers	.245	(.176)
Not classified	-.432	(.278)
Parity (referent: 1st birth)		
2nd birth	-.460	(.152)**
3rd birth	-.996	(.220)***
4th birth	-.469	(.203)*
5th birth or higher	-.429	(.171)*

All tests of significance are two-tailed. * $p < .05$; ** $p < .01$; *** $p < .001$

Table 3. Cox proportional hazards model of **live births** up to 37 weeks of gestation as a function of temperature during gestation, month of conception, and other covariates, Uppsala, Sweden, 1915-1929 (192,116 weeks of observation).

Variable	**Coef.**	**(SE)**
Temperature during gestation	- .006	(.022)
Calendar month of conception (referent: December)		
January	.019	(.131)
February	.0002	(.147)
March	.142	(.146)
April	.141	(.139)
May	.262	(.124)*
June	.0005	(.123)
July	.078	(.132)
August	.214	(.146)
September	.109	(.152)
October	.227	(.142)
November	.142	(.128)
Conception year (continuous)	.00006	(.006)
Male infant (referent: Female)	.067	(.050)
Maternal Age (referent: 18-34yrs)		
< 18 years	.274	(.200)
≥ 35 years	.192	(.073)**
Mother is married (referent: not married)	- .368	(.068)***
Father's occupation (referent: non-manual laborers)		
Manual laborers	.044	(.076)
Entrepreneurs or farmers	-.067	(.093)
Not classified	-.045	(.116)
Parity (referent: 1st birth)		
2nd birth	.004	(.066)
3rd birth	-.244	(.094)**
4th birth	.127	(.094)
5th birth or higher	-.199	(.092)*

All tests of significance are two-tailed. * $p < .05$; ** $p < .01$; *** $p < .001$

Table 4. Ordinary Least Squares regression of **birth weight for gestational age percentile** as a function of temperature during gestation, month of conception, and other covariates, Uppsala, Sweden, 1915-1929.

Variable	Coef.	(SE)
Temperature during gestation	-.239	(.215)
Calendar month of conception (referent: December)		
January	.445	(1.21)
February	-.948	(1.29)
March	-.071	(1.29)
April	-.393	(1.23)
May	-.443	(1.19)
June	-.397	(1.20)
July	-.925	(1.33)
August	-.741	(1.44)
September	-2.36	(1.42)
October	-1.74	(1.32)
November	-1.23	(1.22)
Conception year (continuous)	-.044	(.059)
Male infant (referent: Female)	.024	(.492)
Maternal Age (referent: 18-34yrs)		
< 18 years	-.014	(2.44)
≥ 35 years	-.923	(.725)
Mother is married (referent: not married)	-.108	(.728)
Father's occupation (referent: non-manual laborers)		
Manual laborers	- 2.60	(.730)***
Entrepreneurs or farmers	.895	(.874)
Not classified	-1.91	(1.18)
Parity (referent: 1st birth)		
2nd birth	9.13	(.663)***
3rd birth	11.74	(.813)***
4th birth	12.91	(.972)***
5th birth or higher	16.67	(.878)***

All tests of significance are two-tailed. * $p < .05$; ** $p < .01$; *** $p < .001$

Table 5. Ordinary Least Squares regression of **birth length** as a function of temperature during gestation, month of conception, and other covariates, Uppsala, Sweden, 1915-1929.

Variable	**Coef.**	**(SE)**
Temperature during gestation	.070	(.013)***
Calendar month of conception (referent: December)		
January	-.004	(.074)
February	-.030	(.079)
March	-.159	(.079)*
April	-.146	(.075)
May	.062	(.072)
June	.092	(.073)
July	.301	(.081)***
August	.409	(.088)***
September	.288	(.087)***
October	.235	(.081)***
November	.169	(.075)*
Conception year (continuous)	-.071	(.004)***
Male infant (referent: Female)	.801	(.030)***
Maternal Age (referent: 18-34yrs)		
< 18 years	-.149	(.150)
≥ 35 years	.158	(.044)***
Mother is married (referent: not married)	.090	(.045)*
Father's occupation (referent: non-manual laborers)		
Manual laborers	.001	(.045)
Entrepreneurs or farmers	.015	(.053)
Not classified	.034	(.072)
Parity (referent: 1st birth)		
2nd birth	-.099	(.041)*
3rd birth	-.256	(.050)***
4th birth	-.237	(.060)***
5th birth or higher	-.300	(.054)***
Gestational age (in weeks)	.527	(.001)***
Birth weight for Gestational Age (in %)	.049	(.001)***

All tests of significance are two-tailed. * $p < .05$; ** $p < .01$; *** $p < .001$