Ambient temperature *in utero* and cold-related adult mortality in a Swedish cohort, 1915 to 2002

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Abstract

For all climatic regions, mortality due to cold exceeds mortality due to heat. A separate line of research indicates that lifespan after age 50 depends on season of birth. This and other literature implies that ambient temperature *in utero* may influence cold-related mortality later in life. We use data on over 13,500 Swedes (from 1915 to 2002) to test whether cold-related mortality in adulthood varies positively with exposure to unusually benign ambient temperature *in utero*. We specify a counting process Cox proportional hazards model to analyze the two leading causes of cold-related death: ischemic heart disease and stroke. Results indicate an increased risk of ischemic heart disease mortality during cold spells among persons exposed to relatively warm gestations. We, however, observe no relation for stroke mortality. The ischemic heart disease findings provide the first evidence that temperature during gestation—independent of month of birth—affects cold-related mortality later in life.

Populations living in Arctic and near-Arctic latitudes routinely encounter severely cold temperatures and exhibit elevated adult mortality during cold extremes.[1] In addition, for all three climatic regions on Earth—tropical, temperate and polar—human mortality directly and indirectly due to extreme cold has exceeded mortality due to extreme heat.[2-4] A separate line of research indicates that lifespan after age 50 depends on season of birth.[5] This literature, in addition to experimental reports of temperature sensitivity during fetal development,[6,7] suggests that ambient temperature *in utero* may influence morbidity later in life. In this report, we describe and test the novel hypothesis that the risk of cold-related mortality in adulthood varies positively with exposure to unusually benign ambient temperature *in utero*.

Among adults, ischemic heart disease (IHD) and cerebrovascular disease (stroke) are the two leading causes of cold-related death.[8] Thermoregulatory responses to extreme cold at older ages (e.g., after 50 years) increase arterial thrombosis via a rise in blood viscosity. An increase in blood viscosity raises the risk of a clot and, in turn, ischemic or cerebrovascular death.[9] These deaths may also arise due to the rupture of lipid-containing plaques during hypertension and cold-induced coronary spasm.[10] Such processes may act independently of other meteorological factors (e.g., humidity)[11] and cold-related morbidity due to respiratory infections (e.g., influenza).[12,13]

Although the causes of cold-related IHD and stroke appear multifactorial, research indicates that characteristics of the early-life environment may play a role. Lawlor and colleagues report an association between ambient temperature

after birth and subsequent IHD diagnosis.[14] Evidence from animal models, moreover, indicates that plasticity *in utero* induces long-lasting effects on the biology of offspring.[15] Pregnant meadow voles, for instance, transmit information regarding day length to their fetuses, which affects the pups' speed of development and coat thickness.[16] In mice, cold temperatures in the perinatal period induce permanent physiologic alterations in the offspring to cold tolerance and metabolic heat production later in life.[6] This work, and related literature documenting perturbations in fetal development following unexpectedly high or low temperatures,[17] supports the "developmental plasticity" notion that cold temperature reactivity in adulthood may vary according to ambient temperature experienced *in utero*.

Catalano and colleagues offer a different explanation of how temperature *in utero* may affect mortality later in life.[18] Drawing from the theory of natural selection and results from ecological tests, the authors assert that unexpectedly cold temperatures during gestation may stress mothers and yield more male than female fetal losses. The authors reason that such cold-related "culling" of frail males *in utero* could leave behind a relatively smaller but hardier subset of males that survive to birth. The obverse of this argument, which Catalano and colleagues test in historical Sweden, contends that male cohorts born during unusually benign temperatures— and subjected to relatively less selection *in utero*—will exhibit reduced lifespans when confronted with cold later in life. The authors conduct an ecological time-series test and use average temperature in the birth year as a proxy for temperature *in utero*.[19] Catalano and colleagues find

support for their "oscillations" hypothesis in that Swedish male cohorts subjected to warm temperatures in their birth year but confronted with cold temperatures from age one to four years exhibit shorter lifespans after age five than other males.

Taken together, the literature implies, but does not directly test, that an individual's susceptibility to cold-related adult mortality *during cold spells* increases if exposed to benign (i.e., non-cold) temperatures *in utero.* We perform this test using high-quality life course data from Uppsala, Sweden. We focus on IHD and stroke mortality, the leading causes of cold-related death in adulthood. Support for this hypothesis among males but not females would bolster the male-specific selection *in utero* argument by Catalano and colleagues.[18,19] A discovered general relation across genders, however, would favor the developmental plasticity argument.

Our approach advances the literature in three ways. First, we capitalize on individual-level data from the Uppsala Birth Cohort Study (UBCoS),[20] which includes births from 1915 to 1929 and followed until 2002. This longitudinal dataset links birth records to validated cause-of-death information at older ages. Second, the availability of daily instrument-based temperature measurements in Uppsala, Sweden allows for more precise estimation of ambient temperature exposure during gestation and through an individual's life course (up to 2002). Third, our analytic approach controls for confounding by season of birth and, unlike earlier work, captures the time-varying nature of ambient temperature over the lifespan.

Methods

Variables and Data

Our study population consists of approximately 14,000 live births delivered at Uppsala University Hospital from 1915 to 1929 and linked to the Swedish Cause of Death Register until 2002.[21] These births, referred to as the Uppsala Birth Cohort Study (UBCoS), are regionally representative of live births and account for 75 percent of all births in Uppsala in this time period.[22] UBCoS contains information on social and demographic variables of the mother as well as several birth characteristics. The dataset also includes exact date of birth and estimated gestational age, which allows for linkage of ambient temperature data during gestation. Over 40 peer-reviewed publications use UBCoS data.[20]

Researchers at Stockholm University have linked 97.3 percent of UBCoS birth records to 1960, 1970, and 1980 census registers as well as to death data (beginning in 1952) up to 2002.[21] This process permits cause-of-death estimates for UBCoS births up to 87 years of age (for those born in 1915). UBCoS also contains information on exact date of death. Validation tests of the cause-of-death field show 99.9% agreement between the death registry and the separately administered patient discharge database.[20] The death data are updated yearly, and loss to follow up is less than 0.5% (i.e., fewer than 0.5 percent of all diseased persons have a non-reported cause of death). We used conventional classification schemes, using International Classification of Disease mortality codes, to categorize IHD and stroke deaths.[22]

Concern over climate change has led to the validation and publication of historical temperature data. Much of this work focuses on Sweden, where scientists maintained continuous instrument-based measurements of surface temperature from as early as the mid-18th century. We retrieved daily values from the Moberg and Bergstrom temperature series (in tenths of degrees centigrade) derived from instruments in the Uppsala (59°52' N, 17°38' E) region.[23] These authors calculated daily temperature as the mean of hourly temperatures taken at least four times over each 24 hour period. We used the temperature series from March 1st, 1914 (i.e., earliest estimated date of conception for an UBCoS birth in 1915) to December 31, 2002 (last day of UBCoS follow-up). Consistent with conventions of climatology, scientists have homogenized and validated this series over the test period. The Swedish Meteorological and Hydrological Institute makes the temperature series publicly available.[24]

Approach

For each UBCoS individual with exact date of birth and gestational age information, we assigned an average ambient temperature measure *in utero*. Temperatures in Uppsala fell below 17° C (the nadir on the J-shaped temperature / mortality relation in Scandinavia[25] in over 95 percent of all weeks in our test period. We, therefore, assumed no heat-related stress during gestation. Since our hypothesis focuses on subjects exposed to unusually benign temperatures *in utero*, we specified a "benign gestation" variable as the fraction of weeks in gestation spent in the warmest quintile of Uppsala temperatures from

1915 to 1929 (> 13.5° C, or 56.3°F). Previous research on temperature-related birth outcomes also employs this quintile approach.[26]

Research on cold-related IHD and stroke mortality does not converge on a definition for an acute cold spell.[27] The literature, however, finds non-linear relationships between cold and mortality such that extreme cold events exert the largest IHD and stroke mortality response.[28] We, consistent with this logic and previous climatic research[29], classified extreme cold days as those that fell below the lowest 5th percentile of the average daily temperature for each of the conventional 30-year climate normal periods spanning from 1915 to 2002 (please see reference [30] for more details). Given the reported time lag in which the risk of death remains elevated within one week after extreme cold,[8,27] we classified a binary "cold spell" variable as "1" during a period of at least one extreme cold day including the six days after the last extreme cold day in that week interval. For example, if temperatures on January 3rd and 6th, 1972 (but not other days in January 1972) qualified as extreme cold days, January 3rd through January 12th (inclusive) would score"1" for a cold spell, whereas all other days in January would score "0."

In a life-course setting, a key challenge of estimating the hazard of IHD and stroke deaths during cold spells involves the conditional dependence of these causes of death on the ability to survive to older ages. Selective mortality of frail individuals before older ages, either in response to earlier cold spells or to other insults, may leave behind a non-representative group of older adults. Such

health selection over the life course could complicate tests of cold-related IHD and stroke mortality, which predominantly occurs after age 50.[9]

One recommended approach to control health selection involves a counting process, popularized by Therneau and Grambsch.[31] This time-to-event strategy, which takes the functional form of a Cox proportional hazards model, statistically adjusts for the dependence of older-age mortality on the ability to survive to older age. We employ this counting process in our tests.

The counting process approach also flexibly allows the risk of mortality to vary over the life course based on time-varying characteristics. The procedure essentially divides each subject's person-time of observation into discrete intervals of mortality risk, beginning at their date of study entry (in our case, date of birth). For our test, each discrete interval (in days) receives a cold spell classification (1 or 0) that identifies the temperature through which the individual progresses. Failure to survive beyond a particular interval precludes the subject's exposure to temperatures at future intervals. Furthermore, persons do not contribute time intervals of observation after they die of IHD or stroke, or are lost to follow-up (via deaths due to competing risks, emigration, or survival to December 31, 2002, the last day of observation). Based on this logic and our temperature classification rules, we identified 586 discrete time intervals, of varying lengths, from 1915 to 2002 that an UBCoS subject born in January 1, 1915 has the potential to experience.

Let τ denote current calendar time. We express the mortality rate θ of an individual at a given point of time in terms of their age t, a vector of birth

characteristics X(t), current temperature conditions S(τ), temperature in gestation S(τ-t), and various interaction terms.

We specify a proportional hazards model of the following form:

$$\log\theta(t|X(t),S(\tau),S(\tau\text{-}t)) = \beta_0 + \beta' X_t + \beta_1 S_\tau + \beta_2 S_{\tau\text{-}t} + \beta_3 M_{\tau\text{-}t} + \beta_4 \text{warmxcold} + \varepsilon \quad [1]$$

Where:

θ is IHD death. In a separate specification, we examine stroke death.

X_t is a vector that includes binary indicator variables for month of birth (Jan, Feb, etc.) and binary indicator variables for father's occupation, a measure of socioeconomic status at birth.

S_τ is the binary cold spell variable for that particular time interval.

$S_{\tau\text{-}t}$ is the temperature variable *in utero*, scored as the fraction of weeks in gestation spent in the highest temperature quintile (> 13.5° C).

$M_{\tau\text{-}t}$ is sex of the individual, classified as "1" for male and "0" for female.

warmxcold is the product of $S_{\tau\text{-}t}$ and S_τ. This interaction term takes on a non-zero value during cold spells. The attendant coefficient β_4 is our parameter of interest.

The counting process approach explicitly controls for the subject's age at each discrete time interval. For this reason, we do not include a "right-side" age covariate in the proportional hazards model.

Given that Catalano and colleagues' oscillations hypothesis predicts a male-specific response[19], in a separate model we tested a three-way interaction term of infant sex, the temperature variable *in utero*, and the binary cold spell

variable (with inclusion of all relevant two-way interaction terms). The product of the three-way interaction term takes a non-zero, positive value only among males during cold spells. We then performed additional analyses to assess the stability of results to alternative specifications and assumptions.

Results

The analytic sample comprised 13,625 liveborn subjects with plausible gestational age information and followed after birth. Table 1 describes the characteristics of these UBCoS participants. The mean ambient temperature during gestation was 5.0° Celsius (41°F). Subjects experienced the warmest temperature quintile (>13.5° C) for an average of 19 percent of their gestation. Almost 85 percent of subjects survived to age 50 and over half lived to the end of the observation period (December 31, 2002). After age 50, deaths due to IHD account for over a quarter of all recorded deaths, whereas stroke accounts for about eight percent of these deaths. Less than seven percent of the total IHD and stroke deaths occur before age 50.

Figure 1 plots the proportion of warmest temperature quintile exposure *in utero* for all subjects by calendar month of birth. The temperature variable shows strong seasonality, with the warmest gestations being born in the fall months. Within each birth month, moreover, gestational temperature shows substantial variation around its mean.

Linkage to cause-of-death data began in 1952. We display the results of proportional hazards models for IHD (Table 2) and stroke (Table 3) death with

January 1, 1952 as the left-censored start date of follow-up (540,450 person-years of observation). Males show an elevated IHD mortality risk relative to females. In addition, the risk of IHD death falls with advancing birth year. Births in January and February (relative to births in December) also move positively with the risk of IHD death. Subjects born to the manual labor class show an elevated IHD mortality risk (relative to the non-manual laborer class), but this result appears marginal (p=.09).

For IHD deaths, the warm gestation to cold spell interaction term is positive and reaches conventional levels of statistical significance (p=.0097). This coefficient indicates an increased risk of IHD death among persons subjected to warm gestations but confronted with cold spells later in life. To assist with interpretation, Figure 2 displays the form of the warm gestation x cold spell interaction term as it relates to IHD mortality. We plot the point estimates of the hazard ratios, as well as their 95% confidence intervals, across the warm gestation values in our dataset. The figure shows that, for subjects that spent more than 25 percent of their gestation in the warmest quintile, we estimate an increased risk of IHD death in cold spells (relative to non-cold intervals). Thirty percent of the UBCoS population scores above this level, which (based on the model) places them at a statistically significant increased risk of an IHD-related cold death later in life. An alternative way to interpret this interaction term is that, within a given cold spell, the hazard of IHD death rises 16% (HR: 1.16, 95% confidence interval:1.03 to 1.29) for each one standard deviation (SD) increase

of exposure *in utero* to the warmest temperature quintile (1 SD = 6% more warm days in gestation).

Table 3 indicates an elevated risk of stroke death among males but a decreased risk of stroke with increasing birth year. Calendar month of birth does not predict the risk of stroke death later in life. In addition, unlike the IHD results, we observe no relation between the warm gestation x cold spell interaction term and stroke mortality (p=.74).

We then examined the proposition of a male-specific relation between warm gestations and cold-related mortality later in life. We repeated the tests shown in Tables 2 and 3 but included a three-way interaction term (male x warm gestation x cold spell) as well as all attendant two-way interaction terms. In both the IHD and stroke analysis, the three-way interaction terms show no relation to mortality risk (for IHD: coef: -.88, standard error [SE]= 2.10, p=.67; for stroke, coef: -2.08, SE = 3.48, p=.55). Further analyses that stratified all models by sex also showed no elevated coefficients among males. These results do not support a male-specific mortality response to cold later in life following exposure to warm temperatures *in utero*.

Sensitivity analyses

Availability of cause-of-death data for UBCoS subjects as of 1952, and our analyses of death starting in 1952, raises the possibility that health selection of the study cohort before 1952 may influence our results. We tested this possibility in two ways. First, we re-analyzed the data using all person-years of observation

from birth to death (including before 1952). Inference for all coefficients remained unchanged from those reported in Tables 2 (IHD) and 3 (stroke). Second, we tested the relation between the warm gestation x cold spell interaction term and all-cause mortality *before 1952* to determine if this temperature sensitivity increased the risk of death at earlier ages. Our hazard model found no such association (full results available upon request). Taken together, these checks indicate that health selection before 1952 does not affect inference from our tests.

We checked the assumption of proportional hazards by assessing the stability of our main temperature coefficients in Tables 2 and 3 across discrete age ranges in adulthood (e.g., 30 to 60 years, 55 years or more). We found no substantial change in the magnitude of the temperature coefficients, although the standard errors increased owing to less precision from analyzing fewer deaths within a narrower age range (results available upon request). In addition, we assessed whether results appear sensitive to our definition of a cold spell by re-classifying cold spell intervals over the entire life course as those with days below the 10^{th} percentile of temperature (instead of < 5^{th} percentile). Statistical inference remained the same as the results shown in Tables 2 and 3.

Discussion

We test whether Swedes subjected to unusually benign ambient temperatures during gestation exhibit an elevated risk of cold-related mortality in adulthood. This hypothesis arises from literature that documents both ambient

temperature sensitivity *in utero* and an influence of the prenatal environment on subsequent cold reactivity, adult ischemic heart disease (IHD) and stroke deaths. Using a high-quality longitudinal dataset from Uppsala, Sweden, we find an increased risk of IHD death during cold spells among gestations exposed to relatively warm ambient temperature *in utero*. We, however, observe no relation for stroke mortality. To our knowledge, the IHD results provide the first evidence that ambient temperature during gestation—independent of season of birth—affects cold-related mortality later in life.

Results for IHD mortality cannot arise from seasonal factors related to month of birth (e.g., rainfall, infectious disease burden, fertility timing)[32,5,33] since we controlled for month of birth in all analyses. In addition, sensitivity analyses indicate that health selection before adulthood does not account for our findings. Adjustment for birth year further minimizes confounding by shared secular trends (from 1915 to 1929) between rising temperatures and IHD mortality for the annual UBCoS birth cohorts.

Strengths of our approach include use of what we believe to be the highest quality individual-level cohort and simultaneous local temperature data in the world. Such information allows for assignment of ambient temperature measurements during gestation, as well as longitudinal examination (for up to 87 years) of specific causes of death. In addition, unlike earlier work,[14,19] our counting process hazard model makes explicit the multiple "exposure windows" to cold spells over the life course. This approach allows the risk of mortality to vary over time based on time-varying temperature characteristics. We also

examine subjects from Sweden, the most populous country in a near-Arctic climate whose birth cohorts are forced to adapt to cold but experience relatively little heat stress. Furthermore, the exogenous nature of our independent variables—derived from ambient temperature measurements—minimizes confounding by social, economic, and behavioral causes of IHD and stroke mortality.

We could not acquire information on residential location of UBCoS participants, which precluded a spatial analysis of temperature exposures over the life course. As a proxy, we used validated daily temperatures in Uppsala, Sweden from 1915 to 2002. These daily temperatures correlate quite strongly with temperatures from urban centers in Sweden to which Uppsala residents may likely move (e.g., R^2= .997 with temperatures in Stockholm). In addition, we could not link mortality data to UBCoS subjects that migrated out of Sweden. We, therefore, excluded subjects after their date of emigration (1.4% of the study population). This measurement error and loss of individuals to emigration may have inflated standard errors and biased results toward the null. In addition, the lack of instrument-based measurements of other meteorological factors (e.g., humidity, rainfall) or indoor temperature did not allow for testing of other predictors of climate-related mortality. We expect that increased attention now devoted to the health consequences of climate change may lead to such tests in the future.

Future extensions of this work could include examination of a larger, countrywide census of births followed until death, which may provide adequate

statistical power to study other causes of cold-related death (e.g., respiratory illness) in response to temperatures early in life. In addition, identification of biological or behavioral pathways that mediate the discovered relation between warm temperatures *in utero* and cold-related IHD deaths would strengthen the evidence base in this relatively understudied area. Elucidation of potential pathways would also inform the theoretical debate regarding whether developmental plasticity[15,34] or selection *in utero*[18] best describes our pattern of results. Whereas the failure to observe male-specific reactivity detracts from the male-specific "culling" argument, we note that Uppsala births from 1915 to 1929 may have experienced less selection pressure *in utero* than the 18th and 19th century Swedish populations used in previous studies.[18,19]

Although we focus on a near-Arctic population, our findings may apply to developing countries, in more tropical climates, who are expected to confront extreme heat and exhibit the largest direct and indirect health burden from climate change.[35] We examine cohorts born during times with sub-standard resources to mitigate the adverse consequences of temperature extremes (e.g., no central heating in 1915).[36] Developing countries similarly lack access to appropriate resources as they confront heat waves of greater frequency and magnitude than in the past. Our findings, therefore, should encourage applied longitudinal studies on the consequences of ambient temperature during gestation and adult mortality among populations not sufficiently sheltered from heat waves.

References

1. Young TK, Makinen TM. The health of Arctic populations: Does cold matter? *Am J Hum Biol* 2010 **22**: 129-133.

2. Rau R. Seasonality in human mortality: a demographic approach. 2007. Berlin; Springer-Verlag.

3. Sheridan SC, Kalkstein LS. Progress in heat watch-warning system technology. *Bull Amer Meteor Soc* 2004; **82**: 1931–41.

4. Healy JD. Excess winter mortality in Europe: a cross country analysis identifying key risk factors. *J Epidemiol Community Health* 2003; **57**: 784-789.

5. Doblhammer G, Vaupel JW. Lifespan depends on month of birth. *Proc Natl Acad Sci U S A* 2001; **98**: 2934-2939.

6. Morrison SF, Ramamurthy S, Young JB. Reduced rearing temperature augments responses in sympathetic outflow to brown adipose tissue. *J Neurosci* 2000; **20**: 9264-9271.

7. Canals M, Figueroa DP, Miranda JP, Sabat P. Effect of gestational and postnatal environmental temperature on metabolic rate in the altricial rodent, Phyllotis darwini. *J Therm Biol* 2009; **34**: 310-314.

8. Donaldson GC, Keatinge WR. Early increases in ischaemic heart disease mortality dissociated from and later changes associated with respiratory mortality after cold weather in south east England. *J Epidemiol Community Health* 1997: **51**:643-8.

9. Keatinge WR, Donaldson GC. The impact of global warming on health and

mortality. *South Med J* 2004; **97**: 1093-1099.

10. Farb A, et al. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995; **92**: 1701-1709.

11. Keatinge WR, Donaldson GC. Mortality related to cold and air pollution in London after allowance for effects of associated weather patterns. *Environ Res* 2001; **86**: 209-216.

12. Kunst AE, Looman CW, Mackenbach JP. Outdoor air temperature and mortality in The Netherlands: a time-series analysis. *Am J Epidemiol* 1993; **137**: 331-341.

13. Donaldson GC, Keatinge WR. Excess winter mortality: influenza or cold stress? Observational study. *Bmj* 2002; **324**: 89-90.

14. Lawlor DA, Davey Smith G, Mitchell R*, et al.* Temperature at birth, coronary heart disease, and insulin resistance: cross sectional analyses of the British women's heart and health study. *Heart* 2004; **90**:381-8.

15. Gluckman PD, Hanson MA and Spencer HG. Predictive adaptive responses and human evolution. *TREE* 2005; **20**: 527-533.

16. Lee TM and Zucker I. Vole infant development is influenced perinatally by maternal photoperiodic history. *Am J Physiol Regul Integr Comp Physiol* 1988 **255**: R831-838.

17. Strand LB, Barnett AG, Tong S. The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environ Res* **111**: 451-462.

18. Catalano R, Bruckner T, Smith KR. Ambient temperature predicts sex ratios and male longevity. *Proc Natl Acad Sci U S A* 2008; **105**: 2244-2247.

19. Catalano R, Bruckner T, Smith KR, Saxton K. Temperature oscillations may shorten male lifespan via natural selection in utero. *Climatic Change* 2012; **110**:697-707.

20. Uppsala Birth Cohort Multigeneration Study. Centre for Health Equity Studies, Stockholm University. Available at: http://www2.chess.su.se/ubcosmg/hd/methhospd.htm (accessed on 8/20/12).

21. Modin B. Birth order and mortality: a life-long follow-up of 14,200 boys and girls born in early 20th century Sweden. *Soc Sci Med* 2002; **54**: 1051-1064.

22. Leon DA, et al. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15 000 Swedish men and women born 1915-29. *Bmj* 1998; **317**: 241-245.

23. Moberg A, Bergstrom H. Homogenization of Swedish temperature data. The long temperature records from Uppsala and Stockholm. *Int J Climatology* 1997; **17**: 667-699.

24. Bergström H, Moberg A. Daily air temperature and pressure series for Uppsala (1722-1998). *Climate Change* 2002; **53**: 213-252 (updated series: http://www.smhi.se/klimatdata/meteorologi/temperatur/1.2855).

25. Keatinge WR, Donaldson GC, Cordioli E*, et al.* Heat related mortality in

warm and cold regions of Europe: observational study. *BMJ* 2000; **321**:670-3.

26. Deschênes O, Greenstone M, Guryan J. Climate Change and Birth Weight. *Am Econ Rev* 2009;**99**:211-7.

27. Hong YC, Rha JH, Lee JT*, et al.* Ischemic stroke associated with decrease in temperature. *Epidemiology* 2003;**14**:473-8.

28. Patz JA, et al. The potential health impacts of climate variability and change for the United States: executive summary of the report of the health sector of the U.S. National Assessment. *Environ Health Perspect* 2000; **108**: 367-376.

29. Reid CE, Mann JK, Alfasso R*, et al.* Evaluation of a heat vulnerability index on abnormally hot days: an environmental public health tracking study. *Environ Health Perspect* 2012;**120**:715-20.

30. Anon. “Characterizing Climate from Datasets (Ch 4).” In: Guide to Climatological Practices. World Meteorological Organization, WMO-No. 100. 2011 (ISBN 978-92-63-10100-6).

31. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. (pp. 68-77). 2010. New York: Springer.

32. Maccini S, Yang D. Under the Weather: Health, Schooling, and Economic Consequences of Early-Life Rainfall. *Am Econ Rev* 2009; **99**(3): 1006–26.

33. Darrow LA, Strickland MJ, Klein M*, et al.* Seasonality of birth and implications for temporal studies of preterm birth. *Epidemiology* 2009; **20**:699-706.

34. Barker DJ. In utero programming of chronic disease. *Clin Sci* 1998; **95**:115-28.

35. Smith KR, Ezzati M. How environmental health risks change with development: the epidemiologic and environmental risk transitions revisited. *Annu Rev Energy Resour* 2005*;* **30**: 291–333

36. Modin B. Setting the scene for life. Longitudinal studies of early social disadvantage and later life chances. 2002. Centre for Health Equity Studies, Stockholm University/Karolinska Institutet. Stockholm: Almqvist & Wiksell.

Table 1. Birth and survival characteristics of UBCoS study participants born in Uppsala, Sweden, 1915-1929 and followed until December 31, 2002.

	n	%	Mean (SD)
Temperature during gestation (in ℃)			5.0 (2.4)
Proportion of the gestation spent in warmest temperature quintiile (> 13.5° C)			.19 (.09)
Gestational Age (in weeks)			39.7 (2.3)
Birth weight-for-gestational age percentile			49.0 (29.1)
Birth length (cm)			50.6 (2.7)
Male	7,133	52.3	
Father's occupation			
Non-manual laborer	2,058	15.1	
Manual laborer	8,069	59.2	
Entrepreneur or farmer	2,351	17.3	
Not classified	1,147	8.4	
Successfully tracked after birth	13,625	100.0	
Survived to 1 year	12,773	93.7	
Survived to 50 years	11,495	84.4	
Survived to December 31, 2002	7,004	51.4	
Died after 50 years but before 2003			
Ischemic heart death	1,234	26.2	
Cerebrovascular death	369	7.9	
Death from all other causes	3,096	65.9	

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

Figure 1. Scatterplot of the proportion of the gestation spent in warmest temperature quintiile (> 13.5° C), by calendar month of birth, UBCoS participants born 1915 to 1929.

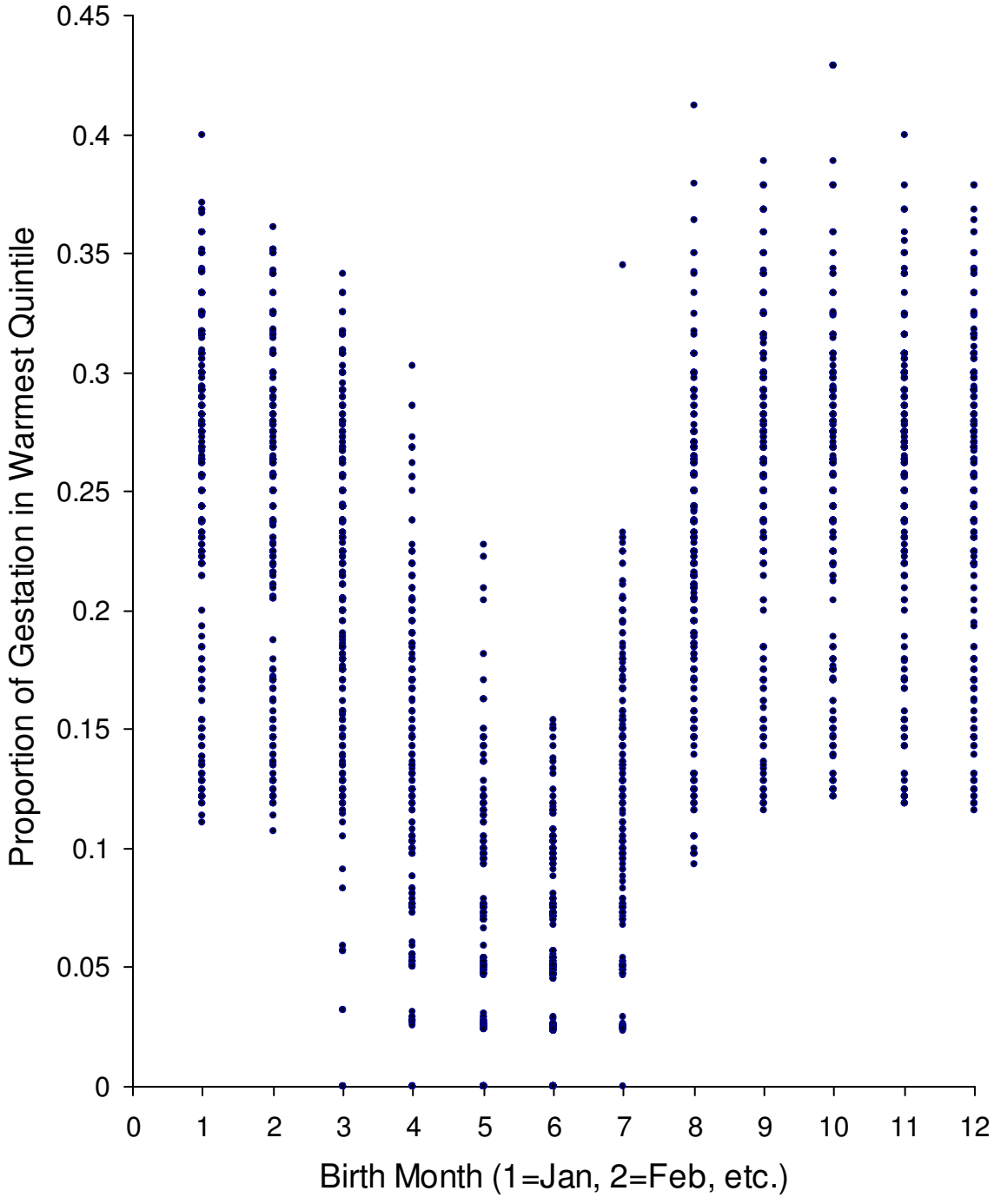

Table 2. Cox proportional hazards model of **ischemic heart disease death** as a function of warm temperature during gestation, cold spells over the life course, the warm gestation/cold spell interaction term, and covariates (1,313 IHD deaths and 540,450 person-years of observation).

Variable	**Coef.**	**(SE)**
Proportion of gestation spent in warmest temperature quintiile	- .052	(.51)
Cold spell (referent: non-cold spell)	-.41	(.21)
Warm gestation x Cold spell	2.47	(.95)**
Male (referent: Female)	1.12	(.06)***
Birth year (continuous)	- .038	(.007)***
Calendar month of birth (referent: December)		
January	.28	(.14)*
February	.28	(.14)*
March	.12	(.14)
April	.18	(.15)
May	.03	(.18)
June	.12	(.17)
July	.23	(.16)
August	.05	(.15)
September	.19	(.14)
October	.07	(.15)
November	.25	(.15)
Father's occupation (referent: non-manual laborers)		
Manual laborers	.14	(.084)
Entrepreneurs or farmers	-.014	(.10)
Not classified	.16	(.12)

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

Figure 2. Plot of the Hazard Ratio (95% Confidence Intervals in light font) of death due to **Ischemic Heart Disease** during a cold spell (vs. non cold spell) across level of warm temperature exposure *in utero* (n=1,313 IHD deaths over 540,450 person-years).

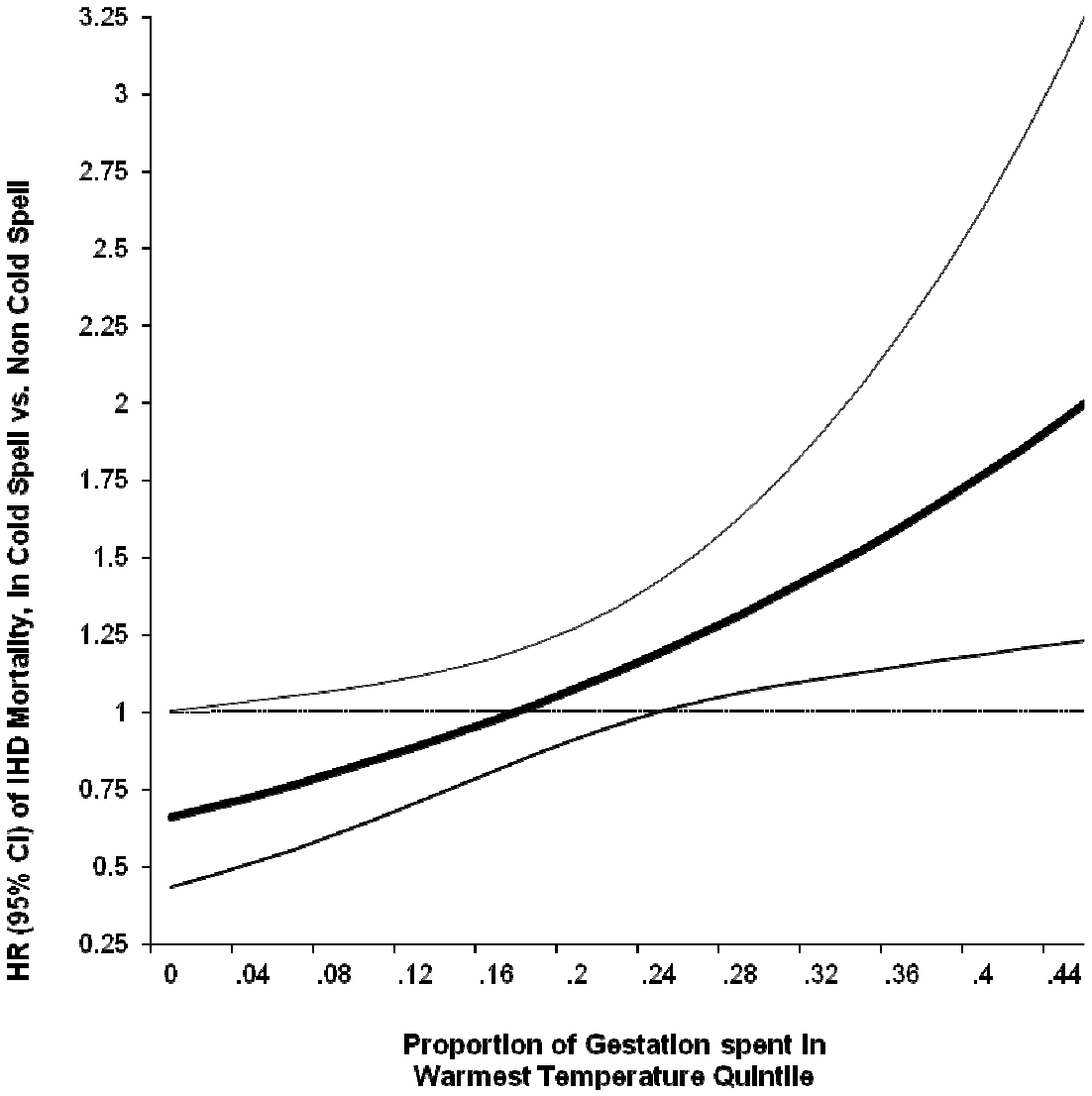

Table 3. Cox proportional hazards model of **cerebrovascular disease (stroke) death** as a function of warm temperature during gestation, cold spells over the life course, the warm gestation/cold spell interaction term, and covariates (406 stroke deaths over 540,450 person-years).

Variable	**Coef.**	**(SE)**
Proportion of gestation spent in warmest temperature quintiile	.13	(.95)
Cold spell (referent: non-cold spell)	.06	(.36)
Warm gestation x Cold spell	-.58	(1.75)
Male (referent: Female)	.30	(.10)**
Birth year (continuous)	- .034	(.014)*
Calendar month of birth (referent: December)		
January	.25	(.25)
February	-.01	(.28)
March	.33	(.24)
April	.25	(.27)
May	.32	(.30)
June	-.02	(.32)
July	.09	(.29)
August	.26	(.25)
September	-.03	(.26)
October	-.05	(.28)
November	.21	(.26)
Father's occupation (referent: non-manual laborers)		
Manual laborers	.22	(.16)
Entrepreneurs or farmers	.10	(.19)
Not classified	.21	(.22)

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