Male lifespan following exposure to benign ambient temperature *in utero* and cold temperature in childhood

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Abstract

Background: Research reports that natural selection has conserved mechanisms that spontaneously abort fetuses, particularly males, least likely to survive in prevailing environmental conditions including cold ambient temperature. These reports imply the hypothesis that males in gestation during relatively warm periods who confront relatively cold climates in early life live, on average, shorter lives than other males.

Methods: We test the above hypothesis using annual cohort lifespan at age 1 for Swedish males from 1850 to 1915 as our dependent variable. For our independent variable, we score a series 1 for birth cohorts that experienced relatively warm temperatures *in utero* but relatively cold temperatures from age 1 through 4, and 0 for other cohorts. We use time-series methods, which adjust the data to remove autocorrelation, to estimate the association between our variables.

Results: We report, consistent with theory, that males in gestation during relatively warm times who encounter relatively cold temperatures in early life have a shorter lifespan than other males. The association survives statistical adjustment for the longevity of women and for the main effects of temperatures during gestation and early life as well as for autocorrelation.

Conclusion: Our findings imply that the increased frequency and amplitude of temperature shifts expected from climate change could influence which humans survive gestation and how long they live.

Introduction

Natural selection has reportedly conserved mechanisms by which women spontaneously abort conceptuses and fetuses least likely to yield grandchildren (Trivers and Willard, 1973). Evidence cited for these mechanisms includes the high risk of spontaneous abortion among small male fetuses. This selection *in utero* supposedly reflects the fact that small males, if born, more likely die in infancy and before reproductive age than similarly small daughters despite relatively greater investments in sons by their mothers (Wells, 2000).

Selection *in utero* suggests at least two hypotheses concerning the effect of environmental stressors on human reproduction. First, stressed populations will yield relatively low ratios of male to female live births (i.e., the secondary sex ratio) because selection against small males *in utero* should increase when pregnant women encounter environmental stressors that would threaten the survival of less robust offspring. Gestations that would yield small or otherwise less fit male infants in benign environments end without live births when ambient stressors turn more virulent. Several reports supporting this hypothesis appear in the literature (Hansen *et al.*, 1999; Kemkes, 2006; Lyster, 1974; Obel *et al.*, 2007; Saadat, 2008). These include 3 tests that used ambient temperature as a population stressor and find lower sex ratios during cold times (Catalano *et al.*, 2008; Grech *et al.*, 2002; Helle *et al.*, 2008).

Second, males in low sex-ratio birth cohorts will, on average, live longer lives than those from higher sex-ratio cohorts because selection *in utero* has removed less robust individuals from the former. Empirical tests also support this hypothesis (Catalano and Bruckner, 2006a, b; Catalano *et al.*, 2008). One of these tests reports that Nordic birth cohorts subjected during gestation to cold ambient temperatures have low sex ratios and that the males in these cohorts live relatively long lives (Catalano *et al.*, 2008).

The possibility that warm ambient temperature reduces selection *in utero* implies that climate change may affect human reproduction and population health in ways not anticipated in the existing literature. These include the possibility that the increasing amplitude and frequency of temperature shifts associated with climate change (Meehl and Tebaldi, 2004; Parry *et al.*, 2007; Schar *et al.*, 2004) will preserve fetuses best suited to unusual warmth but then jeopardize their survival by exposing them early in life to unusual cold. The literature reports an elevated stress response to cold temperature among humans not sheltered against it (Kelsey *et al.*, 2000; Lawlor *et al.*, 2005), which lends biological plausibility to the notion that unusual cold in early life may adversely affect survival. We use data from Sweden, which has kept long time series of ambient temperature and sex-specific lifespan, to explore this possibility. More specifically, we test the hypothesis, implied by the literature summarized above, that males in gestation during relatively warm periods who confront relatively cold climates in early life live, on average, less long than other males.

Materials and Methods

Data

Sweden has kept high-quality vital statistics as well as continuous instrument-based measurements of surface temperature since the mid 19th century. We retrieved annual cohort life table data for Sweden from 1850 (first year of data from consistent record collection methods) to 1915 (most recent year for which demographers can estimate cohort lifespan) from the Human Mortality Database (Human Mortality Database, 2008). Life table data must meet minimum, widely disseminated standards of quality agreed among demographers before inclusion in this database. We chose cohort lifespan at age 1 as our dependent variable. Cohort lifespan gauges the observed lifespan of cohorts born in specific years. Cohort lifespan at age 1 of males born in 1915, for example, equals the average number of years lived from age 1 to death of all males born in that year (i.e., 67.75). We chose lifespan at age 1 rather than lifespan at birth to avoid false rejection of the null hypothesis that could arise from the general effect of cold weather on infant mortality.

We constructed our warm-to-cold shift variable from the mean of two annual temperature series derived from instruments in the Uppsala (59°52’ N, 17°38’ E) and Stockholm (59°20’ N, 18°03’ E) regions of Sweden. Climate scientists have used these instrument-based data to estimate daily, monthly, and annual average temperatures for Scandinavia (Moberg and Bergstrom, 1997). Consistent with the recording of these data, we use tenths of degrees centigrade as the temperature metric.

We scored our warm-to-cold variable 1 for years in which the birth cohort experienced relatively warm temperatures *in utero* but relatively cold temperatures during childhood (i.e., from age 1 through age 4). We defined relatively warm gestation years as birth years with average temperatures above the median for all years. We defined childhood as relatively cold if the average of annual temperature for ages 1 through 4 fell below the median temperature for all years. All other years received a “0” score.

Our test equations included four variables in addition to the warm-to-cold shift indicator. We added cohort lifespan for females at age 1 to make our tests specific to males as required by the theory and research described above. We also included continuous variables measuring birth year temperature and average of annual temperatures for age 1 through 4. These variables test the possibility that cold in either the birth year or during ages 1 through 4 independently predict male lifespan at age 1. We included the interaction of these two as well as their main effects. Low values of the interaction would characterize cohorts experiencing relative cold in both gestation and childhood while high values imply exposure to relative warmth from gestation through childhood. We also controlled, as described below, for autocorrelation in the male lifespan variable.

Analyses

Our test turns on whether male cohort lifespan at age 1, adjusted for the four covariates described above, falls below its statistically expected value among annual cohorts exposed to warm-to-cold shifts. Researchers typically assume that, under the null hypothesis, the statistically expected value of a variable is its mean. Cohort lifespan, however, may exhibit trends, cycles, oscillations, and the tendency to remain elevated or depressed after high or low values. These patterns, referred to collectively as autocorrelation, complicate hypothesis tests because the expected value of an autocorrelated series is not its mean.

Researchers dating to Fisher have overcome autocorrelation by “decomposing” time series into predictable and residual components (Fisher, 1921). The residual components of each series, which become the analyzed variables, have no autocorrelation thereby precluding spurious associations due to shared temporal patterning.

We implemented Fisher’s approach in the following steps. First we modeled male cohort lifespan at age 1 as a function of the four covariates described above. Second, we used Dickey-Fuller (Dickey and Fuller, 1979) and Box-Jenkins (Box *et al.*, 1994) methods to detect and specify autocorrelation in the residuals of the equation estimated in step 1. These methods use iterative model building routines to identify and express autocorrelation in time series as a function of autoregressive and moving average processes. The estimated values of the best-fitting model can be thought of as the expected component of the modeled series while the differences between the observed and estimated values are the unexpected component. We then estimated the following test equation formed by adding the binary warm-to-cold oscillation variable to the model derived in steps 1 and 2.

$$\nabla Y_t = \mathrm{C} + \omega\nabla X_{1t} + \omega_2 X_{2t} + \omega_3 X_{3t} + \omega_4 X_{4t} + \omega_5 \nabla I_t + \frac{\left(1-\theta \mathrm{B}^{\mathrm{q}}\right)}{\left(1-\phi \mathrm{B}^{\mathrm{p}}\right)} \mathrm{a}_{\mathrm{t}}$$

∇ is the difference operator that indicates the variable has been differenced (i.e., values at year t subtracted from values at year t+1) to remove secular trends.

Y_t is cohort lifespan at age 1 for males born in year t.

C is a constant.

X_{1t} is cohort lifespan at age 1 for females born in year t.

X_{2t} is a continuous variable measuring annual temperature in tenths of degrees centigrade in the year of birth.

X_{3t} is a continuous variable measuring the average temperature in tenths of degrees centigrade of years 1 through 4 after year of birth.

X_{4t} is the product of X_{3t} and X_{2t}.

ω through ω_5 are effect parameters.

I_t is a binary variable scored 1 for years in which the birth cohort experienced relatively warm temperatures *in utero* but relatively cold temperatures from age 1 through 4.

θ is the moving average parameter.

ϕ is the autoregressive parameter.

B is the value of the variable at month t-q for moving average and t-p for autoregressive processes.

a_t is the residual, or unexpected value, at month t.

We inspected the residuals for autocorrelation to estimate the efficiency of the parameters. We added Box-Jenkins parameters to the equation, if needed, and estimated the test equation again.

Results

Figure 1 shows the annual mean temperature over our test period. Temperatures ranged from 3.4º to 7.4º centigrade.

Figure 2 shows the first differences in male and female lifespan at age 1 over the test period. Cohort lifespan at age 1 ranged from 51.44 to 67.75 for males and from 54.13 to 73.21 for females. Both series trend upward and, therefore, required differencing.

Table 1 shows the results of our test. Annual changes in female cohort lifespan at age 1 predicted, as expected, similar, though smaller, changes in male cohort lifespan at age 1. Temperature in neither the year of birth nor averaged over age 1 through 4, nor their interaction, predicted male-specific lifespan at age 1. The residuals of the model exhibited no autocorrelation.

Consistent with the theory and research described at the outset, males in gestation during warm years but confronted with cold years in childhood had shorter cohort lifespan at age 1 than expected from female cohort lifespan at age

1, temperature in the birth year, temperature averaged over years 1 through 4 of life, and the interaction of the two temperature variables. The coefficient suggests a drop of approximately 2.46 months in lifespan among males in birth cohorts exposed to temperature mismatches.

We repeated our test with the male and female cohort lifespan variables transformed to their natural logarithms to determine if variability in variation over time, seen in figure 2, could have affected our findings. The results, with the obvious exception of the metric of the coefficients, did not change.

We estimated our test equation again after excluding the three temperature variables that yielded statistically nonsignificant coefficients. The results of the test did not change.

We also tested the association between cold-to-warm temperature shifts and male cohort lifespan at age 1. The literature summarized at the outset predicts no association because cold temperatures would have culled the cohort of frail male fetuses. We replaced the temperature variable in the test equations with a binary variable scored 1 for years in which the birth cohort experienced relatively cold temperatures *in utero* (i.e., below the median of annual temperature values) but, on average, relatively warm temperatures from age 1 through 4 (i.e., mean of the 4 years above the median of annual temperature values). We found no association.

Some males spared spontaneous abortion during unusually warm gestational years may have been hardy enough in childhood to survive a temperature mismatch, but less hardy through the remainder of life than individuals from cohorts with more selection *in utero* against presumably less fit males. To test this possibility we repeated our original test but replaced cohort lifespan at age 1 with that at age 5. Results showed a significantly lower (i.e., -0.1806, SE = 0.0562, $\underline{p} < .01$; two-tailed test) cohort lifespan at age 5 for males in cohorts subjected to the temperature mismatch. The coefficient suggests that males exposed to the warm to cold temperature shift experience a lifespan of approximately 2.16 fewer months than expected at age 5. Taken together, these results suggest that premature deaths associated with warm-to-cold shifts occurred predominantly after age 5.

Discussion

Our findings imply that increases in the size of temperature shifts could induce similar shifts in the intensity of selection *in utero* and its sequelae. Climate change, in other words, could affect human reproduction and longevity through mechanisms not anticipated in the earlier literature.

A loss of 2.46 months of lifespan among males exposed to shifts from warm temperatures *in utero* to cold temperatures in childhood may not seem important. We note, however, that the average change in male lifespan at age 1 over annual birth cohorts in Sweden during our test period was an increase of 2.9 months. Warm to cold temperature shifts, therefore, decreased male lifespan in affected cohorts roughly as much as salutary forces increased it in the average annual cohort during the test period.

Mechanisms other than selection *in utero* could have contributed to our findings. Evidence from animal models implies that plasticity *in utero* can have long-lasting effects on the biology of offspring (Gluckman *et al.*, 2005). Pregnant meadow voles, for example, transmit information regarding day length to their fetuses, affecting the speed of development and coat thickness of pups (Lee and Zucker, 1988). This work suggests that human infants in gestation during relatively warm times may not adapt well to cold and suffer health consequences as a result of encountering cold years later in life. Although such “fetal programming” would predict shorter lifespan among cohorts exposed to temperature shifts like those we measure, nothing in the theory would suggest greater vulnerability among males and attendant lower sex ratios reported after population stressors.

Limitations include that we did not have information on lifespan or age-specific mortality by month of birth. Aggregation of cohorts by calendar year may have masked heterogeneity in temperature exposure among cohorts in gestation at different months of that year. As a result, the averaging of the temperature variable across calendar year may lead to measurement error which, in our case, may bias findings toward the null. Our findings, therefore, may underestimate the true relation between warm to cold temperature shifts and reduced male lifespan.

The Intergovernmental Panel on Climate Change's most recent report concludes that human impacts will change both the mean climate and the variability of climate. Projections based on global climate models indicate that not only will the planet generally become warmer, particularly in high latitudes, but also that it is virtually certain (>99%) that warmer days and nights will increase in frequency over the 21st century. In addition, the Panel forecasts very likely (>90%) temperature variability in the form of more frequent heat waves (Parry *et al.*, 2007). The increased frequency and intensity of these temperature shifts implies that climate change may affect male lifespan in future generations through processes such as those reported here. The effects would more likely appear in less well-developed than developed countries assuming collective wealth provides means for populations to shield themselves against temperature extremes. People subjected to stressful environments, and who have relatively few resources with which to cope, will, therefore, have to make yet another adaptation that could shorten their already relatively short lifespans.

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Table 1. Estimated parameters of equation predicting male cohort lifespan at age 1 in Sweden from 1850 through 1915 (Standard errors in parentheses).

Female cohort lifespan at age 1	0.8956 (.0700) *
Temperature in birth year	0.0034 (.0034)
Average of temperature over ages 1 through 4	-0.0021 (.0036)
Interaction of above 2 temperature variables	-0.00002548 (.0001)
Binary variable score 1 for cohorts experiencing shifts from warm birth years to cold years while age 1 through 4.	-0.1682 (.0489) *

* $p< .01$, two-tailed test

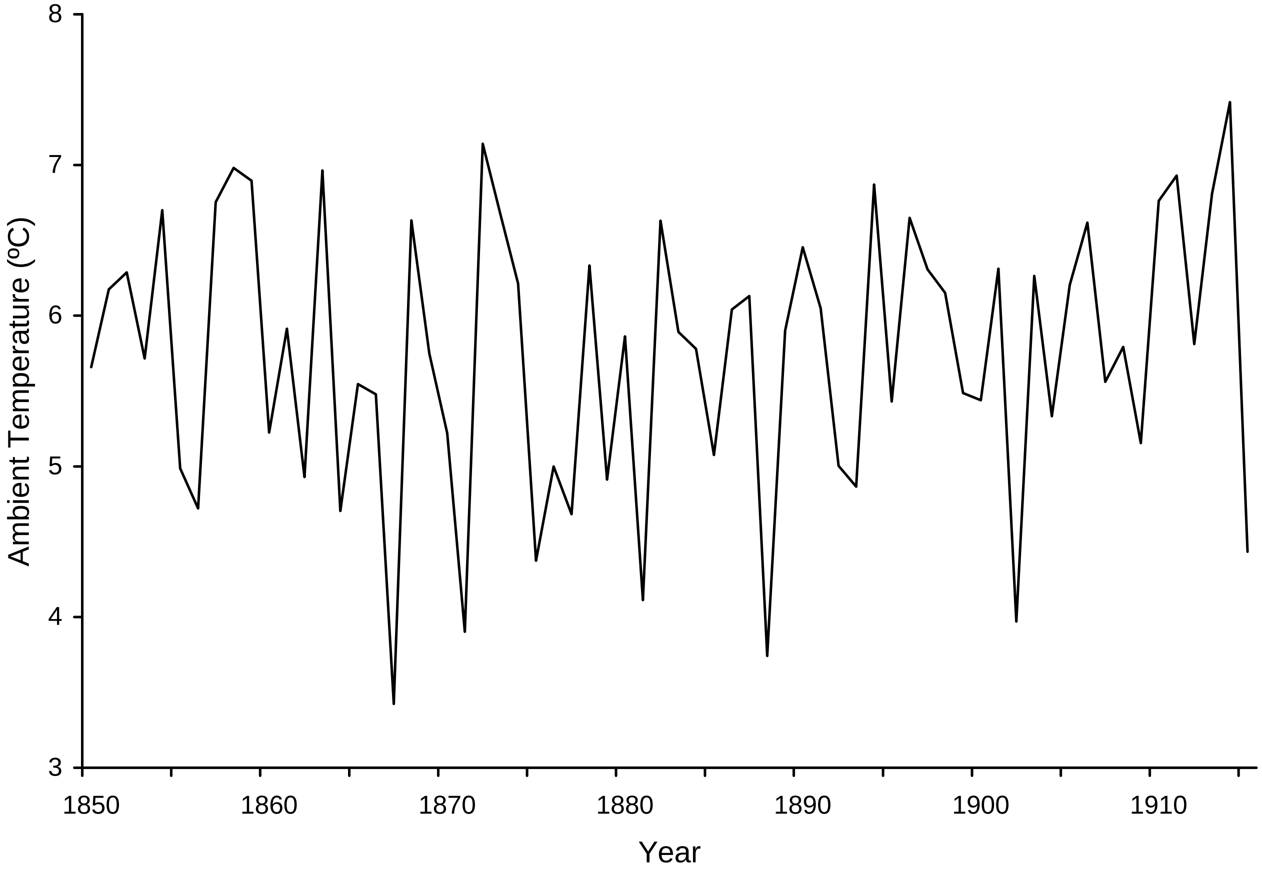

Figure 1. Mean annual ambient temperature for Sweden, in degrees centigrade, from 1850 to 1915.

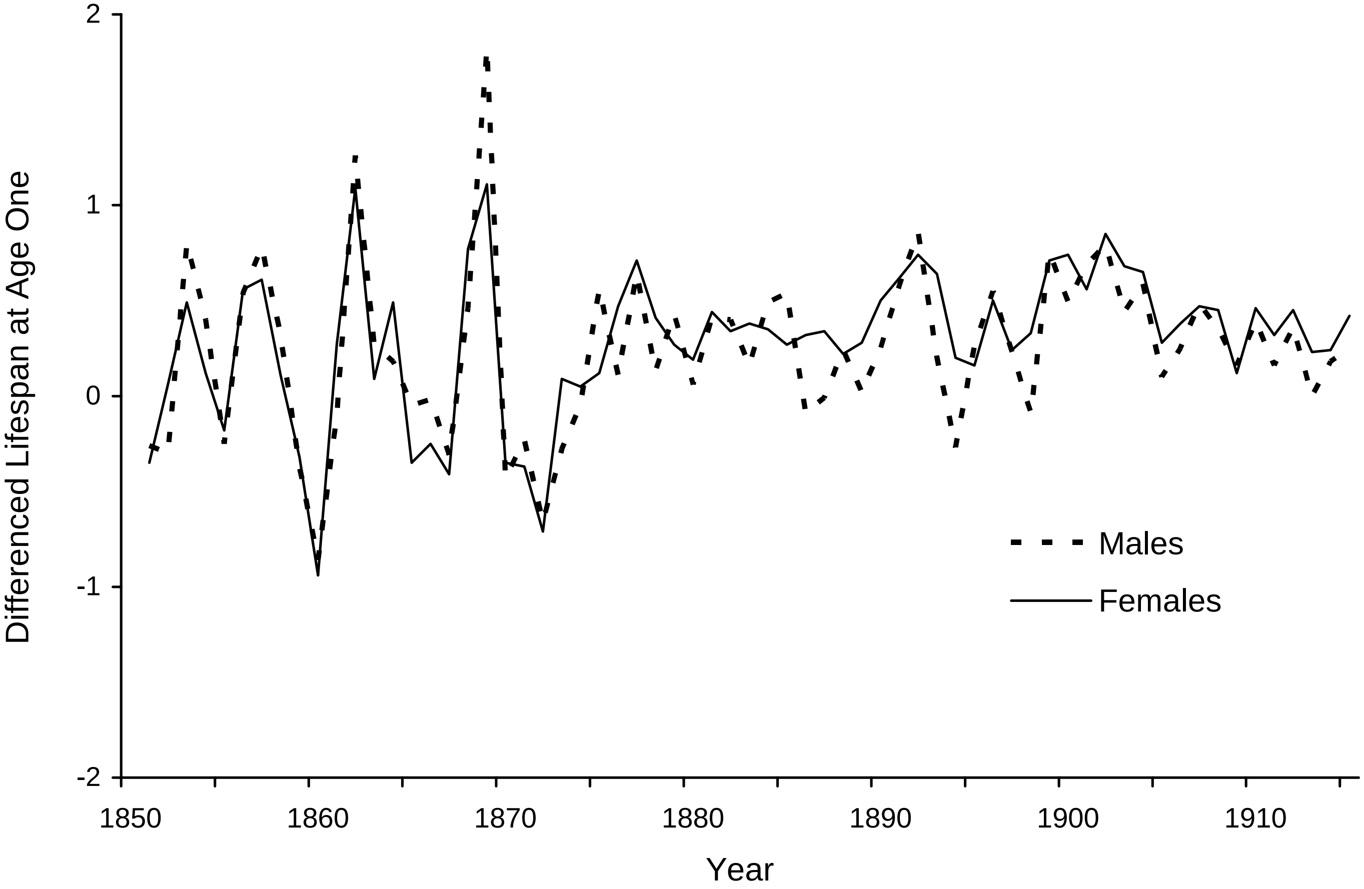

Figure 2. First differences of cohort lifespan at age one for males and females born in Sweden from 1850 to 1915.