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Ambient temperature during gestation and cold-related adult mortality in a Swedish cohort, 1915–2002

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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 season of birth predicts lifespan after age 50. This and other literature implies the hypothesis that ambient temperature during gestation may influence cold-related adult mortality. We use data on over 13,500 Swedes from the Uppsala Birth Cohort Study to test whether cold-related mortality in adulthood varies positively with unusually benign ambient temperature during gestation. We linked daily thermometer temperatures in Uppsala, Sweden (1915–2002) to subjects beginning at their estimated date of conception and ending at death or the end of follow-up. We specified a Cox proportional hazards model with time-dependent covariates to analyze the two leading causes of cold-related death in adulthood: ischemic heart disease (IHD) and stroke. Over 540,450 person-years, 1313 IHD and 406 stroke deaths occurred. For a one standard deviation increase in our measure of warm temperatures during gestation, we observe an increased hazard ratio of 1.16 for cold-related IHD death (95% confidence interval: 1.03–1.29). We, however, observe no relation for cold-related stroke mortality. Additional analyses show that birthweight percentile and/or gestational age do not mediate discovered findings. The IHD results indicate that ambient temperature during gestation—independent of birth month—modifies the relation between cold and adult mortality. We encourage longitudinal studies of the adult sequelae of ambient temperature during gestation among populations not sufficiently sheltered from heat or cold waves.

1. Introduction

Populations living in Arctic and near-Arctic latitudes routinely encounter severely cold temperatures and exhibit elevated adult mortality during cold extremes (Young and Makinen, 2010). In addition, for all three climatic regions—tropical, temperate and polar-mortality due to cold has exceeded mortality due to heat (Rau, 2007; Sheridan and Kalkstein, 2004; Healy, 2003). A separate line of research indicates that season of birth predicts lifespan after age 50 (Doblhammer and Vaupel, 2001). This literature, in addition to reports of temperature sensitivity during fetal development, suggests that ambient temperature during gestation may influence morbidity later in life (Morrison et al., 2000; Canals et al., 2009). We describe the hypothesis, and offer the first empirical test in humans, that the risk of cold-related mortality in adulthood varies positively with exposure to unusually benign ambient temperature during gestation.

Among adults, ischemic heart disease (IHD) and cerebrovascular disease (stroke) rank as the two leading causes of cold-related death (Donaldson and Keatinge, 1997). Although the causes of cold-related IHD and stroke appear multifactorial, research implicates two mechanisms. 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 (Keatinge and Donaldson, 2004). These deaths may also arise due to the rupture of lipid-containing plaques during hypertension and cold-induced coronary spasm (Farb et al., 1995). Such processes may act independently of other meteorological factors (e.g., humidity). Heightened morbidity due to respiratory infections (e.g., influenza) during the winter, moreover, does not account for the positive relation between cold temperature and IHD and stroke (Keatinge and Donaldson, 2001; Kunst et al., 1993; Donaldson and Keatinge, 2002).

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Research further suggests that the early-life environment may adversely affect cold reactivity and increase the risk of cold-related mortality in adulthood. Fetal temperature remains relatively constant despite fluctuations in ambient temperature. However, cold during gestation may perturb development via several indirect pathways (Strand et al., 2011). Evidence from animal models indicates that the fetal response to external temperature induces long-lasting sequelae on the biology of offspring (Morrison et al., 2000; Gluckman et al., 2005; Lee and Zucker, 1988).

Although less work appears in humans, Lawlor and colleagues report an association between ambient temperature after birth and subsequent IHD diagnosis among British women (Lawlor et al., 2004). This report and related literature documenting perturbations in fetal development following maternal exposure to high or low temperatures supports the "developmental plasticity" notion that cold reactivity in adulthood may vary according to ambient temperature during gestation (Bruckner, Modin & Vagero, 2014; Wolf and Armstrong, 2012; and systematic review by Strand et al., 2011). We employ the term developmental plasticity to refer to the ability of a range of human phenotypes to develop from a single genotype in response to environmental cues during the critical period of gestation (Gluckman et al., 2005). According to this argument, a mismatch between the temperature environment *in utero* and that experienced later in life may accelerate mortality in adults.

Catalano and colleagues offer a different explanation of how temperature *in utero* may affect mortality later in life, especially among males (Catalano et al., 2008). They assert that cold during gestation selects especially against male fetuses least adapted to prevailing conditions. Such "culling" of frail males *in utero* could leave behind a smaller but hardier cohort of surviving males. The obverse of this argument, for which Catalano and colleagues find support using ecological life table data in 18th and 19th century Sweden, contends that male cohorts born during benign temperatures exhibit reduced lifespans when confronted with cold later in life (Catalano et al., 2012).

Taken together, previous research in humans identifies pregnancy as a critical period in which gestations adversely respond to perturbations in ambient temperature. We, however, know of no research in humans that tests whether susceptibility to cold-related adult mortality *during cold spells* increases if exposed to benign (i.e., non-cold) temperatures during gestation. We provide such a test using individual-level life course data from Uppsala, Sweden (Uppsala Birth Cohort Multigeneration Study, 2012). This test requires assignment of temperature exposure to individuals throughout their life—from gestation until death in adulthood. We focus on IHD and stroke mortality, the leading causes of cold-related death in adulthood. 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.

2. Methods

2.1. Variables and data

We retrieved data from approximately 13,500 live births delivered at Uppsala University Hospital from 1915 to 1929. These data are linked to the Swedish Cause of Death Register until 2002 (Modin, 2002a). These births, referred to as the Uppsala Birth Cohort Study (UBCoS), are regionally representative of live births in terms of socioeconomic status and rural/urban composition. Rajaleid et al. (2008) further demonstrate that UBCoS is representative of births in Sweden for the years 1915–1929. UBCoS accounts for 75% of all births in the city of Uppsala and 50% of births in the surrounding region (<20 km) in this time period (Leon et al., 1998). UBCoS contains sociodemographic data on the mother and characteristics at birth including exact date of birth and estimated gestational age.

Researchers have linked 12,161 UBCoS birth records to 1960, 1970, and 1980 census registers as well as to cause of death data (beginning in 1952) up to December 31, 2002 (Modin, 2002a). We did not link UBCoS birth records to adult death data if the subject died in infancy ($n = 852$), out-migrated ($n = 190$), or could not be followed for other reasons ($n = 422$). 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 (Uppsala Birth Cohort Multigeneration Study, 2012). Less than 0.5% of the deceased have a non-reported cause of death. We used conventional classification schemes to categorize cause of death. We applied the following ICD codes for IHD death: 420–422 and 410–414 for ICD versions 6/7/8/9, and I20–I25 for the ICD-10 version. For stroke mortality, we applied the following codes: 330–334 for ICD-6, 430–438 for ICD versions 7/8/9, and I60–I69 for the ICD-10 version.

We retrieved the continuous, daily temperature series (in tenths of degrees centigrade) derived from thermometers in the Uppsala (59°52′ N, 17°38′ E) region (Bergström and Moberg, 2002). Daily temperature was calculated as the mean of hourly temperatures taken at least four times over each 24 h 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 publicly-available series to permit temperature comparisons across the test period (Moberg and Bergström, 1997).

2.2. Approach

For each UBCoS individual with date of birth and gestational age information, we assigned an ambient temperature measure during gestation. Temperatures in Uppsala fell below 17 °C (the nadir on the J-shaped temperature/mortality relation: see Keatinge et al., 2000; Kunst et al., 1993) in over 95% 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 during gestation, 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 (i.e., >13.5 °C, or 56.3 °F). This variable summarizes absolute weekly temperature values over the pregnancy and classifies any week as "benign" if temperature falls in the warmest quintile. Previous research on temperature-related birth outcomes employs this approach (Deschênes et al., 2009). For UBCoS subjects, the proportion of the gestation spent in the warmest quintile ranged from 0.0 to 0.44. We also summarized weekly temperatures as the mean over the entire gestation to assess sensitivity of results to the "benign gestation" classification.

The literature on cold-related mortality does not converge on a definition for an acute cold spell (Hong et al., 2003). Research, however, finds non-linear relationships between cold and mortality such that extreme cold events exert the largest IHD and stroke mortality response (Patz et al., 2000). Consistent with this logic and previous climatic research (Reid et al., 2012), we 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 (see World Meteorological Organization, 2011, for more details). For example,

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