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LETTER

Sex differences in adult mortality rate mediated by early-life environmental conditions

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Abstract

Variation in sex differences is affected by both genetic and environmental variation, with rapid change in sex differences being more likely due to environmental change. One case of rapid change in sex differences is human lifespan, which has become increasingly female-biased in recent centuries. Long-term consequences of variation in the early-life environment may, in part, explain such variation in sex differences, but whether the early-life environment mediates sex differences in life-history traits is poorly understood in animals. Combining longitudinal data on 60 cohorts of pre-industrial Finns with environmental data, we show that the early-life environment is associated with sex differences in adult mortality and expected lifespan. Specifically, low infant survival rates and high rye yields (an important food source) in early-life are associated with female-bias in adult lifespan. These results support the hypothesis that environmental change has the potential to affect sex differences in life-history traits in natural populations of long-lived mammals.

Keywords

Development, environmental variation, humans, life-history, sexual dimorphism.

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INTRODUCTION

The extent of phenotypic differences between the sexes, affected by both genetic and environmental changes, can vary considerably over very short periods of time. For example, lifespan has increased dramatically in humans over the last 200 years in most industrialised nations (Beltrán-Sánchez *et al*. 2015) and, interestingly, this increase has been stronger in females. As a result, lifespan has become progressively more female-biased in many contemporary populations (Austad & Fischer 2016; Colchero *et al*. 2016). Changes in sex differences are generally unlikely to occur rapidly through evolutionary processes because selection favouring sex differences frequently affects genes with similar effects in either sex, thus inducing intralocus sexual conflict (Lande 1979; Bonduriansky & Rowe 2005; Griffin *et al*. 2013). This suggests a role for environmental effects to mediate rapid shifts in sex differences in human lifespan, and life-history traits in other natural populations. However, for life-history traits, the link between ecology and sex differences remains poorly understood, not just in humans, but across taxa (Brooks & Garratt 2017). Longitudinal series of data available on human populations (Stearns *et al*. 2010) can therefore prove to be a valuable asset when assessing the potential importance of environmental conditions for sex differences in life-history traits for natural populations of long-lived animals, a critical issue given current rates of environmental change.

Particularly poor environmental conditions during development and early-life have been linked to long-lasting adverse effects on health, reproductive success, and mortality rates in a range of species (Lindström 1999; Metcalfe & Monaghan 2001), including humans (Lummaa & Clutton-Brock 2002). However, whether such factors are associated with variation in sex differences in human life-history traits remains unexplored (Austad 2006; Austad & Fischer 2016). While evidence that changing patterns of sex differences in key life-history traits can result from variation in early-life environments is very limited, two recent studies, in a bird (Wilkin & Sheldon 2009) and a mammal (Garratt *et al*. 2015), do provide some support to this hypothesis. In great tits (*Parus major*), variation in both altitude and size of the natal territory have been linked to recruitment and lifespan in males respectively, but not females, suggesting that variation in the natal environment can drive sex differences in life history traits. In roe deer (*Capreolus capreolus*), higher juvenile mortality rates, which may be indicative of a less favourable environment, were associated with higher adult lifespan in females and lower adult lifespan in males. As a result, lifespan is expected to become more female-biased in more harsh early-life conditions (Garratt *et al*. 2015). Harsh early-life conditions are proposed to either better prepare individuals for similar conditions later in life (predictive adaptive response, PAR, see Gluckman & Hanson 2004), or reduce adult lifespan because of lasting damage to the individual, as suggested by the silver-spoon hypothesis (Wilkin & Sheldon 2009). Alternatively, weaker individuals may be less likely to survive to adulthood when conditions are harsh, leaving only the most viable individuals within the adult population and thus increasing average adult lifespan of the cohort (viability selection, see Garratt *et al*. 2015).

We use longitudinal data from individuals born across a 60-year period in a pre-industrial Finnish population combined

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with detailed data on year-to-year environmental conditions to test for associations between sex differences in life-history traits (adult mortality and adult life expectancy) and environmental variation. Sex differences in adult lifespan in humans may have a number of underlying causes, such as sex differences in the tendency to access and use medical care (Bertakis *et al*. 2000; Vaidya *et al*. 2012), which may also be associated with industrialisation. By using data from a pre-industrial population (Bolund *et al*. 2015) with no access to such advances, we are able to assess the ecology of sex differences in adult mortality linked to variation in early-life conditions, across cohorts with variable magnitude of sex differences, while minimising such confounding effects. During the study period (1791–1850) the Finnish population depended on small-scale farming of rye and barley for their livelihood, supplemented by fishing and hunting. Unpredictable climatic conditions led to frequent crop failures and, subsequently, famines and disease outbreaks were common (Hayward *et al*. 2013, 2016). Environmental variation occurred throughout the study period, which we first quantify as variation in the infant survival rate, as previously used in a similar study in roe deer (Garratt *et al*. 2015) and other species as a broad-scale indicator of environmental severity (e.g. Robinson *et al*. 2008; Martin & Festa-Bianchet 2011). We then extend the study to a more specific ecological context, utilising data on annual crop yields and climate in a subset of cohorts for which this data is available.

MATERIAL AND METHODS

Human data

The Lutheran Church in Finland has been required to record births, deaths and marriages since the 1700s and we use these data for 1988 individuals born in the parish of Ikaalinen in south-west Finland between 1791 and 1850 (60 birth cohorts). The number of individuals born per cohort over the 60 years averaged 67.2 ± 23.96, ranging between 28 and 114, with 49.3% of those born surviving to adulthood (15 years of age). The individuals included in our study sample survived to adulthood, did not migrate before adulthood, and had known socio-economic status during childhood (socio-economic status of the father). Childhood socio-economic status may affect the relationship between adult mortality risk and the environment by determining susceptibility to environmental factors. We therefore estimate and compare the sex-specific responses to environmental variation while controlling for childhood socio-economic status.

Environmental data

We explored the environment which individuals were exposed to in childhood taken as both (1) a 3-year mean around the birth year, combining gestation and the early post-natal period, and (2) the average environment over the first 10 years of life (juvenile period). Throughout the study, infant survival rates were calculated per cohort as the proportion of individuals surviving to the age of 5 years such that; for estimates at the birth year, it is the proportion of individuals born in the focal year, the preceding year, or the following year that survive to age 5; for the 10-year juvenile period estimates, it is the proportion of individuals born in the focal year, or the following 9 years, that survive to age 5. The annual infant survival rates were highly variable among the 60 cohorts, ranging between 50% and 96% survival to the age of five and at an average of 73% survival.

We use data on crop sowing success (yields) as indicators of local grain availability and nutritional stress. Crop yield is measured as the ratio of grain sown to grain harvested by weight, and the annual success varied between 2.71 and 10.47 for barley, and 2.81 and 11.06 for rye, with mean yields of 6.07 and 6.27 for barley and rye respectively. Crop yields, while not measuring the *per capita* availability of crops, indicate the between-year variation in harvest success without being biased by factors such as cultivation area or intensity, providing a relative measure of nutritional stress (Hayward *et al*. 2012). Data on barley yield was available to produce 3-year estimates for 1543 individuals across 37 cohorts (mean cohort size = 41.7), and 10-year estimates for 1345 individuals across 30 cohorts (mean cohort size = 44.8). Data on rye yield was available for 3-year estimates for 1588 individuals across 40 cohorts (mean cohort size = 39.7) and for 10-year estimates for 1345 individuals across 30 cohorts (mean cohort size = 44.8). We also use data on spring temperature to assess the effect of variation in climatic conditions. Reconstructed annual spring temperature data for south-west Finland (Holopainen *et al*. 2009) showed a mean temperature of 2.56 °C and range of 0.28–7.19 °C for the study period. Data on spring temperature was available for 3-year estimates for 1762 individuals across 46 cohorts (mean cohort size = 38.3), and for 10-year estimates for 1789 individuals across 47 cohorts (mean cohort size = 38.1).

Crop yields and spring temperatures are known to have affected life-history traits in the study population (Rickard *et al*. 2010; Hayward *et al*. 2013): a great famine during the late-1860s largely resulted from failed crops following a late onset of spring bringing unusually high infant mortality; in 1867, 48.0% of children born in Ikaalinen died before the age of five. There were no secular trends (Fig. S1) for annual measures of infant survival (generalised linear model: $\beta = 0.001 \pm 0.017$, $P = 0.951$), barley yield (linear model [lm]: $\beta = -0.004 \pm 0.023$, $P = 0.851$), rye yield (lm: $\beta = -0.011 \pm 0.021$, $P = 0.589$), and spring temperature (lm: $\beta = -0.010 \pm 0.015$, $P = 0.481$).

Statistical analysis

Effects of the environmental factors on sex differences in adult mortality were assessed in Cox proportional hazards models using the 'coxph' function in the 'survival' R package (Therneau 2012), using the individuals that survived to adulthood as the study population. Individual models were constructed for each environmental factor, with lifespan as the response variable, and including fixed effects of sex (two-level factor), childhood socio-economic status (two-level factor; 'land-owners' and 'landless'; see Bolund *et al*. 2015), and the environmental factor of interest, as well as their interactions (sex × environment × socio-economic status, sex × environment, socio-economic status × environment) and the random effect of cohort. These models estimate values of the sex-

specific regression coefficients (β), herein denoted by subscript M (male) and F (female) as appropriate. Cox proportional hazards models were used as they also allow the inclusion of individuals with 'censored' lifespan, i.e. those with a minimum known lifespan inferred from records of other events ($n = 663$) such as church attendance, child birth, marriage, and migration, rather than limiting analyses to a potentially biased sample of individuals with a known lifespan. We did not control for: mother identity, because only a small number of offspring per mother survive to adulthood (with many only producing one offspring surviving to adulthood) and thus mother identity would largely explain the same variation as individual identity; maternal mortality during childhood, because this information was not available for all our study subjects and the negative effects of maternal death on individual mortality risk appear to be short-term in the study population, with effects present in childhood (Lahdenperä *et al.* 2011); and reproductive status of the individual (or number of children), as this may have been inherently biased by survival because short-lived individuals had less opportunity to reproduce. We did not test models that contain multiple environmental factors simultaneously (e.g. barley and rye yield) and their interactions because; (1) there were strong correlations among the fixed environmental effects measured over the 10-year juvenile period ($r_{\text{Barley, Rye}} = 0.69$, $P < 0.001$; $r_{\text{Barley, Temperature}} = -0.55$, $P = 0.001$; $r_{\text{Rye, Temperature}} = -0.44$, $P = 0.013$), and (2) not all individuals included in the analyses had data for all factors for the same years, thus doing so would reduce sample size and power.

Models were reduced by backwards elimination, retaining terms which substantially improved model fit (as judged by AIC, Table S2), the two-way interaction of interest in this study (sex × environmental factor), and any main effects for factors retained in higher order terms. The assumption of proportional hazards was checked using the 'cox.zph' function and all models considered in the analyses satisfy this assumption. From the model summaries, we extracted estimates of the sex-specific coefficients, and differences in sex-specific coefficients, along with estimates of the standard error and P values for a null hypothesis that the coefficient, or difference between coefficients, is zero. Predictions of sex-specific adult life expectancy in relation to infant survival rate and environmental factors were also drawn from these reduced models, using the 'survfit' function in the 'survival' R package, while removing the random effect of cohort as survfit cannot handle models containing random effects terms. Two further Cox proportional hazards models were fitted with fixed effects of only cohort, and both sex and cohort, and compared by likelihood ratio testing to test for variation in sex-specific adult mortality risk. Population-wide predicted life expectancy at adulthood was also estimated using the latter model and survfit function.

RESULTS

Within this study population, there was considerable variation in sex differences in adult mortality ($\chi^2 = 17.73$, $P < 0.001$) illustrated by clear sex differences in survival curves (Fig. 1a). As a result, adult life expectancy was predicted to be female-biased, to a varying degree, in all cohorts (Fig. 1b), with expected lifespan at adulthood on average being 62.30 years in males and 66.41 years in females.

Sex-specific responses to early-life environmental variation

Cohorts which were exposed to lower rates of infant survival at the time of birth (3-year) expressed increased adult mortality risk in males ($\beta_M = -1.128 \pm 0.562$, $P = 0.045$), consistent with the silver-spoon hypothesis, while no association was present in females ($\beta_F = 0.132 \pm 0.587$, $P = 0.820$). When considering the early-life environment over the 10-year juvenile period, males show a qualitatively similar but not statistically significant association with infant survival rate ($\beta_M = -1.148 \pm 0.927$, $P = 0.215$), while a stronger association closer to statistical significance was found in females, with a lower adult mortality risk in cohorts exposed to low infant

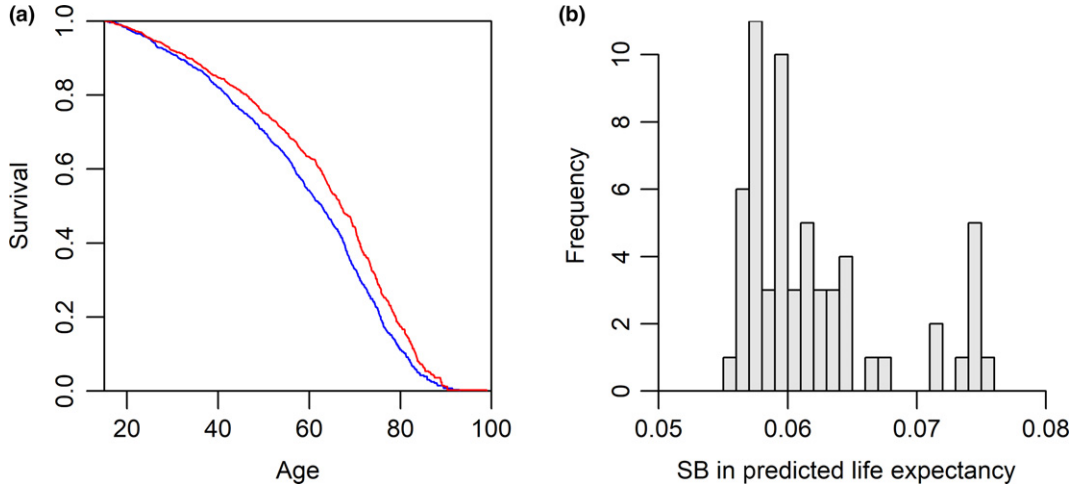

Figure 1 Survival and sex differences in expected adult lifespan. (a) Survival curves for the 1988 individuals used in the study (see methods), with males (blue) showing lower survival than females (red). (b) Sex-bias (SB; 1 − [M/F]) in life expectancy at adulthood, as predicted by the model, was female-biased for all cohorts.

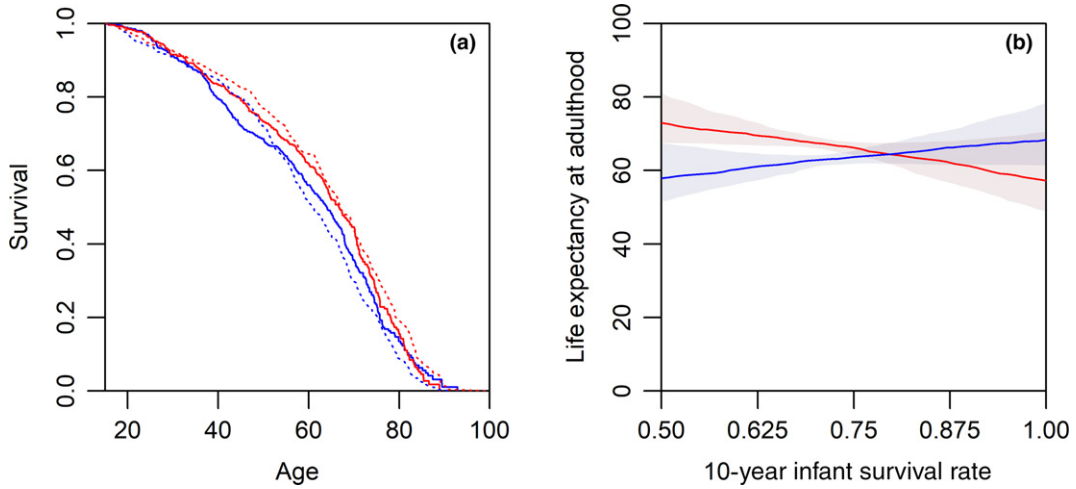

Figure 2 The relationship between 10-year infant survial rates and adult life-history. (a) Females (red) showed consistently higher rates of survival than males (blue), and this difference appears to be smaller in cohorts with above average 10-year infant survival rate (solid lines) than in cohorts with infant survival rates below average (dashed lines). (b) Life expectancy at adulthood was expected to be higher in females (red) than males (blue) when infant survival rates were low, and for males to outlive females when infant survival rates were high, though 95% confidence intervals (shaded areas) overlap for much of this area. Sample size of 1988 individuals across 60 cohorts.

survival rates during early-life ($\beta_F = 1.890 \pm 0.989$, $P = 0.056$, Fig. 2a), consistent with the viability selection hypothesis. While averaging the environment over a longer period of time will reduce the environmental variation between cohorts and potentially weaken the ability to detect effects early in childhood, the developmental period in humans is extraordinarily long compared to other long-lived mammals, thus the longer time period allows us to test for any effects which accumulate through later phases of development which would be missed in analysing just the birth period. Because our results illustrate that the environment experienced during the entire early-life period is important in determining adult mortality risk, we herein focus on effects over the 10-year juvenile period for brevity (but see Table S1 for the corresponding results for environmental conditions around the time of birth).

Cohorts exposed to better nutritional conditions during the juvenile period, as measured by higher yields of barley, have lower adult mortality risk in females ($\beta_F = -0.272 \pm 0.111$, $P = 0.015$) but not males ($\beta_M = -0.037 \pm 0.107$, $P = 0.733$). Inspection of survival curves (Fig. 3a) shows that adult mortality is decreased for females when yields of barley are high in early life. Similarly, exposure to high yields of rye during the juvenile period was also associated with reduced adult mortality in females ($\beta_F = -0.187 \pm 0.065$, $P = 0.004$) but not males ($\beta_M = 0.038 \pm 0.056$, $P = 0.501$, Fig. 3c). These results support that the nutritional environment during early-life has the potential to affect adult mortality and life expectancy, such that nutritionally rich environments were associated with longer life expectancy in females, a result consistent with the silver-spoon hypothesis, but not males (Fig. 3b, d). Spring temperature during the juvenile period was positively associated with adult mortality in males ($\beta_M = 0.107 \pm 0.052$, $P = 0.039$) but not females ($\beta_F = 0.068 \pm 0.052$, $P = 0.192$), such that males from cohorts which endured colder conditions during the juvenile period had lower adult mortality risk (Fig. 4a). This supports that variation in adult life expectancy may be mediated by climatic variation in early-life, with expected lifespan decreasing in males more than females as spring temperatures during the juvenile period increase (Fig. 4b).

Sex differences in responses to early-life environmental variation

Comparison of sex-specific coefficients in response to infant survival rates during the juvenile period suggests that sex differences in adult mortality risk were associated with variation in the early-life environment ($\beta_F - \beta_M = 3.039 \pm 1.326$, $P = 0.022$). Survival curves suggest that sex differences in mortality were smaller in cohorts exposed to high rates of infant survival (Fig. 2a). As a result, adult life expectancy was female-biased in cohorts exposed to low rates of infant survival during the juvenile period (Fig. 2b). For all three ecological factors (barley yield, rye yield, and spring temperature), we find statistically significant responses in one sex and smaller non-detectable responses in the other, supporting that various aspects of the environment experienced during the juvenile period simultaneously contributed to sex differences in adult mortality risk. Formal comparison of the sex-specific estimates suggests that adult mortality risk in males and females showed different responses to rye yields ($\beta_F - \beta_M = -0.224 \pm 0.084$, $P = 0.008$). However, we find no statistically significant differences between male and female specific associations with barley yields ($\beta_F - \beta_M = -0.235 \pm 0.151$, $P = 0.120$) or spring temperature ($\beta_F - \beta_M = -0.039 \pm 0.072$, $P = 0.591$) experienced during the juvenile period. Overall, these results support that variation in early-life environment can have lasting consequences mediating variation in sex differences in life-history traits.

DISCUSSION

The early-life environment is known to have lasting effects on life history traits in humans (Hayward *et al.* 2013), but

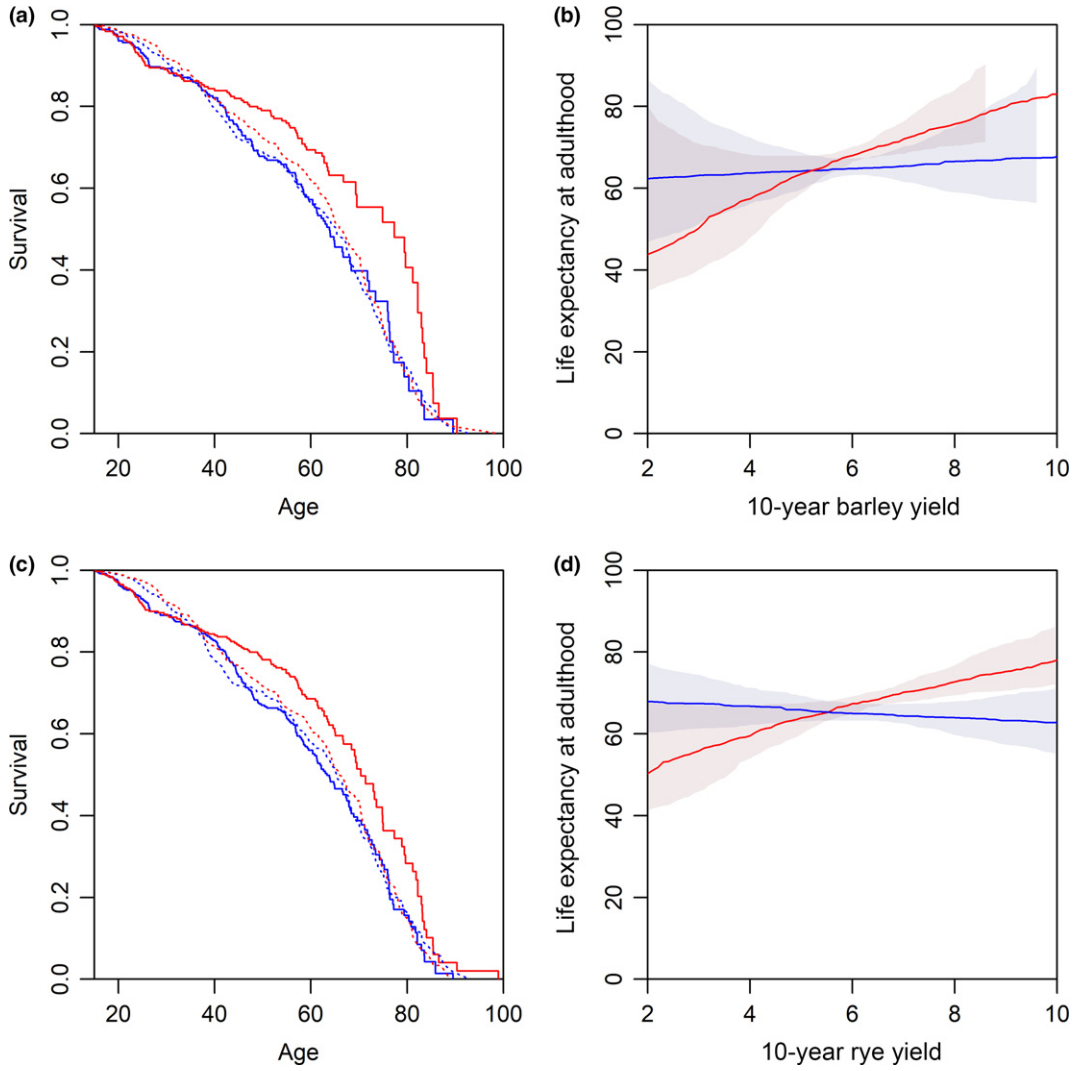

Figure 3 The relationship between 10-year crop yields and adult life-history. (a) Survival in males (blue) in cohorts exposed to below average barley yields (dashed lines) were similar to those exposed to above average yields of barley (solid lines), while female (red) survival was increased when yields of barley were high. (b) Life expectancy at adulthood was more strongly associated with barley yield in females (red) than males (blue), such that lifespan was predicted to become female-biased when barley yields were high, and male-biased when barley yields were low. Confidence intervals do not show for higher yields of barley because few cohorts experience high yields (Fig. S1). (c) Similarly to barley yield, rye yield showed greater effects in females than males, with survival increasing in females when rye yields were high, leading to (d) predictions of increasing female-biased lifespan when rye yields were high. Sample size of 1345 individuals across 30 cohorts.

whether variation in the early-life environment is linked to variation in the extent and direction of sex differences in such traits is poorly understood in natural animal populations. Our study supports the conjecture that the environment experienced during early-life can have long-lasting consequences for sex differences in life-history traits such as adult mortality risk and expected lifespan, highlighting the importance of determining the ecological drivers of sex differences both in humans and other natural animal populations, particularly in this era of rapid environmental change (Simmonds & Coulson 2015). The recent transitions in human mortality and fertility patterns as a consequence of rapid environmental change are among the most striking described for any species (Scranton *et al*. 2016), and the longitudinal records available on humans across varying environmental conditions make them a valuable system which can be used to study the effects of environment on sex differences in life-history traits in a general context which is informative across taxa (Briga et al. 2017).

Using infant survival rate as an indicator of environmental severity, as in previous ecological studies, we show that harsh early-life environments were associated with increased sex differences in mortality risk and female-bias in adult life expectancy. This result is concordant with a recent study in roe deer (Garratt *et al*. 2015), but not with modern human trends which are characterised by increasing infant survival and female-bias in life expectancy. While infant survival rates are used within ecology as a proxy for the severity of environmental conditions, they can be simultaneously affected by a wide range of ecological factors including nutritional and abiotic

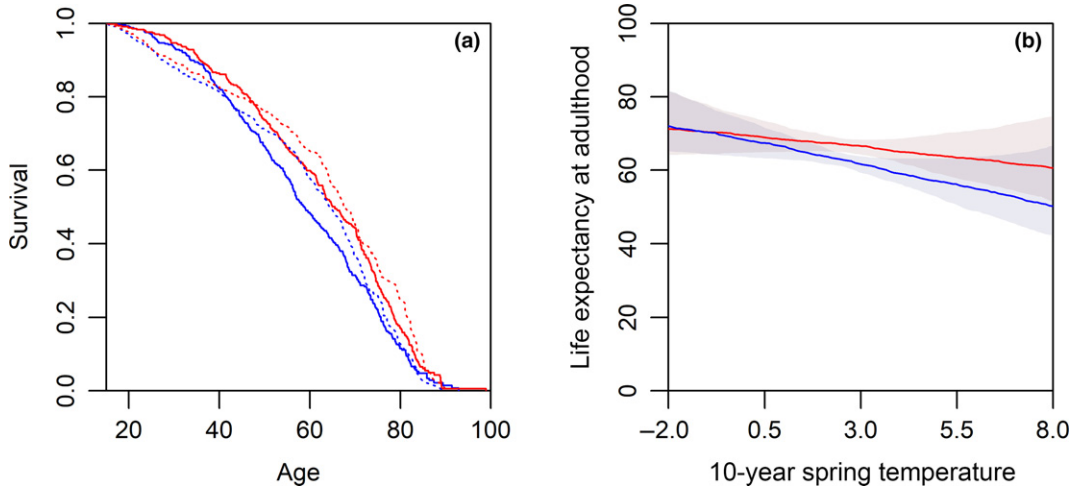

Figure 4 The relationship between 10-year spring temperature (°C) and adult life-history. (a) Survival was reduced in cohorts exposed to above average spring temperatures (solid lines) in both males (blue) and females (red) relative to cohorts exposed to below average spring temperatures. (b) Adult life expectancy showed mild declines in both sexes in cohorts exposed to higher spring temperatures, but predicted increasing female-bias in lifespan as temperature increases. Sample size of 1789 individuals across 47 cohorts.

stressors, as well as epidemics of infectious disease which were common at the time of our study population (Hayward *et al.* 2016) and were not incorporated into our study. It is likely that the factors determining infant survival rates differ greatly between our study population and current human populations, which could offer an explanation for the discrepancy between our results and modern trends. Our results from three environmental factors (barley yields, rye yields, and spring temperature), which more directly assess potential environmentally induced stress, suggest that less harsh environments, those with better food availability and warmer temperatures, led to further male-bias in adult mortality risk and female-bias in expected lifespan. This latter result can be considered as being consistent with trends over recent generations of humans. Taken together, these results highlight that conclusions drawn using coarse demographic measures of the environment, such as infant survival rates which are affected simultaneously by many different factors such as disease and more stochastic events, may differ to those using more direct measures of the environment due to the complex nature of coarse measures.

Sex differences in life-history traits have been linked to early-life environmental variation in a limited number of studies in natural environments; in a mammal (Garratt *et al.* 2015) and a bird (Wilkin & Sheldon 2009) species. While such links have not previously been demonstrated in human populations, knowledge of the general importance of early-life effects in determining sex differences in life-history traits is certainly also lacking for natural populations (Brooks & Garratt 2017). Further female-bias in adult life expectancy was predicted to occur in our study population when there were good crop yields or warmer spring temperatures, with these occurring through decreasing female mortality in the case of crops, and increasing male mortality in the case of spring temperature. The sex-specific associations with rye yield, and the general sex-specific pattern found across environmental factors, suggest that improved access to food and reduced environmental stress lead to increased sex differences in adult mortality risk, and increased female-bias in life expectancy. In the birth-year centred results on crop yields, models featuring the three-way interaction between sex, environment, and childhood socio-economic status, further support that the environment and susceptibility to the environment, which may be mediated by socio-economic status, can affect sex differences in life history traits (Fig. S3). While human populations in most industrialised nations have moved far beyond the levels of nutritional and climatic stress that the population in our study would have experienced, our results nonetheless give the first evidence that sex-specific responses to the early-life environment may contribute to sex differences in life-history traits in humans. Indeed, ecological variation during early development even in contemporary developed countries has been linked to a range of health outcomes in adulthood (Huxley *et al.* 2007; Mandl *et al.* 2009; Belbasis *et al.* 2016), showing that between-individual differences in developmental conditions continue to exert long-term effects in humans. Furthermore, these results make a valuable contribution to our broader understanding of the link between variation in the early-life environment and sex differences in life-history traits.

Sex differences in life expectancy and mortality could be linked to the environment if lifespan responds differently to environmental effects in males and females. At the individual level, harsh environments may either increase (PAR) or decrease (silver spoon) expected lifespan, while cohorts may also bear the signature of viability selection. In the latter case, weaker individuals that would be short-lived as adults are more likely to die prior to adulthood when exposed to harsh conditions and, if environmentally determined rates of viability selection are sex-specific, sex-bias in pre-adulthood mortality would be associated with sex differences in adult lifespan. Males typically invest more than females in the development of costly sexually selected traits (Vinogradov 1998; Bonduriansky *et al.* 2008), such as large body size, at the expense of reduced survival probability. Under harsh environmental

conditions, expensive male growth requirements could thus lead to male-biased pre-adult mortality, thereby increasing viability selection in males and increasing male lifespan more so than in females in the resulting cohort. Our data indicates that this may be the case in humans, as female-bias in expected adult lifespan was lower when pre-adulthood mortality was male-biased, which would be expected to remove low quality males and leave low quality females in the cohort, such that sex-biased rates of infant mortality are associated with the sex differences in adult life expectancy (Fig. S4). Disentangling the mechanisms underlying sex differences in life-history traits is a substantial challenge which is yet to be addressed, and while our results indicate that sex-differences in viability selection may be a factor here, there is a pressing need to address this issue more thoroughly both in humans and other natural systems. Our results from the Finnish pre-industrial population offer support to the hypothesis that environmental changes can help to explain increasing sex differences in life-history traits such as lifespan, mortality, and ageing, as has been increasingly common in human populations since industrialisation. In a broader context, our results suggest that accelerating environmental change could alter patterns of sex differences in life-history traits in natural populations of other animals.

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AUTHORSHIP

RMG and VL designed the study, VL collected data and RMG analysed data, all authors contributed to writing of the manuscript.

DATA ACCESSIBILITY STATEMENT

Data available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.b31h1

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SUPPORTING INFORMATION

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