CHAPTER 6

Making the Case for Mutation Accumulation

Introduction

Previous chapters have examined relevant aspects of the pre-industrial (specifically medieval) and modern Western worlds, along with factors likely responsible for the transition between them. We have placed special emphasis on selective processes that apparently enhanced the levels of g and K in Western populations over time, such that these groups became (in historical context) unusually cooperative, hardworking, future-oriented, and innovative. A large body of convergent evidence suggests that these characteristics have been essential to the unparalleled standards of living that Westerners have achieved (Clark, 2007; Rindermann, 2018; Woodley of Menie, Figueredo et al., 2017).

But we have also indicated that the effects of this biological modernization have not been exclusively good, especially in the immediately preceding chapters. Notably, the group-level fitness of Western peoples has been declining precipitously for around a century and shows no signs of recovering (Inglehart, 2018; Meisenberg, 2007). Moreover, and to partially reiterate, a number of dimensions of phenotypic quality in these groups have been degrading: their mental health (Twenge et al., 2010; Twenge, 2013), developmental stability[1] (Woodley of Menie & Fernandes, 2016; Woodley of Menie, Fernandes, Kanazawa & Dutton, 2018), and (in

[1] Developmental stability refers to an organism's resilience to insults (genetic and environmental) that occur in the process of biological development.

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certain respects) physical well-being (Levine et al., 2017[2]; Staub et al., 2018; You & Henneberg, 2016, 2017, 2018) potentially have been worsening, as have correlates of dominance in males (e.g. testosterone levels [Travison et al., 2007] and strength [Fain & Weatherford, 2016]). There are various distinct proximate-level explanations of these phenomena, which invoke, for example, xenoestrogens and other pollutants to explain testosterone and fecundity[3] declines in males (Levine et al., 2017; Toppari et al., 1996), or rapid social change and attendant stress to explain increasing rates of mental health problems (Rosa, 2013), but the possibility of a common factor underlying all of these trends has not been adequately explored.

One candidate factor is *deleterious mutation accumulation*, or the buildup of fitness-depressing mutations in the Western gene pool. Accumulation of such mutations could be reasonably expected as a consequence of the probable relaxation of negative selection in Western populations, that is, selection that removes deleterious genetic variants (which occur due to imperfections in the process of DNA replication and environmental factors that induce genetic damage). Since the opportunity for such negative selection to act, at least through mortality, has been massively diminished following industrialization, insofar as the subsequent improved standards of living have all but eliminated reproductively relevant human mortality (i.e. mortality that prevents an individual from having the opportunity to participate or fully participate in reproduction) from the period of infancy on, mutation accumulation is a serious concern: Given that every human trait is under some degree of genetic control, progressively larger burdens of harmful mutations threaten to impair the quality of every human trait. Unsurprisingly, over the last 80 years, a number of prominent biologists have called attention to the potential problem of deleterious mutation accumulation. These include Muller (1950), Haldane (1937), Hamilton (2001), Crow (1997), Kondrashov (2017), and Lynch (2016). The average estimated impact of these mutations on human "fitness" is on the order of a 1% loss per generation, which over the course of a century (approximately four generations) would be fairly substantial, potentially rendering mutation accumulation an existential risk (Lynch, 2016).

[2] Given the association between sperm count and general health (Levine et al., 2017), the massive declines in sperm count that Levine et al. (2017) find are especially troubling.

[3] But as it happens, "there is currently very little epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders (including reduced sperm counts)" (Pacey, 2017; see Bonde et al., 2017).

Importantly, not all relevant academics are in agreement about the threat of mutation accumulation. Arslan et al. (2018) suggest[4] that negative selection has not relaxed in the shift from pre-industrial to industrialized, or modernized, life. They draw this conclusion from the fact that paternal age effects on fitness-relevant outcomes are comparable across one industrialized and three pre-industrial populations. Paternal age effects are germane in that older fathers are thought to bequeath larger burdens of *de novo* (newly acquired, i.e. not present in the genome of either parent) deleterious mutations to their offspring than younger ones on average (Moorjani, Gao & Przeworski, 2016). Older mothers also bequeath larger burdens of *de novo* mutations to their offspring than younger ones on average, but the effect is much smaller compared to that of paternal age (Wong et al., 2016).

A recent exchange of papers in *Proceedings of the Royal Society B* (Arslan et al., 2018a, 2018b, 2018c; Woodley of Menie, Sarraf, & Fernandes, 2018), in which two of the current authors were involved, in part concerns the adequacy of paternal age effects on fitness-relevant outcomes as a proxy for negative selection, allowing comparison of the strengths of negative selection across populations and over historical time. Arslan et al. (2018a) find differential fitness-relevant outcomes among the children of fathers[5] of different ages in three historical populations and one modernized population (controlled for multiple covariates). This is taken to support the hypothesis that older fathers bequeath greater burdens of deleterious *de novo* mutations to their offspring on average compared to younger fathers. Arslan et al. (2018a) furthermore report evidence of slight declines in average paternal age over time. Given seeming implicit assumptions about the operation of negative selection acting on the *relative* fitness differences of genomes exhibiting different loads of deleterious mutations (e.g. the fitness of a given genome relative to the average genome of the population), and apparent minimal change in average age at paternity over time, Arslan et al. (2018a) reject claims of serious mutation accumulation in human populations (though Arslan et al., 2018b deny that they rejected these, an issue to which we will return):

[4] In subsequent relevant publications, they have denied that they made any such suggestion. In the course of this chapter, we explain why we disagree.

[5] Arslan et al. (2018a) also find evidence of grandpaternal age effects in one historical population.

> While advanced parental ages at first birth may entail smaller families, pre-industrial populations had similar average ages at birth and were not overwhelmed by mutational stress. So, we do not predict that contemporary reproductive timing will lead to unprecedented or unbearable de novo mutational loads and concomitant changes in the prevalence of genetic disorders. The decline in fitness with paternal age suggests that purifying selection is still effective in a modern population with hormonal contraception, social transfers and modern medicine. This runs counter to oft-repeated predictions of mutational doom by relaxed selection. (p. 8)

In response, Woodley of Menie, Sarraf, et al. (2018) observe that fitness variation as a function of paternal age is not sufficient to rid populations of deleterious mutations if the personal fitness costs of those variants are becoming increasingly attenuated via general reduction of environmental harshness through, for example, industrialization; simply put, the *relative* intra-population costs of larger burdens of *de novo* mutations could remain similar over time but change in the "absolute" costs could be great enough to allow accumulation of increasingly mildly deleterious mutations "across the board" (where the increase in mildness is driven by decreases in environmental harshness). Woodley of Menie, Sarraf, et al. (2018) point to research on the biological state index (I_{bs}; Henneberg, 1976), which operationalizes opportunity for mortality selection (i.e. selection which acts through differential mortality) in a population via the computation of a probabilistic index capturing the likelihood of a randomly selected individual within a given population having the opportunity to fully participate in the reproduction of the next generation. Essentially as the opportunity for selection decreases (as captured by factors such as diminishing infant mortality), an individual's likelihood of having the opportunity to fully participate in reproduction approaches unity. Thus, I_{bs} values are scaled from 0 to 1, with some contemporary countries having I_{bs} values around 0.99 (meaning that almost everyone born has the opportunity to fully participate in the reproduction of the next generation; Henneberg, 1976; Rühli & Henneberg, 2013).

If increases in I_{bs} generally correspond to attenuation of negative selection through differential mortality, then, in the absence of some countervailing negative-selective factor(s), as I_{bs} rises, a larger proportion of *de novo* deleterious variants will tend to persist across generations as *legacy load*, which will contribute to mutation accumulation. This phenomenon allows the average genome's burden of deleterious mutations to increase,

even though fitness variation among individuals as a function of, for example, paternal age effects will continue to be observed. What is preserved in this instance is the *rank order* of the paternal age effect on relative fitness (specifically, older fathers' children remain on average less fit than those of younger fathers, all else equal[6]).

Another crucial issue concerns the adequacy of I_{bs} as a proxy for negative selection in populations. There is no contemporary, modernized national population in which 99% of people who are born reproduce, despite the ~0.99 I_{bs} values in some of these populations; however, the index simply indicates the percentage of people who have the opportunity for full participation in reproduction by virtue of survival through all reproductively relevant years. The index is derived from mortality and fertility schedules, with the effect of mortality at different ages weighted according to the fertility rate in the population associated with each age. Mortality, especially child and infant mortality, may be a highly significant source of negative selection in historical and also certain contemporary populations—indeed childhood has been termed the *crucible of human evolution*, owing to the historically extremely high rates of child mortality (in particular) in certain regions and times (Volk & Atkinson, 2008, 2013). Woodley of Menie, Sarraf, et al. (2018) make the key claim that this mortality likely *has not been random* with respect to mutation load, especially if mutations have pleiotropic effects on multiple fitness-critical domains (pleiotropy is the phenomenon of one gene affecting more than one phenotypic trait), which is the basis for the existence of the *f* or "general fitness" factor among different sources of individual differences, such as cognitive ability, body symmetry, health, height, and so on, first proposed independently by David Houle (2000) and Geoffrey Miller (2000):

[6] For the purpose of illustration, suppose that those born in Population A to 30-year-old fathers have a 20% chance of dying in infancy due to the effects of *de novo* deleterious mutations and those born to 40-year-old fathers have a 40% chance of this outcome (and so the higher mortality risk for the offspring of the older fathers is due entirely to the tendency for the *de novo* burdens of harmful mutations that fathers bequeath to their offspring to increase with paternal age); the respective figures for Population B are 0.5% and 1% (assume that all else is equal between Population A and B, apart from differences in environmental conditions that render the same deleterious *de novo* variants more harmful in A compared to B). In both cases, the effect of ten additional years of paternal age is a doubling of the risk of infant death, but the overall strength of mortality selection in infancy against deleterious variants is clearly lower in B compared to A.

> If child and infant mortality were random with respect to deleterious variants, then they could not have been major sources of negative selection. There are reasons to doubt this possibility, however…the presence of the general fitness factor…suggests that in very competitive ecologies and in the absence of factors that would attenuate the fitness costs of mutations… pleiotropic mutations may have been especially lethal due to their potential to impair functionality across a number of fitness-critical domains. (Woodley of Menie, Sarraf, et al., 2018, pp. 1–2)

The *f* factor therefore serves to unite multiple vulnerabilities in historical populations (e.g. poor health should correlate with poor impulse control, which should in turn correlate with low cognitive ability and thus relatively high vulnerability to selection via "evolutionarily novel hazards," etc.); this might explain why, historically, infant and child mortality were highest among those with low socioeconomic status, who had concomitantly lower relative lifetime reproductive success as compared with those of higher status (Clark, 2007), reflecting the potential action of efficient negative selection (this model assumes that increasing mutation load puts descendants at risk of downward social mobility and reproductive failure).

Woodley of Menie, Sarraf, et al. (2018) further argue that the *f* factor is a plausible explanation for the so-called mutation load paradox—or the fact that premature death and reproductive failure are quite uncommon in modernized populations despite the high human deleterious mutation rate, which seems to entail that modernized populations should be in mutational meltdown, with very high reproductive failure (88%) and concomitantly very high compensatory reproduction (16 children per viable woman) needed to prevent this outcome (Kondrashov & Crow, 1993). Historical infant and child mortality might have approached the levels needed to remove deleterious mutations *if* the death was non-random with respect to mutations targeting *f* (in some countries historical child mortality was as high as 50%; Volk & Atkinson, 2013). This observation could substantially reduce the paradoxical quality of the discrepancy between theoretical predictions of mutational meltdown in modernized societies and their actual relevant conditions, in that it highlights that a substantially weaker "mutation load paradox" may well have been observed throughout most of human history (with selection on the relative fitness differences of genomes perhaps accounting for whatever disconnect would remain; Lesecque, Keightley & Eyre-Walker, 2012). The departure of modernized societies from high rates of premature death and reproductive

failure may in part be due to the mitigation of environmental harshness and its negative selective effects on mutation load through industrialization and its *sequelae*, and thus the average human genome historically may have been much closer to freedom from deleterious mutations than the contemporary genome (Woodley of Menie et al., 2017; Woodley of Menie, Sarraf, et al., 2018).

In a response to these and other arguments, Arslan et al. (2018b) make the following claim: "Woodley of Menie, Sarraf, et al. [2018] argue that opportunity for selection strongly corresponds to strength of purifying selection. However, there is no necessary correspondence between the two" (p. 2). Strictly speaking, this is incorrect, since opportunity for selection sets a limit on the strength of negative selection, as Arslan et al. (2018b) go on to acknowledge: "Selection strength cannot exceed opportunity, but it can be smaller and can vary independently" (p. 2). That aside, the lack of *necessary* correspondence does nothing to contradict the claim that there *likely is* meaningful correspondence (as a matter of empirical fact), and Arslan et al. (2018b) fail to provide any compelling basis to doubt this idea (their arguments are considered more fully in the Discussion). They refer to the role of "non-genetic social factors and random chance" (Arslan et al., 2018b, p. 2) in determining variation in fitness, but they do not mention the role that genetic factors would play in mediating the effects of many "non-genetic" environmental influences on fitness outcomes in humans. For example, one of the greatest causes, if not *the* greatest cause, of historical infant and child mortality, namely infectious disease (Caldwell, Caldwell, Caldwell, McDonald & Schindlmayr, 2006), would vary substantially in its effects on individual fitness as a function of the immunological integrity of children and infants. Arslan et al. (2018b) do not discuss the *f* factor or the challenge it implicitly poses to claims of high randomness with respect to genotype of historical infant and child mortality. Moreover, given that reproductively relevant mortality *from infancy on* (i.e. not including subinfant mortality, although as we will see this also seems to have decreased) has been nearly eliminated in many modernized societies, the point Arslan et al. (2018b) raise has limited importance: in periods of life where there is hardly any mortality, there can be hardly any negative mortality selection (consider Kondrashov, 2017: "An almost complete elimination of pre-reproductive mortality abolished the opportunity for selection through differential viability and, thus, definitely reduced its strength" [p. 193]). Unless one assumes that all or nearly all of the mortality from infancy through the subsequent reproductively relevant periods of life has been random with respect to del-

eterious mutations throughout human evolutionary history, and thus that the negative-selective fraction of this mortality has been at most minuscule, it is difficult to believe that modernization has not substantially relaxed negative *mortality* selection in these periods of life. Elective abortions, a source of subinfant mortality, are quite common in modernized populations, but the vast majority of these abortions are non-therapeutic, that is, not prompted by known medical problems with the aborted child, which lowers the likelihood that they have negative-selective effects (Woodley of Menie, Sarraf, et al., 2018; Arslan et al., 2018b offer a response on this score, which we consider in the Discussion of this chapter).

Woodley of Menie, Sarraf, et al. (2018) also offer a quasi-empirical simulation to illustrate their point about the possibility of mutation accumulation occurring despite persistent (and even declining) paternal age effects on *de novo* burdens of harmful mutations, using data on paternal age and imputed *de novo* mutation loads sourced from a study of the Icelandic population by Kong et al. (2012). The model was based on a simplifying assumption, namely that for birth cohorts separated by intervals of 20 years (as available from Kong et al., 2012), the *de novo* load of a particular cohort would persist to the next as legacy load in proportion to the historical I_{bs} value associated with that cohort. I_{bs} was modeled as increasing linearly from a value of 0.35 for the cohort with mid-year 1654.5 to 0.99 (equal to the observed contemporary value for Iceland, 0.99; Budnik & Henneberg, 2017) for the cohort with mid-year 2014.5, using data from Rühli and Henneberg (2013). The model indicated that mutation load should have increased linearly across cohorts (temporal $r = 0.987$), *despite* a significant decrease in paternal age across the cohorts (temporal $r = -0.714$). When the simulation was re-run fixing the I_{bs} value to 0.35 (approximately equal to the value for most of human history; Rühli & Henneberg, 2013), no significant change in cohort-by-cohort load was detected (temporal $r = -0.003$). Nonetheless, it must be emphasized that this model was not intended to give an estimate of the extent of mutation accumulation, or deleterious mutation accumulation, in the Icelandic population. Its purpose was to show that variation in (a proxy for) the strength of negative selection through mortality can vary rates of mutation accumulation even assuming positive paternal age effects on *de novo* load and declining paternal age. While it could be objected that the model cannot differentiate between neutral and deleterious mutation accumulation, the results of the condition in which I_{bs} was fixed to 0.35 for the full range of years indicate that the level of opportunity for mortal-

ity selection typical of human evolutionary history (at least in the period from infancy on) renders the probability of deleterious mutation accumulation extremely low (though there are further possible objections to our claims here that will be considered later).

Arslan et al. (2018b) critique the realism of this model on a number of grounds (see Discussion; Arslan et al., 2018b offer some irrelevant criticisms only because of an error on the part of the journal in which the critical exchange occurred—specifically, they were not provided with the final version of Woodley of Menie, Sarraf et al., 2018 before Arslan et al., 2018b was published). Most saliently, they assert that Woodley of Menie, Sarraf, et al. (2018) assume 10-year generations, but in a corrigendum (Arslan et al., 2018c) correctly note that 20-year generations were assumed (although the data used in Woodley of Menie, Sarraf, et al., 2018 are on cohorts, consistent with Kong et al.'s 2012 analysis); they (2018c) deem 20-year "generation" lengths to be unrealistic and inconsistent in the context of the model itself, given the variation in "generation" lengths implied by the variability of paternal ages. As it happens, the data that Woodley of Menie, Sarraf et al. (2018) sourced from Kong et al. (2012) concern birth cohorts, not generations, separated by 20-year intervals, and these birth cohorts are associated with variable average paternal ages simply because the paternal age at conception associated with those born in a year varies across years.[7]

What could be thought problematic, although we are unsure if this is what Arslan et al. (2018b, 2018c) had in mind, is Woodley of Menie, Sarraf, et al.'s (2018) use of data on each preceding cohort to approximate the legacy load bequeathed to each subsequent cohort in their model. Given that this model was intended only for the purposes of illustration and was explicitly a simplified representation of the relevant evolutionary dynamics, this choice of proxy was reasonable. The 20-year spacing between cohorts was the distance between mid-years, with each cohort spanning 10 years, thus the 1954.5 mid-year cohort contains those born from 1950 to 1959. At minimum, those born in the earlier part of the span of years likely contributed non-negligibly to the procreation of the

[7] Some confusion here perhaps results from a claim by Woodley of Menie, Sarraf, et al. (2018) that was mistakenly not removed from their text, namely that their analysis assumes "unchanging" "generation lengths" (p. 2). In fact, the analysis does not depend on this assumption, and the claim that it does was, again, not supposed to be published. This is reflected in the use of the term "cohort" rather than "generation" in all relevant places elsewhere in the article.

subsequent cohort. In light of the immediately foregoing, the simplified nature of the model, and the fact that no finer breakdown of the data is available from Kong et al. (2012), the 20-year spacing Woodley of Menie, Sarraf, et al. (2018) assume is acceptable for the purpose of roughly modeling the basic pattern of changes in mutation load across cohorts. Nevertheless, Arslan et al. (2018c) make a valid point concerning model realism—one that can be profitably addressed by re-examining the assumptions that went into the "legacy load" simulation, and re-estimating parameters on the basis of the addition of more realistic assumptions. To that end we will reanalyze the data from Kong et al. (2012) in an effort to test the robustness of the quasi-empirical simulation from Woodley of Menie, Sarraf, et al. (2018). We will also examine the pattern of temporal correlations between simulated changes in mutation load and one proposed driver of mutation accumulation—climatic mildness (Woodley of Menie, Figueredo et al., 2017). If the results of the new simulation correlate with this proposed driver, it will augment the finding via external validity.

Methods

Data

Mean Paternal Age at Cohort Birthyear

Icelandic data on mean paternal age at conception by cohort's birth year are displayed in Kong et al.'s (2012) figure 4 (p. 474), for ten-year spans with mid-year spacings between cohorts of two decades—starting with mid-year 1654.5 (for the span 1650 to 1659) to "2010+" (which if made equivalent to the spacing for the previous cohorts would correspond to a mid-year of 2014.5; Kong et al.'s data of course do not extend this far, indeed their paper was published in 2012, so simulated data corresponding to this mid-year must be considered a projection). These data were harvested using the *WebPlotDigitizer* (Rohatgi, 2017), which allows data to be extracted directly from figures with high accuracy. This yielded a total of 37 data points, spanning mid-years (rounded to nearest year) 1655 to 2015.

Estimating De Novo Mutation Load

Kong et al. (2012) convert the mean paternal age at conception into an equivalent burden of *de novo* mutations by simply multiplying paternal age

at conception by about two. Thus, a cohort born to fathers at a mean age of 35 would have an average of ~70 *de novo* mutations. (This is not to suggest that, for instance, mutations accumulate in the sperm from birth—of course, that would be impossible since males do not begin to produce sperm until puberty; rather, we are simply describing the operation used to derive the approximate average number of *de novo* mutations that males will bequeath to their offspring at different ages in light of Kong et al.'s [2012] study.) Since the publication of Kong et al. (2012), there have been several additional estimates of the paternal age effect on offspring *de novo* mutation counts. The results of seven of these studies are summarized in Moorjani, Gao, and Przeworski (2016), and the values for the mean numbers of *de novo* mutations bequeathed to offspring at the age of 30 range from 30 to 86.1. The weighted average across the seven studies is 1.38 per year of father's age (combined $N = 532$); thus mean *de novo* mutation values are assigned to each cohort by multiplying the mean paternal age at conception associated with each cohort by 1.38.

Estimating Legacy Load

It is a potentially important problem that the mid-year gap between cohorts (20 years) is unrealistic in a model of the transmission of legacy load, especially given that variable average paternal ages imply variable legacy loads. A new protocol was devised to compute generational (as opposed to cohort) changes in mutation load. This involved using the mean cohort paternal age, rounded to the nearest decade, to estimate generation length, which was used to assign a cohort's legacy load to a subsequent *generation's de novo* load. Thus, for example, the legacy load from the 1755 cohort is estimated by multiplying the estimated I_{bs} for 1755 in Iceland by that cohort's average received *de novo* load (as in Woodley of Menie, Sarraf, et al., 2018 I_{bs} was allowed to rise linearly from 0.35 in 1655 to 0.99 in 2015); this result is added (as legacy load) to the *de novo* load estimated for the 1795 cohort—this cohort being separated from the last by approximately one whole generation, on the basis that the mean paternal age for the 1795 cohort rounds up to 40 years. Owing to inconstant generational lengths over time, this led to a small number of decades for which there were no estimates of mutation load, which were left blank. In total, this yielded *generational* changes in mutation load spanning 28 decades. As with Woodley of Menie, Sarraf, et al. (2018), the decadal values were rescored as increases relative to a reference year (1695), which was assigned a reference value of zero mutations. *Contra*

Arslan et al.'s (2018b) *claim*, *this does not mean that the 1695 cohort had "mutation-free" genomes*—it is simply that this cohort serves as an anchor cohort against which the loads of subsequent decades are computed (Carter & Sanford, 2012 use effectively the same approach).

A second analysis was conducted in which the value of I_{bs} was set to 0.35 (the value for most of human history [Rühli & Henneberg, 2013]), as in Woodley of Menie, Sarraf, et al. (2018), in order to examine the effect on mutation accumulation of (probable) strong negative selection.

Icelandic Decadal Temperature Anomaly Estimates

Decadal running averages on temperature anomaly for Iceland (i.e. the degree to which that decade's temperature is higher or lower in degrees Celcius relative to a reference temperature) were extracted from data made publicly available via the Berkeley Earth Observatory (2017). It was assumed that it would take one generation for the effects of climatological mildness and its selective consequences (e.g. the impact on crop productivity, disease prevalence, and both intra- and inter-group violence; Woodley of Menie et al., 2017; Zhang et al., 2011) to impact mutation load, therefore the temperature means were lagged by one generation (e.g. the 1765 mean was correlated with the total load [expressed as a difference score relative to the reference cohort] of the 1805 cohort, etc.). This yielded 16 cohorts for which data on both were available. The running decadal means are only available going back to 1760.

Analyses

The first analysis involves correlating both sets of decadal mutation accumulation values with year in order to determine whether there is a temporal trend. The second analysis involves correlating the decadal mutation accumulation values derived from the first analysis (the values derived from the relaxing negative selection condition) with the Icelandic decadal temperature anomaly values, lagged by one generation.

Results

Analysis 1

In the first analysis, two separate temporal correlations are computed between the decadal change in mutation values and year, one for the

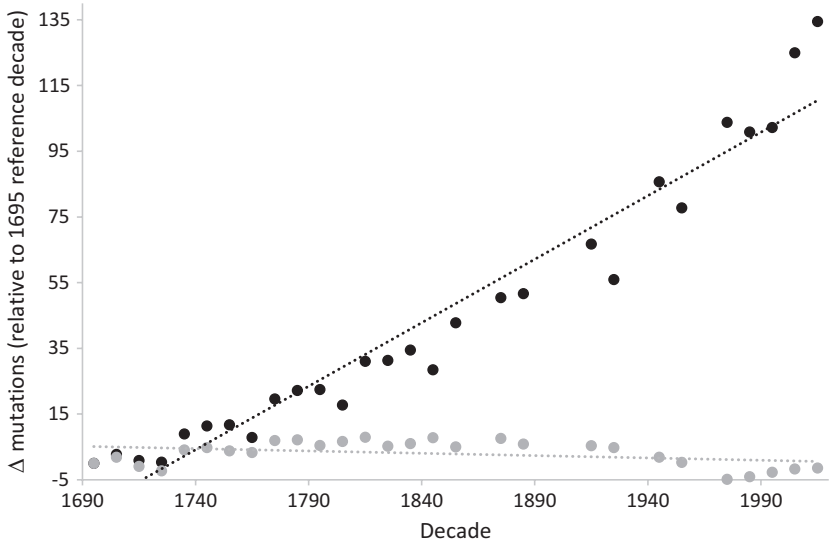

Fig. 6.1 The decadal change in mutation load (estimated relative to the 1695 reference cohort) under increasing I_{bs} (0.35 to 0.99, black points) and fixed I_{bs} (0.35, gray points), 1695 to 2015

relaxed negative selection condition (where I_{bs} is allowed to rise from 0.35 to 0.99) and one for the strong negative selection condition (where I_{bs} is fixed to a value of 0.35). The first correlation was 0.97 ($p < 0.05$, $N = 28$ decades), indicating mutation accumulation with time at a rate of 3.87 per decade. The second correlation was −0.37 (*ns*, $N = 28$ decades) indicating no significant change in mutation load. These temporal correlations are graphed in Fig. 6.1.

Analysis 2

In the second analysis (Fig. 6.2), the decadal change in mutation load (from the relaxing negative selection condition) is correlated with the generation-lagged Icelandic decadal temperature means. The two are correlated at 0.5 ($p < 0.05$, $N = 16$ decades), indicating, consistent with predictions, that increasing climatic mildness might have some role in mutation accumulation in Iceland. All analyses and computations were conducted using Excel.

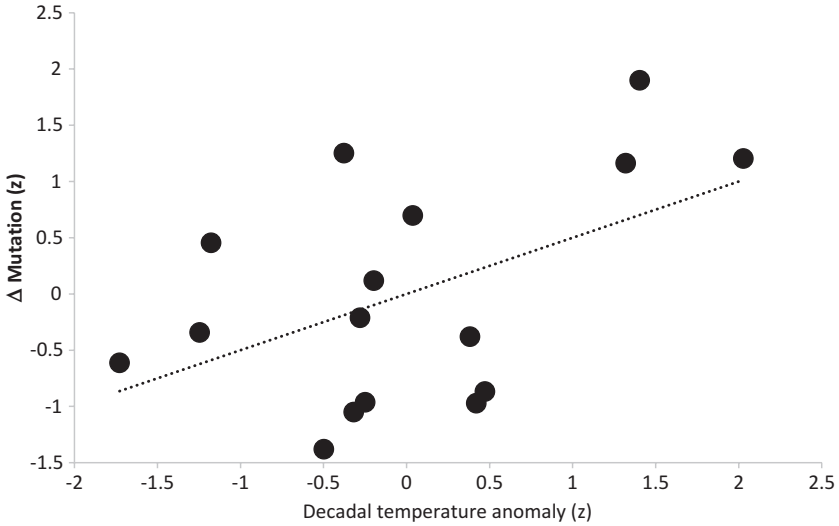

Fig. 6.2 The association between the decadal change in mutation load and the Icelandic decadal mean temperature anomaly, lagged by one generation, 1805 to 2005

Discussion

The results of our simulation, despite increased model realism, align well with those of Woodley of Menie, Sarraf, et al. (2018). The latter model estimated a yearly increase in mutation load of 0.8 mutations per year whereas the current model's estimate is 0.4, and the linear correlation of mutation load with time is 0.99 in the former and 0.97 in the latter, reflecting a high level of convergence between the simulations and that Woodley of Menie, Sarraf, et al.'s (2018) model is robust to increased realism of at least some assumptions (the discrepancy in the mutation accumulation rate is perhaps largely driven by the lower *de novo* mutation rate assumed in the current analysis compared to the earlier one; but in any case, neither analysis was or is intended to precisely estimate the count of accumulated mutations). Furthermore, the trend in mutation accumulation is consistent with predictions of Woodley of Menie, Figueredo et al. (2017), namely that increasing climatic mildness relaxes selection against deleterious mutations. Nevertheless, it must be understood that the use-

fulness of these quantitative estimates is in the fact that they allow evaluation of the importance of certain simplifying assumptions on the part of Woodley of Menie, Sarraf, et al. (2018). To reiterate, the original model was not intended to estimate the extent of mutation accumulation in the Icelandic population; instead, the point was to show that it may well be unwise to ignore legacy load in analyses of negative selection, and to instead pay attention only to paternal age and associated *de novo* mutation loads, insofar as the model illustrates the possibility of variable levels of mutation accumulation as a function of variation in (a proxy for) the strength of negative selection through mortality *even in a population with declining mean paternal age*. The primary purpose of the current model is the same. But since it is more realistic, the current model may somewhat approximate the rate of change in mutation load in the Icelandic population (on the assumption that mortality selection is the major source of negative selection and that a substantial proportion of the opportunity for selection historically corresponded to negative selection, about which more in what follows). Analysis 2, conducted above, provides some support for this possibility, and so adds robustness to Analysis 1, insofar as its results align with one prior prediction concerning a driver of relaxed selection against deleterious mutations (i.e. increasing climatic mildness).

Several criticisms of our model are possible. First, given the rounding that we had to use because of the nature of Kong et al.'s (2012) data, and the fact that the paternal age values concern age at conception and not at birth, our generation length estimates are not ideally precise. Second, one could observe that through our simulation we effectively do not consider fertility variance as a potential source of negative selection. Understanding the force of this possible criticism requires several considerations. The maximum possible intensity of negative selection equals the sum of fertility and (reproductively relevant) mortality variance multiplied by the heritability of this variance (Rühli & Henneberg, 2017). Estimates of the genetic variance of fertility generally range from around 0.10 to 0.20, when high-quality data are used (Bolund, Hayward, Pettay & Lummaa, 2015; Kondrashov, 2017). But in perhaps the most extensive analysis of the heritability of human fertility to date, including 80 samples, Henneberg (1980) estimated that genetic fertility variance may be less than 0.01 (see also Staub et al., 2018; if non-additive effects are involved, one can expect the broad-sense heritability of fertility to be higher—however, most estimates of the heritability of fertility depend on genealogical data, from

which the effects of dominance and epistasis are notoriously difficult to measure).

Unfortunately, high-quality estimates of the heritability of early-life mortality do not seem to be available. The earliest period for which estimates of this sort have been offered seems to be infancy, and even these are limited. Philippe (1977) finds a heritability of infant mortality of about 0.27, although in the absence of sophisticated variance partitioning he speculates that this estimate may reflect non-additive and shared environmental variance. A large genealogical study yields estimates of the additive heritability of infant and child mortality from 0.15 to 0.19 (Hanson, Smith & Hasstedt, 2014). Cavalli-Sforza and Bodmer (1971) use twin data to estimate a broad-sense heritability of mortality of 0.29, but this only pertains to individuals who survived at least to the age of five (p. 611). Ulizzi, San Martini, and Terrenato (1979) maintain that "perinatal mortality…early fetal losses apart, is universally considered as the most 'genetically' determined fraction of pre-adult deaths" (p. 140), making the absence of heritability estimates for pre-infant mortality, which is very difficult to measure (M. Henneberg, personal communication), especially challenging for those trying to ascertain the role of mortality in negative selection.[8] Moreover, the heritability of neither mortality (Philippe, 1977) nor fertility (Bolund et al., 2015; Briley, Harden & Tucker-Drob, 2015) has been stable over time. Crucially, it is a distinct possibility that attempts to establish genetic influences on mortality using classic heritability analyses will substantially underestimate those influences (to a more limited extent, this may apply to such analyses of genetic effects on fertility variance). The reason is that deleterious mutations idiosyncratic to individuals, occurring as a result of developmental noise and tending to cause subinfant and infant death in sufficiently harsh environments, may have had a greater role in early-life mortality before industrialization. (Note that even monozygotic twins typically are *not* genetically identical; see Liu, Molenaar & Neiderhiser, 2018.)

These results on the whole *might* indicate that mortality variance is much more heritable than fertility variance, indeed that fertility variance may have negligible heritability, and thus that failing to model the impact of fertility

[8] Nevertheless, Ulizzi et al.'s (1979) observation makes substantial declines in the perinatal mortality rate over time especially noteworthy (see Rahman et al., 2013; Sugai, Gilmour, Ota, & Shibuya, 2017; Woods, 2008).

variance potentially does little to bias our simulation. But the aforementioned temporal instability in the heritability of both parameters, and the high variability of estimates and limited set of studies to consider, weakens this argument. Therefore, future work simulating changes in mutation load ideally would account for changes in fertility variance, which we were not able to do in the current work; still, we do think that evidence indicates that, for probably most of human evolutionary history, mortality selection has had a substantially greater role in negative selection than sexual selection and variation in fecundity (which account for variance in reproductive success not explained by mortality variance, along with, e.g., non-fatal differences in organismal condition due to morbidity differences that do not affect fecundity and do not affect reproductive success exclusively through sexual selection). Setting aside for a moment the issue of which variance component bearing on reproductive success has been most determinative of negative selection throughout most of human evolutionary history, we can inquire into what trends these variance components have likely taken over time. Evidence generally indicates that just as opportunity for mortality selection has been profoundly diminished over the long run of human evolutionary history (Rühli & Henneberg, 2017), so has opportunity for sexual selection (Lippold et al., 2014). Janicke, Ritchie, Morrow, and Marie-Orleach (2018), in a study of many animal species, claim that an index that "sums up all variance in reproductive success arising from viability, fecundity and sexual selection … can be considered a proxy for net selection" (p. 6), and report evidence consistent with its being such a proxy. Since in humans it appears that opportunity for mortality selection and sexual selection have substantially declined, and that the impact of genetic differences in fecundity probably has been somewhat reduced through reproductive technologies (e.g. in vitro fertilization; Rühli & Henneberg, 2017), one can claim with confidence that the overall opportunity for selection has declined (see also Kondrashov, 2017, on apparent decreases following industrialization of Crow's index of opportunity for selection in human populations), which, if Janicke et al. (2018) are right, approximates changes in actual selection strength; this certainly gives some reason to predict that the strength of negative selection acting on human populations has fallen over time. Interestingly, Arslan et al.'s (2018a) model of paternal age effects indicates that in Sweden, negative selection on relative fitness differences may have relaxed slightly (for the other two historical populations considered, Arslan et al., 2018a lack corresponding data for these populations in modernized conditions, a point to which we return below). Briley et al. (2015) do note increases in the heritability of fertility in

recent decades in the United States, but this was followed by a decline. Additionally, and perhaps most importantly, Arslan (2017) notes, in a different publication concerning the paternal age effect data presented in Arslan et al. (2018a) and a separate analysis of sexual desire over the course of the menstrual cycle, that "[b]oth of my approaches' results were consistent with sexual selection not playing a major role in the selection against deleterious mutations…. Quantitatively, it seems likely that survival selection plays a bigger role in selection against mutations than sexual selection" (p. 29). With respect to his paternal age effect data specifically, the basis for this conclusion of Arslan's (2017) was the absence of clear paternal age effects on marriage success, which Arslan et al. (2018a) also report: "We found no robust pattern of effects on survival to age 15 and the odds of getting married" (p. 6; exactly the same sentence is found in Arslan, 2017, p. 95). These empirical results, although most germane to selection on relative fitness differences, align with theoretical claims to the effect that differential mortality is a greater (perhaps much greater) contributor to negative selection than differential fertility, at least in the case of differential fertility due to sexual selection—although these theoretical claims, as already indicated, have been based on estimates suggesting that genetic influences on mortality variance are larger than those on fertility variance (e.g. Henneberg, 1980; Rühli & Henneberg, 2017).

Moreover, recent changes in fertility behavior resulting from the availability of contraceptives may mostly have had the effect of promoting certain patterns of selection, such as those reducing genotypic intelligence (Woodley of Menie, Figueredo et al., 2017), which could relate to indications of relaxed negative selection on fitness differentials in the course of recent decades alone (to the extent that these are present). Pflüger, Oberzaucher, Katina, Holzleitner, and Grammer (2012) find that among women *not* using hormonal contraception, attractiveness (a potential signal of low mutation load) positively predicts reproductive success, whereas this association was not found in women *using* such contraception (their sample, however, was small). In a similar vein, Kanazawa (2003) replicates another researcher's (Pérusse, 1993) finding that higher status does not tend to advantage the reproductive success of men in modernized societies (Kanazawa operationalizes status using income, whereas Pérusse uses a composite measure), but does positively associate with their number of sexual partners and frequency of intercourse (*cf* Hopcroft, 2015); this indicates that were it not for the availability of contraception, wealth would tend to positively associate with male fertility in modernized popu-

lations (but if Hopcroft, 2015 is right that those variables *do* tend to positively correlate in men of modernized populations, there is a further question of whether the strength of the association has relaxed over time; evidence of severe lopsidedness in reproductive participation ratios in most of human evolutionary history, favoring women over men and suggesting strong sexual selection acting on men, selection that was likely in large part for status given standard evolutionary theory, certainly suggests such relaxation—see Brown, Laland, and Mulder, 2009; Lippold et al., 2014).

Third, one could argue that our model's results are implausible, given that molecular genetic studies have failed to find substantial variation in the frequency of at least certain kinds of mutations across populations (e.g. Simons & Sella, 2016; see Arslan et al., 2018b), which seem to have been subjected to widely variable legacies of mortality selection. This would appear to indicate that mortality has been highly random with respect to deleterious mutations and thus is of limited relevance to our understanding of negative selection in humans. Controversy in this area of molecular genetic inquiry is very high, however[9] (Gravel, 2016); moreover, comparing the mutation load of different geographical populations may not be the optimal approach (a point on which Arslan et al., 2018b *might* agree). One study restricted to European populations found substantial increases in burdens of disease-related mutations over many thousands of years, especially mutations related to common diseases such as obesity and diabetes (Aris-Brosou, 2019). In any case, the molecular genetic analyses currently possible are unlikely to fully register the effects of relaxed negative selection stemming specifically from industrialization and its *sequelae*: "[Molecular genetic comparisons of human and related populations] cannot rule out relaxation of selection after the Industrial Revolution, because even a free accumulation of *de novo* mutations in the course of a few generations would be hard to detect by studying genotypes alone" (Kondrashov, 2017, p. 192; see also Woodley of Menie, Sarraf, et al., 2018). Arslan (2017) offers a related observation—"similar molecular genetic indices [to those of Simons and Sella (2016)] have not yet been used to test for changes in mutation load over recent periods in the same populations, but molecular genetic methods are probably not sufficiently

[9] Arslan et al. (2018b) do not adequately acknowledge the depth of this controversy.

powerful at present genome sequence sample sizes to detect the small expected changes over short periods" (p. 33).

Fourth, one could maintain, in spite of the arguments already offered, that there is not enough evidence that I_{bs}, or opportunity for mortality selection, substantially corresponds to the strength of negative selection. Against this possible counter, we note that I_{bs} has been shown to significantly positively associate with the prevalence and incidence of certain diseases and medical conditions across populations, even after controlling for salient covariates; these include the prevalence of obesity (Budnik & Henneberg, 2017; You & Henneberg, 2018; see also Voss, Goodson & Leon, 2018; Zheng & Tumin, 2015), the prevalence of type-1 diabetes[10] (You & Henneberg, 2016) and the incidence of many cancers (You & Henneberg, 2017). The findings of robust and significant positive associations between I_{bs} and obesity and diabetes prevalence, controlled for several possible confounds such as indicators of economic development, should be considered alongside the molecular genetic evidence of mutation accumulation that Aris-Brosou (2019) reports; Aris-Brosou notes that variants predictive of obesity and diabetes have increased in frequency even into the twenty-first century, and if in recent centuries this mutation accumulation is due at least in part to relaxed negative selection, the positive association between I_{bs} and obesity and diabetes prevalence may indicate that I_{bs} tracks the strength of negative selection against these variants to at least some extent (though note that Aris-Brosou does not provide any evidence that the mutation accumulation he reports is due to relaxed negative selection; it is merely possible that the mutation accumulation in the more recent centuries for which he presents evidence is to some extent a consequence of relaxed negative selection, a possibility that he seems to hint at via a citation of Lynch, 2016). Moreover, the idea that rising I_{bs} over time reflects relaxation of negative selection aligns with concurrent trends in the increasing prevalence of various medical abnormalities (Rühli & Henneberg, 2013), as well as indications of progressively greater developmental instability (such as sinistrality [Woodley of Menie, Fernandes, Kanazawa, & Dutton, 2018] and craniofacial fluctuating asymmetry [Woodley of Menie & Fernandes, 2016]). The possibly very recent origins of certain diseases, such as schizophrenia (Hare, 1988; Turner, 1985),

[10] Type-2 diabetes prevalence has been shown to associate in the expected direction with opportunity for selection through differential mortality (Rühli, van Schaik, & Henneberg, 2016), but it is unclear if this correlation would survive relevant controls.

which is highly heritable (Keller & Miller, 2006), in addition to those related to instability of the 11p15.5 chromosomal region (Shterenshis, Roitblat, Ilani, Lumbroso & Padilla-Raygoza, 2018), are also consistent with relaxation of negative selection around the time of industrialization. In the absence of adequate genomic data, information on phenotypes should be considered in examining possible changes in negative selection over time (Kondrashov, 2017, p. 192). Moreover, historically mortality selection was clearly non-random with respect to social class (Woodley of Menie, Sarraf, et al., 2018), which is under substantial genetic control (Clark, 2014; Clark & Cummins, 2018) and is thus plausibly open to being adversely impacted via the action of pleiotropic mutations reducing *f* and thus impairing relevant cognitive and conative phenotypes (Houle, 2000; Miller, 2000).

Arslan et al. (2018b, 2018c) strongly criticize a simplified version of the model presented here (Woodley of Menie, Sarraf, et al., 2018), and we now turn to the points that they raise.

Arslan et al.'s (2018b) main response contains errors due ultimately to a publisher mistake (see above), which were corrected in a corrigendum (Arslan et al., 2018c); so here we will only deal with the parts of Arslan et al.'s (2018b) critique that were not corrected by Arslan et al. (2018c). At the outset, Arslan et al. (2018b) assert that their "data did not permit conclusions about *accumulated* genetic load" (p. 1, emphasis in original), indicating that Woodley of Menie, Sarraf, et al.'s (2018) arguments concerning mutation accumulation are irrelevant to the original article of Arslan et al. (2018a). But their original piece presents its findings as "run[ning] counter to oft-repeated predictions of mutational doom by relaxed selection" (Arslan et al., 2018a, p. 8) from, among others cited, Lynch (2016), whose major basis for expecting "mutational doom" (as Arslan et al. put it) *is* mutation accumulation, which cannot be dismissed with the mere finding that paternal age effects on fitness across three pre-industrial and one industrialized populations are comparable, per Arslan et al.'s own admission (to recapitulate, such paternal age effects in three historical populations and one modernized population were the key findings of Arslan et al., 2018a). At least for that reason, Woodley of Menie, Sarraf, et al. (2018) reasonably took mutation accumulation to be relevant. (Elsewhere, Arslan et al. [2018b] interpret the claim of Simons and Sella [2016, p. 150] concerning evidence that there is "little or no difference in the load of non-synonymous mutations among human populations" as "[i]n line with our own conclusions" [p. 2]. But how can this

result of Simons and Sella's [2016] be "[i]n line" with the conclusions of Arslan et al. if the latter's data do not allow conclusions about "*accumulated* genetic load"? Arslan et al. [2018b] indicate that they take the "opportunity to clarify and expand on the conclusions that can potentially be drawn from our data [from Arslan et al., 2018a] with respect to mutation load" [p. 1]. But what they offer in light of further consideration of their data does not meaningfully differ from what Arslan et al. [2018a, including the supplement] present, and in any case Arslan et al. [2018b] contend that it was their "data" that did not allow "conclusions about *accumulated* genetic load"; yet it is that data that they use to reach "conclusions" that they believe to be "[i]n line" with the findings of Simons and Sella [2016], whose work they say "address[es] the issue of accumulated mutation load more directly" [Arslan et al., 2018b, p. 2].)

Arslan et al. (2018b) further argue that Woodley of Menie, Sarraf, et al. (2018) "muddle," "[occlude]," and "confus[e]" the distinction between opportunity for selection and negative selection. This is incorrect, as Woodley of Menie, Sarraf, et al. (2018) indicate that mortality and negative mortality selection theoretically could be independent: "If child and infant mortality were *random with respect to deleterious variants*, then they *could not have been major sources of negative selection*" (p. 1, emphasis added). They then go on to argue at length for the view that mortality selection is unlikely to have been random with respect to deleterious mutations historically. Furthermore, at no point do Woodley of Menie, Sarraf, et al. (2018) state or suggest that opportunity for selection and negative selection in fact fully overlap—it would be incorrect to posit this total correspondence given what we do know about the heritability of reproductively relevant mortality.[11]

[11] Arslan et al. (2018b) write the following in an endnote to their discussion of the opportunity for selection/negative selection distinction: "This confusion between opportunity (variation) and actual selection strength is also at the heart of the [sic] [Woodley of Menie, Sarraf, et al.'s] reiterated concern about a potential selective role of abortions that may compensate for selection that no longer occurs through infant mortality. Yes, the majority of abortions are elective, but in England and Wales 1–2% are therapeutic. Likewise, our estimate of the regression coefficient of paternal age on infant survival in the preindustrial populations is also only a few per cent and thus a fraction of the 12–20% infant mortality. According to our estimates, the majority of the variance in mortality and fertility is not explained by paternal age" (2018b, p. 3, n. 1). In observing that "most…abortions [in modernized populations] are elective rather than therapeutic" (p. 2), Woodley of Menie, Fernandes, et al. (2018) already conceded that some abortions are therapeutic. Furthermore, if Arslan et al.'s (2018b) point is that only the infant mortality variance "explained by paternal age" should

In criticizing the simulation of mutation accumulation from Woodley of Menie, Sarraf, et al. (2018), Arslan et al. (2018b) make several claims. First, they assert that the model assumes that "Icelanders" in "1654" were free of mutations. This is false: the birth cohort (not the total population of Iceland) assigned 1654.5 as a mid-year was taken to be a *reference sample* relative to which the accumulation of mutations could be tracked for the purpose of illustrating mutation accumulation—no assumption of freedom from mutations was involved. Second, they assert that the simulation "assum[ed]" that mutations are "incurred" at a rate of 70 on average per generation (Arslan et al., 2018b, p. 2); we assume that Arslan et al. are objecting to our use of Kong et al.'s (2012) estimate of the rate at which *de novo* mutations occur in sperm with age (which entails that at age 35 males will on average bequeath ~70 *de novo* mutations to their offspring)—in the current analysis, a lower rate was assumed, as explained above. Further, they argue that the model entails the objectionable assumption that these are "70 *equally deleterious* mutations" (p. 2; emphasis in original); but it is obvious that, all else equal, as negative selection (approximated using I_{bs}) relaxes, any harmful variant that varies in its harmfulness as a function of environmental and genomic conditions (and so, for instance, does not eliminate carrier fitness in all environments) will have a lower probability of being selected against, even though this probability will vary from allele to allele as a function of deleteriousness. A similar point could be raised against Arslan et al.'s (2018b) objection to the model's implicit assumption that all accumulated mutations are additive. Again, it is reasonable to assume that even non-additive deleterious mutations are *generally more likely* to be selected against the stronger negative selection is. Arslan et al. (2018b) of course are correct that the fact that our simulation does not model various differences among mutations renders it less precise than it would be if it did, but for the reasons we have just given we doubt that accounting for these factors would undo the basic finding of mutation accumulation.

Arslan et al. (2018b) also claim that the model assumes that only viability selection is relevant to negative selection and that "all" pre-reproductive mortality is due to mutations. But as even Arslan (2017) observes, there is evidence that "sexual selection [does] not [play] a major role in

be thought to track negative selection through infant mortality, we think that they are mistaken, for reasons given in the main text about the probable inadequacy of paternal age effects to capture the full extent of negative selection.

the selection against deleterious mutations" (p. 29); so while modeling the effect of fertility variance would be ideal, especially fertility variance not related to sexual selection (negative selection related to which we expect has declined due to the use of reproductive therapies), we do not suspect that this is a source of large bias in our simulation. Moreover, that deleterious mutations cannot account for all pre-reproductive deaths does not change the probable fact that such mutations tend to be removed *in proportion to* the opportunity for selection through differential mortality, if one accepts the evidence that there is some substantial correspondence between opportunity for and strength of negative mortality selection (given above); it could be that even if negative selection through mortality, from infancy on, has decreased, increased negative selection through fertility differences or through subinfant mortality could offset this decline, although for reasons already given we doubt that this has happened to the extent needed to prevent deleterious mutation accumulation.

The alleged assumption of short generation lengths—and the supposed assumption that "every 10 years everybody dies after reproducing and is replaced by their children"—also draws the critical attention of Arslan et al. (2018b, p. 2; see also 2018c). As noted earlier, Woodley of Menie, Sarraf, et al.'s (2018) model merely employs the estimated *de novo* load and I_{bs} of the birth cohort preceding any given one to *approximate* the *average* legacy load that the latter cohort received. Even after adjusting the model here by adding dynamical generation lengths and more realistic assumptions concerning *de novo* load, the results remain consistent with our earlier claims, indicating that the proxies assumed in the prior model were reasonable.

Arslan et al. (2018b) conclude their direct critique of Woodley of Menie, Sarraf, et al.'s (2018) model with the following: "Merely by discarding the incorrect assumption that Icelanders in 1654 were mutation-free or by doing away with the false equivalence between I_{bs} and strength of purifying selection, their results would change completely, no longer showing an increase in mutation load. We argue, therefore, that these simulations do not demonstrate anything relevant to the question of whether *deleterious* genetic load has risen and what role relaxed selection may play in this rise. We already knew that neutral mutations accumulate: this is the basis of the evolutionary clock" (p. 2).

We reject Arslan et al.'s (2018b) confident predictions about the adjustments that would nullify the results of the analysis. Again, since the 1654.5 birth cohort is an anchor, the "assumption" of mutation-free Icelanders

was never made—and clearly altering the values associated with the first cohort in our time series would not affect the *relative* simulated increase in mutation load. Since we have already addressed the issue of the correspondence between I_{bs} and strength of negative selection, we will not repeat ourselves in response to one of Arslan et al.'s (2018b) objections quoted just above; moreover, our argument is compatible with most mutations being essentially neutral—it need only be the case that there is a tendency for deleterious mutations to accumulate the smaller the opportunity for mortality selection is, as the research of Henneberg and colleagues suggests. Certainly Aris-Brosou's (2019) findings give some reason to believe that the mutation accumulation that has occurred for many thousands of years, in some European populations, has not been irrelevant with respect to at least one fitness-salient aspect of human phenotypic condition, namely health.

There are aspects of Arslan et al.'s research that should be mentioned. A peculiar choice of Arslan's (2017) is to highlight the fact that "the effect on overall offspring fitness was descriptively smaller in Québec than in 20th-century Sweden" (p. 32). It is unclear why this was done given that the paternal age effect analysis lacks data on modernized Québec. On the other hand, data for both pre-industrial and modernized Sweden are available and indicate that the paternal age effect on offspring fitness is "descriptively" greater in historical than in modernized Sweden (a decade of advanced paternal age predicts a 3.4% reduction in reproductive success in twentieth-century Sweden but a 7.3% reduction in pre-industrial Sweden; Arslan, 2017, p. 89; Arslan et al., 2018a, p. 4).

A critical point that Woodley of Menie, Sarraf, et al. (2018) offer, but which Arslan et al. (2018b, 2018c) leave unanswered, is that paternal age effects may poorly track the overall strength of negative selection, given that these effects, which are relative by nature, could remain comparable (at least across a certain range of negative-selective regimes) even as, for example, absolute death rates due to deleterious mutations differ. That is, the relative fitness costs of a given increase in deleterious *de novo* mutation load across different regimes of negative selection could remain similar—so long as there is non-negligible negative selection in all cases. The persistence of these *relative* fitness costs, as indexed by, for example, paternal age effects, would indicate that negative selection is present in all cases, but not that the overall strength of negative selection is equivalent in all cases. In some places, it seems that Arslan recognizes this—for example, where he claims that his findings of paternal age effects in a modernized

population permit the modest conclusion that "purifying selection is still effective in a modern population with hormonal contraception, social transfers, and modern medicine" (2017, p. 101; same passage, with the exception of one comma, in Arslan et al., 2018a, p. 8). He is correct about this. But it does not clearly follow where he goes on to argue in the very next sentence that "[t]his runs counter to oft-repeated predictions of mutational doom by relaxed selection" (Arslan, 2017, p. 101; exactly the same sentence in Arslan et al., 2018a, p. 8). The mere fact that negative selection has not been fully eliminated is compatible with its having been relaxed compared to some prior point in time. Therefore, Arslan has not offered evidence that is definitely inconsistent with predictions of relaxed selection and adverse consequences from it.

Nevertheless, Arslan et al. (2018a, 2018b) seem to lean heavily on the possibility that a great deal of negative selection may occur on relative fitness differences, but ignore Lynch's (2016) point that "soft" selection, "in the sense that individual performance is simply measured against the moving mean" is compatible with "decline in the baseline performance of physical and mental attributes in populations with the resources and inclination toward minimizing the fitness consequences of mutations with minor effects": "physical defects involving cancer, metabolic disease, and psychiatric disorders have very real costs regardless of the average population state" (p. 873). And again, even if negative selection on relative fitness differences has not much changed, this together with relaxation of negative selection on absolute fitness differences would have the net effect of reducing negative selection. Arslan et al. (2018a, 2018b, 2018c) ignore the evidence that this has in fact occurred in the voluminous germane research of Maciej Henneberg and colleagues, which Woodley of Menie, Sarraf, et al. (2018) discuss.

Finally, it should be noted that certain important classes of deleterious mutations may be unrelated to paternal age (see Girard et al., 2016; Gratten et al., 2016).

It is important to establish the plausibility of the basic mutation accumulation scenario, since in the next chapter the effects of the accumulation of deleterious mutations of a specific kind, which impose fitness costs not just on their carriers, but also on those with whom they transact within a social-epistatic context, will be discussed and explored empirically. The mutation accumulation phenomenon will be shown to be potentially far more central to understanding the decline of modernized civilizations than has previously been thought, although the mechanisms for this process have been only recently elucidated.

References

Aris-Brosou, S. (2019). Direct evidence of an increasing mutational load in humans. *Molecular Biology and Evolution*, in press. https://doi.org/10.1093/molbev/msz192

Arslan, R.C. (2017). *Secular changes in sexual and natural selection against deleterious genetic mutations in humans*. Unpublished doctoral dissertation, University of Göttingen, Göttingen, Germany.

Arslan, R. C., Willführ, K. P., Frams, E. M., Verweij, K. J. H., Paul-Christian, B., Myrskylä, M., … Penke, L. (2018a). Older fathers' children have lower evolutionary fitness across four centuries and in four populations. *Proceedings of the Royal Society B: Biological Sciences, 284*, 20171562.

Arslan, R. C., Willführ, K. P., Frans, E. M., Verweij, K. J., Bürkner, P., Myrskylä, M., … Penke, L. (2018b). Relaxed selection and mutation accumulation are best studied empirically: Reply to Woodley of Menie et al. *Proceedings of the Royal Society B: Biological Sciences, 285*, 20180092.

Arslan, R. C., Willführ, K. P., Frans, E. M., Verweij, K. J., Bürkner, P., Myrskylä, M., … Penke, L. (2018c). Correction to: Reply to Woodley of Menie et al. *Proceedings of the Royal Society B: Biological Sciences, 285*, 20181427.

Berkeley Earth. (2017). Regional climate change: Iceland. Retrieved September 1, 2018, from http://berkeleyearth.lbl.gov/regions/iceland

Bolund, E., Hayward, A., Pettay, J., & Lummaa, V. (2015). Effects of the demographic transition on the genetic variances and covariances of human life-history traits. *Evolution, 69*, 747–755.

Bonde, J. P., Flachs, E. M., Rimborg, S., Glazer, C. H., Giwercman, A., Ramlau-Hansen, C. H., … Bräuner, E. V. (2017). The epidemiologic evidence linking prenatal and postnatal exposure to endocrine disrupting chemicals with male reproductive disorders: A systematic review and meta-analysis. *Human Reproduction Update, 23*, 104–125.

Briley, D. A., Harden, K. P., & Tucker-Drob, E. M. (2015). Genotype × cohort interaction on completed fertility and age at first birth. *Behavior Genetics, 45*, 71–83.

Brown, G. R., Laland, K. N., & Mulder, M. B. (2009). Bateman's principles and human sex roles. *Trends in Ecology & Evolution, 24*, 297–304.

Budnik, A., & Henneberg, M. (2017). Worldwide increase of obesity is related to the reduced opportunity for natural selection. *PLOS ONE, 12*, e0170098.

Caldwell, J. C., Caldwell, B. K., Caldwell, P., McDonald, P. F., & Schindlmayr, T. (2006). *Demographic transition theory*. Dordrecht: Springer.

Carter, R. W., & Sanford, J. C. (2012). A new look at an old virus: Patterns of mutation accumulation in the human H1N1 influenza virus since 1918. *Theoretical Biology and Medical Modelling, 9*, 42.

Cavalli-Sforza, L. L., & Bodmer, W. F. (1971). *The genetics of human populations*. San Francisco, CA: W.F. Freeman.

Clark, G. (2007). *A farewell to alms: A brief economic history of the world*. Princeton, NJ: Princeton University Press.

Clark, G. (2014). *The son also rises: Surnames and the history of social mobility*. Princeton, NJ: Princeton University Press.

Clark, G., & Cummins, N. (2018). *Nature versus nurture in social outcomes. A lineage study of 263,000 English individuals, 1750–2017*. Working paper.

Crow, J. F. (1997). The high spontaneous mutation rate: Is it a health risk? *Proceedings of the National Academy of Sciences, 94*, 8380–8386.

Fain, E., & Weatherford, C. (2016). Comparative study of millenials' (age 20–34 years) grip and lateral pinch with the norms. *Journal of Hand Therapy, 29*, 483–488.

Girard, S. L., Bourassa, C. V., Perreault, L.-P. L., Legault, M.-A., Barhdadi, A., Ambalavanan, A., … Rouleau, G. A. (2016). Paternal age explains a major portion of *de novo* germline mutation rate variability in healthy individuals. *Plos ONE, 11*, e0164212.

Gratten, J., Wray, N. R., Peyrot, W. J., McGrath, J. J., Visscher, P. M., & Goddard, M. E. (2016). Risk of psychiatric illness from advanced paternal age is not predominantly from *de novo* mutations. *Nature Genetics, 48*, 718–724.

Gravel, S. (2016). When is selection effective? *Genetics, 203*, 451–462.

Haldane, J. B. S. (1937). The effect of variation on fitness. *The American Naturalist, 71*, 337–349.

Hamilton, W. D. (2001). The hospitals are coming. In W. D. Hamilton (Ed.), *Narrow roads to gene land. Evolution of sex* (Vol. 2, pp. 449–509). Oxford, UK: Oxford University Press.

Hanson, H. A., Smith, K. R., & Hasstedt, S. (2014). *Heritability of longevity and the role of early and mid-life environments*. Working Paper.

Hare, E. (1988). Schizophrenia as a recent disease. *British Journal of Psychiatry, 153*, 251–231.

Henneberg, M. (1976). Reproductive possibilities and estimations of the biological dynamics of earlier human populations. *Journal of Human Evolution, 5*, 41–48.

Henneberg, M. (1980). Natural selection through differential fertility in human populations: Quantitative evaluation of selection intensity. *Przeglad Antropologiczny, 46*, 21–60.

Hopcroft, R. (2015). Sociobiology at work in modern populations. In J. H. Turner, R. Machalek, & A. Maryanski (Eds.), *Handbook on evolution and society: Toward an evolutionary social science* (pp. 122–135). Boulder: Paradigm.

Houle, D. (2000). Is there a *g* factor for fitness? In G. R. Bock, J. A. Goode, & K. Webb (Eds.), *The nature of intelligence* (pp. 149–170). Chichester, UK: Wiley.

Inglehart, R. F. (2018). *Cultural evolution: People's motivations are changing, and reshaping the world*. Cambridge: Cambridge University Press.

Janicke, T., Ritchie, M. G., Morrow, E. H., & Marie-Orleach, L. (2018). Sexual selection predicts species richness across the animal kingdom. *Proceedings of the Royal Society B: Biological Sciences, 285*, 1878, 20180173. https://doi.org/10.1098/rspb.2018.0173

Kanazawa, S. (2003). Can evolutionary psychology explain reproductive behavior in the contemporary United States? *The Sociological Quarterly, 44*, 291–302.

Keller, M. C., & Miller, G. (2006). Resolving the paradox of common, harmful, heritable mental disorders: Which evolutionary genetic models work best? *Behavioral and Brain Sciences, 29*, 385–404.

Kondrashov, A. S. (2017). *Crumbling genome: The impact of deleterious mutations on humans*. Hoboken: Wiley Blackwell.

Kondrashov, A. S., & Crow, J. F. (1993). A molecular approach to estimating the human deleterious mutation rate. *Human Mutation, 2*, 229–234.

Kong, A., Frigge, M. L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., … Stefansson, K. (2012). Rate of *de novo* mutations and the importance of father's age to disease risk. *Nature, 488*, 471–475.

Lesecque, Y., Keightley, P. D., & Eyre-Walker, A. (2012). A resolution of the mutation load paradox in humans. *Genetics, 191*, 1321–1330.

Levine, H., Jørgensen, N., Martino-Andrade, A., Mendiola, J., Weksler-Derri, D., Mindlis, I., … Swan, S. H. (2017). Temporal trends in sperm count: A systematic review and meta-regression analysis. *Human Reproduction Update, 23*, 1–14.

Lippold, S., Xu, H., Ko, A., Li, M., Renaud, G., Butthof, A., … Stoneking, M. (2014). Human paternal and maternal demographic histories: Insights from high-resolution Y chromosome and mtDNA sequences. *Investigative Genetics, 5*, 13.

Liu, C., Molenaar, P. C., & Neiderhiser, J. M. (2018). The impact of variation in twin relatedness on estimates of heritability and environmental influences. *Behavior Genetics, 48*, 44–54.

Lynch, M. (2016). Mutation and human exceptionalism: Our future genetic load. *Genetics, 202*, 869–875.

Meisenberg, G. (2007). *In God's image: The natural history of intelligence and ethics*. Kibworth, UK: Book Guild Publishing.

Miller, G. F. (2000). Mental traits as fitness indicators: Expanding evolutionary psychology's adaptationism. *Annals of the New York Academy of Sciences, 907*, 62–74.

Moorjani, P. G., Gao, Z., & Przeworski, M. (2016). Human germline mutation and the erratic evolutionary clock. *PLoS Biology, 14*, e2000744.

Muller, H. J. (1950). Our load of mutations. *American Journal of Human Genetics, 2*, 111–176.

Pacey, A. (2017, July 25). Expert reaction to meta-analysis of sperm count among men in Western countries. Retrieved from https://www.sciencemediacentre.org/expert-reaction-to-meta-analysis-of-sperm-count-among-men-in-western-countries/

Pérusse, D. (1993). Cultural and reproductive success in industrial societies: Testing the relationship at the proximate and ultimate levels. *Behavioral and Brain Sciences, 16*, 267–322.

Pflüger, L. S., Oberzaucher, E., Katina, S., Holzleitner, I. J., & Grammer, K. (2012). Cues to fertility: Perceived attractiveness and facial shape predict reproductive success. *Evolution & Human Behavior, 33*, 708–714.

Philippe, P. (1977). La mortalité infantile: hérédité et milieu. *Acta Geneticae Medicae et Gemellologiae: Twin Research, 26*, 185–187.

Rahman, S., El Ansari, W., Nimeri, N., El Tinay, S., Tohid, H., Yousafzai, M. T. (2013). Achieving excellence in maternal, neonatal and perinatal survival: Executive synopsis of PEARL study annual report 2011. *Journal of Postgraduate Medical Institute*, *27*, 4-7.

Rindermann, H. (2018). *Cognitive capitalism: Human capital and the wellbeing of nations.* Cambridge, UK: Cambridge University Press.

Rohatgi, A. (2017). *WebPlotDigitizer*. Retrieved from https://apps.automeris.io/wpd/

Rosa, H. (2013). *Social acceleration: A new theory of modernity.* (J. Trejo-Mathys, Trans.). New York, NY: Columbia University Press.

Rühli, F., & Henneberg, M. (2017). Biological future of humankind – Ongoing evolution and the impact of recognition of human biological variation. In M. Tibayrenc & F. J. Ayala (Eds.), *On human nature: Biology, psychology, ethics, politics, and religion* (pp. 263–275). London: Elsevier.

Rühli, F., van Schaik, K., & Henneberg, M. (2016). Evolutionary medicine: The ongoing evolution of human physiology and metabolism. *Physiology, 31*, 392–397.

Rühli, F. J., & Henneberg, M. (2013). New perspectives on evolutionary medicine: The relevance of microevolution for human health and disease. *BMC Medicine, 11*, 115.

Shterenshis, M., Roitblat, Y., Ilani, J., Lumbroso, J., & Padilla-Raygoza, N. (2018). The 11p15.5 chromosomal region: When did the instability occur? *Medical Hypotheses, 121*, 21–25.

Simons, Y., & Sella, G. (2016). The impact of recent population history on the deleterious mutation load in humans and close evolutionary relatives. *Current Opinion in Genetic Development, 41*, 150–158.

Staub, K., Henneberg, M., Galassi, F. M., Eppenberger, P., Haeusler, M., Morozava, I., … Bender, N. (2018). Increasing variability of body mass and health correlates in Swiss conscripts, a possible role of relaxed natural selection? *Evolutionary Medicine and Public Health*, (*1*), 116–126.

Sugai, M. K., Gilmour, S., Ota, E., & Shibuya, K. (2017). Trends in perinatal mortality and its risk factors in Japan: Analysis of vital registration data, 1979–2010. *Scientific Reports, 7*. https://doi.org/10.1038/srep46681

Toppari, J., Larsen, J. C., Christiansen, P., Giwercman, A., Grandjean, P., Guillette, L. J., Jr., … Skakkebaek, N. E. (1996). Male reproductive health and environmental xenoestrogens. *Environmental Health Perspectives, 104*, 741–803.

Travison, T. G., Araujo, A. B., O'Donnell, A. B., Kupelian, V., & McKinlay, J. B. (2007). A population-level decline in serum testosterone level in American men. *Journal of Clinical Endocrinology & Metabolism, 92*, 196–202.

Turner, T. H. (1985). Was insanity on the increase? *The British Journal of Psychiatry, 146*, 325–325.

Twenge, J. M. (2013). Overwhelming evidence for generation me. *Emerging Adulthood, 1*, 21–26.

Twenge, J. M., Gentile, B., Dewall, C. N., Ma, D., Lacefield, K., & Schurtz, D. R. (2010). Birth cohort increases in psychopathology among young Americans, 1938–2007: A cross-temporal meta-analysis of the MMPI. *Clinical Psychology Review, 30*, 145–154.

Ulizzi, L., San Martini, A., & Terrenato, L. (1979). Changes of selection opportunities with a changing environment: Regional heterogeneity in Italy. *Annals of Human Genetics, 43*, 137–141.

Volk, T., & Atkinson, J. (2008). Is child death the crucible of evolution? *Journal of Social, Evolutionary & Cultural Psychology, 2*, 247–260.

Volk, T., & Atkinson, J. (2013). Infant and child death in the human environment of evolutionary adaptation. *Evolution & Human Behavior, 34*, 182–192.

Voss, J. D., Goodson, M. S., & Leon, J. C. (2018). Phenotype diffusion and one health: A proposed framework for investigating the plurality of obesity epidemics across many species. *Zoonoses and Public Health, 65*, 279–290.

Wong, W. S., Solomon, B. D., Bodian, D. L., Kothiyal, P., Eley, G., Huddleston, K. C., & Niederhuber, J. E. (2016). New observations on maternal age effect on germline *de novo* mutations. *Nature Communications, 7*, 10486.

Woodley of Menie, M. A., & Fernandes, H. B. F. (2016). The secular decline in general intelligence from decreasing developmental stability: Theoretical and empirical considerations. *Personality and Individual Differences, 92*, 194–199.

Woodley of Menie, M. A., Fernandes, H. B. F., Kanazawa, S., & Dutton, E. (2018). Sinistrality is associated with (slightly) lower general intelligence: A data synthesis and consideration of the secular trend in handedness. *HOMO: Journal of Comparative Human Biology, 69*, 118–126.

Woodley of Menie, M. A., Figueredo, A. J., Fernandes, H. B. F., Peñaherrera-Aguirre, M., Sarraf, M. A., & Hertler, S. (2017). *The Rhythm of the West: A Biohistory of the Modern Era AD 1600 to the Present. Journal of Social Political and Economic Studies, Monograph Series No. 37*. Washington, DC: Council for Social and Economic Studies.

Woodley of Menie, M. A., Sarraf, M. A., & Fernandes, H. B. F. (2018). Mutation accumulation is still potentially problematic, despite declining paternal age: a comment on Arslan et al. (2017). *Proceedings of the Royal Society B: Biological Science, 285*, 20172511.

Woods, R. (2008). Long-term trends in fetal mortality: Implications for developing countries. *Bulletin of the World Health Organization, 86*, 460–466.

You, W., & Henneberg, M. (2016). Type 1 diabetes prevalence increasing globally and regionally: The role of natural selection and life expectancy at birth. *BMJ Open Diabetes Research & Care, 4*, e000161.

You, W., & Henneberg, M. (2017). Cancer incidence increasing globally: The role of relaxed natural selection. *Evolutionary Applications, 11*, 140–152.

You, W., & Henneberg, M. (2018). Relaxed natural selection contributes to global obesity increase more in males than in females due to more environmental modifications in female body mass. *PLOS ONE, 13*, e0199594.

Zhang, D. D., Lee, H. F., Wang, C., Li, B., Pei, Q., Zhang, J., & An, Y. (2011). The causality analysis of climate change and large-scale human crises. *Proceedings of the National Academy of Sciences, 108*, 17296–17301.

Zheng, H., & Tumin, D. (2015). Variation in the effects of family background and birth region on adult obesity: Results of a prospective cohort study of a Great Depression-era American cohort. *BMC Public Health, 15*. https://doi.org/10.1186/s12889-015-1870-7