The transition to modernity and chronic disease: mismatch and natural selection

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Abstract | The Industrial Revolution and the accompanying nutritional, epidemiological and demographic transitions have profoundly changed human ecology and biology, leading to major shifts in life history traits, which include age and size at maturity, age-specific fertility and lifespan. Mismatch between past adaptations and the current environment means that gene variants linked to higher fitness in the past may now, through antagonistic pleiotropic effects, predispose post-transition populations to non-communicable diseases, such as Alzheimer disease, cancer and coronary artery disease. Increasing evidence suggests that the transition to modernity has also altered the direction and intensity of natural selection acting on many traits, with important implications for public and global health.

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The Industrial Revolution and the accompanying ecological, epidemiological and demographic transitions — a combination that we call the transition to modernity (TTM) — have had a profound impact on human populations. Fundamental ecological changes driven by modernization include permanent improvements in nutrition and food security[1], a dramatic decline in exposure to pathogens and a global increase in exposure to air and water pollutants[2]. Biological changes include shifts in our physiology, development, immunobiology, microbiota and life history traits (BOX 1) and the age structures of our populations.

In the process, mismatches between our evolved capacities and our rapidly changing environment have emerged, with many consequences for health and disease. Previously evolved genetic effects mediated by antagonistic pleiotropy may now account for a substantial proportion of the increasing burden of non-communicable diseases, which are currently responsible for over 63% of the world's deaths[3]. Of these deaths, 80% occur in low-income and middle-income countries, and half are in men and women of working age. Although important progress has been made in the past decade in stemming the rising death toll from non-communicable diseases[3], they remain a substantial threat both to health and to global economic development[4,5].

If evolution in prior environments favoured alleles that are harmful to fitness in current environments, then selection should eventually either modify their effects or remove them from contemporary populations. Indeed, growing evidence suggests that the rates and sizes of recent phenotypic responses to mismatch can substantially alter the direction and intensity of natural selection for genes that contribute to important traits, such as age and size at first birth, body mass index (BMI) and age at menopause (TABLE 1).

In this Review, we focus on the impact of the ecological, epidemiological and demographic changes driven by the TTM on human biology. We aim to answer two questions: how compelling is the evidence that once advantageous gene variants now contribute to the growing burden of non-communicable disease, and how compelling is the evidence that natural selection has started to improve survival and reproduction in humans living in recently changed environments? Our aim is to make clear the degree to which the TTM has revealed the ecological and evolutionary origins of much of the increasing burden of non-communicable diseases by changing both age structures and the leading causes of death. By informing our basic understanding of disease causes, this knowledge can help to guide the search for novel therapies.

The transition to modernity

The demographic transition, an unprecedented change from a regime of high fertility and high mortality to one of low fertility and low mortality, began in northwestern Europe around 1800 (FIG. 1) and has now spread to all parts of the world. During the transition, first mortality and then fertility declined, causing population growth rates to first accelerate and then slow again, eventually resulting in lower fertility, longer life and an ageing population (FIG. 2). Projected to be completed by 2100,

Industrial Revolution
Period of time in Europe and North America in the late 1700s to early 1800s that saw the mechanization of agriculture and textile manufacturing and a revolution in the use of power that produced steamships and railroads, with profound impacts on social, cultural and economic conditions.

Demographic transitions
Transitions that result from changes in birth and death rates that yield dramatic, qualitative changes in population age distributions.

Modernity
The historical period that started with the Industrial Revolution and then experienced the ecological, demographic and epidemiological transitions that led up to and include the present.

Life history traits
Traits directly associated with reproduction and survival, including size at birth, growth rate, age and size at maturity, number of offspring, frequency of reproduction and lifespan.

Antagonistic pleiotropy
A single gene has positive effects on fitness through its impact on one trait or age class but negative effects on fitness through its impact on another trait or age class.

Non-communicable diseases
Also known as chronic diseases, these diseases, which are characterized by slow progression and long duration, include cancer, cardiovascular diseases, chronic respiratory diseases, diabetes mellitus and dementias, such as Alzheimer disease.

Fitness
The property of an individual in one generation that reflects its representation in subsequent generations.

Natural selection
The difference between the trait mean before and after weighting it by fitness; also, the covariation between a trait and fitness.

Box 1 | Life history theory and life history traits

Life history theory[97–99] was developed to predict the coordinated evolution of the major traits that contribute directly to fitness: age and size at maturity, number and size of offspring, interbirth interval, number of reproductive events per life, ageing and lifespan. It views the evolution of these traits as the product of interactions between intrinsic constraints and trade-offs — features that organisms inherit or acquire during development — and extrinsic factors in the environment that affect mortality risk and resource availability. It then asks how extrinsic factors shape the entire combination of intrinsic traits to maximize lifetime reproductive success.

Together with evolutionary game theory, life history theory is a model for phenotypic evolution in general. Everything in biology has both a mechanistic explanation that answers the question 'How does this work?' and an evolutionary explanation that answers the questions 'How did this get here, and what maintains its state?' Both questions can be considered in the long term, to understand why a species has particular traits as a result of past exposure to natural selection, and in the short term, to understand why individual organisms respond to environmental factors with phenotypic plasticity, that is, developmental responses that have themselves evolved.

the demographic transition is fundamentally reshaping economic conditions and restructuring populations[6].

Mortality. Before the 16th century, there was little to distinguish the standard of living of unskilled workers and farmers in the poorer areas of Europe, the Ottoman Empire, Egypt, India, China and Japan[7,8]. In pre-industrial populations, the death rate varied from an annual minimum of 30 deaths per 1,000 to many times higher during famines or epidemics[9]. In Western Europe, this volatile pattern of mortality began to recede in the 16th and 17th centuries[10], although total mortality remained high because of a marked increase in childhood mortality, especially from smallpox[11].

Beginning in Europe in the 18th century, improvements in agriculture, transport and food distribution uncoupled cycles of mortality and fertility from the price of grain[1,10]. Associated nutritional improvements led to the earliest and most important increases for both child and maternal survival, in part by increasing resistance to infectious diseases[12–14].

From about 1800 onwards in England and then progressively throughout Europe, urbanization imposed a mortality penalty that was only partially compensated for by the invention and then adoption of civic hygiene, the creation of a public health infrastructure, the emergence of safe milk and clean water supplies and sewage disposal[15]. Mortality from enteric and water-borne diseases, such as cholera and typhoid, fell sharply in response[16]. The introduction of vaccination in 1796 dramatically reduced the number and magnitude of smallpox epidemics[17]. Mortality from other airborne diseases, such as tuberculosis, diphtheria and whooping cough, also declined steadily in the latter half of the 19th century in response to improvements in the built environment and other living conditions. Improved hygiene and cleanliness, made possible by greater availability of soap and washable cotton clothing[18] and better, less-crowded housing, reduced the exposure to pathogens[19]. The introduction of new childhood vaccines and antibiotics starting in the 1930s furthered the reduction in mortality from infectious diseases[12] (FIG. 3) as did technological developments, such as refrigeration and antisepsis, and improvements in health education, health promotion and public health and environmental regulation[12,15]. In the developed world in the 21st century, communicable diseases now account for fewer than 10% of years of life lost compared with 20–80% in less developed countries[20].

Lifespan. Life expectancy at birth in countries with the highest global life expectancy increased remarkably between 1840 and 2000 (REF.[21]). Average life expectancy at birth was 37–40 years in pre-industrial Sweden and England, comparable to contemporary hunter–gatherer populations and to forager and horticulturalist societies[21,22], for which life expectancy at birth is 27–37 years and 40–42 years, respectively. In Sweden, the maximum age at death increased by 0.4 years per decade from 1860 to 1969 and by 1.1 years per decade between 1969 and 1999 (REF.[23]). Similar trends in maximum lifespan were found in six other North European countries with complete and validated data on centenarians[24]. Before 1950, most of the gains in lifespan were due to reductions in mortality at younger ages. Since then, gains have mostly been due to improved survival in those over 45 years of age[21] (FIG. 4). In contemporary high-income countries, average life expectancy was 80.7 years in 2015 (REF.[25]). Continuing increases in lifespan will probably depend on further major medical advances[26].

Fertility. Fertility in pre-industrial populations ranged from 30 to 50 births per 1,000, or a total fertility rate of 3.5 to 10 births per woman[27,28]. Births in most pre-industrial populations were strongly seasonal, with a nutritionally mediated nadir in conceptions occurring in seasons of hunger[29,30]. The proximate determinants of fertility were, in descending order, the duration of lactational amenorrhoea (the temporary infertility that occurs with breastfeeding), nuptiality (the proportion married), fecundability (the probability of pregnancy in one menstrual cycle), age at menarche, proportion of women who were sterile, age at menopause, rate of fetal loss and length of gestation[31].

The transition from high to low fertility, one hallmark of a demographic transition, began in France in the decades after the French Revolution and extended to most of Europe by 1940 (REFS[32–35]). By 2015, crude birth rates in high-income countries were 10.9 births per 1,000, or 1.7 births per woman, and 20.6 births per 1,000, or 2.6 births per woman, in low-income and middle-income countries[36]. By 2003, 60 countries with 43% of the world's population were at or below the replacement level of 2.1 children per woman[6,37].

Across the TTM, age at menarche fell by approximately 5 years from 17–18 years in pre-industrial populations to 12–13 in post-TTM populations. Age at natural menopause is determined by a complex array of sociodemographic, reproductive and lifestyle factors.

Table 1 | **Examples of estimates of selection acting on a variety of traits in modern human populations**

Trait	Sex	Selection	*P*	*n*	Population	Refs
Life history						
Age at first birth	F	–	***	2,227	USA (20th)	84
	F	–	**	314	Finland (20th)	103
	F	–	***	306	Finland (17th–19th)	104
	F	–	***	395	Finland (18th–19th)	105
	F	–	***	1,459	Australia (20th)	106
	F	–	**	2,443	USA (20th)	107
	M	–	**	395	Finland (18th–19th)	105
	M	–	**	2,443	USA (20th)	107
Interbirth interval	F	–	***	306	Finland (17th–19th)	104
Age at last birth	F	+	***	306	Finland (17th–19th)	104
	F	+	*	314	Finland (20th)	103
Age at menopause	F	+/S	**/**	2,227	USA (20th)	84
	F	+	**	1,459	Australia (20th)	106
Age at death	M	+	***	746	USA (19th)	108
Post-50 lifespan	M/F	+/–	***/NS	128,129	USA (19th)	81
Mating success	M/F	+/+S/S	***/*** ***/*	65,561	USA (19th)	109
Morphology						
Weight	F	+	**	1,278	USA (20th)	110
	F	+/S	***/***	2,227	USA (20th)	84
	M	S	***	2,616	USA (19th–20th)	111
Height	F	+	*	216	The Gambia (20th)	112
	F	S	***	3,552	UK (20th)	113
	F	–	**	1,278	USA (20th)	110
	F	–	***	2,227	USA (20th)	84
	M	S	***	2,616	USA (19th–20th)	111
	M	+	*	322	USA (20th)	114
	M	+	***	3,201	Poland (20th)	115
Physiology						
Cholesterol	F	–	**	2,227	USA (20th)	84
Systolic blood pressure	F	–	*	2,227	USA (20th)	84
Blood glucose	F	S	**	2,227	USA (20th)	84

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Highest *P* value for trait (not all may have been significant). Several studies estimated fitness as number of offspring that survived to age 14 or to age 18 years. Two assumed that reproduction was complete by age 42 years[112] or 45 years[103–105]. The association of traits with fitness was estimated in most cases with multiple or partial regression. Most populations were post-industrial; the Gambian population was pre-industrial with natural fertility. +, positive directional; – negative directional; F, female; M, male; *n*, sample size (largest reported in study); NS, not significant; S, stabilizing.

A recent meta-analysis of studies of women born during the 20th century in 24 countries across 6 continents found that the mean age at natural menopause was 48.8 years. After adjustment for the factors mentioned, levels of economic development accounted for a 2-year to 3-year difference in age at natural menopause, which ranged from 46 to 52 years[38], suggesting that the age at menopause increased with the TTM.

The combination of the trends in menarche and menopause could extend the potential reproductive lifespan by more than a decade. However, the actual reproductive lifespan for women decreased during the TTM. The postponement of age at first birth, first observed in some Scandinavian countries in the 1960s[39], reached the rest of Europe by 2000. This trend has been accompanied by declines in fertility that reflect conscious limitation of family size driven by the perceived costs and value of children[6], by increasing life expectancy and literacy, by a better understanding of the risks of pregnancy and childbirth and by cultural factors that include who controls female reproduction[40]. Effective contraceptive technologies, involuntary infertility through delayed marriage or divorce and changes to the stability and nature of sexual unions have also contributed[41].

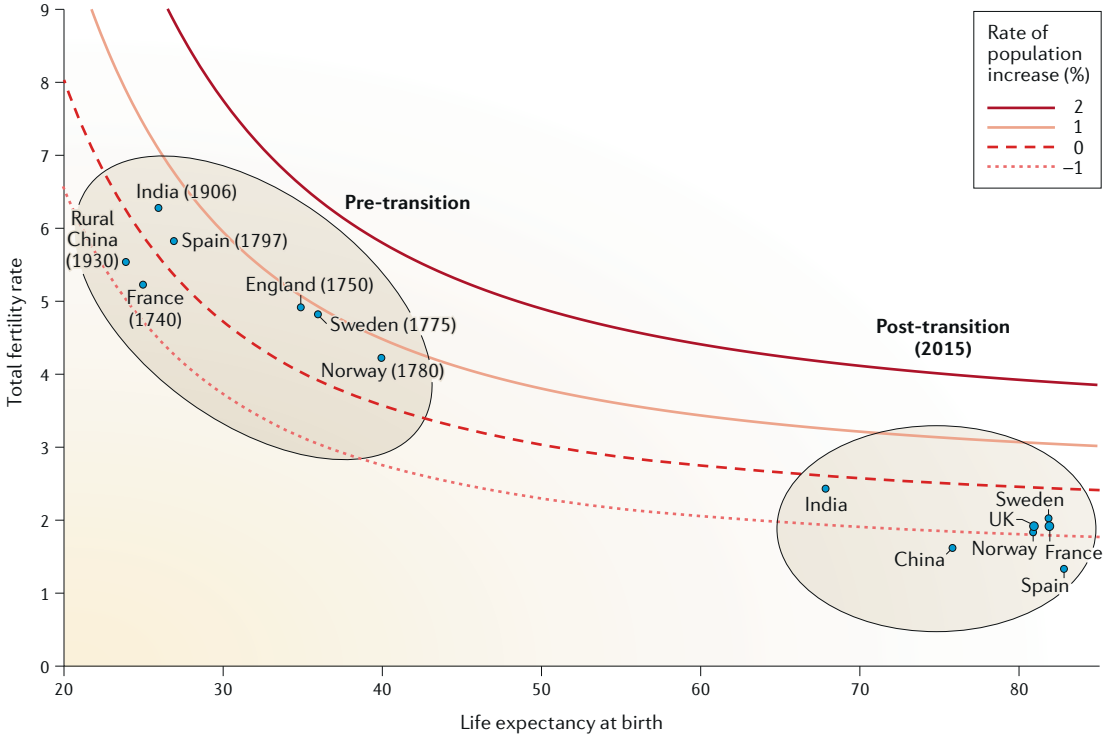


Fig. 1 | **Total fertility rate and life expectancy in selected countries before and after the demographic transition to modernity.** Figure is adapted with permission from Princeton University Press, from The Decline of Fertility in Europe, Coale, A., 1986, REF.[32]; permission conveyed through Copyright Clearance Center, Inc.

Changing patterns of disease. Changing patterns of mortality, lifespan and fertility in populations undergoing the TTM have led to a shift in population age structure (FIG. 4). As a greater proportion of the general population survives to older ages, the major causes of mortality have shifted from the infectious diseases of childhood to the non-communicable diseases associated with ageing. Although infectious diseases remain an important public health concern and a major cause of mortality and morbidity, particularly in developing countries, non-communicable diseases — including cardiovascular and chronic respiratory disease, neurodegenerative disease, diabetes mellitus and cancer — accounted for four of the top five causes of death globally in 2016, according to the Global Burden of Disease (GBD) database (Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA). In high-income countries in 2015, nine of the top ten leading causes of death were non-communicable diseases[42].

It may be possible to check the absolute increase in non-communicable disease by concerted national and global action. The most recent GBD study[3,43] shows a 12.1% decrease globally in mortality from non-communicable diseases between 2006 and 2016. Within countries, marked socioeconomic inequalities influence the rate and magnitude of this decline[44]. The decline, particularly for cardiovascular disease, is attributable both to preventive programmes, such as smoking cessation, and to effective medical treatment[45], although in low-income countries, the impact of preventive programmes has so far been modest[46]. As the mortality from cardiovascular disease has declined, especially in developed countries[47], the relative contributions to mortality of other non-communicable diseases associated with ageing, including cancer and dementia, have increased.

The rising cost of antagonistic pleiotropy

Do gene variants that were once advantageous now contribute to the growing burden of non-communicable disease? This, our first question, is motivated by Williams[48], who proposed that ageing is caused by the combined effect of many genes that each convey benefits in younger ages but with costs paid at older ages. Such genes are pleiotropic because they each have effects on two or more traits or two or more age classes, and their effects are antagonistic because each gene has both beneficial and detrimental effects on fitness. The rapid changes in both environment and age structure caused by the TTM have brought the costs and benefits of this trade-off into sharp relief (FIG. 5).

Several studies now provide either direct or indirect evidence that genes linked to increased disease risk in old age are associated with increases in juvenile survival, fertility or lifetime reproductive success.

Direct evidence. First, germline mutations in the *BRCA1* and *BRCA2* genes in industrialized populations, albeit rare, account for between 1–13% of ovarian cancer and 1–5% of female breast cancer[49]. Despite their cost, the persistence of such harmful alleles in the population[50] suggests that they have been maintained owing to large fertility benefits associated with the same alleles[51]. In a longitudinal study of women in Utah and Idaho, women

Lifetime reproductive success
The number of children per parent per lifetime, also called children ever born (CEB) or number of ever born (NEB). It is a measure of fitness that combines survival and reproduction.

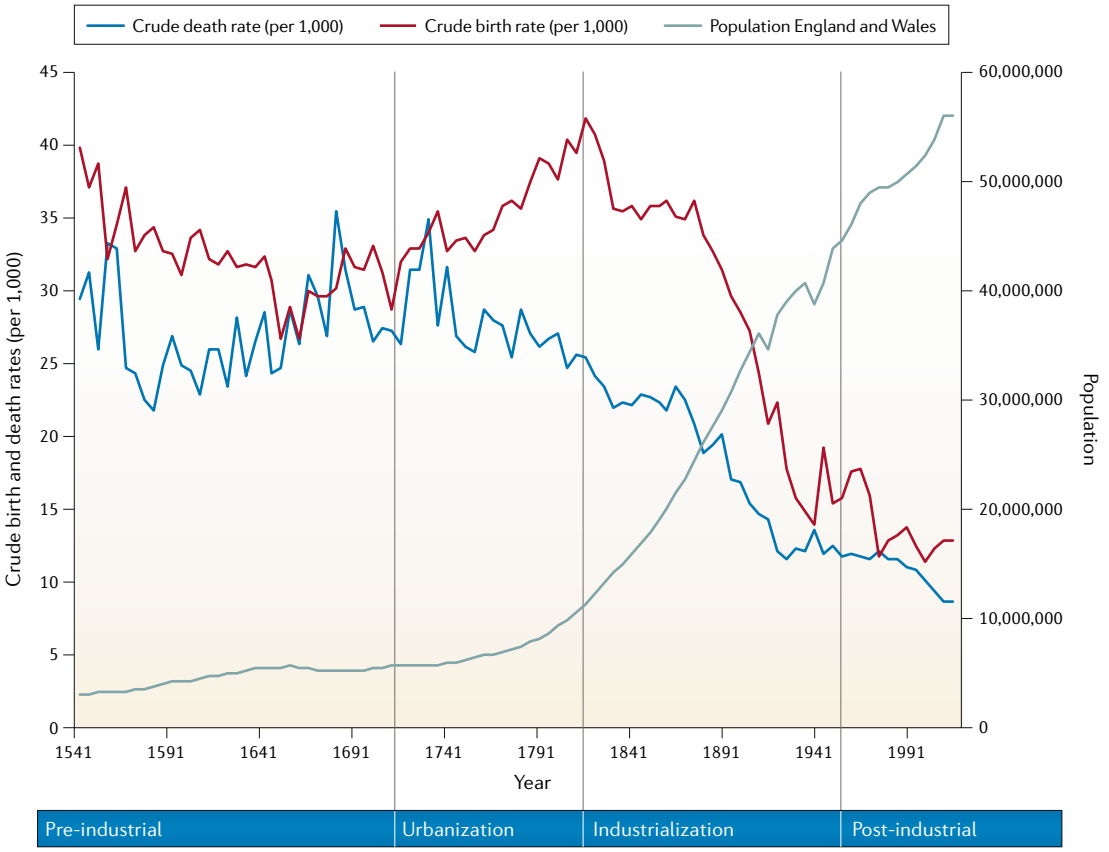


Fig. 2 | **Changes in vital rates and population growth across the demographic transition in England and Wales, 1551–2011.** Data were sourced from REF.[10], and mid-1838 to mid-2012 population estimates (total persons, single year of age and quinary age) were obtained from the UK Office of National Statistics in March 2018.

carrying these mutations produced an average of two more children if they were born before 1930 (REF.[52]). This effect on fertility may have further mitigated the carcinogenic potential of these mutations in the past because multiple pregnancies are an independent protective factor for breast cancer[53].

Second, the tumour suppressor protein p53 plays a pivotal role in coordinating cellular responses to DNA damage and in maintaining genomic stability. A common polymorphism, the p53 Pro allele, is associated with increased lifespan, but it is also associated with increased rates of blastocyst implantation failure and infertility[49,54]. Despite these costs, past positive selection for alleles in the p53 pathway has been identified in contemporary white and Asian populations, as indicated by their increase in haplotype frequency relative to African Americans[54].

Third, the *ε4* allele of the *APOE* gene is associated with increased risks of Alzheimer disease and atherosclerosis in later life[55]. This allele is carried by more than 10% of the individuals in more than half of 299 populations sampled worldwide across 6 continents[56], suggesting that it is maintained by selection. The *ε4* allele also seems to protect the cognitive development of poorly nourished infants with frequent diarrhoea[57] and may be associated with higher fertility in women[58]. In a rural population in Ghana, where infectious diseases remain the main cause of death[59], *APOE-ε4* was associated with higher fertility in women drawing water from open wells and rivers rather than boreholes, a risk factor for both gastrointestinal infection and mortality in this community[58]. Those carrying one allele copy had on average 1 more child, and those with two copies had 3.5 more children than women carrying no *ε4* copies. In this population, the cost to survival of carrying an *APOE-ε4* allele was small because most individuals died of infectious disease before the ages at which the negative effects of *APOE-ε4* are expressed, and it therefore contributed a net fitness benefit.

Finally, a recent genome-wide association study (GWAS) of 12 human populations found evidence that risk alleles for cardiovascular disease known to be under positive selection were also linked to increases in lifetime reproductive success[60]. Evidence for positive selection was found in 40 of the 76 genes known to be associated with risk of coronary artery disease (CAD). To determine whether pleiotropy drove this selection, associations of these CAD genes with lifetime reproductive success were analysed for women in the Framingham Heart Study. A systematic literature search on the 40 genes with strongest associations with CAD risk found associations with twinning, number of offspring produced, age at menarche, age at menopause, lactation capacity and pregnancy loss in 14 of those 40 genes. These antagonistic relationships between CAD and reproductive success suggest that

Positive selection
Type of natural selection that increases the frequency of alleles contributing to reproductive success in a population.

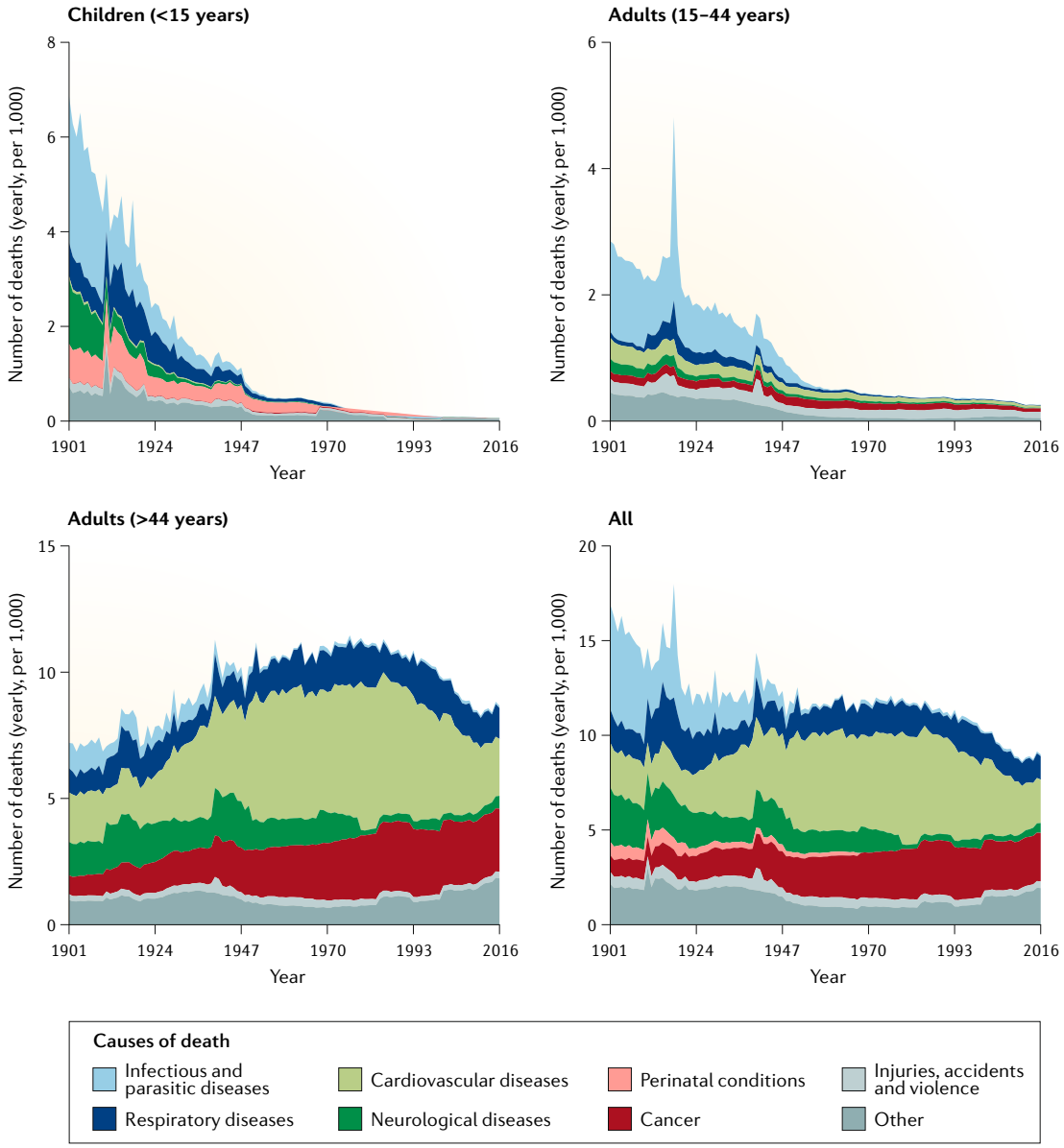


Fig. 3 | **The epidemiological transition to modernity.** The figure shows changes in causes of death between 1901 and 2016 for the entire population of England and Wales ($n = 61,256,163$ records). The categories are arranged in layers to represent the overall change in mortality. Three plots provide details for distinct age categories; the fourth summarizes trends for the entire population. Note that the scale on the *y* axis differs between plots. Causes of death have been classified into the broadest categories defined by the International Classification of Diseases, 10th revision (ICD-10). Modern death records were readily associated with ICD-10 labels. For earlier reports, we manually allocated each cause of death to one of the possible categories. We aggregated several categories among the 22 defined by the ICD-10 to reduce their number to the 8 displayed here. Precisely, each category directly corresponds to the equivalent ICD-10 chapter except for 'Injuries, accidents and violence', which pools diseases from chapters XIX and XX and 'Other', which pools diseases from chapters III, IV, V, VII, VIII, XI, XII, XIII, XIV, XV, XVII, XVIII, XXI and XXII (see the ICD-10 for details). Several historical events linked to surges in mortality can be seen, including the heatwave in the summer of 1911, which triggered deaths from enteritis and diarrhoea among children, the 1918 flu pandemic and the two World Wars. Data were retrieved from the UK Office for National Statistics in February 2018.

natural selection has maintained genetic variants that contribute to CAD because of their beneficial effects on lifetime reproductive success[60].

These four studies provide the strongest evidence to date that genes with antagonistically pleiotropic effects were previously favoured by natural selection because they conferred benefits to fertility and survival in early life, but the same genes now increase the risks of non-communicable disease.

Indirect evidence. Risk alleles associated with late-onset diseases tend to have higher frequencies than those associated with early-onset diseases[61], an observation consistent with stronger directional selection on

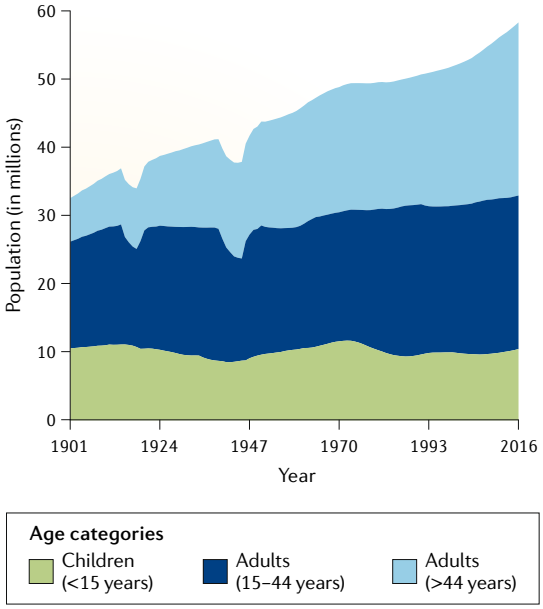


Fig. 4 | **The demographic transition to modernity.** The figure shows changes in population age structure between 1901 and 2016 for the entire population of England and Wales. The age categories are stacked to represent the overall change in population size, which is increasingly dominated by adults >44 years of age. Data were retrieved from the UK Office for National Statistics in February 2018.

early-onset than on late-onset diseases. Signatures of selection that occurred at a time in the past that cannot be accurately determined were found in three genes (*CDKN2A*, *RREB1* and *IL13*)[61]; in all three cases, alleles that protect against early-onset disease were found to increase the risk of late-onset disease, suggesting antagonistic pleiotropy. However, childhood infectious diseases were excluded in this analysis, and the direct impact of the alleles in question on mortality and fertility was not considered.

A GWAS of human reproductive behaviour combining information from 62 European cohorts found that alleles linked to decreased age at first birth in both men and women were associated with a higher genetic risk of smoking and type 2 diabetes mellitus[62]. The decrease in age at first birth represents a benefit for reproduction and the lowered risk of smoking and diabetes a cost to survival[63]. The case for antagonistic pleiotropy in this study would be strengthened if the association were also found within each cohort.

We conclude that reliable but somewhat limited evidence suggests that genes with antagonistically pleiotropic effects are now increasing the risks of non-communicable disease. Studies on antagonistically pleiotropic effects of genes require analyses of large databases that contain information on genomics, fertility, mortality and health status, but at present few such databases exist.

Adaptive responses to modernity

The second question we asked was whether natural selection has started to alter human responses to recent environmental changes. To answer this question, we next consider the impact on evolution in contemporary human populations of the changes associated with the TTM in the ecological and demographic environment.

Environmental changes caused by the TTM can induce the expression of new phenotypes without causing changes in gene frequencies. However, the TTM also may have triggered genetic change by means of phenotypic evolution by natural selection. Phenotypic evolution is driven by the association of traits with differences in fitness. A response to selection occurs if some portion of the variation in the traits is genetically heritable. If the TTM has altered phenotypic evolution, then it must have changed either the association between a trait and fitness, which sets the direction and magnitude of phenotypic selection, or the degree to which genetic variants determine phenotypic differences, which sets the magnitude of heritability and genetic correlations between traits.

Changes in fitness and vital rates. Fisher's fundamental theorem of natural selection[64] posits that variance in relative fitness determines the maximum possible change in a phenotypic trait after one generation of selection[65,66]. Crow defined this variance as the "opportunity for selection" (REF.[67]); he also pointed out that only a fraction of differences in vital rates, that is, death rates and fertility rates, is genetically effective, for how strongly selection acts on a trait depends both on the association between that trait and fitness and on its heritability[67]. Despite this limitation, the opportunity for selection has been used as a metric to compare the potential for evolutionary change caused by selection in human populations under different demographic conditions[68,69].

Estimates of the opportunity for selection (I) taken at multiple time points have shown that I has decreased in most populations with modernization[68–72]. However, the potential for adaptive evolution remains, as values of I remain significantly higher than zero.

To better understand the change in adaptive potential at a finer scale, it helps to define two components of I: the opportunity for selection caused by variation in juvenile mortality (I_m) and that caused by variation in adult fertility (I_f). Two methods have been used to measure the two components. The first method defines the two components crudely: I_m is deduced from the probability of surviving to an age that marks the onset of adulthood; I_f is interpreted as the variance in fitness generated by differences in fertility, but it more accurately describes the variance in fitness among adults because it conflates fitness variance generated by among-individual differences in reproduction with that from adult survival. Partitioning the variance in fitness into these two components reveals that the decrease of I during demographic transitions is largely attributable to decreased variance in mortality during childhood[70,71], although there can be a simultaneous increase in adult fitness variance. These relationships can be illustrated by plotting the components of the opportunity for selection over time using historical demographic data[10,30] (FIG. 6).

The second method partitions I into components more exactly by using age-specific rates of mortality and fertility[72,73]. One benefit of this approach is that the contributions of adult mortality and reproduction to I are made distinct. In this way I_m and I_f are more reliably

Phenotypic evolution
The change in trait value distributions from one generation to the next.

Heritability
The proportion of the variation in a phenotypic trait that is due to inherited variation among individuals in a population.

interpreted as arising from variation in mortality and fertility, respectively. In the female population of 19th century Utah[74], the trends in I_m and I_f measured in this way were similar to those reported in other populations: I_m decreased and I_f increased. Because the increase in variance in relative fitness attributed to fertility more than compensated for the decrease in fitness variance caused by decreased death rates, the total opportunity for selection in Utah increased.

The changes in vital rates that mark the TTM imply increases in lifespan, and selection for lifespan may be changing in parallel, because changes in age-specific mortality, fertility and reproductive timing combine to determine how selection acts to increase lifespan. For example, selection in late life for greater lifespan will increase if mortality is decreased more in adulthood than in earlier life[11]. Conversely, a reduction of infant or juvenile mortality alone will reduce selection for survival in older individuals[75]. Reductions in reproductive rates decrease population growth rates, which can either increase or decrease selection for late-life mortality depending on the ages at which these fertility reductions occur.

Clearly, the effects of demographic transitions on the selection for lifespan are complex and can only be discerned in multigenerational studies with complete ascertainment of fertility and mortality. In one such study in Utah, improved infant and childhood mortality, reduced reproductive rates in older women and continued exposure to infections combined to reduce selection for late-life survival[74].

How fitness relates to traits. Mortality and fertility rates — the vital rates — result from the combination of behavioural, morphological and physiological traits; selection acts on these traits through their relationships with the vital rates. However, both selection for vital rates and the relationship between other traits and mortality or fertility can change across the TTM[76].

Evidence of recent natural selection acting on a diversity of traits has been reported in more than 15 longitudinal studies in pre-industrial and post-industrial populations. In several studies of post-industrial populations, both sexes experienced selection for earlier age at first birth, and women experienced selection for greater age at last birth and at menopause, greater weight, lesser height and lower levels of cholesterol and systolic blood pressure (TABLE 1).

A study on changes in selection on phenotypes across the demographic transition that occurred in several villages in The Gambia between 1956 and 2010 yielded results on the direction of selection that contrasted with those found for Western populations but confirmed that selection recently changed[68]. Before 1974 and the establishment of a medical clinic that provides health care and contraception, selection decreased height and increased BMI; after 1974, selection increased height and decreased BMI. These changes were in part due to altered relationships between height and BMI and fertility. Although this study did not investigate the proximate mechanisms underlying that change, changes in selection for fertility are likely to have been mediated by improvements in health care[68].

The recent drop in the cost of high-throughput, genome-wide genotyping has made it possible to study the relationship between genes and fitness directly. Studies using this approach suggest that selection acting on alleles known to be associated with functional traits has changed in contemporary humans[77–80]. For example, there have

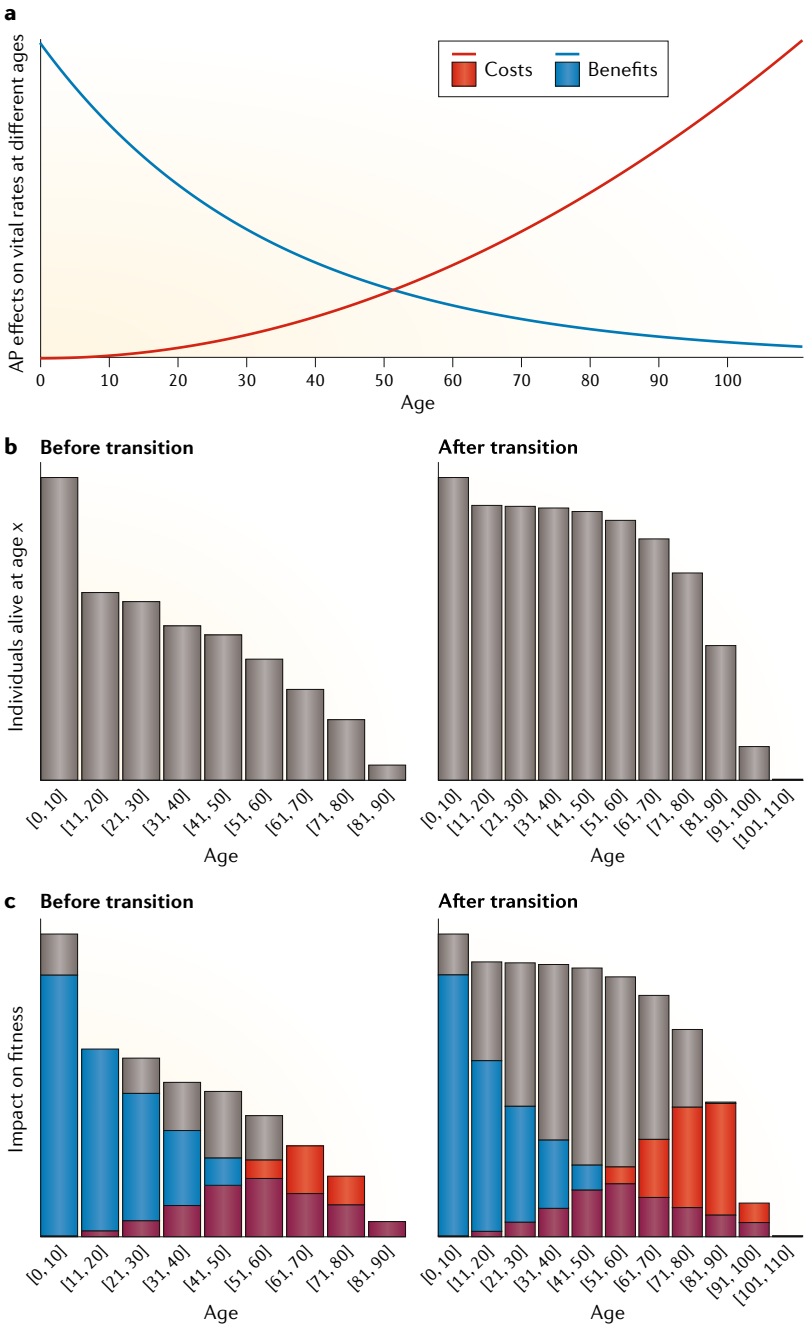
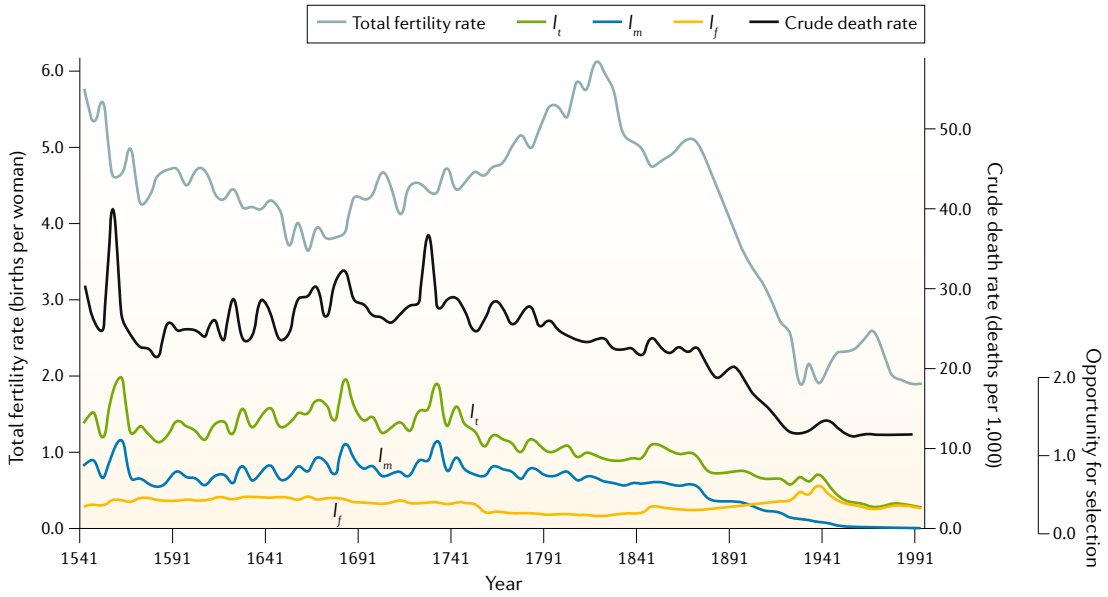


Fig. 5 | **The costs and benefits of antagonistic pleiotropy, before and after the transition to modernity. a** | The antagonistic pleiotropy (AP) hypothesis assumes that many genes, each of which has benefits at early ages and costs at later ages, combine to affect birth and death rates through their impact on many traits. **b** | The left panel, based on data from Sweden in the 1750s and hunter–gatherer populations in the 20th century[22], models conditions before the transition to modernity (TTM). The right panel models conditions after the TTM based on data from France in 2016 that were obtained from the Human Mortality Database (University of California, Berkeley, and Max Planck Institute for Demographic Research). **c** | Projecting the cost–benefit curves in part **a** onto the age structures in part **b** reveals that before the TTM, the costs were a small portion of the benefits, whereas costs are much higher after the TTM.



Calculation of Crow's indices: $I_t = I_m + \left(\frac{1}{P_s}\right) I_f$ where $I_m = \frac{P_d}{P_s}$ and $I_f = \frac{V_f}{\bar{x}^2}$

Fig. 6 | **The opportunities for mortality (*Im*), fertility (*If*) and total selection (*It*) in England, 1541–1991.** We derived secular estimates of Crow's indices[65] for total opportunity for selection and its components from compiled fertility and mortality data for England between 1541 and 1871 (REF.[10]). Quinquennial estimates of probability of death before age 20 years between 1541 and 1871 were calculated from the Second English Life Table[30] and based on estimates of life expectancy for the same period. Data between 1871 and 2000 were taken directly from estimates by Kiefitz and Fleiger[100,101]. The total fertility rate between 1541 and 1871 (REF.[30]) and between 1871 and 2000 (REFS[100,101]) was derived by inflating quinquennial estimates of gross reproductive rate (GRR) by 2.05 (REF.[87]). Estimates of fertility variance were interpolated from three point estimates between 1541 and 1871 of the proportion of married women having 0, 1, 2, 3, 4 and ≥5 children[30,102]. *If*, index of opportunity for selection caused by fertility; *Im*, index of opportunity for selection caused by mortality; *It*, index of total opportunity for selection; *Pd*, probability of death before age 20 years; *Ps*, probability of survival until age 20 years (1–*Pd*); *Vf*, fertility variance; $\bar{x}^2$, average number of children. Figure is adapted with permission from Stearns, S. & Medzhitov, R. *Evolutionary Medicine* Ch. 10, p. 259 Fig. 10.1 & p. 260. Fig. 10.2 (2016), REF.[116], Oxford University Press (www.oup.com).

been recent genetic responses to selection against educational attainment in Iceland[80] and the USA[77]. A study of reproductive and social fitness in the USA[78] confirmed that those carrying genes associated with less education had more children per lifetime; however, it found no evidence that the relationship between genes related to education and the number of children produced by parents born between 1919 and 1955 changed over the study period. While improved statistical approaches and computing power now allow direct estimates of selection acting on genes for life history traits in historical populations with sufficiently large pedigrees[81], this method has not yet been applied to explicitly estimate changes in the genetic responses to selection over demographic transitions.

How genes relate to traits. How genes produce phenotypes often depends on the environment; we refer to such context-dependent gene action as gene-by-environment (GxE) interactions. With GxE interactions, environmental changes that accompany modernization could either augment or diminish genetic responses to selection by changing the amount of additive genetic variation with which natural selection can work. For example, improvements in civic hygiene, maternal and child nutrition and the use of effective vaccines and antibiotics may have buffered the effects of genetic differences in immune responses, thereby leading to a decrease in additive genetic variation.

Results from two studies provide evidence for GxE interactions. First, a Danish cohort study of twins born between 1945 and 1952 found no variation in early-age fertility that could be attributed to heritable influences. By contrast, in a cohort born between 1961 and 1968, 47% of the variation in the determinants of early fertility was due to genetic factors — a rapid and significant increase[82]. The change in additive genetic variation was related to the socioeconomic status of the cohorts. The authors concluded that improvements in socioeconomic conditions relaxed environmental constraints and facilitated individual decision-making that served to strengthen the influence of genes on fertility[82]. A second study using 300 years of genealogical data from Finland found that while key life history traits (ages at first and last reproduction, number of offspring and lifespan) were heritable both before and after the demographic transition, there was again a tendency for additive genetic variance to increase[83]. In fact, even though reproductive timing and number of offspring are often thought to be

Additive genetic variation
The portion of the total genetic variation for a trait (not influenced by dominance or epistasis) that is capable of responding to selection.

largely volitional in post-TTM populations, studies show that expressed genetic variance in these traits may even have increased precisely because of individual freedom to choose[82], and therefore, reproductive traits can continue to evolve by natural selection.

Predicting evolution. Predicting the contemporary and future relevance of the evolutionary impacts of modernization on human health is inherently difficult because substantive evolutionary change is often slow, requiring many generations to leave a clear signature on the genome. Concurrent demographic and environmental changes can obscure the impact of genetic change. For example, selection for reduced height and lifespan in women in Framingham (MA, USA) occurred over a period when height and lifespan actually increased[74,84]. This apparent contradiction can occur when environmental effects, such as improved nutrition, push traits in a direction opposite to that driven by selection[79,85]. A similar explanation accounts for the negative selection on genes related to educational attainment in the USA[77,78] and Iceland[80] in a period when educational attainment increased[85].

Separating phenotypically plastic responses to environmental change from those that are evolutionary is important because the timescales over which these changes occur differ. Of the alternative hypotheses for the mechanisms that could mediate mismatch between the functions of genes selected in the past and their functions in contemporary populations, short-term changes caused by phenotypic plasticity, which include GxE interactions, seem more likely than changes in allelic frequencies, which take generations to accumulate to a detectable level. We should therefore assume that plastic responses to environmental changes are responsible for phenotypic change until evidence forces us to admit a role for recently evolved genetic changes.

Rapid genetic change is possible, but it is subject to the amount of genetic variation for a trait in the general population, the genetic architecture of the trait (for example, many genes of small effect or few genes of major effect)[86,87] and the influence of the trait on vital rates. For example, a recent study of green anole lizards in Texas showed that extreme winter events produced selection strong enough to change adaptation to cold at genetic, physiological and regulatory levels in approximately one generation[88]. Similar to this, rapid changes in human populations driven by the TTM are conceivable. The TTM may also have influenced trait evolution through several other factors. The influence of genetic drift should decrease as populations expand. Migration should blend the contributions of genes and the influences of selection from different areas, slowing the global response. While one can expect increased human migration to reduce the scope for local adaptation, at the same time, increases in population size should strengthen the efficacy of selection that acts in the same direction globally. Disentangling such effects and determining whether the ability of humans to adapt has increased or decreased with the TTM when all factors are considered remains a challenge.

How compelling is the evidence that natural selection is already starting to improve human health by altering our genetic response to recently changed human environments? The answer is suggestive but not yet overwhelming — there is evidence for adaptive responses of some traits to selection in some contemporary populations[68,81].

Conclusions and perspectives

Over the past two centuries, rapid improvements in health and the standards of living linked to the TTM have been accompanied by well-documented changes in patterns of disease, fertility, mortality and population growth. These improvements are now under threat by the growing global burden of non-communicable disease[4]. Efforts to understand the impact of modernization on the ecology and evolution of health and disease should now complement global efforts to prevent and treat non-communicable disease by reducing risk factors, promoting healthy environments, strengthening national policies and health systems and monitoring changing patterns of disease[89]. Some evidence suggests that changes linked to the TTM have revealed antagonistic pleiotropic effects that contribute to this burden of non-communicable disease.

Studies of multigenerational cohorts traversing demographic transitions suggest that the TTM changes the direction and intensity of phenotypic selection[55] and that the pace and magnitude of the evolution of life history traits are modest and similar to those observed in other species[68,84]. However, evolutionary changes need not be slow, and we may simply have not yet measured rapidly evolving traits for two reasons: there are not yet many adequate databases, and not all those working on the appropriate databases have prioritized this issue. Rapid adaptation can occur in polygenic traits that respond quickly to changes in selection with shifts in the frequencies of many polymorphisms already present in the population[90,91]. To respond quickly, traits need to be sufficiently heritable[86,87] and highly correlated with fitness. The fulfilment of those conditions deserves broader attention.

We close with two recommendations. First, mismatches between past adaptations and the current environment are a major theme in evolutionary medicine, but we do not yet have accurate estimates of the timing of most of the signatures of selection now being detected in the human genome (lactase persistence being one exception[92,93]). Neither do we have good methods for estimating the ages and natures of the environments in which past selection occurred. We need studies that can discriminate with confidence whether selection occurred as a result, for example, of the agricultural revolution 8,000–10,000 years ago or the TTM 100–300 years ago. Promising new techniques include the singleton density score[92], Bayesian inference[94], simulation based methods[95] and multilocus haplotype models of coalescence[96]. Given enough evidence, these approaches may be able to detect very recent signals of selection attributable to the environmental changes linked to the Industrial Revolution. Such advances will be important to identify the causes of changes in health and disease more precisely and thereby improve the search for therapies.

Second, we need large, multigenerational prospective cohort studies that allow direct measurements of genetic

Phenotypic plasticity
The sensitivity of the developing phenotype to differences in the environment.

Genetic drift
Random change in allele frequencies due to chance factors that occurs in populations of all sizes and can become strong enough to overshadow selection in small populations.

variation and selection intensity for common traits in contemporary populations, performed in a range of nutritional, cultural and geographic settings. These types of studies are the best way to characterize the magnitude and importance of complex changes that are simultaneously ecological, epidemiological, demographic and evolutionary. In addition to the Framingham cohort in the USA, such cohorts now include the Uppsala Birth Cohort in Sweden, the Lifelines Cohort in the Netherlands and the Tohoku Medical Megabank Project in Japan. Longitudinal studies of individuals supplemented with genomic and medical information will further our understanding of the antagonistic pleiotropic effects that contribute to the burden of non-communicable diseases and provide new clues to disease causes, potential therapies and possible adverse effects of novel therapies.

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