Measuring selection in contemporary human populations

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Abstract | Are humans currently evolving? This question can be answered using data on lifetime reproductive success, multiple traits and genetic variation and covariation in those traits. Such data are available in existing long-term, multigeneration studies — both clinical and epidemiological — but they have not yet been widely used to address contemporary human evolution. Here we review methods to predict evolutionary change and attempts to measure selection and inheritance in humans. We also assemble examples of long-term studies in which additional measurements of evolution could be made. The evidence strongly suggests that we are evolving and that our nature is dynamic, not static.

Given the recent emphasis on the roles of genes in disease and evolution, we tend to forget that in the short run evolution is driven by differences in fitness among phenotypes, not genotypes. We can learn a lot about the speed and direction of evolution in humans by examining the transmission of phenotypes from one generation to the next. This focus on phenotypes contrasts with the attention recently paid to the signatures that selection has written in the human genome since our last common ancestor with chimpanzees[1,2], and more recent signatures, as our genomes have responded to the domestication of plants and animals[3–6] and the spread of agriculture[7] — a fascinating area of research that is well reviewed elsewhere[1,3,4,8–11]. Less attention has been paid to the possibility that we are currently experiencing natural selection on our phenotypes and that its intensity can be measured and used to predict responses (BOX 1). The phenotypic approach focuses on one of the three central mechanisms through which natural selection drives evolution: selection works on phenotypes; genomes record and transmit the intergenerational response to selection; and development determines the phenotypes that are presented to selection. This article reviews methods for measuring our phenotypic responses to contemporary natural selection.

Knowing that we are currently evolving and understanding our responses to selection changes our basic concept of the human condition from static to dynamic. This also reveals how our rapidly changing culture, particularly through its delivery of public health and medical care, is changing our biological nature. Such knowledge is important for both applied and basic research because of the insights it offers into short-term changes in the health and demography of human populations. Research on evolution in contemporary human populations could also change our understanding of the long-term implications of recent medical innovations. Medical practice and publicity about its results affect the direction and intensity of selection on traits of medical interest. An example is the decline in selection on cholesterol level in the Framingham Heart Study between 1950 and 1990 (REF. 12). The decline probably resulted from publicity about the effects of cholesterol on heart disease detected by that very study[13].

Responses to contemporary selection can be estimated using data from multigeneration clinical, demographic and epidemiological studies that have been assembled at great expense over many years (TABLE 1); however, much of this data has not yet been used to study natural selection. This missed opportunity is the result of historical and professional biases. Physicians and epidemiologists developed methods to understand risk factors for complex diseases, and evolutionary biologists focused primarily on non-human organisms and developed methods to measure selection on phenotypic traits and predict the responses to selection. Therefore, the medical community has been unaware of phenotypic methods for measuring selection and evolutionary biologists have been unaware of large, multigeneration studies. Because of the recent surge in interest in evolutionary medicine, the two communities are just now starting to appreciate each other's insights[14]. Here, we link the phenotypic methods used in evolutionary biology to the medical and epidemiological data to illustrate

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Box 1 | **Why humans continue to evolve despite the many benefits of hygiene and modern medicine**

Within a decade of the publication of *On the Origin of Species*, the misconception developed that modern hygiene and medicine have caused natural selection to stop working on human populations[58]. This was fuelled by another misconception: that selection operates only through differences in survival. We now know that natural selection on traits occurs whenever there is variation among individuals in fitness and in traits and when the variation in traits is correlated with the variation in fitness. A response to selection will then follow if some portion of the variation in the traits is heritable. A good proxy for fitness is lifetime reproductive success (LRS) or number of children per parent per lifetime. LRS has both a survival component — one must survive to reproduce — and a reproductive component. Good hygiene and medical care that reduce prenatal, infant and child mortality rates reduce the variation among individuals in the survival component but that does not eliminate natural selection, as substantial variation among individuals in the reproductive component remains. For example, consider an extreme case in which medical and public health measures were so good that everyone who was born survived to age 80. This would not eliminate natural selection, as individuals would still differ in their LRS and that variation would drive natural selection. The potential for natural selection only vanishes when all individuals have exactly the same reproductive success or when no trait is correlated with the variation in reproductive success that still exists. These states are unlikely ever to occur in any population.

The effect of culture on biology raises interesting issues. Birth control, assisted reproductive technology and the increased prevalence of late marriage and divorce complicate the evolutionary genetics of reproduction. These factors can be dealt with by regarding them as part of a changing environment that is changing selection intensities. A more fundamental solution awaits the development of methods of analyzing gene–culture co-evolution that can be applied to large, longitudinal human data sets.

the insights that can be gained. First, we present a list of human data sets in which natural selection could be analyzed and identify a few that have already been used for this purpose. We then describe how to measure multitrait evolution and discuss the special issues that arise in humans. We finish by reviewing previous studies that measured selection or genetic parameters and by drawing some conclusions.

The emerging picture is that selection is acting in post-industrial societies to reduce age at first reproduction in both sexes, to increase age at menopause in females and to improve traits such as total blood cholesterol that are associated with the risk of disease and mortality.

Sources of data

Large, long-term, multigeneration human data sets. The sources of human phenotypic data (TABLE 1) are well known to the medical and public health community but have been underused by evolutionary biologists. They include epidemiological studies designed to measure risk factors for diseases; demographic studies designed to explore social factors affecting health; national health and twin registers[15] designed to document and analyze national health trends; and registers collected by churches and municipalities to monitor births, deaths and marriages.

Longitudinal studies are rich in phenotypic information and are easily accessed but information on fertility, which is crucial for measuring selection (see below), is often missing. National health registers, a valuable source of information on disease phenotypes, can be accessed through local authorities. In some countries, personal identification numbers allow social, familial and biological information from various registers to be combined at the individual level. For example, in 2005 the Danish National Board of Health had more than 8 million people registered[16] and had collected detailed health data since the mid-1970s, including births, deaths, abortions, disease and psychiatric diagnoses, pedigree data and information on birth defects. Sweden, Norway, Finland, Iceland and other developed nations keep similar records. Because most national health registers record visits to doctors, they usually do not report as complete and regular measurements as do epidemiological studies. Parish registers have also been used in an evolutionary context[17].

None of these data sets is perfect; in all of them some data are missing or measured irregularly. The most useful are those that record completed family size and attempt to measure traits repeatedly at regular intervals on all individuals in the population under study.

Measuring evolution

To estimate selection intensities on traits, one needs a measure of fitness, reliable measurements of traits and the phenotypic and genetic correlations among those traits for a large number of individuals in a single population. Although acquiring molecular genetic data has become increasingly cheap and easy, getting equivalent phenotypic data remains expensive and difficult. Connecting genotypes to phenotypes is a top priority but to do so we need both the genetic and phenotypic levels to be described with similar detail and precision: we need a phenome to match the genome (BOX 2). The studies highlighted here are a starting point, as they describe at least part of the human phenome.

Measuring fitness. How best to measure fitness[18] is an issue of more theoretical than practical consequence in modern human populations, in which most individuals survive from birth through the peak ages of childbearing. In such populations, fitness is reasonably approximated by completed family size (lifetime reproductive success; LRS)[12], a measure that incorporates survival and reproduction. Even in contemporary populations with moderately high mortality, the proportion surviving from birth to age 50 is so high that the number of

Longitudinal study
An observational study in which individuals are followed for a long period of time, often many decades, and in which the same traits are measured repeatedly.

Table 1 | **Examples of clinical cohorts that could be used in evolutionary studies**

Study and data analysed	Focus	Origin	Sample size	Sex or cohort	Date initiated	Refs
The Framingham Heart Study • LRS, births, deaths; genetic, cardiovascular, physiological and morphological traits; family and pedigree data	Cardiovascular disease	USA	~14,000	Both sexes; three cohorts	1948	12
The Wisconsin Longitudinal Study • LRS, birth year and sex of child, education, marital history, fertility; anthropometric, socioeconomic, family and pedigree data	General health	USA	~10,317	5,326 women, 4,991 men born 1937–1940	1957	98,99
Medical Research Council studies in Gambia • LRS, marriages, migration, health, mortality, height and weight	General health	Gambia	~ 684 women, ~ 500 men	Both sexes; different villages	1950 (annually 1950–1980)	43
The National Child Development Study • LRS, fertility, height, occupation, education, health data, birth weights; obstetric, disability, medical and psychological assessments	Social, economic and health outcomes	Great Britain	~17,414	All children born in a single week in March	1958 6 sweeps to gather information	100
The Helsinki Birth Cohort Study	Multidisciplinary epidemiological cohort	Finland	~13,345	Individuals born 1934– 1944	1971	101, 102
The Hutterite Study • LRS, fertility, genetic, pedigree and family data, medication use and illness	Reproduction and fertility	USA	Varies by study; >23,000 in population	Both sexes	1982	93, 103
The Nurses' Health Study* • Reproductive history, family history, diet, physical activity, disease incidence, medication, psychosocial and physical data	Long-term effects of oral contraceptives	USA	First generation: ~122,000 Second generation: ~117,000	Women	1976	
The Jackson Heart Study* • Anthropometric, blood chemistry, genetic, inflammation and hormone data; reproductive history, family and pedigree data	Cardiovascular disease in African–Americans	USA	~3,360 women, ~1,941 men	Both sexes	2000	
Atherosclerosis Risk in Communities* • Reproductive history; anthropometric, cardiovascular and socioeconomic traits	Atherosclerosis	USA	15,792 (3 years)	Both sexes	1987	
The Women's Ischaemia Syndrome Evaluation Study* • Reproductive status; demographic, clinical, symptomatic and psychosocial data (menarche, menopause, pregnancy)	Ischaemic heart disease in women	USA	936	Female	1996	
The Danish Civil Registration System* • Fertility, family and pedigree, health and disease data‡; hospitalizations, psychological data and malformations	National health monitoring	Denmark	8,176,097	Men, women and children	1978	16

Pleiotropy
The action of a single gene on two or more distinct phenotypic characters.

Linkage disequilibrium
A measure of whether alleles at two loci coexist in a population in a nonrandom fashion; one common cause is that the loci are neighbours on the same chromosome and therefore do not recombine.

newborn per female per lifetime that survive childhood is a reasonable estimate of fitness (BOX 1). Reproductive success can be more reliably estimated for females than for males and data are often only collected from women. This restricts the study sample to women who have reached menopause or for whom there is another reliable way to conclude that they will not have more children. Not all attempts to measure contemporary evolution have limited their sample this way (TABLE 1). Counting the number of children or grandchildren that survive to reproduce would be an improvement but is rarely done. In cases in which the mothers' ages at birth of all offspring are available, a fitness measure should be used that incorporates timing effects[19].

Multiple traits and indirect effects on fitness. Traits have a direct correlation with fitness and indirect connections through their phenotypic correlations with other traits. Therefore, a trait can evolve simply because it is correlated with another trait that is subject to selection pressures. For example, high cholesterol levels are associated with obesity. If obesity is associated with reproductive success, then cholesterol levels will tend to evolve. The genetic correlations, caused by pleiotropy and linkage disequilibrium, are also needed because they affect responses to selection. In humans, both types of correlations can be affected by the cultural transmission of behaviours such as diet, education and smoking.

Table 1 (cont.) | **Examples of clinical cohorts that could be used in evolutionary studies**

Study and data analysed	Focus	Origin	Sample size	Sex or cohort	Date initiated	Refs
The Maternal and Child Health Research Database* • Linked registers with births, deaths, health, maternal physical, sociodemographic, pregnancy and perinatal data, family data for mothers and children	Maternal and child health monitoring	Australia	>All births (450,000) from 1981	Women and children	1980	104
Coronary Artery Risk Development in Young Adults* • Birth and fertility, diet, exercise, behaviour, psychological, anthropometry and women's reproductive health	Coronary artery risk development	USA	5,115	Both sexes	1985–1986	
The San Antonio Family Heart study	Heart disease in Mexican–Americans	USA	1,431	Both sexes	1991	105
The Utah Population Database*	Cancer records	USA	> 7 million	Both sexes	1971	106
The Family Heart Study*	Coronary heart disease	USA	14,592	Both sexes	1970	107
Biological Ageing in Mennonites*	Genetics of ageing	USA	~1,450	Both sexes	1979	
The Stanislas Cohort*	Cardiovascular disease	France	4,295	Both sexes	1993	108
The Sardinia Cohort*	Personality and cardiovascular traits	Italy	6,148	Both sexes	2002	96

*In these studies, data on reproductive history or fertility are collected but we do not know whether this represents completed lifetime reproduction. ‡According to the international classification of diseases by the World Health Organization. LRS, lifetime reproductive success.

The problem of disentangling correlated traits can be illustrated by a real example. For women in the Framingham Heart Study population, total cholesterol has a positive phenotypic correlation with weight, systolic and diastolic blood pressure, blood glucose and age at first birth, but a negative phenotypic correlation with height and age at menopause. It has a negative genetic correlation with weight, height and age at first birth, but a positive genetic correlation with systolic and diastolic blood pressure, glucose and menopause. The correlations of these traits with lifetime reproductive success are positive for weight, diastolic blood pressure and age at menopause, but negative for total cholesterol, height, systolic blood pressure and age at first birth[12]. The outcome for total cholesterol depends on the intensities of selection on the entire set of correlated traits and on the strengths and signs of the genetic and phenotypic correlations. In general, a trait under directional selection could respond positively, negatively or not at all depending on the contributions of the phenotypic and the genetic correlations. In this case, after phenotypic and genetic correlations were taken into account, it was found that selection is operating to lower total cholesterol[12].

Cultural versus genetic transmission of traits. The methods used to estimate genetic variances and covariances of traits in humans rely on correlations among relatives. If we have hundreds of pedigrees, we can estimate the genetic parameters fairly precisely. However, the precision of the estimates should not distract us from an issue in the logic: parents transmit genes and culture to their offspring and both effects are confounded in the data. This complicates the assumption of the model that there are no interactions between genetic and environmental effects[20]. Because the environment includes cultural effects and the transmission of traits across generations is in part cultural, a change in culture might change the transmission of traits between generations. Culture matters less for some traits than for others but in observational studies the only practical solution is to note the issue and remain modest in drawing conclusions. Estimates of the evolution of traits in humans provide a description of evolutionary change over a brief historical period and may not predict future changes. That estimates of genetic transmission of traits based on phenotypic data may be biased by environmental factors is a general problem that is not limited to studies of human populations[21].

Dealing with age and year effects on traits. Many of the traits measured in the large studies mentioned in the 'Sources of data' section change with the age of the individual and the year of measurement. Complex models have been developed to examine selection in age-structured populations with secular change[22]. A more practical approach in some situations is to express individual traits relative to other individuals of the same age measured at the same time. If sample sizes are large and traits have been measured several times on each individual, then these effects can be accommodated by taking the average of the individual residuals from a three-dimensional surface generated by a generalized additive model[23] or a locally weighted regression[24] of each trait by age and year of measure. This yields one estimate of the trait value per individual that is more reliable than the individual measurements and adjusts for changes in the trait mean over time and with age. These average residuals can then be input to the procedures that yield the phenotypic and genetic covariance matrices.

Directional selection
Natural selection that favours values of a quantitative trait at one extreme of the population distribution. In positive directional selection, natural selection favours values of a quantitative trait at the upper extreme of the population distribution.

Generalized additive model
A statistical model that blends properties of generalized linear models with additive models (parametric or non-parametric) and is often used to estimate smoothing functions for scatter plots.

Box 2 | **The need for phenomes**

In the post-genomic era, it is well recognized that we need to be able to describe phenomes as precisely as we describe genomes[59,60]. For example, large-scale phenotyping is expected to improve our resolution of phenotype–genotype associations[61], to better predict candidate genes for disease[62], to improve our understanding and treatment of complex diseases[63] and to enhance our opportunities to discover and predict evolutionary changes in contemporary humans. The issue of how best to define, collect, store, analyze and share phenomic data, however, remains open[64].

As various high-throughput technologies allow more detailed biomolecular phenotypes (biomarkers) to be obtained, they will enable selection studies on phenomes with hundreds and even thousands of traits. We are not yet aware of any long-term multigeneration studies that have built such data collection into their regularly executed protocols. It is likely that future studies that do so will understand selection in unprecedented detail.

When one studies multitrait evolution, there are technical as well as conceptual reasons to include measurements on as many traits as possible. Because the projections of response to selection are made using both phenotypic (*P*) and genetic variance–covariance (*G*) matrices, the predictions for change in a focal trait depend on the other traits included in the study — on the number of rows and columns in the *P* and *G* matrices. The greater the number of traits included, the better the chance that the analysis will reflect reality. For example, in the women in the Framingham Heart Study, the predicted evolutionary change in systolic blood pressure is a decrease of 0.4 mmHg over 10 generations or 0.35% when the trait is considered by itself, but when its phenotypic and genetic correlations with 6 other traits are included, the prediction changes to a decrease of 2.3 mmHg over 10 generations. This is 1.82% of the starting value and 5.25 times larger than the prediction made when the trait is considered by itself.

This modest example, which suggests the importance of correlated complexes of traits, indicates what we might find if we could analyze the entire phenome, which consists of thousands of traits and is the object on which natural selection works. Large-scale phenotyping may require improved methods for measuring natural selection because as we add traits to a multiple regression, the probability of multicollinearity increases and larger samples may be needed to generate sufficient statistical power to detect differences.

Dealing with substantial environmental change over periods shorter than a generation. Humans are long lived, their culture changes rapidly and the data assembled in multigeneration studies reflect a range of biological and cultural environments. For example, individuals born in 1920 experienced the Great Depression, the Second World War and the post-war economic recovery. They lived through major shifts in fertility patterns (low during the 1930s and early 1940s and high in the 1950s) and encountered substantial changes in technology, public health and medical practice, including antibiotics, vaccinations, treatments for high blood pressure, diabetes, heart disease and the management of reproductive health.The method of residuals described in the previous paragraph represents the traits measured on an individual relative to others in the population. For fertility trends, which can be dramatic (the 'baby boom' of the 1950s and the 'baby bust' in the 1960s and 1970s), the period of observation can be divided into cohorts of approximately 25 years to match the periods that have major differences. The LRS of an individual can then be expressed relative to others in its cohort. One could also use locally weighted regressions to express individual reproductive success relative to others of a similar age who are reproducing at nearly the same time[24]. In any population, some individuals have completed reproduction and others are still fertile. This issue can be dealt with for women by limiting the sample of completed family sizes to individuals who have completed menopause. Getting a reliable measure of completed family size for men is problematic because paternity can be cryptic or intentionally concealed and the ability to reproduce often continues to high ages.

Status of the research. Although we now know that some contemporary humans may be evolving, we do not know how general the evolutionary patterns are. We need several comparable studies of post-industrial and pre-industrial populations to get a more complete picture of the variation in selection patterns in time and space. In so doing, a major challenge will be to develop better methods to measure the effects of culture on selection and inheritance. A starting point to do this will be the analytical framework developed by evolutionary biologists.

Analytical framework

Phenotypic evolution, which is the change in the mean value of traits between generations, is driven in the short term by natural selection — that is, by the association of heritable traits with differences in fitness (LRS). Differences in fitness only lead to evolution if the traits with which fitness is associated are inherited. Therefore, phenotypic models describing natural selection include three components: differences in fitness, heritability of the trait and the amount of variation in the trait. The simplest model examines a single binary trait whereas a more useful model simultaneously examines several quantitative traits. The basic model is described below and the progression from the simplest model to the more complete model is shown in BOX 3.

Basic phenotypic model of natural selection. Most research on natural selection uses a framework developed by Lande and Arnold[25]. Lande[26] expressed the change in the mean value of a trait, z, in terms of the three components described above. The first component, the difference in fitness, is measured by the selection differential, s, which is the difference between the mean of z and the mean of z when individuals are weighted by their reproductive success, w_i. The second, genetic component, g, which represents the additive genetic variance in the trait (commonly represented as σ_A^2), can be estimated as the covariance between the z_i values of the children and their parents. The third component, the amount of phenotypic variation in the trait, is simply the variance of z, σ_z^2. The change in the mean of z between generations is sg/σ_z^2.

This framework leads to two ways of thinking about natural selection. Animal and plant breeders, who have substantial control over the fertility of individuals and experimental design, focus on heritability. 'Narrow-sense heritability', h^2, is g/σ_z^2. In humans, this can be estimated as the regression coefficient relating z in offspring to the mean z of their two parents. Then, the 'breeder's equation' expresses the change between generations due to selection as h^2s; this is the response to selection, R (REF. 27).

Heritability
The proportion of the total phenotypic variation in a trait that can be attributed to genetic effects.

Selection differential
The average superiority of the selected parents; it is expressed as the mean phenotypic value of the individuals selected as parents and expressed as a deviation from the population mean.

Additive genetic variance
The part of the total genetic variation that is due to the main (or additive) effects of alleles on a phenotype. The additive variance determines the response to selection.

More natural situations in which fertility cannot be controlled require us to focus on the fertility differentials. Lande and Arnold[25] show that s can be expressed as the covariance between the traits and fitness, z_i and w_i. They then note that s/σ_z^2 is the regression coefficient, b, relating fitness, w_i, to the trait, z_i. In this perspective, the change between generations is expressed as $\sigma_A^2 \times b$. Extending the model to examine multiple traits then involves the slopes from a multiple regression between a measure of fitness and multiple traits, β. In matrix form, σ_z^2 is replaced by a variance–covariance matrix, *P*. The multivariate equivalent of *g*, the genetic variance–covariance matrix, *G*, can be estimated from data on the traits of family members, such as parents and children or siblings, using one of several computer packages (for example, SOLAR[28], MERLIN[29] and VCE[30,31]; please see Further information for links to these analysis tools). The change in the traits can then be compactly expressed as $\Delta z = G\beta$ (BOX 3). The model can be applied to reproductive success or to any component of fitness, such as child mortality or total live births. Within this general framework, the methods used to test, quantify and display the effects of natural selection have grown in variety over the years[32–38].

Table 2 | **Estimates of selection on traits in modern human populations**

Trait	Sex	Selection	*p*	*n*	Population (century)	Refs
Life history						
Age at first birth	F	–	***	306	Finland (17th–19th)	109
	F	–	***	395	Finland (18th–19th)	17
	F	–	***	2,227	USA (20th)	12
	F	–	**	314	Finland (20th)	110
	F	–	***	1,459	Australia (20th)	111
	F	–	**	2,443	USA (20th)	112
	M	–	**	395	Finland (18th–19th)	113
	M	–	**	2,443	USA (20th)	112
Interbirth interval	F	–	***	306	Finland (17th–19th)	109
Age at last birth	F	+	***	306	Finland (17th–19th)	109
	F	+	*	314	Finland (20th)	110
Age at menopause	F	+/s	**	2,227	USA (20th)	12
	F	+	**	1,459	Australia (20th)	111
Age at death	M	+	***	746	USA (19th)	114
Morphology						
Weight	F	+	**	1,278	USA (20th)	115
	F	+/s	***	2,227	USA (20th)	12
	M	s	***	2,616	USA (19th–20th)	116
Height	F	+	*	216	Gambia (20th)	43
	F	–/s	**	3,552	Great Britain (20th)	100
	F	–	**	1,278	USA (20th)	115
	F	–	***	2,227	USA (20th)	12
	M	s	***	2,616	USA (19th–20th)	116
	M	+	*	322	USA (20th)	44
	M	+	***	3,201	Poland (20th)	117
Physiology						
Cholesterol	F	–	**	2,227	USA (20th)	12
Systolic blood pressure	F	–	*	2,227	USA (20th)	12
Blood glucose	F	s	**	2,227	USA (20th)	12

Several studies went beyond lifetime reproductive success to estimate fitness as number of offspring that survived to age 14 (REF. 43) or to age 18 (REFS 109,110,113). Two assumed that reproduction was complete by age 42 (REF. 100) or 45 (REF. 118) – for example, 96% and 99% of all male and female reproduction occurred before the age of 45 in a Swedish cohort[118]. The association of traits with fitness was estimated in most cases using multiple or partial regression; one study used analysis of variance (ANOVA)[115]. Most populations were post-industrial; the Finnish Sami and Gambian populations were pre-industrial with natural fertility. Only two studies used lifetime reproductive success to measure fitness, estimated both phenotypic and genetic correlations among multiple traits and combined them to estimate evolutionary change[12,111]. Only one study attempted to project the response to selection[12]. +, positive directional selection; –, negative directional selection; F, female; M, male; *n*, sample size (largest reported in study); *p*, Highest *p*-value for trait (not all may have been significant; *p<0.05; **p<0.01; ***p<0.001); s, stabilizing selection.

Projecting evolution over more than one generation. The true relationship between a component of fitness and a series of traits is rarely described exactly by a multiple linear regression. For example, binary traits such as the survival status of a child are best described by a logistic regression. This is not a problem for studying evolutionary change over a single generation. However, in each generation, natural selection moves the population to a different point on the surface that relates traits to fitness. Therefore, projecting more than one generation ahead requires calculating how the variance–covariance matrix among traits will change and what effects this will have on the mean effects of each trait on fitness. Lande and Arnold[25] suggested that this can be accomplished using a quadratic regression that includes the traits, the traits squared and the cross-products of each pair of traits. The use of a simple quadratic regression has been questioned and several alternatives such as logistic regression have been proposed[39,40]. However, the rapid nature of environmental change in human populations and the likely importance of gene–environment interactions mean that it is not useful to project evolution in humans beyond a few generations; here the quadratic model is probably adequate[40].

Nonlinear selection. The issue of nonlinear selection is not yet well explored. There are three types of nonlinear selection: stabilizing (convex), disruptive (concave) and correlational. The first two are often estimated by a quadratic regression. Many studies of natural populations have not tested for quadratic effects. Many of those that have tested for them had small sample sizes and the effects that were found suggest that stabilizing selection is weak and uncommon, but this inference is not very reliable[41]. Correlational selection is dealt with by estimating the interactions of traits in affecting fitness. Only 7 of 63 studies of natural populations[41] and only 3 of 14 studies of human populations (TABLE 2) tested for nonlinear selection using interaction terms. A reorientation of the matrices that express interactions, for example, using factor analysis, can reveal substantial nonlinear selection where little had previously been detected[32,35,39]. We have yet to uncover the prevalence and intensity of nonlinear selection in natural and human populations.

In human cases, in which environmental change is rapid compared to generation length, the issue of non-linear selection is real but may be less important than in species in which generations are shorter than the periods of environmental change. Worrying about the exact shape of the selection differentials should not be the top priority if the shape of the surface and the genetic correlations will change in the next generation. More important in human evolution are rapid cultural and environmental change; the challenge is to measure their effects and represent them in models.

Insights from previous studies

Studies of evolution in contemporary human populations are beginning to suggest a few generalizations. When summarizing these results, it is important to distinguish studies in low mortality populations from those in populations with higher levels of infant and child mortality. Until the start of the last century, all contemporary humans experienced low infant survival rates but many populations now experience much better survival at all ages. Because reproductive success is composed of survival and reproduction and very low mortality rates imply little variation among individuals in survival, we would expect to see a shift in selection intensities towards the more variable reproductive parameters, such as age at first birth, interbirth interval, age at menopause and use of modern contraceptives to limit total births.

Studies of selection. More than 14 studies have reported significant selection in contemporary human populations (TABLE 2). Those reported here differ in whether a single trait or multiple traits were measured, in whether genetic parameters were estimated and in whether estimates of evolutionary change were made. Methods for detecting natural selection in humans have been changing. Early studies considered the association of one or two traits with LRS but often did not consider both biological and cultural evolution. Most early studies did not adjust for temporal changes in traits and fertility, did not include nonlinear terms to test for stabilizing selection and did not account for correlations among traits. Many did not estimate genetic parameters. From the point of view of this paper, these are deficiencies, but many of the papers reviewed had different aims and were written before current methods were broadly appreciated.

Box 3 | **Models for studying the evolution in blood pressure caused by differences in fertility**

The table below uses the example of blood pressure to show the progression from simple models of natural selection to more complex multitrait models. It illustrates each of the three components described in the text: measures of differentials in fitness by phenotype, measures of the amount of variability in the phenotype in the parental population and measures of the extent to which children inherit the phenotype of a parent.

Binary trait

The example focuses on the fertility component of lifetime reproductive success. The second column examines how a simple model describes the effect of fertility differentials on the proportion of individuals in the population who are hypertensive (a binary trait). We could measure the difference in fertility (row 2) as the ratio of mean number of children born to hypertensive individuals divided by the mean number born to normotensive individuals. The amount of variation in the parental population (row 3) would simply be the proportion that is hypertensive. We describe the heritability (row 4) using the proportions of hypertensive individuals among the children of hypertensive and normotensive individuals. The final row gives the equation for change in the proportion hypertensive between generations.

Continuous trait

Column 3 shows the equivalent measures for changes in systolic blood pressure (SBP), a continuous trait. In this case, the change between generations can be described in terms of heritability, h^2, and the covariance between fertility and SBP or in terms of the regression coefficient relating fertility to SBP and the covariance between the SBP of parents and their children, *b*. Column 4 shows the matrix notation used for describing the co-evolution of multiple traits, such as SBP, diastolic blood pressure and high-density lipoprotein cholesterol.

Component	Single binary trait (% hypertensive, π)	Single continuous trait (SBP)	Multiple traits ($X_1 \ldots X_k$)
Fertility differences	The ratio of the numbers of children born to groups 1 and 2 (F_1/F_2)	Covariance between fertility and SBP, Cov (*F*, SBP)	Vector of covariances between fertility and each phenotype, V
Variation in parental generation	Percent hypertensive among parents, π_1	Variance in SBP among parents, Var (SBP_1)	Variance–covariance matrix among phenotypes in parents, *P*
Inheritance component	Percentages hypertensive among children of hypertensives and others, p_1 and p_2	Variance in SBP attributed to genetics, *g* (commonly represented as σ_A^2)	Matrix of genetic variances and covariances from additive model of inheritance, *G*
Change in mean phenotype(s)	$\pi_1 \times (F_1/F_2 * p_1 + (1 - \pi_1)) \times p_2$	$G \times \mathrm{Cov}(F, \mathrm{SBP}) / \mathrm{Var}(SBP_1) = h^2 \times \mathrm{Cov}(F, \mathrm{SBP}) = g \times b$	$\Delta z = G P^{-1} V = G \beta$

β, a vector of regression coefficients relating multiple traits to a measure of fitness; *b*, the regression coefficient relating a single trait to a measure of fitness; h^2, the common measure of heritability.

Narrow-sense heritability
The proportion of phenotypic variation that can be accounted for by additive genetic effects. By contrast, broad-sense heritability includes effects of interactions among genes that are caused by dominance and epistasis.

Quadratic regression
A quadratic regression estimates the parameters of an equation for a parabola that best fits the data. Here it is incorporated in a larger model that also has linear elements.

Stabilizing selection
Natural selection that favours intermediate values of a quantitative trait.

These studies report three striking findings. First, both women and men are under selection for earlier age at first birth in both pre-industrial, natural fertility populations and in post-industrial populations. Second, women are under selection for later age at last birth in a pre-industrial population and later age at menopause in two post-industrial populations. Third, women are under selection for increased height in one pre-industrial population and for decreased height in three post-industrial populations.

The trend to earlier maturation at smaller body sizes may be a consequence of the widespread decrease in juvenile mortality rates caused by modern hygiene, public health measures and medical care. If we assume that age and height at maturity had been in an evolutionary equilibrium determined by a life–history trade-off in which earlier maturation implies higher juvenile mortality of offspring, then the lowering of juvenile mortality rates would decrease the cost of earlier reproduction and selection would then favour earlier age at first birth at a shorter height[42]. In pre-industrial societies, the advantages of earlier birth at a shorter height may be outweighed by the greater mortality of children of shorter, younger women[43].

The combination of earlier age at first birth and later menopause or age at last birth, which is consistently found across multiple populations, indicates that the temporal window of reproductive opportunity is broadening. This can be interpreted as a response to a shift in the balance of selection components from mortality-dominated to fertility-dominated components.

Selection may be either directional (consistently for an increase or a decrease) or stabilizing (consistently for an intermediate value). Selection on height in men includes both directional selection for increased height[44–46] and stabilizing selection for intermediate height in some populations[47]. Stabilizing selection for height may be due to poorer health overall for short men[48] and increased risk for musculoskeletal problems[49] and certain cancers[50,51] in very tall individuals.

We have only begun to detect the human traits that are under selection. The extensive evidence of natural selection on diverse traits in plant and animal studies[41] suggests how much remains to be discovered in humans.

We have chosen not to discuss the many other studies that used age-adjusted fertility rather than LRS because they did not measure lifetime reproduction completely. Results on traits with a large cultural component — such as education, measures of cognition and wealth — are reported separately in BOX 4 because there are serious issues with the inference of their heritabilities and because expectations have not been borne out that a trait such as intelligence quotient (IQ) would respond to selection[20,52].

Studies of heritability and genetic correlations. Measuring selection intensities is necessary but not sufficient to predict the response to selection. We also need to know the heritabilities[53] of the traits and the genetic correlations among them, which then require transformation to represent additive genetic variances and covariances (G). Heritabilities of single human traits have been measured far more often than have genetic correlations between pairs of traits. FIGURE 1 shows 4 representative patterns of heritability estimates from our analysis of 75 studies with a combined sample size of more than 130,000 individuals. This analysis makes the following points. First, most human traits have measurable heritability and will respond to selection if they are not constrained by phenotypic and genetic correlations with other traits. Second, traits directly related to LRS tend to have lower heritabilities than traits that have a less direct relationship to fitness. The mean heritabilities of age at first birth (~0.11), LRS (~0.23), cardiovascular function (~0.34) and blood phenotypes (~0.36) are lower than the mean heritabilities of weight (~0.55), measures of many body dimensions (~0.59), age at menopause (~0.59) and height (~0.75). This pattern is consistent with the expectations of evolutionary genetics, as selection reduces the standing genetic variation of traits in proportion to its intensity. Similar patterns have been found in comparisons of the heritabilities of different classes of traits summarized from 1,120 wild animal populations[54]. Third, for a given trait, estimates of heritabilities from twin studies are consistently higher than estimates from population studies. Two common problems with twin studies involve the assumptions about shared environment and how measurement error is handled as a source of error[20].

Lessons learned

The phenotypic data available in large data sets hold the key to how natural selection is currently acting on many human populations. This information will benefit basic science in the short term and medical science in the long term by changing our view of human populations from static to dynamic, genetically and culturally. The most interesting potential insights will be into how human interventions are changing human evolution.

The major unresolved issues are how to deal with cultural evolution and gene–culture co-evolution. Culture includes socially transmitted information that affects the behaviour of individuals (such as marriage patterns, diet, education and smoking) and the larger social environment (including public health and clinical practices). Cultural change can affect selection gradients by altering the correlation of traits with LRS. It can also change the expression of genetic variation and, therefore, heritabilities and genetic correlations[55]. Therefore, culture can affect both selection and the response to selection. At this point, the data and analytical methods needed to understand these processes are sparse. In modern societies, the cultural environment changes so rapidly that, even if these data and methods were available, the best that could be expected would be retrospective analyses of gene–culture interactions rather than reliable predictions of future states.

The next step will be to see whether the phenotypic changes measured with the methods described here

Box 4 | **Selection on traits with a large cultural component**

We present this Box with the warning that it should be used 'with great caution'. Heritability estimates in humans for traits such as intelligence are derived from observational studies using correlations that are not from experiments designed to isolate the additive genetic component of phenotypic variance. This means that they can be seriously confounded by undetected cultural transmission. In addition, there are many dimensions to intelligence and each test measures something different. Therefore, these heritabilities might better be described in terms of performance on a given test, not some grand concept called intelligence quotient (IQ). We have nevertheless chosen to present these estimates of selection pressures, as there is widespread interest in the evolution of such traits. The heritability of cognition is perhaps more intensely studied than that of any other human trait and for decades there have been discussions on the apparent paradoxical evolution of cognitive abilities. The issue was recently reviewed by Visscher *et al.* (Box 4 in REF. 53). Estimates of the heritability of IQ derived from comparing the IQs of monozygotic and dizygotic twins range from 0.5 to 0.8. When maternal effects are taken into account, estimates drop to 0.3, which is still significant. Visscher *et al.* conclude that "a large proportion of the variation in IQ between individuals within a population is associated with additive genetic factors." Bouchard agrees, noting that the influence of shared environment on IQ predominates early in life but dissipates to near zero by adulthood[65].Therefore, IQ is heritable and varies among individuals. Does it respond to selection as would be expected? It does not. Ramsden[52] discusses the striking case of the large repeat survey of Scottish schoolchildren that was conducted to see whether IQ measured at age 11 in parents had declined in their offspring, who were measured with the same test at the same age. It was expected that IQ would decline, as it is negatively correlated with family size and is heritable. IQ did not decline, despite being under negative directional selection. In fact, it increased. This striking result suggests that projecting evolutionary change for traits that have a large cultural component encounters difficulties that go beyond the estimation of heritability.

With this in mind, consider the table shown above. Taken at face value, it suggests that contemporary humans are under directional selection for less education, less income in women, and more income and wealth and higher rank in men, and decreased intelligence in both sexes. However, as the Scottish study makes clear, we can only conclude from these results that these traits were significantly correlated with reproductive success in the environment in which they were measured. We cannot say that these correlations would lead to an evolutionary response.

Such examples re-emphasize the need to develop and apply methods to partition the contributions of cultural and biological evolution to changes in human traits.

Trait	Sex	Selection	*p*	*n*	Population (century)	Refs
Education	F	–	**	2,443	USA (20th)	112
	F and M	–	*	1,906	USA (20th)	119
	M	–	*	2,443	USA (20th)	112
Income	F	–	**	2 443	USA (20th)	112
	F	–	*	1,278	USA (20th)	115
	F	–	*	14,000	Sweden (20th)	120
	F	–	**	5,576	Great Britain (20th)	121
	F and M	–	*	1,906	USA (20th)	119
	M	+/–	**	10,436	USA (20th)	122
	M	+	**	2,443	USA (20th)	112
	M	+	**	5,576	Great Britain (20th)	121
	M	+	***	14,000	Sweden (20th)	120
Wealth	M	+	***	164	Kenya (20th)	123
	M	+	*	746	USA (19th)	114
	M	+	***	302	Sweden (19th)	124
Occupational status	F and M	–	*	1,906	USA (20th)	119
Rank	M	+	***	746	USA (19th)	114
	M	+	*	322	USA (20th)	44
Hunting ability	M	+	*	18	Botswana (20th)	125
Intelligence	F and M	–	***	1,906	USA (20th)	119

+, positive directional selection; –, negative directional selection; F, female; M, male; *n*, sample size (largest reported in study); *p*, highest *p*-value for trait (not all may have been significant; *p<0.05; **p<0.01; ***p<0.001); s, stabilizing selection.

are tracked by changes in the allele frequencies of the genes associated with the traits[56,57]. This can be done by identifying the genomic variants (for example, SNPs and copy number variants) associated with the selected traits in studies in which such data have been gathered for the parental and the offspring generation.

Conclusion

The studies reviewed here make clear that traits in many human populations are experiencing natural selection and have the genetic potential to respond to it. In at least two populations, selection acting on multiple traits has been measured and responses have been estimated.

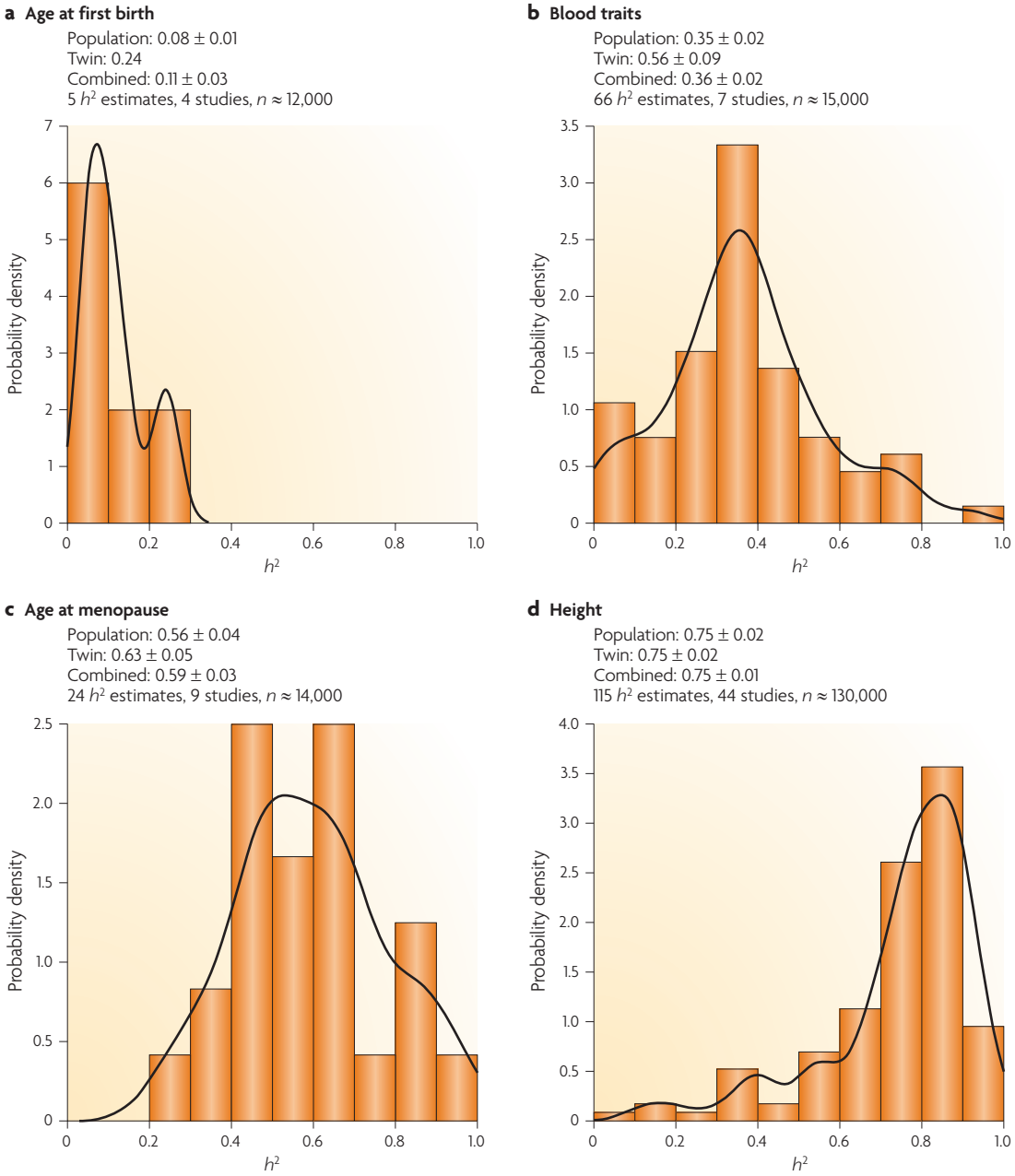

Figure 1 | **Heritabilities (h^2) of human traits.** The heritabilities of four human traits are shown: age at first birth (**a**), blood traits (many measures of blood chemistry; **b**), age at menopause (**c**) and height (**d**). Note that traits that are tightly correlated with fitness such as age at first birth have lower heritabilities than traits relatively uncorrelated with fitness, such as age at menopause and height, as is consistent with the predictions of theoretical evolutionary genetics[54]. Population refers to the mean h^2 from population-based studies, twin refers to the mean h^2 from twin-based studies and combined refers to the mean h^2 using data from population and twin studies. ± followed by a number refers to the standard error of the mean. Other values indicate number of h^2 estimates plots were based on (h^2), the number of studies h^2 values were obtained from and the approximate sum of individuals across all studies that were used to obtain these estimates (n). The data shown in the plots are from REFS 12,66–97.

Measuring selection on contemporary human populations is important because it changes our views of the populations for which clinical and public health interventions are designed. Our biological nature is not static; our interventions are changing it with uncertain direction and magnitude. Measuring such change is not easy. Large samples are needed over multiple generations and many traits should be measured repeatedly and reliably. Future large, long-term, multigeneration studies should regularly record at least all births and deaths and those measures of culture — including medical intervention, diet and education — that influence selection and inheritance.

The importance of culture becomes clear in the contrast between the developed and the developing world. In the developed world, it is primarily variation in fertility rather than mortality that shapes variation in LRS. In developing countries, the variation in mortality has a greater contribution to selection, particularly the variation in infant and child mortality that is associated with infectious disease and deficiencies in child nutrition. The next important insights from the measurement of selection in contemporary human populations will come from the comparison of populations from the developed and the developing world.

The rapid rate of change in the social and cultural environment offers opportunities for studying the dynamics of selection and the plasticity of genetic correlations. Humans are not the only species affected by environmental changes. Research on human evolutionary responses to sudden environmental changes will contribute to cross-species comparisons that will help us understand the role of evolution in a rapidly changing world.

1. Barreiro, L. B. & Quintana-Murci, L. From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nature Rev. Genet.* **11**, 17–30 (2010).
2. Bradley, B. J. Reconstructing phylogenies and phenotypes: a molecular view of human evolution. *J. Anat.* **212**, 337–53 (2008).
3. Han, Y. *et al.* Evidence of positive selection on a class I *ADH* locus. *Amer J. Hum. Genet.* **80**, 441–456 (2007).
4. Laland, K. N., Odling-Smee, J. & Myles, S. How culture shaped the human genome: bringing genetics and the human sciences together. *Nature Rev. Genet.* **11**, 137–148 (2010).
5. Tishkoff, S. A. *et al.* Convergent adaptation of human lactase persistence in Africa and Europe. *Nature Genet.* **39**, 31–40 (2007).
An excellent example of detecting signatures of selection in the human genome.
6. Perry, G. H. *et al.* Diet and the evolution of human amylase gene copy number variation. *Nature Genet.* **39**, 1256–1260 (2007).
7. Cavalli-Sforza, L., Menozzi, P. & Piazza, A. *The History and Geography of Human Genes.* (Princeton University Press, Princeton, 1994).
8. Biswas, S. & Akey, J. Genomic insights into positive selection. *Trends Genet.* **22**, 437–446 (2006).
9. Grossman, S. R. *et al.* A composite of multiple signals distinguishes causal variants in regions of positive selection. *Science* **12**, 883–886 (2010).
10. Novembre, J. & Di Rienzo, A. Spatial patterns of variation due to natural selection in humans. *Nature Rev. Genet.* **10**, 745–755 (2009).
11. Sabeti, P. *et al.* Positive natural selection in the human lineage. *Science* **312**, 1614–1620 (2006).
12. Byars, S. G., Ewbank, D., Govindaraju, D. R. & Stearns, S. C. Natural selection in a contemporary human population. *Proc. Natl Acad. Sci. USA* **107**, 1787–1792 (2010).
By detecting significant selection on height, weight, age at first birth and menopause, this paper illustrates in detail the methods discussed in this Review.
13. Castelli, W. P. & Anderson, K. A population at risk. Prevalence of high cholesterol levels in hypertensive patients in the Framingham Study. *Am. J. Med.* **80**, 23–32 (1986).
14. Stearns, S. C., Nesse, R. M., Govindaraju, D. R. & Ellison, P. T. Evolutionary perspectives on health and medicine. *Proc. Natl Acad. Sci. USA* **107**, 1691–1695 (2010).
A recent overview of the diverse applications of evolutionary thought to issues of medical importance.
15. Boomsma, D. I. Twin registers in Europe: an overview. *Twin Research* **1**, 34–51 (1998).
16. Pedersen, C. B., Gotzsche, H., Moller, J. O. & Mortensen, P. B. The Danish Civil Registration System — a cohort of eight million persons. *Danish Med. Bull.* **53**, 441–449 (2006).
17. Kaar, P., Jokela, J., Helle, T. & Kojola, I. Direct and correlative phenotypic selection on life-history traits in three pre-industrial human populations. *Proc. R. Soc. Lond. B* **263**, 1475–1480 (1996).
18. Charlesworth, B. *Evolution in Age-Structured Populations* 2nd edn (Cambridge University Press, Cambridge, 1994).
19. McGraw, J. & Caswell, H. Estimation of individual fitness from life-history data. *Am. Nat.* **147**, 47–64 (1996).
20. Schonemann, P. On models and muddles of heritability. *Genetica* **99**, 97–108 (1997).
21. Stinchcombe, J. *et al.* Testing for environmentally induced bias in phenotypic estimates of natural selection: theory and practice. *Am. Nat.* **160**, 511–523 (2002).
22. Coulson, T. & Tuljapurkar, S. The dynamics of a quantitative trait in an age-structured population living in a variable environment. *Am. Nat.* **172**, 599–612 (2008).
23. Hastie, T. J. & Tibshirani, R. J. *Generalized Additive Models.* (Chapman and Hall, London, 1990).
24. Cleveland, W. S. Robust locally weighted regression and smoothing scatterplots. *J. Am. Stat. Assoc.* **74**, 829–836 (1979).
25. Lande, R. & Arnold, S. The measurement of selection on correlated characters *Evolution* **37**, 1210–1226 (1983).
A classic paper in which methods were presented that transformed evolutionary quantitative genetics.
26. Lande, R. Quantitative genetic-analysis of multivariate evolution, applied to brain–body size allometry. *Evolution* **33**, 402–416 (1979).
27. Robertson, A. A mathematical model of the culling process in dairy cattle. *Anim. Prod.* **8**, 95–108 (1966).
A prescient contribution that anticipated both Lande and Arnold's approach and Price's covariance theory and provided the basis for much of selection theory in plant and animal breeding.
28. Blangero, J., Almasy, L., Dyer, T. & Peterson, C. Sequential oligogenic linkage analysis routings. *Solar* Version 1.4.1. SOLAR [online], http://solar.sfbrgenetics.org (1999).
29. Abecasis, G. R., Cherny, S. S., Cookson, W. O. & Cardon, L. R. Merlin — rapid analysis of dense genetic maps using sparse gene flow trees. *Nature Genet.* **30**, 97–101 (2002).
30. Neumaier, A. & Groeneveld, E. Restricted maximum likelihood estimation of covariances in sparse linear models. *Genet. Selection Evolution* **30**, 3–26 (1998).
31. Pettay, J., Kruuk, L., Jokela, J. & Lummaa, V. Heritability and genetic constraints of life-history trait evolution in preindustrial humans. *Proc. Natl Acad. Sci. USA* **102**, 2838–2843 (2005).
32. Blows, M. W. A tale of two matrices: multivariate approaches in evolutionary biology. *J. Evol. Biol.* **20**, 1–8 (2007).
33. Brodie, E., Moore, A. & Janzen, F. Visualizing and quantifying natural selection. *Trends Ecol. Evol.* **10**, 313–318 (1995).
34. Janzen, F. & Stern, H. Logistic regression for empirical studies of multivariate selection. *Evolution* **52**, 1564–1571 (1998).
35. Kruuk, L. E. B. & Garant, D. A wake-up call for studies of natural selection? *J. Evol. Biol.* **20**, 30–33 (2007).
36. Ovaskainen, O., Cano, J. M. & Merila, J. A Bayesian framework for comparative quantitative genetics. *Proc. R. Soc. Lond. B* **275**, 669–678 (2008).
37. Schluter, D. Estimating the form of natural selection on a quantitative trait *Evolution* **42**, 849–861 (1988).
38. Stinchcombe, J. R., Agrawal, A. F., Hohenlohe, P. A., Arnold, S. J. & Blows, M. W. Estimating nonlinear selection gradients using quadratic regression coefficients: double or nothing? *Evolution* **62**, 2435–2440 (2008).
39. Blows, M. W. & Brooks, R. Measuring nonlinear selection. *Am. Nat.* **162**, 815–820 (2003).
40. Schluter, D. & Nychka, D. Exploring fitness surfaces. *Am. Nat.* **143**, 597–616 (1994).
41. Kingsolver, J. G. *et al.* The strength of phenotypic selection in natural populations. *Am. Nat.* **157**, 245–261 (2001).
A comprehensive review of measurements of natural selection in a broad range of plants and animals.
42. Stearns, S. & Koella, J. The evolution of phenotypic plasticity in life history traits — predictions of reaction norms for age and size at maturity. *Evolution* **40**, 893–913 (1986).
43. Sear, R., Allal, N., Mace, R. & Mcgregor, I. Height and reproductive success among Gambian women. *Am. J. Hum. Biol.* **16**, 223–223 (2004).
44. Mueller, U. & Mazur, A. Evidence of unconstrained directional selection for male tallness. *Behav. Ecol. Sociobiol.* **50**, 302–311 (2001).
45. Pawlowski, B., Dunbar, R. I. M. & Lipowicz, A. Evolutionary fitness — tall men have more reproductive success. *Nature* **403**, 156–156 (2000).
46. Sear, R. Height and reproductive success — how a Gambian population compares with the West. *Hum. Nat.* **17**, 405–418 (2006).
47. Nettle, D. Height and reproductive success in a cohort of British men. *Hum. Nat.* **13**, 473–491 (2002).
48. Silventoinen, K., Lahelma, E. & Rahkonen, O. Social background, adult body-height and health. *Int. J. Epidemiol.* **28**, 911–918 (1999).
49. Heliovaara, M., Makela, M., Knekt, P., Impivaara, O. & Aromaa, A. Determinants of sciatica and low-back-pain. *Spine* **16**, 608–614 (1991).
50. Michaud, D. S. *et al.* Physical activity, obesity, height, and the risk of pancreatic cancer. *J. Am. Med. Assoc.* **286**, 921–929 (2001).
51. Shors, A. R., Solomon, C., McTiernan, A. & White, E. Melanoma risk in relation to height, weight, and exercise (United States). *Cancer Causes Control* **12**, 599–606 (2001).
52. Ramsden, E. A differential paradox: the controversy surrounding the Scottish mental surveys of intelligence and family size. *J. Hist. Behav. Sci.* **43**, 109–134 (2007).
A superb study in the recent history of science. This paper tells the intriguing story of how intelligence was predicted to decline under selection but in fact increased.
53. Visscher, P. M., Hill, W. G. & Wray, N. R. Heritability in the genomics era — concepts and misconceptions. *Nature Rev. Genet.* **9**, 255–266 (2008).
A masterly introduction to the heritability concept.
54. Mousseau, T. & Roff, D. Natural selection and the heritability of fitness components. *Heredity* **59**, 181–197 (1987).
55. Stearns, S., De Jong, G. & Newman, B. The effects of phenotypic plasticity on genetic correlations. *Trends Ecol. Evol.* **6**, 122–126 (1991).
56. Hill, W. G. Genetics. A century of corn selection. *Science* **307**, 683–4 (2005).
57. Laurie, C. C. *et al.* The genetic architecture of response to long-term artificial selection for oil concentration in the maize kernel. *Genetics* **168**, 2141–55 (2004).
A thorough test of the additivity assumption of quantitative genetics. It demonstrates that responses to selection for oil content in corn continued for over 100 generations despite small population sizes.
58. Tait, L. Has the law of natural selection by survival of the fittest failed in the case of man? *Dublin Quart J. Med. Sci.* **47**, 102–113 (1869).
59. Groth, P. & Weiss, B. Phenotype data: A neglected resource in biomedical research? *Curr. Bioinform* **1**, 347–358 (2006).
60. Houle, D. Numbering the hairs on our heads: the shared challenge and promise of phenomics. *Proc. Natl Acad. Sci. USA* **107**, 1793–1799 (2010).
61. Denny, J. C. *et al.* PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene–disease associations. *Bioinformatics* **26**, 1205–1210 (2010).

62. van Driel, M., Bruggeman, J., Vriend, G., Brunner, H. & Leunissen, J. A text-mining analysis of the human phenome. *Eur. J. Hum. Genet.* **14**, 535–542 (2006).
63. Oti, M., Huynen, M. A. & Brunner, H. G. The biological coherence of human phenome databases. *Am. J. Hum. Genet.* **85**, 801–808 (2009).
64. Bilder, R. M. Phenomics: Building scaffolds for biological hypotheses in the post-genomic era. *Biol. Psychiatry* **63**, 439–440 (2008).
65. Bouchard, T. J. Genetic influence on human intelligence (Spearman's g): how much? *Ann. Hum. Biol.* **36**, 527–544 (2009).
66. Austin, M. A. *et al.* Genetics of LDL subclass phenotypes in women twins — concordance, heritability, and commingling analysis. *Arterioscler. Thromb.* **13**, 687–695 (1993).
67. Baare, W. F. C. *et al.* Quantitative genetic modeling of variation in human brain morphology. *Cereb. Cortex* **11**, 816–824 (2001).
68. Beardsall, K. *et al.* Heritability of childhood weight gain from birth and risk markers for adult metabolic disease in prepubertal twins. *J. Clin. Endocrinol. Metab.* **94**, 3708–3713 (2009).
69. Bella, J. N. *et al.* Genetic influences on aortic root size in American Indians — the Strong Heart Study. *Arterioscler. Thromb. Vasc. Biol.* **22**, 1008–1011 (2002).
70. Brown, W. M. *et al.* Age-stratified heritability estimation in the Framingham Heart Study families. *BMC Genet.* **4** (Suppl. 1), 32 (2003).
71. Busjahn, A. *et al.* β-2 adrenergic receptor gene variations, blood pressure, and heart size in normal twins. *Hypertension* **35**, 555–560 (2000).
72. Byard, P. J., Poosha, D. V. R. & Satyanarayana, M. Genetic and environmental determinants of height and weight in families from Andhra Pradesh, India. *Hum. Biol.* **57**, 621–633 (1985).
73. Carmichael, C. M. & Mcgue, M. A cross-sectional examination of height, weight, and body-mass index in adult twins. *J. Gerontol. A Biol. Sci. Med. Sci.* **50**, B237–B244 (1995).
74. Clark, P. J. The heritability of certain anthropometric characters as ascertained from measurements of twins. *Am. J. Hum. Genet.* **8**, 49–54 (1956).
75. Dahlberg, G. *Twin Births and Twins from a Hereditary Point of View* (Tidens Tryckeri, Stockholm, 1926).
76. Darocha, F. J., Salzano, F. M., Callegar, S. M. & Pena, H. F. New studies on heritability of anthropometric characteristics as ascertained from twins. *Acta Genet. Med. Gemellol.* **21**, 125–134 (1972).
77. de Bruin, J. P. *et al.* The role of genetic factors in age at natural menopause. *Hum. Reprod.* **16**, 2014–2018 (2001).
78. de Oliveira, C. M., Pereira, A. C., de Andrade, M., Soler, J. M. & Krieger, J. E. Heritability of cardiovascular risk factors in a Brazilian population: Baependi Heart Study. *BMC Med. Genet.* **9**, 1–8 (2008).
79. Decastro, J. M. Genetic influences on daily intake and meal patterns of humans. *Physiol. Behav.* **53**, 777–782 (1993).
80. Deng, H. W. *et al.* A whole-genome linkage scan suggests several genomic regions potentially containing QTLs underlying the variation of stature. *Am. J. Med. Genet.* **113**, 29–39 (2002).
81. Fischbein, S. Intra-pair similarity in physical growth of monozygotic and of dizygotic twins during puberty. *Ann. Hum. Biol.* **4**, 417–430 (1977).
82. Furusho, T. On manifestation of genotypes responsible for stature. *Hum. Biol.* **40**, 437–455 (1968).
83. Garner, C. *et al.* Genetic and environmental influences on left ventricular mass — a family study. *Hypertension* **36**, 740–746 (2000).
84. Hammond, C. J., Snieder, H., Spector, T. D. & Gilbert, C. E. Factors affecting pupil size after dilatation: the Twin Eye Study. *Br. J. Ophthalmol* **84**, 1173–1176 (2000).
85. Hansen, P. S. *et al.* Genetic and environmental causes of individual differences in thyroid size: a study of healthy Danish twins. *J. Clin. Endocrinol. Metab.* **89**, 2071–2077 (2004).
86. Harrap, S. B., Stebbing, M., Hopper, J. L., Hoang, H. N. & Giles, G. G. Familial patterns of covariation for cardiovascular risk factors in adults — the Victorian Family Heart Study. *Am. J. Epidemiol.* **152**, 704–715 (2000).
87. Hauspie, R. C., Bergman, P., Bielicki, T. & Susanne, C. Genetic variance in the pattern of the growth curve for height — a longitudinal analysis of male twins. *Annals Hum. Biol.* **21**, 347–362 (1994).
88. Hawk, L. J. & Brook, C. G. D. Family resemblances of height, weight, and body fatness. *Arch. Dis. Child.* **54**, 877–879 (1979).
89. Hewitt, J. K., Stunkard, A. J., Carroll, D., Sims, J. & Turner, J. R. A twin study approach towards understanding genetic contributions to body size and metabolic-rate. *Acta Genet. Med. Gemellol.* **40**, 133–146 (1991).
90. Hunter, D. J., Snieder, H., March, L. & Sambrook, P. N. Genetic contribution to cartilage volume in women: a classical twin study. *Rheumatology* **42**, 1495–1500 (2003).
91. Kohler, H. P. & Christensen, K. in *Genetic Influences on Human Fertility and Sexuality* (eds Rodgers, J. L., Rower, D. C. & Miller, W. B.) 67–84 (Kluwer, Boston, 2000).
92. Kohler, H. P., Rodgers, J. L. & Christensen, K. Between nurture and nature: the shifting determinants of female fertility in Danish twin cohorts. *Soc. Biol.* **49**, 218–248 (2002).
93. Kosova, G., Abney, M. & Ober, C. Heritability of reproductive fitness traits in a human population. *Proc. Natl Acad. Sci. USA* **107**, 1772–1778 (2010).
94. Liu, X. Q., Hanley, A. J. G. & Paterson, A. D. Genetic analysis of common factors underlying cardiovascular disease-related traits. *BMC Genet.* **4**, S56 (2003).
95. Peccei, J. S. Genetic correlation between the ages of menarche and menopause. *Hum. Nature* **11**, 43–63 (2000).
96. Pilia, G. *et al.* Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genet.* **2**, e132 (2006).
97. Wang, Z. Q., Ouyang, Z., Wang, D. M. & Tang, X. L. Heritability of blood-pressure in 7-year-old to 12-year-old Chinese twins, with special reference to body size effects. *Genet. Epidemiol.* **7**, 447–452 (1990).
98. Jokela, M. Physical attractiveness and reproductive success in humans: evidence from the late 20th century United States. *Evol. Hum. Behav.* **30**, 342–350 (2009).
99. Wollmering, E. *Wisconsin Longitudinal Study Handbook* (12.10.07) (University of Wisconsin—Madison, Madison, 2007).
100. Nettle, D. Women's height, reproductive success and the evolution of sexual dimorphism in modern humans. *Proc. R. Soc. Lond. B* **269**, 1919–1923 (2002).
101. Barker, D. J. P., Osmond, C., Forsén, T. J., Kajantie, E. & Eriksson, J. G. Trajectories of growth among children who have coronary events as adults. *N. Engl. J. Med.* **353**, 1802–1809 (2005).
102. Pesonen, A.-K. *et al.* Reproductive traits following a parent–child separation trauma during childhood: a natural experiment during World War II. *Am. J. Hum. Biol.* **20**, 345–351 (2008).
103. Abney, M., McPeek, M. S. & Ober, C. Estimation of variance components of quantitative traits in inbred populations. *Am. J. Hum. Genet.* **66**, 629–650 (2000).
104. Glasson, E. J. *et al.* Perinatal factors and the development of autism — a population study. *Arch. Gen. Psychiatry* **61**, 618–627 (2004).
105. Mitchell, B. D. *et al.* Genetic and environmental contributions to cardiovascular risk factors in Mexican Americans. The San Antonio Family Heart Study. *Circulation* **94**, 2159–2170 (1996).
106. Niazi, T. N., Cannon-Albright, L. A. & Couldwell, W. T. Utah Population Database: a tool to study the hereditary element of nonsyndromic neurosurgical diseases. *Neurosurg. Focus* **28**, E1 (2010).
107. Higgins, M. *et al.* NHLBI Family Heart Study: objectives and design. *Am. J. Epidemiol.* **143**, 1219–1228 (1996).
108. Siest, G. *et al.* Objectives, design and recruitment of a familial and longitudinal cohort for studying gene–environment interactions in the field of cardiovascular risk: the Stanislas cohort. *Clin. Chem. Lab. Med.* **36**, 35–42 (1998).
109. Helle, S., Lummaa, V. & Jokela, J. Are reproductive and somatic senescence coupled in humans? Late, but not early, reproduction correlated with longevity in historical Sami women. *Proc. R. Soc. Lond. B* **272**, 29–37 (2005).
110. Helle, S. A tradeoff between reproduction and growth in contemporary Finnish women. *Evol. Hum. Behav.* **29**, 189–195 (2008).
111. Kirk, K. M. *et al.* Natural selection and quantitative genetics of life-history traits in Western women: a twin study. *Evolution* **55**, 423–435 (2001).
112. Weeden, J., Abrams, M. J., Green, M. C. & Sabini, J. Do high-status people really have fewer children? Education, income, and fertility in the contemporary US. *Hum. Nat.* **17**, 377–392 (2006).
113. Kaar, P., Jokela, J., Helle, T. & Kojola, I. Direct and correlative phenotypic selection on life-history traits in three pre-industrial human populations. *Proc R. Soc. Lond. B* **263**, 1475–1480 (1996).
114. Mealey, L. The relationship between social-status and biological success — a case-study of the Mormon religious hierarchy. *Ethol. Sociobiol.* **6**, 249–257 (1985).
115. Bailey, S. M. & Garn, S. M. Socioeconomic interactions with physique and fertility. *Hum. Biol.* **51**, 317–333 (1979).
116. Vetta, A. Fertility, physique, and intensity of selection. *Hum. Biol.* **47**, 283–293 (1975).
117. Pawlowski, B., Dunbar, R. & Lipowicz, A. Evolutionary fitness — tall men have more reproductive success. *Nature* **403**, 156–156 (2000).
118. Fieder, M. & Huber, S. The effects of sex and childlessness on the association between status and reproductive output in modern society. *Evol. Hum. Behav.* **28**, 392–398 (2007).
119. Hopcroft, R. L. Sex, status, and reproductive success in the contemporary United States. *Evol. Hum. Behav.* **27**, 104–120 (2006).
120. Fieder, M. & Huber, S. The effects of sex and childlessness on the association between status and reproductive output in modern society. *Evol. Hum. Behav.* **28**, 392–398 (2007).
121. Nettle, D. & Pollet, T. V. Natural selection on male wealth in humans. *Am. Nat.* **172**, 658–666 (2008).
122. Bean, F. D. & Wood, C. H. Ethnic variations in relationship between income and fertility. *Demography* **11**, 629–640 (1974).
123. Mulder, M. B. On cultural and reproductive success — Kipsigis evidence. *Am. Anthropol.* **89**, 617–634 (1987).
124. Low, B. S. Occupational status, landownership, and reproductive behavior in 19th-century Sweden: Tuna Parish. *Am. Anthropol.* **92**, 457–468 (1990).
125. Wiessner, P. Hunting, healing, and hxaro exchange — a long-term perspective on!Kung (Ju/'hoansi) large-game hunting. *Evol. Hum. Behav.* **23**, 407–436 (2002).

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Competing interests statement

The authors delare no competing financial interests.

FURTHER INFORMATION

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