Evolutionary public health 1

Evolutionary public health: introducing the concept

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See Editorial page 430

This is the first in a Series of three papers about evolutionary public health

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See Online for appendix

The emerging discipline of evolutionary medicine is breaking new ground in understanding why people become ill. However, the value of evolutionary analyses of human physiology and behaviour is only beginning to be recognised in the field of public health. Core principles come from life history theory, which analyses the allocation of finite amounts of energy between four competing functions—maintenance, growth, reproduction, and defence. A central tenet of evolutionary theory is that organisms are selected to allocate energy and time to maximise reproductive success, rather than health or longevity. Ecological interactions that influence mortality risk, nutrient availability, and pathogen burden shape energy allocation strategies throughout the life course, thereby affecting diverse health outcomes. Public health interventions could improve their own effectiveness by incorporating an evolutionary perspective. In particular, evolutionary approaches offer new opportunities to address the complex challenges of global health, in which populations are differentially exposed to the metabolic consequences of poverty, high fertility, infectious diseases, and rapid changes in nutrition and lifestyle. The effect of specific interventions is predicted to depend on broader factors shaping life expectancy. Among the important tools in this approach are mathematical models, which can explore probable benefits and limitations of interventions in silico, before their implementation in human populations.

Introduction

The aim of public health is to prevent disease, promote health, and prolong life in human populations through the organised efforts of society.[1] It is intuitive that improving living conditions should benefit peoples' health, but from an evolutionary perspective this assumption is simplistic. Natural selection has not shaped organisms for maximum health, but rather to maximise their reproductive success (or genetic fitness; appendix). Consequently, public health interventions might not always achieve exactly what they intended.

Consider an example from rural Ethiopia, where a water development scheme aimed to decrease the daily energy burden on women who carried water up to 30 km in clay pots.[2] One might anticipate that by reducing this stress and maintaining the energy supply, maternal nutritional status would improve, transmitting health benefits to the next generation. But the outcome was different: a pioneering evolutionary analysis by Gibson and Mace[2] concluded that the energy saved by the installation of village water taps enhanced maternal fertility, which was associated with worsening childhood malnutrition. They suggested that the outcome might have been better if the intervention had included a family planning component.

This example highlights the potential benefits of an evolutionary perspective in public health. Human physiology and behaviour have been selected to transmit genes to future generations. Health is sometimes compromised in favour of immediate survival or reproduction, and particularly so under conditions of deprivation and environmental harshness. Public health has benefited substantially from incorporating a life-course perspective that is capable of integrating the effects of physical, biological, and societal stresses or stimuli at different life stages.[3–6] Evolutionary approaches could extend these benefits, providing new insight into the health consequences of efforts to change behaviour patterns or the environment.

In 1973, Dobzhansky[7] observed that "nothing in biology makes sense except in the light of evolution". Throughout the 20th century, evolutionary approaches permeated most areas of biological enquiry, and they are increasingly

Key messages

What we know

- Evolutionary theory is likely to improve the effectiveness and integration of public health interventions, in view of its use in other areas of public policy
- Evolutionary life history theory is integrative, and can inform both physiological and behavioural components of public health interventions
- On the basis of optimisation principles, life history theory allows potential interventions to be modelled using mathematical techniques, identifying likely consequences before implementation in vivo

What we need to know

- How do predictions from life history theory change when populations occupy affluent and benign environments, and many individuals choose not to produce offspring?
- How should we balance benefits versus costs that appear in different parts of the life course, such as when interventions promoting early health adversely affect long-term health?
- How can we incorporate the insights generated by applying life history theory to plasticity into personalised medicine?
- How can we use life history theory to improve public health campaigns promoting behaviour change?

employed by policy makers in the management of agriculture and fisheries.[8,9] Surprisingly, an evolutionary perspective on medicine emerged only recently.[10]

A key benefit of evolutionary approaches is the availability of solid overarching theory. Most natural sciences have a strong theoretical basis— eg, quantum theory in physics and molecular theory in chemistry.[11] Evolution is also a "basic science",[12] and it is no exaggeration to suggest that its application in medicine could revolutionise the discipline. In the 19th century, for example, pre-Darwinian biology was mainly descriptive. Variability was well documented, but poorly understood.

Medicine remains largely pre-evolutionary—excelling in description and mechanistic explanations, but only beginning to explain the variability in disease susceptibility in individuals and populations. Evolutionary theory generates testable hypotheses regarding how organisms should respond to environmental stimuli, and these hypotheses are widely supported in diverse species, including humans.[13–15]

To date, evolutionary medicine has primarily aimed to go beyond understanding how people become ill by considering why the body is susceptible to disease. This approach helps understand why people present at clinics, but it might not help prevent illness from developing. Building on earlier work,[16] we argue that evolutionary approaches could benefit outcomes most directly in the arena of public health.

In particular, these approaches could improve understanding of the effect of ecological change on health, whether this relates to non-human or societal factors. Traditionally, public health efforts targeted risk factors related to pathogens. To prevent disease transmission, hygiene and sanitation were improved, as were nutrition and living conditions, to promote resilience. Although pathogens remain a major source of disease, the global burden of ill health is shifting towards non-communicable diseases (NCDs), for which individuals' constitutions and behaviour are key to susceptibility and prevention.[17] Although some overt risk factors have been identified (eg, tobacco, dietary trans-fats, carcinogens), many lie nested within normal lifestyles (eg, enjoyable behaviours) or the normal range of physiological variability (eg, patterns of growth and maturation). In turn, our lifestyles are shaped by broader societal phenomena, connecting health with cultural and political factors.[18] By shedding more light on how physiology and behaviour respond to such compound stresses, evolutionary approaches could improve societal efforts to prevent NCDs, just as they already help reduce the burden of infectious disease.[19]

This Series paper has three objectives. First, we describe two primary components of evolutionary theory—natural selection and population genetics, and life history theory, which provide a predictive framework for investigating plasticity, the range of phenotypes that could be elicited by the environment from one genotype. Second, we briefly discuss the physiological and behavioural mechanisms that underpin plasticity, to elucidate how our evolved biology responds to environmental change. Last, we show how mathematical models could help predict the effects of interventions before their implementation. Two other papers in this Series focus in more detail on reproduction and human–microbe interactions.[20,21]

Evolution, heritability, and genetics

Darwin's and Wallace's theory of natural selection provided new insight into how ancestral environments shape contemporary biological variability.[22] The theory proposed that traits varied, that this variability had a heritable component, and that organisms producing more offspring transmitted their traits with greater frequency to subsequent generations. Over time, a lineage acquires the genes and phenotypes of those reproducing most successfully.[23] Though simply a purposeless algorithm,[24] natural selection shapes traits to enhance genetic fitness.[25] In Darwin's time, scientific understanding of the mechanisms of heredity was rudimentary. Modern genetics emerged from the rediscovery of Mendel's work in the late 19th century, laying the foundation of the modern evolutionary synthesis.[26]

It is well established that genetic variants influence disease risk,[27] prompting interest in gene-based personalised medicine. Concerning treatment, differences between ethnic groups in the frequency of genes that influence drug metabolism have attracted attention.[28] Most clinicians looking at pathogens in combination with their human hosts will be familiar with the evolutionary emergence of new infectious diseases, such as those caused by HIV, hantaviruses, SARS, and Ebola virus,[29] with the possibility that imperfect vaccines can make pathogens more virulent,[30] and with the striking threats posed by the evolution of drug-resistant or antibiotic-resistant strains of some pathogens.[31]

Genetic variability is also relevant to public health, particularly for understanding population variability in physiology. For example, where malaria is prevalent it has selected for protective haemoglobin variations, though these might also generate health penalties such as high prevalence of haemoglobinopathies deriving from autosomal recessive genes in malaria-exposed populations.[32] High-fitness genotypes do not maximise pathogen defence, but rather optimise trade-offs with other biological functions.[33] Several evolutionary theories have been proposed for ethnic genetic differences in NCD susceptibility (appendix), although the supporting evidence is variable.

However, about 85% of human genetic variation occurs within, rather than between, populations.[34] Pedigree and twin studies indicate that NCDs cluster within families,[35,36] and a key aim of the Human Genome Project was to identify individual contributing alleles.[37] The

additive effect of common alleles, potentially favoured through selection, explains little variance in NCD risk. Instead, rare deleterious alleles that evolved too recently to have been selected out of the gene pool seem to be better genetic predictors of ill health.[38] It is often suggested that natural selection has ceased in humans, but a more realistic scenario is that it has accelerated in concert with the population boom of the last 10 000 years, increasing the number of new mutations.[39]

Genes clearly contribute to individual variability in disease susceptibility, and genetic analyses can help identify biological pathways to be targeted by pharmaceutical treatment.[40] Nevertheless, the importance of genotypes in public health is limited by our inability to target them directly for interventions. Genes do not change within generations, and with few exceptions, such as the use of pre-implantation diagnosis in assisted reproduction to screen out rare deleterious alleles, efforts to influence allele frequencies across generations are ethically unacceptable.[41] We therefore turn to a second component of biological variability that is highly amenable to intervention: plasticity.

Evolution and plasticity

Plasticity refers to the range of phenotypes potentially elicited by the environment from a single genotype. Plasticity has several different dimensions including behaviour, physiology and development, and responses that range from the momentary to the transgenerational. The primary evolutionary approach to plasticity is life history theory, which aims to predict how developing organisms respond to environments to maximise their chances of survival and reproduction.[42]

Life history theory provides a framework for understanding how organisms make physiological and behavioural decisions—though behavioural decisions do not need a basis in conscious deliberation. Patterns of growth, maturation, reproduction, and metabolism account for substantial variation in the risk of NCDs and diverse cancers, but the very normality of these traits has hindered deeper understanding of how they contribute to the causes of ill health, and how they might be targeted by public health programmes. Crucially, the associations of these traits with health outcomes could also differ substantially between high-income and low-income and middle-income settings. Life history theory can help explain this complexity, and it offers a holistic framework that can integrate different components of human health.

Life history theory

Life history theory was developed to predict the coordinated evolution of the traits contributing directly to fitness: age and size at maturation, number and size of offspring, number of reproductive events, and ageing and lifespan. The theory views the evolution of these traits as the product of interactions between intrinsic constraints and trade-offs—features inherited or acquired during development—and extrinsic factors in the environment that affect mortality risk and resource availability. It then considers how extrinsic factors shape the combination of intrinsic traits to maximise fitness.[42,43]

Life history theory models 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?" Although these questions can be considered over the long term, to comprehend why a species has particular traits, they can also be considered within the life course, to understand why individual organisms respond to environmental factors in particular ways. Plastic responses to environmental stimuli include physiological adaptations implemented by homoeostatic feedback loops that can react in seconds or minutes, acclimations (eg, adjustments to altitude) that can react in days to weeks through changes in the setpoints of feedback loops, and finally, developmental plasticity, in which reactions usually last a lifetime.[44,45]

The medical importance of plasticity is most apparent in the developmental origins of adult health and disease.[4,46] Variation in early life experience has many consequences, for example undernutrition in utero increases the risk of NCDs in late life,[4,46] delivery by caesarean section increases the risk of asthma and obesity,[47,48] and receiving more antibiotic treatments than average before 2 years increases the risk of obesity and allergies.[49,50]

Although consistent with genetic theories of evolution, the predictions of life history theory explain much more phenotypic variation, thus justifying its simplifications. Because physicians and public health professionals deal with phenotypes, they can gain substantially from a theory that predicts phenotypic states and how they are expected to change over an individual's life course. Going beyond standard care, an understanding of each individual's ongoing life history could guide personalised decisions concerning the prevention, diagnosis, and treatment of disease.

Trade-offs and reaction norms

Two key concepts in life history theory are trade-offs and reaction norms. A trade-off occurs whenever a change in one trait that increases fitness is connected to a change in another trait that decreases fitness. The major functions involved in trade-offs are maintenance, growth, reproduction, and defence, in which energy can be invested (appendix). Changes in allocations among these functions are shaped both by resource availability and extrinsic mortality risk, of which key components in humans include infectious disease, poverty or deprivation, and violence or conflict. Generally, organisms with high mortality risk invest in rapid growth and reproduction at the expense of maintenance and defence, in which organisms with low mortality risk

invest more. Thus the life histories of species occupying contrasting environments diverge, creating a continuum from small, fast-living, short-lived species to large, slow-living, long-lived species (figure 1).

This continuum also characterises individual variation within species, including humans. Natural selection has shaped individuals to respond to cues of extrinsic mortality risk and resource availability with phenotypic change that maximises fitness. Specific responses include variation in age and size at maturity, the interval between births, and investment in offspring. The quality of the external environment therefore shapes the entire schedule of growth, maturation, reproduction, and ageing. This helps explain the profound variability in life tables, which describe age-specific mortality rates and life expectancies in human populations, highlighting slower and faster life history trajectories within our species (appendix).

Each individual represents a bundle of many trade-offs. For example, the trade-off between reproduction and survival (maintenance or defence) shapes the rate of ageing and NCD risk.[51] Trade-offs are crucial for physicians and public-health planners because they force us to recognise that one trait cannot be changed without also changing others, sometimes for the worse. Two trade-offs especially relevant to public health, namely immune function versus growth and reproduction versus longevity, are summarised in panel 1.

The second key concept, the reaction norm, describes the spectrum of phenotypes produced by a single genotype across a range of environmental conditions. Life history theory predicts the evolution of reaction norms themselves, and the state of traits expressed in specific environments. This approach clarifies how nature always interacts with nurture during development to produce the state of the observed organism. Examples of human reaction norms include age and size at maturity,[42] and variation in inter-birth interval induced by changes in nutritional status (panel 2, figure 2).

Several issues are important when applying life history theory to humans. First, our sociality connects the life histories of multiple individuals. Humans show cooperative breeding, whereby several individuals can contribute to a pooled energy budget for investment in offspring.[62] Sociality can also expose individuals to stresses, such as social hierarchy and inter-group conflict.[19] Second, cultural values that influence behaviour might themselves evolve over time; examples include attitudes to wealth, risk, or the costs and benefits of raising children.[63,64] Cultural goals can be pursued at the expense of genetic fitness. Finally, evolved behaviour need not necessarily benefit health or fitness, an example being the use of narcotic substances that trigger reward centres in the brain while compromising physiological function.[65]

One might question whether humans in affluent environments still experience trade-offs. Energy can be stored outside the body in material form or social relationships, or inside the body as adipose tissue.[66] Although wealthy human beings acquire energy to invest in each of growth, health, and reproduction, subtle trade-offs are both predicted[67] and observed, for example between family size and the growth rate of individual children.[68] Similarly, while obesity might suggest a surfeit

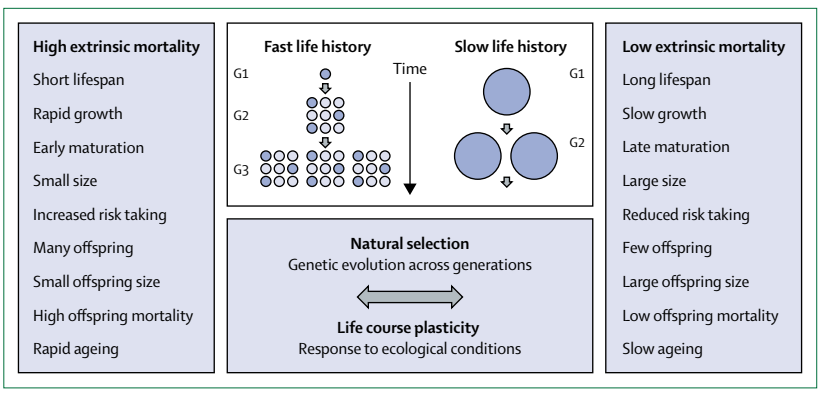

Figure 1: **Life history contrasts across a fast–slow continuum**
Fast life histories are favoured in environments with high mortality risk, whereas slow life histories can evolve when mortality risk reduces. These strategies might evolve under natural selection, but physiology can also respond to cues during the life course through plasticity. The size of the circles is proportional to adult body size, and filled circles indicate individuals that survive to reproduce. G1=first generation. G2=second generation. G3=third generation.

Panel 1: Life history theory predicts trade-offs relevant to public health

- Immune function is metabolically costly;[52] for example, in children, each degree of temperature rise from fever increases metabolic rate by 11·3%,[53] hence the costs of fighting infections impair child growth[54]
- This relationship can account for epidemiological associations linking secular declines in infant mortality rate (a proxy for the energy costs of immune function in the survivors) with secular increases in adult height and longevity.[55] Developmental exposure to infectious diseases shapes the entire life history strategy, and might propagate effects to subsequent generations[56]
- Another key trade-off is between reproduction and longevity, with several studies showing that parental survivorship declined in proportion to the number of children produced, more strongly in mothers than fathers.[57] However, the magnitude of this effect varies by living standards,[58] and reproduction might protect against some cancers (see Paper 2 in this Series)[21]
- Such trade-offs also apply across generations: throughout 27 sub-Saharan African countries, the odds of child survival fell in relation to the number of offspring produced by the mother[59]
- Public health programmes targeting infant infections or adult reproduction are thus expected to shape long-term health outcomes and disease susceptibility through influencing these trade-offs. For example, nutritional interventions to resolve stunting might be ineffective unless also reducing the burden of infections and parasites[60]

Panel 2: Reaction norms and the trade-offs that shape them

- Life history theory predicts that maternal age and size at first birth will vary depending on the conditions encountered during development, thereby maximising reproductive success across the range of environments frequently encountered. Life history theory predicts optimal reaction norms consistent with shifts caused by recent changes in nutrition and mortality risk.
- Figure 2A distinguishes the plastic developmental reaction to environmental change from the genetic evolution of that reaction (ie, between nurture and nature).
- The upper curve shows the optimal response to environmental improvement: the reproduction event slides up the reaction norm to the left, occurring earlier. While this represents a developmental response, the shape and position of the reaction norm itself have evolved and are genetically determined.
- The lower curve shows the evolution of that reaction norm. Through demographic and epidemiological transition, infant mortality rates fell as public health and medical efforts decreased the impact of infectious disease.[61] This drove the entire reaction norm down and to the left, resulting in a further decrease in age at first birth and a modest decrease in maternal weight.
- Why does the reaction norm change in this way? One major trade-off affecting human maturation relates infant mortality to maternal age (figure 2B). As infant mortality declines, mothers are selected to have their first baby earlier than their ancestors under the same nutritional and growth conditions.
- In this way, cultural evolution (ie, improved health care) is interacting with biological evolution. It is important to understand that efforts of physicians and public health workers in the interest of promoting health could also shape human evolution itself.

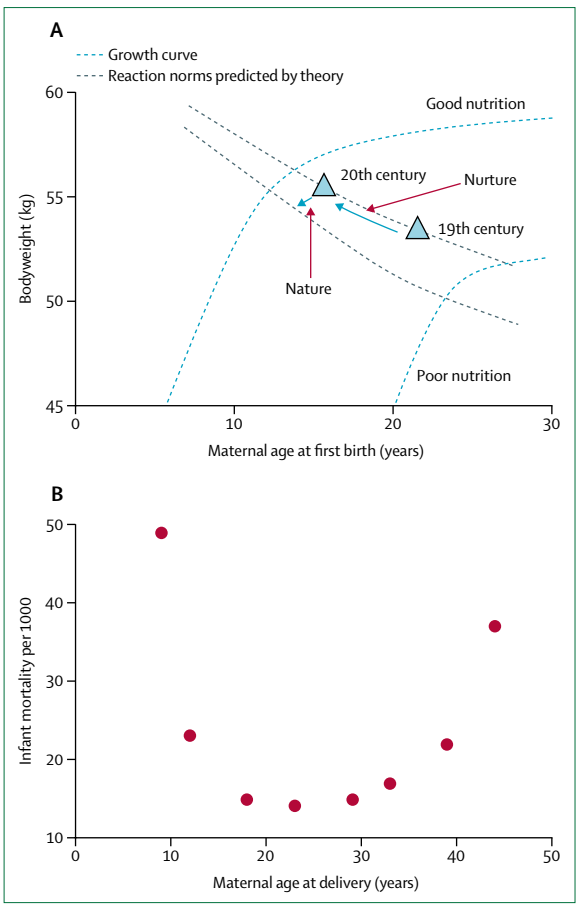

Figure 2: **Reaction norms for age and size at first birth in women**
(A) The triangles are observations from the literature. The blue dashed lines curving up and to the right are growth curves, the left one under good nutrition, the right one under poor nutrition. The black dashed lines are reaction norms predicted by theory. The long blue arrow describes the observed plastic response in maturation between the 19th and 20th centuries. The short blue arrow describes the inherited shift in the entire reaction norm predicted by theory. Reproduced with permission from Stearns and Medzhitov.[42] (B) The relationship between infant mortality and maternal age in the USA, 1960–61. This relationship is the key trade-off that shapes the evolution of the reaction norm (panel 1). Infant mortality per 5-year group of maternal ages (n=107 038 infant deaths). Reproduced with permission from Stearns and Medzhitov.[42]

of calories, it is better considered as a state of metabolic perturbation, in which perturbed insulin dynamics provoke cellular starvation.[69] Finally, some trade-offs involve conflicts in signalling between immune cells or in gene expression networks, and they are mediated not by energy but by information. These trade-offs exist regardless of nutritional status.

The specific decisions that constitute each individual's life-history trajectory are enacted at levels that include physiology and behaviour. Many of the relevant mechanisms are already well understood to shape disease risk. What we emphasise is that these are the same mechanisms that permit adaptation through plasticity to ecological stimuli and stresses. Both hormonal and behavioural plasticity represent mechanisms of risk management that are inherently sensitive to physical and societal stimuli.[66]

Life history plasticity and hormones

Hormones allow organisms to respond to both endogenous and exogenous environmental factors by modifying cell functions variably across tissues and organs.[70] Hormones are now recognised to generate multiple physiological effects, a scenario known as pleiotropy.[70]

For example, insulin plays a key role in allocating energy across competing physiological functions. Conventionally, clinicians think of insulin as responsible for regulating blood glucose, and variability in its production or activity is central to the constellation of diseases grouped as diabetes.[71] However, its total metabolic profile is far more complex, and it affects diverse functions in tissue-specific ways.[72] Insulin modulates the regulation of peripheral metabolism, including appetite, reproductive function, thermoregulation, and adiposity, via receptors in the brain.[72,73] Within the brain, insulin also regulates cognitive functions such as learning and memory.[74] Although muscle insulin resistance increases the risk of diabetes, it also allows the diversion of fuel to other tissues.[72]

Leptin, which is secreted by adipose tissue, signals the magnitude of energy stores to the brain but also has broader functions, contributing to the regulation of reproduction, cognitive function, and immune function.[75,76] For example, leptin influences the functions

of T cells, monocytes, macrophages, and natural killer cells, as well as the release and expression of cytokines and other inflammatory markers, and these molecules likewise contribute to the regulation of energy balance.[76] Although early linear growth benefits long-term health and human capital,[77] the association between low leptin and mortality in malnourished children indicates the short-term survival value of body fat.[78]

Another influential hormone is cortisol, produced by the adrenal glands in response to diverse types of stress including illness, trauma, fear, pain, and psychosocial stress. It too affects diverse metabolic activities, for example suppressing immune function while increasing blood pressure and blood glucose.[79]

In each case, therefore, these hormones implement the allocation of energy between life history functions. Although such plasticity might be adaptive, especially in the context of reproduction (see Paper 2 by Jasienka and colleagues[21]) it can also impose metabolic costs, accelerating the rate of ageing. Furthermore, human societies generate stresses for which their biology is unprepared or mismatched,[80] such as pollutants, processed foods, and sedentary environments.

Many trade-offs pertain to individual organisms. However, mammalian reproduction inherently brings the life-history strategies of two generations together, through placental nutrition and lactation. This interaction could be characterised as a tug-of-war over maternal metabolic resources,[81] because the energy allocation decisions that are optimal for maternal fitness might not maximise offspring fitness. In such parent–offspring conflict (appendix),[82] hormones now function as signals between individuals, and each party can not only read the signals of the other, but can also potentially manipulate them with their own hormonal secretions. For example, placental lactogen promotes maternal insulin resistance, allowing the fetus to gain from prolonged increases in maternal blood sugar levels after meals.[83] The consequences of this tug-of-war are expressed in several outcomes relevant to public health, including the prevalence of low birthweight, the incidence of colic, the duration of breastfeeding, and the management of infant sleep.[83–85] The tug-of-war can itself be targeted by interventions; for example, results from a randomised trial showed that promoting relaxation in breastfeeding mothers was associated with faster weight gain in their offspring, compared with mothers not receiving this therapy.[86]

Life history theory and behaviour

Conventionally, public health models of behaviour emphasise purpose and individual autonomy; in other words, how a person thinks rather than what he or she does,[87] hence campaigns often target conscious deliberation. By contrast, life history theory makes predictions about behaviour itself, and makes no assumptions about whether decisions are made consciously or unconsciously. In other species, this question does not arise. Some conscious thought could simply provide post-hoc rationalisation—more a consequence of behaviour than of cause.

Particularly in high-income, low-fertility populations, contemporary behaviour is not maximising fitness. This is partly because of cultural preferences (for wealth, social status, health, or hedonic pleasure) that evolve independently of genes, and partly because of adaptive lag, whereby environments change more rapidly than does human biology.[88] But we can still use evolutionary principles to understand associations between behaviour and health outcomes.

In long-lived species such as humans, which produce offspring at regular intervals, the value of investing in somatic maintenance and future reproduction is expected to vary with ecological conditions. Higher extrinsic mortality risk favours diverting energy from maintenance to earlier reproductive effort. Why stint on reproduction if one is likely to die soon? Conversely, lower mortality risk favours higher investment in somatic maintenance, which could benefit future reproduction and longevity. Variation in mortality risk can therefore help explain variation in behaviours relevant to public health, both with and between populations, including reproductive decisions and engagement in risky behaviours (appendix).

For example, reproductive timing varies in association with environmental harshness. In high-income countries,

Panel 3: An optimisation model of maternal nutritional supplementation programmes

- To assess the consequences of supplementing mothers to improve the growth of their offspring, we consider a mother producing single offspring sequentially.
- The mother accrues resources (energy) to invest in offspring growth at a rate of *r* per unit time. She is also exposed to a mortality risk of m per unit time. The decision she faces is how long to support each offspring before producing the next. Longer support means more resources for the offspring, but greater risk the mother will die before the offspring reaches independence.
- We assume that maternal death before independence leads to offspring death, whereas there is no risk of offspring death while the mother survives to care for it.
- After independence, offspring survival depends upon the resources it received. We assume that some minimum level of resources is required for viability; beyond this, survival prospects increase with resources, but at an ever-diminishing rate (appendix).
- In view of these assumptions, we can determine the optimal duration of support that maximises the mother's expected lifetime fitness, and the resulting size and viability of her offspring (figure 3). We can also ask how these outcomes change if we alter the level of resources available, either during the period of dependency of the current offspring, or throughout the remainder of the mother's life.

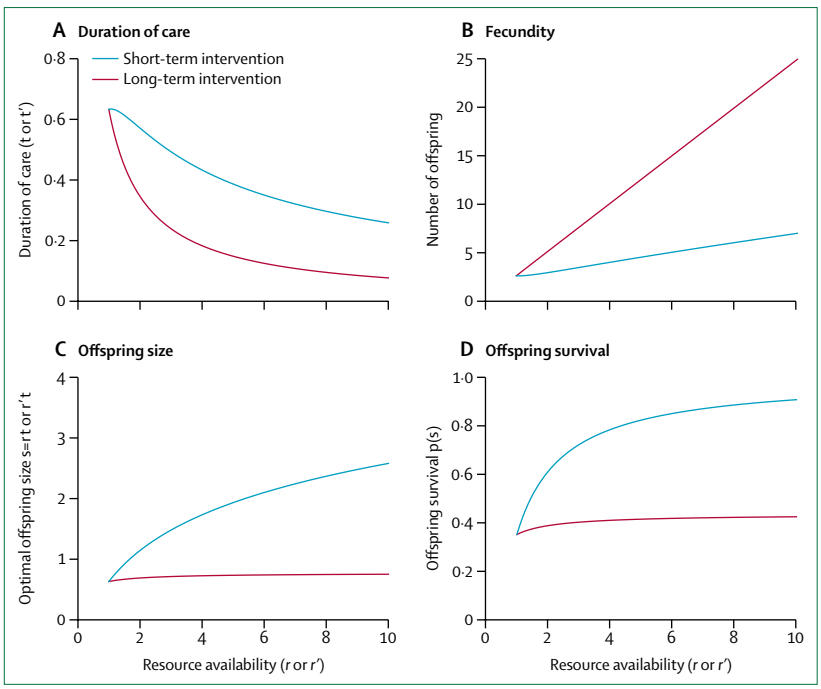

Figure 3: **An optimisation model of maternal nutritional supplementation programmes**
Results of a model predicting how maternal and offspring traits vary in accordance with ecological conditions, if the goal is to maximise maternal reproductive fitness. A short-term intervention increasing energy availability increases maternal investment in the current offspring, leading to larger offspring size, and an increased chance of offspring survival, but it has negligible effect on maternal fecundity. By contrast, the benefits of a long-term intervention are primarily captured by the mother through increased fecundity, whereas there is little effect on offspring investment, growth, or chance of survival. Y-axes scales refer to model variables, described in detail in the appendix.

low socioeconomic position correlates with earlier reproduction, and poorer health status could be an important explanatory variable. Data from 2009 to 2011, showed that in England, living in areas with the highest deprivation (measured in deciles) was associated with a life expectancy that was 7 years shorter for women and 9 years shorter for men, compared with those in the least-deprived areas.[89] Equivalent differences in healthy life expectancy were twice as large.[89] Early reproduction in women of low socioeconomic position might therefore reflect both their lower expectancy of a healthy life and the absence of benefits of waiting to reproduce, since they typically have fewer chances to capitalise on educational and career opportunities. A link between deprivation and early age at first birth also remains across populations worldwide.[90] In turn, increased energy investment in reproduction indicates decreased investment in homoeostasis (panel 1), and this might contribute to elevated NCD risk in populations of low socioeconomic position.[19]

In behavioural terms, low investment in self-preservation could be mediated by time preferences, in which short-term gains are favoured over long-term rewards.[91] For example, individuals unable to assume that a long and healthy life lies ahead of them are expected to discount the future and prioritise immediate rewards, whether through conscious or subconscious mechanisms (appendix). Individuals who are oriented to the present report more risk-prone attitudes than those oriented to the future.[92] However, the trade-off between longevity and reproduction can also be exploited for health benefit by interventions designed to appeal to personal attractiveness, rather than health benefits that are only realised some time in the future, as shown for diet and cancer risk.[93,94]

Extrinsic mortality risk therefore predicts many unhealthy behaviours (smoking, drug consumption, poor diet, and risky sexual behaviours) as well as decreased commitment to healthy behaviours, such as physical activity. Such unhealthy behaviours are consistently linked with low socioeconomic position in high-income countries,[95] and this relationship appears to be mediated through increased perceptions of extrinsic mortality risk experienced by individuals of low socioeconomic position.[96] Although such behaviours contribute to socioeconomic health inequalities, they are not sufficient to entirely explain observed differences in life expectancy by socioeconomic position, indicating that structural and economic constraints are also important. Public health campaigns targeting such unhealthy behaviours might therefore have greater success if supported by efforts to reduce deprivation and increase access to health care. Currently, however, medical treatment in some countries can be withheld from those who smoke or are obese.

Mathematical modelling

A strength of life history theory is that it can be expressed in terms of equations, enabling mathematical modelling. This could allow potential benefits and costs of interventions to be considered before their implementation in vivo. Although models inevitably have limitations related to the assumptions involved, they might flag up, in advance, issues that merit more attention. Though applicable to many contexts—eg, predicting reaction norms or examining host–pathogen dynamics—models are particularly valuable for understanding parent–offspring dynamics, through which life histories interact.

To illustrate this, we briefly consider the challenge of reducing child malnutrition, a major global health problem.[97] Logic suggests a simple solution: increased energy supply. Since low birthweight contributes to subsequent malnutrition, logic also suggests that interventions should target pregnant mothers. Protein-energy supplementation programmes have thus been provided for pregnant mothers in several countries.[98]

As the Ethiopian example showed, however, mothers face a trade-off between investing in current versus potential future offspring.[99] Additional energy might either support growth and survival of existing offspring, or accelerate production of more children. Assuming that maternal metabolism has been selected to optimise lifetime reproductive fitness, models can predict the optimal energy allocation (panel 3, figure 3). Even simple models can clarify the issues and suggest qualitative predictions.

Our model suggests that maternal supplementation can lead both to improved offspring survival and to a

shorter period of dependency, increasing maternal fecundity. The balance between these effects, however, differs markedly according to the duration of the intervention. A short-term boost in resources promotes offspring growth and survival, whereas a long-term improvement primarily benefits maternal fecundity with little benefit for the size of individual offspring.

The underlying reason is that mothers must balance the benefit of prolonged care for the current offspring against the risk that she will die and lose the opportunity to produce additional children. A short-term energy windfall increases the benefit of extending care for the current offspring, while leaving the mother's long-term prospects unchanged. By contrast, a long-term improvement in resources increases the chances of future reproductive success, devaluing investment in the current offspring. Once again, this example highlights how reproductive fitness might take priority over the health of individuals.

The emerging field of evolutionary public health

Life history theory improves the understanding of human variability in disease susceptibility, and of how the organised efforts of societies to change behaviour or environments can affect health outcomes. Both physiology and behaviour respond to ecological stimuli through the medium of trade-offs and reaction norms that favour survival and behaviour over health. Both physiology and behaviour have been selected to discount the future in high-risk environments. One key insight is that a given intervention should not be expected to produce identical consequences in populations that contrast in resource availability and extrinsic mortality risk.

This helps understanding of why poverty and deprivation have such a powerful impact on health and lifespan, and why they themselves should be a key target for interventions. Experience in early life might affect the entire trajectory of maturation and ageing, generating trade-offs between reproduction and homoeostasis.[19] Consequently, programmes targeting individual behaviour might have increased health benefits if linked with broader efforts to combat poverty, deprivation, and extrinsic mortality risks. Another key insight is that every individual phenotype reflects an accumulated history of trade-offs. This information could potentially improve the personalisation of disease prevention, diagnosis, and management.

Evolutionary approaches are likely to be particularly valuable for addressing the challenges of global health, in which populations are differentially exposed to multiple metabolic costs deriving from high fertility, diverse infectious diseases, and rapid changes in nutrition and lifestyle. Given such heterogeneity, mathematical modelling could be used to explore the likely costs and benefits of local interventions in silico, before their implementation in vivo. More broadly, evolutionary approaches offer a unique predictive framework with which to understand the basis of human disease and improve the efficacy of public health interventions.

Contributors

All authors wrote sections of this report, provided feedback on drafts, and approved the final version.

Declaration of interests

We declare no competing interests.

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References

1 Winslow C. The untilled field of public health. *Mod Med* 1920; **2:** 183–91.
2 Gibson MA, Mace R. An energy-saving development initiative increases birth rate and childhood malnutrition in rural Ethiopia. *PLoS Med* 2006; **3:** e87.
3 Kuh D, Ben-Shlomo Y. A life course approach to chronic disease epidemiology, 2nd edn. Oxford: Oxford University Press, 2004.
4 Barker DJ. Fetal and infant origins of adult disease. London: *BMJ*, 1992.
5 Krieger N, Davey Smith G. "Bodies count," and body counts: social epidemiology and embodying inequality. *Epidemiol Rev* 2004; **26:** 92–103.
6 Marmot M. Social determinants of health inequalities. *Lancet* 2005; **365:** 1099–104.
7 Dobzhansky T. Nothing in biology makes sense except in the light of evolution. *Am Biol Teacher* 1973; **35:** 125–29.
8 Jørgensen C, Enberg K, Dunlop ES, et al. Ecology: managing evolving fish stocks. *Science* 2007; **318:** 1247–48.
9 Wade N. Green revolution (I): a just technology, often unjust in use. *Science* 1974; **186:** 1093–96.
10 Nesse RM, Williams GC. Why we get sick: the new science of Darwinian medicine. New York: Times Books, 1994.
11 Wilson EO. Consilience: the unity of knowledge. London: Little, Brown and Co, 1998.
12 Nesse RM, Bergstrom CT, Ellison PT, et al. Making evolutionary biology a basic science for medicine. *Proc Natl Acad Sci USA* 2010; **107** (suppl 1)**:** 1800–07.
13 Stearns SC, Ackermann M, Doebeli M, Kaiser M. Experimental evolution of aging, growth, and reproduction in fruitflies. *Proc Natl Acad Sci USA* 2000; **97:** 3309–13.
14 Winterhalder B, Smith EA. Analyzing adaptive strategies: human behavioral ecology at twenty-five. *Evol Anthropol* 2000; **9:** 51–72.
15 Nettle D, Gibson MA, Lawson DW, Sear R. Human behavioral ecology: current research and future prospects. *Behav Ecol* 2013; **24:** 1031–40.
16 Omenn GS. Evolution in health and medicine Sackler colloquium: evolution and public health. *Proc Natl Acad Sci USA* 2010; **107** (suppl 1)**:** 1702–09.
17 WHO. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization, 2011.
18 Doyal L, Pennell I. The political economy of health. London: Pluto Press, 1979.
19 Wells JC. The metabolic ghetto: an evolutionary perspective on nutrition, power relations and chronic disease. Cambridge: Cambridge University Press, 2016.
20 Rook G, Backhed F, Levin B, McFall-Ngai M, McLean A. Evolution, human-microbe interactions and life history plasticity. *Lancet* 2017; **390:** 521–30.
21 Jasienska G, Bribiescas RG, Furberg A-S, Helle S, Nunez-de la Mora A. Human reproduction and health: an evolutionary perspective. *Lancet* 2017; **390:** 510–20.
22 Darwin C. On the origins of species by means of natural selection. London: Murray, 1859.
23 Dobzhansky T, Boesinger E. Human culture: a moment in evolution. New York: Columbia University Press, 1983.
24 Dennett DC. Darwin's dangerous idea. London: Penguin, 1995.

25 Hamilton WD. The genetical evolution of social behaviour. I. *J Theor Biol* 1964; **7:** 1–16.

26 Jablonka E, Lamb MJ. Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic variation in the history of life. Cambridge, MA: MIT Press, 2005.

27 Frazer KA, Murray SS, Schork NJ, Topol EJ. Human genetic variation and its contribution to complex traits. *Nat Rev Genet* 2009; **10:** 241–51.

28 Ono C, Kikkawa H, Suzuki A, et al. Clinical impact of genetic variants of drug transporters in different ethnic groups within and across regions. *Pharmacogenomics* 2013; **14:** 1745–64.

29 Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature* 2008; **451:** 990–93.

30 Gandon S, Mackinnon MJ, Nee S, Read AF. Imperfect vaccines and the evolution of pathogen virulence. *Nature* 2001; **414:** 751–56.

31 Arias CA, Murray BE. Antibiotic-resistant bugs in the 21st century—a clinical super-challenge. *N Engl J Med* 2009; **360:** 439–43.

32 Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. *Blood* 2010; **115:** 4331–36.

33 Ardia DR, Parmentier HK, Vogel LA. The role of constraints and limitation in driving individual variation in immune response. *Funct Ecol* 2011; **25:** 61–73.

34 Barbujani G, Magagni A, Minch E, Cavalli-Sforza LL. An apportionment of human DNA diversity. *Proc Natl Acad Sci USA* 1997; **94:** 4516–19.

35 Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994; **86:** 1600–08.

36 Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease. Evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 1989; **320:** 1161–65.

37 Collins FS, Mansoura MK. The Human Genome Project. Revealing the shared inheritance of all humankind. *Cancer* 2001; **91** (suppl 1)**:** 221–25.

38 Cohen JC, Kiss RS, Pertsemlidis A, Marcel YL, McPherson R, Hobbs HH. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* 2004; **305:** 869–72.

39 Keinan A, Clark AG. Recent explosive human population growth has resulted in an excess of rare genetic variants. *Science* 2012; **336:** 740–43.

40 Hirschhorn JN. Genomewide association studies—illuminating biologic pathways. *N Engl J Med* 2009; **360:** 1699–701.

41 Sermon K, Van Steirteghem A, Liebaers I. Preimplantation genetic diagnosis. *Lancet* 2004; **363:** 1633–41.

42 Stearns SC, Medzhitov R. Evolutionary medicine. Sunderland, MA: Sinauer Associates, 2016.

43 Roff DA. Evolution of life histories: theory and analysis. London: Chapman and Hall, 1992.

44 Lasker GW. Human biological adaptability. The ecological approach in physical anthropology. *Science* 1969; **166:** 1480–86.

45 Wells JC, Stock JT. The biology of the colonizing ape. *Am J Phys Anthropol* 2007; **134** (suppl 45)**:** 191–222.

46 Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med* 2008; **359:** 61–73.

47 Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy* 2008; **38:** 629–33.

48 Darmasseelane K, Hyde MJ, Santhakumaran S, Gale C, Modi N. Mode of delivery and offspring body mass index, overweight and obesity in adult life: a systematic review and meta-analysis. *PLoS One* 2014; **9:** e87896.

49 Trasande L, Blustein J, Liu M, Corwin E, Cox LM, Blaser MJ. Infant antibiotic exposures and early-life body mass. *Int J Obes (Lond)* 2013; **37:** 16–23.

50 Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics* 2011; **127:** 1125–38.

51 Wells JC, Yao P, Williams JE, Gayner R. Maternal investment, life-history strategy of the offspring and adult chronic disease risk in South Asian women in the UK. *Evol Med Public Health* 2016; **2016:** 133–45.

52 Lochmiller RL, Deerenberg C. Trade-offs in evolutionary immunology: just what is the cost of immunity? *Oikos* 2000; **88:** 87–98.

53 Benhariz M, Goulet O, Salas J, Colomb V, Ricour C. Energy cost of fever in children on total parenteral nutrition. *Clin Nutr* 1997; **16:** 251–55.

54 Lee G, Yori P, Olortegui MP, et al. Comparative effects of vivax malaria, fever and diarrhoea on child growth. *Int J Epidemiol* 2012; **41:** 531–39.

55 Crimmins EM, Finch CE. Infection, inflammation, height, and longevity. *Proc Natl Acad Sci USA* 2006; **103:** 498–503.

56 Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. *Clin Microbiol Rev* 2004; **17:** 760–69.

57 Penn DJ, Smith KR. Differential fitness costs of reproduction between the sexes. *Proc Natl Acad Sci USA* 2007; **104:** 553–58.

58 Le Bourg E. Does reproduction decrease longevity in human beings? *Ageing Res Rev* 2007; **6:** 141–49.

59 Lawson DW, Alvergne A, Gibson MA. The life-history trade-off between fertility and child survival. *Proc Biol Sci* 2012; **279:** 4755–64.

60 Panter-Brick C, Lunn PG, Baker R, Todd A. Elevated acute-phase protein in stunted Nepali children reporting low morbidity: different rural and urban profiles. *Br J Nutr* 2001; **85:** 125–31.

61 Stearns SC, Byars SG, Govindaraju DR, Ewbank D. Measuring selection in contemporary human populations. *Nat Rev Genet* 2010; **11:** 611–22.

62 Hrdy SB. Mothers and others: the evolutionary origins of mutual understanding. Cambridge, MA: Belknap Press, 2009.

63 Alvergne A, Lummaa V. Ecological variation in wealth-fertility relationships in Mongolia: the 'central theoretical problem of sociobiology' not a problem after all? *Proc Biol Sci* 2014; **281:** 20141733.

64 Colleran H, Jasienska G, Nenko I, Galbarczyk A, Mace R. Community-level education accelerates the cultural evolution of fertility decline. *Proc Biol Sci* 2014; **281:** 20132732.

65 Wise RA. Addictive drugs and brain stimulation reward. *Annu Rev Neurosci* 1996; **19:** 319–40.

66 Wells JC. The capital economy in hominin evolution: how adipose tissue and social relationships confer phenotypic flexibility and resilience in stochastic environments. *Curr Anthropol* 2012; **53** (suppl 6)**:** 466–78.

67 Van Noordwijk AJ, de Jong G. Acquisition and allocation of resources: their influence on variation in life history tactics. *Am Nat* 1986; **128:** 137–42.

68 Lawson DW, Mace R. Sibling configuration and childhood growth in contemporary British families. *Int J Epidemiol* 2008; **37:** 1408–21.

69 Lustig RH. Childhood obesity: behavioral aberration or biochemical drive? reinterpreting the first law of thermodynamics. *Nat Clin Pract Endocrinol Metab* 2006; **2:** 447–58.

70 Finch CE, Rose MR. Hormones and the physiological architecture of life history evolution. *Q Rev Biol* 1995; **70:** 1–52.

71 Gale EA. Is type 2 diabetes a category error? *Lancet* 2013; **381:** 1956–57.

72 Watve M. Doves, diplomats and diabetes: a Darwinian interpretation of type 2 diabetes and related disorders. New York: Springer, 2013.

73 Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. *Diabetes* 2014; **63:** 2232–43.

74 McGregor G, Malekizadeh Y, Harvey J. Minireview: food for thought: regulation of synaptic function by metabolic hormones. *Mol Endocrinol* 2015; **29:** 3–13.

75 Schneider JE. Energy balance and reproduction. *Physiol Behav* 2004; **81:** 289–317.

76 Li J, Li F, Zhao A. Inflammation and leptin. *Drug Discovery Today: Dis Mech* 2006; **3:** 387–93.

77 Victora CG, Adair L, Fall C, et al. Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 2008; **371:** 340–57.

78 Bartz S, Mody A, Hornik C, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab* 2014; **99:** 2128–37.

79 Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85:** 109–17.

80 Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. *Trends Endocrinol Metab* 2010; **21:** 199–205.

81 Moore T, Haig D. Genomic imprinting in mammalian development: a parental tug-of-war. *Trends Genet* 1991; **7:** 45–49.

82 Trivers RL. Parent-offspring conflict. *Am Zool* 1974; **14:** 249–64.

83 Haig D. Genetic conflicts in human pregnancy. *Q Rev Biol* 1993; **68:** 495–532.

84 Wells JC. Parent-offspring conflict theory, signaling of need, and weight gain in early life. *Q Rev Biol* 2003; **78:** 169–202.

85 Haig D. Troubled sleep: Night waking, breastfeeding and parent-offspring conflict. *Evol Med Public Health* 2014; **2014:** 32–39.

86 Shukri NH, Wells JC, Mukhtar F, Lee MS, Fewtrell MS. Mother-infant signalling during breast-feeding: a randomised trial investigating the effects of a relaxation intervention in breastfeeding mothers on breast milk production, breast milk cortisol and infant behaviour and growth. *Matern Child Nutr* 2016; **11:** 110.

87 Elder JP, Talavera GA, Gorbach PM, Ayala GX. Theories and structures of public health behavior. In: Scutchfield FD, Keck CW, eds. Principles of public health practice, 2nd edn. New York: Delmar Learning, 2003: 253–72.

88 Laland KN, Brown GR. Niche construction, human behaviour and the adaptive-lag hypothesis. *Evol Anthropol* 2006; **15:** 95–104.

89 Office for National Statistics. Inequality in healthy life expectancy at birth by national deciles of area deprivation: England, 2009–11. Office for National Statistics, 2014.

90 Caudell MA, Quinlan RJ. Resource availability, mortality, and fertility: a path analytic approach to global life-history variation. *Hum Biol* 2012; **84:** 101–25.

91 Chisholm D. Death, hope and sex. Cambridge: Cambridge University Press, 1999.

92 Schecter DE, Francis CM. A life history approach to understanding youth time preference: mechanisms of environmental risk and uncertainty and attitudes towards risk behaviour and education. *Hum Nat* 2010; **21:** 140i64.

93 Hillhouse JJ, Turrisi R. Examination of the efficacy of an appearance-focused intervention to reduce UV exposure. *J Behav Med* 2002; **25:** 395–409.

94 Whitehead RD, Ozakinci G, Perrett DI. A randomized controlled trial of an appearance-based dietary intervention. *Health Psychol* 2014; **33:** 99–102.

95 Pampel FC, Krueger PM, Denney JT. Socioeconomic disparities in health behaviors. *Ann Rev Sociol* 2010; **36:** 349–70.

96 Pepper GV, Nettle D. Perceived extrinsic mortality risk and reported effort in looking after health: testing a behavioural ecological prediction. *Hum Nat* 2014; **25:** 378–92.

97 Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008; **371:** 243–60.

98 Ceesay SM, Prentice AM, Cole TJ, et al. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997; **315:** 786–90.

99 Smith CC, Fretwell SD. The optimal balance between size and number of offspring. *Am Nat* 1974; **108:** 499–506.