Many ways to die, one way to arrive: how selection acts through pregnancy

Many Ways to Die; One Way to Arrive:

How selection acts through pregnancy

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Abstract

When considering selective forces shaping human evolution, the importance of pregnancy to fitness should not be underestimated. Although specific mortality factors may only impact a fraction of the population, birth is a funnel through which all individuals must pass. Human pregnancy places exceptional energetic, physical, and immunological demands on the mother to accommodate the needs of the fetus, making the woman more vulnerable during this time period. Here, we examine how metabolic imbalances, infectious

diseases, oxygen deficiency, and nutrient levels in pregnancy can exert selective pressures on women and their unborn offspring. Numerous candidate genes under selection are being revealed by next-generation sequencing, providing the opportunity to further study the relationship between selection and pregnancy. This relationship is important to consider to gain insight into recent human adaptations to unique diets and environments worldwide.

Selection and Pregnancy

Some of the earliest records of mortality from London in John Graunt's "Bills of Mortality" for 1632 reveal a number of distinct causes of death in the population [1]. Any specific cause of death impacts only a fraction of the population, lessening each particular factor's importance to fitness (Figure 1). Managing to be born, however, is a universal requirement for fitness. Thus, factors that influence fecundity and pregnancy are likely to strongly shape human evolution.

The many physiological compromises of pregnancy make it a tremendous challenge for both mothers and infants and a potential selective force. In order to provide for the growing fetus, mothers increase blood sugar [2], blood volume, and hemoglobin count [3]; remodel uterine arteries [4]; and decrease vascular resistance [5]. These changes put the mother at risk of diabetes, high blood pressure, strokes, hemorrhaging, and seizures [2, 6-8]. Moreover, properties of the immune system are down-regulated to prevent immune response to the "foreign" fetus, potentially contributing to pregnant women's greater susceptibility to infectious disease [9].

These difficulties for mothers translate into problems for infants as well: pre-industrial data show nearly a quarter of babies died during labor and infancy, while maternal mortality was nearly 1.5% per birth due to infectious diseases, diabetes, eclampsia, and jaundice [10]. Similarly, modern foraging populations and sub-Saharan African nations in 1970 also had infant mortality rates of 20% to 25%, in contrast to Norway, for example, at only ~1.6% [11, 12]. Maternal mortality in sub-Saharan Africa was ~1.0% in the year 2000 (comparable to 16th and 17th century England) with hemorrhage, hypertension (preeclampsia/eclampsia), and infectious diseases as the major causes. By contrast, maternal mortality in Northern Europe was only 0.02% in the year 2000 [13]. These data from historic, foraging, and developing country populations only serve as rough proxies for the conditions facing humans during recent evolution, but they give some indication of the difficulty of pregnancy experienced by pre-modern foraging and Neolithic populations.

In addition to the challenges of pregnancy, the number of babies a woman births, compounded across generations, can have huge evolutionary impact. For example, landless Finnish women living 1760-1849 had an average of 4.27 babies, whereas landowning women had an average of 4.55 babies: a change in absolute fitness of this magnitude would cause a geometric rise in the number of descendants in a few generations [14] (Figure 2a). The nutritional benefits of the Industrial Revolution (circa 1880) boosted average Finnish fertility to 5.3 babies [15]. Any such increase in fertility from either environmental or genetic factors will dramatically increase women's fitness (Figure 2b). An earlier revolution, the development of agriculture and pastoralism, may have conferred similar fertility benefits, especially to women with genetic mutations allowing them to maximally

exploit these new resources—lactase persistence, described below, may be an example of this [16]. Furthermore changes in female fertility could have played an important role during human population migrations. For example, a large study of Quebecois settlers indicated that women on the wave front of territory expansion had a fertility 15-20% advantage and a heritable component for fertility, suggesting that genes influencing fertility may be shaped by selection [17].

Considering the impact of female fertility alongside the challenges of pregnancy may be critical for understanding recent human adaptations. This review explores how selection may have acted through pressures on mothers and infants during pregnancy given the changing environment, diet, and behavior of the last 10,000 years. These factors are critical to bear in mind as opportunities for evolutionary geneticists to generate new adaptive hypotheses proliferate, fueled by next-generation-sequencing data and new statistical tools for predicting adaptive variants in diverse populations.

Metabolic Disorders and Selection during Pregnancy

Theories of human adaptation surrounding metabolic disorders, such as hypertension and type 2 diabetes, are constrained by the fact that these diseases typically strike at post-reproductive ages. The related disorders of gestational diabetes mellitus (GDM) and preeclampsia (hypertension in pregnancy), however, occur precisely during the critical reproductive period of pregnancy. GDM occurs as a mother's blood glucose level rises to nourish the fetus, increasing risk of maternal diabetes [18]. Preeclampsia occurs as a mother increases blood volume and remodels vasculature for

fetal ventilation, raising the risk of maternal hypertension [6]. Women predisposed for these conditions can be pushed into metabolic dysfunction.

GDM and preeclampsia are common diseases with grave consequences in pregnancy and thus may strongly impact reproductive fitness. GDM affects 4%-20% of pregnancies in different populations worldwide [19]. It can cause macrosomia, in which the fetus grows too large to fit through the maternal pelvis [20-23]. Before the advent of Caesarian-sections, GDM could lead to fetal morbidity and mortality and maternal hemorrhage and tearing during delivery [7, 20]. Preeclampsia is the leading cause of maternal mortality worldwide accounting for 10%-19% of deaths [24-26]. It can cause fetal hypoxia and oxidative stress, low birthweight, and maternal hemorrhage and seizures (eclampsia) if not treated by premature delivery [24]. (See Box 1 for a discussion of high-altitude adaptation and the risks of preeclampsia.)

The rates of GDM and preeclampsia vary significantly in different populations, even when controlling for environmental factors like obesity [27, 28]. This raises the possibility that selective pressures during pregnancy have fine-tuned metabolism to suit different environments and diets around the world, resulting in the current distribution of disease prevalence. On the other hand, alternative explanations, discussed in Box 2, may also account for these patterns—distinguishing between these competing hypotheses is an important avenue for future research.

Intriguingly, incidence of GDM among modern populations is inversely related to traditional consumption of dietary components known to increase risk for diabetes and GDM (Table 1). These include high glycemic carbohydrates, which produce large glucose responses in the blood, and dairy products, which produce large insulin responses due to

the effect of whey proteins [29-33]. Europeans have the lowest prevalence of GDM in the world—3.6% in a study of over a million births in New York City (NYC) [19]—yet have the longest history of high glycemic diets. In the past 10,000 years, European grain-based agriculture increased carbohydrate consumption to roughly 70% of diet, while hunter-gatherers consume only 3-50% [34]. In the past 8,000 years, Europeans also began consuming dairy products in large quantities [35]. In comparison, South Central Asians had a much higher incidence of GDM in the NYC cohort (14.3%) with Bangladeshis the highest at 21.2% [19]. Traditionally, Bangladeshis have had high consumption of fish, a low glycemic food; rice, of moderate glycemic index due to little processing; and no dairy [36, 37]. Finally, among African-Americans, incidence of GDM was intermediate at 4.3% [19]. This is consistent with their admixed ancestry and the mixed consumption of dairy across populations in West Africa, the origin of most U.S. African-Americans.

Given the inverse correlation between traditional consumption of dietary components increasing GDM risk and current incidence of GDM, high glycemic foods and dairy may have acted as selective agents on metabolism during pregnancy. Since GDM is very likely to have a genetic basis - 67% of the risk of type 2 diabetes for adults younger than 60 is heritable [38], and women with GDM have 7-12x elevated risk for type 2 diabetes [39, 40] - natural selection can act on its underlying risk factors. Therefore, any population environmentally at risk for GDM without access to C-sections should experience selection against genetic risk factors for GDM. Conversely, any population without access to high glycemic food items should experience selection to make blood sugars more available to the fetus, perhaps through increasing insulin resistance by increasing the frequency of genetic risk factors for GDM. Supporting these predictions, evidence suggests Europeans

may have a blunted glycemic response to food compared to other populations, which could be a result of this selection on maternal metabolism to suit diet [41, 42].

Like GDM, preeclampsia has an incidence that varies across populations, and it appears to have an inverse relationship with the dietary risk factor of salt-intake (Table 1) [43]. In a study of preeclampsia in NYC, preeclampsia rates were lower among immigrants from East Asia (1.4%), especially Japan (1.2%) and Taiwan (0.9%), and lowest in the world among Iranians (0.6%) [44] compared to an incidence of 3-5% of pregnancies in other developed countries [24]. Although these populations are less obese than Americans, Japanese and Iranians have historically high salt-intakes due to consumption of coastal foods (Japan) and high soil salinity (Iran) [45-47].

High salt-consuming populations, such as Japanese and Iranians, may have experienced strong selection to protect them from the deadly threat of preeclampsia. Since the heritability of preeclampsia is 0.55 according to a study done in a Swedish cohort [48], this provides variation for selection to act on. Populations consuming large amounts of salt should experience strong selection against genetic risk factors for preeclampsia in the absence of modern medical support for premature deliveries. Supporting this, insensitivity to salt in the diet is common in Japanese: women consuming the most salt (20.6g/day) have no more hypertension than those consuming the least 8g/day [49]. For comparison, the WHO recommends less than 5g/day of salt consumption for adults [50].

Adaptation for consuming a high glycemic, high dairy diet may have been the result of selection in Europeans through the pressure of GDM, whereas adaptation for consuming a high salt diet may have evolved in Japanese and Iranians through the selective pressure of preeclampsia. On the other hand, alternative hypotheses may also explain the trends

described (see Box 2). In the past several thousand years, populations migrated to new environments and invented new methods of food extraction and processing, such as agriculture, pastoralism, and fishing. The hypotheses presented here focus on how selective pressures during pregnancy may cause strong selection in response to changing diets in recent human evolution.

Nutrients and Selection during Pregnancy

Access to nutrients has been critical in human evolution, contingent upon dietary resources and the physiological processes that determine the bioavailability of ingested nutrients. Two selective pressures in humans that changed the amount and bioavailability of nutrients in the diet were exposure to solar UV radiation and adult milk-drinking. The ways in which these impacted fecundity and pregnancy may explain why UV radiation and milk-drinking exerted such strong fitness effects.

Skin pigmentation closely correlates with UV radiation worldwide [51], perhaps partly because UV radiation exerted strong selection across populations during pregnancy in addition to other stages of life. Lighter or darker pigmentation impacts absorption of UV radiation on folate and vitamin D3, critical micronutrients during pregnancy [51, 52]. Folate—obtained from eating plants—is stored in cutaneous blood vessels and can be destroyed by UV radiation [53]. Folate deficiency causes failure of neural tubes to close during fetal development, resulting in anencephalus and spina bifida, defects lethal to the fetus [54]. Neural tube defects rarely occur in darkly pigmented people as their melanin protects their folate stores in equatorial areas [51]. Therefore, increased melanin production among equatorial populations of Africa, as well as Asia, Australia, and the

Pacific where populations migrated, was potentially selected to protect folate stores in the skin during pregnancy.

On the other hand, melanin in the skin also blocks synthesis of vitamin D3 at higher latitudes [55]. Vitamin D3 enables absorption of calcium for skeletal formation in the fetus and maintenance in the mother [56]. Deficiencies cause malformation of the maternal pelvis, maternal osteoporosis, and rickets in fetuses and growing children [57, 58]. In addition, vitamin D3 may assist development of the fetal innate immune system and critical organs [59, 60]. Therefore, balancing the synthesis of vitamin D3 with protection of folate-stores for pregnancy probably played a role in the strong selection for graded melanation with UV-radiation clines worldwide [51, 52].

Signatures of strong selection have been found in diverse populations surrounding genes with variants associated with skin pigmentation—notably *SLC24A5*, *MATP*, and *TYR* in Europeans, *DCT*, *EGFR*, and *DRD2* in East Asians, and *TYRP1*, *KITLG*, *ASIP* and *OCA2* in both populations [61-64]. In addition, ancestral alleles of these genes that tend to be associated with darker pigmentation and occur at a high frequency in Africans also tend to be highly frequent in darkly pigmented Melanesian populations. This may indicate convergent selection on the same genetic variants in diverse populations [61], although many populations remain to be tested.

Alternatively, UV radiation may have selected for appropriate skin pigmentation at other life stages such as childhood. Some detrimental effects of UV radiation on skin, such as skin cancer, occur post-reproductively, mitigating their importance to fitness [52, 65]. However, sun-burn alone causes significant morbidity for lightly pigmented people living in high UV regions because it damages the skin, increasing infection and water loss and

decreasing thermoregulatory control. Furthermore, while vitamin D3 is critical for pregnancy, it is also important for bone density, immune function, and other effects in childhood and throughout life. To address this, one piece of evidence indicating that pregnancy, specifically, may have been important to selection on skin pigmentation is that women exhibit slightly lower levels of skin pigmentation on low exposure patches of skin than men, across world populations, indicating that the need for vitamin D3 may have been more critical to women than men [51]. Research clarifying the importance of vitamin D3 status to human health at different life stages could shed more light on this hypothesis.

Likewise, the ability to drink milk among pastoralists who keep dairy animals may also have been driven by selection on reproductive fitness. These pastoralists experienced strong selection in the past 10,000 years to continue digesting the lactose found in milk into adulthood, rather than losing this ability shortly after birth, as in most mammals [66]. Strong selection has been detected surrounding a number of different polymorphisms in diverse pastoralist populations from Europe, Africa, the Middle East, and Central Asia, each associated with regulation of *LCT* expression, encoding the enzyme lactase, which is responsible for cleaving lactose, the disaccharide in milk [35, 67-70]. Researchers have been surprised by the strength of this selection and have struggled to develop plausible explanations for it. Milk from animals provides an extra source of sugar, protein, fat, calcium, and hydration, beneficial not only for survival but also for reproduction. Several possible hypotheses could link milk to reproductive fitness. First, milk from animals provided a sterile source of hydration, especially for those living in hot, arid climates like Africa and the Middle East [66]. Considering the sensitivity of pregnant women to contaminated food and drink [71], pregnant women able to drink sterile fresh

milk may have experienced special fitness benefits. Second, the extra calcium in milk could be beneficial due to its role in skeletal development and maintenance and to female reproductive maturation, as large pelvises are required for vaginal delivery [72]. Third, because fat is more calorically dense than proteins and carbohydrates, fat from milk could help the mother nourish her infant during pregnancy and lactation. Fat stores and energy balance have also been linked to age of menarche and length of anovulatory period post pregnancy [73, 74].

A final hypothesis involves the fact that milk and other animal fats contain cholesterols used to synthesize reproductive hormones, critical for fecundity and early fetal development and growth [75]. The grain-based diets of Neolithic farmers were lower in cholesterol than the diets of hunter-gatherer ancestors who consumed more wild game [34]. Less cholesterol in the diet correlates with lower levels of reproductive steroids [76], reducing ovarian function and fecundity, suggesting that milk drinking could have provided a much-needed cholesterol and fertility boost for Neolithic Europeans. Therefore, the increase in fat, cholesterol, and calcium from drinking milk may have accelerated female skeletal maturation, increased caloric resources, and increased fecundity among women who could consume dairy, creating strong fitness benefits.

Infectious Disease and Selection during Pregnancy

Infectious diseases have exerted some of the strongest forces of selection on humans, most notably since the increase in population densities following the transition to agriculture and pastoralism 10,000 years ago. For example, genetic variants conferring resistance to malaria, such as alleles in the region of *HBB*, *HBA*, *FY*, *CD36*, *G6PD*, etc., were

strongly selected among African populations and others where malaria is endemic [77]. Though infectious diseases are threats to survival generally, their differential impact on infants and pregnant women makes them especially powerful selective agents.

During pregnancy, the maternal immune system is suppressed so that the mother does not launch an adaptive immune response to the fetus's foreign cellular antigens [9]. Though details are still being clarified, this response may make pregnant women less able to clear infections requiring strong inflammatory responses [9]. The outcome is that pregnant women experience spontaneous abortion and have higher morbidity and mortality in response to many infections than the general population [9].

Malaria, influenza, and cholera are three infectious diseases that pose severe risks for pregnancy. In particular, African Plasmodium falciparum can infect the placenta [9]. As a result, pregnant women with malaria die 2-3 times more often than the general infected population [78]. In sub-Saharan Africa, malaria causes 20% of the cases of low infant birthweight, along with slow growth, spontaneous abortion, maternal anemia, and infant mortality [9, 78, 79]. Intriguingly, positive selection on a genetic variant of the gene *FLT1*, which reduces spontaneous abortions in cases of placental malaria, has been found for a malaria-endemic population in Tanzania [80]. This indicates that in the case of malaria resistance, selection mediated by pregnant women and their fetuses alone is sufficient for adaptive change in allele frequency in a population. Based upon this evidence, although genetic variants conferring general resistance to malaria experienced positive selection that could have been mediated by a broader subset of the population, pregnant women likely comprised an important portion of this selection.

During the 1918 influenza pandemic, ~50% of all infected pregnant women contracted pneumonia, and ~50% of this subset died (~27% total mortality for infected pregnant women), far more than the ~1% mortality for all individuals of reproductive age with influenza [81, 82]. Along with fetal abortion, this caused a 5-15% drop in birth rate the following spring [83]. This pattern is typical of other influenza pandemics [84]. Mortality by influenza is heritable [85], so resistance to influenza may have been strongly selected for in recent human evolution, although this has been understudied.

Cholera causes diarrhea, vomiting, dehydration, and cramping, which can induce spontaneous abortion, preterm small birthweight babies, and maternal death [86]. Similar to influenza, smallpox, and dysentery, cholera decreases birthrates significantly during epidemic years [10, 87], indicating it has strong potential as a selective agent in humans.

Many other infectious diseases are particularly dangerous for pregnant women. Among female Lassa Fever patients of childbearing years admitted to a hospital in Sierra Leone, death was significantly higher for pregnant women (25%) than non-pregnant women (13%) [88]. Tellingly, symptoms improved with delivery [88]. The Ebola virus killed more pregnant patients (95.5%) than the population average (77%) during an outbreak in the DRC [89]. Some infectious agents, for example the parasite Toxoplasma gondii, cause disease only in pregnant women, who are likely to experience abortion [9]. Evidence from mice suggests that another parasite, Leishmania, also exploits immunological changes in pregnant women [90]. Finally, Varicella zoster, the chicken pox virus, causes pregnant women to develop more skin lesions and pneumonia at higher rates than the average adult with chicken pox [91].

Pregnant women are clearly especially vulnerable to infectious disease. Although many of these diseases also cause significant morbidity in non-pregnant adults, the dramatic impact on pregnant women makes it likely that selective effects would have been strongly mediated by this population, though the adaptive benefit of genetic resistance to infectious disease is felt across all life stages for both males and females. As researchers discover functional genetic variants in areas under selection in the human genome, we predict that many are likely to confer resistance to infectious diseases that severely impact pregnant women who lack resistance in addition to those causing high infant mortality.

Concluding remarks

The field of human evolutionary genomics is in a period of transition. Currently, only a few examples of selection in response to environmental pressures felt by particular populations have been elucidated —malaria resistance, lactase persistence, etc. These examples were already under study prior to the development of evolutionary genomics, and the signatures of selection surrounding the genetic variants under selection merely served to substantiate strong adaptive hypotheses already presented. However, next-generation sequencing data, conducted in diverse populations, now provides the raw material to detect many more strong candidates for selection. Thus, the field of evolutionary genomics now has the potential to provide many new testable hypotheses of selection, which were not developed a priori. For example, a catalog of candidate variants for selection was recently published and one of these variants was experimentally characterized [102].

At this turning point in the field, we seek to underscore that many aspects of human evolution are best understood by investigating the life-history bottleneck of pregnancy and birth from the perspective of both the mother and the infant. During pregnancy, nutritional, energetic, physical, and immunological requirements are constrained in the mother to support the fetus, concentrating selective forces upon the mother at a sensitive life stage. The pressures that have been most important in recent human evolution—infectious diseases from high population densities, adult dairy consumption from pastoralism, grain consumption from agriculture, changes in UV radiation and oxygen levels from moving to extreme latitudes and altitudes—have left genetic signatures of their selective impact. Although these selective factors may be felt across the lifespan, nowhere are they more serious than during infancy and pregnancy. We should thus remain cognizant of these phases of life as next-generation sequencing now provides evolutionary genomicists with the data to generate many new testable hypotheses of why loci are under selection in humans.

Box 1 **Oxygen and Selection during Pregnancy**

Another environmental pressure detrimental to pregnant women is high-altitude hypoxia. When brought to high-altitudes, people from sea-level populations increase hemoglobin levels to carry more oxygen to the tissues. With long-term exposure and old age, increased hemoglobin causes altitude sickness and even death. However, pregnant women experience a special danger: preeclampsia caused by oxygen-restriction for the fetus. As described in the main text, preeclampsia often results in premature labor, small birth-weight babies, and hemorrhaging, seizures, and death for the mother [24].

Tibetans, Andeans, and the Ethiopian Amhara have each adapted to hypoxic high-altitude conditions possibly due to its impact on pregnancy. In these populations, strong signatures of selection surround genetic loci related to hypoxia and hemoglobin concentration, including *EGLN1,*

EPAS1, *PPARA, THRB*, and *ARNT2* [92-95]. However, Andeans are still at risk for altitude sickness in old age because they exhibit the same elevated hemoglobin levels of low-landers at high-altitudes, indicating that selection for post-reproductive survival was not the primary force in this population [96]. Yet, some studies find that Andeans and Tibetans giving birth at high-altitudes have fewer instances of low-fetal birth weights and preeclampsia than low-landers at high-altitudes, possibly due to increased uterine capillary density [97-99]. Also, some genes under selection among the Amhara are involved in fetal hemoglobin levels (*BCL11A*) and angiogenesis (*AIMP1* and *VAV3*), an important feature of pregnancy [92]. These pieces of evidence indicate that pressures during pregnancy may have been significant in adapting to high altitude hypoxia for Tibetans, Andeans, and the Amhara.

Box 2 **Alternative Hypotheses and Avenues of Research**

Although the evidence described in the main text support the importance of pregnancy to recent selection in humans, alternative hypotheses could also explain some phenomena that we argue suggest selection in pregnancy. Take, for example, the differences in GDM prevalence across populations, and the inverse correlation with historical glycemic intake. When mothers born in energy-poor environments emigrate to energy-rich environments, fetal programming may contribute to the pattern as these women have heightened risk of GDM and type 2 diabetes [100]. Maternal epigenetic modifications could be the mechanism underlying this programming to suit the early life environment. Another contributor could be the differences in patterns of adipose storage across populations—Asian women tend to have more central adiposity than women in other populations, and this is thought to increase insulin resistance [101]. However, this proximate cause of increased GDM among Asians is not at odds with a history of natural selection acting on the trait.

Distinguishing among these competing explanations for the patterns we see could be a fruitful line of research. For example, first, one could conduct association studies in diverse ethnic populations to identify genetic loci linked to GDM risk. Second, these loci associated with GDM could be analyzed for signatures of recent selection in order to test whether selection has influenced GDM incidence across populations. Finally, one could test whether incidence of GDM among immigrants approaches that of the rest of the population across generations. GDM is reduced for South Asians born in the US compared to first generation immigrants, but it is still elevated above the level of European-Americans [19], indicating fetal programming may explain a large fraction of differences in GDM risk, but is probably not the only factor.

Similar approaches could be used to test hypotheses of selection for resistance to preeclampsia, infectious disease, hypoxia and other reproductive factors. In a broad sense, this will require a better understanding of the axes of human variation—genetic and phenotypic. Next-generation sequencing data from diverse populations of humans will contribute to this understanding. However, the phenotypic data is just as critical. We need a clearer understanding of the susceptibility of pregnant women to infectious diseases and metabolic diseases across populations, and how this is mediated by nutritional status, UV radiation, hypoxia, and other external factors. Testing these hypotheses will be important both for evolutionary genetics and for improving care for human health across diverse ethnicities.

Table 1—Relationship between Metabolic Diseases of Pregnancy and Traditional Diets

GDM Incidence, Glycemic Index, and Dairy Consumption

Population	**GDM Incidence**	**Diet**	**Dairy**	**Agriculture**	**Glycemic Index**	**Reference**
European-Americans	3.6%[a]	70% Carbohydrate; Grain-based	Yes	Yes	High	15, 30, 31
Hunter-Gatherers	?	3-50% Carbohydrate; Game, Tubers, Vegetables, Fruits, Nuts, etc	No	No	Moderate	30
Bangladeshis	7-9%[b] 21.2%[a]	Rice, Fish	No	Yes	Moderate	15, 32, 33
African-Americans	4.3%[a]	Agriculture, Pastoralism, or Hunter-Gatherer	Mixed	Mixed	Moderate	15

Preeclampsia Incidence and Traditional Salt Consumption

Population	**Preeclampsia Incidence**	**Salt Consumption**	**Obesity**	**Reference**
European-Americans	2%[a]	?	High	40, 41
Sub-Saharans	3.3-3.9%[a]	Low, especially in rainforests	Low	40, 41
African-Americans	4.6%[a]	Low, mixed ancestry	High	40, 41
Iranians	0.6%[a]	High, due to soil salinity	Medium	40, 41, 42

Japanese	1.2%[a]	High, due to seafood	Medium	40, 41, 43

[a]Incidence for populations living in New York City
[b]Incidence for populations living in Bangladesh

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Figure 1. Multiple Varied Causes of Death in Modern and Historic Populations

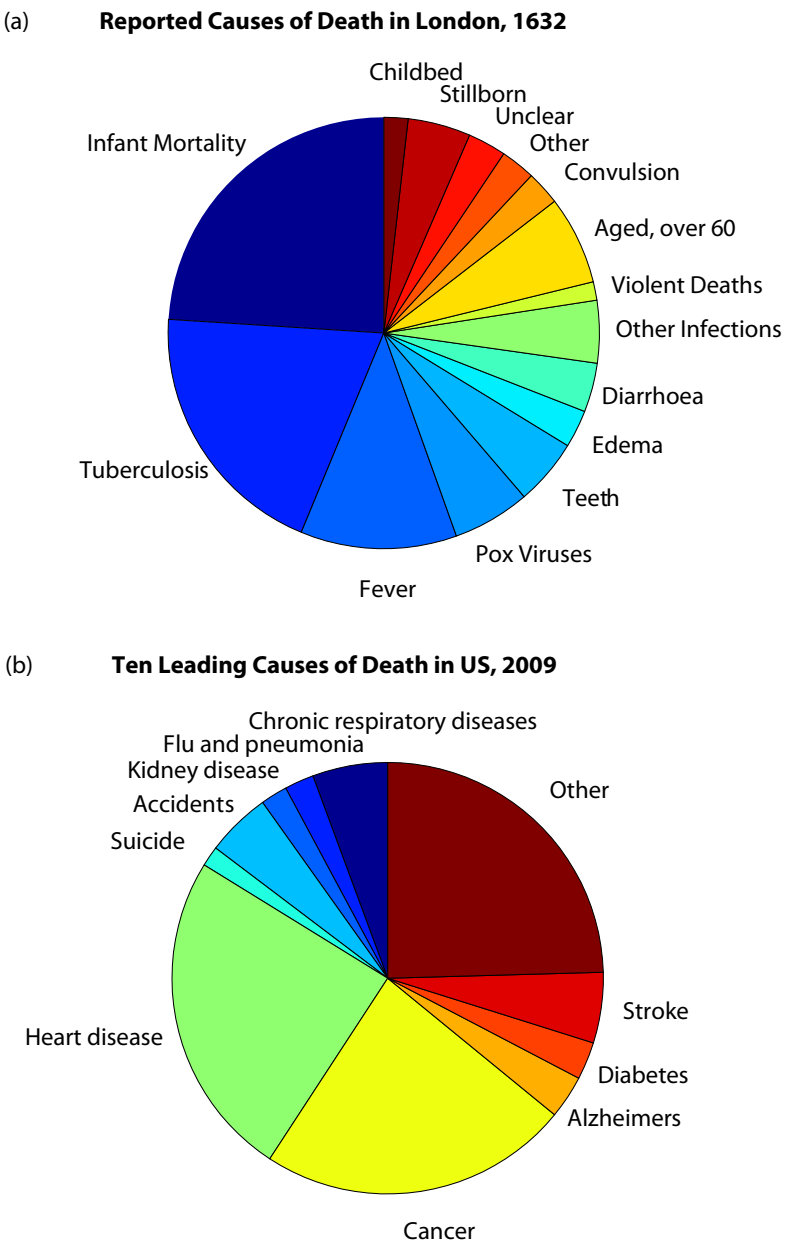

Figure 1 **Multiple Varied Causes of Death in Modern and Historic Populations** (a) Many different factors caused death for individuals who died in London in 1632 [1]. "Childbed" referred to mothers who died during or after labor, often due to infections. Over a quarter of deaths occurred in infants and unborn fetuses. (b) By contrast, the leading causes of death in modern, developed countries, such as the US in 2009, are very different with heart disease and cancer accounting for fully half of the deaths [103].

Figure 2. Rapid Change in Prevlance of Fertility Enhancing Traits

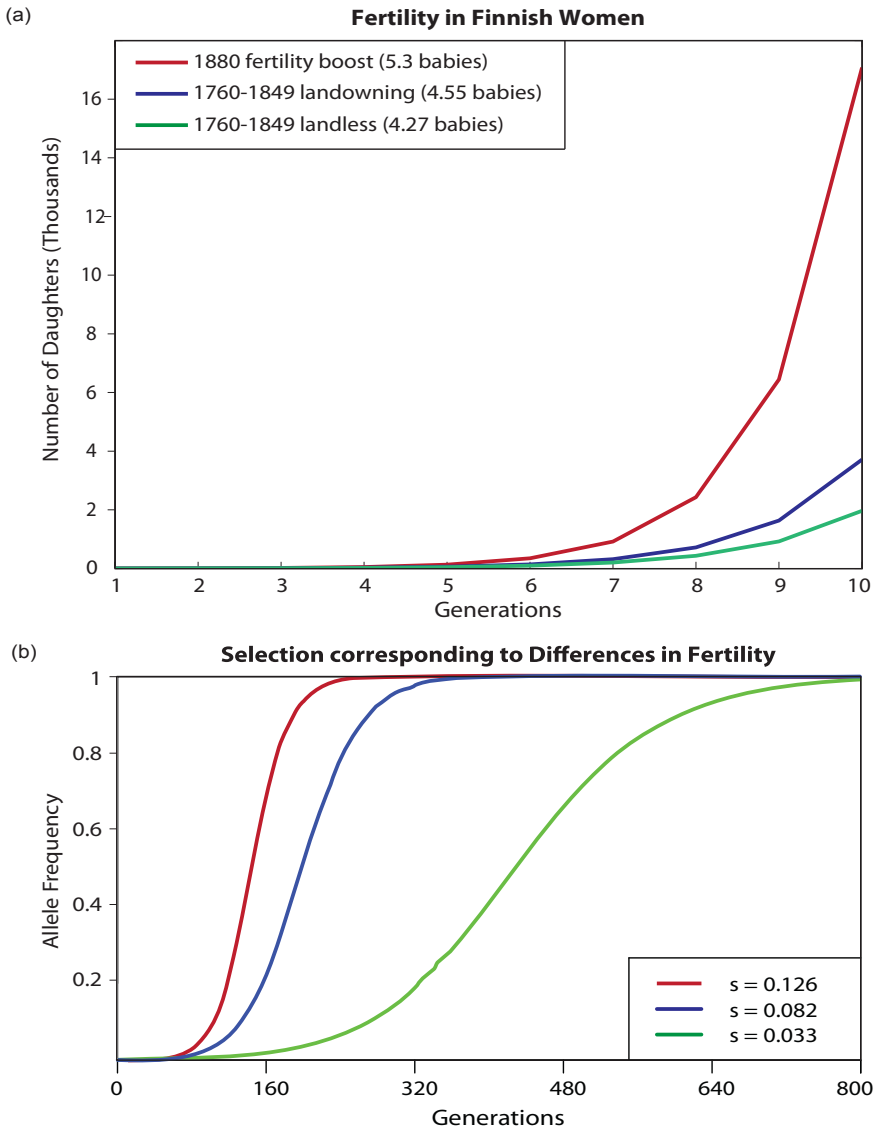

Figure 2 **Rapid Change in Prevalence of Fertility Enhancing Traits** (a) The increase in number of female descendants (y-axis in the thousands), compounded across generations, for maternal lineages with an average of 5.3, 4.55, or 4.27 babies over a lifetime, based on pre-industrial data on differences in female fertility in Finland [14, 15]. (b) The increase in frequency of new mutations conferring fertility advantages that correspond to the differences in fertility for the three groups of Finnish women (s = 0.126 for 5.3 versus 4.27 babies; s = 0.82 for 5.3 versus 4.55 babies; s = 0.033 for 4.55 versus 4.27 babies). This demonstrates how readily any mutation with a positive impact on female reproduction will sweep through a population over a very short time due to the compounding effect across generations.