Innate immune response and regulation of human life-histories under adverse conditions

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CHAPTER 2

REGULATION OF HUMAN LIFE-HISTORIES: THE ROLE OF THE INFLAMMATORY HOST RESPONSE

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ABSTRACT

Most species with a long life span have few offspring while species with a short life span have many offspring. This evolutionary trade-off between fertility and body maintenance, based on the theory of r/K-selection, is a central theme in the theory of life history regulation. This trade-off is not only found between various species but also between individuals within one species. There is accumulating evidence for this trade-off in humans. We hypothesize that the innate immune system is a critical factor skewing an individual into the direction of either a high fertility or better maintenance strategy. As over thousands of years human survival has been highly dependent on resistance to infectious diseases, genetic adaptations resulting in inflammatory responses were favored. An inflammatory host response is critical to fight infection necessary to survive up to reproductive age. An inflammatory host response is also negatively associated with fertility and can explain for the trade-off between fertility and body maintenance. After human reproductive age, these inflammatory responses contribute also to development of chronic degenerative diseases. These will especially become apparent in affluent societies where the majority of individuals reach old age. Identifying the inflammatory host response as a critical factor both in the regulation of human life histories and in the occurrence of chronic diseases at old age implies means for intervention allowing individuals to live healthier for longer.

INTRODUCTION

The fitness of a species is determined by the capability of an organism to pass its genes to the next generation under defined environmental conditions. Fitness is therefore dependent on fertility *per se*, and maintenance, in order to survive up to reproductive age. Limited resources have to be divided between body maintenance and fertility. This can be described by the r/K-selection theory as proposed by MacArthur andWilson[1]. The symbols r and K refer to two ends of a continuum, where a compensatory exchange occurs between investment in fertility (r-selection) and in body maintenance (K-selection). Both r- and K-strategies are adaptive survival strategies employed by species in different habitats. By means of natural selection, dependent upon environmental conditions, each species will be pushed to its own fitness optimum somewhere on this continuum between an extreme of r- or K-strategies. If extrinsic mortality is high, organisms tend to have their fitness optimum more at the r-side of the r/K continuum. In a more stable environment, organisms invest more in K at the cost of r. Support for this evolutionary trade-off between investment in body maintenance and fertility is pictured in **Figure 1**, which shows the relation between body maintenance (life span) and fertility (number of offspring) of different mammals.

The r/K-selection theory also helps us to understand differences in the life histories within one species and between individuals of one species[3,4] Several experiments with the fruit fly *Drosophila melanogaster* support the existence of this trade-off between body maintenance and fertility within one species[5-7]. A selection regime favouring flies with prolonged fertility at later ages did result in populations with reduced fertility early in life and increased life span. Direct selection for longevity also produced long-lived populations with significantly reduced fertility[8]. A similar experimental trade-off has been found in the nematode *Caenorhabditis elegans*; a series of mutations in the insulin pathway are associated with an increase in life span of up to 200%, but at the cost of fertility[9,10].

There is accumulating evidence that the evolutionary trade-off between body maintenance and fertility is also present in humans[11,12]. Earlier we have studied a historic data set, so as to investigate humans in an environment where evolutionary selection was still present. In the pedigrees of the British aristocracy who lived before 1700, we found that long-lived women had

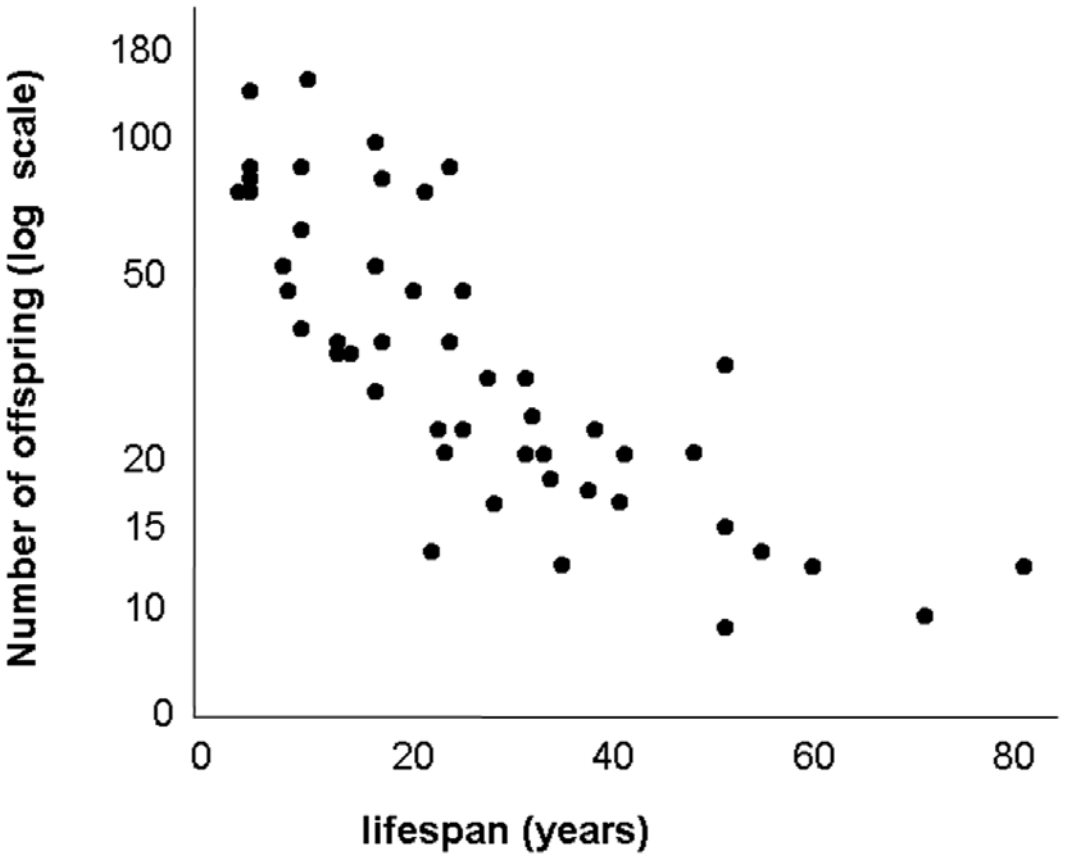

Figure 1. Life span and number of offspring in mammal species.
(Adapted from Holliday[2].)

fewer offspring, as shown in **Figure 2**[13]. Several other studies have confirmed these findings in populations resembling the human "natural habitat." Korpelainen found the trade-off between reproductive success and longevity in women in a Finnish population between 1700 and 1899[14]. Thomas *et al*. found a trade-off in both sexes using data from 153 countries[15]. Some studies only found the trade-off to be present in women[16,17]. Other studies, however, did not find evidence for the trade-off[15,18-21]. This could in part be explained by the fact that the populations under study resided in a modern affluent environment characterized by low mortality and fertility rates, that is, having past the demographic transition. In line with this reasoning, Lycett *et al*. demonstrated that the trade-off was stronger under poverty conditions[22]. We also showed that the trade-off disappeared when environmental conditions of the British aristocracy markedly improved after 1700 and ini-

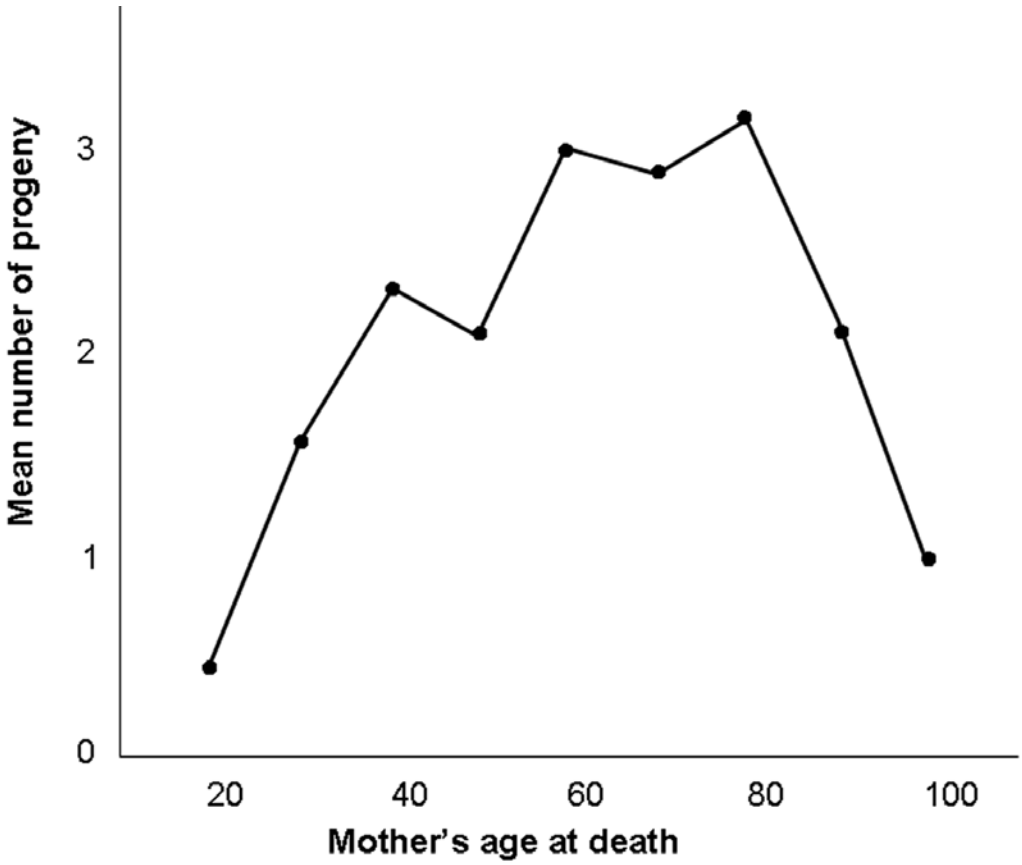

Figure 2. Progeny number for married aristocratic women from different birth cohorts as a function of age at death. (Adapted from Westendorp & Kirkwood[13].)

tiated a demographic transition[13]. Similar trends over time were found by Korpelainen, who demonstrated that the trade-off in women[14] had disappeared upon further improvement of the environment[23].

Nowadays, the demographic transition has taken place in most countries resulting in low fertility and low mortality rates under affluent conditions[24]. It is therefore not surprising that the r/K trade-off may not be found in contemporary populations. At present the population genome is not yet in evolutionary equilibrium with the dramatically improved environmental conditions in which we live. To understand which factors have contributed to the regulation of human life history, we first look at the r/K-selection forces that have shaped our body under adverse conditions in our "natural habitat." From there we develop a line of thought in five steps to understand the consequences of this selection for our present day life.

FUNDAMENTALS

Human survival is strongly dependent on resistance to infectious diseases

The selections that took place during evolution of *Homo sapiens* in his natural habitat differ from other mammals, in that he constantly created new ways of living. First he eliminated the danger of cold with the mastery of fire some hundreds of thousands of years ago. Additional contributions to the reduction of death from cold were the use of clothing, the transition from hunter/gatherer ways of living to agricultural civilization during the Neolithic period, and the construction of houses. Farming also managed to create a far more constant supply of food, reducing the selection of individuals withstanding hunger and shortage of food. The use of tools, superior intellect, the ability of speech, and group cooperation reduced the number of deaths through predation. The result of expelling the major threats predation, hunger, and cold is that selection pressure on infectious diseases became more prominent[25]. Resistance to infectious diseases (parasites, bacteria, and viruses) became an even more important selection criterion when humans moved closer together. The developing farming societies were also able to feed a far greater population, leading to increased population sizes. The growing populations with a more sedentary lifestyle were a perfect niche for different infectious diseases. In more recent history, with the rise of cities some thousands of years ago, the first epidemics occurred, sometimes killing as many as one-third of a city population. This all has resulted in a predominant selection for resistance to infection to survive up to reproductive age, that is, humans had to invest in K in order to maintain their fitness.

Resistance to infectious diseases is strongly dependent on an inflammatory host response

As, over the last thousands of years, *Homo sapiens* has developed in an environment with a high pathogenic burden, it can be hypothesized that selection has taken place on an inflammatory host response[26]. Evidence for genetic adaptations for resistance to infection is widely demonstrated and many of these adaptations have occurred in the innate immune system[27]. The innate immune system is the first line of defense and suffices for the overwhelming majority of invading pathogens[28]. Its components have evolved under high selective pressure in our ancient predecessors. The innate immune system is triggered by pathogens that are among others, identified by Toll-like receptors on antigen-presenting cells[29]. Stimulation of

these receptors results in a series of pro- and anti-inflammatory signals to adequately fight infection and to offset the immune response[30-32]. Survival up to reproductive age thus necessitates balancing of the pro- and anti-inflammatory responses. The elicited aspecific pro-inflammatory signals have a synergistic role in the inflammatory host response, mediated by cytokines, such as tumor necrosis factor-α (TNFα). Cytokines also induce an adaptive, specific cell-mediated immune response, able to attack a further number of pathogens that cannot efficiently be cleared by the innate, aspecific immune response alone. Anti-inflammatory cytokines regulate activation of the innate and adaptive immune response. They inhibit pro-inflammatory signals thus preventing collateral damage of a too abundant inflammatory host response. Moreover, these cytokines mediate recruitment of B cells, antibody responses, mast cells, and eosinophils by cytokines like interleukin-10 (IL10). Not surprisingly, we have found the production and regulation of pro- and anti-inflammatory cytokines to be under tight genetic control, in line with the assumption that the inflammatory host response is submitted to evolutionary selection pressure[33].

Earlier we studied the production capacity of TNFα and IL10 in first-degree relatives of patients suffering from meningococcal infections and showed that the ratio of TNFα/IL10 was lower in cases in which the infection was fatal. Our interpretation of these data is that subjects with an innate tendency toward anti-inflammatory signalling are at an increased risk of death through infection[34]. Many other studies now have demonstrated that pro-inflammatory signals are critical to protect against death from infection[35-37]. It is therefore likely that over the last thousands of years evolutionary selection favoured genes that associate with an adequate inflammatory host response.

Pro-inflammatory signals are negatively associated with fertility

As humans have to be able to survive up to reproductive age, the immune system elicits pro-inflammatory signals in order to fight non-self-antigens. However, protection against infection does not go well with fertility *per se*. Half of the fetus' antigens are from paternal origin, and are therefore considered non-self by the mother. These non-self-antigens thus elicit a strong immunologic response resulting in pro-inflammatory signalling, local inflammation, and rejection of the fetus. Successful reproduction necessitates an adequate immunotolerance to allow pregnancy to proceed.

During pregnancy the mother physiologically enhances anti-inflammatory signalling, even though this makes her more susceptible to infection[38,39]. Several studies report increased pro-inflammatory signalling among women with spontaneous abortions and higher anti-inflammatory signalling among women with reproductive success[40-42]. These studies support the hypothesis that pro-inflammatory signalling is negatively associated with fertility. In line, we have demonstrated that genetic variants that associate with increased pro-inflammatory signalling were enriched in married but infertile women[42,43]. We have concluded that investment in fertility and body maintenance is under tight genetic control, balancing between pro-inflammatory and anti-inflammatory signals. The pro-inflammatory signalling increases resistance to infections and is thus a component of K-selection, whereas selection for anti-inflammatory signalling increases fertility and can therefore be considered as a component of r-selection. Depending on the environment, and especially the risk of fatal infection, the balance between these various responses results in an optimal level of fitness, as shown in **Figure 3**.

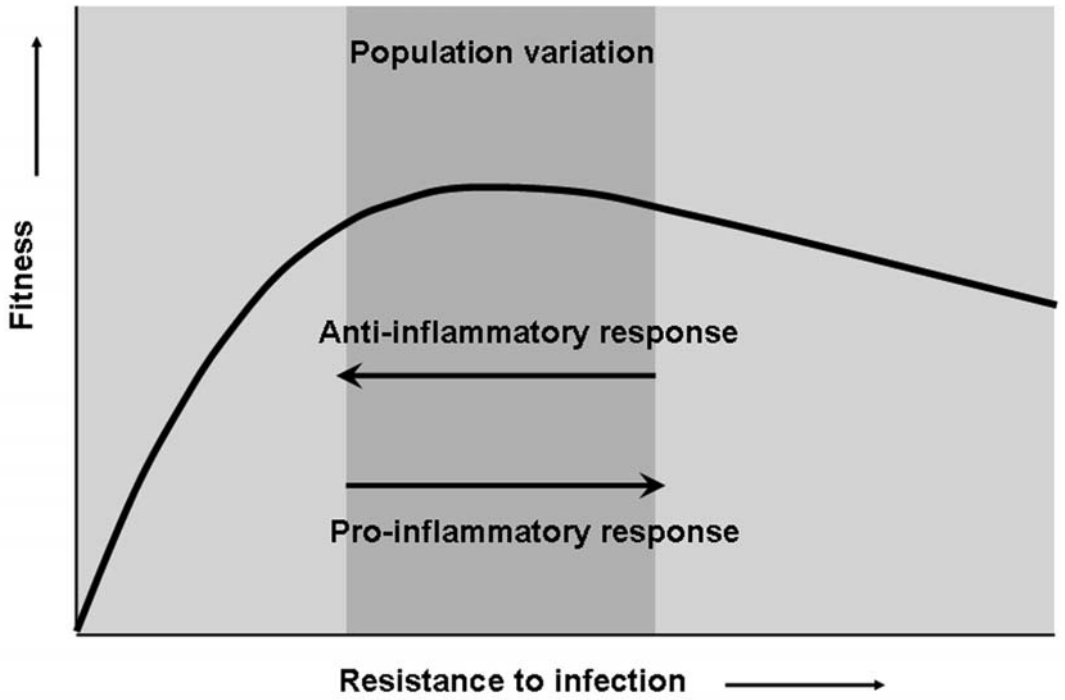

Figure 3. Schematic diagram showing fitness for different genes encoding pro- and anti-inflammatory signals. (Adapted from Westendorp[12])

Pro-inflammatory signalling promotes degenerative diseases after reproductive age

In our ancient, natural habitat not many individuals will have survived beyond 40 to 50 years. Not coincidental this is the age up to which we can bear offspring. In natural societies the durability of the body is optimized only to guarantee survival up to reproductive age and to raise one's offspring[44]. **Figure 4** shows the decline of survival probabilities under adverse conditions. Mutations that have an effect after the age of 40 to 50 years will neither be selected for nor against, for the sole reason that most individuals did not have a postreproductive life span. Events that occur after the reproductive period fall in the "selection shadow," since these effects are not under an evolutionary selection pressure[45].

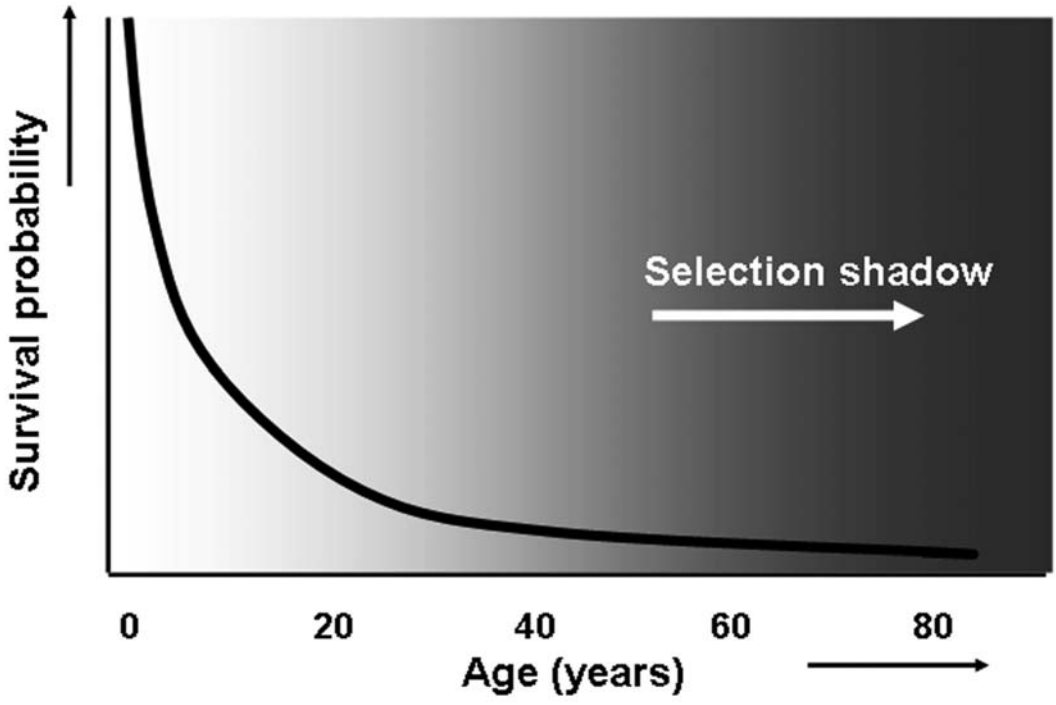

Figure 4. Human survival probabilities in our natural habitat. After reproductive age humans enter the selection shadow. (Adapted from Kirkwood & Austad[46].)

One may also consider that genes that have a beneficial effect early in life have detrimental effects later on, as is proposed by the theory of antagonistic pleiotropy[47]. It says that chronic, degenerative diseases at later age are in fact the consequence of selection for genes that were beneficial at early age. Selection for a pro-inflammatory signalling that is protective in early life may in fact promote for what are generally called "age-related" or "degenerative diseases," among which are atherosclerosis and the cardiovascular diseases, multiple sclerosis, rheumatoid arthritis, autoimmune thyroid diseases, osteoporosis, and diabetes[48-51]. Dementia, may also become more likely as a consequence of inflammatory responses that were selected for because of their beneficial effects at child age[52,53]. This chronic inflammatory host response contributing to the occurrence of age-related diseases has thus been referred to as "inflammaging"[54].

It is tempting to speculate that the chronic degenerative diseases in old age are part of our evolutionary shaped life history and do not directly result from our recent affluent life style. Arguments for this reasoning can be found in the research of Magee *et al*. who demonstrated atherosclerosis in Egyptian mummies from individuals who lived until their 50s or 60s[55]. Now the demographic transition has taken place, our life expectancy has increased tremendously[56]. The simple fact that about half of our present life—with a life expectancy of 80 years—takes place in what used to be the selection shadow, indicates that we are for a long time subjected to the deleterious effects of genes that encode for inflammatory responses[24].

Detrimental effects at late age get worse when humans improve their natural habitat

Our genome has evolutionarily been shaped following environmental changes that occurred over millions of years. The improvement of our environment began slowly (see above) but accelerated during the last hundred of years. Now we have almost dealt with death from infection. In developed countries clean drinking water, sanitation systems, improved hygiene, vaccination, antibiotics, and improved medical care have changed human life histories forever. We have converted our adverse natural habitat into a well-protected environment. All these changes have resulted in a greatly reduced mortality risk from external causes and it is clear that a far larger proportion of recent birth cohorts will survive up to an age that can be considered as residing in the selection shadow. This is illustrated in **Figure 5**. A larger pro-

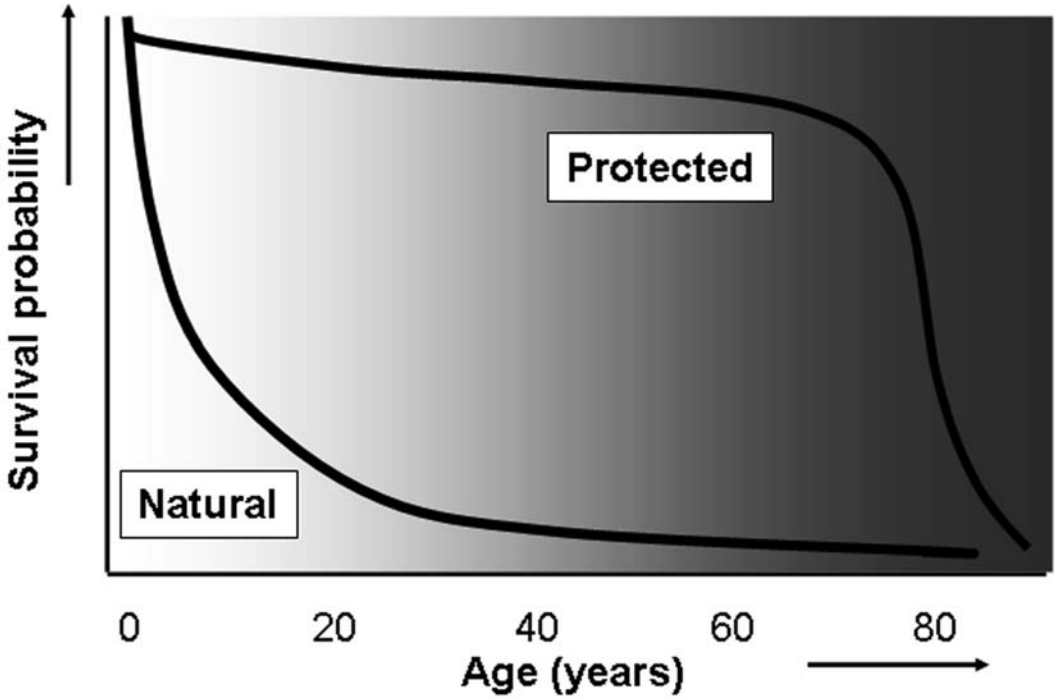

Figure 5. Survival probabilities in wild (natural) and domesticated (protected) populations. (Adapted from Kirkwood & Austad[46].)

portion of the population is thus likely to suffer and die from chronic degenerative diseases. These radical demographic changes have not taken place everywhere at the same time, leaving large parts of the world still in environmental conditions resembling our natural habitat or in a transition phase.

This brings us to what can be considered as the ultimate test of our hypothesis, that is, the inflammatory host response is the main regulator of the trade-off between maintenance of our bodies and fertility. What happens if immigrants, who were selected in order to survive under natural conditions, grow old in a protected environment? We assume that individuals who originated in an adverse environment are still under evolutionary pressure for inflammatory host responses when compared to individuals from protected environments. Quite often, immigrants to wealthy, affluent countries come from places with an adverse environmental condition where death from infection is still rampant. Thus still being selected for pro-inflammatory signalling, we expect them to suffer more from age-related diseases when they live up to postreproductive age in the protected environment to which they

have emigrated. Numerous studies have indeed reported that chronic degenerative diseases, such as atherosclerosis[57-60], diabetes[61], and risk factors, such as obesity and hypertension[61-63] are far more prevalent among African Americans compared to Caucasian Americans. Other studies line up with the hypothesis that the excess of chronic diseases in immigrants has to be explained by a genetic predisposition[64-68]. Immigrants who are more heavily selected for an inflammatory response thus should also suffer from a reduced fertility (see above). Indeed several studies found preterm deliveries and spontaneous abortions to be more common among African Americans than among Caucasians[69,70] and this finding appears to have a strong genetic explanation[71].

DISCUSSION

Organisms need to maintain their body up to reproductive age to show their reproductive success. Above we have reasoned that among other critical phenotypes man has strongly been selected for resistance to infection. As the necessary inflammatory responses come with a cost at fertility, investments in body maintenance are not maximized. This explains why humans are still susceptible to fatal infection despite fierce evolutionary selection over thousands of years. As such it provides a biological mechanism for optimizing rand K-strategies to maximize fitness under adverse conditions in our "natural habitat"[72].

Health and disease after the reproductive age can best be understood from the theory of antagonistic pleiotropy, which argues that the pro-inflammatory signalling that we have been selected for under adverse conditions negatively influences body maintenance at old age. As humans have increased their life span by improving the environment in which we live, a far greater proportion of people now reach older age and will suffer from late consequences of the inflammatory responses that were so beneficial at an early age. The costs of this selection for inflammatory responses are likely to be biggest among those who were born under conditions where death from infection was still present, but age under affluent conditions.

This line of reasoning is not only applicable to individuals but also to populations who have successfully improved their living conditions. A recent

report from the WHO found that age-specific rates of many cardiovascular diseases are currently higher among adults in sub-Saharan Africa than in industrialized countries[73]. Hence a fast transition from a natural to a protected environment leaves us with an ancient genome set for pro-inflammatory signals to be expressed in an environment where this is not a necessity and comes at a cost. The future of the developing countries is an emerging epidemic of chronic diseases[74,75] with cardiovascular diseases on top[76].

When concluding we emphasize three points. First, by no means have we wanted to suggest that inflammation is the only human phenotype that is under evolutionary selection, nor that it is the only factor that determines the occurrence of chronic degenerative diseases in old age. For instance, humans were also selected for handling a shortage of food. We are set to store as much energy as possible during periods of abundance so as to increase our survival chances during the lean season. In the sedentary lifestyle of our protected environment with a plethora of foods this has led to the epidemic of adipositas, which is nowadays one of the most threatening phenotypes from which we suffer[77].

Second, apart from evolutionary selection for specific genetic variants, it can be argued that differences in early phenotypic expression, that is, plasticity, contribute also to the risk of chronic diseases at later age. A lucid example is the idea that fetal deprivation increases risk of mortality from cardiovascular diseases in old age[78]. The principle of plasticity can also be applied to the expression of the innate immune system. Children who grew up in an environment with high infectious pressure have skewed their host response toward pro-inflammatory signalling and this may last a lifetime. Plasticity may thus contribute also to the increased risk of chronic degenerative diseases for those who moved from an adverse to an affluent environment.

Finally, man adapts genetically to his new environment. This Darwinian logic emphasizes that our population genome is on the change. In populations that have undergone a demographic transition, several birth cohorts have not been exposed to the fierce selection of resistance to infection. Instead of selective survival up to reproductive age, a period during which half of the original birth cohort may have died, under affluent conditions virtually all newborns will survive and pass their genotypes to the next generation. This includes individuals who have below average inflammatory responses

and under adverse conditions would have suffered from fatal infection. These individuals can now escape selection pressure, are reproductively successful, and may suffer less from chronic degenerative diseases as their genome encodes for less pro-inflammatory signalling. The population genome is likely to shift toward a predisposition for living healthier for longer.

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