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Evolution of senescence in humans - The rift between lifespan and healthspan

Introduction

Due to recent improvements in our food, the environment, and medicine, humans are living longer lives than ever before. Our lifespan has doubled over the past two centuries, as infection and communicable disease no longer pose a considerable threat to our species (Finch, 2010). However, human healthspan, or the time in which we are free from disease, has not demonstrated the same trend. The American population has become debilitated by a rise in chronic disease both physically and financially, sharing a paralleled increase in healthcare expenditure (Anderson & Horvath, 2004). We may be living longer, but we are not necessarily healthier. Human healthspan seems to be declining at an unprecedented rate, with the onset of this deterioration occurring sooner and sooner with each new generation.

Senescence in humans is inevitable, but its origins are unclear. A senescent state has evolved with no clear adaptive benefit and an obvious detriment to individual fitness. Four notable evolutionary hypotheses of aging have been proposed: mutation accumulation, disposable soma, DNA damage, and antagonistic pleiotropy. Mutation accumulation posits that deleterious mutations accumulate throughout an individual's life and, as a result, selection is very weak once their effects become debilitating (Medawar, 1952). The disposable soma hypothesis asserts that resources are finite in nature, and therefore the body must budget which of these resources to invest in growth, reproduction, and ultimately body maintenance and repair (Kirkwood & Rose, 1991). It has also been suggested that DNA damage increases over the course of an individual's life, and that damage through mitotic division and excessive oxidative

stress may yield a senescent state (Fagagna et al., 2003). Lastly, antagonistic pleiotropy suggests that traits conferring even a slight advantage near sexuality maturity will be selected for despite being detrimental later on in life (Williams, 1957). These hypotheses are not mutually exclusive, but the first three are insufficient in and of themselves to describe the origins of senescence.

In this review, I will argue that antagonistic pleiotropy must be considered in order to properly address the origins of senescence, selecting exclusively for traits that are advantageous early on in life even if they are injurious later on. A state of decline has become inexorable, but the novel and evolutionarily-inconsistent environment we find ourselves in today has only exacerbated the rate of this decline. An inflammatory diet, coupled with increasingly sedentary lifestyles and constant stress, highlights a mismatch between the world today and the world in which humans have evolved to endure. The current paradigm in modern medicine of suppressing these once-advantageous phenotypes through pharmaceutical intervention does nothing to address or understand the root cause of what is instigating these symptoms to arise in the first place. Our healthspan will never be as long as our lifespan without first understanding human physiology within the evolutionary context that it was selected for.

Four Hypotheses of Aging

Antagonistic Pleiotropy

Pleiotropy is ubiquitous within the biological world, meaning that a gene's effects may not be entirely harmful or beneficial, and that they need not present themselves at one single moment in an individual's life. Antagonistic pleiotropy recognizes that traits will only be weakly selected for the older an individual gets, so a trait with pleiotropic effects will best be served by delaying any disadvantages toward the latter half of life. From an adaptive perspective, species

evolve through individuals who optimize their cost to benefit ratio as close to reproductive maturity as possible (Williams, 1957). Therefore, a trait that confers a fitness advantage at puberty, but becomes crippling one year later, will still be favored and spread rampantly throughout a population.

Specific genes have been found to possess these antagonistic pleiotropic effects (Parker et al., 2020). Two distinct lines of *Drosophila melanogaster* were compared: those that were long-lived and selected for postponed reproductive senescence and those that were unselected for. RNA interference (RNAi) of fifty-seven candidate genes possessing high genetic divergence between the two illustrated that twenty-three had antagonistic pleiotropic effects on lifespan and productivity. Genes which increased lifespan decreased productivity, and genes which increased productivity decreased lifespan. Of the fifty-seven candidate genes that were analyzed, forty-nine were found to have human orthologs. This experiment illustrates that evolutionarily conserved genes do in fact possess antagonistic pleiotropic effects, but more importantly, senescence is not explained by any one gene. Senescence is orchestrated by many genes that may modulate the expression of one another and is the result of a biological tradeoff between their costs and benefits.

Two distinct evolutionary strategies have presented themselves: reproducing more at the expense of living a shorter life or reproducing less and living longer to ensure progeny are reared all the way to sexual maturity. However, this is just one example of antagonistic pleiotropy and most human studies do not include a measure of reproductive success to analyze senescence. For that reason, fitness and being disease-free are assumed to be correlated with one another. It is quite possible that many other minor adaptations are causing problems down the road, explaining the underlying mechanism differentiating a longer from a shorter healthspan.

Genome-wide association studies (GWAS) have been used to detect genetic patterns that may be contributing to certain diseases, leading to a senescent state (Rodríguez et al., 2017). Using data gathered from the NHGRI-EBI GWAS Catalog, 2,559 unique single nucleotide polymorphisms (SNPs) were associated with 120 non-communicable diseases. The researchers used a contingency table to find at what age threshold antagonistic pleiotropies related to diseases occurring in early and late stages of life (early-late) significantly differed from those occurring in the same period of life (Figure 1). Notably, a significant excess of early-late antagonistic effects were seen at the age threshold from forty to fifty years old. This age range possesses biological significance to humans, being about the age in which women enter menopause. One specific gene that was found in this study was *CDKN2A*, being associated with four antagonistic pleiotropic effects with five SNPs and five diseases. The T allele has been found to be protective against glioma, an often fatal form of cancer presenting itself early on in life, but also increases the risk of type II diabetes, glaucoma, coronary heart disease, and nasopharyngeal cancer. The adaptive benefit of being a carrier for this allele is clear, bypassing an early childhood death even if it means developing any of the other four later on in life.

It is possible that the optimum balance of costs and benefits to survive through reproductive maturity is not as intuitive as previously thought. It would seem as though a defensive strategy would be optimized to a point whereby the cost of defending one's self never exceeds the cost of the harm itself. However, frequent damaging defenses resulting in false alarms may actually be beneficial if the harm they are defending against is substantial. In other words, defense expression will continue to increase so long as this incremental investment results in less overall damage to the individual (Figure 2). Such a case is known as the "Smoke Detector Principle" (Nesse, 2001). From this perspective, the costs of a defense may be senselessly high

but have actually achieved an optimum since an error in responding to harm could be more deleterious to the individual than each defense combined. An example of this would include stress and anxiety. These sympathetic responses have ingrained our minds to flee from a source of danger at a moment's notice, but long, sustained cortisol secretion can increase blood pressure, decrease bone density, suppress immune activity, and lead to hyperglycemia (Chrousos, 2000). Each of these make a stress response appear highly maladaptive and questions why it has been conserved within our species, but that is easily answered when observing those suffering from Addison's disease. With the adrenal glands not producing enough cortisol to warrant a response, the slightest stressors may result in extreme fatigue, dizziness, and even death with such a steep drop in blood pressure.

Similarly, humans have evolved a highly inflammatory system to ward off pathogens and protect themselves from infection. This has led to the "cohort morbidity hypothesis" suggesting that survivors of early infectious disease carried a burden of higher inflammatory loads, increasing the likelihood of developing chronic disease later in life (Finch, 2010). It has been proposed that low-grade, systemic inflammation has resulted in chronic activation of both the innate and adaptive immune systems. Increased coagulation factors and serum pro-inflammatory cytokines such as IL-6, IL-15, and IL-18, would have prevented our Paleolithic ancestors from bleeding out and succumbing to infection, but could be causative factors in "inflammaging" later on in life (Franceschi et al., 2007).

The evolution of our immune system has evolved through our shift in eating patterns and an attempt to deter parasitic exploitation. Apolipoprotein E (*ApoE*) alleles, whose primary role is the metabolism of fats and the transport of cholesterol to neurons, provides a great candidate to explore these changes. A more meat-centric diet must have been accompanied by an increase in

fat consumption, making apoE a powerful tool to cope with an influx of dietary fat. *ApoE4* is considered to be the ancestral allele, owing to the presence of an arginine at amino acid 112 in the protein it encodes for, which is shared with other primates of the *Homo* genus. The other two common variants arising from *ApoE4*, *ApoE2* and *ApoE3*, substitute a cysteine for the arginine. This substitution results in loss of a domain-domain interaction, preventing these lipoproteins from associating with lipophilic pathogens.

Mice that are genetically modified to express human apoE4 exhibit an increased production of pro-inflammatory cytokines and nitric oxide compared to that of wild-type mice (Trotter et al., 2011). The same observation is seen in human carriers for *ApoE4*, with the addition of having more severe neurologic complications following trauma and an increased risk of Alzheimer's disease, cardiovascular disease, and cognitive deficits if infected with HIV relative to *ApoE3* carriers. Additionally, *ApoE2* is consistently found to be prevalent in longer-living populations, with a surprisingly large deficit of *ApoE4* carriers in older individuals of developed countries. Despite carrying a much more proinflammatory phenotype and being considered to be highly correlated with the onset of disease later in life, it is worth exploring the context in which the *ApoE4* allele may be favored to answer why it is still apparent within the population today.

Traditional hunter-gatherer societies possess a concerningly high proportion of *ApoE4* carriers within their genetic pool, yet are not met with a parallel incidence of these chronic diseases. Such populations include the Pygmies (40%), Khoisian (37%), aborigines of Malaysia (24%) and Australia (26%), Papuans (37%), and some Native Americans (28%), suggesting there is an adaptive role of being an *ApoE4* carrier within these contexts (Trotter et al., 2011). Seventy-two Brazilian shantytown children were phenotyped and followed longitudinally,

measuring childhood diarrhea and cognitive performance (Oriá et al., 2005). Those with *ApoE4* were consistently found to have lower diarrhea burdens and perform better on cognitive tests than non-carriers, even after adjusting for family income, maternal education, and breast-feeding. Here lies a rift between the benefits of eliminating parasitic infection through developing a high inflammatory immune response early in life, despite possibly being detrimental to the individual by constantly being activated. Clearly the evolution of these divergent phenotypes are context dependent and the same strategy may be adaptive in one environment but maladaptive in the next. No matter the environment an individual finds themselves in today, their physiology has evolved to maximize its cost to benefit ratio at reproductive maturity.

Mutation Accumulation

The mutation accumulation hypothesis and its implication within senescence is rooted in the observation that somatic cell division is innately imperfect (Blokzijl et al., 2016). Incorrect base pairs are substituted during DNA replication resulting in mutation. Thereby, deleterious mutations are thought to gradually accumulate throughout an individual's life due to their weak effect on fitness in later years. Medawar (1952) proposes a thought experiment to illustrate why selection acts so weakly in older individuals, even in an ageless species. Using test-tubes as an inanimate model organism, whereby ten percent are broken stochastically each month and replaced, he argues that older individuals will always be outnumbered by the younger generation. These older individuals do not deteriorate with age and are not any more prone to breaking, but they will make up less and less of the population as time transpires, simply by having more exposure to these breakage events. Even if a beneficial trait exposes itself late in life, it will be

unable to spread, simply by being outnumbered by a larger, younger population. However, this hypothesis only narrates half of our evolutionary story.

Mutation accumulation ignores the fact that beneficial mutations may also present themselves early in life, thereby impacting the direction of selection with each new variation. It assumes that aging arises strictly by cumulative damage but overlooks that one beneficial trait may be equivalent or even more damaging later on than all accumulating mutations put together. Medawar's explanation of the decline in selection with age only accentuates why genes that are advantageous early on, but detrimental later, will still be favored. Thus, an individual's genes will spread invariably throughout the population, not because the rate of mutation is alleviated, but because it only requires one single adaptive benefit during puberty to alter the composition of the next generation. That trait may have antagonistic pleiotropic effects later on in life, but the carrier of the trait will have already reproduced.

Discrete generations of *Drosophila melanogaster* were used to compare the hypotheses of mutation accumulation and antagonistic pleiotropy (Rose & Charlesworth, 1980). The researchers observed that the mean daily egg lay decreased from seventy eggs per day on the first day of the assay to only thirty eggs a day on the twenty-fifth, or last day. This significant drop in productivity throughout these individual lives suggested that a senescent state was achieved. However, looking at each female individually, it appeared that the longer living individuals were reproducing more at later ages, albeit having a lower overall reproductive output (Figure 3). In addition, the researchers found that the additive genetic variation of the population was not significantly divergent throughout a single individual's lifespan. Such observations illustrate that mutations are not gained to a considerable degree throughout short-lived organisms' lives, the mutations that are gained may have a much smaller proportional effect compared to those gained

early in life, and that an increase in fecundity later is accompanied by a decrease in fecundity earlier on. Only antagonistic pleiotropy allows us to fully understand why a shorter lifespan would be favored, and why longer lived individuals are not free from the tradeoff of sacrificing something else.

Disposable Soma

The disposable soma hypothesis contests that there is an intrinsic tradeoff between the costs and benefits of energy expenditure in growth, reproduction, and bodily maintenance and repair. The resources an individual accumulates through food acquisition is limited and hence must be budgeted toward expending energy toward fitness and repairing itself from the damage it incurs when attempting to reproduce. It is in a constant state of flux whereby investing more energy in reproductive success will lead to less investment in bodily maintenance, yielding a senescent state. Disposable soma stemmed from the “error catastrophe theory,” asserting that errors in proof-reading could be sacrificed to produce faulty proteins if it meant saving more energy to be directed toward reproductive growth and success (Gavrilov & Gavrilova, 2002).

Caloric restriction has been shown to slow the onset of aging in rodents, primates, and humans. However, a calorically restricted individual will not behave in the same manner. Using mice as a model, a mere 20% reduction in caloric intake resulted in a significantly extended lifespan relative to mice which were free to eat *ad libitum*, or as much as they pleased (Figure 4). This diet altered the body composition and size of the calorically restricted mice, but was suggested to have been met with a decreased need for calories when confined to the realms of a cage (Weindruch, 1996). Therefore, investment in maintenance and repair will not be of as great importance when compared to those in the wild. Similarly, a randomized control including forty-

eight calorically restricted humans were studied for six months. Lifespan was indirectly measured using proxies of longevity, finding that caloric restriction significantly decreased fasting insulin levels and core body temperatures, both associated with longer lifespan through superior glycemic control and a lower overall metabolic rate (L. K. Heilbronn et al., 2006).

I would argue that disposable soma is simply a specific example of antagonistic pleiotropy and not comprehensive enough to describe the origins of senescence. Its effects are most evident in a clean, controlled environment and does not acknowledge the body's investment in protecting itself through an inflammatory response. A state of autophagy achieved through caloric restriction may extend lifespan through degrading and recycling defective proteins, but it may also be modulated based on an individual's inflammatory phenotype (Jiang et al., 2019). Both IL-6 and CCL2 are integral in an inflammatory response and induce autophagy. Upon binding to their receptors, these two cytokines induce autophagy in a tumor microenvironment by polarizing macrophages to the M2 phenotype, leading to tissue remodeling and hence, destruction of cancerous cells. However, an inflammatory phenotype may increase metabolic rate and amino acid turnover by as much as 100-fold in the liver to produce these proinflammatory cytokines (Trotter et al., 2011). Autophagy is more nuanced than budgeting resources between reproduction and a longer life. Disposable soma neglects the resources that must be budgeted toward mounting an immune response, not only to maintain and repair the body, but to protect itself as well. An individual's inflammatory signature is at the root of these pleiotropic effects, and must be considered to describe the origins of senescence.

DNA Damage

Cumulative DNA damage has also been implicated as the causative agent in yielding a senescent state in later life. The most common example of this is the noticeably shortened telomere length in the DNA of senescent individuals. Telomeres are essentially caps found at the end of our chromosomes. They are repeating strings of nucleotides that are suggested to be protective against the imperfections of cell division, effectively providing a buffer at the beginning and end of our DNA to preserve protein-encoding, life-sustaining segments. These repeat sequences are added through the catalyst known as telomerase, a ribonucleoprotein that works at the 3' end of extending telomeres. The assumption is that when an individual's telomeres are depleted, this buffer no longer exists and the cell enters a permanent cell-cycle arrest (Saretzki et al., 1999).

Telomere length decreases as a function of mitotic division (Harley et al., 1990). Five strains of human fibroblasts were grown *in vitro*, and telomeres were extracted and measured through Southern blot analysis. Telomere length shortened by as much as 2kb with cumulative population doublings - half of the estimated 4kb of telomeres found within somatic cells. The distribution of ninety-two telomeres varies widely in length, so a loss of 2kb may render half our chromosomes “naked” while the other half remain fully intact. Additionally, transformation and induction of telomerase in cell culture reduces B-galactosidase staining, preserves telomere length, and retains a normal karyotype, exceeding normal lifespan by more than twenty generations and suggesting a causal role between telomere length and senescence. (Bodnar et al., 1998).

However, environmental factors have also been found to reduce telomere length, independent of cellular division. Fifty-eight pre-menopausal women rearing either a healthy

(control) or chronically-ill (caregiver) child were studied and controlled for age (Epel et al., 2004). Telomeres were obtained from peripheral blood mononuclear cells (PBMCs) and quantified through PCR, while telomerase activity was measured by the Telomerase Repeat Amplification Protocol (TRAP). An oxidative stress index was also utilized and standardized as the ratio of isoprostanes per milligram of creatinine to vitamin E. What the researchers found was that caregivers possessed higher perceived stress, shorter telomeres, reduced telomerase activity, and higher oxidative stress relative to the control.

Stress, as mentioned above, is a physiologic adaptation that has evolved to protect the body, but overstimulation may promote the early onset of age-related disease. Oxidative stress, through the production of reactive oxygen species (ROS), may play a role in the shortening of telomeres. ROS are integral to cell signaling but overproduction may yield a highly inflammatory state, replete with lipid peroxidation, DNA damage, and protein carbonylation. These cellular messengers are vital to our health and responding quickly to our external environment, but oxidative stress has dramatically increased through novel environmental stressors. Novel environmental factors such as particulate matter (Pope III & Dockery, 2006) and the overconsumption of inflammatory omega-6 fatty acids (Turpeinen et al., 1998) provide an exaggerated glimpse of the pleiotropic effects behind our evolution as humans, and how we have not yet adapted to the rapidly changing society that surrounds us today.

In summary, humans have evolved to be pro-inflammatory, hypercoagulable, and obesity-prone to stave off infection, avoid bleeding out, and survive the next famine. These traits have been optimized at an early age despite being harmful later on. The deleterious nature of these effects likely would never have been seen in our Paleolithic ancestors, succumbing to one of these three early deaths and possibly never achieving the age at which senescence presents

itself. Our new environment has allowed us to live longer, but also made it clear that our bodies are not evolved to live extended lives. Our physiology as humans has had minimal time to acclimate to our new surroundings, and our once advantageous phenotypes are slowly morphing into burdens.

Evolutionary Mismatch

Death from infection has decreased dramatically, the most calorically dense food is now the cheapest, and modern medicine has made a broken arm nothing to worry about other than the inconvenience of wearing a cast for the next couple of months. However, chronic disease in America has never been more of a problem. Obesity, as well as cardiovascular, neurodegenerative, and autoimmune disease have become endemic, so what has changed in the past centuries to make these disorders appear as a normal part of aging?

A mismatch disease is defined as a condition arising from the body being inadequately adapted to the recent and profound changes brought to us since the Industrial Revolution. (Gurven & Lieberman, 2020). I believe the majority of the nation's chronic diseases are the result of this mismatch and have their roots in both chronic inflammation and metabolic disorder. A large interventional trial known as the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) consisted of 4,833 stable atherosclerosis patients and grouped individuals into one of four categories: those who received doses of 0, 50, 150, and 300 mg of the anti-inflammatory drug, canakinumab, subcutaneously for three months (Ridker et al., 2018). Canakinumab is an anti-IL-1 β monoclonal antibody, preventing this proinflammatory cytokine from binding to its receptor and suppressing inflammation as a result. The study showed that canakinumab reduced cardiovascular events, cardiovascular mortality, and all-cause mortality by

32%, 52%, and 48%, respectively, for those that achieved an IL-1 β level below the study median. These observations suggest that an inflammatory state may be a large contributing factor to the progression of cardiovascular disease, and that inflammation may be an overlooked, but underlying theme of many diseased states.

This inflammation is not entirely genetic, but must be analyzed through an evolutionary lens in terms of what we are eating, being exposed to, and to what extent, answering whether or not our bodies are adapted to cope with all the world now has to offer. In terms of food, excessive caloric intake induces pro-inflammatory cytokines and the expression of p53 at the level of the adipocyte, resulting in insulin resistance (Minamino et al., 2009). These researchers used Ay mice with overexpression of agouti peptide, inducing over consumption and later an obese, diabetic state. The excessive caloric intake resulted in increased B-galactosidase, higher adipose tissue amounts of p53, and cyclin-dependent kinase inhibitor-1A expression, all characteristics of senescent cells and illustrating that a senescent-like state was achieved independent of age.

Inflammation may be stemming from the level of the adipocyte, but our microbiome is also immunologically active and may be modulated through dietary intervention (Tran et al., 2019). In this study, mice were fed a Western-style diet (WSD) with 60% kcal from fat for eight weeks, and given a series of antibiotics to kill off microbiota of the gut. The loss of these microorganisms led to a marked decrease in adipose inflammation, suggesting obesity to just be a proxy for metabolic disturbance and systemic inflammation. Diet, mediated through the composition of the microbiome, may contribute to many diseases of the Western world.

The food we eat is one of the greatest contributors to our overall metabolic health, and metabolic disorder, mediated through insulin resistance, seems to be at the heart of many age

related diseases. A recent study (Araújo et al., 2018) consisting of 8,721 Americans, found only 12.2% of them to be in good metabolic health. The data was obtained from the National Health and Nutrition Examination survey and viewed individual metrics within the light of waist circumference, fasting glucose and hemoglobin A1C, blood pressure, triglycerides, high-density lipoprotein cholesterol, and the absence of prescription medications. This finding suggests that many individuals, even with a normal weight, are not metabolically healthy, and that fixing metabolic health may help put a dent in our nation of chronic disease.

Currently, chronic diseases are not being viewed through an evolutionary scope and suppressing these adaptations through pharmaceutical intervention may be counterproductive. Rather than suppressing inflammation such as in CANTOS, it may be more fruitful to address what is instigating that inflammation to arise in the first place, understanding how it can be eliminated and resolved rather than just suppressed. For this reason, Serhan et al. (2002) have channeled their investigations to a form of specialized pro-resolving mediators (SPMs) known as resolvins. They investigated the biochemical pathways of these molecules and how they work to attenuate the damaging effects of inflammation rather than block them from occurring. In this study, human COX-2, an enzyme responsible for inducing inflammation (Minghetti, 2004), was overexpressed in *Sf9* insect cells. Supplementing these cells with acetylsalicylic acid (otherwise known as Aspirin), and the anti-inflammatory omega-3 fatty acid, docosahexaenoic acid (DHA), resulted in the enzymatic production of two previously unknown compounds: 17*R*-HDHA and 13*R*-HDHA, respectively. Human microglial cells were then treated with these two molecules, measuring the degree to which they were able to mediate inflammation. At nM concentrations, they found these compounds to inhibit TNF- α -induced cytokine production, as measured through IL-1 β expression (Figure 5). This was the same cytokine that was blocked from binding to its

target in the CANTOS trial, illustrating that a diet rich in DHA could potentially achieve the same effect. These observations question the current balance between omega-3 and omega-6 fatty acids that comprise the Standard American Diet, and allow us to start to comprehend the efficacy of nutrition when it comes to treating those with chronic disease.

The body needs help resolving its inflammation because it evolved in an environment with no anti-inflammatory medications. This resolving effect is seen in mice when presented with an inflammatory challenge (Guerreiro et al., 2012). One hundred and fifty adult mice were exposed to *Escherichia coli* lipopolysaccharide (LPS) that is recognized by toll-like receptor 4, resulting in systemic inflammation. The balance between proinflammatory IL-6 and anti-inflammatory IL-10 was able to predict mortality once exposed to LPS. Those possessing similar serum levels of the two interleukins fared far better than those with increased IL-6 relative to IL-10, illustrating that both pro- and anti-inflammatory pathways are crucial to survival (Figure 6).

Centenarians provide a great model to understand the archetype of longevity. These are individuals who live over the age of one hundred, and their offspring seem to demonstrate the same trend, indicating that their healthspan has some genetic basis (Vasto et al., 2006). They seem to evade certain age-related diseases, but does this come at the cost of something else? Would these individuals be more susceptible and prone to infectious diseases at a young age if they grew up in a different environment?

Franceschi et al. (2007) seem to suggest they would, however little data exists to demonstrate this trend. Instead they compiled a list of phenotypic and genetic variants that seek to explain why centenarians were able to “slip past” an early childhood death. Interestingly, one of these variants was high plasma levels of the proinflammatory interleukins: IL-6, IL-8, and IL-15. The upregulation of these three while not being met with increased expression of resolving

mediators suggests something else to be afoot, something environmental. For the most part, these individuals live in what are referred to as the Blue Zones, specific regions that house some of the oldest living individuals in the world (Buettner & Skemp, 2016). The inhabitants of these zones, which include Sardinia, Okinawa, Loma Linda, Nicoya, and Icaria, live simple lives and have retained much of the culture and traditions of their ancestors within their daily lives. These societies place a heavy emphasis on food preparation, exercise, stress reduction, and most importantly, community. Their extended lives are not met with prescriptions and are mostly absent of chronic diseases.

Living an Evolutionarily-Consistent Life

The efficacy of diet, exercise, and stress management cannot be overlooked, especially at a time when cultural evolution seems to be outpacing our own biological evolution. Many ailments within the world today are viewed as inevitable, predominantly by possessing some type of genetic predisposition. However, the Danish Twin Study found only 1% of longevity to be significantly impacted by zygosity, or the genetic fidelity between two individuals (Herskind & McGue, 1996). In this study, 2,872 pairs of twins born from 1870-1900 were tracked longitudinally until all but 0.6% had died. Age of death was obtained from various registers including the Danish Central Person Register and the Danish Cause-of-Death Center to record longevity. With such a small degree of similarity in lifespan, the authors attributed an individual's longevity to be weighted less on that individual's genes, and more on the degree of the environment those individuals found themselves living in. With this knowledge, how can we live more in accordance with the life we have evolved for?

Diet

In my view, the greatest contributor to our chronic disparity has been a shift in our dietary regime, matched with an increasingly sedentary lifestyle and novel stressors that we are now being exposed to on an everyday basis (Kaplan et al., 2000). In terms of diet, humans have been grain-consuming for only 10,000 of the 1.7 million years of our existence. Even in the era of the Paleolithic, our human ancestors would have relied largely on fruits and vegetables for their carbohydrate intake, resorting to cereal grains only in rare instances and having no means to cultivate farmland or process these grains into flour (Eaton et al., 1996). Similarly, vegetable oils are relatively new to us. Many vegetable oils, such as canola or corn oil, come from foods that are not intrinsically oily. They require not only a tremendous supply of these plant derived resources but also a tremendous amount of processing to receive a mere tablespoon worth of cooking oil. These oils are replete in omega-6 fatty acids, essential to the human diet, but have reached a proportion within our diet that is highly evolutionarily-inconsistent thanks in large part to the technologies since the Industrial Revolution.

The ratio of omega-6 to omega-3 fatty acids within the diet of early humans was about 1, but Western diets today have a ratio of around 15/1 to 16.7/1 (Simopoulos, 2002). Omega-6 fatty acids are generally regarded as proinflammatory molecules, especially when they outnumber and or are not supplemented with a comparable quantity of anti-inflammatory omega-3 fats. The principal ingredient of vegetable oils is linoleic acid, and the major omega-6 that humans are receiving in greater quantities than ever before, comprising 8%-10% of total intake in the Western world and subcutaneous adipose tissue concentrations increasing from 9.1% to 21.5% from 1959 to 2008 (Guyenet & Carlson, 2015). Linoleic acid is a polyunsaturated fat, making it a potential target for oxidation by ROS. These oxidized omega-6s can then be esterified onto cholesterol molecules and incorporated into LDL particles, producing oxidized LDL (oxLDL).

OxLDL has been shown to increase recruitment and entry of monocytes into the subendothelial layer of arteries, inducing foam cell formation, a surrogate marker for atherosclerosis.

Atherosclerotic aortas have actually been found to contain a higher proportion of cholesteryl linoleate (12.3%-20%) compared to those of healthy individuals (5.8%-9.5%) (DiNicolantonio & O'Keefe, 2018). Statin drugs, which inhibit HMG-CoA reductase, the rate-limiting enzyme of cholesterol biosynthesis, are usually prescribed for atherosclerotic patients. However, these observations suggest cholesterol to be wrongly accused for causing cardiovascular disease, and that eliminating linoleic acid from one's diet may reduce their risk for cardiovascular events.

Viewed in the light of antagonistic pleiotropy, a diet rich in linoleic acid may just be adding coals to the fire. Our evolution has selected for a highly-inflammatory phenotype, unsuitable for pathogen colonization, and to be activated at a moment's notice, but is now constantly turned on. Diets high in polyunsaturated fatty acids (PUFAs) were systematically analyzed in thirty-eight individuals aged 20-48 years old (Turpeinen et al., 1998). Subjects were placed on a baseline diet rich in saturated fat for four weeks and then transitioned to a diet high in either linoleic acid or oleic acid (omega-9 fatty acid). Urinary excretion of 8-iso-PGF_{2α} was significantly increased in the group with a diet rich in linoleic acid. 8-iso-PGF_{2α} is an isoprostane and a downstream product of non-enzymatic peroxidation of arachidonic acid in membrane phospholipids, making it one of the most common biomarkers to measure oxidative stress. The group whose diet consisted of oleic acid did not have this effect, suggesting omega-6 intake to be a greater contributor to oxidative stress than total PUFA intake. Additionally, it should be highlighted that foods rich in omega-9 oleic acid, such as olives and avocados, are more oily foods, and a tablespoon-worth of olive or avocado oil would have been much more easily obtained during our evolutionary past.

The effects of conjugated linoleic acid (CLA) supplementation was tested in a double-blind placebo-controlled trial consisting of 60 men with metabolic syndrome (Risérus Ulf et al., 2002). Participants were split into three groups receiving either *n10c12* CLA, a CLA mixture, or a placebo for twelve weeks. Those given *n10c12* CLA saw a 578% increase and a 110% in C-reactive protein (marker of inflammation) compared to the placebo group (Figure 7).

Additionally, insulin resistance was aggravated in individuals subjected to *n10c12* CLA provisions, as measured through a euglycemic hyperinsulinemic clamp, and independently predicted by changes in 8-iso-PGF_{2α} (Figure 8). Pathologic insulin resistance at the level of the adipocyte is not an inert biological process. It is now recognized that adipocytes are immunologically active, capable of secreting numerous adipokines, cytokines, and chemokines contributing to an inflammatory response that is always activated (L. Heilbronn & Campbell, 2008).

Besides increasing oxidative stress and inducing insulin resistance, what else is an excessive intake of omega-6 PUFAs doing to our bodies? Data from the Offspring Cohort from the Framingham Heart Study, including 327 Caucasian men, illustrated that both oxidative stress and insulin resistance were associated with shorter leukocyte telomere length (Demissie et al., 2006). As stated above, oxidative stress may result in shortened telomeres, either by damaging DNA itself through ROS production or by inhibiting the expression and activity of telomerase. Reconstitution of telomerase activity has been noted *in vitro* through exogenous supplementation of human telomerase RNA component (hTR) and TP2, the catalytic subunit of human telomerase (Beattie et al., 1998). Research is just beginning to scratch the surface of how to increase telomerase activity *in vivo*, and many successes have been free of pharmaceutical intervention. A study using thirty-three adults over 65 years of age had subjects supplement with omega-3

eicosapentaenoic acid (EPA), DHA, or omega-6 linoleic acid for six months (O’Callaghan et al., 2014). The authors did not see an increase in telomere lengths with omega-3 supplementation, however those supplementing with linoleic acid during this time saw the greatest reduction in telomere length, measured in whole blood by quantitative polymerase chain reaction (qPCR). It seems as though omega-3 supplementation may help attenuate telomere degradation, reemphasizing that it may be more advantageous to focus on resolving oxidative stress through SPMs rather than blocking a once adaptive response through pharmaceutical intervention.

Exercise

Our changing diet toward highly processed, linoleic acid-rich “food” has not been unaccompanied. We are now more sedentary than ever before and being exposed to novel stressors on a frequent basis. Exercise, too, has shown to retard telomere shortening even in the presence of substantial perceived stress (Puterman et al., 2010). Sixty-three healthy, post-menopausal women were assessed and quantified based on their level of stress within the month prior to study, and grouped into either “active” or “sedentary” groups based on their self-reported physical activity the next three days (increased heart rate and/or sweating). Those with higher perceived stress levels were found to have shorter telomeres, measured through qPCR. However, physical activity seemed to mitigate perceived stress in the “active” group, demonstrating longer telomeres for the same degree of stress found in those that were sedentary (Figure 9). Level of stress seems to correlate well with rate of telomere shortening, but this study suggests that exercising just enough to break a sweat or elevate a heart rate on a frequent basis may be protective and delay the onset of a senescent state.

Stress

We have many more stressors today than we did in the past, whether it be psychological or environmental. In a mindfulness-based stress reduction and eating awareness trial, forty-seven obese women were examined for telomerase activity pre- and post-intervention (Daubenmier et al., 2012). The study focused on attention to breath, thoughts, and emotions, as well as how to be more in tune with physiological cues related to hunger, satiety, and emotional triggers of eating. Over the four month period, the treatment group saw a 39% increased mean telomerase activity, as measured via TRAP using PBMCs. Being the first study to examine effects of lifestyle intervention on telomerase activity, the paper suggests reduced stress to play a role in attenuating the onset of senescence, possibly by reducing the secretion of cortisol and downregulating stress pathways.

But what about the stressors that are beyond our control? Particulate matter (PM) is a sum of all solid and liquid substances that are suspended in the air through aerosols. While most of these atmospheric particles are naturally occurring, a growing number are anthropogenic with the rise of air pollution. Acute exposure to metal-rich PM has been analyzed in humans (Dioni Laura et al., 2011). Leukocyte telomere length (LTL), as well as the mRNA expression and promoter DNA methylation of human telomerase reverse transcriptase (*hTERT*), was measured in sixty-three newly-recruited steelworkers, and again after three days of exposure to PM. Surprisingly, LTL increased significantly following the three-day exposure, but was not met with any increase in either mRNA expression or DNA methylation. A longer telomere length seems to stand in contrast to findings that steelworkers who are exposed to substantial PM have an increased incidence of cardiovascular disease (Andjelkovich et al., 1990). However, this study only measured the effects of a three-day exposure. Evolutionarily, it may have been beneficial to

increase telomere length when subjected to a stressed state, but over time this effect may wear off. While the exact mechanism of these effects remain elusive, it is crucial to view these findings in light of antagonistic pleiotropy in order to adequately understand why a short-lived increase in telomere length would have been adaptive when paralleled with such an easily-induced stress response.

Conclusion

It is apparent that the human body has not evolved to live a long life, but rather ensure survival both to and through reproductive maturity. However, the environment humans have evolved in and adapted to protect themselves from has changed dramatically. Just in the last few hundreds of years, we are eating, moving, and surviving in an ancestrally-inconsistent manner, not giving our bodies sufficient time to acclimate to their new surroundings. Despite powerful innovations made possible by modern medicine, the rift between lifespan and healthspan is becoming increasingly divided, with health beginning to decline earlier and earlier with each new generation. The adaptations that helped individuals survive the cruel, unforgiving world are still within us today and are summoned at a moment's notice, "protecting" our naive bodies from all the novel stressors that are a commonplace within society today. Simply suppressing these once-advantageous phenotypes through pharmaceutical intervention makes no attempt to address the root cause of disease or prevent it from occurring again in the future. The efficacy of diet, exercise, and stress management should not and cannot be ignored for any longer. The American population is clearly sick and in dire need of help. Maintaining lives has become the norm rather than optimizing their well-being for as long as they live. Our healthspan can only be extended by

viewing our bodies in light of the environment that shaped it, and reconstructing a life that is more consistent with our evolutionary past.

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Appendix

Figure 1. A significant excess of early-late antagonistic pleiotropies when ages 40-50 are used as a threshold to differentiate early from late diseases. The y-axis represents the $-\log_{10}(P \text{ value})$ of the chi-squared tests performed for pleiotropies of each age threshold, illustrating an age of 46 as an example and highlighting it in yellow.

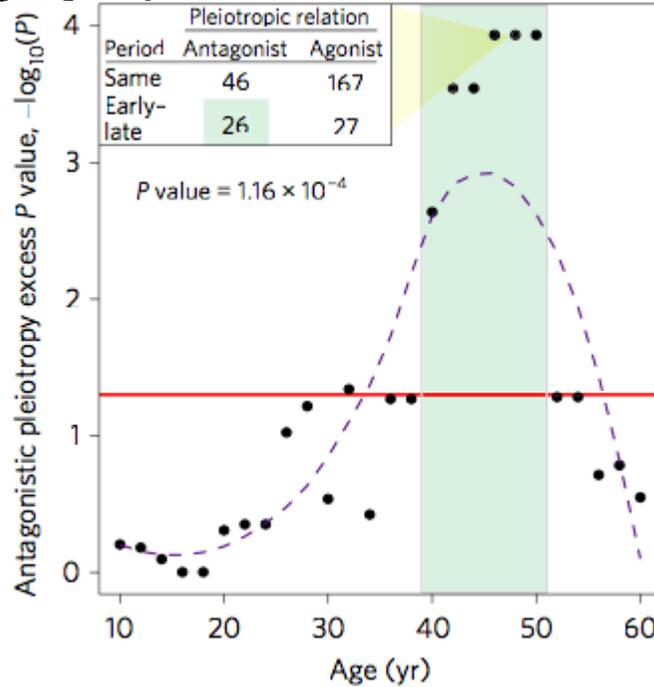


Figure 2. The optimum expression of graded defenses as predicted by the smoke detector principle. Incremental investments in defense give large decrements in harm. Abbreviations: C(H): cost of harm; C(D): cost of defense; C(Tot): total cost.

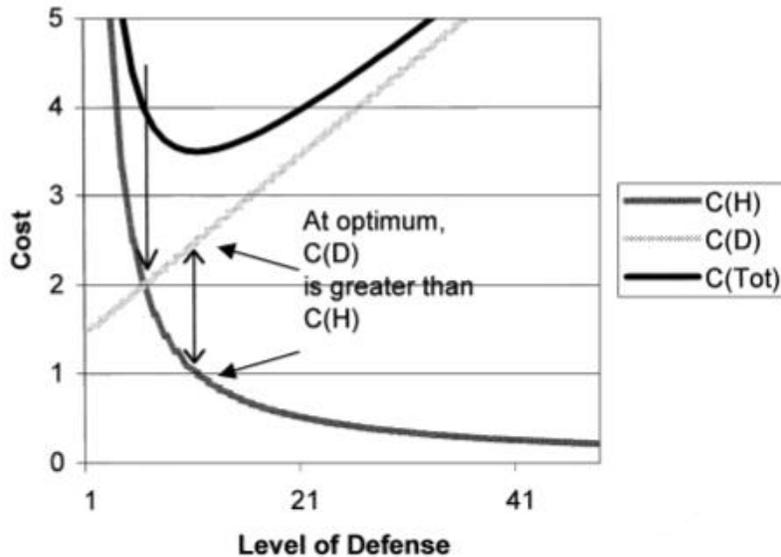


Figure 3. Difference in 24 hour mean egg counts between a population born from those reproducing at late ages, L, and a population born from those reproducing at early ages, E.

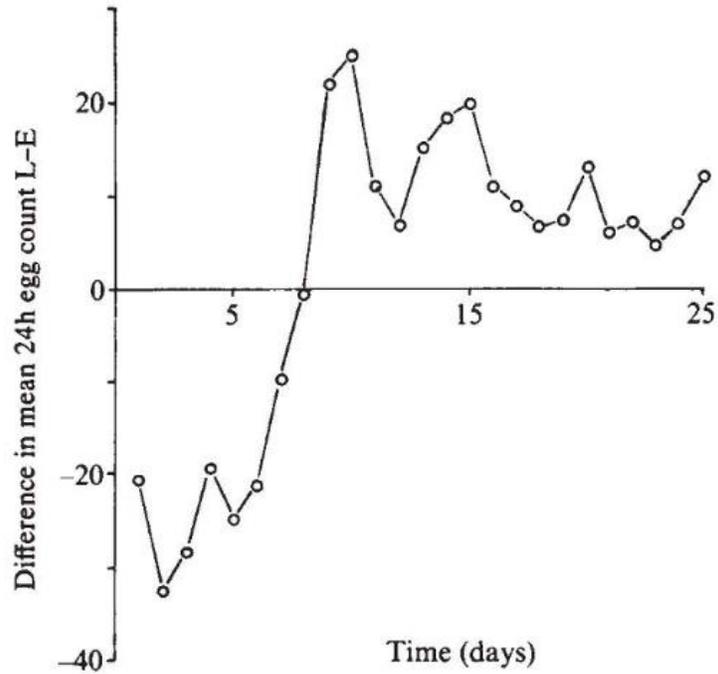


Figure 4. Effect of caloric restriction in mice on both (A) body weight and (B) survival.

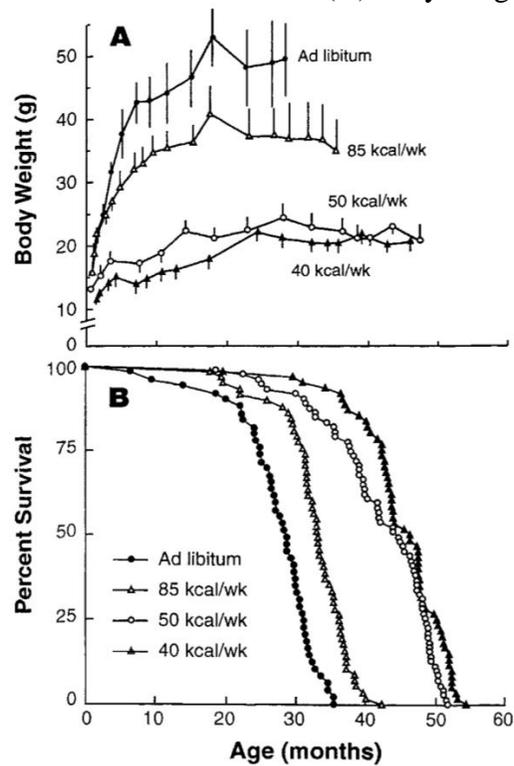


Figure 5. Inhibition of TNF- α -induced cytokine production in human microglial cells by 13-HDHA and 17-HDHA supplementation, as measured through IL-1 β expression.

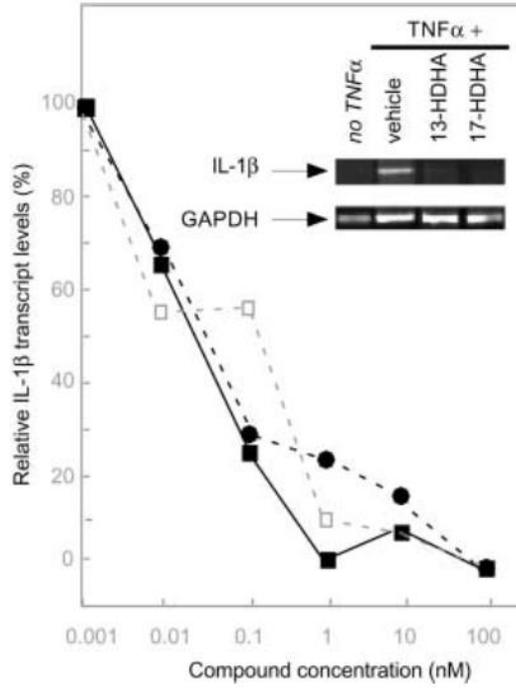


Figure 6. Adaptive landscape for serum IL-6 and IL-10 produced in mice when exposed to an LPS inflammatory challenge.

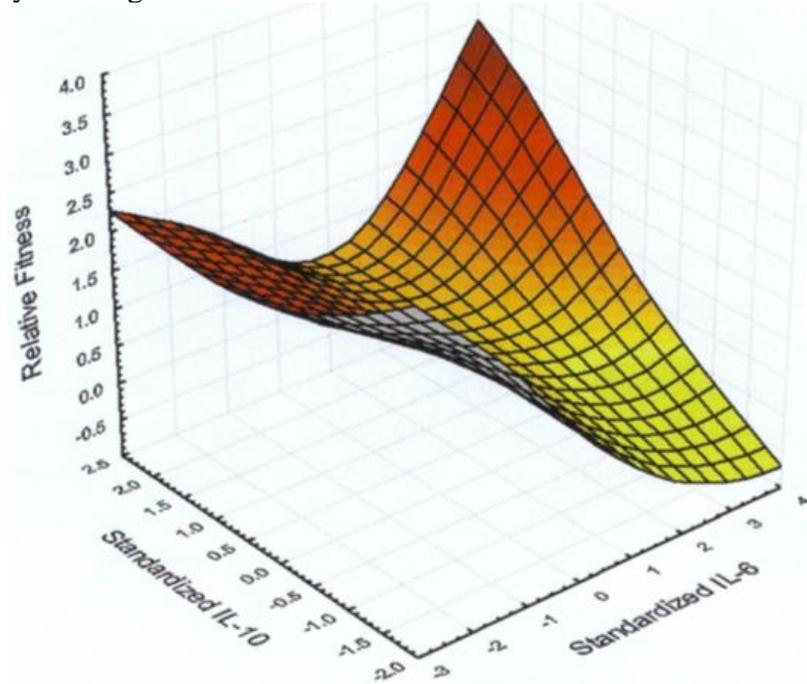


Figure 7. Changes from baseline to twelve weeks in (A) 8-iso-PGF_{2α} and (B) plasma CRP following supplementation with *t10c12* CLA, a CLA mixture, or a placebo among men with metabolic syndrome (n=56).

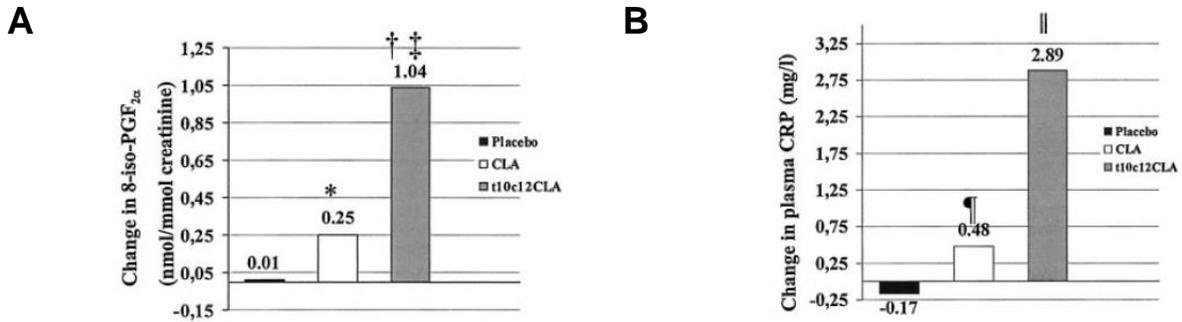


Figure 8. Correlation between insulin sensitivity and oxidative stress, as measured using 8-iso-PGF_{2α}, following a twelve week intervention of supplementation with *t10c12* CLA, a CLA mixture, or a placebo among men with metabolic syndrome (n=56).

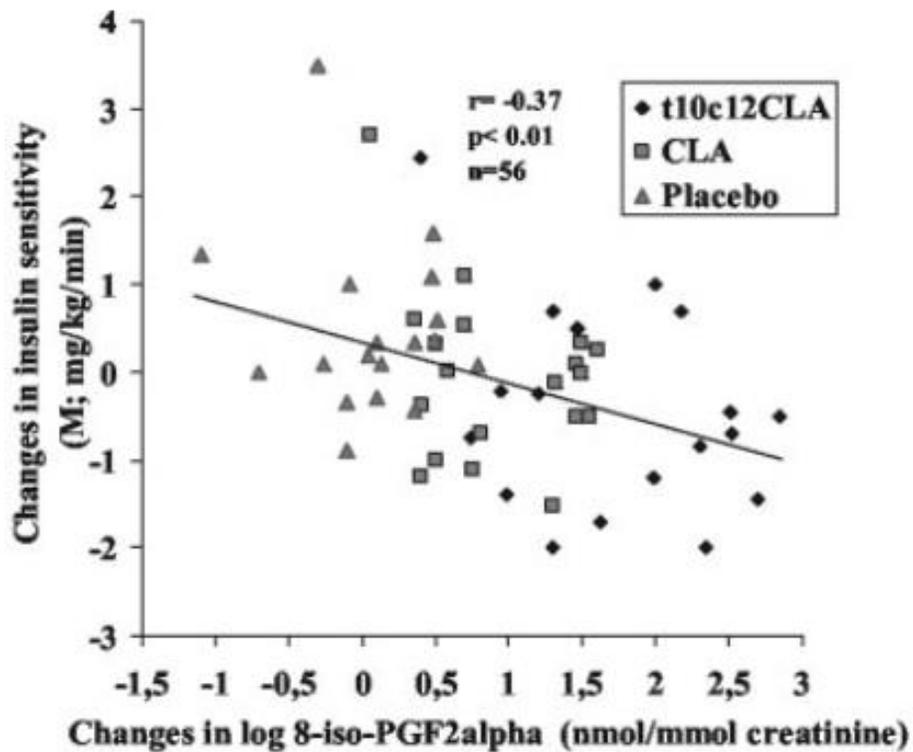


Figure 9. Relationship between perceived stress and telomere length as a function of physical activity in post-menopausal women (n=63).

