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Review Article

DISEASE MECHANISM

Evolutionary Mismatch and Chronic Psychological Stress

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Abstract *Stress and disease.* Although psychological stress is an adaptive phenotypic state necessary for survival, chronic psychological stress in developed, industrialized human populations can be characterized as an immune-altering factor associated with a wide range of allergic, autoimmune, and other inflammatory-related diseases. *Modern lifestyles, chronic disease, and psychological stress.* Here we present a synopsis of factors in industrialized populations which might increase or decrease psychological stress compared with preindustrialized populations. Several sources are identified which might increase chronic stress in postindustrialized society, although the stress induced by half of those is counterbalanced to some degree by decreasing the likelihood that individuals will be consigned to undesirable social roles that developed following the agricultural revolution. *The environment of evolutionary adaptedness and disease.* It is hypothesized that chronic stress in industrialized society might exceed that found in our environment of evolutionary adaptedness, particularly for those individuals who, for whatever reason, have not found satisfying social roles among the wide range of options available.

Keywords evolutionary medicine; stress; mismatch; modernization; industrialization; human evolution; biome depletion

1. Stress and disease

The purpose of a stress response is to marshal and conserve body resources in preparation for a crisis. Hormones associated with the stress response include (1) glucocorticoids from the adrenal cortex and (2) epinephrine (adrenaline) from the adrenal medulla. Epinephrine, typically associated with the "fight-or-flight" response of Walter Cannon's "emergency theory of adrenal function" [1], is immediately released (within seconds) following activation of the sympathetic nervous system. Glucocorticoids, associated with Hans Selye's "general adaptation syndrome" [2], are more slowly released (within minutes) following activation of the hypothalamic-pituitary-adrenal axis (corticotropin-releasing hormone [CRH] from the hypothalamus, adrenocorticotropin hormone [ACTH] from the anterior pituitary, and cortisol or corticosterone from the adrenal cortex).

An acute stress response is necessary to prepare the body to cope with crisis. Plasticity in our phenotype in response to stochastic environmental signals is hypothesized to represent a suite of complex adaptations, reaction norms produced by natural and sexual selections [3]. This phenotypic variability allows organisms to make adaptations to their current environments. Environments are always changing, and often times this phenotypic plasticity allows us to adjust accordingly.

Despite the clearly adaptive nature of the stress response, chronic psychological stress in industrialized populations today is associated with allergy [4], autoimmune disease [5], and a variety of other inflammatory diseases [6]. The connection between stress and disease can be traced back to the latter part of the 19th century, during the Industrial Revolution. During that time, when allergic diseases were increasing in prevalence and starting to gain attention, the noted physician Charles Harrison Blackley stated "if there is one temperament which, more than another, predisposes to attacks of hay-fever, it is the nervous temperament" [7, p. 163]. The association between inflammatory disease and psychological stress is now widely appreciated, with the most common example probably being the connection between stress and ulcers. As pointed out by Thoits [8], forty years of sociological stress research have shown that the damaging impact of psychological stress on human health and well-being is substantial. Here and throughout this manuscript we refer to the psychological stress response as that response associated with threat and danger, although this response does share many similarities with the "excitement" response associated with opportunity

or the anticipation of reward. Clearly, it is the chronic stress response associated with danger, not the typically acute responses to opportunity or reward, that is associated with inflammatory disease.

Constant exposure to stressors and overactivation of the stress responses can produce pathological effects ("allostatic load"), including impaired cognition, growth, reproduction, and immunity [9]. Studies in animal models show dramatic, sex-related differences between the impacts of acute versus chronic stress on immunity. For example, acute stress enhances whereas chronic stress suppresses cell-mediated immunity in rats [10]. At the same time, acute stress in addition to isolation-induced chronic stress enhances the inflammatory response of female rats only; acute stress in addition to chronic stress further suppresses immunity in male rats [11]. Chronic stress is associated with structural deficiencies in the brain [12,13], and these and other studies provide insights into the mechanisms underlying the connection between stress and immune dysfunction. Mechanisms linking stress and mast cell function, particularly important in allergic disease, have been extensively reviewed [14].

Many studies demonstrate effects of chronic stress on immune-related disease in humans [4,5,6,15,16,17,18]. For example, mothers who report significant stressors during pregnancy can produce children of low birth weight who later are more likely to develop cardiovascular problems and insulin resistance [19]. Furthermore, women abused as children are more likely to produce children with autism [20]. Stressors experienced during childhood have been associated with the subsequent onset of wheezing in children between birth and one year as well as inhibiting specific immune responses toward vaccines [5,21,22,23,24].

Chronic stress in humans is also associated with increased psychopathology and poor mental health. The increased stress of childrearing on parents can result in decreased marital quality and life satisfaction, which typically coincide with the birth of a first child [25,26,27]. Parental stress, in turn, has a direct effect on child mental health, as high parental stress and low parental social support are associated with psychiatric hospitalization of their children [28,29]. Parental depression has well-documented deleterious effects on child physical and mental health [30,31,32].

Psychosocial stressors such as abuse, neglect, and household dysfunction during childhood are associated with depression, alcoholism, attempted suicide, intimate partner violence, and other negative behaviors and poor health outcomes in adulthood [33]. Even when not in abusive households, children living with nonrelatives or single parents without kin support are ill more frequently than children living with both parents, single mothers with kin support, or grandparents [34]. The same can be said for stepchildren compared with genetic offspring living in the same households [34]. Stressors during early childhood also alter the functioning of the hypothalamic-pituitary-gonadal axis, which appears to negatively interact with mental health symptoms such that each exacerbates the other [35].

The experience of stressors in early childhood is associated with adult depression [36], as well as the onset and persistence of mood disorders, anxiety disorders, and substance use disorders in children, adolescents, and adults [37,38]. In adults, chronic stress has been shown to alter monoaminergic neural systems associated with psychopathology [39, 40], and has repeatedly been associated with negative mental health outcomes, including depression [41] and schizophrenia [42]. Our species is clearly sensitive to the effects of stressors throughout our development. So how has our exposure to many of these stressors changed over time?

2. The environment of evolutionary adaptedness and disease

The environment of evolutionary adaptedness [43] represents to some scholars the ancestral environment and conditions under which an adaptation has evolved. Notwithstanding the arguments for the correct definition of an adaptation, or when in time all of our different traits coevolved (as well as which ones are ancestral versus derived), the general idea to follow is that these past environments were probably very different from those experienced by most humans today. Our own species, anatomically modern *Homo sapiens*, appears to have evolved approximately 200,000 years before present [44]. It is unlikely that a significant proportion of our genotype has changed since then, but our lifestyles have [45]. Examining the potential consequences of the incongruities between some human lifestyles and environments today from the conditions under which we originally evolved is growing in popularity by practitioners and advocates of evolutionary (or Darwinian) medicine [46]. "Evolutionary mismatch" is the term typically applied to the negative consequences of the incompatibilities between modern lifestyles/environments and the conditions under which traits originally evolved. This explanation implies both spatial and temporal misalignment and can be applied to explain the origins of some physical and psychological disorders today [47]. As a species, most of us have experienced accelerated cultural changes that have arguably outpaced our physical and mental capacities to have a healthy lifestyle in many modern environments. For a vast majority of our evolutionary history, we had a hunter-gatherer lifestyle, and a discordance now exists, with many of our behaviors/traits that were advantageous no longer serving the adaptive purpose for which they originally evolved. This evolutionary paradigm offers an explanatory tool for a number of medical conditions today, and may explain the role of chronic psychological stress in many modern diseases.

Table 1: Some factors in developed populations leading to INCREASED stress.

Increased incidence of chronic disease due to factors such as biome depletion, inflammatory diets, and vitamin D deficiency that can be attributed to evolutionary mismatches
Less exercise to relieve stress
Overloaded schedules
Automobile accidents
Commutes
Disruption of circadian rhythm
Unrealistic personal expectations due to media exposure
Frequent exposure to violence, death, and other stress-inducing issues through the media
Frequent superficial social interactions
Inefficient bureaucracies
Vocational uncertainty
Educational system not suited to all individuals
Social pressure to climb the ladder of success (the Peter Principle)
Number of options exceeds evolved ability to decide
Loss of self-identity and self-worth in some individuals due to changes in social rules
Decreased security due to changing social rules and loss of nuclear family
Increased difficulty in child rearing due to loss of nuclear family
Decreased sense of security due to decreased influence of religion
More time to contemplate dissatisfaction

Table 2: Some factors in developed populations leading to DECREASED stress.

More options, freeing some people from roles for which they are unsuited[a]
Decreased sense of fear due to less influence of religion
More time for recreation, entertainment, and methods of stress reduction such as yoga, meditation, and biofeedback
Ability to prevent, cure or treat many diseases through modern medicine[b]
Institutionalized emergency services, insurance, and social welfare improves security[b]
Predation eliminated[b]
Less concern about difficulty in finding food and water[b]
Less concern about effects of unpredictable and harsh natural phenomena (drought, floods, pestilence) on daily life[b]

[a]Factors in developed populations which lead to reduced stress relative the agrarian societies and other hierarchal societies, but not relative to the hunter-gatherer societies. "More options, freeing some people from roles for which they are unsuited" in particular refers to the effect of social freedoms in potentially allowing individuals to avoid cultural roles for which they feel unsuited. Importantly, this effect of modern, social freedom alleviates sources of stress that emerged during the agricultural revolution, not sources of stress that would have been present in hunter-gatherer societies. (i.e., relative to the egalitarian hunter-gatherer societies, modern social freedoms afford no obvious advantages in terms of stress reduction.)

[b]Factors in modern society which potentially lead to reduced stress relative to hunter-gatherer societies.

3. The hunter-gatherer lifestyle and psychological stress

The hunger-gatherer lifestyle, unlike the agricultural way of life that followed, apparently depended on intense cooperation and sharing, backed up by a strong egalitarian (non-hierarchical) ethos [48]. While certainly still experiencing some acute and chronic physical and social stressors, those living in such an environment absolutely did not experience many of the factors in modern industrialized societies that create chronic psychological stress (Table 1). Social pressures were exerted in hunter-gatherer societies to squelch deviant behavior (first teasing and then, if necessary, shunning), but use of this pressure was rare since adherence to the social norm was necessary for survival [49]. Although hunter-gatherers likely had different levels of social stress than in more developed human populations, they dealt with a variety of life-threatening factors. Predation, harsh natural elements (extreme temperatures and storms), and sometimes difficulty in obtaining food and water, all plagued hunter-gatherers. However, the stress induced by many of these factors could have been offset or relieved by strenuous physical activity, which alters physiological and neurochemical responses to stress and is discussed in greater detail below.

4. Agrarian lifestyles and psychological stress

During the agricultural revolution, the cooperative, egalitarian hunter-gatherer lifestyle rapidly gave rise to hierarchal agrarian societies. Indeed, even a brief contact between hunter-gatherer societies and other populations can cause substantial social changes in the hunter-gatherer lifestyle [50]. The agricultural revolution resulted in the widespread appearance of many social roles (e.g., slave, prostitute, soldier, criminal, serf, etc.; [51]) that can be considered extremely stressful. Stress-inducing issues regarding oppression of women, particular social classes, and minorities emerged. Additional chronic stress emerged as a result of pressure to maintain or improve social status and infrastructure. Furthermore, the higher population densities made possible by agrarian society profoundly increased the impact of infectious disease and parasitism on the population, thus inducing further chronic stress. At the same time, problems with life-threatening factors that affected hunter-gatherers, including predation, harsh natural elements (extreme temperatures and storms), and difficulty in obtaining food and water, were still present in many cases. Thus, the agricultural revolution was a key element leading to chronic, psychological stress. It is upon this background that the modern lifestyles of developed and developing populations are built, although our genes and our ability to cope with stress have their foundation in the hunter-gatherer lifeway.

5. Modern lifestyles, chronic disease, and psychological stress

Modern industrialization has tremendously changed the way we interact with our physical and social environments. Tables 1 and 2 present a diverse list of factors associated

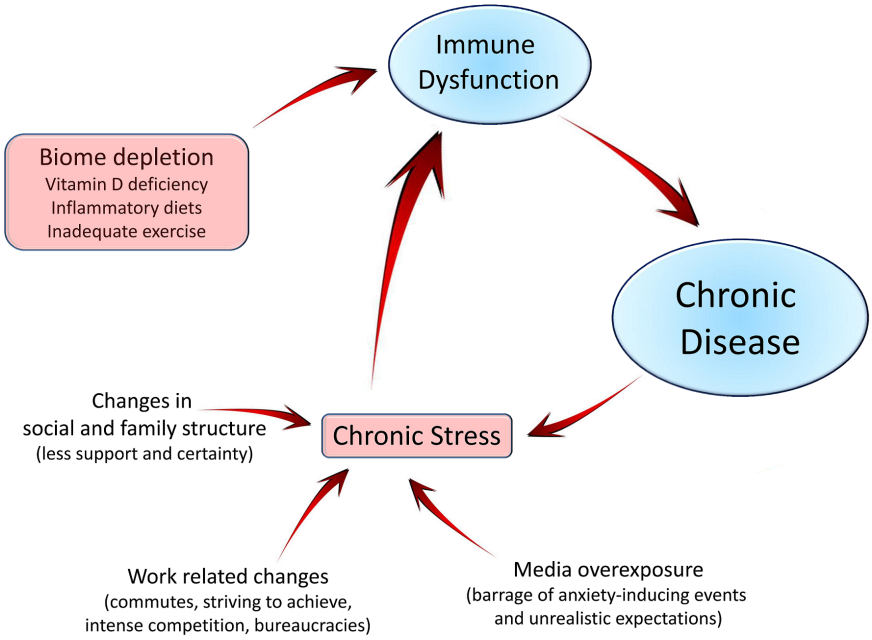

Figure 1: Schematic diagram showing (a) factors in modern, industrialized society that lead to chronic stress, (b) how chronic stress in addition to other evolutionary mismatches (e.g., biome depletion) induce immune dysfunction and chronic disease, and (c) how chronic disease and chronic stress form key components of a vicious cycle. In this diagram, "changes" refer to changes implemented since the agricultural revolution. Factors in developed populations that induce chronic stress are listed in groups according to their associations with particular cultural factors, although other groupings are certainly reasonable. For a more detailed list of factors inducing chronic stress, see Tables 1 and 2.

with modern lifestyles that either increase or decrease psychological stress. High on the list of factors that increase stress is chronic disease. The effect of these diseases on stress should not be underestimated. For example, severe food allergies in children can cause significant psychological stress for parents [52], and the physiological effects of stress on mothers with children having autism resemble effects seen in other groups experiencing chronic stress, including combat soldiers, Holocaust survivors, and individuals suffering from PTSD [53]. In this section, four major factors leading to chronic disease are examined (biome depletion, inflammatory diets, lack of exercise, and vitamin D deficiency), and all are the result of evolutionary mismatches with our current environment. Whether or not a fifth factor, chronic psychological stress, is an evolutionary mismatch is the underlying focus of this paper. However, chronic psychological stress does interact with the evolutionary mismatches described below, exacerbating disease in industrialized society (Figure 1).

5.1. Biome depletion

One evolutionary mismatch that affects many of us today is the loss of keystone species, or "old friends," from the ecosystem of the human body (the "human biome"). This "biome depletion" is probably the single most influential evolutionary mismatch leading to chronic immune disease in industrialized societies [54,55,56]. Depletion or alteration of various species from the human biome is due to modern sanitation, water treatment, modern storage and refrigeration, and many other factors that include widespread use of antibiotics and replacement of breast milk with infant formulas. A large body of evidence indicates that the removal of species from the human biome over the course of several decades in modern industrialized populations underpins pandemics of chronic immune-related conditions. These pandemics include allergies, autoimmune diseases, and a range of inflammation-associated cognitive disorders, from autism to migraine headaches [57]. In this manner, practices of industrialized populations aimed at reducing infectious disease have apparently created the single most potent element destabilizing the immune system in hundreds of millions of humans, resulting in a wide range of chronic inflammatory diseases.

Biome depletion may also be linked with a number of psychological conditions, including autism, depression, and schizophrenia. For example, gut bacterial composition, as influenced by hygiene, diet, antibiotics, and other factors, likely plays some important role in the manifestation of these mental illnesses, probably through metabolic and immunological mechanisms [58]. There is increasing evidence that many mental illnesses may derive from early neuroinflammatory events and may therefore be a result

of the same factors that lead to allergy and autoimmunity (e.g., [59,60]). Given that autism and schizophrenia each affect about 1% of industrialized populations and lifetime depression affects 16% of the population [61], the impact of these and other hyperimmune-associated diseases on human health and quality of life is potentially one of the greatest challenges ever faced by medicine.

5.2. Inflammatory diets

Biome depletion is not the only evolutionary mismatch to cause chronic disease. With such a large, energetically expensive brain relative to body size [62], anatomically modern *Homo sapiens* and our hominin ancestors have been characterized as being omnivorous, with a diet including meat and other nutrient-dense foods requiring extraction and processing [63]. This dietary flexibility was important for obtaining enough calories and balanced nutrients. During the Paleolithic Revolution, the use of tools to obtain foods from plants or animals that are underground or otherwise protected by natural defenses was likely widespread [64]. The end of the Pleistocene Epoch and the beginning of the Holocene Epoch were marked by a glacial retreat and warming trend. The Neolithic Revolution was marked by increases in population size and sedentism. The beginnings of livestock domestication and widespread plant cultivation also correspond with this period, sometime around 11,000 years ago [65].

The "nutritional transition" [66] was characterized by reduced dietary diversity and has had huge consequences for human health, particularly with the eventual globalization of processed foodstuffs [67]. Changes in food production resulted in changes in consumption patterns. Industrialized populations obviously consume much more salt, sugar, and fat than did our hominin ancestors. These ancestors likely consumed a more balanced diet with much less saturated fat, more fruits, vegetables, protein and fiber, and much less grain [68,69]. Today, overnutrition, perhaps more appropriately labeled "misnutrition," contributes to a number of chronic disorders like obesity, diabetes, cancer, cardiovascular disease, and associated morbidities ("diseases of affluence"). It is as if many food products today produce a supernormal stimulus, eliciting a response much greater than for which sugar, salt, and fat originally evolved [70]. Modern human health is now dependent on a certain amount of dietary restraint.

5.3. Lack of exercise

Intensive physical activity is also no longer required by most members of industrialized populations to obtain adequate nutrition. Today, physical inactivity contributes a significant amount of disability-adjusted life-years to the global burden of disease [71]. This must have been less of a problem in our evolutionary past, which was characterized by physical exertion to procure food prior to the development of a sedentary lifestyle. Such physical activity would contribute to increased aerobic capacity, muscle strength, and skeletal robusticity [45]. Exercise also clearly protects against depression and anxiety [72,73,74,75,76,77]. In fact, exercise has been shown to be as effective as cognitive behavioral therapies and antidepressant medication [76].

5.4. Vitamin D deficiency

Spending less time outdoors has clear consequences. For some, artificial lighting can have significant mental health effects [78]. Decreased exposure to ultraviolet radiation, due mostly to an indoor working environment, reduces production of vitamin D. This deficiency has become epidemic in many industrialized populations, with about a quarter of us being deficient [79]. It is clear that a wide range of immune-related diseases, including allergies and a variety of autoimmune disorders, are associated with low vitamin D levels [80]. Such deficiency is also associated with several mental health disorders, including depression [81]. Obtaining proper nutrition, including vitamin D, is particularly important for pregnant and lactating women [82], with health consequences for both mother and offspring.

6. Changes in choices, uncertainty, and chronic psychological stress

The number of daily choices in modern life vastly exceeds that encountered by our hunter-gatherer ancestors and by most of our agrarian ancestors. People today can choose from literally thousands of items for breakfast, whereas our hunter-gatherer ancestors had a small selection limited by season and availability. And the number of choices modern humans face obviously extends beyond food and clothing selections. Our species evolved under conditions where options for a vocation and for other cultural/social roles (e.g., family and gender roles, community leadership roles) were generally very limited, and where such societal roles were necessary for survival of the group. Industrialized populations have seen a profound expansion of the choices available to many individuals for vocational and family roles. This freedom of choice involves considering a multitude of factors that probably exceed the limited number of factors (four to nine) that the human brain has evolved to consider simultaneously [83,84]. Thus, not only is the choice of vocational and family roles relatively recent to the human condition, but also the overwhelming manner in which the choice is presented may be incompatible with our cognitive capacities. At the same time, the availability of choices in most industrialized populations probably reduces the number of individuals who are relegated to vocational or family roles (e.g., soldier or father) for which they are personally not suited (Table 2). It is important to note that highly undesirable (e.g., stressful) vocational roles and the stress associated with those roles were probably not present prior to the agricultural revolution.

Once the vocational role has been decided, another source of stress in industrialized populations has been the rise of bureaucracies and middle management. This component of daily work has left many individuals with daily job tasks that do not require physical activity, have tight timelines, are generally inefficient, counterproductive, and fail to provide personal satisfaction [85]. This stands in profound contrast to work in preindustrial populations, where most tasks were aimed directly at providing food and shelter, childrearing, or other necessary goals.

Unclear societal expectations, particularly for adolescents who may look physically mature but lack the cognitive social skills to enter adulthood, are also problematic. The loss of ceremony as a sign of adulthood, and a general blurring of the lines between childhood and adulthood, have created substantial social uncertainties in many cultures [86, 87]. This uncertainty regarding societal roles has created chronic stress as individuals wrestle with basic questions of self-worth that did not confront our preindustrial ancestors: How does my effort contribute to my group? What is my importance? Why am I needed? Acceptable answers to these questions are important for psychological well-being, and inadequate answers to these questions may lead to a variety of psychological problems [88]. The differences in this regard cannot be underestimated. When a hunter-gatherer matures to a particular age or level of ability, their role in life and their sense of self-worth are determined by default: They hunt and gather and care for children as does any member of their small group of individuals. In profound contrast, modern humans are often faced with daunting tasks when attempting to find rewarding work and eventually a career after completing school.

The transition from childhood to adulthood has changed significantly. While the delay of adult responsibilities could be considered a luxury of many societies, problems establishing age-typical autonomy are predictive of depression among adolescents [89]. Youth have also lost meaningful roles that contribute to the survival of the group, and lack of participation in meaningful societal roles and loss of adult-to-child mentorship in adolescents may contribute to increased stress and societal alienation manifested through mental health symptoms and delinquent behaviors [90]. Interventions that target these relationships and identification of meaningful societal roles have shown to decrease deleterious behaviors such as school dropout and teen pregnancy [91]. Additional research on these interventions and direct indices of adolescent stress could help clarify associations between social relationships in adolescence and stress.

Loss of meaningful societal roles may be attributed in part to the development of educational systems that separate children from parents during a large portion of the day during primary and secondary education, and often encourage if not demand relocation during advanced education (undergraduate and postgraduate work). Similarly, career pathways often lead offspring to vocations that do not require mentorship from parents or extended family members and that also require relocation, often on a long-term basis. Thus, vast geographic dispersal of family members is now a common phenomenon. Such relocation is in conflict with a fundamental drive that has evolved as a means of self-preservation: maintenance of the extended family and community bonds. It is expected that this phenomenon may indeed result in increased chronic stress, especially as offspring attempt to raise children without the benefit of extended family with experience in child rearing.

7. Modern social life and chronic psychological stress

Familial and community social support are critical for buffering against life's stressful events. For example, women with higher levels of family support are more resistant to the negative health effects of life stress [92], and family support moderates the effects of daily stress on health and mood for married couples [93]. The nuclear and extended families have certainly played important roles throughout our evolutionary history. For most of this history, however, people had social interactions with likely many fewer people than those experienced by people living in urbanized areas today, as well as for those who have access to social media websites. Dunbar [94] estimates the average number of significant interaction partners (adult, stable relationships) that humans are capable of maintaining is limited by our cognitive ability to approximately 150. However, modern humans are surrounded by more strangers today than we were many thousands of years ago, and are thus forced to engage in far more social interactions than our cognitive ability allows. Of course, no singular value can accurately describe complex human social interactions, as there are stark differences in social personalities as well as differences in relationship qualities. However, the end result of these changes is that we now have more social interactions, well beyond what we are likely capable of processing and maintaining, with less time for individual interactions and fewer social interactions with immediate family members.

Technological advances now allow us to remain connected to a tremendous number of people across far distances. The use and overuse of social media may result in anxiety due to differential self-presentation to various social groups, such as friends, family members, and employers on Facebook [95], and the associated stress might even result in increased risk of upper respiratory tract infections [96]. While some researchers suggest that social media could result in increased self-esteem and self-awareness [97, 98], online social networking may contribute to body dysmorphia and other traits associated with eating disorders

by increasing exposure to idealized images [99]. This is consistent with other research indicating that media presentations of perceived and often narrowly defined standards of beauty may play a role in the development of eating disorders [100, 101]. Instantaneous comparisons with the most beautiful and talented people on the planet have moved measures of social success, whether in finances or appearance, outside of the immediate social circle with the potential to be defined by unrealistic goals.

Given such a barrage of information in the face of decreased social support, it is no wonder that people turn to a variety of outlets to ease frustration and stress. A propensity for drug use and addiction [102], as well as the development of other behavior pathologies like addictive gambling [103], may result. Modern humans are particularly vulnerable to abuse of psychoactive drugs because we have developed the technology to produce artificial substances that mimic the activation of neural mechanisms involved in regulating feelings of pleasure and other necessary emotions [102, 104]. We have been programmed by natural selection to pursue behaviors that produce such chemical incentives. Reward-seeking behaviors that evolved in times of scarcity are now being coopted by molecules (including ethanol and tobacco) that hijack neurotransmitter levels, leading to self-destructive behaviors. Such drugs are readily available in forms, concentrations, and delivery systems that are all too potent.

8. What should we be doing?

We contend that levels of stress in most modern industrialized populations are quantitatively or qualitatively different from those in our early evolutionary past, and that evolutionary mismatch is to blame for many of these stressors today. Psychological stress can be viewed much the same as the genetic factors associated with immune disease: an evolutionarily ancient condition that becomes pathological as a result of manifestation in a modern industrialized environment. The levels and type of psychological stress in modern industrialized populations also function as triggers that, like ragweed pollen and wheat gluten, have long been with humanity but are now joined by a combination of several evolutionary mismatches that cause disease. This includes biome depletion and subsequent immune hypersensitivity with accompanying allergic and autoimmune diseases.

No one claims that our ancestors did not experience psychosocial stressors, or that modern hunter-gatherer populations do not also experience stress. Furthermore, most industrialized populations have now been buffered from a variety of stressors (Table 2), including many infectious diseases and death by predation or (depending on socioeconomic and political factors) other violent acts (with automobile accidents being among notable exceptions). Some may even experience too much reduction in social stressors, so much so that they lack motivation to achieve personal goals and contribute to society, or so that they develop socially aberrant behaviors. The capacity to experience changes in our emotional state is an adaptation to conserve and allocate resources for different opportunities [105], and some anxiety is useful for removing oneself from dangerous situations [106]. Studies of temperament and personality have identified "sensation-seeking" or "reward-seeking" individuals with lower levels of anxiety compared to most others, who exhibit a higher propensity for seeking novelty and excitement (e.g., [107]). Sensation-seeking behaviors are encompassed in normal personality traits and, in and of themselves, are not problematic. However, these traits are highly associated with problematic behaviors, including antisocial behaviors in children and adults [108] and substance abuse [109]. Personality characteristics that may have provided an evolutionary advantage before (e.g., low anxiety, willingness to take on risk and novel situations) may become problematic now.

It would be inappropriate to make any judgment regarding the suitability of a hunter-gatherer lifestyle versus life as a business executive. Nevertheless, evaluating the evolutionary mismatches that underpin diseases has the potential to promote improved health and well-being through changes in medical and psychological diagnosis and treatment. This view does not necessarily encourage a return to our environment of evolutionary adaptedness. Indeed, we have reached a point of no return for many factors, and alternatives must be considered. For example, babies probably slept between parents in our ancestral environment [110], and this may be associated with reduced stress compared to being placed in a crib. However, such sleeping arrangements today are potentially associated with an almost 30-fold increased risk of sudden infant death syndrome (SIDS) for infants less than eleven weeks old [111], probably due to aberrant inflammatory reactions [112] that are prevalent in modern populations. As another example, we know that elimination of large swaths of the biome in many people has contributed to the widespread development of stress-inducing allergies and autoimmune diseases, but no one recommends that we return to a lifestyle filled with infectious diseases so as to compensate for immunopathologies. Rather, for example, the development and use of "domesticated helminths" may be a solution [57]. Similarly, no medical professional would suggest introducing large, free-roaming predators to urban areas to facilitate human exercise, but most if not all professionals would strongly support regular exercise.

To avert the negative effects of chronic stress in modern industrialized populations, regular physical exercise is almost certainly the most important consideration. Indeed, the addition of physical exercise is known to ameliorate the effects of chronic stress, and was probably the key factor that attenuated the effects of chronic psychological stress

in hunter-gatherer populations. Furthermore, awareness of the factors that cause chronic stress (Table 1) and avoidance of these factors (e.g., by reducing the amount of exposure to stress inducing news media) or resolution of these factors (e.g., by reducing the number of commitments in an overburdened schedule) are effective stress-reducing strategies. Chronic stress reduction for modern humans can also include mindfulness training and counseling/coaching to promote adaptive cognitive and emotional strategies (e.g., reappraisal of dangers as opportunities for self-growth, and finding personal strengths in the face of anxiety-inducing events), two approaches which act synergistically [113]. Furthermore, massage therapy [114] and acupuncture [115] are known to be effective stress mediators. In summary, there is no shortage of approaches to stress reduction and stress management for modern industrialized populations. While a wide range of approaches to stress management have been implemented for a range of mental health disorders, substance abuse, and chronic pain [116, 117, 118], a shift in the health care and health policy in industrialized populations is desperately needed for the purpose of prevention. Awareness of chronic stress and prophylactic use of preventive measures has the potential to slow the increasing dependence on psychotropic medications with their unwanted side effects, particularly those that contribute to chronic metabolic conditions. This preventative approach is critical, since addressing fundamental evolutionary mismatches is far more effective than attempting to treat the diseases resulting from those mismatches using modern medical approaches. By analogy, placing the proverbial fish-out-of-water in a suitable environment is much more likely to lead to a healthy fish than is attempting to stabilize that fish with chemicals (pharmaceuticals) outside of the water.

We will not argue the pros or cons of particular cultural values or practices. We do recognize, however, that in everyone the nervous, endocrine, and immune systems are intimately interconnected [119, 120, 121], and changes in exposure to psychological stressors will therefore alter not just the nervous system, but also the endocrine and immune systems as well. Although this assessment implicates evolutionary mismatches as a source of increased chronic stress, future studies might be envisioned to evaluate levels of stress in preindustrial societies (e.g., remaining hunter-gatherer, pastoral, and basic horticultural populations undergoing market integration now) and provide a more direct assessment of this issue. Although such studies may be difficult to perform, we have known for several decades that animals removed from their natural environment can rapidly develop significant psychological disturbances [122]. Thus, it seems prudent to be more sensitive to the differences between today's environment and the environment of evolutionary adaptedness for our own species.

Conflict of interest The authors declare that they have no conflict of interest.

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