The multiple faces of the human immune system
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 2. Physical inactivity


Physical Activity Protects the Human Brain against Metabolic Stress Induced by a Postprandial and Chronic Inflammation

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Abstract

In recent years, it has become clear that chronic systemic low-grade inflammation is at the root of many, if not all, typically Western diseases associated with the metabolic syndrome. While much focus has been given to sedentary lifestyle as a cause of chronic inflammation, it is less often appreciated that chronic inflammation may also promote a sedentary lifestyle, which in turn causes chronic inflammation. Given that even minor increases in chronic inflammation reduce brain volume in otherwise healthy individuals, the bidirectional relationship between inflammation and sedentary behaviour may explain why humans have lost brain volume in the last 30,000 years and also intelligence in the last 30 years. We review evidence that lack of physical activity induces chronic low-grade inflammation and, consequently, an energy conflict between the selfish immune system and the selfish brain.

Although the notion that increased physical activity would improve health in the modern world is widespread, here we provide a novel perspective on this truism by providing evidence that recovery of normal human behaviour, such as spontaneous physical activity, would calm proinflammatory activity, thereby allocating more energy to the brain and other organs, and by doing so would improve human health.
1. **Introduction**

Chronic inflammatory diseases are a major cause of morbidity and impaired work and social functioning and are responsible for 35 million to 52 million annual deaths worldwide (WHO 2014) [1]. A state of low-grade inflammation might be considered the “cause of causes” for these deadly and disparate conditions. In contrast to inflammatory patterns observed in hunter-gatherer groups living more in accord with lifestyles that were prototypical across human evolution and in which inflammatory responses are brisk and time limited (i.e., resolving within a maximum of 42 days), in the modern world chronic proinflammatory activity can last for weeks, months, or even years [2]. Many of the inflammatory diseases that plague modern societies were uncommon until some 200 years ago [3] but are nowadays increasingly prevalent. However, treatment is still in its infancy [4], and interventions addressing the genuine etiologies of the diseases have typically been less than fully satisfactory [5].

Although the abnormalities that promote allergy, asthma, autoimmunity, and othermore systemic inflammatory states, such as cardiovascular disease, are usually characterized in terms of their immune effects, it is less appreciated that the underlying activation of both innate and adaptive immune inflammatory pathways has costly consequences in terms of resource use of energy, proteins, and minerals such as calcium [6] and magnesium [7–9]. In addition, chronic activation of the immune system produces a constant flux of energy and blood to the immune system itself, which leads to metabolic stress on other organs and, in certain circumstances, also the brain. Stress on the brain is unexpected in light of the brain’s selfish character and humans’ high encephalization quotient, which is the highest of all mammals and provides evidence of how evolution prioritized energy allocation to the human brain [10].

Thus, as we discuss in this paper, these metabolic and nutrient imbalances have wide ranging effects on health-relevant physiological functioning that go beyond the straightforward costs of immune activation per se. One of the major risk factors for chronic low-grade activity of the immune system is frequent and abundant food intake. Postprandial inflammation can put a high burden on energy availability for the whole body, including the brain, as shown by the typical “post-lunch dip” in energy and mental activity observed after high-fat and high-glycemic load meals [11]. Postprandial inflammation increases with meal size, meal frequency, and consumption of foul food, and these factors reduce brain growth in mammals, illustrating the metabolic conflict between the immune system and the brain [12].

Our ancestors experienced rapid and consistent brain growth for 2.5 million years, despite the likelihood that they frequently consumed spoiled food in the absence of food preservation
technology [13]. This pattern of rapid and sustained brain growth despite consumptive patterns known to activate postprandial inflammation suggests that other mechanisms inhibited chronic inflammation—and by extension also attenuated postprandial immune activation. While a number of factors may have contributed to this inhibition, in this review we will focus on evidence suggesting that preprandial physical activity attenuates postprandial inflammatory activity while simultaneously protecting from infection via the induction of immunoglobulins, including lysozymes, and especially, lactoferrin.

In human adults, lactoferrin is produced during and after exercise independent of sex, age, and menstrual cycle [14]. In infants, lactoferrin is obtained through breast milk, consumed 6 to 7 times daily by newborns. Newborns allocate 74% of their energy intake to brain growth and differentiation [15–17]; an energy allocation that would be impossible if they experienced a high-cost bout of postprandial inflammation after every meal. Fortunately, constituents found in breast milk are capable of downregulating the newborn’s immune system, while they also protect against possible pathogens. Lactoferrin is probably the most abundant immunologically active constituent of breast milk that reaches concentrations as high as 8 mg/g in colostrum and 1.5 to 4 mg/g in mature milk [18]. A breastfed newborn who consumes 600 mL of breast milk daily can ingest up to 2.4 grams of lactoferrin daily, an amount that is probably more than enough to protect against infection, while simultaneously inhibiting postprandial inflammatory activity of adipocytes and the immune system, thereby saving energy for constant brain growth.

The hominin brain experienced unprecedented growth despite the challenges that the immune system faced as our ancestors sought novel experiences and colonized the world.

However, in the last 30,000 years, brain size has shrunk from 1,490 mL to 1,350 mL, a loss of 11% [19]. Here we suggest that this reduction in brain size happened because of new environmental inflammatory factors such as novel pathogens, high meal frequency, food abundance, and lack of solar radiation but most of all because of the absence of regular physical activity.
2. **Energy and Energy Conflict as the Driving Force behind Evolution**

In all animals, energy conflicts shaped physiology during evolution. These conflicts seem to have caused changes in energy allocation among organs. Nowhere have these conflicts been more relevant than in the rapid expansion of the brain during hominin evolution [20, 21]. In principle, a proportionally larger and metabolically expensive brain could have been supported through an increase in the basal metabolic rate, but no evidence of such a relationship has been found in humans or other primates [22]. Because of this, several ideas have been advanced to explain how this larger brain might have been metabolically supported. For example, the expensive tissue hypothesis [20] and, more recently, various energy-allocation scenarios [16, 22] propose that the development of the metabolically expensive human brain must have had consequences for other organs, leading to lower energy allocation to those organs in favour of the brain.

Navarrete et al. [23] examined evidence for the expensive tissue hypothesis in 100 different mammalian species, including 23 primates. They found that, controlling for fat free body mass, brain size is not inversely correlated with the mass of the digestive tract or any other expensive organ, thus refuting the expensive tissue hypothesis. However, they did find evidence for a negative correlation between brain size and fat depots in mammals, raising the intriguing possibility that encephalization and fat storage both evolved as compensatory strategies to buffer against starvation. When these two strategies are combined, fat might provide extra energy for the brain during starvation, but only if this fat storage did not negatively impact locomotor efficiency. Central fat storage (which does not hamper locomotion efficiency) has probably favoured encephalization, redirecting energy allocation from growth, reproduction, and high-energy locomotion to brain development and more efficient locomotion, including during starvation [23].

The observation that human bipedal locomotion and foot anatomy lead to less energy use than the bipedal or quadrupedal locomotion of chimpanzees is supporting this theory [24]. Bipedal locomotion in humans also facilitates higher central fat depots without major energy demands during movement [23].

A recent study provides new evidence for the expensive tissue hypothesis [25]. The study shows that guppies with a bigger brain have smaller guts and produce fewer offspring. This is in line with the expensive tissue hypothesis and adds a second factor to this hypothesis relating brain size, gut length, and reproductive capacity [25]. Humans are “under-muscled” compared with other primates, although this difference is too small to provide sufficient energy for brain growth [22]. Nevertheless, it is the energy consumed by human muscles during locomotion which is almost twice as low compared with, for instance, in chimpanzees
(332 versus 564 kcal/day) [22] providing enough energy for brain development and function. The consequence is that humans’ brains are three times bigger than the brains of chimpanzees, and brain metabolism accounts for 25% of the basal metabolic rate in humans and only 7 to 8% in other primate species [26].

Overall, there seems to be sufficient scientific support to suggest that the increase of human brain size and metabolism has been possible because of a change of locomotion, higher central fat depot storage [27], and (although not addressed in this review) a change of food intake (see review [24]). In addition, the human brain may have benefitted from a change in the expression of glucose transporters [28] and the same holds for the immune system. Higher expression of GLUT1, supporting high and constant glucose uptake, is seen in activated immune cells, where energy is needed to protect against pathogens and other immune challenges [29]. This occurs at the expense of GLUT4 that needs insulin for glucose uptake and is notably expressed in muscles and adipocytes [30–33]. Thus, immune function may have benefitted from a smaller gut, reduced energy needs for locomotion, increased fat mass, and tissue specific differences in the expression of glucose transporters.

The work of Fedrigo et al. [28] provides a new explanation for this intriguing “mystery,” that is, the evidence that during human evolution energy allocation has been directed to brain and immune system development. They showed that human brain cells express more activity of the SLC2A1 gene responsible for the production of GLUT1 glucose transporters compared with the chimpanzee and macaque (human > chimpanzee > macaque). At the same time, SLC2A4 expression (i.e., GLUT4) in muscle is significantly higher in chimpanzee > human > macaque. Given a certain circulating glucose concentration, an increase in the amount of SLC2A1 or SLC2A4 protein per gram tissue results in more glucose being captured by that tissue and less by others. It is important to note that GLUT1 transporters are insulin-independent whereas GLUT4 in muscles depends on insulin for glucose uptake. An increase in SLC2A1 expression in the brain and a decrease in SLC2A4 in skeletal muscle would work synergistically to change the distribution of glucose between these two most energy-demanding tissues in the human body, in a manner allowing more energy to become available for the brain.

A similar line of reasoning explains glucose allocation to the immune system. The energy demands of lymphocytes and leukocytes increase dramatically upon activation \[3, 5\] and all activated immune cells express GLUT1 glucose transporters \[29, 34\]. Not surprisingly, several signals and stimuli such as pathogen associated molecular patterns (PAMP), including lipopolysaccharide (LPS), can promote GLUT1 expression, giving rise to an increase of insulin-independent glucose transport into all immune cells that supports T-cell receptor stimulation, immune cell migration, and inflammation \[35, 36\]. Thus, higher expression of GLUT1 promotes energy allocation to the immune system, which could be considered an "energy demand reaction," mobilizing fuel stocks and suppressing the resource demand of other organs/systems with the overall purpose of preferentially allocating fuels to activated immune cells \[37\]. Glucose allocation to the immune system maintains its function even under strong energy restriction \[38\].

Metabolic mechanisms and immune control coevolved, conceivably because both processes are interrelated and essential to survival \[39\], and both seem to have originated in a single fat body organ, as can still be seen in Drosophila melanogaster \[40, 41\]. The integration of metabolism and immunology persists in higher organisms, in which lymph nodes are embedded in perinodal adipose tissue that may influence immune responses. In humans, adipose tissue is well infiltrated with macrophages, and the production of inflammatory cytokines by both adipocytes and macrophages contributes to systemic inflammation \[42\]. Activation of the immune system through danger signals utilizes and redistributes energy in a manner that favours the brain and the immune system. However, prolonged activation of the immune system, as observed in people with chronic inflammatory states, allocates glucose chronically to the immune system through immune-controlled down regulation of GLUT1 transporters at the level of the blood-brain barrier and a reduction of GLUT4 transporters at the level of muscle and adipose tissue \[43–45\]. This selfish behaviour of the immune system is responsible for the majority of chronic diseases, if not all \[46\].

Our hypothesis is that chronic exercise reallocates energy primarily to the brain and muscles, reducing energy distribution to the immune system, and by doing so recovers metabolic homeostasis.
4. **Muscle as a Defence Mechanism in Humans**

Muscle is a “forgotten” organ of the immune system. Indeed, the physical activity permitted by muscles changes the phenotype of immune function from proinflammatory to antiinflammatory, while maintaining protection against possible lethal pathogens. Interestingly, chronic exercise is only seen in humans and allowed us to discover and inhabit widely divergent habitats around the world, while remaining able to survive and reproduce. Hominins in general and humans in particular tended to seek novelty in their environments, and this practice would have led them to encounter new pathogens, climatological challenges, and food scarcity, all of which would have threatened survival and prompted activation of the immune system. If proinflammatory activity had dominated the biology of our ancestors when they were challenged with pathogens such as *Plasmodium falciparum* malaria, tuberculosis, *Salmonella*, or pathogenic *Escherichia coli*, brain growth from 450mL in early *Homo erectus* to the current 1,350mL in modern humans would unlikely have been possible. The energy costs of a consistently active immune system would have been enormous and would probably have impeded the growth of the brain as well as the body. An overly active immune system would also have harmed reproduction [47], as evidenced in modern fertility issues among autoimmune patients [48].

Hominins are not the only organisms in which such a trade-off occurs. Green plants and hominins probably share one and the same ancestor [49]. The difference is that plants have chosen an evolutionary path in which locomotion had low or no priority, which implies that they have not learned to escape from danger in a physical manner [50]. Animals’ ability to physically flee prevents them from being wounded and thereby from experiencing the ensuing cytotoxic and self-damaging reaction of the highly expensive innate immune system [51]. Without the means to physically escape from predators or other direct threats, plants employ toxins to defend themselves against predators. These toxins (e.g., perforin) are defence substances similar to those used by animals to kill invading pathogens and are part of the immune system of the plant [52]. Plants do not have the “migrating” immune cells found in animals and are therefore dependent on an immune system in each individual cell [53], which has the potential to be very robust. As a result, in plants a chronic pathogenic load can lead to overactivity in their equivalent of an immune system causing a change in energy distribution that favours immune functions at the expense of functions related to growth and reproduction [54].

Similar to plants, humans and other mammals may experience damage following a robust reaction of their immune system, such as in sepsis. Long-term and very intense activation of the immune system in individuals with sepsis can cause loss of lean body mass, tissue breakdown for use as a source of amino acids and energy, growth impairment, and
reproductive disturbances [48, 55]. Even motor and mental functions in later life may be affected [55, 56]. In addition, a robust inflammatory reaction following acute trauma, such as a stroke or any other neuro-trauma, often produces severe secondary damage [57]. The strength of the immune reaction results from the complexity of the human immune system, which has high receptor diversity that greatly enhances the efficiency of microbial detection. However, these same qualities also make humans uniquely vulnerable to autoimmune disease (AID) [58], as high receptor diversity increases the risk of misinterpretation of self-molecules as foreign, potentially provoking autoimmune responses [59].


The prevalence of autoimmunity is markedly increased in sedentary people [60], who, by definition, infrequently engage in physical activity. It is interesting to consider whether the expensive immune reaction seen in sedentary individuals can be considered adaptive in a manner similar to the strategy plants use to defend against invaders and danger, given that—like plants—sedentary individuals are less able than others to flee danger.

Exercise has powerful immune effects. Even nonstrenuous exercise, when engaged in regularly, promotes better health and increases life expectancy [61]. Nonstrenuous exercise also induces the expression of anti-inflammatory molecules such as lactoferrin and lysozymes, which provide defence against a large number of invaders, including bacteria, viruses, and other microbes [62]. A bout of forty five minutes of running at 75% of VO2 max increases the production of lysozyme and lactoferrin in saliva significantly, independent of sex and menstrual phase [14]. Serum lactoferrin concentrations also increase immediately after strenuous exercise, such as running, and may play an antibacterial role in host defences prior to the mobilization of neutrophils into the circulating pool, thereby attenuating the need for a possible inflammatory response with high-energy demand [63, 64]. Sedentary individuals, obese people, and patients with diabetes mellitus type 2 exhibit lower lactoferrin levels [65, 66], while suffering from an energy-demanding, chronic low-grade inflammation [10]. All organisms share a need for food intake, and food intake produces postprandial immune activation as a result of the possible presence of danger signals. This immune reaction is normally based on the production of inflammation-preventing defence molecules such as lactoferrin, immunoglobulin A (IgA), and lysozyme, which prevent the high-energy demands incurred from activation of innate immune cells [65]. However, when this mechanism fails or is inadequate, as often happens in obese/sedentary individuals, an inflammatory response ensues [67]. Increasing evidence suggests that this type of postprandial inflammatory response may contribute to the development of metabolic syndrome, endothelial dysfunction, cardiovascular diseases, obesity, insulin resistance, and chronic low-grade inflammation [60, 65].
Just as postprandial inflammation is more common in those who are sedentary or obese, postprandial inflammation is also observed after consumption of a meal that is high in fat, consists of refined carbohydrates, or contains sugar, fructose, linoleic acid, or other high-caloric nutrients. Interestingly, a postprandial inflammatory reaction may occur after an even modestly sized meal that contains cereal-fed meat which should be considered “new” on an evolutionary time scale [68–70]. The same holds for consumption of a new form of hybridized beef. The postprandial immune response after ingestion of “new” wagyu beef is significantly higher than when humans ingest “old” kangaroo meat [70]. All these data raise the intriguing possibility that the increased immune activity against new nutrients reflects a “borrowed” ancient immune reaction against evolutionary unknown danger signals, causing low-grade, systemic, inflammation [70, 71]. Another factor increasing inflammatory activity of the immune system is chronic food availability. The relationship between food availability and development of the metabolic syndrome has been investigated in mice [72, 73] and more recently in humans.

Hatori et al. [72] showed that obesity and metabolic syndrome are caused not only by caloric content, but also by food being constantly available. Koopman et al. [73] showed that meal frequency impacts development of fatty liver. Using a 40% hypercaloric diet, they showed that a high meal frequency (6/day) as compared to a lower frequency (3/day) increases intrahepatic triglycerides and abdominal fat, independent of caloric content and body weight gain. Constant food availability further decreases overall physical activity and especially spontaneous physical activity [74]. In contrast, starvation upregulates glucose transport through the blood-brain barrier by increasing the number of insulin-independent glucose transporters 1 (GLUT1) [75], whereas starvation leads to spontaneous physical activity and even hyperactivity [76].
5. **Exercise Protects the Body against the Expensive and Damaging Postprandial Inflammatory Response: Our Hypothesis and Its Putative Mechanism**

Interestingly, exercise prior to meal consumption markedly lowers the postprandial inflammatory reaction [77]. Evidence suggests that this effect may result from muscle contraction inducing anti-inflammatory myokines (i.e., myokines), including IL-6, IL-15, and IL-8, that subsequently stimulate production and release of anti-inflammatory molecules such as lysozyme and lactoferrin by the immune system [64, 78]. The previously mentioned anti-inflammatory myokines are increased up to 100-fold during exercise [79] and thereby are responsible for the production of anti-inflammatory molecules such as lactoferrin during and after physical activity [80]. Elevated concentrations of lactoferrin in serum have been reported 30 minutes after intense running and are associated with elevated serum antibacterial activity to viable Micrococcus luteus [62]. Furthermore, higher levels of serum lactoferrin have also been observed two hours after submaximal cycling followed by a bout of eccentric resistance exercise [81]. The lactoferrin increase appears to be related to intense exercise and eccentric contraction, which has also been observed in relation to the production of anti-inflammatory myokines [82]. There seems to be a direct relationship between glycogen depletion and the production of muscle-derived IL-6, which, despite its inflammatory activities, also demonstrates anti-inflammatory and metabolic-sensing and regulating properties when expressed as a muscle myokine [82]. Lactoferrin stimulates the expression of a protein in adipocytes and in newly identified cells of the innate immune system called six-transmembrane protein of prostate 2 (STAMP-2) [83].

STAMP-2 links obesity, inflammation, and insulin resistance. When STAMP-2 is activated, the production of proinflammatory cytokines is inhibited through down regulation of nuclear factor kappa B (NFkB), the key transcription factor for activation of genes responsible for the production of proinflammatory cytokines and enzymes such as IL-1-beta, TNF-alpha, COX2, and LOX5 [84]. STAMP-2 deficiency can lead to several disorders, including atherosclerosis, metabolic syndrome, and diabetes [85]. NFkB contributes to the development of insulin resistance, and STAMP-2 restores insulin sensitivity by inhibiting NFkB [86]. All members of the STAMP family possess both ferric and cupric reducing activities, which indicate that STAMP-2 might regulate iron or copper entry into cells [87]. STAMP-2 requires iron or copper as cofactors, suggesting that STAMP-2 is needed to maintain metabolic homeostasis. STAMP-2 further protects against atherosclerosis and stabilizes plaques in diabetic mice [88]. Decreased activity of STAMP-2 and similar proteins creates a signalling bottleneck that leads to insulin resistance [86, 88]. Lactoferrin is an “iron” carrying protein, which could explain its activating function on STAMP-2 [89]. Considering all these factors, it seems plausible that...
preprandial (before meal intake) exercise induces the production of anti-inflammatory myokines and that these myokines stimulate neutrophils to produce lactoferrin [89].

The release of lactoferrin into the circulation activates visceral adipocytes, which subsequently react with increased expression of STAMP-2 [83]. STAMP-2, in turn, inhibits NFκB and Janus kinase (JNK) activation and prevents the inhibition of insulin signalling.
6. **Physical Activity Was Spontaneous during Evolution and Causes a Phenotypical Shift of the Immune Response during Immune Challenges**

That exercise prevents postprandial inflammation makes good sense from an evolutionary perspective. From 2 million years ago until approximately 200 years ago, common threats to human health included starvation, dehydration, predation, climate, accidents, violence, and infectious disease [90]. With the exception of infectious disease, all these threats induced spontaneous activity (SPA) through activation of dopaminergic neuroanatomic nuclei in the brain, including the ventral tegmentum and the striatum [75]. The major neuropeptide systems that have been studied relative to spontaneous physical activity include cholecystokinin, corticotropin-releasing hormone, neuromedin U, neuropeptide Y, leptin, agouti-related protein, orexins, and ghrelin. All these systems influence dopaminergic signalling [91]. SPA stimulates the production of anti-inflammatory myokines by energy depletion of the contracting muscles. As mentioned earlier, these myokines drive neutrophils to produce antimicrobial/anti-inflammatory molecules (e.g., lactoferrin) and STAMP-2 in adipocytes and cells of the innate immune system, thus preventing over-activation of NFkB and the subsequent proinflammatory/insulin resistance response. The cascade of neurochemical reactions in the brain, when faced with old danger factors such as starvation, prompted patterns of SPA that reflected the daily lives of our ancestors.

To starve off hunger and obtain food, both men and women often engaged in fishing, while men also engaged in leg-based long-term hunting and women employed arm based gathering. Our ancestor’s use of the upper body during physical activity is an important factor in stimulating an anti-inflammatory reaction. Upper body muscles are energetically more efficient than lower body muscles and are normally conserved even during severe metabolic conflicts, as observed in people suffering from chronic obstructive pulmonary disorders (COPD) [92, 93]. Preservation of upper body muscles may seem counterintuitive considering that scientists unequivocally recognize horizontal running as the evolutionarily conserved flight direction and considering that the maximum running speed of predators such as lions, tigers, and jaguars is by far much higher than the maximum speed of the fastest human. Conceivably, conserving upper body muscles during metabolically stressful situations may have occurred because humans could more easily escape threats by climbing/fighting than by running, making maintenance of the upper body muscles a priority. This view is supported by the observation that energy is first allocated to arm muscles during fear situations, manifesting in warm, sweating hands and an instantaneous increase of circulation [94–96].

Palm sweating has a surprising benefit; hands are important parts of the body to eliminate
excessive body heat during exercise and increased heat elimination through palm sweating augments exercise resistance and prevents fatigue. Use of the upper body is also likely to have led to optimal levels of IL-6, which is anti-inflammatory only when produced in small amounts. These amounts depend on the amount of metabolic stress on contracting muscles during exercise, which is significantly less when using the upper body for fishing, digging, and other gathering functions. Our ancestors were merely gatherers/fishers and part-time hunters, and they therefore often relied on their upper body, thus producing the optimal anti-inflammatory cocktail of myokines to cause an anti-inflammatory postprandial response. As a result, although our ancestors suffered from stress, these patterns of activity made them less likely than most modern humans to experience a metabolically expensive inflammatory response of the innate immune system and subsequent low-grade inflammation-based disorders. The energy thereby conserved would have been used to feed the metabolically expensive brain, and the absence of immune stress induced insulin resistance would prevent the development of neurodegenerative diseases and other maladies affecting the central nervous system in general, but especially the brain [97].
7. Spontaneous Physical Activity and the Immune System

Evidence that SPA is caused by ancient stress factors such as food scarceness comes from research with people suffering from anorexia nervosa and individuals with obesity, that is, the opposite phenotype [74]. However, SPA and even hyperactivity in periods of reduced food availability are not unique to humans: animals need to be active to search for more food if the food supply is limited, as is commonly the case in the natural habitat. Already in 1922, the psychologist Curt Richter observed that if food is served for a limited period of time, the meal is preceded by an increase in physical activity [98]. This phenomenon is referred to as “food anticipatory activity” (FAA), and the biological explanation for FAA preceding meals is similar to the above-mentioned evolutionary approach to human SPA in starvation.

The SPA pathway, activated through food restriction, seems to be dependent on orexin and dopamine [74]. Activation of orexin receptors leads to an increase in physical activity, while orexin is released in response to food restriction [99]. Orexin-producing hypothalamic neurons project on dopaminergic neurons in the ventral tegmentum, which are highly involved in SPA [100]. The same is true for the gut-derived orexigenic hormone ghrelin, which also activates dopaminergic pathways in the ventral tegmentum and induces SPA [101]. Dopaminergic pathways responsible for spontaneous physical activity have gained importance during evolution. These dopaminergic neurons belong to the group of the so-called emotional motor neurons [102–104] and these neurons are part of the behavioural column.

The behavioural column and its emotional motor neurons literally facilitate muscle contraction through "gain setting" pathways and motivation. It can be concluded that motivated activity is energetically less costly (“cheap”) than voluntary exercise and motivated activity is dopamine dependent [105]. Comparison of the human substantia nigra and ventral tegmentum with those of other mammals or vertebrates revealed tremendous differences in the number of dopaminergic neurons.

For example, lizards (Gekko) have about 2,000 dopaminergic neurons and turtles (Pseudemys) about 5,500, while rats have 45,000 dopaminergic neurons, macaques 165,000, and humans 590,000 in the first four decades of their lives [106]. Vernier states: “The large number of dopaminergic neurons in humans is remarkable given that the human brain is only three times larger than that of the macaque. Normally, the number of dopaminergic neurons correlates closely with body weight, but humans are a clear exception. This peculiarity is even more striking because a single dopaminergic neuron of the substantia nigra or ventral tegmental area (VTA) sends many collaterals with large arborization trees to several areas of the forebrain. The projections of these neurons are essentially similar among the different vertebrate species, though they tend to abundantly innervate the striatal areas.
and, less abundantly, pallial (cortical) areas, under-scoring their role in the control of incentive and sensorimotor behaviours. Details of these connections are well described only in mammals and especially in humans [107]. As mentioned before, the dopaminergic motor system belongs to the behavioural column defined by Swanson [103], and this system facilitates and permits behaviour [51].

The opposite response is observed in people with a variety of diseases such as fibromyalgia syndrome, multiple sclerosis, panic disorder, obesity, and Parkinson's disease, all of whom show non-permissive behaviour such as exercise avoidance [108]. Dopamine-induced preprandial SPA firstly saves energy for brain function and secondly helps to induce a protective anti-inflammatory response of the immune system after food intake through upregulation of the production of lactoferrin and its accumulation in dopaminergic neurons might protect against neurodegeneration and Parkinson’s disease [109]. As mentioned before, several specific aspects of human locomotion have made it possible to save energy for the brain [23], but this is not the only way the brain gained access to more resources to grow and develop during hominin evolution. Chronic exercise shaped the immune system, creating a highly protective anti-inflammatory phenotype that maintains protection against possibly lethal invaders while saving energy [82].
8. Physical Activity: Part of the Combined and Coordinated Neuroendocrine-Immunological Stress Response

Another intriguing effect of spontaneous or voluntary exercise is related to its ability to convert dopamine to codeine and morphine, although in low amounts [110]. Codeine and morphine are known for their analgesic effects, but much less is known about their influence on the immune system. Endogenous codeine and morphine induce constitutive nitric oxide synthetase (cNOS) in immune cells. The resulting NO inhibits mitochondrial energy (ATP) production in white blood cells and thereby immune inflammatory activity [111]. Voluntary motivated exercise also produces the immunoregulatory/anti-inflammatory cytokine IL-10, which may further elicit anti-inflammatory effects through dopamine-regulated physical activity [112, 113]. This anti-inflammatory response might be dangerous when the bacterial load is so high that the host would be in serious infectious danger when the immune system would maintain an anti-inflammatory activity. It is in this context not surprising that recent research showed that when the pathogenic load is high, the immune response will maintain proinflammatory capacity and drive sickness behaviour and thereby outweigh the anti-inflammatory potential of voluntary exercise [114]. This observation in mice further supports the selfish character of the immune system.

Taken together, both the emergence and function of dopamine, morphine, and nitric oxide seem to be related to evolutionary pressures to maintain chronic physical activity (for an excellent review see [115]). The combined production of lactoferrin, anti-inflammatory myokines, and IL-10 and also the dopamine/morphine/NO triad through motivated and spontaneous exercise make it at least plausible that SPA has driven the immune system to an anti-inflammatory phenotype, thereby saving energy for the brain and the muscles, which is in support of our hypothesis and observed mechanisms.
9. **Physical Activity Protects against the Damaging Effect of the Proinflammatory Activity of the Selfish Immune System: Clinical Evidence**

Clinical research in patients suffering from different disorders of the central nervous system supports the notion that physical activity protects against proinflammatory activity. Patients with neuroinflammatory diseases such as amyotrophic lateral sclerosis (ALS) react positively to exercise [116], probably through down regulation of the immune response directed against brain tissue. Patients with Parkinson’s disease who engage in ‘forced’ exercise show significant improvement of typical Parkinson symptomatology and less progression of the disease [117]. These and other neurodegenerative and many other diseases seem to be related to disturbances in energy metabolism in the brain [118] and also to energy distribution between the central nervous system and the peripheral organs [119], all caused, at least in part, by a chronically activated immune system [10, 120].

In summary, SPA and recreational voluntary exercise seems to override the chronically active immune system [121] and reduce its selfish behaviour. Strenuous obligatory exercise produces immune suppression, possibly leading to increased susceptibility to infection [114, 122], although recent human research shows that the immune system reactivates when challenged with a high load of pathogens in people engaging in strenuous exercise. Physical activity (ancestors = SPA, contemporary = voluntary) induces anti-inflammatory myokines which inform the immune system and literally relax it. A relaxed immune system (which is distinct from “suppressed”) only reacts to the danger signals it was designed to respond to, such as bacteria and viruses, which conserves energy for the benefit of phylogenetically younger organs such as the liver, kidneys, and brain and gives rise to normal behaviour and a so-called permissive brain phenotype. A subject’s permissive brain literally facilitates free will, as opposed to those suffering from a non-permissive brain syndrome [51, 123–126].

Behavioural changes have high energetic cost and lack of brain energy prevents flexibility and loss of free will. Spontaneous and voluntary activity can also be considered a strategy belonging to the proactive behavioural immune system. Avoiding danger, psycho-emotional problems, social contact with infected individuals, dirt, and other unknown, possibly dangerous, triggers relax the expensive reactive immune system, once again providing energy for the human brain. Recent research in insects shows that an acute flight/fight reconfigures the type of immune reaction from a pro- to an anti-inflammatory phenotype, just as in humans. Once more, it is this low-cost anti-inflammatory immunological response that protects against infection and saves energy for brain development and function. In contrast, the sedentary lifestyle, a disease in itself, demands a proinflammatory response of
the immune system and chronic allocation of energy/resources to this system. Low-grade inflammation is the ultimate consequence and the cause of causes of most, if not all, noncommunicable chronic diseases [46].
10. Conclusions

Because regular muscle contraction diminishes the need for proinflammatory activity of the innate immune system [127], we suggest that muscles should be considered part of the immune system [128]. The phylogenetic development of muscles, together with that of human locomotion, increased fat storage. Differences in glucose transporters between muscle and the brain have been responsible for patterns of energy allocation that enabled the brain to grow to its evolutionary maximum of 1,490mL approximately 30,000 years ago.

Throughout hominin evolution, our ancestors encountered dangerous situations, such as violence and dehydration, that threatened the survival of the individual or the species and usually triggered a survival response in which more ancient systems tend to dominate younger ones [129], although brain functions and anatomy seem to maintain the highest priority.

The normal response to survival threats is SPA, and SPA is capable of controlling the immune system by saving energy for the brain during stressful situations [130]. The absence of SPA or voluntary exercise, as is occurring in sedentary people living modern lifestyles, provides a framework in which the immune system overrides the interests of the normally selfish brain, which could be the reason why brain size shrunk in the last 30,000 years from the maximum of 1,490mL to the current average of 1,350 mL.

Conflict of Interests

Dr. Raison reports the following activities in the prior 12 months: consulting for Pamlab, Merck, and Otsuka; speaker’s bureau for Pamlab and Sunovion; delivery of nondisease state presentations for Merck and Otsuka; steering committee membership for North American Center for Continuing Medical Education (NACCME); preparation and delivery of continuing medical education material for NACCME, Haymarket, and Medscape.
References


Physical inactivity is a disease
Synonymous for a non-permissive brain disorder

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University of Graz (Austria), Uni for Life.

Running Title: Physical inactivity; protective?
Abstract

The evolution of human kind has taken millions of years in which environmental factors gradually shaped the actual genome adapted to those circumstances. One of the most vital behavioural adaptations of mammals in general and especially humans is their capability of self-sufficiency through physical activity. Physical activity abilities, including long distance running, jumping, climbing and carrying things have probably been necessary to outrun wild animals, search for food and hide for danger. In contrast, individuals physically or psychologically unable to “take care of themselves” were more susceptible for early death and therefore for genetic extinction.

The actual society is characterized by sedentary instead of “moving” individuals. Physical inactivity is not just a possible factor related with chronic disease, but should be considered the actual cause of the majority of human illness. Individuals know that exercise is necessary and beneficial. Nevertheless almost 75% of the actual population doesn’t reach the estimated minimum of necessary activity. Physical inactivity belongs to the characteristics of sickness behaviour; the latter which probably is protective for the organism. Sickness behaviour, including depressive mood, seems to protect against infection, injury, social conflict and facilitates energy conservation. Sickness behaviour is based on immune-brain mechanisms and can be defined as non-permissive behaviour. Long-term non-permissive behaviour can lead to chronic disease because of reduction of physical activity and self-defeating coping styles, converting non-permissive behaviour in a non-permissive brain disorder. We propose that physical inactivity disease is synonymous for a non-permissive brain disorder and that NPBD produces a so called “reptile phenotype”, characterized by hypothermia, poor hair growth, decreased fertility and low basal metabolic rate.

Keywords

Physical inactivity, depression, non-permissive, brain, evolution, self defeating behaviour
Introduction

Physical inactivity is related to almost every type of chronic disease including heart insufficiency, diabetes type II, metabolic syndrome, obesity, gall stones depression, early aging, neurodegeneration and even early death (1). Clinical research about the effect of exercise on parameters such as blood flow, energy metabolism and immune system activation is not conclusive because of a basic mistake; the use of “healthy sedentary” individuals as the control group (2). The human genome has been shaped through several evolutionary pressure factors including the need of self-sufficiency. Self-sufficiency is defined sociologically as each human or small group of humans being responsible for their own food, water, defence, and shelter (3, 4). The self-sufficient phase has dominated human behaviour for almost 2 million years and only perhaps the last 100 years individuals are “served” dinner, warmth, drinks and shelter. This non-self-sufficiency is defined here as humans obtaining a constant supply of food until reproductive age through a distribution network composed generally of farmers to transporters to sellers to buyers to consumers.

Homo sapiens is the most resistant being to long term exercise, capable of outrunning animals such as wildebeest and other big mammals, which have been part of the natural nutritional sources of humans till very recently (5, 6). The capability of outrunning other animals demands the following unique characteristics of human physiology and morphology (7):

- Thermoregulation in homo sapiens is unique through the absence of body hair and the presence of more than 2 million eccrine sweat glands (8, 9)
- Short toes, reducing the energetic cost of running (10, 11)
- The capability of producing great amounts of glucose out glycogen, amino acids and glycerol; gluconeogenesis
- Expensive organs such as the heart muscle and the brain can use different energy sources when necessary; the so-called metabolic flexibility (12). This metabolic flexibility facilitates endurance running, climbing, jumping, swimming, throwing, crawling, carrying and sprinting (13).
Table 1 The relationship between evolutionary based life threatening danger factors, the developed survival reaction, the benefit and the contemporary consequence of disease.

<table>
<thead>
<tr>
<th>Danger</th>
<th>Response</th>
<th>Evolutionary benefit</th>
<th>Actual burdens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen</td>
<td>HSR</td>
<td>angiogenesis</td>
<td>Cancer, fibrotic fat</td>
</tr>
<tr>
<td>Starvation</td>
<td>IR, IR</td>
<td>Energy storage</td>
<td>Obesity, Metabolic syndrome, Low grade inflammation</td>
</tr>
<tr>
<td>Dehydration</td>
<td>AVP</td>
<td>Water and Na retaining</td>
<td>Hypertension, Oedema</td>
</tr>
<tr>
<td>Infection</td>
<td>Hyper IS</td>
<td>Anti-sepsis</td>
<td>Allergy</td>
</tr>
<tr>
<td>Violence</td>
<td>NA, A</td>
<td>Flight/refight</td>
<td>Fear, aggression</td>
</tr>
<tr>
<td>Anticipation</td>
<td>NA, SER</td>
<td>Social withdrawing</td>
<td>Restlessness, sleeping disorders</td>
</tr>
<tr>
<td>Wound healing</td>
<td>HIF-1</td>
<td>Tissue maintenance</td>
<td>Depression, autism?</td>
</tr>
<tr>
<td>Reproduction</td>
<td>High fertility</td>
<td>Long lasting</td>
<td>Social Isolation</td>
</tr>
</tbody>
</table>

A = adrenalin; AVP = arginine vasopressin; HIF-1 = hypoxia inducible factor 1; HSR = hypoxia stress reaction; IIS = innate immune system; IR = insulin resistance; LR = leptin resistance; NA = noradrenalin; SER = serotonin (adapted from 4)

Homo sapiens “is made for walking”, so inactivity is a disease

As it seems that homo sapiens is “made for walking”, it is very strange that so few people engage in physical activity nowadays. Troiano et al (14) using an accelerometer showed that only 5% of the adults and 8% of the adolescents reach the minimal amount of recommended physical activity (figure 1). Nevertheless, looking at Haile Gebreselassie finishing the Berlin marathon and breaking the world record with a big smile on his face makes it plausible that exercise, although intense, has to be fun. So knowing why people fail to engage in regular exercise, leading to possibly severe damage to their body, is of mayor clinical importance. We state that the background of choosing for a sedentary life is based on a so-called non-permissive brain syndrome (NPBS, our hypothesis, see further, 17). This syndrome protects the individual for a certain period (a disorder), while long lasting NPBS is a disease itself (defined as such by Heskha and Allison, 18), related with increased mortality risk. NPBS is characterized by low basal metabolism, impaired hair growth, thermoregulation disorders and, naturally, inactivity.

![Figure 1](image1.png)

*Figure 1 The actual percentage of individuals reaching the minimal physical activity level (adapted from 14)*
The burden of physical inactivity

The systemic changes caused by physical inactivity occur fast and are specific for a disease. In response to excessive inactivity (continuous bed rest or go into the microgravity environment of space) individuals exhibit a rapid loss of tissue mass and disruption of normal function in many cells and tissues. Within weeks of the onset of continuous bed rest by humans, numerous adaptations occur, including 25% decreases in maximal stroke volume, maximal cardiac output, and peak consumption of O2 during maximal aerobic exercise. Orthostatic intolerance occurs due to attenuated baroreflex-mediated sympatho-excitation in response to incremental declines in arterial blood pressures. Bones lose mass at 10 times their normal rate. Skeletal muscles become weaker with less endurance for light physical effort. In addition, metabolic pathways adapt to inactivity by decreasing mitochondrial concentration in skeletal muscles, lowering the capacity to oxidize fatty acids, affecting metabolic flexibility. Whole body insulin sensitivity declines within the first 3 days of inactivity, whether it is sedentary or active individuals stopping daily exercise. Constipation ensues. Deep vein thrombosis can occur within a time frame as short as an international flight with possible pulmonary thrombo-embolism in susceptible individuals. In summary, the body’s reaction to physical inactivity result in a loss of many structural and physiological processes, which often lead to unhealthy, in some cases life-threatening, conditions (3, 19, 20, 21). Another consequence of inactivity is the loss of strength of respiratory muscles (22). This effect can cause severe loss of muscle strength of peripheral muscles through more severe inactivity, oxygen deficiency and higher insulin resistance (23). On cellular level, changes are even more dramatic. Inactivity decreases neurogenesis in specific parts of the brain responsible for memory, motor learning and programs and need-catering factors (food, water, no-drugs, no-alcohol abuse, etc.). Parts included are the cerebellum (motor programs), the olfactory bulb (need – catering) and the hippocampus (24). On the contrary, exercise combined with enriched environment is able to recover earlier lost neurons also in elder animals and humans (25, 26). Decision-making can be considered the most important trait of Homo sapiens. The actual environment demands self-control and discipline to make the right decision regarding food choice, physical activity, smoking, alcohol and other factors that affect hedonic choices. The hippocampus is essential for decision-making together with other parts of the brain such as the striatum and the frontal cortex (27, 28). Loss of hippocampus volume (and the subsequence increased susceptibility for developing inactive behaviour) can further be produced by stress, sleep disruption, smoking, alcohol abuse and inflammation (26, 29, 30). Another consequence of physical inactivity is its resistance-inducing effect on insulin, leptin, serotonin, dopamine, thyroxin and cortisol signalling, affecting the function of the immune system, the endocrinological system and distribution of energy (50, 53, 54, 55, 56). Resistance to the mentioned hormones is part of the development of sterile chronic inflammatory diseases (65). Inactivity can also affect the expression of glucose transporter 4 (GLUT4). GLUT4 is responsible for muscular glucose
trafficking in rest (insulin dependent) and activity (insulin independent, 19, 20, 62). GLUT4 is decreased in sedentary individuals, increased in active ones and persons with high GLUT4 are more engaged in exercise (62, 63, 64, 65, 66). Increase of GLUT4 expression enables muscle to uptake more than 80% of the daily glucose load. This would make our high glycemic society less toxic and therefore less pathological. In resume, the great amount of literature supports the overall necessity of increase of physical activity as a normal way of living and in one way or another people have to get conscious about the severe deleterious effects of sedentary lifestyle on health and life expectation (67, 68).

**Possible explanations for the “lazy phenotype”**

Chronic intake of food (high meal frequency and abundant meals) can have an important influence on various forms of physical activity (32), including spontaneous and voluntary exercise. Spontaneous physical activity, the activity related with daily life, plays a mayor role in maintaining body weight, caloric intake and overall health (33, 34, 35, 36). Spontaneous physical activity (SPA) is not chosen and bypasses higher cortical regions while voluntary exercise is a choice and therefore dependent on neocortical activity and “free will” (36, 37, 38, 39). Brain stem and spinal centres responsible for the maintenance and recovery of homeostatic balances regulate SPA. Hunger, thirst, cold, warmth, itch, libido, curiosity and pain are homeostatic feelings inducing movement beyond any doubt. The problem in modern society is just that the refrigerator, air conditioner and heating are very nearby and eliminate the SPA stimulus within seconds, whereas our ancestors were obliged to move till they would find food, water, a place to hide or would have produced so much body heat that they could survive in the cold (the self-sufficiency period). Homeostatic feelings are related with the production of certain neuromodulators, including orexin and cholecystokinin (CCK, for a excellent review see 34). Orexin, related with appetite and environmental food and liquid exploration, favours SPA (40,41, 42). On the contrary, CCK, produces postprandial satiety, inhibits SPA and induces sleep (43). Postprandial CCK production influences the body arousal system probably by inhibiting the sympathetic nervous system and by activating the non-myelinated vagus nerve (44, 45, 46, 47). This appetite-satiety/exercise-rest rhythm has probably been developed through evolutionary mechanisms, giving raise to the so-called feast-rest/famine-exercise hypothesis of Chakravarthy and Booth (3, 47, 48). Several interventions to promote SPA have failed so far; although something so simple as less sedentary behaviour and reduction of television hours could already be effective (49).

Human evolution has shaped the genome in such a way that the majority of genes are selected against physical inactivity (3, 70, 71, 72, 73). Current scientific research shows that a few genes seem to play a mayor role in engagement in physical activity, including dopamine receptor 1 (Drd1) and the so-called nescient helix loop helix (Nhlh2, 82). The involvement of a
dopamine-signalling pathway in physical activity should not be surprising. Dopamine is involved in several locomotor disorders such as Parkinson, attention deficit hyperactive disorder, Tourette syndrome and restless legs. Quite a few studies have been carried out relating Drd1 expression with activity-level in animals and humans (see review 74). Dopamine is the key-player in functions such as drive, motivation, "cheap movement", decision-making, future thinking, reward searching and control of emotional-obsessive behaviour (7).

Dopamine is fun, but an overload can be responsible for hyperkinetic disorders, paranoia, fanatic religious behaviour and even uncontrollable aggressive behaviour (75, 76). Dopamine receptors 1 and 2 are the most studied in humans. Theoretically, Drd2 receptor binding signals the presence of important (often reward-based) information and allows the prefrontal cortex (PFC) network to respond to this new information by updating its working memory system. Drd1 receptor stimulation, on the other hand, plays a gating role by controlling the threshold of significance above which information may pass before it can be admitted to working memory and processed by the PFC. Drd1 receptor activation stabilizes the pattern of activity within the PFC neural network and protects the system from distracters until the appropriate behavioural response is generated (77). Different research groups have found that animals and humans with a lower expression of Drd1 in the nucleus accumbens belong to the high-active sample while high expression of Drd1 produces a more inactive phenotype (77, 78, 79, 80, 81).

Dopamine signalling in the brain is very much dependent on the intra-uterine environment and especially of the presence of enough iodine, L-tyrosine and omega 3 fatty acids (82, 83, 84, 85, 86, 8, 88, 89, 90). Chronic inflammation is especially important in dopamine signalling and therefore will be considered separately proposing our hypothesis.

**Our Hypothesis: “The non-permissive brain disorder; laziness as a protection?”**

We hypothesize that physical inactivity is part of a non-permissive brain syndrome caused by (adaptive?) disorders of dopamine signalling; not only genes will be involved but also environmental factors including a lack of brain nutrients during brain development and maturation (iodine, DHA, L-tyrosine, Cunnane 2005), vitamin D deficiency, increased protein turnover and energy distribution disturbances (17). The pathways leading to insufficient dopamine signalling include hyper activation of indoleamine 2,3 dioxygenase pathway in chronic inflammation (for an excellent review see 61) and decrease of the conversion of the amino acid L-tyrosine in dopamine (75). Chronic disease is characterized by higher energy demand of the immune system and dramatically increased protein turnover (60). The increased protein/energy demand can be so severe that multiple organs could suffer functional disorders and even failure, leading to acute death (59). Chronic immune activation leads to sickness behaviour resembling the non-permissive brain syndrome (91, 92, 93).
- Exercise avoidance
- Thermoregulation disorders
- Social isolation
- Reduction of libido
- Gluttony or
- Lack of appetite
- Increased pain sensitivity
- Fatigue
- Concentration deficiency
- Attention disorders
- Memory problems
- Change of body composition (muscle atrophy and increased fat deposits)
- Decreased fertility
- Impaired hair growth and boldness
- Decrease of top-down decision making
- Self-defeating behaviour
- Depressive mood

The physical characteristics lined up belong to a species with low basal metabolism such as a reptile (51). Low activity belonging to sickness behaviour and NPBS could help to defend the organism against infection, conflict, injury, exhaustion and perhaps the most important factor, low activity conserves energy for the immune system to combat infection, although it would be a sterile one (96, 97, 98). Certain depressive states are part of the non-permissive brain disorder (NPBS) and therefore depression and low activity should probably be considered protective at start. Long-term inactivity is deleterious per sé because of the tremendous damage at physical and mental level. We define NPBS as a behavioural strategy to prevent more severe damage, conserve energy and proteins to support immune function and provide protection of the most expensive organs of the human body at start. NPBS can also protect people against repeated physical abuse (social withdrawal in people who have suffered childhood abuse, 119) and severe loss of lean body mass during chronic immune system activity (52, 58, 59). Long lasting NPBS is severely deleterious to the host and should be treated as one of the most important clinical identities in modern medicine. Humans have the highest encephalisation quotient of all living animals on earth. Big brains need more energy. The development of bigger brains, mostly in mammals, has changed the morphology of these mammals in such a way that more central energy allocation was needed in stead of high
allocation to "dismissible" organs such as guts and muscles (99, 100). Possible threat to brain energy supply will lead to NPBS.

The "selfish brain" will continuously scan energy status in the peripheral body through neurological and endocrinological communication, including sympathetic interoceptors and hormones such as insulin (informing about muscle energy) and leptin (informing about the amount of stored fat. Peters et al (101, 102) showed that the brain would always give priority to its own energy need although others organs could suffer. Even in insulin resistant states, in which energy allocation is disturbed, the brain will cover its needs through up regulation of alternative substrate usage such as creatine and fatty acids (103, 104). NPBS will therefore protect primarily the brain on behalf of muscle tissue. Muscle tissue uses an average of 13 kcal/24 hours in rest and up to 10 times more during exercise (table 2, 107). Muscle waisting and physical inactivity conserves a substantial amount of energy and provide proteins to be used by the immune system.

Chronic immune system activation is just one possibility of energy and protein deficiency (105). Hepatic overload (through chronic fructose intake, environmental toxins, hormonal stress) demands a higher energy turnover in the liver. Situations in which an expensive organ demands more energy and protein, other organs will have to reduce their metabolic rate, conserving energy and proteins for the demanding organ (103, 106).

![Table 2 The energy rate/24 hours of different human organs and tissues.](image)

Muscle, contributing to more than 40% of the body mass, uses approximately 13 kcal/24 hours. Fat tissue and bones belong to the cheapest tissues and demand 4.6 kcal/24 hours and 2.2 kcal/24 hours respectively (107).

An excellent example of a NPBS is chronic fatigue. The majority of people suffering from chronic fatigue syndrome (CFS) show symptoms, which should be considered as consequence of the huge energy and protein demand of the chronic activated immune system. Another topic in CFS is the high incidence of people suffering from fatty liver disease, low thyroid hormone function and insulin resistance (108, 109, 110, 111). Impaired thyroid hormone function induces low basal metabolism and inactivity (¿??).
Resuming, it seems plausible to state that physical inactivity as part of NPBD could actually be a protective strategy against severe or more damage and infection, an energy conservation strategy and an avoidance strategy against possible psycho-emotional conflicts. If so, treatment for people with physical inactivity disease (PID) should be based upon inhibition of the immune system, improvement of energy distribution, recovery of insulin sensitivity and reduction of psychosocial stress. Even other factors such as shame coping style (117), socio-demographic conditions (118), childhood abuse (119) and lack of employment (120), causing an inactive phenotype should be considered just part of the etiological factors leading to NPBS.

**NPBS and engaging in physical activity; discussion**

As it is stated in this article, physical inactivity disease should be considered a non-permissive brain syndrome, based on multiple factors but all related with a possible threat for brain energy deficiency. Our hypothesis can be easily tested through measurement of biomarkers such as basal metabolic rate, acute phase proteins, the use of validated questionnaires and the influence of integrative “motivational” treatment and the measurement of engaging in spontaneous and voluntary exercise after intervention. Basic part of the treatment of people suffering from NPBS is in depth information about the pathways leading to it and the subsequence physical inactivity.

Physical inactivity is a disease and should be considered one of the most damaging behavioural traits not only in developed but also in developing countries. Multiple etiological factors have been identified to explain this rather strange way of living (without exercise). Strange because of the fact that exercise has saved Homo sapiens during thousands of generations and is therefore programmed against inactivity. The impact of physical inactivity on systemic, metabolic, cellular, molecular and genetic level is so diverse and severe that the effort to find a so called “exercise pill” will probably will be too good to be true (121). Engaging people in physical activity needs an integrative intervention based upon deep learning, immune system regulation, recovery of insulin sensitivity and normalizing of energy and energy distribution (50). Part of the optimal treatment is based on motivation, increase of inevitable spontaneous exercise (absence of elevators) and on promoting evolutionary biorhythm, including a feast/famine rest/exercise rhythm (51). Education in the need of engagement in physical activity should probably begin when the next generation starts; at school (69).
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Influence of a 10 days mimic of our ancient lifestyle on anthropometrics and parameters of metabolism and inflammation.

The ‘Study of Origin’.

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Abstract

Background: Chronic low-grade inflammation and insulin resistance are intimately related entities that are common to most, if not all, chronic diseases of affluence. We hypothesized that a short-term intervention based on ‘ancient stress factors’ may improve anthropometrics and clinical chemical indices.

Objective

Study whether a 10-day-mimic of a hunter-gatherer lifestyle favorably affects anthropometrics and clinical chemical indices.

Methods

Fifty-three apparently healthy subjects and two patients with fibromyalgia (22–69 years, 28 women), in 5 groups, engaged in a 10-day trip through the Pyrenees. They walked 14 km/day on average, carrying an 8-kilo backpack. Raw food was provided, self-prepared and water was obtained from waterholes. They slept outside in sleeping bags and were exposed to temperatures ranging from 12–42 °C. Anthropometric data and fasting blood samples were collected at baseline and the study end.

Results

We observed median decreases (p≤0.002) of body weight (-3.5 kg), BMI (-1.1 kg/m²), hip (-3 cm) and waist (-5 cm) circumferences, glucose (-0.6 mmol/L), HbA1c (-0.1%), insulin (-4.7 pmol/L), HOMA-IR (-1.2 mmol•mU/L²), triglycerides (-0.14 mmol/L), total cholesterol (-0.7 mmol/L), LDL-cholesterol (-0.6 mmol/L), triglycerides/HDL-cholesterol (-0.55 mol/mol) and FT3 (-0.8 pmol/L). Changes in anthropometrics were unrelated to changes in clinical chemical indices, except for FT4 and FT3. ASAT (11 IU/L), ALAT (6 IU/L), ASAT/ALAT ratio (0.14) and CRP (0.56 mg/L) increased, and their changes were interrelated.

Conclusion

Coping with ‘ancient mild stress factors’, including physical exercise, thirst, hunger and climate, may influence immune status and improve anthropometrics and metabolic indices in healthy subjects and patients with fibromyalgia.
1. Introduction

Chronic non-communicable diseases (CNCD), including diabetes type 2, cardiovascular diseases, autoimmune diseases, chronic fatigue, depression and neurodegenerative diseases, are the major causes of morbidity, work absence and invalidity. They may be responsible for 35 million out of 52 million annual deaths worldwide (1). CNCD has recently become the major topic for the World Health Assembly. In 2013, the Lancet issued a special on CNCD (2, 3).

Treating patients with CNDC is complex and of limited availability in many countries because of costs, while its proximate treatment has many side effects. Compliance is often low (e.g. lipid lowering drugs, anti-hypertensives) and many interventions have proven unsuccessful (4).

The vast majority of CNCD are caused by unhealthy lifestyle and other anthropogenic factors. It seems that none of us is immune for the damaging effects of modern lifestyle (5, 6). Not surprisingly, many of these diseases are preventable by changes in behavior, including nutrition, physical activity and coping strategies (7, 8, 9, 10). The anthropogenic factors responsible for the CNCD pandemic include physical inactivity, unhealthy diet (e.g. high energy density refined food, too low vegetables, fruits and fish), chronic psycho-emotional stress, insufficient sleep (loss of biorhythm) and environmental toxins, including smoking (5, 11, 12, 13, 14, 15, 16, 17, 18). All of these may be considered ‘danger signals’ that activate central stress axes [sympathetic nervous system (SNS) and hypothalamus-pituitary-adrenal gland axis (HPA)] and the immune system (19, 20).

Inflammation is characterized by the five classical symptoms of rubor, dolor, calor, tumor and torpor. Inflammation requires metabolic adaptations (12). Overt injury and infection bring about short-term allostatic responses aiming at the removal of the infectious agent, engaging in repair, and, ultimately, recovering homeostasis in a highly coordinated fashion (21). While ancient infectious challenges induce optimal responses with self-resolving capacity, anthropogenic inflammatory stimuli deriving from modern society provide us with weak and long-lasting immunological responses that take us to a condition of chronic systemic low-grade inflammation with accompanying chronic hypometabolic adaptations (22, 12, 23). It has become clear that many, if not all, CNCD are characterized by a state of low-grade inflammation (LGI, 24, 25) that comes along with (e.g.) insulin resistance, hyperleptinemia, cortisol resistance, subclinical hypothyroidism and nerve-driven immunity. Jointly, they are responsible for the gradual development of multiple comorbidities together referred to as the typically Western diseases of affluence (26, 11, 27, 28, 29, 30, 31).
The absence of ancient immune challenges in current Western societies inspired us to hypothesize that acute stress from ancient danger signals causes redistribution of the immune system towards its evolutionary preferred locations, and thereby favorably affects the state of chronic systemic low-grade inflammation, normalizes stress axes activities, recovers rhythmic function and restores insulin-insensitive pathways. Mild stress factors may activate resolution responses based on survival mechanisms that originate from millions of years of evolutionary pressure. In this study we investigated whether such ‘ancient stressors’, provided by a 10-day trip through the Pyrenees, improved anthropometrics and various clinical chemical parameters of low-grade inflammation, stress and metabolic control in 53 apparently healthy adults and two patients with fibromyalgia. The objective was to provide proof of principle that humans can influence their immune and metabolic systems by exposure to ancient mild acute stress factors. Our intervention mimicked, to some extent, the ‘conditions of existence’ of ancestral and current hunting/fishing-gathering populations.

2. **Subjects and methods**

**Study group**

The participants were students, scientists, physicians and other health professionals who were engaged in clinical Psycho-Neuro-Immunology (PNI) courses throughout Europe. They were interested to experience the impact of ancient lifestyle on their own health and well-being and therefore jointly decided to engage in this study. No consent from a medical ethical committee was deemed necessary, for which we refer to the constitutional law of self-determination, in which people have a basic right to decide what they want to do with their health (included in the patients self-determination act, United States 1991 and the Council of Europe 2009). The participants were part of their own team, united in a research consortium (see acknowledgments). They covered their own expenses and there were no grants. They appointed one of us (LP) as the study coordinator. All volunteers signed an informed consent and all were informed about the trip details. The Catalan Government and the local government of Tremp (Spain) gave permission to execute our study without any restrictions.

We included apparently healthy adults and two patients with fibromyalgia. The fibromyalgia syndrome was diagnosed by medical specialists. Exclusion criteria were cardiovascular diseases, psychiatric diseases and chronic use of medication for serious illnesses.

**Study design**

Groups of 11 subjects, at most, participated in this 10-day trip through the Spanish Pyrenees during the summers of 2011 (n=10), 2012 (n=32) and 2013 (n=11). The participants lived outdoors and walked from one water-source to another. Food was provided by the organization and with help of forest-guards from official institutes of the Catalan county.
Food intake was planned before the trip, based on the average daily food intake by the traditionally living Hadzabe people in Tanzania (Supplementary Tables 1 and 2). The use of mobile phones or other electronic devices was not allowed.

The detailed activities and condition during the 10-day study were as follows:

- First day, arrival at the hospital of Tremp (Catalonia, Spain) with an air-conditioned bus from Barcelona (2.5 h drive). Participants were once again informed about the trip. Anthropometric data and blood samples were collected in the fasting state.

- Daily walking trips from waterhole to waterhole, with an average walking distance of about 14 km/day, including altitude differences up to approximately 1,000 m. The participants carried their own backpacks with an average weight of 8 kg. The trip took place in the part of the pre-Pyrenees with a maximum altitude of 1,900 meters above sea level.

- Participants consumed two meals daily. The first was provided by the organization halfway and the second on arrival at the camping site. Animals, including ducks, chickens, turkeys, rabbits and fish, were delivered alive and killed by the participants. Fish were caught with nets in the Noguera river. All foods were prepared on the spot by the participants. Nutritional details are in Supplemental Table 2.

- The participants slept outside in sleeping bags on small inflatable mattresses. Outside temperatures varied from 22 to 42 °C during daylight, whereas night temperatures varied from 12 to 21 °C. One group experienced a day of snow in the middle of July, which prompted the organization to provide hotel accommodations for a single night.

- Bulk (intermittent) drinking behavior was recommended by drinking as much as possible (up to satiety) after reaching a waterhole. The waterholes contained non-chloritized drinking water.

- Some manual work was done to clean mountain trails as agreed upon with the Catalan Government.

**Anthropometric data, sample collection and analyses**

Sixteen anthropometric and clinical chemical parameters were measured before departure to the Pyrenees and after return. Anthropometric measurements were measured by one of us (LP) at the hospital of Tremp. The subgroup of two participants with fibromyalgia syndrome was followed for more than two years. Fasting heparin-, oxalate- and EDTA- anti-coagulated blood samples were collected by venipuncture in the first morning and the morning of the 10th day at the study end. All samples were transported at 5 °C and processed within 1 h. Analyses were done in the clinical laboratory of the hospital of Tremp.
HbA1c, total-cholesterol, HDL-cholesterol, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and glucose were determined with a Cobas c-501 analyzer (Roche, Madrid, Spain). Serum insulin was measured by chemo-luminescent assays, using Dxi-600 (Beckman, Barcelona, Spain) and Liaison XL (Diasorin, Madrid, Spain), respectively. High sensitivity C-reactive protein (CRP) was measured with a Behring Nephelometer II Analyzer System. HOMA-IR (\text{mmol}\cdot\text{mU/L}^2) was calculated by glucose (in mmol/L)*insulin/22.5 (in mU/L) (Hill 2013)

**Statistics**

Statistical analyses were performed with IBM SPSS statistics version 23.0 (IBM Corp). Changes during the intervention were analyzed with the Wilcoxon signed rank test at p<0.05. Interrelations between variables were analyzed by Spearman’s correlation coefficient at p<0.05.

**Results**

**Study group**

There were 55 participants. Their median age was 38 years (range 22-67). The number of women was 28 (50.9%). Baseline anthropometrics are in Table 1.

**Course of the trip**

The 10-day trip went through the low and middle-high part of the Pyrenees. The majority of participants did very well. If one of them got too tired, LP or JA carried his/her backpack for as long needed. Trips were made from one waterhole to another, with a consistent midday pause of 1-1.5 h. The Mountainside of the Pyrenees is composed of hard soil and many of its vegetation carries thorns. Most participants suffered from small wounds on arms and legs, caused by the thorns of the aliaga, a plant belonging to the original vegetation of the Pyrenees. None of them suffered from infected wounds and most appeared fully cured at the end of the trip. Participants suffered from hunger feelings during the first three days, but gradually got used to eating only twice daily. Only one participant discontinued the trip, because she had different expectations. The local organization arranged transport and she left. The other participants enjoyed the trip for the full 10 days, without exceptions. Interestingly, the majority, including LP, wanted to go home after 7 days (see discussion).

Feelings of thirst were moderate at the beginning, but ameliorated after 3 days. Participants noticed that they could drink increasingly more water upon arrival at a waterhole and gradually experienced less needs for ‘in-between water stops’. Three participants suffered from what might have been neuroglycopenic periods, feeling weak, hungry, cold, dizzy and
trembling. However, measurement of their blood glucose level by finger prick did not reveal hypoglycemia. One of these participants was grossly overweight and exhibited fasting glucoses highly surpassing the normal range. He was not able to carry his backpack during the first three days, but managed surprisingly well during the last. At night, some participants were affected by the cold. They needed a thicker sleeping bag, which was supplied. Participants went asleep at sunset and rose at sunrise. Overall, participants felt good, occasionally tired, but not at all overloaded. Mosquitoes were a nuisance at night and therefore a liquid mosquito repellent was provided by the organization. Several participants suffered from diarrhea at the trip’s end, probably from drinking water from the non-chloritized waterholes. Taken together, the vast majority of the participants enjoyed the trip and recognized the benefits by feeling more healthy and recovered from Western stressful life.

**Anthropometrics and clinical chemical indices**

Anthropometric and clinical chemical data collected before and after the excursion were available from 23-53 participants (Table 1). The missing values were attributable to the 2012 groups. Probably because of procedural imperfections in the Tremp lab, the outcome of the insulin assay could not be performed in various series.

We found (Table 1) that body weight decreased with a median (range) of -3.4 kg (-7.5 to -0.7), BMI with -1.2 kg/m² (-4.4 to -0.2), hip circumference with -3 cm (-17 to +5), waist circumference with -5 cm (-18 to +9) and waist/hip ratio with -0.02 (-0.14 to +0.10).

We also observed decreases (median; range; Table 1) of: glucose (-0.6; -1.7 to +0.5 mmol/L), HbA1c (-0.1; -0.4 to +0.2 %), insulin (-4.7; -31.4 to -0.2 pmol/L), HOMA-IR (-1.2; -7.0 to -0.4 mmol*mU/L²), triglycerides (-0.14; -6.12 to +2.18 mmol/L), total cholesterol (-0.7; -2.8 to +0.4 mmol/L), LDL-cholesterol (-0.6; -3.1 to +0.6 mmol/L), triglycerides/HDL-cholesterol ratio (-0.55; -8.98 to 1.34 mol/mol), and FT3 (-0.8; -3.4 to +3.1 pmol/L).

On the other hand we found that ASAT and ALAT activities increased with 11 IU/L (-8 to 54) and 6 IU/L (-13 to 52), respectively, while CRP increased with 0.56 mg/L (-15.72 to +41.07). Figure 1 shows the median and individual changes of ASAT (panel A), ALAT (panel B) and CRP (panel C). The ASAT/ALAT ratio before the intervention was 1.23 (0.68 – 2.00) and increased with 0.08 to 1.31 (0.48 – 2.06).

Figure 2 shows the medians of the percentage change for the anthropometric and clinical chemical parameters that were found to change significantly during the 10 days trip through the Pyrenees.
Two subjects with fibromyalgia

The two female participants (ages 37 and 38 years) were part of the 2011 group. Both managed surprisingly well. The first three days they still suffered from overall pain, but these gradually disappeared after 7 days. From the start, they preferred to carry their own backpacks but were in too much pain. LP and one of the others carried their backpacks most of time during the first three days. They were able to carry their own backpacks from then. Fatigue symptoms were severe during the first 4 days but diminished substantially after the fifth. Sleeping problems vanished almost immediately. Bowel movement was compromised at start, but improved during the trip to become almost normal in one of them at the end. The second patient kept complaining about abdominal pain, but stool consistency and frequency were normal. No notable differences were observed in the changes of their clinical chemical indices when compared with other participants. Both showed increases of ASAT (from 26 to 48; and 36 to 53 IU/L), ALAT (18 to 30; 25 to 39 IU/L) and CRP (0.37 to 2.71; 0.17 to 0.64 mg/L). while their HOMA-IR decreased (0.48 to 0.31; 1.04 to 0.52 mmol*mU/L²). Their ASAT, ALAT and CRP values decreased during the months after the trip. Three months after the trip her ASAT had decreased from 48 to 22 IU/L in one of them, while ALAT decreased from 30 to 19 IU/L, and CRP from 2.71 to 0.5 mg/L. The other showed changes from 53 to 18 IU/L for ASAT, 39 to 16 IU/L for ALAT and 0.64 to 0.2 mg/L for CRP. Follow-up of both patients occurred during three years. At present both women are healthy. One became pregnant and mother of a healthy child. She started her own clinical PNI institute, while the other is completing an University master.

One subject with arrhythmia.

One of the participants suffered from cardiac arrhythmia since 2000, following a sternum fracture in a car accident. He was on medication since then. During the trip he stopped taking treatment and did not suffer from arrhythmic periods during the 36-month-period that passed since the study end.

Interrelationships

Relationships between changes of the anthropometric and clinical chemical indices are presented in Supplemental Table 3. Importantly, we found that the changes in weight, BMI, hip circumference, waist circumference and waist/hip ratio were generally unrelated to the changes of clinical chemical indices. Exceptions were the negative associations (p<0.05) between waist circumference and FT3 (r = -0.359), and waist/hip ratio and FT4 (r = -0.360). The change in HOMA-IR was negatively related to changes in total cholesterol (r = -0.457) and LDL-cholesterol (r = -0.436). Finally, we found that the changes in ASAT, ALAT and CRP were positively interrelated (ASAT vs. ALAT r= 0.777; ASAT vs. CRP r=0.508; and ALAT vs. CRP
Age proved positively related to the change of ASAT ($r=0.371$), but was unrelated to the changes of ALAT and CRP.

**Discussion**

The aim of this study was to investigate whether a 10-day trip through the Pyrenees favorably affects anthropometric-, metabolic- and inflammatory-parameters in apparently healthy subjects and two patients with the fibromyalgia syndrome. The trip mimicked to some extent the ‘conditions of existence’ of ancient and contemporary hunting-gathering populations. We found that the intervention was well tolerated and that all participants, except for one dropout, experienced a better subjective feeling of health following its completion. Also the two patients with fibromyalgia experienced improvements: they were able to meet the needed physical activity after 7 days. The pain vanished and favorable effects seemed to remain during a subsequent follow up of three years. The trip caused decreases in body weight and BMI (median change 4.8%), hip circumference (3%), waist circumference (5.6%) and waist/hip ratio (2.5%)(Table 1; Figure 2). Among the clinical chemical indices we found decreases of glucose (12.5%), insulin (55%), HOMA-IR (58.1%), HbA1c (1.8%), triglycerides (20%), total-cholesterol (13.7%), LDL-cholesterol (21.9%) and triglycerides/HDL-cholesterol ratio (19.3%). On the other hand, the medians of ASAT and ALAT increased with 48.0% and 35.7%, respectively, while CRP increased with 110.1%.

**Favorable effects**

Altogether we found that 3 features of the metabolic syndrome improved, i.e. body mass, glucose homeostasis and circulating lipids. The fourth, i.e. blood pressure, was not recorded. The metabolic syndrome, also named the insulin resistance syndrome, is a well-established risk factor for various diseases of affluence, including type 2 diabetes, cardiovascular disease, essential hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease, certain types of cancer (colon, breast, pancreas), sleep apnea and pregnancy complications, such as preeclampsia and gestational diabetes (32). Although we did not aim at hard endpoints, our results suggest that the 10-day intervention could be of value to both primary and secondary prevention of the ‘typically Western diseases of affluence’.

**Potential mechanisms**

Our intervention is based on causing ‘mild acute stress’ in humans who in their usual daily lives are exposed to the chronic stress commensurate with our modern lifestyle. Acute stress promotes release of stress hormones, including adrenaline, noradrenaline and cortisol, that each cause profound metabolic and immunologic adaptations (33). For instance, a recent study by the group of Pickkers (34), showed that extreme cold exposure, combined with breathing exercise (producing intermittent hypoxia), profoundly increases adrenaline secretion. This study and others (35, 33) show that acute stress factors increase autonomic.
activity, accelerate immune cell proliferation and differentiation, and also stimulate the anti-inflammatory component of the immune system (i.e. production of IL10, lactoferrin, lysozymes) (26). Nevertheless, mild stress initially produces a pro-inflammatory response, which may subsequently give rise to recovery from the reigning state of chronic low grade inflammation and the return to homeostasis (36, 37).

In line with the above, we found that the observed changes in HOMA-IR and lipids were independent of weight loss, suggesting that a combination of lifestyle factors might be at stake. Major, highly interacting, lifestyle factors contributing to typically Western diseases are poor diet, insufficient physical activity, chronic stress, insufficient sleep, abnormal microbial flora and environmental pollution (smoking included) (38, 11). However, other mismatches with our ancient lifestyle are less appreciated. For instance, the participants suffered from thirst. Thirst relates to oxytocin production and the inhibition of stress axis activity (39, 40).

The participants were also disconnected from daily trouble and 'self-made' stress, which reduced the number of anthropogenic stress factors and possibly other inflammatory 'danger signals' (16). Another factor might be the prohibited use of mobile telephones and other electronic devices. Although controversial, chronic mobile telephone usage may activate stress systems as evidenced by a recent study of Hamzany et al. (41). Chronic use of mobile telephones also negatively affects the production of anti-inflammatory substances in saliva (42). Absence of artificial light might be another factor. The trip forced the participants to adopt a 'natural day-night rhythm' in which the sleep-wake cycle was not dominated by social life, but rather by sunlight (43, 44, 45).

Spontaneous physical activity prior to food and water intake might be another beneficial factor. The postprandial inflammatory response has been identified as an independent risk factor for cardiovascular, metabolic and other non-communicable disorders (26, 46, 47, 48). Pre-prandial exercise did not only blunt the pro-inflammatory response after food intake, but also produced a shift towards the production of anti-inflammatory mediators by the immune system and adipose tissue, conferring protection against possible pathogens present in food (49, 50). Another important difference between Western life and the 10-day trip in the Pyrenees might be the presence of 'cutaneous- and other body surface- directed danger signals'. All participants suffered from little wounds on hands, arm and legs because of small injuries inflicted by sharp thorns and other natural obstacles. In addition, several participants suffered from mild gastrointestinal disorders and diarrhea. Fiuza-Luces et al. (51) attributed positive health effects to so-called hormetic triggers, including small external wounds and light muscle damage. Although speculative, the immune system might have migrated to sites that have been most susceptible to the damaging effects of the environment during evolution, including those affecting the skin, the gastrointestinal tract and the lungs, jointly being the sites with the highest need of immune surveillance (33).
Taken together, we propose that we are dealing with complex interacting lifestyle factors (5, 11) and that the current tendency to perform interventions aiming at single components, whether or not designed as RCTs, might suffer from a reductionist approach.

**Possible adverse effects**

We found increases of ASAT, ALAT and CRP, which at first glance might be regarded as genuine adverse effects. Increases of ASAT and the ASAT/ALAT ratio are related to cardiac muscle damage (52), while those of ALAT (53) and CRP (54) are intimately related to liver damage and infection, respectively.

Extreme sports, such as marathon and triathlon, are well known to elicit increases of lactate dehydrogenase, creatine kinase, ALAT, ASAT, ASAT/ALAT ratio, CRP and cardiac troponins (55, 56, 57, 58). The responses may easily exceed the upper limit of the reference range into the myocardial infarction area. The increases of cardiac troponins were similar when exercise was performed under controlled normoxic or hypoxic conditions, but proved dependent on exercise duration and intensity, possibly aggravated by hypoxic conditions (56). Noakes et al. (59) also observed that novice runners had much higher responses than experienced runners and these results were confirmed in a later study (60). We found that the augmentation of ASAT increased with age, as previously reported by Jastrzebski et al. (57). Increases of cardiac markers under these conditions have not been firmly associated with irreversible cardiac muscle damage and are at present considered benign, at least in well-trained subjects. On the other hand, there are currently no data from long-term follow-ups (61).

The increases of both ALAT and CRP might also point at moderate liver damage and inflammation due to environmental exposure, the latter causing mild gastrointestinal infections from drinking water from waterholes, and small injuries on legs and arms inflicted by thorns and falls. Although the aforementioned plausible adverse effects will definitely require more attention in future interventions, they are not unexpected in the light of hunter-gatherer populations. For instance, the Pygmies exhibit huge gamma-globulin bands in the classical electrophoretic profiling of serum proteins, pointing at exposure to a host of different microorganisms and parasites (62). Therefore, apart from the effects of intensive physical activity, the current findings remind us of the super-hygienic conditions of our current lifestyle. Hygiene is a major factor in longevity, but may, as a trade-off, also be at the basis of e.g. autoimmune disease; the so-called ‘hygiene hypothesis’ (63, 64, 65). For instance, a recent study in pregnant and newborn mice revealed that helminth colonization exerts beneficial effects on the infectious response of the offspring brain and also on microglial
sensitization and cognitive dysfunction at adult life (66).

**Comparison with previous studies**

Our study is not the first to suggest that mimicking the lifestyles of traditional hunter-gatherer populations may be beneficial to our health. Already in 1984, O’Dea et al. showed that overweight Australian Aborigines with type 2 diabetes who reverted to their original lifestyle for 7 weeks, were able to improve, or even normalize, the characteristic abnormalities of diabetes, including improvements of body weight and fasting glucose, insulin and triglycerides. The favorable changes were attributed to weight loss, low-fat diet and increased physical activity (67). Another example of the protective effects of our ‘ancient conditions of existence’ against modern lifestyle and ‘Western diseases of affluence’, may be compiled from the studies of the Kitava people in Papua New Guinea (68, 69). Lindeberg et al. showed that these people, living a traditional lifestyle (e.g. consuming wild foods with profound physical activity) showed low rates of cardiovascular disease, obesity and other modern diseases, probably because of higher insulin sensitivity and lower levels of insulin, uric acid and leptin (70).

**Limitations**

Our study has many limitations. There was no control group and we also did not employ a cross-over or RCT-like design. The investigated group was relatively small and we only measured a small number of ‘soft’ parameters. Hard endpoints can obviously not be expected in short-term interventions in small groups with good general health. The findings of the two patients with fibromyalgia and the single subject with arrhythmia should be regarded as ‘anecdotal’. However, whether a placebo effect or not, the subjective feeling of better health is certainly important and so are the observed changes in anthropometric and clinical chemical parameters. Our primary objective was to provide a proof of principle. More studies with more participants are certainly needed, including the recording of more parameters to objectivize e.g. the feeling of improved health. Also the minimum duration and intensity needed to demonstrate favorable effects are uncertain as yet.

**Conclusions**

The outcome of this 10-day ‘Study of Origin’ suggests that a short period of return to the ‘conditions of existence’ similar to those on which our genome is based may improve anthropometrics and metabolism by favorably challenging the immune system in apparently healthy subjects and possibly patients with fibromyalgia. The ‘return’ may come with some costs in more active infection, as a trade-off for the ‘chronic systemic low grade inflammation’ typical of our current lifestyle of affluence. We may increasingly appreciate that we cannot have it all, while the evolutionary lessons of Darwin and intervention studies (71) teach us that
prevention might be more rewarding and affordable than the current culture of medical treatment.
Acknowledgments

We thank the Catalan Government and the local government of Tremp for permission to execute the study. Mr. José Ángel Alert Rafel, head of environmental issues of the city of Tremp, is gratefully acknowledged for arranging all licenses needed for fishing, hunting, outdoor sleeping and fire making. We further thank all members of the consortium: Laura Alapont, Estefanía Alayón, Cristina Alayon Rocio, Josep Angel Alert, Sheila Backus, Timo Bartel, Rita Beldman, Azemina Bennet, Jeroen Bierman, Jacoline Bogaerds, Dick van Bolhuis, Mike Budd, Jens Johannes Freese, Anja Gehring, Michaela Gostner, Thomas D´Have, Jan Willem Den Hollander, Sabine de Hooghe, Javier de la Hoz, Daniel König, Richard de Leth, Nicolai Loboda, Jorge López, Tjaliing Kramer, Anouk Leek, Bianca Manzano, Ivan Maria, Nennie van der Matten Pablo Medina, Willemijn Melle, Raymond Niemeyer, Willeke v.d. Oord, Sarai Perez Martinez, Leo Pruimboom, Ralph Ree, Claire Rother, Sandra Rossi, Irine Schmid, Carolina Sigalat, Maike Slikker, Michael Stary, Monika Barbara Stary, Lucy Stephens, Fernando Luca De Tena, Wilma Tuk, Johannes Ullrich, Jerome Jacques Verbeek, Vet-Gos (Proj. Soto), Boukje Vogel, Robin Witte.
References


Figure 1. Median and individual changes of ASAT (panel A), ALAT (panel B) and CRP (panel C) during the 10 days trip through the Pyrenees.
Figure 2. Medians of the percentage changes of anthropometric and clinical chemical parameters during the 10 days trip through the Pyrenees.

*Only significant changes are shown (see Table 1). For abbreviations see legend of Table 1.*
Table 1. Anthropometrics and clinical chemical indices at baseline and at the study end

Data are medians (range). Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-estimated insulin resistance; LDL, low-density lipoprotein; N.M. Not measured; TG, triglycerides; TSH, thyroid-stimulating hormone. *, Significant difference between the values before and after the intervention by Wilcoxon signed rank test at p<0.05.
<table>
<thead>
<tr>
<th>Food consumed</th>
<th>Hadza en%</th>
<th>kcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>25</td>
<td>625</td>
</tr>
<tr>
<td>Tubers</td>
<td>17</td>
<td>425</td>
</tr>
<tr>
<td>Wild Berries</td>
<td>25</td>
<td>625</td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green Vegetables</td>
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<td></td>
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<td>Baobab</td>
<td>11</td>
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<tr>
<td>Honey</td>
<td>22</td>
<td>550</td>
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<td>Total</td>
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**Supplemental Table 1. Average food intake of Hadzabe hunter-gatherers**


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<tr>
<th>Nutrient</th>
<th>Average amount</th>
<th>kcal /unit</th>
<th>total kcal</th>
<th>kcal/part/10 days</th>
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<td>80</td>
<td>105</td>
<td>8400</td>
<td>840</td>
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<tr>
<td>Apple</td>
<td>70</td>
<td>20</td>
<td>1400</td>
<td>140</td>
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<tr>
<td>Melon</td>
<td>10 kilo</td>
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<td>3000</td>
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</tr>
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<td>4,5 kilo</td>
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<td>Pineapple</td>
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<td>2260</td>
<td>226</td>
</tr>
<tr>
<td>Dates</td>
<td>1,1 kilo</td>
<td>2760</td>
<td>3036</td>
<td>304</td>
</tr>
<tr>
<td>Onions</td>
<td>12 kilo</td>
<td>400</td>
<td>4800</td>
<td>480</td>
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<tr>
<td>Lettuce (6 types)</td>
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<td>160</td>
<td>480</td>
<td>48</td>
</tr>
<tr>
<td>Cucumber</td>
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<td>112</td>
<td>336</td>
<td>33</td>
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<tr>
<td>Garlic</td>
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<td>132</td>
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<td>26</td>
</tr>
<tr>
<td>Olives</td>
<td>1,5 kilo</td>
<td>1660</td>
<td>2500</td>
<td>250</td>
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<tr>
<td>Carrots</td>
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<td>410</td>
<td>985</td>
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<td>220</td>
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<td>Pumpkin</td>
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<td>1100</td>
<td>110</td>
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<td></td>
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<tr>
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<td>6300</td>
<td>6300</td>
<td>630</td>
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<td>3 liters</td>
<td>8400</td>
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<td>2520</td>
</tr>
<tr>
<td>Honey</td>
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<td>14000</td>
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<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>3290</td>
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</tr>
<tr>
<td>Deer</td>
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<td>2628</td>
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<tr>
<td>Rabbit</td>
<td>2 kilo</td>
<td>2764</td>
<td>5528</td>
<td>553</td>
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<tr>
<td>Sweat water fish</td>
<td>8 kilo</td>
<td>1590</td>
<td>12720</td>
<td>1272</td>
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<tr>
<td>Tuna in olive oil</td>
<td>5 kilo</td>
<td>4030</td>
<td>20150</td>
<td>2015</td>
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<tr>
<td>Duck</td>
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<td>Eggs</td>
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<td>7700</td>
<td>770</td>
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<td>Nuts</td>
<td>3,7 kilo</td>
<td>575</td>
<td>20275</td>
<td>2027</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>12394</td>
<td></td>
</tr>
<tr>
<td><strong>Total/pp/trip</strong></td>
<td></td>
<td></td>
<td>22216</td>
<td></td>
</tr>
<tr>
<td><strong>Total/pp/day</strong></td>
<td></td>
<td></td>
<td>2222</td>
<td></td>
</tr>
</tbody>
</table>

**Supplemental Table 2.** Average food intake of participants during the ten days trip through the Pyrenees (amount/10 persons)
### Supplemental Table 3. Spearman’s correlation coefficients for the relations between the changes in anthropometric and clinical chemical indices during the study

Changes refer to the difference between pre- and post-intervention data. Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CRP, C-reactive protein; FT3, free triiodothyronine; FT4, free thyroxine; HBA1c, hemoglobin A1c; HDL, high-density-lipoprotein; HDL-C, high-density-lipoprotein-cholesterol; LDL, low-density lipoprotein; N.M. Not measured; TG, triglycerides; TSH, thyroid-stimulating hormone. *, Significant at p<0.05; **, significant at p<0.01.

<table>
<thead>
<tr>
<th>Δ Weight</th>
<th>Δ Hip</th>
<th>Δ Waist</th>
<th>Δ Glucose</th>
<th>Δ HBA1c</th>
<th>Δ ALAT</th>
<th>Δ ASAT</th>
<th>Δ CRP</th>
<th>Δ FT3</th>
<th>Δ Total cholesterol</th>
<th>Δ Appendicular mass</th>
<th>Δ Waist/Hip ratio</th>
<th>Δ HOMA-IR</th>
<th>Δ TGFβ1</th>
<th>TGFβ1/TGFβ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
<td>0.250</td>
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<tr>
<td>Δ Glucose</td>
<td>0.226</td>
<td>0.038</td>
<td>0.113</td>
<td>0.212</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
<td>0.320</td>
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</tr>
<tr>
<td>Δ ALAT</td>
<td>0.299</td>
<td>0.092</td>
<td>0.369</td>
<td>0.369</td>
<td>0.369</td>
<td>0.369</td>
<td>0.369</td>
<td>0.369</td>
<td>0.369</td>
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<td>0.369</td>
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<tr>
<td>Δ ASAT</td>
<td>0.389</td>
<td>0.046</td>
<td>0.206</td>
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<td>0.206</td>
<td>0.206</td>
<td>0.206</td>
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<td>0.206</td>
</tr>
<tr>
<td>Δ CRP</td>
<td>0.330</td>
<td>0.046</td>
<td>0.206</td>
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<td>0.206</td>
<td>0.206</td>
<td>0.206</td>
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</tr>
<tr>
<td>Δ FT3</td>
<td>0.330</td>
<td>0.046</td>
<td>0.206</td>
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<td>0.206</td>
<td>0.206</td>
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Summary and Future perspectives

This thesis describes the multiple ways by which the human immune system can react upon direct and indirect challenges, such as infection and wounds on the one hand, and chronic multi metabolic stress factors on the other. The immune system exhibits a type of selfish behaviour during both acute- and chronic activity states. Acute activation of the immune system is normally finalized in a short time through multiple mechanisms exerting immune inhibiting effects. Several of these mechanisms are intrinsic to the immune system itself, such as the negative biofeedback function of lactic acid produced by the anaerobic metabolism of an activated immune system (Hoque 2014, Fischer 2007). Systemic inhibitors include cortisol, testosterone and adrenalin and all these have protective short-lasting immune suppressive roles. An immune suppressive period serves four purposes. First of all it facilitates the recovery of energy sources and energy distribution to those organs and systems disposed-of during the inflammatory phase. Second, wound healing can only start when the inflammation has been finalized. The third purpose is to prevent the development of lymphocytes with sensitivity against auto-antigens, which could cause autoimmune disease. Finally, since the opposite also occurs, increased self-tolerance through long-term contact between activated lymphocytes and auto-antigens, the immune suppressive state also decreases the chance of developing cancer. Short-term immune suppression prevents self-tolerance against cancer cells, which implies that when tumour cells develop they will be recognized as non-self.

A state of chronic activity of the immune system can only be achieved when this state becomes supported by reactivation and gluconeogenic strategies, of which the development of insulin resistance with compensatory hyperinsulinemia is an example. Chronic activity of the immune system is caused by the total number of so-called anthropogenes, which include proximal lifestyle factors, such as overeating, sitting time, and insufficient sleep, but also economy, environmental toxins and politics, the latter as examples of distal factors. The sum of risk factors produces chronic activation of stress axes and endotoxaemia, causing a chronic infectious state that is referred to as chronic low-grade inflammation. This low-grade inflammation should be considered as the cause of most, if not all, chronic non-communicable diseases (CNCD).
Chapter 1. Chronic systemic low-grade inflammation

Paragraph 1.1
The brain and the immune system are the only two systems of the human body capable of dominating all other organs and systems with respect to the use of resources, including glucose. The brain dominates during daytime hours and stressful situations, whereas the immune system protects us during the night, infectious periods and wound healing. Both systems exhibit similar capacities to pull on energy and other essential resources, using strategies favouring their own functional and anatomical benefits. Human evolution has put the brain on top of the body’s systems, resulting in a shift from strong to smart. However, the immune system is very old and robust. If necessary, it is activated through a variety of non-specific factors and most often when problems are not solved in an appropriate time frame. If chronically activated the immune system demonstrates an even more selfish behaviour than the selfish brain, inducing chronic low-grade inflammation and multiple related diseases. But before castigating the immune system for this behaviour it is crucial to recognize that it is only doing what it is made for: trying to protect us.

Paragraph 1.2
In this paragraph, we focus on lifestyle changes, especially dietary habits, that are at the basis of chronic systemic low-grade inflammation, insulin resistance and ‘typically Western’ diseases. Our sensitivity to develop insulin resistance traces back to our rapid brain growth in the past 2.5 million years. An inflammatory reaction jeopardizes the high glucose needs of our brain, causing various adaptations, including insulin resistance, functional reallocation of energy-rich nutrients and by changing the serum lipoprotein composition. The latter aims at redistribution of lipids, modulation of the immune reaction, and active inhibition of reverse cholesterol transport for damage repair. With the advent of the agricultural and industrial revolutions, we have introduced numerous false inflammatory triggers in our lifestyle, driving us to a state of chronic systemic low grade inflammation that eventually leads to ‘typically Western’ diseases via an evolutionary-conserved interaction between our immune system and metabolism. The underlying triggers are an abnormal dietary composition and microbial flora, insufficient physical activity and sleep, chronic stress and environmental pollution. The disturbance of our inflammatory/anti-inflammatory balance is illustrated by dietary fatty acids and antioxidants. The current decrease in years without chronic disease is rather due to ‘nurture’ than ‘nature’, since less than 5% of the ‘typically Western’ diseases are primary attributable to genetic factors. Resolution of the conflict between environment and our ancient genome might be the only effective manner for ‘healthy aging’, and to achieve this we might have to return to the lifestyle of the Palaeolithic era, as translated to culture of the 21st century.
Paragraph 1.3
In 1996, Serhan and colleagues introduced the term ‘Resoleomics’ as the mechanistic process of inflammation resolution. Their major discovery is that the onset to the conclusion of an inflammatory reaction is a highly controlled process orchestrated by the immune system itself, and not simply the consequence of an ‘extinguished’ or ‘exhausted’ immune reaction. Resoleomics can be considered as the evolutionary conserved mechanism of restoring homeostatic balances after injury, inflammation and infection. Under normal circumstances, Resoleomics should be able to conclude inflammatory responses. However, considering the modern pandemic increase of chronic somatic and psychiatric illnesses involving chronic inflammation, it has become apparent that Resoleomics is currently not fulfilling its potentially resolving capacity. We suggest that recent drastic changes in lifestyle, including diet and psycho-emotional stress, are responsible for inflammation and for disturbances in Resoleomics. In addition, current treatments, chronic use of anti-inflammatory medication included, suppress Resoleomics. These, from an evolutionary point of view, new lifestyle factors should be considered health hazards, as they are capable of causing long-term or chronic activation of the central stress axes. The immune system is designed to provide solutions for fast, intensive, hazards and not to cope with long-term, chronic, stimulation. The never-ending stress factors of recent lifestyle changes have pushed the immune system and the central stress system into a constant state of activity, leading to chronically unresolved inflammation and increased vulnerability for chronic disease. Our hypothesis is that modern diet, increased psycho-emotional stress and chronic use of anti-inflammatory medication disrupt the natural process of inflammation resolution, i.e. Resoleomics.

Paragraph 1.4
Nowadays, CNCDs are the leading causes of work absence, disability and mortality worldwide. Most of these diseases are associated with low-grade inflammation. Here we hypothesize that stresses (defined as homeostatic disturbances) can induce low-grade inflammation, which augments the need of water, sodium and energy-rich substances to meet the increased metabolic demand induced by the stressor. One way of triggering low-grade inflammation is by augmented intestinal barrier permeability through activation of various components of the stress system. Although beneficial to meet the demands necessary during stress, increased intestinal barrier permeability also raises the chance of translocation of bacteria and their toxins, i.e. their passage from the intestinal lumen into the blood circulation. In combination with modern life-style factors, increased bacteria/bacterial toxin translocation, arising from a more permeable intestinal wall, causes a low-grade inflammatory state. We support this hypothesis with numerous studies, showing associations with CNCDs and markers of endotoxaemia, and thereby suggest that this mechanism plays a pivotal, and perhaps even causal, role in the development of low-grade inflammation and its related diseases.
Paragraph 1.5
Wheat is one of the mostly consumed cereal grains worldwide and makes up a substantial part of the human diet. Although government-supported dietary guidelines in Europe and USA advise individuals to eat ample amounts of (whole) grain products per day, cereal grains contain ‘anti-nutrients’, such as wheat gluten and wheat lectin, that in humans can elicit dysfunction and disease. In this review we discuss evidence from in vitro, in vivo and human intervention studies that describe how the consumption of wheat, but also other cereal grains, may contribute to the manifestation of chronic inflammation and auto-immune diseases by increasing intestinal permeability and initiating a pro-inflammatory immune response.

Paragraph 1.6
Various recent, positively selected, adaptations to new nutrients have been identified. Lactase persistence is among the best known, enabling exposed populations to drink milk, notably to digest lactose, at post-weaning age. An augmented number of amylase gene (AMY1) copies, giving rise to higher salivary amylase activity, has been implicated in the consumption of starch-rich foods. Higher AMY1 copy numbers has been demonstrated in populations with recent histories of starchy diets. It is, however, questionable whether the resulting polymorphisms have merely exerted positive selection pressure by providing easily-available sources of macro- and micronutrients. Humans have explored new environments more than any other animal. Novel environments challenge the host, but especially its immune system with new climatic conditions, foods and especially pathogens. With the advent of the agricultural revolution and the concurrent domestication of cattle came new pathogens and diseases (zoonoses). We contend that specific new food ingredients (e.g. gluten) and novel pathogens drove selection for lactase persistence and higher AMY gene copy numbers. Both adaptations provide ample glucose for activating the sodium glucose-dependent co-transporter 1 (SGLT1), which is the principal transporter of glucose, together with sodium and water, in the small intestine and to a lesser extent the stomach (Chen 2010). Following starch ingestion, people with higher AMY1 copy numbers have more rapid increases of insulin and concomitantly lower plasma glucose, compared with counterparts with lower AMY1 copies (Mandel 2012). Rapid uptake of glucose, sodium and water confers protection against potentially lethal dehydration, hyponatraemia and ultimately multiple organ failure, especially during infection accompanied by diarrhoea and vomiting. Also oral rehydration therapy aims at SGLT1 activity and is the current treatment of choice for these conditions. We hypothesize that lifelong lactase activity and rapid starch digestion should be looked at as the evolutionary precursor of the current oral rehydration therapy.
Chapter 2. Physical inactivity

Paragraph 2.1
In recent years, it has become clear that chronic systemic low-grade inflammation is at the root of many, if not all, ‘typically Western’ diseases associated with the metabolic syndrome. While much focus has been given to sedentary lifestyle as a cause of chronic inflammation, it is less often appreciated that chronic inflammation may also promote a sedentary lifestyle, which in turn causes chronic inflammation. Given that even minor increases in chronic inflammation reduce brain volume in otherwise healthy individuals, the bidirectional relationship between inflammation and sedentary behaviour may explain why humans have lost brain volume in the last 30,000 years and also intelligence in the last 50 years. We review evidence that lack of physical activity induces chronic low-grade inflammation and, consequently, an energy conflict between the selfish immune system and the selfish brain. Although the notion is widespread that increased physical activity would improve health in the modern world, we here provide a novel perspective on this truism by providing evidence that recovery of normal human behaviour, such as spontaneous physical activity, would calm pro-inflammatory immune activity, thereby allocating more energy to the brain and other organs, and by doing so would improve human health.

Paragraph 2.2
The evolution of humankind has taken millions of years, during which environmental factors gradually shaped its genome with the aim to adapt to the reigning circumstances (Darwin). One of the most vital behavioural adaptations of mammals in general, and humans in particular, is their capacity to be self-sufficient through physical activity. Physical activity abilities, including long distance running, jumping, climbing and carrying things have probably been necessary to outrun wild animals, to search for food and to hide from danger. In contrast, individuals physically or psychologically unable to ‘take care of themselves’, were more susceptible to early death and therefore genetic extinction.

The current society is characterized by sedentary, instead of ‘moving’, individuals. Physical inactivity is not just a possible factor related with chronic disease, but should be considered the actual cause of the majority of human illness. The majority of people know that exercise is necessary and beneficial. Nevertheless, almost 75% of the current population doesn’t reach the estimated minimum of the necessary activity. Physical inactivity belongs to the characteristics of sickness behaviour; which is probably protective for the organism. Sickness behaviour, including depressive mood, seems to protect against infection, injury, social conflict and facilitates energy conservation. Sickness behaviour is based on immune-brain mechanisms and can be defined as non-permissive behaviour. Long-term non-permissive behaviour can lead to chronic disease because of reduced physical activity and self-defeating
coping styles, converting non-permissive behaviour into a non-permissive brain disorder. We propose that physical inactivity disease is synonymous with a non-permissive brain disorder and that this disorder produces a so called ‘reptile phenotype’, characterized by hypothermia, poor hair growth, decreased fertility and low basal metabolic rate.