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Intermittent living; the use of ancient challenges as a vaccine against the deleterious effects of modern life – A hypothesis

Leo Pruimboom[a,*], Frits A.J. Muskiet[b]

[a] Natura Foundation, Numansdorp, The Netherlands
[b] Laboratory Medicine, University Medical Centre Groningen (UMCG), University of Groningen, The Netherlands

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ABSTRACT

Chronic non-communicable diseases (CNCD) are the leading cause of mortality in developed countries. They ensue from the sum of modern anthropogenic risk factors, including high calorie nutrition, malnutrition, sedentary lifestyle, social stress, environmental toxins, politics and economic factors. Many of these factors are beyond the span of control of individuals, suggesting that CNCD are inevitable. However, various studies, ours included, show that the use of intermittent challenges with hormetic effects improve subjective and objective wellbeing of individuals with CNCD, while having favourable effects on immunological, metabolic and behavioural indices. Intermittent cold, heat, fasting and hypoxia, together with phytochemicals in multiple food products, have widespread influence on many pathways related with overall health. Until recently, most of the employed challenges with hormetic effects belonged to the usual transient live experiences of our ancestors. Our hypothesis; we conclude that, whereas the total inflammatory load of multi-metabolic and psychological risk factors causes low grade inflammation and aging, the use of intermittent challenges, united in a 7–10 days lasting hormetic intervention, might serve as a vaccine against the deleterious effects of chronic low grade inflammation and it's metabolic and (premature) aging consequences.

Introduction

The number of people with chronic diseases such as cardiovascular diseases (CVD), diabetes, respiratory diseases, mental disorders, autoimmune diseases (AID) and cancer has increased dramatically over the last three decades. The increasing rates of these chronic systemic illnesses suggest that inflammation [171,199], caused by excessive and inappropriate innate immune system (IIS) activity, is unable to respond appropriately to danger signals that are new from the perspective of evolution. The challenges lead to unresolved or chronic inflammatory activation in the body and a state of low-grade inflammation (LGI).

Known risk factors for LGI and chronic disease are premature aging, smoking, socioeconomic status, obesity, chronic psychosocial stress, sedentary lifestyle, toxins, insufficient sleep, nutritional factors (dose, composition, time, frequency), abuse of legal and illegal drugs, alcohol included, politics and economy [87,180,179,57,58]. These, mostly environment-driven, risk factors seem inevitable in current Western societies and their shares and intensities are most likely destined to further increase in the future. Importantly, many of these risk factors exhibit interaction, while contemporary humans are likely to suffer from these challenges in concert. This current 'conditions of existence' (Darwin) contrast with the stress factors experienced by traditionally living populations who still live in the environment of our ancestors. In that environment, they had to cope with short-term mono-metabolic danger factors (e.g. hunger, thirst, cold, heat), whereas modern humans are exposed to multi-metabolic risk factors that stimulate an energy conflict between organs and major systems [223]. The ensuing conflict between current experience and to what our genes and stress systems

Abbreviations: AA, arachidonic acid; AID, autoimmune diseases; ALAT, transaminases alanine aminotransferase; ARE, antioxidant response element; ASAT, aspartate aminotransferase; ADHD, attention deficit hyperactive disorder; BAT, brown adipose tissue; BMR, basal metabolic rate; CRP, C-reactive protein; CVD, cardiovascular diseases; CIRBP, cold-inducible RNA binding protein EPO; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HIF1, hypoxia inducible factor 1; IF, intermittent fasting; IL8, interleukin 8; IHT, intermittent hypoxia training; KEAP1, Kelch-like ECH associated protein 1; LFD, low food diversity; LGI, low-grade inflammation; MOP, mitochondrial oxidative phosphorylation; NFkB, nuclear factor kappa B; PON, plasma paraoxonase-1-arylesterase activity; mTOR, mammalian target of rapamycin; MOP, mitochondrial oxidative phosphorylation; Nrf2, N-erythroid derived -related factor 2; PD, panic disorder; PPARs, peroxisome proliferator activated receptors; RAAS, renin-angiotensin-aldosterone system; SAD, separation anxiety disorder; TNF-alpha, tumour necrosis factor alpha

* Corresponding author.
E-mail addresses: cpni.pruimboom@icloud.com, pruimboom@naturafoundation.nl (L. Pruimboom).

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are adapted is the basis of the so-called 'mismatch hypothesis' of 'typically Western' diseases.

Mono-metabolic stress factors have shaped adaptive mechanisms for survival and reproduction, such as short-lasting inflammation, insulin resistance, activation of the sympathetic nervous system and others. All of these responses emerged with the purpose to first protect the brain from damage and energy deficits [163]. Whereas mono-metabolic challenges increases basal metabolic rate, multi-metabolic risk factors may, on the other hand, cause LGI and a hypo-metabolic state [223]. The latter might be the principal reason for the deleterious effects of LGI, since a hypometabolic state causes energy deficits in multiple organs, and consequently multi-organ damage [198]. While among our ancestors, cold, heat, starvation and repetitive infections were among the major causes of death, exposure to mild cold, mild heat, short fasting periods and the regular consumption of small amounts of 'toxic' nutrients provided hormetic triggers. Mildly toxic insults, for example, derive from plant secondary metabolites, many with bitter tastes. The discovery of the Nrf2 receptor has revolutionized toxicology by unveiling the benefits of low amounts of toxins [16,83]. Ultimately, it is all about hormesis: every dose response curve is U-shaped (for further reading [22,142,138,137,26,21,20] (Calabrese, 2014)), as opposed to the saturation curves that are usually depicted in textbooks and lectures, and are the first to pop-up when entered into Google-pictures. Establishment of 'dietary reference intakes' (e.g. AIs, RDAs, ULs) have for long used dose–response curves, showing a dynamic intake range that initially causes deficiency and via adequacy moves into toxicity. The step to a general concept of 'what does not kill you makes you stronger' has, however, only recently become appreciated. This notion deserves rethinking of the definition of 'essential nutrients', but at the same time begs for extrapolation to non-nutritional lifestyle factors.

Mild triggers might at least in part reset physiologic and metabolic dysfunctioning in patients with 'typically Western' diseases [142,138]. In other words: they may provide low-cost opportunities for secondary prevention. Conversely, the chronic absence of mild stress factors may have rendered modern 21st century humans less resistant to major toxic insults and susceptible to the development of many, 'typically Western', chronic diseases of affluence, including metabolic disorders, some types of cancer, depression and cardiovascular diseases [142,138,27,140]. Re-introduction of exposure provides low-cost opportunities for primary prevention with huge favourable potential for the society as a whole. Many changes in lifestyle are involved and their adoption is not necessarily unpleasant, as is frequently claimed. For instance, a recent study suggested that men taking sauna bathing sessions at a frequency of 4–7 times/week have 63% lower risk of all-cause and CVD mortality, compared with those having one sauna session/week. There was also a significant trend of lower fatal CVD mortality of 19 min sessions, compared with sessions lasting less than 11 min [117]. A sauna session may be regarded as a mild, heat-based, stress factor with hormetic actions and broad protecting ability from the insults of the 21st century environment [183,170].

Several of our studies including the "Study of Origin" (see below) in the Spanish Pyrenees [166], a smaller one in Germany [70], and a third also in the Spanish Pyrenees (Pruimboom in preparation) showed that the combination of certain intermittent stress factors produce a hormetic early stress response with a compensatory improvement of multiple metabolic and immunological indices, and wellbeing. The employed hormetic triggers included: intermittent fasting, intermittent heat, intermittent cold, intermittent hypoxia, intermittent drinking and the consumption of a great number of nutrients with hormetic effects. Simultaneously, biorhythm became re-established by living in a natural environment without electric light. The influence of the latter was recently shown in a small observational study [197].

The use of intermittent challenges, combined in a homework-protocol, could serve as a vaccine against the deleterious effects of modern life. We named this concept "*intermittent living*", defined as the daily intermittent use of known ancient triggers for a period of seven days per month. We propose to use this concept as a basis for interventions for individuals with chronic disease and/or its prevention. Intermittent living is no more than the reintroduction of mild environmentally-based short lasting stress (including cold, heat, hunger, thirst,). It were those triggers that made us human, reflecting a part of the ancient lifestyle that in our ancestors produced a shift from strong to smart [155]. However, the feelings accompanying these hormetic stress factors are not necessarily comfortable. The resulting opponent emotion will nevertheless provide individuals with a higher level of well-being, health and even happiness [194].

Hormesis; the role of Nrf2

Hormesis refers to the evolutionary conserved adaptive responses of all living organisms to mild environmental, nutritional or even voluntary challenges through which the system amends its tolerance to more dangerous stress factors [29]. Hormetic triggers, also named hormetins, stimulate multiple effects at cellular and systemic levels. Molecular mediators include hypoxia inducible factor 1 (HIF1), nuclear factor kappa B (NFkB), peroxisome proliferator activated receptors (PPARs) and N-erythroid derived -related factor 2 (Nrf2). Three of these are key-transcription factors for the hypoxia stress response (HIF1), inflammation (NFkB) and the adaptive stress response, respectively [168] (Lee, 2014). The discovery of the major evolutionary conserved transcription factor Nrf2 has been crucial for the understanding of the process of hormesis. Nrf2, also known as CNC in flies and SKN-1 in worms, exerts its functions via more than 270 different genes through binding to an antioxidant response element (ARE, [T/C] TGCTGA [C/G]) in the gene promotor [114].

Interestingly, the Nrf2 gene itself contains several AREs and is therefore subject to a positive biofeedback loop initiated by its agonists (ARE inducers) [121]. Nrf2 can either induce (230 genes) or repress (30–40 genes) the expression of its target genes [89]. Nrf2 is the key-transciption factor for the activation of redox and the detoxifying systems, including phase I, II and III enzymes [201]. Other genes involve intermediary metabolism, the production of growth hormones and inflammation [83]. During non-stress conditions, Nrf2 is deactivated by Kelch-like ECH associated protein 1 (KEAP1) that maintains a short Nrf2 half-life through polyubiquination and proteosomal degradation. However, upon stress (oxidative stress or otherwise, see below), changes in KEAP1 inhibit ubiquination and thereby Nrf2 degradation. The now activated transcription factor migrates into the cell nucleus where it binds to its target genes, eliciting expression of cytoprotective molecules [9].

Although oxidative stress is sufficient for activating the Nrf2 pathway, the presence of certain compounds with redox/electrophilic properties enhance Nrf2's activity to its full range [185]. Important members of such substances are sulforaphane in broccoli and curcumin in the turmeric plant [88]. Nrf2 stimulation exerts strong cytoprotective effects in multiple organs and tissues, including neuroprotection and maintenance of pancreatic beta-cells. Next to the cytoprotective effects, increased expression of Nrf2 exerts anti-inflammatory effects, induces detoxification of a wide range of xenobiotics, is anti-apoptotic, and influences metabolism through multiple pathways [120]. The relevant influence of Nrf2 on intermediary metabolic pathways has only recently been clarified. Effects range from inhibition of lipogenesis, facilitation of the pentose phosphate pathway, purine biosynthesis, NADPH regeneration, and support of beta-oxidation. The sum of these observations suggests that hormetic activation of Nrf2 helps the reprograming of metabolism during stress situations [83].

The hormetic response is usually biphasic and occasionally multiphasic. Knowledge of dose-responses is of crucial importance for the understanding of mechanisms in pharmacology, inflammation, aging and cancer [29]. An example of a hypothetical multiphasic hormetic response is the dosage of vitamin C in relation with mitochondrial viability and overall health (Fig. 1). Whereas a chronic vitamin C intake

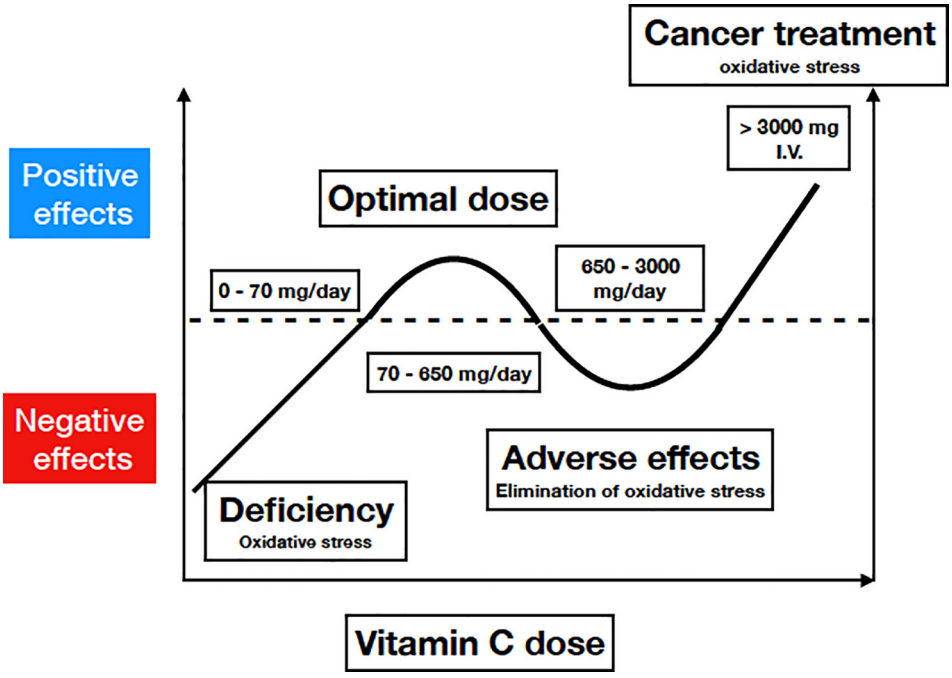

Fig. 1. A hypothetical multiphasic hormetic curve of vitamin C intake and its influence on overall health and mitochondrial biogenesis. The amounts are estimates based on Carr [34], Ohno [158], Ristow [173], Viña [216].

below 70 mg/day may cause mitochondrial damage with multiple consequences, the optimal preventive dose range amounts to 70–650 mg. An average intake of 120 mg vitamin C/day seems optimal for maintaining human health and vitamin C electron donor function [34]. However, a vitamin C intake above 650 mg (1000 mg) affects mitochondrial metabolism and mitohormesis negatively as evidenced in various human studies [173,216]. Mitohormesis (mitochondrial hormesis) refers to the damaging effect of high levels of reactive oxygen species, and the improvement of systemic defence by low levels of reactive oxygen species through an adaptive response. Gomez-Cabrera [216] compared the impact of physical training in two groups of sedentary people with and without receiving 1000 mg vitamin C/day during 8 weeks. The primary outcome was the improvement of VO_2-max as a parameter of mitohormesis. The VO_2-max improvement of the control group was found to be two times higher than the improvement of the vitamin C group. It was shown that the anti-oxidative function and the inhibitory effect of vitamin C on the Nrf2 pathway were responsible for the diminished effect of physical training on mitochondrial biogenesis [216]. Ristow [173] evaluated the effects of a daily combination of 400 mg vitamin E and 1000 mg vitamin C on insulin sensitivity in previously trained (n = 20) and untrained (n = 19) healthy young men before and after a four-week training program. Insulin sensitivity, measured by glucose infusion rates during a hyperinsulinemic euglycemic clamp, improved only in the non-vitamin group. The improvement paralleled an increase of oxidant-sensitive transcriptional factors, PPAR and the PPAR co-activator PGC1 (part of the Nrf2 pathway) but only in the absence of vitamins [174,173]. In summary, both studies showed that oxidative stress is needed for mitochondrial biogenesis and that at high intakes vitamin C's anti-oxidative function may interfere with the health promoting effects of exercise. The evidence of both studies is rather strong, although both studies lacked a placebo group. Along a similar vein it might as well be that even higher vitamin C intakes improve mitochondrial biogenesis by its pro-oxidative effects, while inducing apoptosis in cells with low mitochondrial capacity, such as cancer cells [158].

Overactivation of the Nrf2 pathway may have played a role in the adverse effects of bardoxolone methyl in patients with type 2 diabetes melitus and stage 4 kidney disease. The synthetic triterpenoid bardoxolone methyl and its analogues are the most potent known activators of the Nrf2 pathway. The patients exhibited more heart failure events and composite outcome events of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes [234]. The current notion is that there is likely to be a narrow therapeutic window for the beneficial effects of Nrf2 activators, also referred to as "a sweat spot" [84,213].

It seems clear that mild oxidative stress and certain compounds have hormetic effects through multiple pathways. Not surprisingly in the concept of hormesis, Nrf2 itself also shows a hormetic biphasic curve, merely because of its influence on other mechanisms next to protection against oxidative stress. Overexpression of Nrf2 in cancer cells could provide protection against chemo- and radiotherapy, inhibit cancer cell apoptosis and even increase proliferation [39]. Overexpression of Nrf2 could have both pro- and anti-inflammatory effects [39] but the opposite of Nrf2 overexpression may also occur. Many modern lifestyle factors produce chronic stress and down-regulation of Nrf2 and its related pathways. A remarkable example of how such a factor in the current lifestyle of modern humans could influence Nrf2 activity comes from mycotoxins in frequently eaten food items. Ochratoxin and aflatoxin have been demonstrated to inhibit Nrf2 activity, which seems in part causative for their effects in nephropathy and nephro-carcinogenicity [127,126]. Mycotoxins are ubiquitously present on cereals and other starchy foods [164,237]. The average exposure of a European adult amounts to 1 ng/kg body weight, although intake can be eight times higher [40].

Mycotoxins accumulate in many organs including the liver, but especially the kidneys. Accumulation of mycotoxins in the kidneys is able to cause severe renal damage by inhibition of the Nrf2 pathway [126]. The use of ginger, a known hormetin and potent Nrf2 enhancer, shows hepato-cytoprotective effects against mycotoxins in vitro and in vivo through upregulation of multiple anti-oxidative and detoxifying mechanisms, including the Nrf2 pathway [217]. These results support the notion that mycotoxins exhibit their toxicity through dysregulation of Nrf2.

The use of hormetic challenges is not only effective as a preconditioning approach to increase stress-tolerance, but also as a possible post-conditioning countermeasure following even severe ischemic

trauma [30]. Li [124] demonstrated that a pre- or a post-conditioning intervention with therapeutic hypercapnia attenuates ischemia-reperfusion injuries in laboratory rats. Therapeutic hypercapnia belongs to the self-imposing interventions with hormetic capacity as evidenced by multiple preconditioning studies (see Chapter 3.7. Intermittent hypercapnia).

The biology of Nrf2 is complicated, while Nrf2 effects themselves are characterized by a biphasic hormetic curve. Nevertheless, it seems that *intermittent* activation of Nrf2 by mild hormetic stressors is safe and provides overall health promoting effects. Responses to hormetic triggers are not confined to the exposed tissues or organs, but also involve communication between tissues and organs [29]. This could imply that triggers from local skin hyperthermia may provide beneficial effects for the whole body. A recent study of the group of Raison [97] demonstrated that hyperthermia is effective against depression (see Chapter 3.4. Intermittent heat), suggesting cross influence of hormesis between organs and tissues.

It can be concluded that intermittent oxidative stress exerted by environmental challenges and chemical electrophylic substances produce a health promoting adaptive reaction in most, if not all, living organisms.

Ancient triggers with health benefits,

The founder of evolutionary medicine, Dobzhansky (Dobzhansky, 1973), has stated that "*Nothing in biology makes sense except in the light of evolution*". To these legendary words may be added that "Nothing in medicine makes sense without biology". Darwin considered 'adaptation to the conditions of existence' as the most powerful driving force in evolution. In other words, evolutionary reasoning argues that health-supporting regimes should be based on the knowledge of "the conditions of existence" of our ancestors. It was recently proposed by Huber et al. that health may be defined as "the ability to adapt and self-manage in the face of social, physical, and emotional challenges" [93]. Thus, important questions are to what conditions our genome has become adapted, what were the triggers and what are the mechanisms that make us adapt.

Many of the mechanisms of hormetic substances have been intensively studied (see Chapter 2. Hormesis; the role of Nrf2). Much less attention has been paid to the mechanisms by which ancient triggers, such as short term cold, heat and hypoxia, have rendered humans resilient against these triggers and other more dangerous stress factors. In the following paragraphs we review those challenges to reunite these into an "intermittent living" protocol; a protocol that has been studied in 138 participants with demonstrated beneficial effects (see Chapter 4. A holistic approach: The 'Study of Origin').

Intermittent fasting

Chakravarthy et al. suggested that, during evolution, humans whose body and brain worked well in a fasted state were the most successful in survival and reproduction [35]. Famine, thirst, infection, violence and temperature stress have been among the most important factors exhibiting selection pressure during evolution. These are likely to have shaped the adaptive stress response that subsequently became encoded in the human genome [163]. It explains the development of one of humans' most exceptional skills, i.e. self-sufficiency. Self-sufficiency refers to individuals or small groups of humans being responsible for their own food, water, shelter and defence [38]. Self-sufficiency has dominated hominin behaviour for almost 2 million years. Homo sapiens was definitely the most resistant animal to long term exercise. Pressured by a feast/famine rhythm, he also developed the biggest brain (encephalization quotient), long before the start of the industrial revolution [125].

Nowadays, and perhaps only since the last 150 years, individuals are "served" drinks, warm meals, antibiotics and shelter. This comfort-life is causative in the development of sedentary behaviour. A sedentary lifestyle may be considered as a disease itself [163]. The employment of regimens of fasting and exercise, followed by meals and rest (feast/famine rhythm), may recover metabolic flexibility and protect the brain from degenerating or even improve cognitive functions [143,71]. Intermittent fasting (IF) is therefore no more than a component of the evolutionary challenges that have made us human.

The positive effects of IF are related to changes in multiple mechanism, including the enhancement of mitochondrial proliferation and aerobic metabolism [140,3,98]. Glycogen depletion of liver and muscles by IF, oblige the brain and other vital organs to use ketones. This metabolic switch benefits the brain, the heart and the muscles, improving their functionality and bolstering resistance against modern life stress in the host [62,215].

Mitochondrial proliferation stimulated by IF is especially important for people with low grade inflammation (LGI). Reduction of mitochondrial viability is one of the damaging effects of LGI that affects overall health [130]. LGI should be considered the main patho-physiological pathway basic to most, if not all, chronic non communicable diseases [179,180,168]. LGI affects cognition by causing direct damage to the brain and these effects have been demonstrated in individuals with the metabolic syndrome [206,233]. IF and the resulting increased metabolic flexibility could protect against, or even reverse, these changes at the level of the brain [143,71].

IF not only stimulates mitohormesis but also improves mitochondrial oxidative phosphorylation (MOP), while inhibiting cytoplasmatic glycolysis [157]. All immune cells, when activated, depend almost fully on cytoplasmatic glycolysis [47,48]. IF "obliges" the immune system to switch to MOP and rest mode [154], putting an end to the chronic state of inflammation.

Another mechanism influenced significantly by IF and CR is the activity of "mammalian target of rapamacyn" (mTOR) pathways. mTOR is a serine/threonine protein kinase that acts as a master of energy and hormonal sensor for cellular growth, activation and metabolism [99]. The functions of mTOR exhibit antagonistic pleiotropy, demonstrated by its fitness increasing influence in early life and its aging effects later on [10]. Rhythmic activation of mTOR is a promising pathway to prevent aging effects, including muscle wasting [108] and IF could serve this purpose [143,141].

Like all interventions, either pharmacological or non-pharmacological, it is important to estimate the potential risk of using IF. Prolonged periods of fasting can produce significant negative secondary effects including excessive weight loss, immune suppression, organ failure and cognitive decline [91]. Nevertheless brief IF periods are well tolerated with only very mild side effects such as light headaches and some dizziness [191]. Obligatory IF has been part of human evolution during thousands of generations and humans are well adapted to it [140,141]. Therefore the occasional skipping of a meal should be considered no more than a challenge that improves overall health and mental functioning [143,142,138]. Perhaps the easiest way to motivate people to engage in IF is the use of an overnight fasting regime of 13–16 h. A recent study showed that an overnight fasting period of more than 13 h decreases the risk for breast cancer recurrence [135]. Individuals fasting for more than 13 h, compared with those fasting less, demonstrated lower glycosylated haemoglobin levels and longer night sleep [135].

Intermittent eating and food variety

The diet of our ancestors was remarkable varied. It was characterized by a broad range of plants and herbs, combined with a diversity of food products from animal sources, including reptiles, eggs, crustacean, amphibians, fish, small mammals, and occasionally a large mammal [113,134,68,133]. Even today modern hunter gatherer populations gather over 400 plant species of which more than a 100 are used for food consumption, while the remaining serve for herbal teas and

natural medicines [196]. Looking further back (135,000 years), data suggest that the plant diversity of homo sapiens' diet was composed of over 3000 species. This variety contrasts with the only 20 different plants contained in the average diet of modern humans living in the developed world [42].

Low nutrient variety is associated with several syndromes and diseases. Nowadays, an alarmingly high number of individuals suffer from food intolerances. Typical food intolerance symptoms are bloating, cramps and diarrhoea. Food intolerance is a risk factor for chronic fatigue and migraine [148]. In relation with low food diversity it is further associated with allergies and asthma [177,156]. Mechanisms clarifying how low food diversity (LFD) may cause these disorders are a more frequent and excessive antigen presentation to the immune system and a low gut microbiome diversity [156]. The latter is a direct consequence of LFD, while low microbiome diversity itself has been associated with a wide variety of diseases [51]. The association of neurodegenerative and developmental disorders of brain functioning such as autism, attention deficit hyperactivity disorder and Parkinson's disease, with low gut microbial diversity, has been demonstrated in different animal models [18,106], but also in humans [63], including post-mortem studies [67]. In populations such as the Hadzabe in Africa and the Yanomami in South America microbiome diversity is higher than in any other world population. This is probably due to food variety depending on resource availability [184,41] . Interesting, but not surprising, is that populations with high microbial diversity present a very low prevalence of neurodegenerative and cardiovascular disorders, partially explained by mechanisms related to microbial functioning [101].

Controversially, a recent study showed that a higher food variety decreased microbe diversity in two species of fish (Stickleback and Persh), when compared with fish eating only a single source of prey [11]. The authors suggest that food generalists can only host a limited number of dominant microbes in their gut that reach the needed quorum sensing limit [11]. The quorum sensing limit is the minimum number of bacteria of the same species that allows gene transcription. It is needed for symbiotic behaviour of the human microbiota [169].

Plant derived materials contain natural toxic substances to defend the plant against several environmental challenges. These phytochemicals show hormetic effects in animals that co-evolved with those plants [150]. Important examples of these hormetic nutrients are the aforementioned sulforaphane in cruciferous vegetables, and curcumin in turmeric roots. Both can activate Nrf2 to its full capacity. However, in line with global hormesis, natural Nrf2 co-factors should be widely available in common food items. It was recently found that certain alkyl-catechols, naturally available in many food sources, can strongly support Nrf2 expression, as demonstrated both in vitro and in vivo [185]. These small electrochemicals, methyl-catechol, vinyl-catechol and ethyl-catechol, are also produced when plant-derived food is fermented by natural or bacterial fermentation in the gut. Potent converters of flavonoids into alkyl-catechols, i.e. Lactobacillus plantarum, Lactobacillus brevis and Lactobacillus collinoides, are common symbionts in healthy humans. These strains also develop when food is fermented [66]. Perhaps the most intruding factor of food variety is provided when the food is fermented.

The clinical importance of high food diversity has been demonstrated in different human studies. High food variety may reduce (fourth vs. first quartile) mortality from coronary heart disease and all causes with 39% and 26%, respectively. This study was part of the Whitehall II cohort in which 10,308 volunteers (age 35–55 years, men/women 75/25%) were followed during five year [136]. Another study in young women (age 27.6 ± 1.7 years at baseline) evidenced that a higher food variety prevented weight gain during a six-year follow-up [1]. Greater healthful food variety was further associated with lower odds of the metabolic syndrome and its components in non-Hispanic whites and non-Hispanic blacks, as established in the NHANES cross sectional study from 2003 to 2006 [210]. A recent *meta*-analysis could not find a significant influence of food variety on the risk of rectal cancer, whereas eating more fruit and vegetables was associated with a reduction [122].

It can be concluded that eating a variety of food seems effective for primary and secondary prevention of different, mainly metabolic, disorders. Fermentation of various food items may amplify the hormetic effects of food variety through the production and presence of alkyl-catechols.

Intermittent cold

Cold exposure has been a factor in selection pressure for thousands of years. Prolonged cold is a risk factor for overall mortality (including infections and cardiovascular death) even in countries with a warm climate such as Thailand and Brazil, where more people die in the winter period [82]. Extreme cold is less deleterious than periods of sustained cold: long winters claimed 89,300 deaths annually from 2003 to 2012 in the USA, whereas extreme cold or heat killed 1100 and 550 individuals, respectively, from 2006 to 2010 [7]. A recent study in China showed that extended cold is a risk factor for stroke mortality [231]. Extreme cold was responsible for 2.0% (1.6–2.2%) deaths from stroke, while chronic moderate cold claimed 12.6% (9.1–15.3%) by stroke in a population of 184.6 million urban residents.

A third epidemiological study examined the association of environmental temperature and mortality of 74,225,200 humans living in 13 countries in different periods between 1985 and 2012 [77]. The overall outcome was similar to previously published studies; moderate long-term cold seemed responsible for the majority of temperature caused deaths (7.29%, range 7.02–7.49%), whereas prolonged heat was responsible for 0.42% (0.39–0.44%) of all deaths. The results also showed that extreme cold and hot temperatures were only minor risk factors for overall mortality (0.86%, 0.84–0.87% range) [77]. Prolonged cold was also found to be associated with mortality caused by pneumonia [19] and total cancer [187] in humans.

While unexpected extreme and prolonged cold adversely affect human health and survival, the opposite is the case for the use of therapeutic cold challenges. Intermittent cold triggers can have strong preconditioning effects and protect against different toxic factors such as chronic heat stress (Le Bourg, 2015), infection [119] and prolonged cold [44].

The human skin contains 3–10 times more cold receptors than heat receptors [95]. Thermal conductance of cold water is 30 times greater than the conductive capacity of cold air [144]. Cold-water immersion or a cold shower therefore causes a kind of shock, similar to electric shock therapy, better known as electroconvulsive therapy [96] and used in people with drug-resistant major depression [6,189]. The use of preconditioning cold triggers and their impact on several cardiovascular risk factors was studied in a group of winter cold-water swimmers compared with a group of physically active, but cold-unadapted, individuals [123]. The cold adapted group showed several differences including 44% lower plasma homocysteine levels, a healthier lipoprotein profile (apolipoprotein A1/apolipoprotein B1 ratio = 0.67 vs. 0.84 g/g) and a better cholesterol efflux capacity (20.74% vs. 18.76%) although the latter value was only borderline significant. This study also showed an increase of plasma paraoxonase-1-arylesterase activity (PON, 220.87 vs. 161.67 U/ml). PON detoxifies certain pesticides. It is part of HDL and known for its cardiovascular disease lowering effects [79]. The final conclusion of Lesna et al. was that cold adaptation enhances the activity of the antioxidant system and protects against the oxidative damage that can be caused by exposure to prolonged cold [123]. Other in vitro and in vivo studies showed that intermittent cold is a hormetic trigger that can support a greater expression of Nrf2 [139].

The hormetic effects of therapeutic cold therapy are not limited to the anti-oxidant system. Cold therapy also induces the development of brown adipose tissue (BAT) and the browning of white adipose tissue

[235]. Brown and beige adipose tissues burn abundant fat and glucose. These tissues release the energy as body heat and increase the basal metabolic rate [4,159] . The latter was confirmed in a study with 17 healthy subjects (male 9, female 8). The participants were acclimated to mild cold by exposure to 16 °C during 6 h/day for a period of 10 days. Both men and women experienced an increase in BMR (females from 6.2 ± 0.7 MJ/24 h to 6.9 ± 1.0 MJ/24 h and males from 7.6 ± 0.7 MJ/24 h to 8.5 ± 0.6 MJ/24 h).

A study in rats found that exposure to mild intermittent cold for 14 days stimulated a complex cold adaptive response. Intermittent cold upregulated the expression of cold-inducible RNA binding protein (CIRBP) and thioredoxin in vital organs including the heart, brain, liver, muscles and BAT [219–221]. Free radical production was also increased in these organs, which is probably the reason that cold not only caused activation of a cold shock response, but also a response of the free radical-scavenger system, including glutathione peroxidase and the aforementioned thioredoxin [230]. Cold shock domain proteins, such as CIRBP, protect against cardiac arrest, liver injury and even brain damage [219–221]. CIRBP shows multiple protective effects against brain and heart damage through inhibition of mitochondrial apoptosis [236,120]. However, CIRBP over-activation can have negative effects and cause inflammation, mostly in people with severe disease, brain injury or sepsis. Over-expression of CIRBP is only observed at very high activity of the immune system [238].

Positive effects of therapeutic cold have been shown in athletes using cold water immersion as a remedy against pain and muscle fatigue [85,2] . Although beneficial on the short run, cold exposure immediately after a training decreases mitochondrial proliferation and loss of training effects. The latter effects depend on a certain inflammatory activity and oxidative load during the rest phase [160]. A recent study performed by the same group demonstrated that cold-water immersion after strength training decreased the acute response related with hypertrophy of the trained muscles. [176]. The logical conclusion is that pain and fatigue after training are signs of inflammation and acidification of the trained tissues. Both mechanisms indicate low level damage that stimulates hormesis. It is as Plato already suggested: to feel pleasure, you first have to feel pain.

Other positive consequences of exposure to intermittent cold triggers are related to the microbiota in the gut. Mice that are shortly exposed to cold triggers exhibit changes in their microbiota that are associated with browning of white adipose tissue, higher energy expenditure, smaller adipocyte cell size and increased insulin sensitivity [37]. If the same mice experienced prolonged cold stress, their microbiota changed into a chronic “cold adapted microbiota”. Specific changes were related with a lower abundance of Akkermansia muciniphilia, a higher Firmicutes/Bacteroidetes ratio and the total absence of Verrucomicrobia [37]. The mice showed increases of the total intestinal surface produced by elongation of villi and microvilli lengths. These changes facilitate energy uptake from food but surprisingly no increase in obesity rate. It was shown that the mice were still protected against obesity, because of increased energy expenditure, improved insulin sensitivity and the browning of white adipose tissue.

Exposure to prolonged cold is usually associated with higher body weight, production of insulate fat and a rounder body shape, which increases the body volume to surface ratio (known as the Bergman’s rule) with the purpose to reduce heat loss [90]. Nowadays climate hardly influences body mass and the universal stress adaptive response, because of the state of continuous normothermia.

Several preconditioning cold protocols have been proposed, including cold shower therapy [188,189], cold water immersion and whole body cryotherapy [85,43], winter swimming [129], and a 10-days cold acclimation (16 °C) for 6 h/day [211]. The use of therapeutic intermittent cold interventions holds great promise, but should be used at the right moment and adapted to the individual. Before definite recommendations can be formulated, more high quality studies should be performed.

Intermittent heat

Prolonged heat has been one of the most devastating pressure factors in evolution and shaped an adaptive system based on multiple heat shock proteins (HSP). HSP are part of a robust system that has assimilated a great number of functions apart from their role in the heat. Known roles of HSP are successful protein folding, degradation of other proteins, secretion of proteins, and the use as chaperones for stress hormone receptors [64]

Humans are better protected against heat than cold stress, which is not surprising considering Homo sapiens’ tropical descent [82]. Gasparrini [77] showed that mortality caused by higher temperatures compared with minimum temperatures was greater in early summer (relative risk 1.15–2.03), but substantially lower at the summer end (0.97–1.41). This argues in favour of a preconditioning effect of heat and the still conserved capacity of humans to adapt to heat stress [77]. It even seems that humans and other animals are in need of heat stress to stay healthy and lean as demonstrated in various studies.

In their daily lives, humans tend to seek for comfortable temperatures, mostly between 20 °C and 23 °C. This temperature range is the “thermoneutral zone” for clothed humans [105]. Individuals living at thermoneutral circumstances are more prone to obesity, whereas higher ambient temperatures (> 23 °C) are associated with lower body mass index [45]. A study in mice [205] showed that animals living in a chronic thermoneutral environment (30 °C) developed atherosclerosis based on metabolic inflammation of adipose tissue whereas the control group exposed to mild temperature stress (22 °C) did not. Surprisingly, it was found that the inflammatory and atherosclerotic state was not accompanied by the development of insulin resistance [205].

Whereas normothermia seems deleterious for humans, the use of mild intermittent heat stress could serve as a remedy against obesity and associated disorders [116]. A recent study showed that a 2 h stay in a mildly hot environment (26–27 °C), as opposed to a neutral environment (19–20 °C), led to augmentation of peripheral body temperature and a reduced caloric intake in both female and male participants (99.5 kcal) [8]. This randomized controlled pilot study (n = 20) further showed that calorie intake was inversely associated with the increase of peripheral temperature; for every 1 °C increase subjects ate on average 85.9 kcal less. It is for long known that higher temperatures decrease appetite and protect against obesity [33,224] . This effect is mediated through hypothalamic pathways [100] combined with peripheral hormones, such as grhelin and leptin [222,103] (Kayala, 2015). Wasse showed that exercise in a hot environment (30 °C) reduces food intake compared with exercise in neutral temperature (20 °C), whereas exercise in a cold environment (10 °C) increases food intake [222,103]. Thus, intermittent heat could serve as a “medicine” against overweight by reducing food intake and increase total energy expenditure.

Intermittent heat has also been used to treat patients with depression. The use of a single session of whole body hyperthermia (WBH) was effective in patients with major depression, compared with controls receiving sham treatment [97]. An open label trial by the same group had already demonstrated the potentially positive effects of WBH in patients with major depression, but this study lacked a placebo group (Hanusch, 2013). WBH produced a direct improvement of depressive symptoms measured with the Hamilton Depression Rating Scale. An important finding in the firstly mentioned study was that the improvement in the WBH-treated group lasted for two weeks, after which the score stabilized. The other surprising outcome was that both the sham and the intervention group did not show an expected relapse during the follow-up period of six weeks. Relapse is usually observed in treatment-resistant depressed individuals using, for instance, the antidepressive drug ketamine [97]. Mild hyperthermia should be regarded as a hormetic trigger with preconditioning effects [26,21,182,49]. The observed 14 days improvement period is in line with the average 14 days duration of a hormetic effect [26].

Mild hyperthermia activates several systemic and cellular pathways

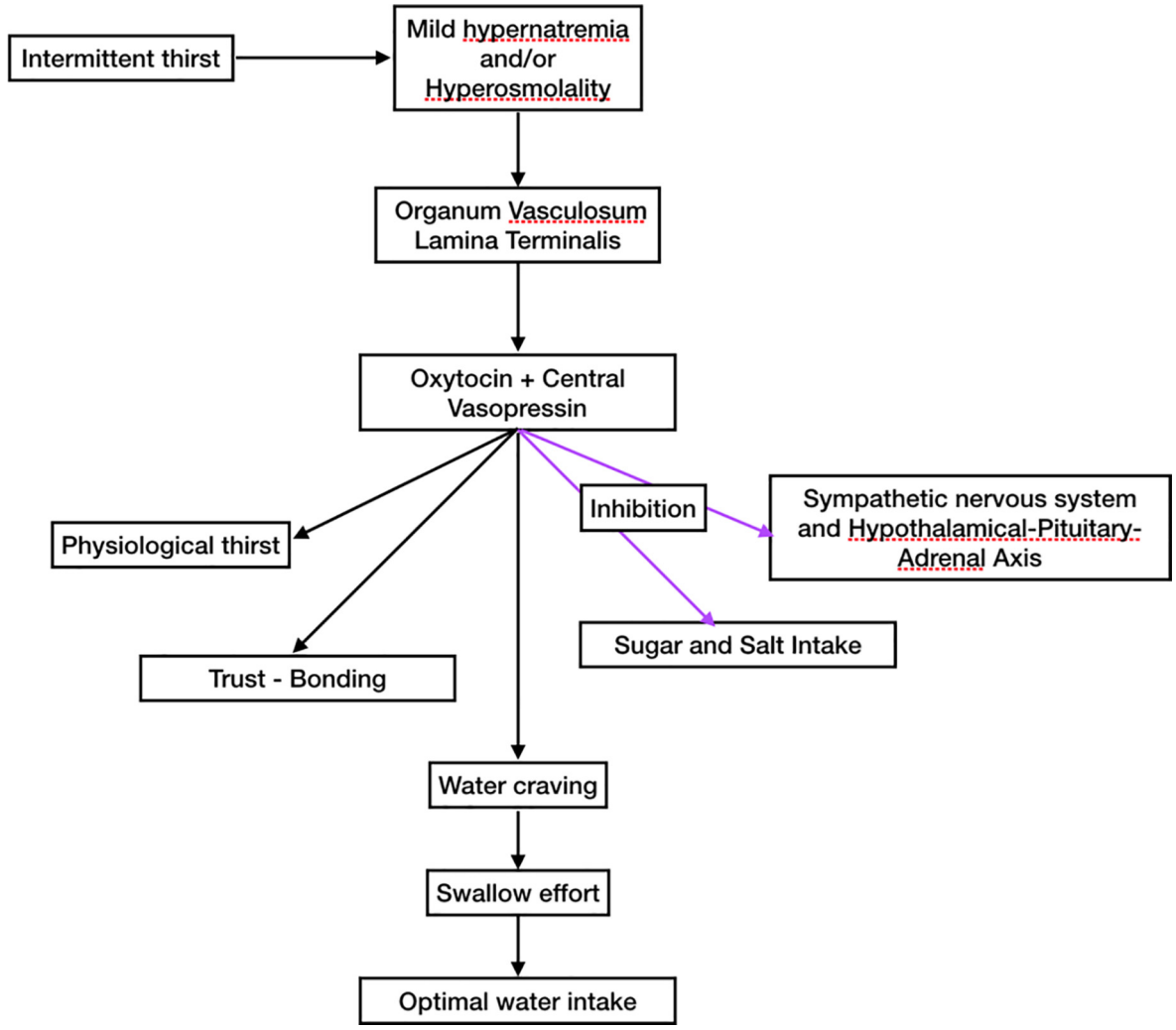

Fig. 2. The major changes caused by intermittent drinking. Thirst, a consequence of mild hypernatremia and/or hyperosmolality, activates the organum vasculosum of the lamina terminalis. This circumventricular organ connects to oxytocin and vasopressin producing neurons in the hypothalamus. Both induce a feeling of physiological thirst, trust and bonding. Simultaneously these substances inhibit activation of the sympathetic nervous system and the HPA axis in combination with rejection of salt and sugar. The ultimate consequence of intermittent drinking is optimal water intake through limiting water intake when swallow effort is increased.

that could explain its positive effects in depression. Depression is characterized by cell damaging oxidative stress (Liu, 2016) and therapeutic heat stimulates a protective heat shock response consisting of an increase of autophagy of damaged cells and an antioxidant response via Nrf2 [49].

Reviewing the literature on hormetic triggers it seems logical that the positive effect of mild hyperthermia in the aforementioned study by Janssen et al. [97] lasted for 14 days. Hormesis is unique as an intervention; effects of hormesis do not adapt, but get stronger, last longer, and start earlier when more often applied [31]. Therefore mild hyperthermia will probably not be toxic when repeated but instead become more effective. The latter hypothesis is supported by the results of a study of Laukkanen et al. [117]. His group investigated the chronic use of sauna in a prospective cohort study of 2315 middle-aged (age range, 42–60 years) men from Eastern Finland during an average follow-up period of 20.7 years. They found that men taking sauna-bathing sessions at a frequency of 4–7 times/week have a 63% lower risk of all-cause and CVD mortality, compared with those having one sauna session/week. There was also a trend of lower fatal CVD mortality with 19 min sessions, compared with sessions lasting less than 11 min [117].

The notion that local hormetic responses, in this case through heat stress applied to the skin, provide systemic benefits has been demonstrated in elderly with cardiovascular disorders. The study investigated 153 in-hospital patients with advanced heart failure and randomized them to two groups [202]. One group received Waon-therapy once daily for a period of 10 days. In Waon therapy the body is heated in an infrared heated room for 15 min at 60 °C. After a core body temperature increase of approximately 1.2 °C, warmth is retained by covering the patient in blankets for an additional 30 min. The treatment group experienced an improvement in walking distance and a reduction of brain natriuretic peptide. The authors concluded that smooth intermittent heating shows clinical advantages in patients with heart failure [202].

It seems clear that heat has profound influence on human immunology and metabolism. Whereas prolonged heat should be considered a risk factor for overall mortality, preconditioning or intermittent heat induce hormesis with strong protective effects from mortality, but also overweight and related metabolic disorders.

Intermittent drinking

Frequent periods of dehydration during evolution have been responsible for the development of a unique stress response in all animals including humans. Mild thirst increases the production of oxytocin and inhibits the typical stress response based on activation of the HPA-axis

and the sympathetic nervous system [166]. Animals never drank from a bottle and were usually dependent on intermittent water drinking, travelling from waterhole to waterhole.

Intermittent drinking in humans was recently defined as 'water (including tea and coffee) drinking up to a feeling of satiety (bulk drinking), regulated by a mild feeling of thirst' [166]. Intermittent drinking is the usual behaviour of all wild animals and also human newborns. The latter are probably the only individuals with an optimal water intake [131]. When newborns cry they probably demand water more frequently than food, which could explain that human breastmilk is 87% water [161].

The rationale of intermittent drinking is based on hypothalamic pathways related to sodium and water regulation [145]. Thirst is the only environmental stress factor producing an increase of oxytocin and inhibiting the activity of stress axes including the hypothalamic-pituitaryadrenal (HPA) axis, as evidenced by diminished cortisol release when exposed to mild thirst [112]. This neuroendocrine response to mild dehydration seems to be responsible for a decrease of anxiety, fear and aggressive behaviour [193,112,192,92]. Optimal hydration is probably associated with weight loss through optimization of mitochondrial metabolism and higher total energy expenditure [204].

Suboptimal water intake is associated with a number of serious health problems such as cancer, the metabolic syndrome, diabetes and cardiovascular diseases, and all involve the renin-angiotensin-aldosterone system (RAAS; [203]). Low plasma volume and low blood pressure are the main factors of RAAS activation, but RAAS is also activated by any other stress-factor being part of the hypothalamus-pituitary-adrenal gland-axis (HPA, [168]). Optimal water drinking is orchestrated by different parts of the brain. Whereas thirst indicates the need for fluid repletion, water satiety is less understood. Human research has demonstrated that over-drinking is prevented by activation of danger sensing parts of the brain, including the amygdala and the prefrontal cortex [181]. Water rejection is achieved by a three times greater swallowing effort and a feeling of unpleasantness. This fluid regulation system is only viable when humans drink with thirst till satiety (increased swallowing effort) and that is what we propose (Fig. 2).

When people would engage in natural drinking habits, they would not drink less quantity but less frequently. Intermittent drinking probably optimizes water and electrolyte balance and attenuates stress responses [166].

Intermittent hypoxia

About 3.5 billion years ago cyanobacteria started to produce oxygen [24]. Life on land became possible from the moment accumulating oxygen formed an ozone layer and thereby protected land creatures from the deleterious effects of the ultraviolet-C radiation emitted by the sun. A subtle rise in oxygen level some 600 million years ago may have given rise to the appearance of the first carnivores and necessitated other organisms to defend themselves against their predatory behaviour [69]. Both events, i.e. oxygen rise and appearance of predators, seem to have caused the so-called Cambrian explosion and the ultimate development of almost all moving eukaryote organisms living on earth today [69].

Oxygen is essential for complex organisms but at the same time can be highly toxic. Oxygen is one of the most electro-negative atoms. It is, in other words, "hungry" for electrons, which is at the basis of its redox behaviour in the production of energy in both plants (photosynthesis in chloroplasts) and animals (oxidative phosphorylation in mitochondria). Oxidation does not only involve carbohydrates (glycolysis, Krebs cycle and oxidative phosphorylation) or fat (beta-oxidation, Krebs cycle and oxidative phosphorylation). It can also affect structural molecules of the body itself. This leads to their oxidation, which may damage cell membranes and cell-organelles, and is thereby involved in the aetiology of many diseases. Chronic hypoxia (ischemia), but also hyperoxia, are both known risk factors for increased oxidation of and damage to tissues, including vital organs such as the brain, heart, lungs and kidneys [55].

Chronic ischemia is, on the other hand, often caused by systemic or local atherosclerosis. Atherosclerotic cardiovascular disease remains the leading cause of mortality worldwide (WHO, 2015). Atherosclerosis can produce cerebrovascular disorders, stroke, coronary heart disease [195], Alzheimer's disease (Liu, 2014) and muscle wasting in patients with chronic obstructive pulmonary disease [147]. Interestingly, a sedentary lifestyle contributes to diseases related with a chronic state of hypoxia. The number of sitting hours is associated with arterial stiffness and obesity, and both symptoms contribute to the development of atherosclerosis and cardiac disease [74]. Sedentary people have a wide range of disorders and the sedentary lifestyle should be considered a disease itself; the sedentary death syndrome [163]. Prolonged sitting time could even be more damaging to human health than classical risk factors such as high cholesterol, smoking and high blood pressure [50,15].

Chronic ischemia causes severe damage to the human body, including the brain and heart. The number of diseases caused by chronic ischemia will only increase because of increasing sedentary behaviour [172,102]. Preconditioning hypoxia could prevent and perhaps even cure the deleterious effects of sedentary lifestyle [209]. During preconditioning hypoxia or intermittent hypoxia an individual is exposed to recurrent periods of hypoxia. A recent case study showed that intermittent hypoxia training and diet during 4 weeks had superior improvement on body weight and glucose homeostasis compared with diet alone [72]. Several protocols of intermittent hypoxia training (preconditioning hypoxia) have been described. Therapeutic hypoxia has been used in cardiology for more than 30 years (see for an excellent review [28,22–23]). Interestingly it seems that angina pectoris (a state of intermittent hypoxia of the heart muscle) protects against major damage after a myocardial infarction [200,178]. In addition to myocardial protection, preconditioning hypoxia may increase anoxic survival by preserving brain metabolism through adaptation to brain anoxia, and protect against ischemic neuronal damage [214]. Intermittent hypoxia may further protect from brain aging and memory loss, although as yet only studied in rats [13].

The mechanisms underlying the positive effects of intermittent hypoxia are multiple and involve protective responses at cellular, systemic and cerebral levels. Kox et al. [110] evaluated the effects of a training program on the sympathetic nervous system and the immune system response. Twenty-four healthy volunteers (all male) were randomized to two groups of 12 each. Subjects in the intervention group were trained for ten days in hypoxia breathing techniques (cyclic hyperventilation and breath retention), exposure to cold (immersions in an ice bath) and third eye meditation. The control group did not receive any training which should be considered a study weakness, because of performance bias. Subsequently all participants were challenged with an experimental i.v. dose of 2 ng/kg Escherichia endotoxin. IL-10 levels were higher and reached maximum concentrations faster in the treatment group. IL-10 was negatively correlated with the pro-inflammatory cytokines IL-8, IL-6 and TNF-alpha, while the latter were also lower in the intervention group. Adrenaline and IL-10 correlated strongly with flu-like symptoms and were significantly lower in the intervention group [110].

Duennwald [54] showed that a single bout of intermittent hypoxia (1 h of intermittend hypoxia, consisting of 6 min breathing of a 13% oxygen mixture 5 times each separated by a 6 min recovery) normalized glucose levels for up to 16 h in patients with diabetes mellitus type 2. Intermittent hypoxia could further serve as a remedy against the effects of aging on, and disturbances of, hypothalamus function and metabolism [36]. Hypoxia induces activation of the transcription factor "hypoxia induced factor 1" (HIF-1). HIF-1 is the first responder during systemic-, tissue- or cellular-oxygen deficiency [36]. Its activation in the hypothalamus, through intermittent hypoxia exercises, is anti-

inflammatory, has anti-oxidative effects, recovers normal functioning of the hypothalamus-pituitary-gonadal axis and inhibits the expression of mTOR [36].

A recent review described the optimal dose-response curve of mild hypoxia [152]. It was concluded that modest hypoxia (9–16% inspired oxygen) and at low frequency (3–15 episodes/day) is beneficial. More severe hypoxia and higher frequency (> 48 times/day) elicit greater pathology. The accumulating evidence supports the notion that "low dose" hypoxia may be a safe, effective, simple and low cost treatment for patients with multiple clinical disorders.

Intermittent hypercapnia – a modern hormetic challenge

Hypercapnia is a state of elevated blood carbon dioxide levels. The normal blood CO_2 partial pressure ($PaCO_2$) ranges from 35 to 45 mm Hg. A 1 mm Hg change of the $PaCO_2$ above or below 40 mm Hg results in a 0.008 unit change in pH in the opposite direction [231]. The $PaCO_2$ in arterial blood is the direct consequence of the amount of CO_2 produced by oxidative metabolism and indirectly of the rate of CO_2 elimination by the lungs. Hypercapnia induces a respiratory response that increases oxygen uptake, arousal and head turning during sleep, based on the brain sensitivity for CO_2 as a panicogen and acidification [61]. This hypercapnia/panic response during sleep protects against a number of possible lethal syndromes, such as sudden death in children, death from epilepsy and sleep apnoea [17].

Chronic hypercapnia can cause multiple dysfunctions, such as dizziness, confusion, drowsiness, shortness of breath, heart rhythm disturbances, headache, mild narcosis, and tremor [80]. Chronic hypercapnia is common in patients with chronic obstructive pulmonary disorders and is the primary cause of death in 10% to 25% of hospitalized patients with COPD [53]. Other syndromes causing chronic hypercapnia with important deleterious effects are obstructive sleep apnoea ([208,219–221] 2X), cor pulmonale and pulmonary hypertension [227,232]. Hypercapnia could become a pandemic problem because of the gradual increase of CO_2 in the air with an actual density of 400 ppm. It seems that human activity is the major cause of the CO_2 rise from 280 ppm up to the aforementioned 400 ppm nowadays in the last 260 years [52]. Predictions of a further increase in the next 100 years range from 540 ppm up to 970 ppm [229].

Hypercapnia causes a decrease in blood pH, inducing a respiratory acidosis and augmentation of tissue carbon anhydrase as a compensatory response [103]. The mechanism responsible for the CO_2-induced increase of respiratory activity is mediated by the effect of CO_2 as a panicogen [104]. The CO_2 panic reaction activates different parts of the panic system in the brain via the chemosensor 'connexin 26' [46]. The "panic" structures include the amygdala (fear, anger), hypothalamus (homeostasis), locus coeruleus (the sympathetic nervous system), solitary nucleus (sensory part of the vagal system) and the midbrain raphe nuclei (serotonin producing part of the brain) [61]. These structures are involved in panic and ventilation and activate other structures involved in panic behaviour such as the prefrontal cortex, hippocampus, thalamus and periaqueductal grey matter [61]. Increased CO_2 sensitivity is associated with panic disorder (PD) and separation anxiety disorder (SAD) [175]. Early life stress, such as parental separation or fear for separation, could predispose individuals for the development of PD and SAD in later life through increased CO_2 sensitivity [5]. Hyperventilation, a typical symptom of PD, produces fear symptoms and seems to protect against feared suffocation symptoms of hypercapnia [146].

It seems clear that chronically disturbed CO_2 levels can have important damaging effects on different functions of the human body. Nevertheless, many recent studies evidence that the use of therapeutic or intermittent hypercapnia shows profound beneficial effects on different functions of vital organs such as the brain and the cardiovascular system, probably in the light of "what doesn't kill you makes you stronger" [76]. It is obvious that intermittent hypercapnia can not be considered as a ancient pressure factor. However, we propose to include intermittent hypercapnia in the group of hormetic challenges with several possible positive effects.

The use of intermittent (controlled, therapeutic) hypercapnia has been extensively studied in animals and humans in a wide spectrum of conditions. A study of Li [124] investigated the use of therapeutic hypercapnia in rats challenged by hepatic ischemia injury. Three groups of rats underwent experimental hepatic ischemia for 1 h. One group was exposed to hypercapnia (5% CO_2) before hepatic ischemia, one group after hepatic ischemia, while a third served as control. Both hypercapnia groups showed lower tumour necrosis factor alpha (TNF-alpha), higher interleukin 10 (IL-10), lower alanine aminotransferase (ALT), lower aspartate aminotransferase (AST) and lower hepatocyte apoptosis index compared with controls [124]. There was also a significant difference between the preconditioned group and the group treated after the ischemic episode, favouring the former. These results indicate that controlled hypercapnia has anti-inflammatory effects by reducing pro-inflammatory cytokines (TNF-alpha), increasing anti-inflammatory cytokines (IL-10) and protecting from severe hypoxia damage (lower AST, ALT and apoptotic rate). A second important conclusion, supporting the conclusions of a recent study of Calabrese [30], is that hormetic triggers (in this case hypercapnia) can have profound protective effects when exploited as a post-conditioning intervention.

A study in humans demonstrated a third conditioning effect of hypercapnia. Next to its proven preconditioning and post-conditioning effects, hypercapnia was demonstrated to decrease inflammation during chirurgical procedures of the lungs. For instance, lobectomy necessitates one-lung ventilation (OLV). The procedure of OLV is known to induce local and systemic inflammation and enhances mortality rate in operated patients after any period of one-lung ventilation [128]. Nevertheless, OLV is needed when low oxygen pressure could cause lung injury and even death in neonates with respiratory distress syndrome, adults with acute respiratory distress syndrome (ARDS) and the aforementioned patients after lobectomy [94]. Gao [73] compared the effects of 210 min of hypercapnia during lobectomy on inflammatory activity in two groups of patients of 25 each. One group was maintained on CO_2 pressures of 35–45 mm Hg (normocapnia), while the other underwent experimental hypercapnia with up to 60–70 mm Hg. Immune cell infiltration in the lungs (neutrophils) was lower in the hypercapnia group. This group also exhibited lower pro-inflammatory cytokines and less protein in their bronchoalveolar lavage fluid. These results provide evidence of anti-inflammatory effects of therapeutic hypercapnia and improvement of respiratory function via lowering of airway pressure [73]. An earlier study with rats had shown the anti-inflammatory effects of therapeutic hypercapnia independent of acidosis in animals with acute lung injury [151].

After an ischemic insult, therapeutic hypercapnia may be a powerful tool to prevent ischemic damage to the brain. Yang [231] employed therapeutic hypercapnia (80 mm Hg for 160 min) in rats following 60 min unilateral ligation of the common carotid arteries, as compared with normoxic respiration. Hypercapnia reduced brain damage and inhibited the apoptotic rate of neurons in the hippocampus [231]. Tregub [207] used preconditioning therapeutic hypercapnia combined with intermittent hypoxia prior to causing focal cerebral ischemic injury in rats. Hypercapnia was shown most effective to prevent major brain damage by ischemic accidents [207].

A phase II trial confirmed the possible positive effects of therapeutic hypercapnia in humans. Eastwood [56] investigated the influence of controlled mild hypercapnia on neurologic damage after cardiac arrest [56]. A group of 42 patients was ventilated mechanically with a CO_2 target of 50–55 mm Hg (mild hypercapnia), compared with 41 patients targeted at 35–45 mm Hg (normocapnia). Neuron specific enolase (NSE) and S100b, two validated parameters for brain damage, were the primary outcomes, whereas global neuromotoric function and mortality after six months were secondary hard end-points. The trial demonstrated that, compared with normocapnia, controlled hypercapnia for 24 h after cardiac arrest appeared safe, reduced the production of NSE

with 50% and improved global neuromotoric functioning after 6 months [56].

We conclude that the effects of therapeutic hypercapnia are promising. The procedures used in animals and humans appear safe and beneficial on the metabolic-, immunological- and neurological-levels.

A holistic approach: the 'study of origin'

We studied a 10 days intermittent lifestyle protocol in the Pyrenees to find profound changes in multiple clinical chemical and anthropometric parameters. The subjects were exposed to several hormetic triggers including mild environmental heat and cold, calorie restriction, overnight fasting of 16 h, intermittent hypoxia, mild thirst and a natural sleep rhythm [166]. The participants lived in the Pyrenees for 10 days and walked from waterhole to waterhole. The average daily walking distance was 14 km and temperatures varied from 12 to 42 °C. Raw food was provided and self-prepared. The trip took place at a height between 1000 and 1900 m. This height produces a mild intermittent hypoxic state. People living at this height have 5.1 times less obesity than individuals living below 500 m. Height and intermittent hypoxia seem responsible for this finding, since correction was made for confounders such as urbanization, temperature, gender, and behavioural and demographic factors [218]. Our study was further characterized by natural sleeping, with exposure to temperature differences between day and night and the absence of electric light. A recent study showed that natural sleeping in a tent without exposure to electrical lightning, for only two days, almost completely recovered normal biorhythm [197]. We observed that after only two days, all participants slept on sunset and woke up at sunrise (personal observation).

In this "Study of Origin", we measured 16 metabolic and immunological parameters, combined with different anthropometric parameters. Fifty-three healthy volunteers and two women with fibromyalgia syndrome participated in our study (28 female and 27 male with an average age of 38 and a range of 22–67 years.). It was found that most anthropometric and metabolic parameters improved after the ten days trip and these improvements were independent of weight loss. As a potentially adverse effect, we found profound increases in the transaminases alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT). These increases were parallel to and interrelated with increases of high sensitive C-reactive protein (hsCRP) (Fig. 3).

Inherent to trials with multiple uncontrolled triggers, our study comes with many limitations. The outcome should at present be regarded to provide a proof of principle. It is virtually impossible to study each of the presumed triggers in a controlled dose-dependent fashion, while the triggers may exhibit multiple interactions. The study lacked a control group, there was a relative small number of participants (55), it aimed at soft end points, and there is no long term follow up. Nevertheless, the results are surprisingly strong.

Similar results were observed in two smaller studies [70] in the Eifel, Germany. One of these included 13 healthy participants [6 women and 7 men with an average age of 39 years (range 22–49)] who mimicked a Stone Age intermittent lifestyle during 4 days and 3 nights [70]. The second study took place in the same area and investigated the same Stone Age intermittent lifestyle in 28 participants of whom 25 finalized the program (12 female and 13 male, with an average age of 40 and a range of 22–75 years). The three drop outs were due to personal stress load related to the study design [70]. Metabolic and anthropometric parameters improved significantly, but hsCRP increased from an average of 0.395 to 1.065 mg/L [70] in the first study, and from 1.334 to 2.229 mg/L in the second [70]. The average increase of hsCRP value in these studies amounted to 169% and 67%, respectively.

We have proposed several hypotheses for the encountered increases in inflammatory activity. Environmental challenges such as drinking water from waterholes (causing mild gastro-intestinal infection) and small wounds (inflicted by thorns and falls) could explain the cause of mild acute infections [166]. In addition strenuous physical exercise, e.g. the running of a marathon, is known to profoundly increase various enzyme and protein markers, such as troponin, CPK and ASAT, which is usually attributed to reversible (cardiac) myocyte leakage [107]. Although these effects warrant more attention in future investigations, they are not at all surprising in the light of our current super hygienic conditions and urban lifestyle with absence of any "external" danger, lack of physical activity and the need of small wound healing [166].

The group of Kaplan studied the coronary health of the South American Tsimane Indians living a typical hunting, gathering, fishing and partially farming lifestyle [101]. These people show surprisingly low blood glucose, cholesterol and blood pressure, and the lowest prevalence of coronary heart disease of all populations studied to date [101]. The Tsimane Indians have protein and fat intakes that derive for 86% from plants and for 14% from animals. Sedentary time is 10% of

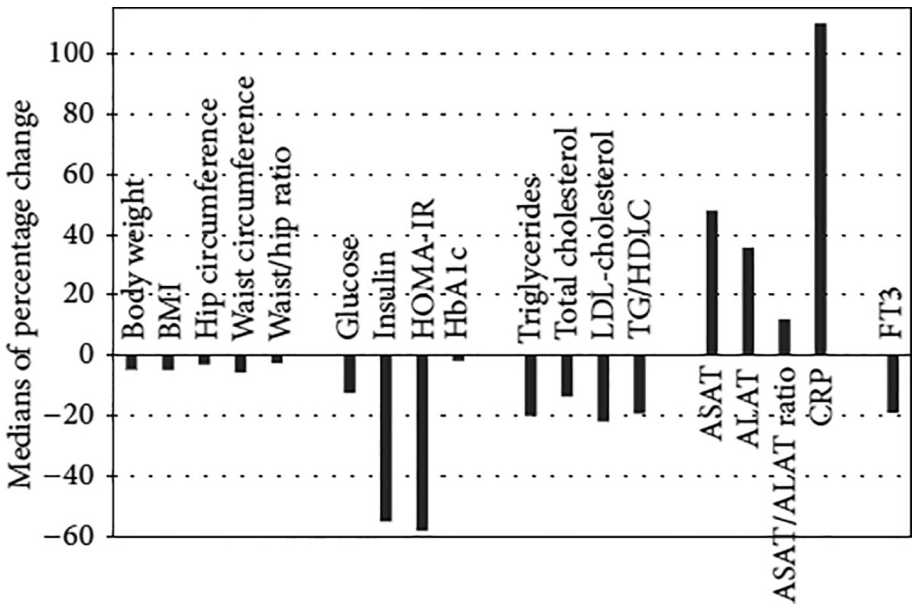

Fig. 3. Medians of the percentage changes of anthropometric and clinical chemical parameters during the 10-day trip through the Pyrenees. Only significant changes are shown (from Pruimboom [166], with permission).

daytime. These percentages are dramatically different from populations living in industrialized countries, who exhibit low consumption of vegetables and fruits and high intakes of animal protein and fat, while being sedentary for at least 54% of their waking hours. Surprisingly in this study, but in consonance with our own findings, is the observation that the Tsimane people exhibit high infectious inflammatory burden, evidenced by average hsCRP levels above 3 mg/L in 51% of the 705 studied individuals [101]. The subjects in our three studies also showed lower glucose, cholesterol and triglycerides, together with an increase of infectious inflammatory activity at the study end [166,70] (Pruimboom in prep.).

The lifestyle offered in our "Study of Origin" mimics, to a certain extent, the lifestyle of the Tsimane people. Although the triggers were not applied separately, and can therefore not be disentangled, the outcome supports the hypothesis that an hormetic lifestyle may include an acute mild inflammatory reaction caused by minor infections. These mild infections may even be protective against chronic low-grade inflammation, while metabolic markers and overall health improve [166]. Acute inflammation could activate different pathways related with resolving mechanisms embedded in the capacity of the immune system to finalize inflammation at time [168]. Low-grade inflammation may not so much develop because of activating triggers, but rather because of insufficient resolving capacity, including the production of inflammation-resolving mediators like resolvins, lipoxins, maresins and (neuro)protectins. These resolvins are produced from their precursors eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [12,186,153].

Taken together, our studies suggest that the use of multiple "low dose" hormetic triggers can have relevant beneficial effects on immunological, metabolic and anthropometric parameters. We found that the intervention is well tolerated and that all subjects, except for one, experienced a better subjective feeling of wellbeing and health immediately after the 10 days intervention.

Discussion and conclusion

Modern life is characterized by multiple "new" anthropogenic risk factors such as smoking, sedentary lifestyle, environmental toxins, overeating and many more, causing states of low grade inflammation and hypometabolism that result in "metaflammation" [59,32]. Metaflammation might be fundamental to most, if not all, contemporary chronic non-communicable diseases [162,32] and the main risk factor for mortality in developed countries at present and in the near future. Because of contemporary society structure, individuals have limited control over the aforementioned risk factors. Programs to prevent or ameliorate chronic diseases, such as based on nutritional changes and augmentation of physical activity, are only partially successful [228,149]. The pathways responsible for the development of most chronic diseases are related to oxidative stress, metabolic disturbances and intoxication [232]. A thoroughly developed intermittent living protocol might support enhanced expression of many cytoprotective mechanism through the activation of Nrf2 pathways and could thereby protect against the deleterious effects of modern life.

Taken together, this review discussed the possibility that the *absence* of "old" known challenges, such as short lasting cold, heat, water and food scarcity and intermittent oxygen 'shortage' should also be considered "*new*" risk factors. Evolution made us adapt to these triggers and they thereby became integral parts of who we are. The regular use of an intermittent living protocol mimics our ancient lifestyle to a certain extent and could thereby function as a vaccine against modern life [174].

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Ethics approval and consent to participate

All participants signed an informed consent and approved the study through the law of self determination.

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