Stock Conference report/Etiology and Pathophysiology

Obesity: lessons from evolution and the environment

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Summary

The 9th Stock Conference acknowledged the complex background of genetic, cultural, environmental and evolutionary factors of obesity. Gene–environment interactions underlie the flexibility in body-weight and body-fat regulation, illustrated by the hunter-gatherers' feast and famine lifestyle, the variation in physical activity over the lifespan being highest at reproductive age, the variation in energy intake through 'eating in the absence of hunger', while running the risk of exceeding the capacity of triacylglyceride storage, leading to lipotoxicity and metabolic problems. Perinatal metabolic programming for obesity via epigenetic changes in response to a 'Western diet' results in production of lipid-poor milk and metabolically efficient pups, contributing to the perpetuation of obesity throughout generations. Evolutionary insight from comparative physiology and ecology indicates that over generations activity-induced energy expenditure has remained the same compared to wild mammals, that energy balance might be dependant on protein balance, while the function of taste changed from detection of poison or energy to social drinking and social behaviour. At present, the impact of assortative mating on obesity prevalence is unambiguously positive. The complexity that appeared can only be fully appreciated by setting the data into the context of our evolutionary history.

Keywords: Comparative ecology and physiology, energy storage, perinatal programming, stock conference.

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Introduction

Although varying in prevalence, overweight and obesity have become evident and intrusive in all societies worldwide, a development that has taken less than half a century. This dramatic increase is often used as the main argument for why obesity must be a strictly environmentally indicated condition, caused by too much food and too little exercise. Whereas it is well established that rapid globalization of the westernized lifestyle is going alongside this obesity epidemic, including the proposal of a direct link between globalization and obesity (1), we still do not fully understand the reasons for the current epidemic of obesity. It is clear that the etiology is a complex mixture of genetic, environmental, psychosocial, cultural and cognitive influences. The recent discovery of robust obesity-susceptibility loci has increased the interest to examine whether lifestyle can attenuate or exacerbate the association between a genetic locus and obesity susceptibility. From an evolutionary point of view, we still possess the genetic heritage of prehistoric man, but new research points towards a possibility of changing gene function without influencing genomic sequences ('epigenetics'), and thus allowing for changes in susceptibility to obesity within one and between two generations.

The 9th Stock Conference, hosted by the International Association for the Study of Obesity (IASO), was held in Budapest, Hungary, from November 10 to 13, 2011, and co-chaired by Berit Heitmann, Klaas and Margriet Westerterp. The focus was on identifying the lessons that could be learned from evolution and the responses to the environment. Already more than 10 years ago, it was recognized by the American Medical Association that obesity is a complex, multifactorial condition in which excess body fat may put a person at health risk. National data indicate that the prevalence of obesity in the United States is increasing in children and adults (2). Although its etiology is not firmly established, genetic, metabolic, biochemical, cultural and psychosocial factors contribute to obesity. Some individuals may become overweight or obese partly because they have a genetic or biological predisposition to gain weight readily. In addition, the increasing prevalence of overweight and obesity reflects changes in society and behaviours over the past 20–30 years (2). Our aim was to acknowledge that the determinants include a complex mix of genetic, cultural, environmental and evolutionary factors. In total, 12 distinguished speakers and 28 attendees were brought together to discuss how in the context of genes and their interaction with physical activity, dietary intake, sleep and circadian rhythm, our evolutionary history and the changing environment have contributed to the current obesity epidemic. Insights were gained not only from Western experiences among children and adults in differing social contexts, but also from indigenous hunter-gatherer populations such as Australian Aborigines.

In her introductory comments, *Berit Heitmann* suggested that such functional changes may come about as a consequence of changes in nutrient intake or in response to a changing environment that includes an enhanced exposure to pollutants, pesticides and other chemicals. Our current understanding that the obesity epidemic is the consequence of disturbances in energy balance is refined by new research showing that changes in energy and nutrient intakes, rather than decreased energy expenditure, may have fuelled the epidemic. Furthermore, new possible etiological players including sleep and circadian rhythm, viruses, changes in the metagenome and temperature changes have been identified.

Gene–environment interactions on energy expenditure, energy intake and energy storage were reviewed by *Ruth Loos*. While lifestyle changes during the past few decades have had a major role in the rise in obesity prevalence worldwide, there is convincing evidence that our genome, which has remained largely unchanged for generations, contributes to obesity susceptibility. After all, not everyone who is exposed to the present-day obesogenic environment is overweight or obese. This inter-individual variation in obesity susceptibility in a population that is exposed to a uniform environment can, at least in part, be attributed to a genetic predisposition to gain weight. Indeed, obesity arises through the joint actions of multiple genetic and environmental factors that not only act additively, but also interact with each other. A classical example of such interaction is that of the Pima Indians. More than two-thirds (69%) of the Pima Indians who live in the obesogenic environment of Arizona are obese, compared to ~30% of the white Americans who live in the same environment (3). However, only 13% of the Pima Indians who live in the restrictive environment of the remote Mexican Sierra Madre Mountains are obese (3). These observations suggest that Pima Indians' genetic make-up makes them overly sensitive to environmental influences in relation to obesity risk. Further observations have been reported in well-controlled lifestyle intervention studies with twins (4–6). For example, 12 monozygotic twin pairs, who were overfed with 1,000 kcal d^{-1} for 100 d, gained on average 8.1 kg with a range of 4–12 kg. Most interestingly, while there was large variation in weight gain between pairs, the variation was three times less within the pairs (4). This supports the notion that the response to these changes depends on an individual's genetic predisposition. Similar results were observed in twin studies that examined the influence of exercise (5) and diet (6) on weight loss.

So far, few studies have reported convincing interactions between lifestyle and genetic loci on obesity risk. For instance, a growing number of studies report that physical activity attenuates the association between variants in the *FTO* locus and obesity-related traits (7), including a large-scale meta-analysis that indicated that physical activity significantly attenuated the effect of *FTO* variants on obesity

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risk and body mass index (BMI) by approximately 30% in adults (8). The physiological mechanisms through which physical activity reduces *FTO* effects remain to be elucidated. The first intron of *FTO* might be sensitive to epigenetic effects, as variants in this region have been shown to influence its methylation capability (9,10).

In another recent study that used a genetic score that summed the BMI-increasing allele across 12 established obesity-susceptibility loci (11), the increase in BMI was ~40% more pronounced in sedentary individuals than in physically active individuals. Similar interaction effects were observed for the risk of obesity.

Joosen and *Westerterp* assessed the magnitude of the *genetic contribution to the range of activity-induced energy expenditure (AEE)*, by measuring this component in the confined and standardized environment of a respiration chamber, which is an indicator of free-living AEE (12–14). The separate genetic and environmental variance components of AEE were analysed with a classic twin design, showing that a genetic influence explained the largest part of the variation in AEE in daily life, whereas AEE was influenced by environment only within the confined area of the respiration chamber (15). So far, this is one of the few studies that quantify the genetic contribution to variation in AEE, using gold standard techniques like doubly labelled water and validated triaxial accelerometers for movement registration.

Taken together, findings on gene–physical activity interactions present an important public health message as they challenge the deterministic view held by many than the genetic susceptibility to obesity is unmodifiable. In contrast, *Loos* suggested that the genetic susceptibility can be overcome, at least in part, by adopting a physically active lifestyle in order to prevent overweight and obesity.

Margriet Westerterp-Plantenga reviewed *gene–environment interactions in relation to food intake*. She emphasized that humans appear to regulate energy balance on a weekly rather than daily basis (16). While energy expenditure, which determines energy requirement, is continuous, energy intake is discontinuous, and requires a mechanism for tuning it to energy expenditure. Hunger and satiety play a role (17), and changes in gut hormone and glucose concentrations have been suggested to act as biomarkers for nutrient-related satiety (18). However, Westerterp-Plantenga and colleagues have shown that these mechanisms show a large variability, as over-eating or under-eating relative to the energy requirement often occurs. This flexibility includes insensitivity to gut-peptide signals especially in overweight and obese individuals (19,20), and sensitivity to modulators such as circadian rhythm and sleep (21,22), ambient temperature (23,24) and hypobaric hypoxia (25).

Over-eating, relative to energy requirement, occurs as eating in the absence of hunger, and is driven by anticipated reward (26,27). Reward is defined as 'liking' and 'wanting', expressing the hedonic value of food or food preference, respectively the motivation to obtain food. Task-related signalling (TRS) for liking and wanting is represented in the brain in overlapping brain areas such as in the thalamus and visual cortex (28), and in separate brain areas, namely in the caudatus for wanting postprandially, and in the insula for liking (28). Before a meal, a high brain activation for wanting TRS is present in the frontal cortex, orbito-frontal cortex and putamen. After the meal, putamen activity decreases. This decrease is strongly present in successful dietary restraint subjects, not only related to wanting TRS but also to liking TRS, but fails to take place under stress, which is related to stress-induced over-eating for reward (27,29).

On the other hand, post-meal wanting TRS in the hypothalamus, implying inhibition of eating, is inversely related to hunger and BMI, thereby facilitating over-eating in the overweight and obese individuals. This phenomenon points towards reward deficiency driven over-eating in those subjects (28).

The genetic contribution to the variation in energy intake and its flexibility appears from studies on gene–environment interactions that are present for pre- to postprandial perceived hunger, satiety, and for orexigenic and anorexigenic hormone concentrations.

Associations with the polymorphisms in LEPR, NPY2R and GHRL have been shown (30). Dietary restraint and disinhibition has been associated with polymorphisms in GHSR (30). In addition, postprandial responses in hunger and satiety were associated with the rs9939609 nucleotide polymorphism in FTO (31), while epistatic interactions involved DNMT3B and LEPR (31).

Finally, polymorphisms of CLOCK, TIMELESS, ARNTL, PROK2 and CSNK2A related to circadian rhythm and sleep appeared to be associated with overweight and obesity (32,33). Taken together, *Westerterp-Plantenga* stated that gene–environment interactions are present for pre- to postprandial changes in hunger, satiety, orexigenic and anorexigenic hormones, circadian alignment of food intake, and dietary restraint, indicating a variation for the ability of eating in the absence of hunger, either to survive fluctuations, including limitations in food availability, or to become obese.

Thorkild Sørensen reviewed *energy storage related to gene–environment interactions*. Triacylglyceride (TAG) is a perfect compound for energy storage – it is energy dense and biologically inert. Sørensen stated that the body has a fine machinery to store it, mobilize it and to use its energy content (34,35). When the available space, as determined by the number and maximum size of normally functioning adipocytes, is filled, ectopic accumulation occurs. When total limits of storage capacity are exceeded and there is no need of the excess fatty acids as a current energy source,

fatty acids accumulate in the blood, which appear to be toxic (lipotoxicity) and lead to metabolic problems (34,35). Storage capacity and distribution of adipose stores within the body varies between populations (e.g. Asians vs. non-Asians), individuals within populations, within individuals over time (age) and across generations. The capacity to store energy may be determined by genes, early life experience, even before conception, and current environmental exposures. It makes little sense to measure how much TAG is stored without knowing the residual storage capacity. For instance, for a given BMI, Asians have a higher body fat percentage, abdominal obesity, a higher intramyocellular lipid and/or a higher liver fat content compared to Caucasians. This contributes to a higher predisposition to insulin resistance at a lower BMI than Caucasians (36). *Sørensen* advocates that the approach of obesity should be directed towards assessment of the adverse effects of fatty acids accumulating in the blood, leading to lipotoxicity and metabolic problems (34,35). Measuring how much TAG is stored is insufficient if one does not know the residual storage capacity.

Karen O'Dea reviewed the insight that could be gained on the development of obesity from studies on *prehistoric variability in body weight*. The flexibility in energy balance as being outlined above was clearly used by the humans living as hunter-gatherers for most of their history – whether we date that from the emergence of modern man (~100,000 years BP) or from the emergence of *Homo habilis*, our tool-making ancestor (1.8–2 million years BP). O'Dea argues that it is to that ancestral diet and lifestyle that humans are primarily genetically adapted. The few remaining hunter-gatherer societies that survived into the 20th century provide a window into that past lifestyle and give insights into its impact on health. In the most remote parts of Australia, small groups of Aborigines continued to live a nomadic lifestyle until 50–60 years ago. Research (37) indicates that they were very lean, with no evidence of the chronic diseases (central obesity, type 2 diabetes, vascular diseases and kidney failure) that occur in epidemic proportions in contemporary westernized Aboriginal communities in Australia today.

In 1982, O'Dea studied the impact of 7-week reversion to hunter-gatherer lifestyle on health in a group of middle-aged, diabetic Aboriginal people from a remote community in northwest Australia, who had retained the knowledge and ability to 'live off the land'. Seven weeks of this traditional hunter-gatherer lifestyle had a profound therapeutic benefit, greatly reducing all of the metabolic abnormalities of diabetes and vascular disease-risk factors (38). Animal foods made the greatest contribution to the diet. Food was consumed when it was available. Everything edible was consumed, and people exhibited a capacity to gorge, eating 2–3 kg of lean meat or fish if available, but eating very little on unsuccessful days ('feast-and-famine').

Significantly, the most highly prized foods were the few that were energy dense: fat depots, bone marrow, organ meats such as brain and liver, fatty insects and honey. Such foods were only available seasonally and/or in small quantities, their procurement was energy intensive, and they needed to be shared with others.

The survival strategies of hunter-gatherers were to maximize energy input (capacity to gorge, preference for energy-dense foods) and minimize energy output (avoid unnecessary physical activity) (38). Throughout human history, food procurement has involved hard physical work, and food shortages were common; never before in human history has there been continual food abundance. Thus, humans have developed many biological adaptations to hunger, but not for over-consumption. Finally, *O'Dea* conveyed the insight that from a hunter-gatherer perspective the modern Western diet and lifestyle would seem to be ideal for survival: an abundance of energy-dense foods high in fat and sugar, readily available at low cost, and for minimal effort. The unintended consequence is the serious epidemic of obesity, type 2 diabetes and related conditions across the world.

Paul Maclean addressed *the role of perinatal metabolic programming in perpetuating the propensity to become obese from one generation to the next*, beyond the inherited genetic predisposition for obesity (39). Maternal malnutrition, both over- and under-nutrition, can impact the development of homeostatic systems that control energy balance and adiposity (40–44). Programming occurs as the maternal environment imposed upon the developing fetus and neonate induces epigenetic changes that may include DNA methylation, genetic imprinting and histone modifications. The programming leads to alterations in gene expression having lasting consequences on growth rates, adaptations to metabolic stress and the susceptibility to metabolic disease.

Diets high in fat and simple sugars (i.e. Western diet) that promote maternal overfeeding during gestation and lactation lead to offspring that exhibit hyperphagia, accelerated growth rates and a propensity to become obese. In addition, these effects may be accentuated with maternal obesity (41,44–46). Prenatal stress yields the same consequences in offspring (44,45), while a transient period of exercise after weaning prevents them (47,48). Maternal obesity, however, imposes distinct developmental challenges during the post-natal period, which can even override a genetic disposition for leanness (41).

Obese women are known to have a difficult time breast-feeding and their offspring have problems maintaining adequate neonatal growth (49,50). A similar impairment with obesity is observed in mice on a Western diet. Obese dams consuming a Western diet produce lipid-poor milk compared to lean dams on the same diet (46). This effect of obesity on lactation performance has two consequences in

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their offspring. First, their pups adapt to energy restriction by becoming more metabolically efficient and slowing their growth rate (46), which may predispose them to 'catch-up' growth favouring fat deposition later in development. Second, their pups oxidize more protein and carbohydrate to produce the energy for growth (46), which may inadvertently program an inability to oxidize fat later in life. Even so, it appears that perinatal metabolic programming provides a distinct path to obesity in early life. These epigenetic events may exacerbate an underlying genetic disposition or yield the same end where no genetic disposition exists. Together, *Maclean* stated, the genetic and epigenetic consequences are likely to contribute to the perpetuation of obesity from generation to generation, so long as the obesogenic pressures persist.

Tina Kold Jensen reviewed *the role of endocrine disruptors to the current epidemic of obesity*. Developmental exposure to environmental pollutants with hormonal activity, whose production and use has increased simultaneously with the rise in these conditions, may play a role in the obesity epidemic (51,52). These endocrine disrupting chemicals (EDCs) have been linked to a growing list of adverse health consequences and those that are oestrogenic or anti-androgenic are most plausibly linked to metabolic changes (53). EDCs are widely detected as pollutants in food because of contamination of food processing and packaging materials and/or bioaccumulation in the food chain (54). They include bisphenol A (BPA), phthalates and perfluorinated chemicals (perfluorinated alkylated substance [PFAS]) (55–58).

These chemicals are widely used and can be measured in urine and serum of almost all humans both adults and children. PFASs are fluorinated compounds that are water and oil resistant and used in a broad range of products, e.g. in waterproofing and protective coatings of clothes, furniture, and in floor polish, paints, non-stick cookware and food packaging (58,59). PFASs are worldwide contaminants of the environment, wildlife, food and drinking water (60). A newly published study found an association between maternal PFAS measured during pregnancy and increased body weight at 20 years of age in the female offspring (61). BPA is a key monomer in production of polycarbonate plastic and epoxy resins (56). It has been found to leak from heated plastic baby bottles into the formula milk and from can lining. Concern has been raised by published studies reporting a relationship between fetal exposure to 'low doses' of BPA and obesity at puberty in experimental studies in laboratory animals (62). A cross-sectional American study found association between BPA levels and obesity and metabolic syndrome-related conditions (63). Phthalates are ubiquitous industrial chemicals used as plasticizers, solvents and lubricants in manufacturing of consumer products such as children's toys, medical equipment, cosmetics, food packaging and building materials. Only few human (cross-sectional) studies have evaluated phthalates and obesity-related outcomes. These reported positive correlations between phthalate metabolites, waist circumference and insulin resistance among adult men (57,64).

Most EDCs accumulate in fat tissue (56), which is of great concern as body fat is not merely a depot for storage of triglycerides, but also an endocrine gland crucially involved in energy regulation (52,55). If exposure occurs in early life stages (fetal and/or childhood), EDCs might interfere with the programming of endocrine-signalling pathways established during vulnerable periods of life. In addition, *Jensen* stated that exposure to EDCs has been associated with obesity-related comorbidities (52,54,55).

Klaas Westerterp and John Speakmann reviewed *the changes in physical AEE over the lifespan*. Physical AEE gradually increases from early age to adulthood and decrease again in old age. Westerterp and colleagues showed the development of physical AEE over the lifespan by expressing it as a fraction of total energy expenditure. At 1 year of age, when children start to walk, about 20% of daily energy expenditure is accounted for by physical activity. The fraction increases to adult values of about 33% at age 15 years soon after reproductive age is reached (65). After 15 years of age, activity energy expenditure remains on average at a constant level during adulthood and then gradually decreases after age 50 years (66). At age 90 years, humans are spending again 20% of daily energy expenditure for physical activity identical to the age of 1 year when they started to walk. Thus, it seems that physical AEE is highest during the reproductive years. Furthermore, *Westerterp* showed that once individuals are obese, they have higher daily energy expenditure because of a higher maintenance requirement for their larger body size. Then, activity energy expenditure is mainly affected by body mass. Body movement but not activity energy expenditure is reduced in the obese (67,68).

The changes in physical activity energy expenditure as we age are inferred from a cross-sectional study of daily energy demands and its components seem to start at around the age of 52 (66). This time also corresponds to the commencement of a number of other changes. Fat-free mass (FFM) also starts to decline and this leads in part to a decrease in basal energy expenditure, although many studies have shown that the decline in basal metabolic rate cannot be completely accounted for by changes in body composition alone, pointing to an independent age-related decrease. The progressive loss of muscle mass with age (sarcopenia) is one of the most significant problems of ageing, and in later life is one of the key factors that influence mobility and dependence. Looking at the coincidence of the cross-sectional patterns of AEE and FFM with age, it would be tempting to speculate that these events are causally linked. That is high levels of activity (reflected in AEE) may protect from FFM loss. However, this seems not

to be the case. Statistically controlling for the effect of age reveals there is no association between age-specific activity levels and FFM (66). More significantly, activity intervention studies in the aged do not significantly preserve FFM and prevent its progressive loss – although resistance-training interventions can prevent muscle loss. *Speakmann* states that it would appear that rather than the amount of FFM being a significant factor driving age-related changes in activity that a much more important issue is muscle quality.

Joey Eisenmann discussed *the role of biocultural changes during childhood and adolescence, related to the variation in physical activity*. In general, children enjoy engaging in physical movement, but, as Eisenmann and colleagues have shown, there is a clear age-related decline in habitual physical activity expressed as time spent in moderate-to-vigorous physical activity particularly during adolescence (69). Several factors influence the development of the physical activity phenotype during childhood and adolescence, and it needs to be recognized that children and adolescents are involved in the 'business' of growing up (70). 'Growing up' is a biocultural experience, which involves interactions with the psychosocial-behavioural aspects of development. The ontogeny of physical activity during childhood and adolescence is a complex multifactorial phenotype influenced directly and indirectly by the multiple demands of 'growing up' including genetics, prenatal exposures and perhaps epigenetics, and a myriad of postnatal factors that include biological, psychological and social factors, as well as the physical environment, that act independently and with each other as a child grows up (69–74). To predict which children are physically active and remain active throughout childhood and adolescence has not been successfully demonstrated in the literature (69–74). Eisenmann suggested that in order to achieve this aim, a comprehensive multivariate, multidisciplinary longitudinal model is necessary that considers the biocultural approach. The period of adolescence seems to be especially a period of decline in physical activity that needs to be better understood from a biopsycho-sociocultural perspective. Yet, on the other hand, Westerterp and colleagues have explained that the increase in body size results in the gradual increase of activity energy expenditure from 20% of total energy expenditure to the adult value of about 33% after 15 years of age, shortly after reproductive age is reached, and the physical AEE is at its highest.

The potential effect of changes in sleep duration during puberty on the development of obesity was addressed by *Margriet Westerterp-Plantenga*. During puberty, BMI increases, and sleep duration decreases, in a related way, independent of possible confounders, as was shown by Westerterp-Plantenga and colleagues (75). In addition, they showed that the influence of polymorphisms of the *FTO* gene changes during puberty (76). The FTO A allele is associated with higher BMI, fat mass index and leptin concentrations from 12 years of age, while the strength of the associations decreases at age 13–14 years, and becomes stronger at age 17 years. The decreased association is presumably caused by the dominating endocrinological changes at mid-puberty (76). In boys and girls during puberty, factors independent of fat mass become (transiently) more important in the regulation of plasma leptin concentrations. In girls, leptin acts as a permissive factor for the onset of puberty, while, in boys, leptin has a different timing and function (77).

The rewiring of the hypothalamus during puberty may help to explain the relationship between BMI and sleep duration. The secondary sex characteristics all originate from shared neuronal systems, with the hypothalamus as the integration point (78,79). The hypothalamus also contains the sleep–wake and feeding circuits (79,80), which are connected through the hypocretin-1 hormone that regulates feeding and locomotor activity via the nucleus accumbens, as well as signals information on the light–dark cycle to the suprachiasmatic nucleus. Changes in hypothalamic functioning, such as disturbed hypocretin-1 signalling, might lead to disturbance of the circadian cycle and feeding behaviour, affecting energy balance and body composition over time (78,79). For instance, children with short sleep duration show decreases in leptin concentrations, decreased insulin sensitivity and altered cortisol concentrations, all promoting lipogenesis (81–83). Thus, Westerterp-Plantenga stated that changes in hypothalamic functioning, such as altered hypocretin-1 signalling, may explain the relationship between the changes in BMI and in sleep duration during puberty, via altered puberty onset, energy balance regulation and circadian rhythm. With respect to adolescents and adults, population statistics show that short sleep duration is a large and severe problem. It is estimated that 50–70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting health and longevity (84). The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes and obesity (84).

An inverse or a U-shaped relationship between sleep duration and BMI has been shown. Adults who slept 7.7 h had the lowest BMI; those with shorter and longer sleep duration had progressively higher BMI. Sleep insufficiency was associated with lower levels of leptin, suppressing appetite, and higher levels of ghrelin, stimulating appetite (85,86). These findings suggest that a hormonally mediated increase in appetite may help to explain why short sleep is related to obesity. Mediating mechanisms may be effects of sleep deprivation on the sympathetic nervous system and/or hypothalamic hormones (86), which also influence appetite. Shorter sleep times were also associated with short-

term impaired glucose tolerance (87); the effect resolved after restoring sleep to normal. Glucose clearance was 40% slower with sleep loss than with sleep recovery. Moreover, the association between sleep loss and diabetes or impaired glucose tolerance may also mediate the relationship between sleep loss and cardiovascular morbidity and mortality (84).

A further focus of the conference was on *the lessons that come from comparative physiology and ecology studies. Klaas Westerterp and John Speakmann* (88) have compared physical AEE levels in modern Western societies with those from third world countries and wild terrestrial mammals while taking into account both body size and temperature effects (88). Daily energy expenditures of individuals from most rural communities were on the expected line determined by gender, age and body mass for individuals in Western societies. The predicted energy expenditure from an equation derived from wild terrestrial mammals for a modern human of 78.6 kg was 9.2 MJ d^{-1}. The actual expenditure across all the Maastricht data was 11.2 MJ d^{-1}, not lower than the prediction. Thus, based on this analysis, physical activity energy expenditure of modern man has not changed in recent times and matches energy expenditures of wild mammals (88). Ambient temperature also affects energy expenditure and, potentially, energy balance when a subject cannot stay in the thermoneutral zone where body temperature can be maintained by changing heat loss. The earliest civilizations developed in climatic regions close to thermoneutrality. Subsequently, new areas could be inhabited by wearing clothing and sheltering for extreme sunshine in daytime or low temperatures overnight. The next developments were heating systems from open fires to air conditioning. Man lives mainly in a thermoneutral environment. The predicted energy expenditure from an equation for wild mammals as presented above was derived for a typical room temperature of 20°C (88).

Stephen Simpson reviewed their approach to *the behavioural strategies of animals in their nutritional environment.* Simpson and Raubenheimer (89) developed a unifying framework that represents the multiple nutritional needs of the animal, the nutritional environment, the behavioural strategies of the animal when faced with that environment, and the associated performance and evolutionary consequences for the animal of these behavioural and physiological responses. This integrative modelling framework, called the geometric framework (GF), was devised and tested using insects but has since been applied to a wide range of organisms, from slime moulds to humans, and problems, ranging from aquaculture and conservation biology to the dietary causes of human obesity and ageing (89).

The GF has been used to show that dietary macronutrient balance plays a critical role in biological processes including growth, development, reproduction, ageing, immunity, and the susceptibility to both non-communicable and infectious diseases. Experimental data indicate that most animal species, including humans, have a separate protein appetite (89,90). Moreover, it is suggested that humans when faced with imbalanced diets prioritize the absolute intake of protein to a 'target' level at the expense of regulating fat and carbohydrate intake (91,92). Such 'protein leverage' has been demonstrated in other species, including non-human primates, pigs, rodents, birds, fish and insects (89), when the percentage of protein in the diet is lowered, total energy intake increases in an effort to maintain constant protein intake. The consequence is that dilution of protein in the diet by fat and/or carbohydrate encourages over-consumption of total energy, which in turn predisposes towards obesity and insulin resistance, causes loss of lean mass (93), and tips metabolic physiology into a vicious cycle towards accelerating obesity and metabolic disease (79,80). Dilution of protein in the modern Western diet (94) is associated with various factors, including increased reliance on processed foods, economic pressures, and an ancestrally derived predilection by humans for the taste of fats and simple sugars (89,95). Weigle *et al.* (96) showed a spontaneous reduction in energy intake upon a high protein diet in 19 subjects who were placed on an *ad lib* 30 EN% protein diet for 12 weeks. Energy intake was reduced to match the original satiety level, resulting in a decrease in body weight of 4.9 kg and fat mass by 3.7 kg. In the meantime, several protein-diet studies have been undertaken, but these are confounded as they include a weight-loss and possibly a weight-maintenance program. These programs first induced body-weight changes and then used a protein diet to sustain satiety, energy expenditure and fat-free body mass at the original level (97). There is insufficient evidence to show a possible relationship between the protein leverage hypothesis and the use of protein diets for the management of obesity.

The changing function of the taste system was reviewed by *Danielle Reed.* A feature of the modern human diet is a decline in the concentrations of bitter-tasting chemicals in foods, a challenge for curious early humans foraging in jungles or savannas, because plant food (while plentiful) is also often poisonous (98). To reduce the risk of accidental poisoning, humans use their sense of taste, especially bitter perception. Bitter chemicals are produced by plants as secondary compounds that provide defence strategies against being eaten and, as such, they are often toxic, even after the consumption of only a few mouthfuls. To capitalize on an easily obtained food source, plants, humans devised strategies to remove or reduce their toxins, which in turn improved their taste (99,100). Nonetheless, person-to-person differences in bitter perception arise (in part) because of genetic variation in the associated sensory receptors, e.g. (101). These genetic differences may have served

a purpose in evolution when tradeoffs between poison detection and eating bitter famine foods were important for survival but now that the food supply is safer, heightened bitter sensitivity may create problems if it leads to the avoidance of healthful plant foods like vegetables (102). One of the mysteries of taste and evolution is why some bitter foods and drinks are liked even when the bitter taste itself is not. Coffee and tea contain several bitter compounds, the most familiar being caffeine and epicatechin. Alcohol, which is bitter to most people, is therefore often consumed with additives such as flavours or sweet solutions. The bitter compounds in these drinks may be pharmacologically rewarding; for instance, the stimulant effects of caffeine in coffee may help make the bitterness more tolerable, perhaps even liked, but at least socially wanted (103). The bitterness of ethanol may be a small detraction in the face of larger post-ingestion rewards (104). Often bitter beverages are shared with friends and family, and there may be social rewards as well as pharmacological ones for the ingestion of bitter-tasting beverages. Social conditioning is well understood in animal models of food preference learning (105) but is often overlooked as a potent force in human food intake (106). Genetic variation in taste perception is rarely studied in a social context, although mothers who are genetically insensitive to some bitter compounds report that their children are more emotional if the child is genetically bitter sensitive (107). If bitterness conveys a warning, sweet taste serves as a beacon for consumption and as an indicator of food desirability (108). Sweet is close to universally liked among humans (109). Sweet liking is present at birth (109) and most intense in children and young adults (99), perhaps as a signal of safe calories for growth (110). In addition to the effect of development on sweet preference, not everyone likes sweet equally, especially at very high concentrations. Differences among people in peripheral sensitivity to sweetness are due (in part) to genetic variants in the sweet receptor (111). Taken together, *Reed* showed that the function of the ability for taste perception has changed, from being used for detection of poison and energy, to being used as an element in social drinks, whose appreciation despite a negative taste needs to be learned, in order to be accepted by one's peers.

Discussion

The conference presentations emphasized that lifestyle and environmental insults operate against a genetic, epigenetic and evolutionary template. Obesity-related risks are lipotoxicity and metabolic problems (34–36) caused by exceeding the health boundaries of gene–environment flexibility (4–15,112). Overall, there were several lessons from evolution and the environment that could be drawn from this meeting.

Lesson 1. Although it is often stated that the rise in obesity over the past 50 years cannot be caused by genetic factors because they could not have changed in such a short time, it is clear that the function of our genome can be changed on this timescale by two important factors. The first is epigenetic programming during our early lives. Perinatal metabolic programming for obesity by which epigenetic changes are induced by a Western diet was underscored (46). In animal models, this has been shown to result in metabolically efficient pups, contributing to the perpetuation of obesity throughout generations, as advocated by McLean (46). The second factor, which was brought up during the final discussion, is assortative mating. Assortative mating (the phenomenon of obese people mating preferentially with other obese people) clearly promotes the development of obesity in offspring that are derived from pairings of obese partners (113–116). The children of obese parents may be at greater risk for development of obesity because of two factors. The lifestyle choices of the children may be conditioned by the lifestyle choices of the parents, or the children may be more likely to be exposed to a greater number of risk alleles because of the genetic make-up of their parents. The evidence strongly suggests that this is a genetic (or potentially epigenetic) effect because the same risks of developing obesity are not present in the offspring that are raised by obese adoptive parents. It is likely that assortative mating has increased since the 1940s for two reasons. First, people now get married and have children at older ages, and second, people now get obese at younger ages. So it is now possible to assortatively mate for obesity when in the past this was probably impossible because people married and had children before it was evident who was going to become obese. Calculations suggest that the shift in assortative mating may have increased the prevalence of obesity by around 5% (113). Thus, this effect may contribute to, but has not completely caused, the epidemic. In the future, this effect may slow down because of possible infertility effects (117), but at present the impact of assortative mating on obesity prevalence is unambiguously positive. Alternatively, the effect of assortative mating may become magnified in the future as the offspring themselves from assortative matings assortatively mate. This would magnify the exposure to 'at risk' recessive alleles because such alleles would become concentrated among the offspring of successive assortative matings. This might lead to a form of 'super obesity' in individuals exposed to such concentrations of alleles. These effects may in fact prove to be more important than the classical genetic effects as the genome-wide association studies have only managed to identify genetic variants that underpin a tiny fraction of the total variation in BMI (8–11). Yet we know from classical twin and family studies that the total variation attributable to 'genetic' factors is much greater than this (4–6,14,15). On the other hand,

the brighter news is that we may not be at the mercy of these genetic and epigenetic effects. It may be possible to overcome our genetic destiny by specific lifestyle choices (7,65–74).

Lesson 2. We evolved in an environment that is very different from that we currently inhabit. We have changed our environment so that many adaptations to our past environment may be inappropriate in our modern world. These include our perception of food tastes, which previously guided us towards consumption of rare but advantageous foods, via macronutrient selection to achieve specific life history aims such as reproduction, to our ability to cope with the variations in food supply on a short timescale (98–111,118,119). A major problem is that these hardwired adaptive systems are less able to cope with a situation where such 'advantageous' foods are no longer rare, where novel macronutrient combinations are available that did not exist in prehistory, and where food is continuously available. Moreover, our environment nowadays contains many chemicals that we never encountered previously (53–58). Evolution leaves us ill equipped to deal with such environmental insults.

Lesson 3: Humans develop over a particularly long time frame compared to most animals. We are constantly changing during this developmental period and indeed through the rest of our lives. Factors that are important at some stages of our development are less important at other stages. The dependencies of different factors on the stage of our lives at which they are studied probably explain many of the inconsistencies in the literature regarding the roles of different attributes on the etiology of obesity. For example, the role of the at-risk allele of the FTO gene (10,31) wanes during puberty (76), and during the first half of our lives we accumulate muscle, but during the second part of our lives we lose it (66–68). Changes in muscle function with age and social factors associated with 'growing up' may underpin changes in physical activity, and hence energy balance with age (66). This developmental dimension of energy balance requires greater attention. We should avoid e.g. statements of the form 'X causes obesity' but rather make more qualified statements that 'X causes obesity at Y stage of life'. In addition, unforeseen changes may also cause social insecurity, implying sensing a future risk of food shortage, involving adaptation of the appetite regulation to serve both the current and future needs (120). When the social insecurity persists and the shortage of food never happens, obesity develops. This theory is compatible with observations of an inverse relation between social class and obesity, and of psychosocial disadvantaged conditions (121–126), but is inconsistent with the observation that the association with social class in developing countries is the reverse – the most socially secure and wealthy are the obese ones. In summary, the rise in obesity over the past 50 years cannot be caused by genetic factors because our genome could not change in such a short time. However, the function of our genome could be changed on this timescale by epigenetic programming and assortative mating. Second, we evolved in an environment that is very different from that we currently inhabit. We have changed our environment so that many adaptations to our past environment such as our perception of food tastes, and being evolutionary ill equipped with environmental insults like the many chemicals that previously we never encountered. Third, humans are developing over a particularly long time frame compared to most animals; we are constantly changing during this developmental period and through the rest of our lives. Factors that are important at some stages of our development are less important at other stages. In conclusion, the complex genetic and environmental interaction underlying the imbalance of energy intake and expenditure includes faster genome changes than had been assumed until now, continuous changes during our development and through the rest of our lives, and new environmental changes we have not been adapted to. This probably can only be fully appreciated by setting the data into the context of our evolutionary history.

Conflict of interest statement

None.

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