

The evolution of human adiposity and obesity: where did it all go wrong?

Jonathan C. K. Wells¹

Because obesity is associated with diverse chronic diseases, little attention has been directed to the multiple beneficial functions of adipose tissue. Adipose tissue not only provides energy for growth, reproduction and immune function, but also secretes and receives diverse signaling molecules that coordinate energy allocation between these functions in response to ecological conditions. Importantly, many relevant ecological cues act on growth and physique, with adiposity responding as a counterbalancing risk management strategy. The large number of individual alleles associated with adipose tissue illustrates its integration with diverse metabolic pathways. However, phenotypic variation in age, sex, ethnicity and social status is further associated with different strategies for storing and using energy. Adiposity therefore represents a key means of phenotypic flexibility within and across generations, enabling a coherent life-history strategy in the face of ecological stochasticity. The sensitivity of numerous metabolic pathways to ecological cues makes our species vulnerable to manipulative globalized economic forces. The aim of this article is to understand how human adipose tissue biology interacts with modern environmental pressures to generate excess weight gain and obesity. The disease component of obesity might lie not in adipose tissue itself, but in its perturbation by our modern industrialized niche. Efforts to combat obesity could be more effective if they prioritized 'external' environmental change rather than attempting to manipulate 'internal' biology through pharmaceutical or behavioral means.

Introduction

Conceptually, obesity can be defined as a level of body weight and adiposity that is sufficiently excessive to damage health, demonstrated by an increased risk of various chronic diseases, including hypertension, stroke, type 2 diabetes, cardiovascular disease and some forms of cancer (Danaei et al., 2009). Although both the mechanisms and the magnitude of effect of these associations remain incompletely understood, there is substantial evidence that secular increases in obesity herald complementary increases in such diseases. For example, migration studies demonstrate linked increases in central adiposity and cardiovascular risk following novel exposure to the industrialized niche (Kinra et al., 2011; Poston and Foreyt, 1999). Obesity is now considered a major public health burden in both industrialized and modernizing countries, stimulating a coordinated strategy for prevention by the World Health Organization.

Despite seemingly compelling evidence that obesity is bad for human health, both public health efforts to reduce its prevalence and clinical efforts to treat it have had only modest success. This scenario can be attributed in part to the persisting poor understanding of what exactly obesity is. Obesity confounds the standard medical model of disease, which developed historically

to address biological pathogens and can be more difficult to apply to other forms of ill health. Obesity is a nebulous concept, defined using statistical criteria rather than explicit diagnosis of a metabolic pathology (Cole et al., 2000; Garrow and Webster, 1985). Its causes remain subject to vigorous debate, owing to the fact that the energy balance equation is a 'truism' and hence offers no explanatory framework for why excess weight gain occurs (Wells and Siervo, 2011). Although diverse phenotypic traits differ between obese and non-obese individuals, it remains unclear which differences are causal in its development.

The fact that high levels of adiposity are associated with poor health has led to many considering adipose tissue a 'toxic' tissue, a perspective that is supported by growing evidence of obesity as a chronic inflammatory state (Bays et al., 2008; Berg and Scherer, 2005; Fernandez-Real and Ricart, 2003; Laclaustra et al., 2007). According to this view, adipose tissue is the disease, and the less body fat, the better health. Yet most research on adiposity is conducted in individuals who are already overweight, thus telling us primarily about a physiological tissue in a pathological state. Much less attention has been directed to understanding the contributions of adipose tissue to health and function. For this, an evolutionary approach is required (Wells, 2006; Wells, 2009c).

Storing energy as fat is a characteristic of many organisms (Pond, 1998). It is best considered a strategy – a strategy that humans use in general, but one in which they also demonstrate substantial variability. The aim of this article is to discuss adipose tissue and its associated metabolism as a flexible 'risk management' strategy, to understand how it is sensitive to a wide variety of ecological cues, and why it is an active endocrine tissue. This then helps to understand why we are changing from a species that is well

¹Childhood Nutrition Research Centre, UCL Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK
e-mail: Jonathan.Wells@ucl.ac.uk

© 2012. Published by The Company of Biologists Ltd
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial Share Alike License (<http://creativecommons.org/licenses/by-nc-sa/3.0/>), which permits unrestricted non-commercial use, distribution and reproduction in any medium provided that the original work is properly cited and all further distributions of the work or adaptation are subject to the same Creative Commons License terms.

adapted to diverse ecological niches into a species in which a large proportion of individuals are characterized by excess body weight that impacts adversely on health.

Influential but insufficient approaches

Previous evolutionary approaches to human obesity, hence relevant to adiposity in general, have been dominated by two hypotheses, each focusing on the concept of thrift. In the 1960s, the 'thrifty genotype' hypothesis suggested that populations varied genetically in their predisposition to store energy, on account of differential ancestral exposure to 'cycles of feast and famine' (Neel, 1962). Those experiencing more frequent famines were assumed to have undergone selection for thriftier genes. This hypothesis was somewhat abstract, with no discussion of when such cycles of feast and famine might have occurred. Nevertheless, it became extremely influential, and is still widely cited today. An alternative hypothesis, focusing on life-course plasticity, proposed that low birth weight babies responded to their low level of nutritional intake in early life through alterations in growth and metabolism, which impact on subsequent obesity risk (Hales and Barker, 1992). According to this 'thrifty phenotype' hypothesis, an increased risk of diabetes following low birth weight could be attributed to poor pancreatic development interacting with excess body weight in later life. Again, this hypothesis has been extremely influential; however, although low birth weight babies are widely assumed to have an increased risk of adult obesity, a recent meta-analysis failed to support this assumption (Yu et al., 2011).

In both of these hypotheses, fat and thrift were considered two sides of the same coin. Thrift remains a very useful concept in evolutionary approaches to human adiposity and metabolism; however, it is essential to emphasize from the outset that there is much more to thrift than fat, and much more to fat than thrift (Wells, 2011).

Thrift implies a degree of prosperity deriving from earlier frugality and careful management of resources (Wells, 2009b). It refers generically to the efficiency with which energy is used, and can derive either from reducing energy expenditure, or storing energy. Fat is only one strategy for storing energy, and organisms show a wide variety of other forms of thrift, including hibernation, torpor and a reduced activity level, along with manipulations of growth rate, body size and relative investment in expensive organs such as brains or secondary sexual characteristics (Wells, 2009b). Storing energy as fat allows some organisms to tolerate ecological uncertainty; however, many organisms respond to such uncertainty in a rather different way – for example, through variation in reproductive success. Boom-bust population dynamics characterize species such as rabbits, which respond to increased energy supply by increasing reproductive rate rather than depositing fat (Wells, 2009b).

For species with energy stores, the allocation of energy between competing functions is potentially subject to greater control, allowing more complex life-history strategies (see Box 1) (Pond, 2003). Indeed, a recent study found that adipose tissue is negatively associated with brain size across mammals (Navarrete et al., 2011), highlighting that storing energy and processing information are alternative ways of dealing with ecological uncertainty. Humans, however, have both large brains and high adiposity (Wells, 2009b), making both strategies possible.

Box 1. Life-history theory

Life-history theory addresses variability in the 'pace' of organisms' life cycles (Stearns, 1992; Hill, 1993). Through the life-course, a series of strategic 'decisions' must be enacted, regarding how fast to grow, when to start breeding and how many offspring to produce at a given time point. Variability across species in life-history strategy reflects genotypic effects of natural selection, whereas variability within species reflects both genetic variability and phenotypic plasticity (Stearns, 1992). In each case, optimizing life-history strategy optimizes reproductive success, or 'fitness'.

The two primary factors influencing life-history strategy are mortality risk and the availability of energy. One of the key tenets of life-history theory is that a finite amount of energy must be divided (i.e. traded off) between competing functions, of which the most important are maintenance, growth, reproduction and immune function, and between current versus future reproduction (Hill, 1993). Adipose tissue, by storing energy in the body, buffers such trade-offs against short-term ecological perturbations, allowing them to be guided by longer-term factors.

Adiposity and risk management

This review emphasizes adiposity and associated components of metabolism as a generic metabolic form of risk management, contrasting with behavioral risk management by the brain (Fig. 1). It is well established that adiposity can fluctuate within individuals in response to a variety of life-course or ecological factors, in addition to accommodating genetic influences. Such fluctuations represent the balance of two competing strategies: on the one hand, individuals have a tendency to maintain a broad profile of adiposity over time, reflecting genetic, developmental and environmental influences; on the other hand, individuals have the capacity to gain or lose fat over short time periods in order to buffer other components of phenotype, and hence manage perturbations in energy balance. Genetic variability in adiposity might likewise be considered to represent ancestral influence on the overall risk management strategy.

Until recently, there was a widespread tendency to consider adipose tissue an inert fuel dump, simply storing energy for it to be drawn upon by other tissues as required. It is now recognized that adipose tissue secretes and responds to a wide variety of signaling molecules (Ahima, 2006). Rather than being supplied by large arteries, adipose tissue depots are maintained by many smaller blood vessels from adjacent tissues, which generate close connections with these tissues (Pond, 1998). Various receptors for the molecular signals that control uptake and discharge of triglycerides, located on the cell membrane and in the internal cytoplasm, provide integration with several regulatory systems (Pond, 1998). Through these complex and multiple signaling systems, adipose tissue is intricately involved in a wide variety of metabolic pathways. Far from being inert, therefore, the risk management strategy represented by adipose tissue plays a proactive role in allocating energy between competing functions (Wells, 2009c), thereby contributing to life-history strategy and promoting reproductive fitness (Hill, 1993).

The genetics of adiposity

Recent studies have emphasized a strong heritable component of variability in adiposity. Heritability estimates from a selection of large classical twin studies from industrialized populations, comparing monozygous and dizygous twins, are provided in Table 1;

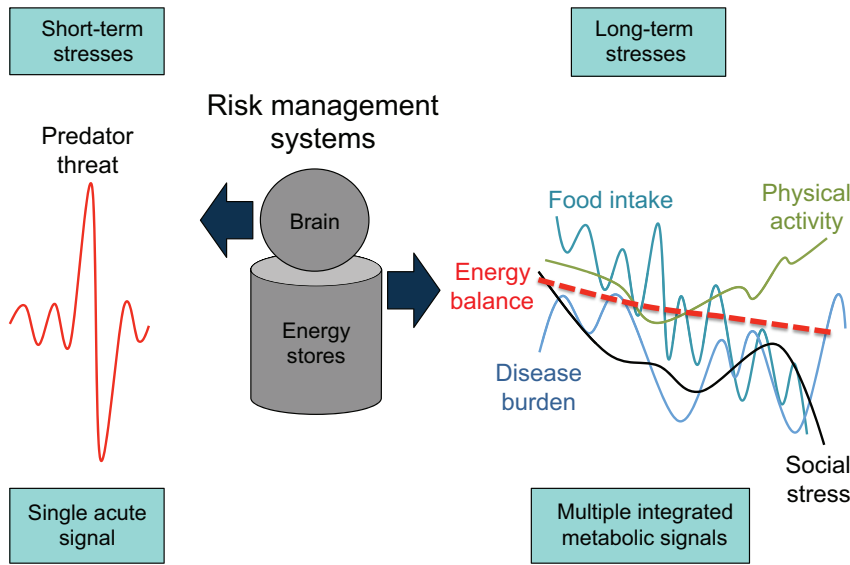


Fig. 1. Adiposity as risk management. This model treats adipose tissue as an endocrine regulatory system integrating multiple signals of energy supply and demand in order to optimize the allocation of energy across competing functions. This slower-response endocrine system contrasts with the faster-response regulation of behavior by the neural system (the brain), in response to acute signals. The example shows an individual responding to negative energy balance caused by increasing energy demand and decreasing supply.

Disease Models & Mechanisms • DMM

adoption studies have also suggested high heritability (Sorensen et al., 1989; Stunkard et al., 1986b). However, these studies have been conducted largely in industrialized populations, where favorable environmental conditions might maximize the contribution of genetic factors to phenotypic variability. Equivalent data from other ecological settings are lacking and, under greater ecological constraint, heritability might well be lower. Genome-wide association studies report an increasing number of individual alleles that are associated with adiposity, although findings often fail to be replicated across populations, a scenario that might be due to variability in study design and sample size as well as in population ethnicity (Elks et al., 2010a; Heid et al., 2010; Speliotes et al., 2010; Willer et al., 2009; Yajnik et al., 2009). Adiposity therefore seems to have the genetic profile of a continuous trait that is affected by numerous different genes, whose number and variability across populations remain to be established.

The reported high heritability values are currently being re-evaluated, following recent developments in our understanding of the biology of phenotypic variability. For example, monozygous twins are not only more similar genetically than dizygous twins, but are also more similar epigenetically (Fraga et al., 2005). This means that the greater similarity of monozygous twins might not be due entirely to genetic factors, and might also reflect a similar environmental experience, especially in early life (Armitage et al., 2008; Yajnik, 2004). This is an extremely important point, because

experience in utero is associated with various subsequent components of phenotype that are relevant to adiposity.

However, genetic variability within populations is not the only important comparison. Humans also appear systematically fatter than other primates (Altmann et al., 1993), although few data are available except from captive primates, themselves likely to be overweight. Even women with a low body mass index (BMI) in foraging populations have ~20% of weight as fat (Wells, 2012c). A genetic perspective on human adiposity therefore emphasizes two key issues: first, that ‘pan-human’ thrift manifests as a continuous trait with substantial plasticity (discussed in the following section), and, second, that it is subject to within- and between-population variability.

Several evolutionary approaches to contemporary genetic variability in adiposity have been proposed. In his classic paper, Neel emphasized differential exposure to ancestral famine (Neel, 1962). Over the last decade, some have argued that there is no evidence for such thrifty genes (Speakman, 2006; Speakman, 2008). Because starvation is rarely the primary cause of death in famines (Mokyr and O Grada, 2002), Speakman argued that famine could not have been sufficiently powerful as a source of selection to generate variability in thrifty genes. Instead, he proposed the ‘drifty genotype’ hypothesis, arguing that multiple alleles impacting adiposity accumulated below the threshold for phenotypic detection over millions of years through genetic drift, and have only

Table 1. Heritability coefficients from a selection of large twin studies for anthropometric indices of adiposity

Population	Age	n	Outcome	Heritability (%)	Reference
China	Adults	1260 twin pairs	BMI	61	Lee et al., 2010
			Waist	75	
Finland	Adults	~5278 twin pairs	BMI	80	Hjelmborg et al., 2008
United Kingdom	4 years	3582 twin pairs	BMI	48	Haworth et al., 2008
	11 years	4251 twin pairs	BMI	78	
United States	20 years	4071 twin pairs	BMI	77	Stunkard et al., 1986a
	Adults	1224 twin pairs	BMI	76	Watson et al., 2010

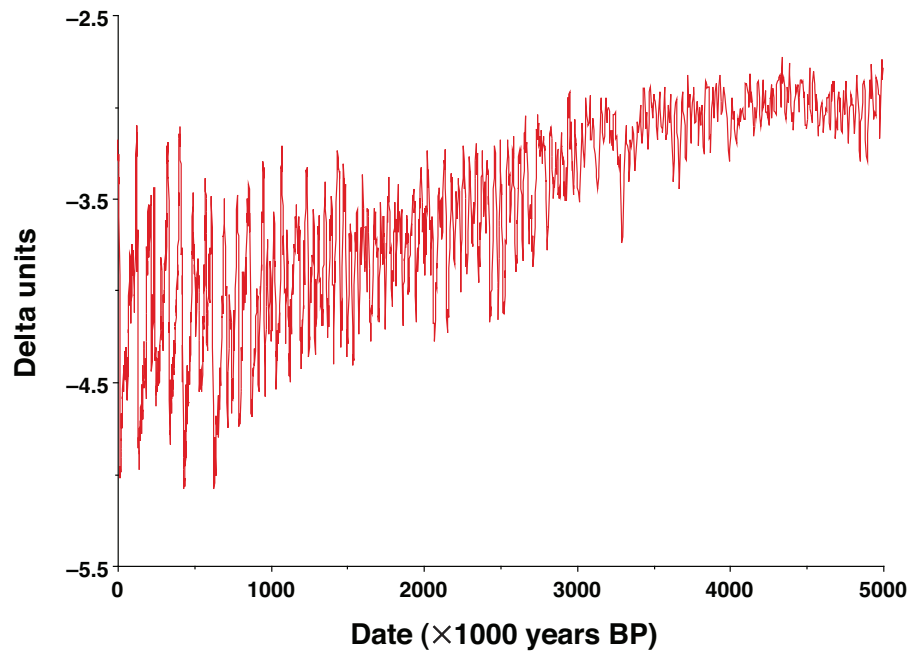


Fig. 2. Isotopic trends over the last 5 million years. Oxygen-18 (^{18}O) isotope levels are directly equivalent to average global temperature. As the world became steadily cooler, shorter-term climate stochasticity also increased substantially, indicating less stable ecological conditions. Based on published data (Lisiecki and Raymo, 2005). BP, before present.

recently been exposed in the modern obesogenic environment (Speakman, 2008).

However, other life-history functions (growth, maintenance of the large *Homo* brain, reproduction and immune function) might have been very important traits exposed to selection on energetics, and this perspective becomes more valuable if the definition of thrifty genes is expanded to those associated with any aspect of adipose tissue biology, rather than those associated with energy stores only. Bouchard suggested five broad types of thrifty gene: those associated with appetite; metabolism or thermogenesis; predisposition for physical activity; adipocyte lipid storage capacity; and lipid oxidation rate (Bouchard, 2007). This list can now be lengthened because genes that are associated with adult BMI have been linked with infant growth, pubertal timing and insulin metabolism (Elks et al., 2010a; Elks et al., 2010b; Hattersley et al., 1998).

Contemporary human genetic variability can be attributed to several different sources. First, some variability has persisted from *Homo erectus*, passing through the population bottleneck that characterized the origin of our own species (Garrigan and Hammer, 2006). Second, there is evidence that the gene pool of *Homo sapiens* received contributions through interbreeding with other hominin species, such as Neanderthals (Green et al., 2010) and a recently discovered type from Siberia (Abi-Rached et al., 2011). Because Neanderthals were well adapted to cold environments and a diet rich in protein, these genes might be very relevant to contemporary adiposity variability (Cochran and Harpending, 2009). Third, the main proportion of global human genetic variability is assumed to have occurred following the exodus from Africa around 60,000 years ago, when populations migrated to most continents and adapted to a wide range of thermal environments, ecosystems, dietary niches and disease loads (Garrigan and Hammer, 2006). Fourth, the rapid expanse in global population size following the emergence of agriculture is predicted to have substantially increased the absolute number of new mutations in the last 10,000 years (Cochran and Harpending, 2009).

When a new mutation occurs, it can increase in frequency in the gene pool if it is beneficial, through a 'selective sweep'. Recent evidence suggests that many local selective sweeps of genes influencing metabolism and adiposity only began relatively recently, and are still continuing (Bender et al., 2011; Pickrell et al., 2009). The specific functions of these genes converge on several important components of biology, including metabolism and digestion, immune defense, reproduction, and cognition (Cochran and Harpending, 2009; Voight et al., 2006).

Genetic evidence indicates that adiposity is a continuous trait, much like other life-history traits such as stature and the timing of puberty (Elks et al., 2010b; Lango Allen et al., 2010). Continuous traits tend to have a polygenic architecture, with each associated gene contributing a small magnitude of effect. The polygenic basis of adiposity maintains numerous small sensitivities to diverse ecological stresses that are relevant to life-history strategy, integrating them into a single phenotype (Wells, 2009b). In this way, it might represent a moderate form of bet-hedging – i.e. increasing variance in offspring to reduce variance in fitness (Wells, 2009b). Perhaps more importantly, the same polygenic architecture further offers a stable platform on which mechanisms of plasticity can function, because the trait becomes robust to individual mutations by constraining their magnitude of effect (Wagner, 2005).

Crucially, this perspective also suggests substantial common ground between the genetic and plastic components of adiposity variability. The genetic component integrates multiple ancestral influences on life-history traits such as growth, pubertal development, metabolism, adipocyte biology, etc., whereas the plastic component allows greater life-course flexibility in the same traits. Next, I consider the long-term evolutionary environment that shaped this overall profile.

What environment shaped human adiposity?

The pan-human profile of adiposity was shaped over our evolutionary past, reflecting ecological pressures that favored a

number of unusual traits that are characteristic of our species (Wells, 2009b). These traits include large brains and fully bipedal locomotion, but also key social and behavioral capacities, and they have been widely assumed to have been favored by the emerging 'savannah' environment in east and southern Africa.

There is a tendency to consider the savannah a relatively stable environment, with our modern fast-changing urban environment generating a stark sudden contrast. An increasing volume of palaeoenvironmental data suggests that this view of past stability is very misleading (Potts, 1996; Potts, 2011). Isotopic data indicating trends in global temperature indicate that, as the world became cooler over the last few million years, this was accompanied by another trend towards increasing climatic volatility (Fig. 2) (Lisiecki and Raymo, 2005). This volatility in turn is assumed to equate to continual ecosystem change, because rises and falls in temperature and precipitation alter patterns of vegetation and associated communities of organisms (Potts, 1996). The last 10,000-year period has paradoxically been relatively stable climatically (Richerson et al., 2001), but has instead been increasingly perturbed by the niche-constructing activities of humans themselves (Wells and Stock, 2007). There has arguably never been a lengthy period of environmental stability during the evolution of the *Homo* genus.

Although outright famines might have been rare in pre-agricultural populations, and severe food shortages could be addressed by nomadism, hominin populations can be assumed to have experienced energy stress repeatedly across and within generations, resulting from various cycles of uncertainty. These include seasonality, longer-term systematic climate shifts, and extreme events such as volcanic eruptions and climatic cycles (Potts, 1996), an example in the contemporary world being El Niño effects. More recently, human activities such as over-hunting and unsustainable agricultural strategies have maintained ecological perturbations (Diamond, 1998; Fagan, 1999). The ability to withstand ecological volatility would furthermore have improved the capacity to probe new habitats and niches, and hence colonize new territories, a process that could have ramped up through positive feedback effects (Wells and Stock, 2007). This issue is of particular interest given the role of energy stores both in promoting reproduction, and in withstanding energy stress, as discussed below.

Although further details of this ecological volatility remain to be established, there is already sufficient evidence to assume that hominin evolution has been strongly shaped by stochastic environments, with regular exposure to energy stress; this assumption underlies the arguments below. Within such environments, adiposity can be assumed to have interacted with other hominin traits, such as large brains, colonizing strategy, cooperative breeding, slow growth and dietary ecology, in complex feedback cycles.

Adipose tissue as a strategy

The notion that adiposity functions as a complex risk management system is supported by previous evaluations of how the tissue evolved in vertebrates. Early mammals, for example, were small and nocturnal. Lactating mice lay down fat by night in order to fund lactation by day (Pond, 1984). In such small species, lactation is too expensive to fund directly from energy intake, hence storing energy during the period of feeding makes high energy output viable

during the non-feeding period. Other ecological stresses favoring fat stores include migration, breeding and hibernation, each of which temporarily overloads energy demand relative to intake (Pond, 1998). Adipose tissue stores are particularly valuable in cold environments, which are more vulnerable to fluctuations in energy supply (Pond, 1998). So important is fat to some hibernating animals that if they are starved as winter approaches, they preferentially preserve adipose tissue, and oxidize lean tissue instead (Dark, 2005).

We can therefore consider adipose tissue as a strategy for energy storage that responds to multiple ecological stresses, interacting with the characteristics of the animal. As body size increases, the energy expenditure per kg body weight decreases (Ofstedal, 2000). Metabolic processes therefore become more efficient as body size increases. In this way, larger body size per se, along with both absolutely and relatively greater energy stores, increases the period of time over which adipose tissue stores can fund energy requirements.

Storing energy as fat is by no means the only strategy for managing the risk of uncertainty in energy supply. A highly social organism such as humans can store energy not only in the body but also extra-corporally (in food hoards) or in social relationships. This 'redundancy' of multiple mechanisms suggests that energy risk management was crucial in the evolution of our species; however, although the different approaches have much in common, they also address different situations. Storing energy in social relationships or food hoards buffers against individual uncertainty and misfortune, such that other group members alleviate the risk. This scenario gives control over the social distribution of energy stores. Storing energy in the body buffers against situations that affect all individuals in the social group, such as major ecological stress. This scenario increases control over the internal distribution of energy, as discussed below. However, storing energy in the body also carries its own risks – the historical record has repeatedly documented widespread cannibalism during severe famine, with some individuals plundering the somatic energy stores of others (Keys, 1999).

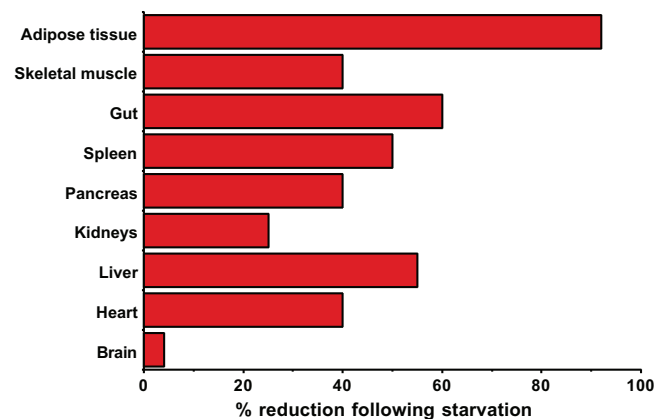


Fig. 3. Percentage reduction in the mass of various organs and tissues during starvation. During starvation, the amount of adipose tissue decreases substantially, but most other tissues also decline. Based on published data (Rivers, 1988).

Fitness functions of fat

Adipose tissue and metabolism are fundamental to each of the primary life-history functions (see Box 1), as briefly described below.

Buffering starvation

It is widely recognized that adipose tissue can buffer against starvation. A typical adult male and female store sufficient energy to meet daily requirements for several weeks, typically longer in females than males due to their higher average body fat content (Norgan, 1997). However, Fig. 3 illustrates that adipose tissue is by no means the only tissue that is broken down during starvation, and that, although it is the most plastic tissue, skeletal muscle, gut, spleen, heart and liver tissue all decrease substantially during prolonged starvation (Rivers, 1988). Fat is therefore only one of a wider range of energy stores. Famines have been recorded regularly throughout human history (Keys et al., 1950), but only in certain circumstances is death from starvation (i.e. extreme exhaustion of energy stores) common. Rather, death commonly occurs from infectious disease (Mokyr and O Grada, 2002), suggesting that, in addition to providing fuel for metabolism, a key role of adipose tissue is to maintain a viable immune system and protect vital homeostatic functions (see below).

Buffering stochasticity

Rather than tolerating absolute famine, energy stores can be considered more important for buffering short- and long-term fluctuations in energy balance that are caused by seasonality in energy supply or other similar stresses. Studies of farming populations in seasonal environments show typical average fluctuations in body weight of 2–3 kg (Ferro-Luzi and Branca, 1993), with 4–5 kg occurring under more extreme conditions (Singh et al., 1989). Detailed studies of Gambian women showed that the majority of such weight change was attributable to losses and gains in fat (Lawrence et al., 1987), although suppression of basal metabolic rate during pregnancy provides another dimension of thrift in this population (Poppitt et al., 1994). Other studies have shown the extraordinary rapidity with which weight can be gained through voluntary over-feeding for brief periods, as demonstrated by the Guru Walla ceremony in rural Cameroon, where daily weight gains approaching 0.25 kg were observed in some individuals (Pasquet et al., 1992).

Adaptation to the cold

Body fatness tends to be greater in populations inhabiting colder environments (Wells, 2012c). Although some have suggested that fat is favored as insulation in such conditions, this is not well supported by evidence, and high fatness impedes heat loss during exercise (Pond, 1998). Instead, increased energy stores in cold environments can ensure a supply of energy for thermogenesis, while also providing greater buffering against negative energy balance, which is potentially more harmful in cold environments. Several stresses co-vary with climate, including dietary ecology, food insecurity and disease load. A recent analysis of non-Western populations showed that climatic variability was more strongly associated with peripheral than central adiposity, suggesting that central adiposity is more strongly influenced by other ecological stresses (Wells, 2012c).

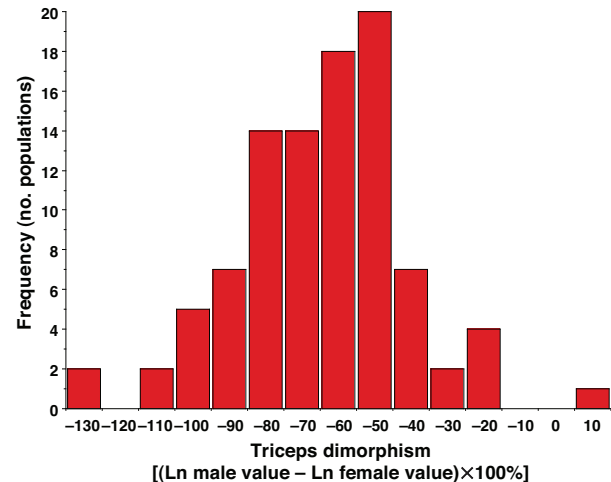


Fig. 4. Histogram of sexual dimorphism in triceps skinfold thickness in 96 non-industrialized populations. These data indicate the trend for substantially greater arm fat in females compared with males, but also substantial variability among populations in this dimorphism. Reprinted with permission (Wells, 2012b).

Growth

Energy stores are important in funding growth, both via the energetics of reproduction and through the individual life-course (Wells, 2009c). Maternal nutritional status regulates the probability of conception (Schneider 2004; Wade et al., 1996), whereas baseline adiposity and pregnancy weight gain contribute to growth of the fetus (Anderson et al., 1984). In early postnatal life, storing energy predicts the amount of lean mass accreted subsequently. This suggests that growth strategy is sensitive to signals of energy availability, although in early life these signals relate more strongly to maternal nutritional status than to the external environment per se (Wells, 2010).

Buffering the brain

Recent studies suggest that brain energy requirements are a function of neuron number (Herculano-Houzel, 2011). Hence, the high neuron number in the human brain [which is associated with upregulation of many brain genes compared with non-human apes (Caceres et al., 2003)] generates a particularly high energy requirement, equivalent to 20% of basal metabolism even in adult life. The high level of adiposity in early life has been attributed to the benefits of buffering the heightened energy needs of the brain at this age (Kuzawa, 1998). At birth, the brain accounts for ~80% of total energy expenditure, a value which decreases to ~20% by adulthood (Holliday, 1978). The brain is not insulin sensitive and has obligatory energy requirements. Body fat might guarantee brain energy supply during early life when infection risk is high, and can provide ketones as an alternative substrate during starvation (Kuzawa, 1998).

Reproduction

The substantial sexual dimorphism that is observable for adult adiposity can be attributed to the primary role that females play in the direct provision of energy for reproduction (Lassek and Gaulin,

2006; Wells, 2009c). Fig. 4 illustrates a histogram of population variability in sexual dimorphism in triceps skinfold thickness. The magnitude of dimorphism varies substantially, in accordance with ecological factors such as energy availability and climate, but the mean female triceps skinfold thickness is greater than that of males in the vast majority of these 96 populations. Importantly, specific fat depots such as gluteo-femoral adiposity might be particularly important in providing essential fatty acids for offspring brain growth (Lassek and Gaulin, 2007; Rebuffe-Scrive et al., 1985), indicating that fat often supplies more than mere energy for biological functions. Notably, such gluteo-femoral fat also seems to be less detrimental to cardiovascular risk than central abdominal fat (Snijder et al., 2004a; Snijder et al., 2004b).

Immune function

Recent work has emphasized the fundamental contribution of adipose tissue to the immune system. Immune function is metabolically expensive, involving a variety of costs, including the defense and repair of specific tissues, the metabolic cost of fever, and the production and maintenance of lymphocytes and other immune agents (Romanyukha et al., 2006). Ironically, these costs also include the growth and metabolism of the pathogens themselves. Again, adipose tissue not only provides energy for immune function, but also anatomically specific molecular precursors for immune agents (Mattacks et al., 2004; Pond, 2003) and a range of pro- and anti-inflammatory cytokines that play numerous roles in both immune defense and the repair of damaged tissues (Atanassova et al., 2007; Badman and Flier, 2007; Permana and Reardon, 2007) (Box 2).

Psychosocial stress

Like many other mammals, humans live in social groups characterized by varying degrees of social hierarchy. In this context, the feeding behavior and metabolism of subordinate individuals is sensitive to behavioral signals from dominant individuals. In humans, as in other primates, subordinate individuals show a different neuroendocrine profile to dominant individuals, having increased cortisol and neuropeptide Y (NPY) levels, leptin resistance, and a greater appetite and central adiposity (Adam and Epel, 2007; Epel et al., 2001; Siervo et al., 2009). Patterns of fat metabolism and deposition therefore represent an adaptive response to the psychosocial environment.

Sexual selection

Given the multiple functions of adiposity, it is no surprise that it represents a key trait that is subject to sexual selection in females, who bear the direct costs of reproduction (Norgan, 1997). Across human populations, female adiposity is generally considered attractive up to a point. However, this association of adiposity and attractiveness is also subject to ecogeographical and cultural variability, indicating that males can facultatively shift their preferences according to local ecological conditions (Tovee et al., 2006).

The sections above have briefly demonstrated that adipose tissue is associated with numerous different biological functions. Importantly, they can all be integrated within the theoretical model of life-history. Adipose tissue can provide energy for each of these

Box 2. Selected cytokines and growth factors secreted by adipose tissue

Pro-inflammatory cytokines:

- Interleukin-1 (IL-1), IL-6, IL-18
- Tumor necrosis factor- α
- Eotaxin
- Resistin
- Leptin

Anti-inflammatory cytokines:

- Adiponectin
- IL-10
- IL-1 receptor antagonist
- Prohibitin

Growth factors:

- Angiopoietin-1
- Fibroblast growth factors
- Epidermal growth factor-like growth factor
- Hepatocyte growth factor
- Insulin-like growth factor
- Nerve growth factor
- Platelet-derived growth factor

functions, and its ability to do so is enabled by two key factors: its involvement in multiple signaling pathways through which energy needs and energy availability interact, and its interaction with fundamental feedback systems that proactively allocate energy between these functions. Hormones such as leptin (secreted by adipose tissue itself), insulin (responsive both to adiposity and ongoing metabolic dynamics) and cortisol (sensitive to a variety of ecological stressors) play key roles in integrating adipose tissue with these competing functions (Harshman and Zera, 2007; Schneider, 2004; Tatar et al., 2003; Wade et al., 1996), but many other signaling molecules are also important.

Fig. 5 presents a schematic diagram of energy metabolism as an 'allocation game', whereby energy is directed to competing functional or storage ends (Wells, 2009a). For example, reductions in adiposity drive reductions in leptin, which in animal studies curtails reproductive function and components of immune function (Drazen et al., 2001; Prentice et al., 2002; Schneider, 2004). Similar signaling systems are expected in humans, although the details are still being established, and the importance of leptin in human adipose tissue biology might have been overemphasized. In addition to the signaling molecules described above, various molecules secreted by adipose tissue influence the relative allocation of energy between these ends. For example, the insulin-sensitizing hormone adiponectin moderates many aspects of reproduction through receptors in the ovaries, oviduct, endometrium and testes, as well as in the central nervous system (Campos et al., 2008; Michalakis and Segars, 2010); adiponectin levels are also sensitive to early-life experience. Although additional work remains to be done, it is already clear that adipose tissue plays a fundamental regulatory role on the allocation of energy between competing life-history functions.

Risk management in operation: the long view

Although humans have a common risk management strategy in their adipose tissue, its characteristics also differ between populations, and between individuals within populations. Unlike

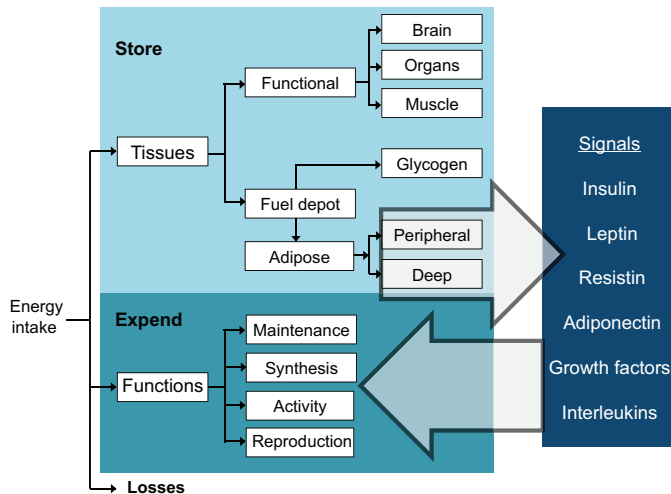


Fig. 5. Energy metabolism as an 'allocation game', with incoming energy allocated to ongoing biological functions (energy expenditure) or a range of energy stores. The allocation 'decisions' are assumed to be orchestrated by various signaling molecules. Adapted with permission (Wells, 2009a).

the brain, which represents another strategy for risk management, adipose tissue biology seems to be somewhat tailored to local ecological conditions. The scenarios described below illustrate how the risk management strategy might be modified by long-term or short-term experience.

Numerous studies have highlighted systematic differences between populations in adiposity and metabolism. For example, compared with Europeans, south Asians have a higher mean body fat content for a given BMI value, whereas West African populations tend to have lower body fat content and greater lean mass. These differences in adiposity are associated with variability in metabolic traits such as insulin sensitivity and blood pressure. Most attention has been paid to these particular ethnic groups, because south Asians and Africans or Afro-Caribbeans comprise significant minority populations in some industrialized populations. Beyond this, a continuum of ethnic variability in adiposity is apparent (Wells, 2012c). What ecological pressures can account for such ethnic variability?

Some of the variability can be attributed to non-genetic factors, potentially incorporating immediate effects of diet and transgenerational growth patterns. However, some of the variability derives from genetic factors, indicating adaptation to longer-term stresses. For example, climate has been associated with physique and adiposity (Wells, 2012c), basal metabolism, and low-density lipoprotein (LDL) concentrations (Snodgrass et al., 2007).

Similarly, I have suggested that adaptation to local disease loads is an important source of such genetic variability. The 'variable disease selection' hypothesis assumes that specific infectious diseases impose different metabolic burdens, favoring variable responses in terms of fat distribution and cytokine biology (Wells, 2009a). For example, a number of infectious diseases have been described as 'unconquerable', in that the pathogen and the immune system develop a 'precarious standoff' in which the immune system remains activated without completely defeating the pathogen (Roth et al., 2011). Such diseases include tuberculosis, malaria, hepatitis

B, schistosomiasis, African trypanosomiasis, Chagas disease and syphilis (Roth et al., 2011).

For each disease, the availability of increased energy stores might boost the immune system, but the optimal depot for storing the energy, and the optimal range of associated cytokine signaling, might vary between the diseases (Wells, 2009a). For example, I have suggested that intramuscular adipose tissue in African populations might have been favored as an adaptation to malaria, providing local fuel for muscle tissue in this disease, for which fever is a key component of immune defense, whereas visceral adiposity might have been favored in south Asian populations as an adaptation to gut-borne infections, which can be promoted by regular monsoon rainfall (Wells, 2009a).

This hypothesis can be placed alongside other hypotheses for ethnic genetic variability in traits relevant to adiposity, such as dietary ecology (Kagawa et al., 2002) and thermal stress (Hancock et al., 2008). However, the reason why the variable disease selection hypothesis merits particular attention is that it offers an explanation for variability in cytokine biology – and it is the cytokine load imposed by obesity that seems to be particularly detrimental in terms of chronic degenerative disease risk (Alvehus et al., 2010; Fernandez-Real and Ricart, 2003; Hotamisligil, 2006; Tilg and Moschen, 2006). The immune system is well established to be under selection in humans, and evidence for ethnic variability in cytokine levels is now emerging (Drazen et al., 2001; Ivanova et al., 2011; Paalani et al., 2011). Although these hypotheses are intriguing, supporting evidence is currently limited and this is an important area for further work.

Risk management in operation: the short view

Within the life-course, experience might also predispose to variability in the adipose risk management system. Recent studies have shown how experience in early life generates differences in life-history strategy, with multiple effects on adiposity. For example, babies born small tend to undergo rapid infant growth (Ong et al., 2000). These traits are then associated with the timing of puberty, and with adiposity both in adolescence (Ong et al., 2009; Ong et al., 2007) and adulthood (Pierce and Leon, 2005). A life-history perspective attributes these associations to different reproductive strategies (Nettle et al., 2010), and therefore different relative allocations of energy to maintenance (longevity), growth, immune function and reproduction. Exposure to psychosocial stress likewise generates metabolic responses, some of which influence adiposity (Brunner et al., 2007).

Mechanistic studies increasingly demonstrate that such life-history plasticity is enabled by several dimensions of physiology, involving hormonal adaptations and epigenetic variability in gene expression. For example, babies born small have low levels of the hormone insulin-like growth factor-1 (IGF1) (Ibanez et al., 2009; Randhawa and Cohen, 2005) but, if nutrition is adequate to support catch-up growth, the expression of insulin receptors and the IGF1 receptor in muscle and related tissues is upregulated (Muhlhauser et al., 2009), with long-term metabolic effects. Other epigenetic effects demonstrated in animal studies target regulatory systems controlling appetite (Coupe et al., 2009). The primary target of such plasticity might be growth variability; however, the metabolic effects often impact the amount, distribution and activity of adipose tissue. In contemporary populations, therefore, each of these early-life

adaptations might interact with the subsequent environment to moderate obesity risk (Wells, 2012a). Importantly, however, the mechanisms underlying such physiological plasticity seem to differ between populations, such that both early-life and subsequent risk factors can vary (Wells, 2012a).

Where is the disease of obesity located?

So far, this article has described adipose tissue as a flexible risk management strategy for allocating energy across competing life-history functions under stochastic conditions. This system is assumed to have evolved under conditions of regular energy stress, and indicates that adipose tissue biology in humans is fundamental to our species' persistence (Wells, 2009c). In modern environments, this adaptive system is paradoxically associated with ill health, through chronic excess weight gain and the metabolic comorbidities of obesity (Hankey, 2012; Lustig, 2008; Prasad et al., 2011).

This scenario can be attributed to the way in which multiple components of modern urban environments interact with the sensitive physiological pathways that confer adaptive plasticity. There is a widespread assumption that factors that are specific to human biology render our species unusually vulnerable to the state of obesity. Yet this leads to the question: at what level of biology is the disease of obesity located? Is obesity 'internal' to the individual – a characteristic of genome and physiology that is amenable to molecular or pharmaceutical manipulation – or is it external and a consequence of environmental factors? Answering this question is relevant to strategies for both prevention and treatment.

Research into the molecular basis of body weight regulation has increased exponentially in recent years, following the discovery of an increasing number of relevant hormones, peptides and other signaling molecules, allowing numerous regulatory pathways to be elucidated (Huda et al., 2006; O'Rahilly et al., 2003; Schwartz and Morton, 2002). Much of this effort has been directed to the development of novel pharmaceutical products that curb appetite or reduce energy absorption. Although a number of such products have been developed, few have been classified safe for human use (Wilding, 2004; Rodgers et al., 2012). The complexity and redundancy of molecular pathways of weight regulation seem to hinder the identification of safe 'entry points' that are still capable of generating substantial effects. Unlike the case of cholesterol, there is no obvious rate-limiting step in energy metabolism and, because adiposity is a continuous trait, no individual gene generates a large magnitude of impact on phenotype. Although further progress, potentially adopting a polytherapeutic strategy whereby multiple pharmaceutical agents are combined (Rodgers et al., 2012), is likely, the extent of potential success remains unknown. Bariatric surgery has proven very effective in reducing type 2 diabetes, one of the primary co-morbidities of obesity (Buchwald et al., 2009), but is clearly an aggressive option with significant effects on quality of life. Furthermore, neither pharmaceutical nor surgical approaches are currently relevant to obesity prevention.

The situation for behavior is more complex. Humans likewise show much behavioral diversity, yet, in non-obesogenic environments, behavioral variability does not typically lead to excess weight. However, humans can deliberately fatten themselves, as reported in various cultures (Pasquet et al., 1992). Obesity can therefore be said to have a specific behavioral component, and

behavior might therefore seem the obvious target for both treatment and prevention. Nonetheless, weight management programs typically achieve only modest weight loss on average (although some individuals perform better) and many who initially lose weight subsequently regain it (Taubes, 2008). The lack of success in behavioral prevention programs is indicated by upward trends in obesity prevalence in many industrialized countries, and even more so in countries undergoing rapid economic development (Misra and Khurana, 2008; Popkin, 2007).

Because obesity is rare in traditional societies, it is clear that environmental factors are essential for its occurrence in the vast majority of individuals, and that these factors drive behavioral change at the level of the individual (Poston and Foreyt, 1999). Molecular variability might account for differential susceptibility to the obesogenic niche, but the niche itself is a prerequisite for obesity except in the case of very rare genetic disorders (O'Rahilly et al., 2003). Significantly, evidence increasingly suggests that many non-human species become overweight if subjected to the human industrialized niche. Many primate species become obese in captivity (Kemnitz and Francken, 1986), and diverse species of pet animals also gain excess weight (German, 2006). These findings remind us that expression of human obesity is dependent on exposure to certain conditions, which are conventionally termed the 'obesogenic niche'. One key element of such environmental effects is their role in eliciting differential susceptibility to obesity. Recently, life-history traits have received attention as being central to the life-course emergence of variability in obesity susceptibility (Dulloo, 2008; Dunger et al., 2006; Wells, 2011; Yajnik, 2004).

The dominant role played by the energy balance equation in obesity research has resulted in particular emphasis on high energy intake ('gluttony') and low energy expenditure on physical activity ('sloth') as the primary determinants of the condition (Prentice and Jebb, 1995). Many studies have sought evidence for gluttony or sloth in those prone to weight gain, and the obesity epidemic is also widely attributed to secular trends in population energy intake or physical activity level (Briefel and Johnson, 2004; Dollman et al., 2005). In popular wisdom, obesity is the product of too much food and too little activity, seemingly implicating personal responsibility. This perspective increasingly seems to be over-simplistic.

The energy balance equation is based on fundamental physics and cannot itself be wrong, but its application in obesity research is increasingly considered problematic (Lustig, 2006; Taubes, 2008; Wells and Siervo, 2011). Attention has begun to turn to a wider range of possible environmental or demographic risk factors, such as central heating, shifts in sleep patterns, chronic psychosocial stress, exposure to television screens, later age at first birth, environmental pollutants, etc. (Brunner et al., 2007; Keith et al., 2006). Although all of these proximate factors merit attention and might prove to be associated with variability in adiposity, almost all researchers pay little attention to why these behavioral trends are taking place.

Risk management meets political economy

A historical perspective, rarely adopted by scientists, offers ample evidence that food supplies fluctuate substantially through the influence of market forces. Importantly, these forces drive both under-nutrition as well as excessive energy intake (Albritton, 2009). A large proportion of the global population remains under-

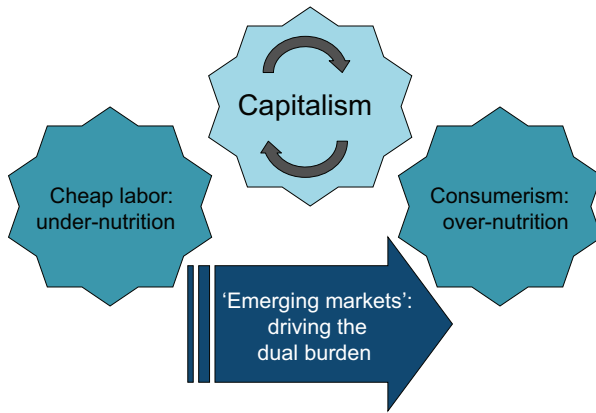


Fig. 6. Schematic diagram of the role of capitalism in global under-nutrition and over-nutrition. In recent decades, the exponential growth of the globalized economy has led to rapid economic development in many countries, resulting in populations further undergoing rapid shifts from chronic under-nutrition to chronic energy excess. In each case, powerful commercial companies privatize the profits arising from manipulating the global supply of food, but socialize the health costs (Albritton, 2009).

nourished, often as a direct consequence of exploitation as cheap labor in agricultural production, industry or new urban economies. Another large and increasing proportion of the population has become overweight, owing to various manipulations that maximize profit for the food retail and associated industries (Albritton, 2009). Recent work on the role of refined-carbohydrate diets in perturbing insulin metabolism highlights how the content of foods might drive changes in human behavior, rather than vice versa (Taubes, 2008; Wells and Siervo, 2011).

Capitalism therefore drives both under-nutrition and excessive energy intake. However, in recent decades, a further effect is for capitalism to drive the transition from one nutritional state to the other (Fig. 6). In 'emerging market' modernizing countries such as India, obesogenic food products interact with metabolic adaptations to chronic malnutrition to produce a high prevalence of obesity that can approach 50% in urban populations (Pandey et al., 2011). A recent study showed, for example, that the transmission of obesity from mother to offspring is much more likely if the mother was herself born small (Cnattingius et al., 2011), demonstrating the impact of prior under-nutrition on susceptibility to the obesogenic niche. These rapid secular trends are driven by the aim of the food industry to target new markets (Stuckler et al., 2012), in the absence of any efforts to address persisting under-nutrition. This is illustrated by a persisting high prevalence of under-nutrition in the same populations in which obesity is rapidly escalating, a situation known as the dual burden (Doak et al., 2000; Doak et al., 2005).

Capitalism therefore stands out from other politico-economic systems in its capacity to drive both under-nutrition, through the demand for cheap labor, and excessive energy intake, through the demand for ever-increasing levels of consumption to boost profits. In the midst of this economic environment, the risk management system represented by adipose tissue swings between extremes of chronic energy deficiency in some, and obesity in others. Chronic psychosocial stress is no longer a signal

of uncertainty in energy availability, but is instead a prevalent component of the modern working environment in which energy-dense foods are readily available, and psychosocial manipulations of appetite are promoted by the food industry (Brunner et al., 2007; Nestle, 2007; Shell, 2002).

The notion that obesity is a disease 'inside' the body, a function of each individual's genotype and phenotypic plasticity, is not well supported by this perspective. As this review has argued, adipose tissue itself is a valuable organ with many beneficial effects on diverse biological functions. In environments of limited food availability, almost no combination of genotype and plasticity will lead to obesity, the exception being very rare genetic conditions such as Prader-Willi syndrome. Instead, obesity can be considered a disease 'outside' the body, deriving from an inappropriate food supply and marketing system, producing a niche to which individuals then vary in their susceptibility.

Efforts to address the global obesity epidemic have been singularly unsuccessful, owing to their focusing at the level of the individual. Most obesity prevention campaigns are characterized by denial at many levels of the fundamental role played by the global economy. As capitalism draws ever more of the global population into its multinational marketplace, the prevalence of obesity rises in concert. A major shift in strategy, from individual-based science to population-based economics, will probably be required to reduce the global health burden of excessive energy intake and obesity. If the disease component of obesity lies not in adipose tissue itself, but in the interaction between adipose tissue biology and our modern industrialized environment, efforts to combat obesity would be much more effective if they prioritized 'external' environmental change rather than attempting to manipulate 'internal' biology through pharmaceutical or behavioral means.

Conclusion

Adipose tissue is found in many vertebrates, where it represents a sophisticated means of accommodating uncertainty in energy supply. The fact that adipose tissue is the source of numerous signaling molecules highlights its role in orchestrating life-history decisions. This risk management system is, however, increasingly destabilized in many human populations. Prevailing economic policies cause individuals to be subjected to a range of 'invasive' cues favoring fat accumulation, in environments in which actual energy availability has high stability. The combination of insulinogenic diets and psychosocial stress on the one hand, and low energy demand for physical exertion, reproduction and immune function on the other, stimulates chronic lipogenesis but reduces lipolysis. At this point, high levels of adiposity become toxic and harmful to health. It is these socio-environmental cues, collectively orchestrated by our capitalist economic system, that are the optimal target for obesity prevention.

This article is part of a special issue on obesity: see related articles in Vol. 5, issue 5 of Dis. Model. Mech. at <http://dmm.biologists.org/content/5/5.toc>.

COMPETING INTERESTS

The author declares that he does not have any competing or financial interests.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

- Abi-Rached, L., Jobin, M. J., Kulkarni, S., McWhinnie, A., Dalva, K., Gragert, L., Babrzadeh, F., Gharizadeh, B., Luo, M., Plummer, F. A. et al.** (2011). The shaping of modern human immune systems by multiregional admixture with archaic humans. *Science* **334**, 89-94.
- Adam, T. C. and Epel, E. S.** (2007). Stress, eating and the reward system. *Physiol. Behav.* **91**, 449-458.
- Ahima, R. S.** (2006). Adipose tissue as an endocrine organ. *Obesity* **14 Suppl. 5**, 242S-249S.
- Albritton, R.** (2009). *Let Them Eat Junk*. London: Pluto Press.
- Altmann, J., Schoeller, D., Altmann, S. A., Muruthi, P. and Sapolsky, R. M.** (1993). Body size and fatness of free-living baboons reflect food availability and activity levels. *Am. J. Primatol.* **30**, 149-161.
- Alvehus, M., Buren, J., Sjostrom, M., Goedecke, J. and Olsson, T.** (2010). The human visceral fat depot has a unique inflammatory profile. *Obesity* **18**, 879-883.
- Anderson, G. D., Blidner, I. N., McClellom, S. and Sinclair, J. C.** (1984). Determinants of size at birth in a Canadian population. *Am. J. Obstet. Gynecol.* **150**, 236-244.
- Armitage, J. A., Poston, L. and Taylor, P. D.** (2008). Developmental origins of obesity and the metabolic syndrome: the role of maternal obesity. *Front. Horm. Res.* **36**, 73-84.
- Atanassova, P., Tonchev, A. B., Peneva, V. N., Chaldakov, G. N., Valchanov, K. P., Fiore, M. and Aloe, L.** (2007). What are subcutaneous adipocytes really good for? Viewpoint 3. *Exp. Dermatol.* **16**, 56-59.
- Badman, M. K. and Flier, J. S.** (2007). The adipocyte as an active participant in energy balance and metabolism. *Gastroenterology* **132**, 2103-2115.
- Bays, H. E., Gonzalez-Campoy, J. M., Bray, G. A., Kitabchi, A. E., Bergman, D. A., Schorr, A. B., Rodbard, H. W. and Henry, R. R.** (2008). Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev. Cardiovasc. Ther.* **6**, 343-368.
- Bender, N., Allemann, N., Marek, D., Vollenweider, P., Waeber, G., Mooser, V., Egger, M. and Bochud, M.** (2011). Association between variants of the Leptin Receptor Gene (LEPR) and Overweight: A systematic review and an analysis of the CoLaus study. *PLoS ONE* **6**, e26157.
- Berg, A. H. and Scherer, P. E.** (2005). Adipose tissue, inflammation, and cardiovascular disease. *Circ. Res.* **96**, 939-949.
- Bouchard, C.** (2007). The biological predisposition to obesity: beyond the thrifty genotype scenario. *Int. J. Obes.* **31**, 1337-1339.
- Briefel, R. R. and Johnson, C. L.** (2004). Secular trends in dietary intake in the United States. *Annu. Rev. Nutr.* **24**, 401-431.
- Brunner, E. J., Chandola, T. and Marmot, M. G.** (2007). Prospective effect of job strain on general and central obesity in the Whitehall II study. *Am. J. Epidemiol.* **165**, 828-837.
- Buchwald, H., Estok, R., Fahrenbach, K., Banel, D., Jensen, M. D., Pories, W. J., Bantle, J. P. and Sledge, I.** (2009). Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am. J. Med.* **122**, 248-256.
- Caceres, M., Lachuer, J., Zapala, M. A., Redmond, J. C., Kudo, L., Geschwind, D. H., Lockhart, D. J., Preuss, T. M. and Barlow, C.** (2003). Elevated gene expression levels distinguish human from non-human primate brains. *Proc. Natl. Acad. Sci. USA* **100**, 13030-13035.
- Campos, D. B., Palin, M. F., Bordignon, V. and Murphy, B. D.** (2008). The 'beneficial' adipokines in reproduction and fertility. *Int. J. Obes.* **32**, 223-231.
- Cnattingius, S., Villamor, E., Lagerros, Y. T., Wikstrom, A. K. and Granath, F.** (2011). High birth weight and obesity—a vicious circle across generations. *Int. J. Obes.* [Epub ahead of print].
- Cochran, G. and Harpending, H. C.** (2009). *The 10,000 Year Explosion. How Civilization Accelerated Human Evolution*. New York: Basic Books.
- Cole, T. J., Bellizzi, M. C., Flegal, K. M. and Dietz, W. H.** (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* **320**, 1240-1243.
- Coupe, B., Grit, I., Darmaun, D. and Parnet, P.** (2009). The timing of "catch-up growth" affects metabolism and appetite regulation in male rats born with intrauterine growth restriction. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **297**, R813-R824.
- Danaei, G., Ding, E. L., Mozaffarian, D., Taylor, B., Rehm, J., Murray, C. J. and Ezzati, M.** (2009). The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med.* **6**, e1000058.
- Dark, J.** (2005). Annual lipid cycles in hibernators: integration of physiology and behavior. *Ann. Rev. Nutr.* **25**, 469-497.
- Diamond, J.** (1998). *Guns, Germs and Steel*. London: Vintage.
- Doak, C., Monteiro, C., Adai, L. S., Bentley, M. E. and Popkin, B. M.** (2000). Coexisting overweight and underweight within households is related to the nutrition transition. *FASEB J.* **14**, A792.
- Doak, C. M., Adair, L. S., Bentley, M., Monteiro, C. and Popkin, B. M.** (2005). The dual burden household and the nutrition transition paradox. *Int. J. Obes.* **29**, 129-136.
- Dollman, J., Norton, K. and Norton, L.** (2005). Evidence for secular trends in children's physical activity behavior. *Br. J. Sports. Med.* **39**, 892-897.
- Drazen, D. L., Demas, G. E. and Nelson, R. J.** (2001). Leptin effects on immune function and energy balance are photoperiod dependent in Siberian hamsters (*Phodopus sungorus*). *Endocrinology* **142**, 2768-2775.
- Dulloo, A. G.** (2008). Thrifty energy metabolism in catch-up growth trajectories to insulin and leptin resistance. *Best Pract. Res. Clin. Endocrinol. Metab.* **22**, 155-171.
- Dunger, D. B., Ahmed, M. L. and Ong, K. K.** (2006). Early and late weight gain and the timing of puberty. *Mol. Cell. Endocrinol.* **254-255**, 140-145.
- Elks, C. E., Loos, R. J., Sharp, S. J., Langenberg, C., Ring, S. M., Timpson, N. J., Ness, A. R., Davey Smith, G., Dunger, D. B., Wareham, N. J. et al.** (2010a). Genetic markers of adult obesity risk are associated with greater early infancy weight gain and growth. *PLoS Med.* **7**, e1000284.
- Elks, C. E., Perry, J. R., Sulem, P., Chasman, D. I., Franceschini, N., He, C., Lunetta, K. L., Visser, J. A., Byrne, E. M., Cousminer, D. L. et al.** (2010b). Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. *Nat. Genet.* **42**, 1077-1085.
- Epel, E., Lapidus, R., McEwen, B. and Brownell, K.** (2001). Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinology* **26**, 37-49.
- Fagan, B.** (1999). *Floods, Famines and Emperors*. New York: Basic Books.
- Fernandez-Real, J. M. and Ricart, W.** (2003). Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocr. Rev.* **24**, 278-301.
- Ferro-Luzi, A. and Branca, F.** (1993). Nutritional seasonality: the dimensions of the problem. In *Seasonality and Human Ecology* (ed. S. J. Ulijaszek and S. S. Strickland), pp. 149-165. Cambridge: Cambridge University Press.
- Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., Heine-Suner, D., Cigudosa, J. C., Urioste, M., Benitez, J. et al.** (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proc. Natl. Acad. Sci. USA* **102**, 10604-10609.
- Garrigan, D. and Hammer, M. F.** (2006). Reconstructing human origins in the genomic era. *Nat. Rev. Genet.* **7**, 669-680.
- Garrow, J. S. and Webster, J.** (1985). Quetelet's index (W/H²) as a measure of fatness. *Int. J. Obes.* **9**, 147-153.
- German, A. J.** (2006). The growing problem of obesity in dogs and cats. *J. Nutr.* **136**, 1940S-1946S.
- Green, R. E., Krause, J., Briggs, A. W., Maricic, T., Stenzel, U., Kircher, M., Patterson, N., Li, H., Zhai, W., Fritz, M. H. et al.** (2010). A draft sequence of the Neandertal genome. *Science* **328**, 710-722.
- Hales, C. N. and Barker, D. J.** (1992). Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* **35**, 595-601.
- Hancock, A. M., Witonsky, D. B., Gordon, A. S., Eshel, G., Pritchard, J. K., Coop, G. and Di Rienzo, A.** (2008). Adaptations to climate in candidate genes for common metabolic disorders. *PLoS Genet.* **4**, e32.
- Hankey, G. J.** (2012). Nutrition and the risk of stroke. *Lancet Neurol.* **11**, 66-81.
- Harshman, L. G. and Zera, A. J.** (2007). The cost of reproduction: the devil in the details. *Trends Ecol. Evol.* **22**, 80-86.
- Hattersley, A. T., Beards, F., Ballantyne, E., Appleton, M., Harvey, R. and Ellard, S.** (1998). Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat. Genet.* **19**, 268-270.
- Haworth, C. M., Carnell, S., Meaburn, E. L., Davis, O. S., Plomin, R. and Wardle, J.** (2008). Increasing heritability of BMI and stronger associations with the FTO gene over childhood. *Obesity* **16**, 2663-2668.
- Heid, I. M., Jackson, A. U., Randall, J. C., Winkler, T. W., Qi, L., Steinthorsdottir, V., Thorleifsson, G., Zillikens, M. C., Speliotes, E. K., Magi, R. et al.** (2010). Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat. Genet.* **42**, 949-960.
- Herculano-Houzel, S.** (2011). Scaling of brain metabolism with a fixed energy budget per neuron: implications for neuronal activity, plasticity and evolution. *PLoS ONE* **6**, e17514.
- Hill, K.** (1993). Life history theory and evolutionary anthropology. *Evol. Anthropol.* **2**, 78-89.
- Hjelmborg, J. B., Fagnani, C., Silventoinen, K., McGue, M., Korkeila, M., Christensen, K., Rissanen, A. and Kaprio, J.** (2008). Genetic influences on growth traits of BMI: a longitudinal study of adult twins. *Obesity* **16**, 847-852.
- Holliday, M. A.** (1978). Body composition and energy needs during growth. In *Human Growth, Vol 2* (ed. F. Falkner and J. M. Tanner), pp. 101-117. New York: Plenum.
- Hotamisligil, G. S.** (2006). Inflammation and metabolic disorders. *Nature* **444**, 860-867.
- Huda, M. S., Wilding, J. P. and Pinkney, J. H.** (2006). Gut peptides and the regulation of appetite. *Obes. Rev.* **7**, 163-182.
- Ibanez, L., Lopez-Bermejo, A., Diaz, M., Marcos, M. V., Casano, P. and de Zegher, F.** (2009). Abdominal fat partitioning and high-molecular-weight adiponectin in short children born small for gestational age. *J. Clin. Endocrinol. Metab.* **94**, 1049-1052.

- Ivanova, M., Ruiqing, J., Kawai, S., Matsushita, M., Ochiai, N., Maruya, E. and Saji, H. (2011). IL-6 SNP diversity among four ethnic groups as revealed by bead-based liquid array profiling. *Int. J. Immunogenet.* **38**, 17-20.
- Kagawa, Y., Yanagisawa, Y., Hasegawa, K., Suzuki, H., Yasuda, K., Kudo, H., Abe, M., Matsuda, S., Ishikawa, Y., Tsuchiya, N. et al. (2002). Single nucleotide polymorphisms of thrifty genes for energy metabolism: evolutionary origins and prospects for intervention to prevent obesity-related diseases. *Biochem. Biophys. Res. Commun.* **295**, 207-222.
- Keith, S. W., Redden, D. T., Katzmarzyk, P. T., Boggiano, M. M., Hanlon, E. C., Benca, R. M., Ruden, D., Pietrobello, A., Barger, J. L., Fontaine, K. R. et al. (2006). Putative contributors to the secular increase in obesity: exploring the roads less traveled. *Int. J. Obes.* **30**, 1585-1594.
- Kemmert, J. W. and Francken, G. A. (1986). Characteristics of spontaneous obesity in male rhesus monkeys. *Physiol. Behav.* **38**, 477-483.
- Keys, A., Brozek, J., Henschel, A., Mickelsen, O. and Taylor, H. L. (1950). *The Biology of Human Starvation*. Minneapolis: University of Minnesota Press.
- Keys, D. (1999). *Catastrophe: An Investigation into the Origins of the Modern World*. London: Century (Random House).
- Kinra, S., Andersen, E., Ben-Shlomo, Y., Bowen, L., Lyngdoh, T., Prabhakaran, D., Reddy, K. S., Ramakrishnan, L., Bharathi, A., Vaz, M. et al. (2011). Association between urban life-years and cardiometabolic risk: the Indian migration study. *Am. J. Epidemiol.* **174**, 154-164.
- Kuzawa, C. W. (1998). Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am. J. Phys. Anthropol. Suppl.* **27**, 177-209.
- Laclaustra, M., Corella, D. and Ordovas, J. M. (2007). Metabolic syndrome pathophysiology: the role of adipose tissue. *Nutr. Metab. Cardiovasc. Dis.* **17**, 125-139.
- Lango Allen, H., Estrada, K., Lettre, G., Berndt, S. I., Weedon, M. N., Rivadeneira, F., Willer, C. J., Jackson, A. U., Vedantam, S., Raychaudhuri, S. et al. (2010). Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* **467**, 832-838.
- Lassek, W. D. and Gaulin, S. J. (2006). Changes in body fat distribution in relation to parity in American women: a covert form of maternal depletion. *Am. J. Phys. Anthropol.* **131**, 295-302.
- Lassek, W. D. and Gaulin, S. J. (2007). Waist-hip ratio and cognitive ability: is gluteofemoral fat a privileged store of neurodevelopmental resources? *Evol. Hum. Behav.* **29**, 26-34.
- Lawrence, M., Coward, W. A., Lawrence, F., Cole, T. J. and Whitehead, R. G. (1987). Fat gain during pregnancy in rural African women: the effect of season and dietary status. *Am. J. Clin. Nutr.* **45**, 1442-1450.
- Lee, J., Chen, L., Snieder, H., Chen da, F., Lee, L. M., Liu, G. F., Wu, T., Tang, X., Zhan, S. Y., Cao, W. H. et al. (2010). Heritability of obesity-related phenotypes and association with adiponectin gene polymorphisms in the Chinese national twin registry. *Ann. Hum. Genet.* **74**, 146-154.
- Lisiecki, L. E. and Raymo, M. E. (2005). A plio-pleistocene stack of 57 globally distributed benthic $\delta^{18}O$ records. *Paleoceanography* **20**.
- Lustig, R. H. (2006). Childhood obesity: behavioral aberration or biochemical drive? Reinterpreting the First Law of Thermodynamics. *Nat. Clin. Pract. Endocrinol. Metab.* **2**, 447-458.
- Lustig, R. H. (2008). Which comes first? The obesity or the insulin? The behavior or the biochemistry? *J. Pediatr.* **152**, 601-602.
- Mattacks, C. A., Sadler, D. and Pond, C. M. (2004). Site-specific differences in fatty acid composition of dendritic cells and associated adipose tissue in popliteal depot, mesentery, and omentum and their modulation by chronic inflammation and dietary lipids. *Lymphat. Res. Biol.* **2**, 107-129.
- Michalakis, K. G. and Segars, J. H. (2010). The role of adiponectin in reproduction: from polycystic ovary syndrome to assisted reproduction. *Fertil. Steril.* **94**, 1949-1957.
- Misra, A. and Khurana, L. (2008). Obesity and the metabolic syndrome in developing countries. *J. Clin. Endocrinol. Metab.* **93 Suppl.** **1**, S9-S30.
- Mokyr, J. and O Grada, C. (2002). What do people die of during famines: the Great Irish Famine in comparative perspective. *Eur. Rev. Econ. Hist.* **6**, 339-363.
- Muhlhauser, B. S., Duffield, J. A., Ozanne, S. E., Pilgrim, C., Turner, N., Morrison, J. L. and McMillen, I. C. (2009). The transition from fetal growth restriction to accelerated postnatal growth: a potential role for insulin signaling in skeletal muscle. *J. Physiol.* **587**, 4199-4211.
- Navarrete, A., van Schaik, C. P. and Isler, K. (2011). Energetics and the evolution of human brain size. *Nature* **480**, 91-93.
- Neel, V. (1962). Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am. J. Hum. Genet.* **14**, 353-362.
- Nestle, M. (2007). *Food Politics: How the Food Industry Influences Nutrition and Health*. Berkeley: University of California Press.
- Nettle, D., Coall, D. A. and Dickins, T. E. (2010). Birthweight and paternal involvement predict early reproduction in British women: evidence from the National Child Development Study. *Am. J. Hum. Biol.* **22**, 172-179.
- Norgan, N. G. (1997). The beneficial effects of body fat and adipose tissue in humans. *Int. J. Obes. Relat. Metab. Disord.* **21**, 738-746.
- O'Rahilly, S., Farooqi, I. S., Yeo, G. S. and Challis, B. G. (2003). Minireview: human obesity-lessons from monogenic disorders. *Endocrinology* **144**, 3757-3764.
- Oftedal, O. T. (2000). Use of maternal reserves as a lactation strategy in large mammals. *Proc. Nutr. Soc.* **59**, 99-106.
- Ong, K. K., Ahmed, M. L., Emmett, P. M., Preece, M. A. and Dunger, D. B. (2000). Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. *BMJ* **320**, 967-971.
- Ong, K. K., Northstone, K., Wells, J. C., Rubin, C., Ness, A. R., Golding, J. and Dunger, D. B. (2007). Earlier mother's age at menarche predicts rapid infancy growth and childhood obesity. *PLoS Med.* **4**, e132.
- Ong, K. K., Emmett, P., Northstone, K., Golding, J., Rogers, I., Ness, A. R., Wells, J. C. and Dunger, D. B. (2009). Infancy weight gain predicts childhood body fat and age at menarche in girls. *J. Clin. Endocrinol. Metab.* **94**, 1527-1532.
- Paalani, M., Lee, J. W., Haddad, E. and Tonstad, S. (2011). Determinants of inflammatory markers in a bi-ethnic population. *Ethn. Dis.* **21**, 142-149.
- Pandey, R. M., Gupta, R., Misra, A., Misra, P., Singh, V., Agrawal, A., Dey, S., Rao, S., Menon, V. U., Kamalamma, N. et al. (2011). Determinants of urban-rural differences in cardiovascular risk factors in middle-aged women in India: A cross-sectional study. *Int. J. Cardiol.* [Epub ahead of print].
- Pasquet, P., Brigant, L., Froment, A., Koppert, G. A., Bard, D., de Garine, I. and Apfelbaum, M. (1992). Massive overfeeding and energy balance in men: the Guru Walla model. *Am. J. Clin. Nutr.* **56**, 483-490.
- Permana, P. A. and Reardon, C. L. (2007). What are subcutaneous adipocytes really good for? Viewpoint 2. *Exp. Dermatol.* **16**, 53-55.
- Pickrell, J. K., Coop, G., Novembre, J., Kudaravalli, S., Li, J. Z., Absher, D., Srinivasan, B. S., Barsh, G. S., Myers, R. M., Feldman, M. W. et al. (2009). Signals of recent positive selection in a worldwide sample of human populations. *Genome Res.* **19**, 826-837.
- Pierce, M. B. and Leon, D. A. (2005). Age at menarche and adult BMI in the Aberdeen children of the 1950s cohort study. *Am. J. Clin. Nutr.* **82**, 733-739.
- Pond, C. M. (1984). Physiological and ecological importance of energy storage in the evolution of lactation: evidence for a common pattern of anatomical organisation of adipose tissue in mammals. *Symp. Zool. Soc. Lond.* **51**, 1-32.
- Pond, C. M. (1998). *The Fats of Life*. Cambridge: Cambridge University Press.
- Pond, C. M. (2003). Paracrine interactions of mammalian adipose tissue. *J. Exp. Zool.* **295A**, 99-110.
- Popkin, B. M. (2007). The world is fat. *Sci. Am.* **297**, 88-95.
- Poppitt, S. D., Prentice, A. M., Goldberg, G. R. and Whitehead, R. G. (1994). Energy-sparing strategies to protect human fetal growth. *Am. J. Obstet. Gynecol.* **171**, 118-125.
- Poston, W. S. and Foreyt, J. P. (1999). Obesity is an environmental issue. *Atherosclerosis* **146**, 201-209.
- Potts, R. (1996). *Humanity's Descent: The Consequences of Ecological Instability*. New York, William Morrow & Co.
- Potts, R. (2011). An African environmental framework for investigating the evolution of early Homo. *Curr. Anthropol.* in press.
- Prasad, S., Sung, B. and Aggarwal, B. B. (2011). Age-associated chronic diseases require age-old medicine: Role of chronic inflammation. *Prev. Med.* **54**, S29-S37.
- Prentice, A. M. and Jebb, S. A. (1995). Obesity in Britain: gluttony or sloth? *BMJ* **311**, 437-439.
- Prentice, A. M., Moore, S. E., Collinson, A. C. and O'Connell, M. A. (2002). Leptin and undernutrition. *Nutr. Rev.* **60**, S56-S67.
- Randhawa, R. and Cohen, P. (2005). The role of the insulin-like growth factor system in prenatal growth. *Mol. Genet. Metab.* **86**, 84-90.
- Rebuffe-Scrive, M., Enk, L., Crona, N., Lonnroth, P., Abrahamsson, L., Smith, U. and Bjorntorp, P. (1985). Fat cell metabolism in different regions in women. Effect of menstrual cycle, pregnancy, and lactation. *J. Clin. Invest.* **75**, 1973-1976.
- Richerson, P. J., Boyd, R. and Bettinger, R. L. (2001). Was agriculture impossible during the pleistocene but mandatory during the holocene? *Am. Anthropol.* **66**, 387-411.
- Rivers, J. P. (1988). The nutritional biology of famine. In *Famine* (ed. G. A. Harrison), pp. 57-106. Oxford: Oxford University Press.
- Rodgers, R. J., Tschöp, M. H. and Wilding, J. P. H. (2012). Anti-obesity drugs: past, present and future. *Dis. Model. Mech.* **5**, 621-626.
- Romanyukha, A. A., Rudnev, S. G. and Sidorov, I. A. (2006). Energy cost of infection burden: an approach to understanding the dynamics of host-pathogen interactions. *J. Theor. Biol.* **241**, 1-13.
- Roth, J., Szulc, A. L. and Danoff, A. (2011). Energy, evolution, and human diseases: an overview. *Am. J. Clin. Nutr.* **93**, 875S-883S.
- Schneider, J. E. (2004). Energy balance and reproduction. *Physiol. Behav.* **81**, 289-317.
- Schwartz, M. W. and Morton, G. J. (2002). Obesity: keeping hunger at bay. *Nature* **418**, 595-597.

- Shell, E. R.** (2002). *The Hungry Gene: The Inside Story of the Obesity Industry*. New York: Grove Press.
- Siervo, M., Wells, J. C. and Cizza, G.** (2009). The contribution of psychosocial stress to the obesity epidemic: an evolutionary approach. *Horm. Metab. Res.* **41**, 261-270.
- Singh, J., Prentice, A. M., Diaz, E., Coward, W. A., Ashford, J., Sawyer, M. and Whitehead, R. G.** (1989). Energy expenditure of Gambian women during peak agricultural activity measured by the doubly-labelled water method. *Br. J. Nutr.* **62**, 315-329.
- Snijder, M. B., Dekker, J. M., Visser, M., Bouter, L. M., Stehouwer, C. D., Yudkin, J. S., Heine, R. J., Nijpels, G. and Seidell, J. C.** (2004a). Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care* **27**, 372-377.
- Snijder, M. B., Zimmet, P. Z., Visser, M., Dekker, J. M., Seidell, J. C. and Shaw, J. E.** (2004b). Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the Aus. Diab Study. *Int. J. Obes. Relat. Metab. Disord.* **28**, 402-409.
- Snodgrass, J. J., Sorensen, M. V., Tarskaia, L. A. and Leonard, W. R.** (2007). Adaptive dimensions of health research among indigenous Siberians. *Am. J. Hum. Biol.* **19**, 165-180.
- Sorensen, T. I., Price, R. A., Stunkard, A. J. and Schulsinger, F.** (1989). Genetics of obesity in adult adoptees and their biological siblings. *BMJ* **298**, 87-90.
- Speakman, J. R.** (2006). Thrifty genes for obesity and the metabolic syndrome-time to call off the search? *Diab. Vasc. Dis. Res.* **3**, 7-11.
- Speakman, J. R.** (2008). Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. *Int. J. Obes.* **32**, 1611-1617.
- Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., Allen, H. L., Lindgren, C. M., Luan, J., Magi, R. et al.** (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat. Genet.* **42**, 937-948.
- Stearns, S. C.** (1992). *The Evolution of Life Histories*. Oxford: Oxford University Press.
- Stuckler, D., McKee, M., Ebrahim, S. and Basu, S.** (2012). Manufacturing epidemics: the role of global producers in increased consumption of unhealthy commodities including processed foods, alcohol, and tobacco. *PLoS Med.* **9**, e1001235.
- Stunkard, A. J., Foch, T. T. and Hrubec, Z.** (1986a). A twin study of human obesity. *JAMA* **256**, 51-54.
- Stunkard, A. J., Sorensen, T. I., Hanis, C., Teasdale, T. W., Chakraborty, R., Schull, W. J. and Schulsinger, F.** (1986b). An adoption study of human obesity. *N. Engl. J. Med.* **314**, 193-198.
- Tatar, M., Bartke, A. and Antebi, A.** (2003). The endocrine regulation of aging by insulin-like signals. *Science* **299**, 1346-1351.
- Taubes, G.** (2008). *The Diet Delusion*. London: Vermillion.
- Tilg, H. and Moschen, A. R.** (2006). Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat. Rev. Immunol.* **6**, 772-783.
- Tovee, M. J., Swami, V., Furnham, A. and Mangalparsad, R.** (2006). Changing perceptions of attractiveness as observers are exposed to a different culture. *Evol. Hum. Behav.* **27**, 443-456.
- Voight, B. F., Kudaravalli, S., Wen, X. and Pritchard, J. K.** (2006). A map of recent positive selection in the human genome. *PLoS Biol.* **4**, e72.
- Wade, G. N., Schneider, J. E. and Li, H. Y.** (1996). Control of fertility by metabolic cues. *Am. J. Physiol.* **270**, E1-E19.
- Wagner, A.** (2005). *Robustness and Evolvability in Living Systems*. Princeton: Princeton University Press.
- Watson, N. F., Buchwald, D., Vitiello, M. V., Noonan, C. and Goldberg, J.** (2010). A twin study of sleep duration and body mass index. *J. Clin. Sleep Med.* **6**, 11-17.
- Wells, J. C.** (2006). The evolution of human fatness and susceptibility to obesity: an ethological approach. *Biol. Rev.* **81**, 183-205.
- Wells, J. C.** (2009a). Ethnic variability in adiposity and cardiovascular risk: the variable disease selection hypothesis. *Int. J. Epidemiol.* **38**, 63-71.
- Wells, J. C.** (2009b). Thrift: a guide to thrifty genes, thrifty phenotypes and thrifty norms. *Int. J. Obes.* **33**, 1331-1338.
- Wells, J. C.** (2009c). *The Evolutionary Biology of Human Body Fatness: Thrift and Control*. Cambridge: Cambridge University Press.
- Wells, J. C.** (2010). Maternal capital and the metabolic ghetto: An evolutionary perspective on the transgenerational basis of health inequalities. *Am. J. Hum. Biol.* **22**, 1-17.
- Wells, J. C.** (2011). An evolutionary perspective on the trans-generational basis of obesity. *Ann. Hum. Biol.* **38**, 400-409.
- Wells, J. C.** (2012a). Obesity as malnutrition: the role of capitalism in the obesity epidemic. *Am. J. Hum. Biol.* **24**, 261-276.
- Wells, J. C.** (2012b). Sexual dimorphism in body composition across human populations: associations with climate and proxies for short- and long-term energy supply. *Am. J. Hum. Biol.* **2**, 411-419.
- Wells, J. C.** (2012c). Ecogeographical associations between climate and human body composition: analyses based on anthropometry and skinfolds. *Am. J. Phys. Anthropol.* **147**, 169-186.
- Wells, J. C. and Stock, J. T.** (2007). The biology of the colonizing ape. *Am. J. Phys. Anthropol. Suppl.* **45**, 191-222.
- Wells, J. C. and Siervo, M.** (2011). Obesity and energy balance: is the tail wagging the dog? *Eur. J. Clin. Nutr.* **65**, 1173-1189.
- Wilding, J.** (2004). Clinical evaluation of anti-obesity drugs. *Curr. Drug Targets* **5**, 325-332.
- Willer, C. J., Speliotes, E. K., Loos, R. J., Li, S., Lindgren, C. M., Heid, I. M., Berndt, S. I., Elliott, A. L., Jackson, A. U., Lamina, C. et al.** (2009). Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat. Genet.* **41**, 25-34.
- Yajnik, C. S.** (2004). Obesity epidemic in India: intrauterine origins? *Proc. Nutr. Soc.* **63**, 387-396.
- Yajnik, C. S., Janipalli, C. S., Bhaskar, S., Kulkarni, S. R., Freathy, R. M., Prakash, S., Mani, K. R., Weedon, M. N., Kale, S. D., Deshpande, J. et al.** (2009). FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia* **52**, 247-252.
- Yu, Z. B., Han, S. P., Zhu, G. Z., Zhu, C., Wang, X. J., Cao, X. G. and Guo, X. R.** (2011). Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes. Rev.* **12**, 525-542.