On the Evolutionary Origins of Obesity: A New Hypothesis

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Obesity is an escalating threat of pandemic proportions, currently affecting billions of people worldwide and exerting a devastating socioeconomic influence in industrialized countries. Despite intensive efforts to curtail obesity, results have proved disappointing. Although it is well recognized that obesity is a result of gene-environment interactions and that predisposition to obesity lies predominantly in our evolutionary past, there is much debate as to the precise nature of how our evolutionary past contributed to obesity. The "thrifty genotype" hypothesis suggests that obesity in industrialized countries is a throwback to our ancestors having undergone positive selection for genes that favored energy storage as a consequence of the cyclical episodes of famine and surplus after the advent of farming 10 000 years ago. Conversely, the "drifty genotype" hypothesis contends that the prevalence of thrifty genes is not a result of positive selection for energy-storage genes but attributable to genetic drift resulting from the removal of predative selection pressures. Both theories, however, assume that selection pressures the ancestors of modern humans living in western societies faced were the same. Moreover, neither theory adequately explains the impact of globalization and changing population demographics on the genetic basis for obesity in developed countries, despite clear evidence for ethnic variation in obesity susceptibility and related metabolic disorders. In this article, we propose that the modern obesity pandemic in industrialized countries is a result of the differential exposure of the ancestors of modern humans to environmental factors that began when modern humans left Africa around 70 000 years ago and migrated through the globe, reaching the Americas around 20 000 years ago. This article serves to elucidate how an understanding of ethnic differences in genetic susceptibility to obesity and the metabolic syndrome, in the context of historic human population redistribution, could be used in the treatment of obesity in industrialized countries. **(*Endocrinology* 155: 1573–1588, 2014)**

Obesity is now a pandemic and is particularly problematic in industrialized countries (1). In the United States and Britain, obesity is rising at a devastatingly rapid rate, and more than half of the population in these countries is now overweight (2, 3). Obesity is a causal factor in numerous metabolic and endocrine disorders including heart disease, diabetes, bone and joint disorders. and some forms of cancer (4–7). Although the social impact and emotional distress obesity can exert are severe, its burden on the economy is crippling. Recent estimates suggest a direct cost in excess of $100 billion per year attributable to the loss of productivity and health care expenditures incurred owing to obesity in the United States (8, 9). It is becoming increasingly clear that whereas detrimental lifestyle changes in recent decades in western societies, particularly of a dietary nature, have contributed to the obesity pandemic, the majority (60%–70%) of individual susceptibility to obesity can be accounted for by genetics (9). The most convincing arguments for this are found twin studies wherein environmental manipulations have

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Abbreviations: BAT, brown adipose tissue; FFA, free fatty acid; GWAS, genome-wide association study; UCP1, uncoupling protein 1.

been shown to be less important than heritable factors in dictating the degree of weight gain or weight loss (10, 11).

The explanation for the genetic basis of the current obesity pandemic in industrialized countries is somewhat circumspect, and various theories that attempt to shed light on our understanding of it abound. These theories attempt to reconcile gene-environment interactions with an understanding of human evolution. Two such theories in particular have gained widespread credibility among geneticists and evolutionary biologists, namely the "thrifty genotype" hypothesis and the "drifty genotype" hypothesis. The thrifty genotype hypothesis argues that the ancestors of present day humans in countries plagued by obesity underwent positive selection for genes that favored "thrift" or energy storage (12). These so-called "thrifty genes" are defined as those that bestow superior energy efficiency such that the energy balance equation is shifted heavily toward energy intake as opposed to energy expenditure (13). The rationale behind this apparent demand for thrifty genes during human evolutionary history is that since the advent of agriculture around 10 000 years ago (13), humanity has been affected by numerous cyclical episodes of "famine" and "feast" whereby periods of food abundance were punctuated by periods of drought. As a result, it is postulated that survival of a population necessitated the selection for thrifty genes that enabled extra fat reserves to be laid down during times of energy surplus to be utilized during harder times. In addition to promoting survival, it is argued that thrifty genes also maintained fertility during periods of famine, a claim that is plausible in light of what is known about the effects of food shortages on reproductive capability (14). The thrifty genotype hypothesis asserts that obesity in industrialized countries is the result of thrifty genes passed down from these ancestors of present day humans who were subject to strong selection pressures that enriched the population with genes that promoted energy storage. Proponents of the theory document various historical famines that occurred on large and devastatingly influential scales in support of it (15).

The "drifty phenotype" hypothesis contends that, contrary to being selected for, obesogenic energy-efficient genes favoring fat storage are present in western populations (and all populations worldwide) because early homonids removed the selection pressure that was previously exerted on them by predation (16, 17). The theory, also referred to as the "predation release" theory was put forward by John Speakman to counter the long-held acceptance of the thrifty genotype hypothesis as the most reliable and plausible model for the genetic basis of obesity. Speakman argued that around 2 million years ago at the dawn of humanity, when the ancient ancestors of modern humans, *Homo habilis* and *Homo erectus*, acquired the capability to use fire and stone tools, manufacture weapons, and band together in organized social structures, for the first time in evolutionary history an animal that was not the top predator in its ecosystem was able to remove the threat of predatory danger (16, 17). Thus, as a result, genes imperative for the evasion of predators, such as those that conferred speed, agility, stamina, athletic ability, and leanness (which ensured "survival of the fittest"), were no longer applicable to humans as it was and continues to be for all other animals (18–20). Therefore, the theory suggests that, in the absence of predation selection pressure, genes that promote energy storage and obesity were not removed by natural selection and simply were allowed to drift in the genetic journey of human evolution, such that they explain the obesity pandemic in modern western societies. Although both the thrifty and drifty genotype hypotheses have considerable merit and may be responsible for the genetic susceptibility to obesity, in a portion of individuals, we believe that neither theory can decisively account for the contemporary obesity pandemic in industrialized countries.

Advocates of the thrifty hypothesis make the argument that in the postagricultural era (since 10 000 years ago), when humans relinquished their hunter-gatherer lifestyle and put their ability to feed at the mercy of climatic and seasonal events, natural selection enriched the population with thrifty genes that enabled survival during famine (15). However, by 10 000 years ago, modern humans were spread over many areas of the globe, populating Asia, Australasia, Europe, and the Americas and inhabiting a wide range of environments (21–23). Did each of these populations experience the same famine events and agricultural strife? In our view, this is unlikely given that famine with drought, the selection pressure that supposedly drove the evolution of people with thrifty genes, is commonly the result of climate, weather, and disease patterns that are largely governed by local geographical phenomena (24–27). In fact, there is very little evidence of any feast or famine events that would have been sufficiently consequential to exert their influence over selection for thrifty genes (28, 29). An alternative view of the thrifty gene hypothesis is that positive selection pressure for thrifty genes has been occurring since the evolution of early humans 2 million years ago, preceding the advent of agriculture and before the geographical redistribution and population of modern humans around the globe (15). However, this concept disregards any selection events that might have occurred after modern humans left Africa and populated a diverse range of climates and habitats. The authors of this notion that thrifty genes have been selected for, for longer than the original thrifty hypothesis claimed,

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state that very few genetic changes have occurred in humans in the last 10 000 years (15). This claim is not, however, borne out by recent evidence. On the contrary, sophisticated and detailed genetic analysis has revealed that a plethora of genetic changes as a result of natural selection in various contemporary human populations have occurred in the last 10 000 to 15 000 years and that these genetic alterations are highly consequential to health and disease in modern times (30). For instance, clear modern selection events in specific geographical populations have greatly enriched genes that confer resistance to malaria (31), enable the ability to digest lactose (32), and protect against kuru (33) and HIV infection (34, 35). Given that immune and digestive functions are intricately linked to metabolism and adiposity (36–39), one cannot dismiss recent selection pressures as being inconsequential to metabolism and the obesity pandemic. Moreover, the global distribution of a large amount of single nucleotide polymorphisms in contemporary human populations has been shown to have a strong latitudinal basis, suggesting a clear climatic and geographical selection influence (40). These observations underscore not only that recent selection events have shaped the genetics of present day humans but also that genetic influences on health and disease, including obesity, must factor in ethnic and geographical considerations. Thus, in our view, the thrifty hypothesis is not an accurate reflection of historical positive selection events. In a similar fashion, the drifty genotype hypothesis assumes that since 2 million years ago the ancestors of modern humans have been subject to the same evolutionary events (ie, release from predation) that have subsequently endowed present day humans in industrialized countries with thrifty genes due to genetic drift. However, this theory makes no attempt to consider the impact on obesity of distinct selection events, specific to geographical influences that may have shaped human evolution since modern humans left Africa 60 000 years ago.

It is becoming increasingly clear that genetic susceptibility to obesity is not equal across the various ethnic groups whose ancestors experienced vastly different geographical and environmental selection pressures (41–44). We believe that to understand the modern obesity phenomenon in industrialized countries, changing population demographics with regard to ethnic variation must be taken into account. Although the ethnic variation in obesity susceptibility has been reviewed extensively and accurately in recent years (45–51), none of this research has served to understand the cause of the variability in obesity susceptibility between ethnicities or how evolutionary forces relating to climate may have shaped the current obesity pandemic. We believe that by understanding the ethnic basis for obesity susceptibility in the light of evolutionary events, western societies will be a step closer to deciphering the mysteries surrounding the genetic predisposition or resistance to obesity.

Although it is our belief that genetic influences are predominantly responsible for explaining the ethnic variation in obesity, it is nonetheless important to recognize that obesity is a complex, multifactorial problem, and therefore other nongenetic factors almost certainly play a role in its pathogenesis. To this end, socioeconomic factors, including education, income, and health care, which have been shown to be ethnically biased, are strongly correlated with obesity trends. Therefore, although the focus of the present article is entirely on the genetic basis for the ethnic variation in obesity, we stress that it does not make an exclusive claim on the origins of obesity.

The Changing Face of the West

The thrifty and drifty genotype hypotheses explain that the genetic susceptibility to obesity is due to heritable factors that are the result of positive selection pressure or an absence of positive selection pressure, respectively, in the course of human evolution. However, because obesity had its origins in industrialized countries and this occurred in the blink of an eye (50–75 years) in geological terms (52, 53), it is clear that the western lifestyle, particularly a greater reliance on fast food and excess calories combined with a lack of physical activity, was a catalyst for obesity to manifest (54, 55). In our view, both the thrifty and drifty gene hypotheses wrongly make the assumption that obesity in the west is due to common evolutionary events that affected all ancestors of present day humans, irrespective of ethnicity and geographical distribution. This simply cannot be true in light of clear evidence for ethnic and racial variations in susceptibility to obesity (45). Interestingly, the last 50 to 75 years coincided with an era of mass emigration and globalization on a scale unparalleled in the history of humanity, although this occurrence receives very little attention in the context of obesity (56–59). The 20th and 21st centuries have seen a large net increase of ethnic minorities (mainly Africans, Indians, Pakistanis, Bangladeshis, and Chinese) in industrialized countries such as Britain, France, Germany, Canada, and the United States (60–65). A report from the US Congressional Research Service articulated the fast changing demographics in this country: "The U.S. population— currently estimated at 308.7 million persons— has more than doubled in size since its 1950 level of 152.3 million" (66). More than just being double in size, the United States has become qualitatively different from what it was in the 1950s. The report goes onto state that within the period since 1950 the

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United States has become more racially and ethnically diverse with large populations of Hispanics, blacks, and Asians (66). Studies assessing the ethnic and racial susceptibility to metabolic dysfunction and obesity in the United States, have identified that blacks, Hispanics, and people of Native American ancestry are more prone to obesity, cardiovascular disease, and diabetes than whites of European ancestry and people of east Asian ancestry such as Chinese, Japanese, and Koreans (44, 48, 67, 68). Similarly in Britain, whose population is equally ethnically and racially diverse, there is a significant ethnic bias in susceptibility to obesity with Caucasians and individuals of Chinese origin being less vulnerable to obesity and cardiovascular disease than those of African, Indian, Pakistani, and Bangladeshi origins (69).

One of the strongest arguments against the thrifty genotype hypothesis and in favor of the drifty hypothesis was conceived by John Speakman (16), who asserted that if positive selection for thrifty genes has been acting for 2 million years as proposed by Chakravarthy and Booth (15), then, assuming a survival advantage (k, coefficient of selection) of 0.001, 100% of the population in the United States should be obese. However, as Speakman countered, obesity affects only 30% of the current US population. Alternatively, as argued by Speakman, if famine has been selecting for thrifty genes only in the postagricultural era (in the last 10 000 years), as proposed by Prentice et al (13), then 100% of the US population should be lean. This argument prompted a reevaluation of the thrifty hypothesis by Prentice et al (70), who have since acknowledged that survival advantages were less important than fertility advantages in promoting the spread of thrifty genes. Thus, this recent revision of the thrifty hypothesis reasons that thrifty genes may not have been necessary for survival but did confer reproductive advantages. Speakman's (16, 17) view is that, when our ancestors became highly organized and sophisticated hunters, they removed predation pressure from the equation and were thus no longer subject to selection for the upper limit or "intervention point" of body weight status. Therefore, according to Speakman, genes that promoted adiposity and increased body weight were not removed by natural selection as they were when predation was a severe threat to survival. In our opinion, the problem with Speakman's "all or nothing" argument that either 100% or 0% of the US population should be obese is that it again assumes that the whole population is genetically similar and that the ancestors of the present day US population were all subject to the same selective pressures. However, we assert that, if predation release 2 million years ago was responsible for the high prevalence of thrifty genes today, then each ethnic group should have the same genetic susceptibility to obesity and contribute equally to the pandemic, but, as we have countered, this is not the case. The highest rates of obesity in the United States are among those of Pacific Island origins at a staggering 43% to 45% (71, 72). Next come Native Americans (mainly due to excessive obesity in Pima Indians) at 39% to 41% (71), closely followed by black Americans at 38% to 40% (71, 72). Obesity rates are also relatively high in Hispanics, at between 31% and 34%. The lowest rates of obesity in the United States are found in Caucasians and East Asians, at 26% and 11%, respectively (71–73). If we assume that being overweight is indicative of obesity propensity, some astounding statistics come to light. Whereas only 30% to 45% and 62% to 67% of US East Asians and Caucasians, respectively, are overweight, a staggering 80% to 85% of Pima Indians, 75% to 80% of black Americans, and 75% to 78% of Hispanics are overweight (71, 72, 74, 75). Neither the drifty hypothesis nor the thrifty hypothesis adequately accounts for such differences in obesity between ethnicities. Given this discrepancy in genetic susceptibility to obesity, it seems counterproductive to look at populations in industrialized countries as a single genetic entity governed by a common set of evolutionary events that played out in the ancient and recent history of mankind.

If neither genetic drift nor selection for thrifty genes can adequately explain the rates and demographics of obesity in industrialized countries, what is the alternative? As we have stated, with regard to selection events, taking a "one size fits all" approach is not an appropriate way to explain the genetic origins of obesity. Certain ethnic groups have a much higher prevalence of obesity than others. Therefore, one single evolutionary principle (genetic drift or selection for thrifty genes) cannot account for the genetic predisposition to obesity, simply because the evolutionary selection events faced by the ancestors of each ethnic group were hugely diverse. We postulate that, selection factors relevant to climate have inadvertently shaped the obesity pandemic in industrialized countries today. We propose here that the ability to thermoregulate in extreme heat or cold afforded powerful survival advantages and therefore commanded much higher selection coefficients (k) than those for thrifty genes, which purportedly provided merely a slight fecundity advantage. Moreover, to reproduce you must survive. Survival advantages must therefore supersede fertility advantages. Genes that were essential to survival, particularly in newborn or young children, such as those that control thermoregulation would be of greater importance than thrifty genes because they would allow an individual to survive to reach reproductive age. One such gene that is essential for body temperature maintenance in cold climates is *uncoupling protein 1* (*UCP1*), which is highly expressed in brown adipose tissue (BAT)

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(76). In response to cold, BAT breaks down stored triglycerides into their constituents, glycerol and free fatty acids (FFAs). FFAs enter BAT mitochondria where they activate UCP1 which, by uncoupling ATP synthesis from oxidative phosphorylation, produces heat via an energy wastage mechanism (76–79). Human infants and young children are born with considerable amounts of BAT, which grows in size and mass up until adolescence, after which it gradually recedes over time until old age (80–82). Given that even a mild reduction in ambient temperature (<19°C) is enough to trigger robust BAT thermogenic activation in healthy adults (83), its heat-generating ability was likely to have been vital for allowing humans to populate the colder regions of the world such as Siberia, Northeast Asia, and Europe. Because effective BAT thermogenic function relies on liberated FFAs and consequent energy-wasting mitochondrial uncoupling, BAT has a secondary fat- and calorie-burning capacity. This meant that, in our view, although the ancestors of modern humans living in colder regions of the world evolved superior BAT thermogenic function, this came with equally efficient fat-burning and energy wastage capability, a useful advantage in the current high-calorie nutritional environment in industrialized countries today. We believe that this explains why Caucasians of European ancestry and East Asians have the lowest rates of obesity in industrialized countries. Whereas Prentice et al state that thrifty genes would have provided a reproductive advantage to modern humans, we argue that genes that promote efficient BAT would have been selected for ahead of genes for effective reproductive health, simply because the lack of BAT would lead to exceedingly high mortality rates in human infants and children born in colder climates, as would have been the case for the present day ancestors of Europeans and east Asians who flourished in ice age Europe and Siberia. Human infants possess abundant amounts of BAT at the time of birth, which accounts for 1.4% of total body weight (84). BAT plays a critical role in thermoregulation in infants and young children (85, 86). Impaired BAT development in the human infant has been implicated in the high mortality rates of preterm infants (87, 88). Thus, genes that augment BAT function would be highly advantageous in cold climates, and we believe that selection for such genes could explain why most east Asians and a large number of Caucasians are resistant to obesity and are not even overweight. Conversely, genes that prevented overheating, heat stroke, and dehydration would have endowed the ancestors of those in tropical and subtropical regions such as Africa, India, Southeast Asia, and much of the Central America with survival advantages. We therefore assert that powerful climatic selection pressures in evolutionary history exerted a strong influence on genes (survival advantage closer to $k = 0.1$ than $k = 0.001$) for efficient thermoregulation that consequently enabled survival. We believe that the differential susceptibility to obesity between ethnicities can be traced to differential exposures of the ancestors of these various populations to climatic selection events that began when modern humans migrated out of Africa around 70 000 years ago. The migration to northern latitudes would have necessitated the selection of genes for cold adaptation, such as those that enhanced thermogenesis. We reason that these genes, due to their secondary effects on metabolism, adiposity, and energy expenditure, became key players in the genetic predisposition to obesity in today's sedentary and overfed western population and explain why the obesity burden is not equally shared across the various ethnicities. The high incidence of overweight and obesity in certain ethnicities, such as Native Americans, black Americans, and Hispanics, in our opinion, reflects a prevalence for genes for heat adaptation, which would greatly have improved survival chances in the hot and arid climate to which the ancestors of these ethnic groups were exposed (89). Conversely, the selection for genes for cold adaptation in Europeans and East Asians may explain the relative resistance to obesity in these populations, because the ability to keep warm in such cold environments would have determined survival rates in ice age Europe and Siberia. Thus, a powerful selection advantage of genes for cold adaptation, in our opinion, would greatly increase the coefficient of selection. As Haldane stated (90), $k = 0.1$ would reflect an appropriate survival advantage/coefficient of selection, if the gene in question was highly consequential to survival. We believe that there would have been no selection advantage for genes for cold adaptation in Africa where modern humans were highly populated in and around Ethiopia. However, as modern humans left Africa 70 000 years ago and reached northerly latitudes by about 40 000 years ago in Siberia and Europe, the survival advantage (k) for genes for cold adaptation would rise, reaching a peak by the time of the first human settlements in Beringa and Alaska. A selection advantage of $k = 0.1$, acting since modern humans left Africa 70 000 years ago, explains why <26% of US Caucasians and East Asians are obese compared with >38% of US blacks, Hispanics, and Pima Indians. To attain a greater understanding of how ethnic and racial differences in today's developed countries such as the United States and Britain might influence genetic susceptibility to obesity, one must go back 70 000 years ago to about the time that a group of modern humans (and the ancestors of all people of non-African ancestry, worldwide) left Africa and went on to populate the world.

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Out of Africa

Accumulating evidence increasingly points to a single migration of a group of modern humans out of Africa 70 000 years ago and the theory that all non-Africans are descended from this small group of pioneers (91, 92). Whereas mammals probably evolved around 200 million years ago in Asia (93–95), the ancient ancestors of early humans, the first primates, evolved in Northern Africa around 65 million years ago (96). By the time early primates had evolved into the first hominid to walk upright, *Australopithecus afarensis*, they were well adapted to the unforgiving heat of the African savannah (96). Present day Africans appear to retain this adaptation to the African climate. Heat exhaustion and heat stroke are associated with elevated mortality in humans (97). As a result, people of African origins exhibit a larger surface area to body mass ratio, longer limbs, more skin pigmentation, reduced body hair, more abundant sweat glands, lower body temperature, and reduced metabolic rates, all of which combine to protect from potential UV damage from solar radiation and maximize heat loss to prevent overheating (98–100). In fact, these adaptations to heat combined with bipedalism are believed to have been the driving force behind the evolution of the first humans, *Homo erectus* (101). Although BAT thermogenic function would have been vital for thermoregulation in cold climates, it would have been detrimental in the African Savannah (102). Thus, BAT and UCP1 function would not have been selected for in these populations. As a result, it is likely that most people of African heritage today have reduced BAT thermogenic/lipolytic capability, which possibly explains the lower metabolic rates in those of African ancestry (103–106). Reduced metabolic rates among Africans have been linked to lower expression of uncoupling proteins and reduced thermogenic function (107).

As modern humans traveled north to colder climates such as Europe and Northeast Asia, selection pressures favored genes for cold rather than heat adaptation. The fairer skin tone in people of Chinese and European ancestry reflects depigmentation in the skin as a direct result of the need for vitamin D absorption and folate production, both of which are dependent on sufficient exposure to solar radiation, which would be lower further away from the equator (108). The unique shape of the skull, particularly the angle of the cheekbones of East Asians (whose ancestors evolved in Northeast Asia), is believed to be an adaptation to cold (109, 110). Today, the successful settlement of the arctic and subarctic regions of indigenous peoples, who share the same ancestry with Chinese and Japanese people, reflects the evolutionary adaption of modern humans to such environments (111). Research in indigenous Siberians (whose ancestors were most closely related to the first humans to populate higher latitudes) revealed a consistently elevated basal energy expenditure compared with that of nonindigenous Siberians (112, 113). This pattern of higher metabolic rates in indigenous peoples living in cold climates has been observed in many populations close to the poles and has a large genetic component (114–116). For example, the Inuit peoples of the Canadian Arctic also have greatly elevated metabolic rates and are thus protected from obesity even with today's western lifestyle influence (117). Similar climatic-driven increases in metabolic rates, can be observed in nonindigenous populations. Such observations suggest that genetic factors relevant to ancestral environmental exposures affect energy expenditure even in peoples from nonhomogeneous populations, indicating a powerful selection advantage of cold-adapted genes. Basal metabolic rates are highest in arctic people (114), intermediate in white Europeans (104), and lowest in African Americans (118). Interestingly, if we further analyze obesity rates in white Europeans, there is a great disparity among this group according to geographical location. Scandinavian countries, whose population's ancestry reflects hundreds of generations of genetic adaptation to extreme cold, have much lower rates of obesity than the rest of Europe, despite having similar lifestyles and caloric intake (119, 120).

Native Americans and East Asians, who share a common evolutionary anthropological classification, "Mongoloid," were also highly cold-adapted (121, 122). A recent study suggests that Native Americans have a significant amount of ancient European genes, potentially due to mating between ancient western Europeans and Siberians (123). Thus, given the climate of Europe and Northeast Asia 20 000 to 40 000 years ago, it is clear that before entering the Americas, the ancestors of Native Americans had genes for cold adaptation. Despite the genetic similarities between East Asians, indigenous Siberians, and Native Americans, the former 2 have higher metabolic rates and are relatively resistant to obesity, whereas the opposite is true for certain Native American groups (124). In fact, the Pima Indians, indigenous peoples of the United States and Mexico, have some of the highest rates of obesity, diabetes, and cardiovascular disease (125). Because of the pronounced genetic basis for obesity in this indigenous group, the Pima Indians were often presented as personifications of the thrifty genotype hypothesis (126). In our view, however, evolutionary forces of a climatic nature, rather than nutritional nature, in the ancestors of Pima Indians are likely to be at the core of their genetic susceptibility to obesity. Having entered the Americas around 20 000 years ago across the Bering Strait from

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present day Russia into Alaska, the first humans to populate the Americas (the ancestors of present day indigenous peoples of the Americas, including Pima Indians) migrated south along the coastline (as much of North America was covered in ice sheets at this time) and by 13 000 years ago developed large settlements in present day Arizona and Mexico where the climate was considerably more arid and hot than in Siberia, a climate to which their ancestors were well adapted (115). Evidence suggests that by this time, Mongoloids in the Americas were reacquiring the capacity for heat adaptation and losing their cold-adapted traits (127). Interestingly, the reduced metabolic rates of Pima Indians have been attributed to lower body temperatures, probably due to reduced sympathetic nervous system activity, alluding to reduced thermogenic capacity in Native Americans who migrated south from Alaska toward the equator (128, 129). Moreover, the elevated genetic predisposition to cardiovascular disease in the Native American population has been linked to a greater capacity for salt retention, which is now believed to be an evolutionary adaptation to heat stress (47). In fact, mutations in the *GNB3* gene, which augment venous tone in response to water loss and have a strong latitudinal basis, are highly prevalent in Native Americans (130). In fact, mutations in several genes associated with improved heat adaptation in Native Americans are as prevalent as in the African population, clearly indicating that, despite their recent descent from cold-adapted Mongoloids, selection for heat adaptation had a profound effect on genes in less than 20 000 years (130). Thus, the genetic switch from cold to heat adaptation may explain the propensity for obesity in US inhabitants of Native American ancestry (48). However, despite a comparable level of heat adaptation, why do Pima Indians have higher obesity rates than African Americans? One reason could be a "founder effect" in this indigenous group, in which a suspected population bottleneck in Beringa, as Mongoloids were entering the Americas, was succeeded by a population explosion, resulting in high frequencies of a specific genetic trait (131). Given the survival advantage of heat adaptation in Arizona and Mexico, it is not surprising that such a genetic trait would have spread rapidly, fueled by a small but growing population that was migrating rapidly southwards (132, 133). Such an amalgamation of diverse genetic influences would have driven a fast-paced evolution of heat adaptive traits from standing variation, in a process known as a "soft sweep," explaining the 80% to 85% obesity rate among Pima Indians (134).

Astonishingly, this was not the final chapter in the rapid evolutionary adaptation to climate in Native Americans. Swift southward migration continued from Central America, through much of South America, aided by glacial retreat during the conclusion of the last ice age around 12 000 years ago. Migration from Central American to the southern tip of South America, known as the Southern Cone, occurred between 13 000 and 10 000 years ago (135). Thus within merely 3000 years, or 150 generations, indigenous populations of the Americas experienced climatic exposures ranging from tropical in Mexico to subantarctic in the Tierra del Fuego Patagonian archipelago. The Yaghan and the now extinct Selknam people, indigenous peoples who descend directly from the first wave of Native American settlers in the Tierra del Fuego, were first documented by Charles Darwin, whom he encountered on his journey toward the Galapagos. Darwin shrewdly observed that, despite living in extreme cold, the Yaghan and Selknam people wore very little clothing and appeared highly adapted to their extreme climate (136). Indeed observations in the Yaghans reveal exceptionally high metabolic rates and inherent heat-producing capabilities (137, 138). Such an abrupt evolutionary change indicates directional evolution, which allows fast changes in allele frequency as a result of altering extremes in environmental pressures (139). Such environmental considerations offer a compelling rationale for why the indigenous peoples of the Tierra del Fuego (and the Canadian Inuits, who descend from a later wave of migrants from Siberia to Alaska within the last 2500 years) exhibit high metabolic rates that would provide obesity resistance, whereas their heat-adapted Native American cousins, the Pima Indians, have low metabolic rates and are obesity-prone.

The clear survival advantage that heat adaptation confers, in our opinion, justifies a selection coefficient (k) of 0.1. Such a coefficient of selection acting over 20 000 years can explain the excessive obesity rates in Pima Indians. US Hispanics, despite being Spanish-speaking, have a much more varied genetic profile than Spanish people. It has been shown that US Hispanics have a significant amount of Native American and African genes (140), which may explain their genetic predisposition to obesity. Interestingly, although evidence exists for humans reaching northern China by 40 000 years ago, evidence also exists for the presence of the first humans in Australia at around the same time (23). Thus, separate migrations from central Asia toward Northeast Asia and through Southeast Asia into Australia are likely to have occurred simultaneously. Given that much of South and Southeast Asia lies on the equator and much of Australia was and still is covered by scorching deserts with tropical temperatures, it is not surprising that the descendants of these first Australians, the indigenous Aborigines, are very dark skinned and have low metabolic rates, making them highly resistant to extreme heat (141). Interestingly, a very recent

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study documented that BAT volume and thermogenic capability were impaired in South Asians compared with those in Caucasians, contributing to the reduced metabolic rates among this ethnic group (142). Therefore, it is likely that the early human inhabitants of South and Southeast Asia did not have the need to adapt to cold and therefore retained their adaptation to heat. The increased prevalence of diabetes and cardiovascular disease among Aborigines in Australia compared with nonindigenous Australians is a testament to this supposition (143, 144). Several reports have documented the increased prevalence of obesity in indigenous Samoan populations compared with that in Native East Asians. However, such reports could not uncover the cause of this discrepancy given that the 2 populations were believed to be culturally and genetically similar (145, 146). The authors of the study in question were equally baffled by the elevated obesity propensity in Native Hawaiians compared with that in East Asians. In our view, these differences can be explained by ancestral exposure to hotter climates. Native Samoans, who descend from the same genetic lineage as Aborigines (147), and all indigenous Pacific Islanders reside near or on the equator and are thus exposed to very hot temperatures all year round. Similarly, Hawaii has a tropical climate; therefore, the descendants of these populations evolved to live in such conditions. In our view, these heat-adapted populations have a reduced metabolic rate and increased susceptibility to obesity as a consequence of their evolutionary climatic exposure. To this end, Native Samoans have been shown to have a thermic response to elevated ambient temperature that is biologically advantageous for minimizing heat stroke and hyperthermia, alluding to their genetic heat-adapted disposition compared with that of Japanese natives who were more susceptible to adverse reactions in response to increased ambient temperature (148, 149). These results confirm that despite sharing a common ancestry and physical features, the lineage that migrated through Indonesia and the Pacific Islands into Australia are more heat adapted and less cold tolerant than the lineage that migrated through Northeast Asia and Siberia. Therefore, in our view European Caucasians and Chinese are more resistant to obesity than other populations because of their genetic adaptation to cold. However, they are not protected from it entirely, as shown particularly by the populations living in warmer regions. Evidence shows that although the obesity prevalence in China is low, its rates are accelerating fastest in southern regions, where the annual temperatures are considerably higher than in colder regions toward the north (150). Similarly, among US populations, obesity rates are higher in the warmer states, whereas colder states tend to have lower rates of obesity. In fact, the coldest state, Colorado, has the lowest prevalence of overweight among US Caucasians (151). It is worth noting here that the correlation between obesity and temperature among contemporary US populations is not likely to reflect evolutionary adaptations as a result of positive selection, as aside from Native Americans (most of whose ancestors did not survive the first colonization by European expeditions), the vast majority of the US population have descended from those who migrated within the last 300 years, from Europe. It is also important to reiterate that lifestyle factors are required for obesity to manifest. A case in point is that Mexican Pima Indians, who retain a more traditional culture with regard to eating habits and hunting, are less susceptible to obesity than US Pima Indians who have increasingly adopted a "westernized" lifestyle (152). Thus, it appears that lifestyle factors as well as inactivation/activation of BAT in response to ambient temperature (as opposed to genetic adaptations), even in contemporary populations whose ancestors probably evolved efficient BAT can negatively influence obesity risk.

Thus, having migrated out of Africa 70 000 years ago, by the time modern humans were thriving in Europe and Siberia 40 000 to 50 000 years ago, changes in climatic selection pressures had a radical effect on selecting for genes for cold adaptation with a secondary effect of increased metabolic rate. Recent evidence has linked human adaptation to cold with gain-of-function mutations in genes that encode for uncoupling proteins and thermogenic genes (153) and their involvement in the pathogenesis of obesity in loss-of-function polymorphisms (154). To understand how BAT thermogenesis influences metabolic rate and how cold exposure can enhance its function, one must explore the molecular basis underlying BAT function.

BAT Thermogenesis and Obesity

The heat-producing qualities of uncoupling proteins and BAT are believed to be a major driving force behind the radiation of mammals 65 million years ago (155, 156). The ability to produce and maintain heat probably contributed to the capacity of eutherian mammals to inhabit all corners of the globe (156). The impact of BAT thermogenesis to survival was so important that it probably drove placental mammalian radiation at the end of the Cretaceous, a global event that led to mammals displacing the dinosaurs as the dominant class of animal on earth (155). The thermogenic capacity of BAT renders it highly specialized for energy expenditure. Although individual cells of white adipose tissue, which is the predominant fat depot in human obesity, contain a single large lipid droplet

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and few mitochondria and receive a limited vascular network, BAT cells contain multiple lipid droplets and numerous mitochondria, have a dense capillary network, and are highly innervated by sympathetic nervous system neurons (76). BAT mitochondria uniquely express UCP1, an inner mitochondrial membrane protein that uncouples ATP synthesis from oxidative phosphorylation, liberating energy in the form of heat (157). Thermogenesis is activated by central stimulation of sympathetic nerves, which innervate BAT and secrete noradrenalin. Noradrenalin-induced activation of β_3-adrenergic receptors on BAT leads to a signaling cascade, resulting in cAMP-dependent lipolysis. The consequent release of FFAs activates UCP1-driven mitochondrial uncoupling (157). β_3-Adrenergic receptor stimulation also induces UCP1 mRNA and protein up-regulation (76, 157). The afferent cues for activation of sympathetic nervous system neurons that innervate BAT in humans include changes in ambient temperature and in photoperiod length (158). Research in rodents has shown that UCP1-driven BAT thermogenesis can account for up to 30% of basal metabolic rate (159, 160) and thus is highly consequential to body weight regulation. This influence of thermogenesis on resting metabolic rate is exemplified in studies in humans showing significantly elevated energy expenditure after acute cold exposure (161). Another emerging activator of thermogenesis is a high-fat diet or hypercaloric nutrition, which has been shown to increase BAT thermogenesis, possibly as a means of prevent body weight gain in rodents (162). High-fat/hypercaloric-induced BAT thermogenesis has also been documented in humans (163, 164). Moreover, one study has documented that a single nucleotide polymorphism in exon 2 of UCP1 leads to the inability to increase energy expenditure in response to a high-fat diet and may be causal in human obesity (165). Interestingly, impaired high-fat diet–induced thermogenesis in UCP1-deficient mice led to high-fat diet–induced obesity only under thermoneutral conditions (when mice were housed at 30°C) (166). This finding suggests that in modern times (with the vast majority of people possessing central heating), the steady increases in the indoor housing temperature experienced throughout industrialized countries in recent decades is exacerbating the deleterious effects of western diets and lifestyle norms, even in those with comparatively effective BAT.

We propose that the selection for genes that favored superior BAT activity in modern humans that migrated to colder climates such as the Europeans and Siberians would have endowed them with the concomitant by-product of a higher energy expenditure and energy-burning capacity. Thus, there appears to be an evolutionary tradeoff between the need for energy storage and the requirement for cold acclimation because although the ancestors of modern humans would have greater resistance to cold as a result of increased BAT function, they would also have a concomitant difficulty in laying down fat as an energy storage mechanism. This is in direct conflict with the thrifty genotype hypothesis, which implies that genes for energy storage were favored during human evolution. UCP1 is often dismissed as a candidate gene for the genetic basis of the obesity pandemic because of an apparent lack of evidence supporting a prominent role for UCP1 in its pathogenesis and a supposed paucity of genome-wide association studies (GWASs) implicating UCP1 in the genetic susceptibility to human obesity (18). Contrary to this belief, a plethora of studies in humans have shown that UCP1 is a causal factor in the genetic susceptibility to obesity (165, 167–173). Moreover, cold-induced thermogenesis in BAT is blunted in obese subjects, indicating a strong link between BAT function and obesity (174). In our view, there are many reasons why UCP1 variants are not more frequently observed in association with human obesity and metabolism, such as those for *FTO* (175). One potential reason for the absence of UCP1 among the list of genes commonly associated with human obesity is that most studies have been conducted in populations of European ancestry (176–178). A recent study failed to replicate most causal variants in obesity from GWASs in European populations and in ethnic minority populations, such as Native Americans and African Americans (179). Moreover, the study in question found that none of the genes previously identified in GWASs in Europeans explain the variation in obesity prevalence among ethnicities, testifying to the need for more robust genetic analysis in non-European populations and the fact that our current understanding of the pathogenesis of obesity remains obscure. Another possible reason for the apparent lack of more frequent association studies implicating UCP1 in human obesity could lie in nonallelic heritable factors. In addition to allelic variants, epigenetic regulation has been suggested to be profoundly influential in determining susceptibility to obesity (180). For instance, the pathogenesis of a rare form of childhood obesity known as Prader-Willi syndrome has been found to lie in epigenetics (181). Recent studies have indicated that DNA methylation is involved in the regulation of UCP1 activity and that such methylation events are critical to the alterations in UCP1 function that affect susceptibility to weight gain and obesity (182–184). Although UCP1 is essential for mitochondrial uncoupling, alterations in other genes could drastically affect thermogenic capacity. Other genes play critical roles in BAT thermogenesis, for instance, increased hypothalamic stimulation of melanocortin receptor 4 (*MC4R*) and increased sympathetic nervous system activity and

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responsiveness enhance BAT function irrespective of UCP1 induction (76, 185). To this end, many GWASs have identified MC4R as having a causal role in obesity (186, 187). Furthermore, studies in Pima Indians have revealed reduced sympathetic responsiveness to adrenergic stimuli compared with that in Caucasians. Taken together, these findings indicate that various elements involved in thermogenesis may shape overall obesity susceptibility in relation to BAT function, not only UCP1 (188).

Given its strong association with increased energy expenditure and lipolysis, BAT research has been put back on the map, ever since the publication of 2 highly cited papers documenting functional BAT in adult humans that was activated by cold (189, 190). Since then, much effort has been channelled into investigation of ways to stimulate BAT function. A recent study suggested that BAT activity may be influenced by ambient temperature and reported a clear correlation between the use of heating/artificial temperature control mechanisms and obesity (191). These findings indicate that the ability to stimulate or reactivate remnant BAT, even in those in whom BAT may be in a dormant state, may be possible by altering ambient temperature. In a similar vein, contemporary BAT research is concentrated on the investigation of pharmacological agents that activate β-adrenergic receptors on BAT or those that increase UCP1 transcription independently of the sympathetic nervous system (192, 193). It is currently unclear, however, to what extent BAT thermogenesis can be activated or rescued in people who have evolved to have minimal or no BAT function. Other efforts to use BAT function to treat obesity have served to stimulate white adipose tissue to acquire BAT characteristics (194, 195). This is an intriguing concept and presents particularly appealing therapeutic prospects; however, such studies are still in their infancy. Another strategy, currently in its conceptual stage, has been proposed by Antonio Vidal-Puig and colleagues (196, 197), who have described the use of knowledge of the genetic and molecular basis for BAT development to stimulate the growth of brown adipocytes from stem cells. Vidal-Puig and colleagues explain that the ability to engineer human stem cell lines that express markers of the brown adipocyte lineage will pave the way for development of large-scale chemical screens for potent inducers of brown adipogenesis and thus promote the cultivation of mature, functional BAT. This strategy of engineering BAT appears to be the most effective option in the treatment of obesity, particularly in relation to our

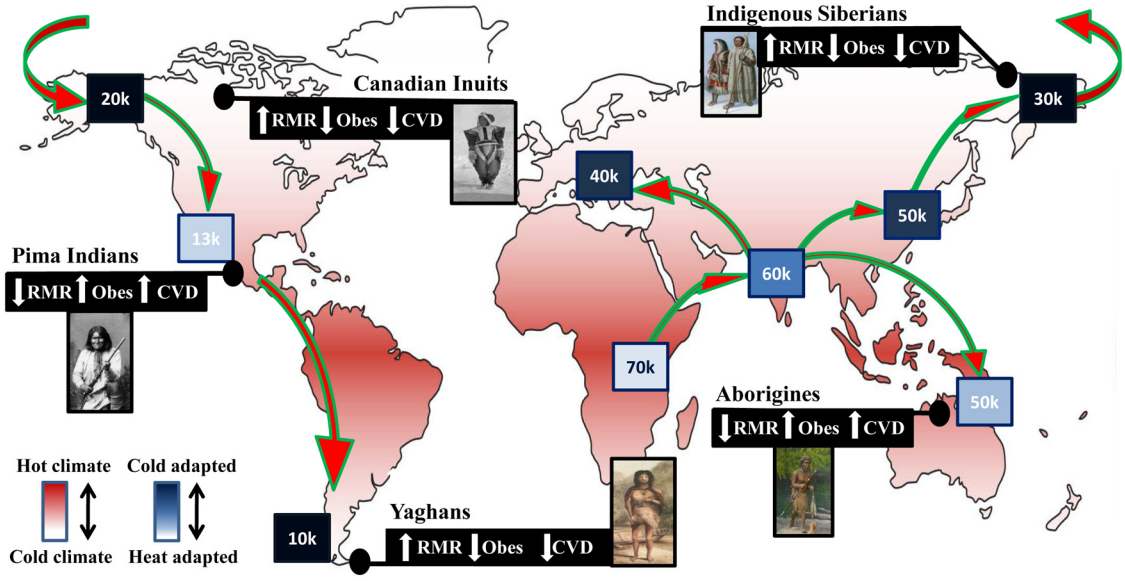

Figure 1. Map of historic human migration out of Africa 70 000 years ago (70k). By 60 000 years ago (60k), humans had reached Central Asia from where a population headed northeast into Siberia and Northeast Asia, acquiring genes for cold adaptation, which also confer higher resting metabolic rates (RMRs) and thus resistance to obesity (Obes). A second group of migrants from Central Asia headed north and west into Europe, also acquiring genes for cold adaptation, displacing the resident Neanderthals. A third group migrated south, through Southeast Asia and into Australia, and maintained genes for heat adaptation. Their descendants, the Aborigines, still inhabit Australia and have low resting metabolic rates and an increased propensity for obesity and type 2 diabetes (T2D). A group of Northeast Asians crossed the Bering Strait 20 000 years ago (20k) into Alaska. Some of their descendants still inhabit the Canadian Arctic and are highly resistant to cold and have exceptionally high resting metabolic rates. Some Mongoloids migrated south along the Pacific coast of North America toward Mexico where they encountered hotter climates and reacquired genes for heat adaptation, discarding those for cold. Their descendants, the Pima Indians, have some of the highest rates of obesity and cardiovascular disease (CVD) in the world. Their evolutionary cousins, the Yaghan people of the Tierra del Fuego whose ancestors continued the southern migration toward the subantarctic South American Cone, probably reevolved BAT capability and have high resting metabolic rates.

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view that those individuals who are most prone to obesity are likely to have very little or no BAT. The implications of this approach to obesity therapeutics is enormous, and it is conceivable that in the future stem cells could be injected into obese patients and molded and manipulated to become mature brown adipocytes, in much the same way that stem cells have recently been used successfully, in vivo, to replace a damaged trachea (198). Alternatively, a patient's own stem cells could be used to grow effective and efficient BAT in vitro, which could then be transplanted back into the patient, in a manner similar to that reported in rodents (199, 200). Each of the aforementioned strategies to maximize BAT function has its relative merits and weaknesses, and it is conceivable in the future that treatments used to tackle obesity will take into account inherent BAT amounts and thermogenic capacity in a manner that resembles a "tailor-made" strategy that best aligns with the biology of the individual. Thus, reinforcing the notion that the success of specific therapies to treat obesity through BAT activation will vary greatly from one individual to the next, depending on evolutionary climatic exposures.

Conclusion

We believe that a fundamental failure to understand the genetic basis for the ethnic variability in susceptibility to obesity in the developed world is a contributory factor in the modern obesity pandemic in these countries. The obesity pandemic has coincided with not only an increase in poor eating habits but also mass immigration of various ethnicities in these countries. Whereas the thrifty and drifty genotype hypotheses make the assumption that the selection pressures faced by the ancestors of all inhabitants of developed countries today were the same, we have argued that this is not entirely accurate. The descendants of early humans who remained in Africa and those who migrated to equally tropical or subtropical environments such as black Americans and Pacific Islanders maintained heat adaption genes. The descendants of those who migrated to colder regions such as Europe and Siberia such as Caucasians and Chinese acquired genes for cold adaptation. A group of early Siberians who migrated to the Americas and settled in subtropical regions in North and Central America lost their cold adaptive genes and reacquired genes for heat adaptation. We postulate that positive selection for cold adaptation in their ancestors equips Caucasians and East Asians such as Chinese, Japanese, and Koreans with efficient BAT and UCP1 function, an advantageous by-product of which is a higher metabolic rate and resistance to obesity. The opposite is true for Africans and South Asians whose ancestors had no need to evolve efficient BAT and UCP1 function, resulting in an increased propensity for obesity in these populations when combined with a sedentary and hypercaloric western lifestyle. Figure 1 is a diagrammatic representation of the impact of historical human migration on selection of genes for heat and cold adaptation and consequent obesity prevalence in industrialized countries today. In summary, we suggest that the modern obesity pandemic in the developed world is largely due to differential climatic exposure of the ancestors of present day people in these countries as a result of historical human migration that began when modern humans left Africa 40 000 to 60 000 years ago. This new perspective has crucial implications for combating obesity in industrialized countries.

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References

1. **Kelly T, Yang W, Chen CS, Reynolds K, He J.** Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)*. 2008; 32:1431–1437.
2. **Zaninotto P, Head J, Stamatakis E, Wardle H, Mindell J.** Trends in obesity among adults in England from 1993 to 2004 by age and social class and projections of prevalence to 2012. *J Epidemiol Community Health*. 2009;63:140–146.
3. **Switzer NJ, Mangat HS, Karmali S.** Current trends in obesity: body composition assessment, weight regulation, and emerging techniques in managing severe obesity. *J Interv Gastroenterol*. 2013; 3:34–36.
4. **Belardi V, Gallagher EJ, Novosyadlyy R, LeRoith D.** Insulin and IGFs in obesity-related breast cancer. *J Mammary Gland Biol Neoplasia*. 2013;18:277–289.
5. **Rader DJ.** Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Am J Med*. 2007;120(3 suppl 1):S12–S18.
6. **Smith SC Jr.** Multiple risk factors for cardiovascular disease and diabetes mellitus. *Am J Med*. 2007;120(3 suppl 1):S3–S11.
7. **Labitigan M, Bahce-Altuntas A, Kremer JM, et al.** Higher rates and clustering of abnormal lipids, obesity, and diabetes in psoriatic arthritis compared with rheumatoid arthritis [published online ahead of print October 7, 2013]. *Arthritis Care Res*. doi: 10.1002/acr.22185.
8. **Zamosky L.** The obesity epidemic. While America swallows $147 billion in obesity-related healthcare costs, physicians called on to confront the crisis. *Med Econ*. 2013;90:14–17.
9. **Aguilera CM, Olza J, Gil A.** Genetic susceptibility to obesity and metabolic syndrome in childhood. *Nutr Hosp*. 2013;28(suppl 5): 44–55.
10. **Naukkarinen J, Rissanen A, Kaprio J, Pietilainen KH.** Causes and

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consequences of obesity: the contribution of recent twin studies. *Int J Obes (Lond)*. 2012;36:1017–1024.
11. **Nan C, Guo B, Warner C, et al.** Heritability of body mass index in pre-adolescence, young adulthood and late adulthood. *Eur J Epidemiol*. 2012;27:247–253.
12. **Neel JV.** Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? 1962. *Bull World Health Organ*. 1999;77:694–703; discussion 692–693.
13. **Prentice AM, Rayco-Solon P, Moore SE.** Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proc Nutr Soc*. 2005;64:153–161.
14. **Song S.** Assessing the impact of in utero exposure to famine on fecundity: evidence from the 1959–61 famine in China. *Popul Stud (Camb)*. 2013;67:293–308.
15. **Chakravarthy MV, Booth FW.** Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. *J Appl Physiol*. 2004;96:3–10.
16. **Speakman JR.** Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis. *Int J Obes (Lond)*. 2008;32:1611–1617.
17. **Speakman JR.** A nonadaptive scenario explaining the genetic predisposition to obesity: the "predation release" hypothesis. *Cell Metab*. 2007;6:5–12.
18. **Speiser DI, Lampe RI, Lovdahl VR, Carrillo-Zazueta B, Rivera AS, Oakley TH.** Evasion of predators contributes to the maintenance of male eyes in sexually dimorphic *Euphilomedes* ostracods (Crustacea). *Integr Comp Biol*. 2013;53:78–88.
19. **Spence R, Wootton RJ, Barber I, Przybylski M, Smith C.** Ecological causes of morphological evolution in the three-spined stickleback. *Ecol Evol*. 2013;3:1717–1726.
20. **Lingle S, Feldman A, Boyce MS, Wilson WF.** Prey behavior, age-dependent vulnerability, and predation rates. *Am Nat*. 2008;172:712–725.
21. **Quintana-Murci L, Semino O, Bandelt HJ, Passarino G, McElreavey K, Santachiara-Benerecetti AS.** Genetic evidence of an early exit of *Homo sapiens sapiens* from Africa through eastern Africa. *Nat Genet*. 1999;23:437–441.
22. **Rasmussen M, Guo X, Wang Y, et al.** An Aboriginal Australian genome reveals separate human dispersals into Asia. *Science*. 2011;334:94–98.
23. **Bowler JM, Johnston H, Olley JM, Prescott JR, Roberts RG, Shawcross W, Spooner NA.** New ages for human occupation and climatic change at Lake Mungo, Australia. *Nature*. 2003;421:837–840.
24. **Emmelin A, Fantahun M, Berhane Y, Wall S, Byass P.** Vulnerability to episodes of extreme weather: Butajira, Ethiopia, 1998–1999. *Glob Health Action*. 2008;2.
25. **Haile M.** Weather patterns, food security and humanitarian response in sub-Saharan Africa. *Philos Trans R Soc Lond B Biol Sci*. 2005;360:2169–2182.
26. **Slingo JM, Challinor AJ, Hoskins BJ, Wheeler TR.** Introduction: food crops in a changing climate. *Philos Trans R Soc Lond B Biol Sci*. 2005;360:1983–1989.
27. **Scrimshaw NS.** The phenomenon of famine. *Annu Rev Nutr*. 1987;7:1–21.
28. **Hanson M, Gluckman P.** Developmental origins of noncommunicable disease: population and public health implications. *Am J Clin Nutr*. 2011;94(6 suppl):1754S–1758S.
29. **Hanson MA, Gluckman PD.** Developmental origins of health and disease: moving from biological concepts to interventions and policy. *Int J Gynaecol Obstet*. 2011;115(suppl 1):S3–S5.
30. **Voight BF, Kudaravalli S, Wen X, Pritchard JK.** A map of recent positive selection in the human genome. *PLoS Biol*. 2006;4:e72.
31. **Kwiatkowski DP.** How malaria has affected the human genome and what human genetics can teach us about malaria. *Am J Hum Genet*. 2005;77:171–192.
32. **Vuorisalo T, Arjamaa O, Vasemägi A, Taavitsainen JP, Tourunen A, Saloniemi I.** High lactose tolerance in North Europeans: a result of migration, not in situ milk consumption. *Perspect Biol Med*. 2012;55:163–174.
33. **Atkins KE, Townsend JP, Medlock J, Galvani AP.** Epidemiological mechanisms of genetic resistance to kuru. *J R Soc Interface*. 2013;10:20130331.
34. **Nkenfou CN, Mekue LC, Nana CT, Kuiate JR.** Distribution of CCR5-Delta32, CCR5 promoter 59029 A/G, CCR2–64I and SDF1–3′A genetic polymorphisms in HIV-1 infected and uninfected patients in the west region of Cameroon. *BMC Res Notes*. 2013;6:288.
35. **Schliekelman P, Garner C, Slatkin M.** Natural selection and resistance to HIV. *Nature*. 2001;411:545–546.
36. **Hur SJ, Kim DH, Chun SC, Lee SK.** Effect of adenovirus and influenza virus infection on obesity. *Life Sci*. 2013;93:531–535.
37. **Molofsky AB, Nussbaum JC, Liang HE, et al.** Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med*. 2013;210:535–549.
38. **Winer DA, Winer S, Chng MH, Shen L, Engleman EG.** B lymphocytes in obesity-related adipose tissue inflammation and insulin resistance. *Cell Mol Life Sci*. 2014;71:1033–1043.
39. **Ridaura VK, Faith JJ, Rey FE, et al.** Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013;341:1241214.
40. **Hancock AM, Witonsky DB, Gordon AS, et al.** Adaptations to climate in candidate genes for common metabolic disorders. *PLoS Genet*. 2008;4:e32.
41. **Albrecht SS, Gordon-Larsen P.** Ethnic differences in body mass index trajectories from adolescence to adulthood: a focus on Hispanic and Asian subgroups in the United States. *PLoS One*. 2013;8:e72983.
42. **Bryant AN, Ford KL, Kim G.** Racial/ethnic variations in the relation between body mass index and cognitive function among older adults. *Am J Geriatr Psychiatry* [published online ahead of print October 11, 2013]. doi: 10.1016/j.jagp.2013.08.006.
43. **Caprio S, Daniels SR, Drewnowski A, et al.** Influence of race, ethnicity, and culture on childhood obesity: implications for prevention and treatment. *Obesity (Silver Spring)*. 2008;16:2566–2577.
44. **Caprio S, Daniels SR, Drewnowski A, et al.** Influence of race, ethnicity, and culture on childhood obesity: implications for prevention and treatment: a consensus statement of Shaping America's Health and the Obesity Society. *Diabetes Care*. 2008;31:2211–2221.
45. **Kuzawa CW, Sweet E.** Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *Am J Hum Biol*. 2009;21:2–15.
46. **Zhang H, Rodriguez-Monguio R.** Racial disparities in the risk of developing obesity-related diseases: a cross-sectional study. *Ethn Dis*. 2012;22:308–316.
47. **Kurian AK, Cardarelli KM.** Racial and ethnic differences in cardiovascular disease risk factors: a systematic review. *Ethn Dis*. 2007;17:143–152.
48. **Crawford PB, Story M, Wang MC, Ritchie LD, Sabry ZI.** Ethnic issues in the epidemiology of childhood obesity. *Pediatr Clin North Am*. 2001;48:855–878.
49. **Kumanyika SK.** Obesity in minority populations: an epidemiologic assessment. *Obes Res*. 1994;2:166–182.
50. **Gordon-Larsen P, Adair LS, Popkin BM.** The relationship of ethnicity, socioeconomic factors, and overweight in US adolescents. *Obes Res*. 2003;11:121–129.
51. **Finkelstein EA, Khavjou OA, Mobley LR, Haney DM, Will JC.** Racial/ethnic disparities in coronary heart disease risk factors among WISEWOMAN enrollees. *J Womens Health (Larchmt)*. 2004;13:503–518.
52. **Heald FP.** Natural history and physiological basis of adolescent obesity. *Fed Proc*. 1966;25:1–3.

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53. **Bray GA.** Obesity: historical development of scientific and cultural ideas. *Int J Obes*. 1990;14:909–926.
54. **Swinburn BA, Caterson I, Seidell JC, James WP.** Diet, nutrition and the prevention of excess weight gain and obesity. *Public Health Nutr*. 2004;7:123–146.
55. **Lichtenstein AH, Kennedy E, Barrier P, et al.** Dietary fat consumption and health. *Nutr Rev*. 1998;56(5 Pt 2):S3–S19; discussion S19–S28.
56. **Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, McKee M.** Migration and health in an increasingly diverse Europe. *Lancet*. 2013;381:1235–1245.
57. **Rafnsson SB, Bhopal RS.** Migrant and ethnic health research: report on the European Public Health Association Conference 2007. *Public Health*. 2008;122:532–534.
58. **Maffla C.** Health in the age of migration: migration and health in the EU. *Community Pract*. 2008;81:32–35.
59. **Friis R, Yngve A, Persson V.** Review of social epidemiologic research on migrants' health: findings, methodological cautions, and theoretical perspectives. *Scand J Soc Med*. 1998;26:173–180.
60. **Loue S, Bunce A.** The assessment of immigration status in health research. *Vital Health Stat 2*. 1999;127:1–115.
61. **Castañeda H.** "Over-foreignization" or "unused potential?" A critical review of migrant health in Germany and responses toward unauthorized migration. *Soc Sci Med*. 2012;74:830–838.
62. **Gagnon AJ, Zimbeck M, Zeitlin J, et al.** Migration to western industrialised countries and perinatal health: a systematic review. *Soc Sci Med*. 2009;69:934–946.
63. **Gagnon AJ, McDermott S, Rigol-Chachamovich J, Bandyopadhyay M, Stray-Pedersen B, Stewart D.** International migration and gestational diabetes mellitus: a systematic review of the literature and meta-analysis. *Paediatr Perinat Epidemiol*. 2011;25:575–592.
64. **Lassetter JH, Callister LC.** The impact of migration on the health of voluntary migrants in western societies. *J Transcult Nurs*. 2009;20:93–104.
65. **Steffen PR, Smith TB, Larson M, Butler L.** Acculturation to Western society as a risk factor for high blood pressure: a meta-analytic review. *Psychosom Med*. 2006;68:386–397.
66. **Shrestha LB.** *The Changing Demographic Profile of the Unites States*. Congressional Research Service Report to Congress. Washington, DC: Congressional Research Service; 2011.
67. **Taveras EM, Gillman MW, Kleinman KP, Rich-Edwards JW, Rifas-Shiman SL.** Reducing racial/ethnic disparities in childhood obesity: the role of early life risk factors. *JAMA Pediatr*. 2013;167:731–738.
68. **Maskarinec G, Grandinetti A, Matsuura G, et al.** Diabetes prevalence and body mass index differ by ethnicity: the Multiethnic Cohort. *Ethn Dis*. 2009;19:49–55.
69. **Gatineau M, Mathrani S.** *Obesity and Ethnicity*. National Obesity Observatory, Oxford, UK; 2011.
70. **Prentice AM, Hennig BJ, Fulford AJ.** Evolutionary origins of the obesity epidemic: natural selection of thrifty genes or genetic drift following predation release? *Int J Obes (Lond)*. 2008;32:1607–1610.
71. **Flegal KM, Carroll MD, Ogden CL, Johnson CL.** Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
72. **Singh GK, Siahpush M, Hiatt RA, Timsina LR.** Dramatic increases in obesity and overweight prevalence and body mass index among ethnic-immigrant and social class groups in the United States, 1976–2008. *J Community Health*. 2011;36:94–110.
73. **Ogden CL, Yanovski SZ, Carroll MD, Flegal KM.** The epidemiology of obesity. *Gastroenterology*. 2007;132:2087–2102.
74. **Singh GK, Kogan MD, Yu SM.** Disparities in obesity and overweight prevalence among US immigrant children and adolescents by generational status. *J Community Health*. 2009;34:271–281.
75. **Wang Y, Beydoun MA.** The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007;29:6–28.
76. **Cannon B, Nedergaard J.** Brown adipose tissue: function and physiological significance. *Physiol Rev*. 2004;84:277–359.
77. **Stock MJ, Rothwell NJ.** Factors influencing brown fat and the capacity for diet-induced thermogenesis. *Int J Obes (Lond)*. 1985;9(Suppl 2):9–15.
78. **Brooks SL, Rothwell NJ, Stock MJ, Goodbody AE, Trayhurn P.** Increased proton conductance pathway in brown adipose tissue mitochondria of rats exhibiting diet-induced thermogenesis. *Nature*. 1980;286:274–276.
79. **Nicholls DG, Bernson VS, Heaton GM.** The identification of the component in the inner membrane of brown adipose tissue mitochondria responsible for regulating energy dissipation. *Experientia Suppl*. 1978;32:89–93.
80. **Gilsanz V, Smith ML, Goodarzian F, Kim M, Wren TA, Hu HH.** Changes in brown adipose tissue in boys and girls during childhood and puberty. *J Pediatr*. 2012;160:604–609.e601.
81. **Ponrartana S, Hu HH, Gilsanz V.** On the relevance of brown adipose tissue in children. *Ann NY Acad Sci*. 2013;1302:24–29.
82. **Lean ME, James WP, Jennings G, Trayhurn P.** Brown adipose tissue uncoupling protein content in human infants, children and adults. *Clin Sci (Lond)*. 1986;71:291–297.
83. **Chen KY, Brychta RJ, Linderman JD, et al.** Brown fat activation mediates cold-induced thermogenesis in adult humans in response to a mild decrease in ambient temperature. *J Clin Endocrinol Metab*. 2013;98:E1218–E1223.
84. **Hu HH, Tovar JP, Pavlova Z, Smith ML, Gilsanz V.** Unequivocal identification of brown adipose tissue in a human infant. *J Magn Reson Imaging*. 2012;35:938–942.
85. **Friedman M.** "Brown fat" as a source of heat production in the newborn. *Midwife Health Visitor*. 1967;3:75–76.
86. **Lutz L, Perlstein PH.** Temperature control in newborn babies. *Nurs Clin North Am*. 1971;6:15–23.
87. **Hackman PS.** Recognizing and understanding the cold-stressed term infant. *Neonatal Netw*. 2001;20:35–41.
88. **Mance MJ.** Keeping infants warm: challenges of hypothermia. *Adv Neonatal Care*. 2008;8:6–12.
89. **Hanna JM.** Human heat tolerance: an anthropological perspective. *Annu Rev Anthropol*. 1983;12:259–284.
90. **Haldane JBS.** *The Causes of Evolution*. Princeton, NJ: Princeton University Press; 1932.
91. **Zhivotovsky LA, Rosenberg NA, Feldman MW.** Features of evolution and expansion of modern humans, inferred from genome-wide microsatellite markers. *Am J Hum Genet*. 2003;72:1171–1186.
92. **Armitage SJ, Jasim SA, Marks AE, Parker AG, Usik VI, Uerpmann HP.** The southern route "out of Africa": evidence for an early expansion of modern humans into Arabia. *Science*. 2011;331:453–456.
93. **Yuan CX, Ji Q, Meng QJ, Tabrum AR, Luo ZX.** Earliest evolution of multituberculate mammals revealed by a new Jurassic fossil. *Science*. 2013;341:779–783.
94. **Luo ZX, Ji Q, Wible JR, Yuan CX.** An Early Cretaceous tribosphenic mammal and metatherian evolution. *Science*. 2003;302:1934–1940.
95. **Ji Q, Luo ZX, Yuan CX, Wible JR, Zhang JP, Georgi JA.** The earliest known eutherian mammal. *Nature*. 2002;416:816–822.
96. **Williams BA, Kay RF, Kirk EC.** New perspectives on anthropoid origins. *Proc Natl Acad Sci USA*. 2010;107:4797–4804.
97. **Anderson BG, Bell ML.** Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States. *Epidemiology*. 2009;20:205–213.
98. **Newman RW.** Why man is such a sweaty and thirsty naked animal: a speculative review. *Hum Biol*. 1970;42:12–27.
99. **Thomson ML.** A comparison between the number and distribution

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of functioning eccrine sweat glands in Europeans and Africans. *J Physiol*. 1954;123:225–233.
100. **Moskowitz DW.** Hypertension, thermotolerance, and the "African gene": an hypothesis. *Clin Exp Hypertens*. 1996;18:1–19.
101. **Ruxton GD, Wilkinson DM.** Avoidance of overheating and selection for both hair loss and bipedality in hominins. *Proc Natl Acad Sci USA*. 2011;108:20965–20969.
102. **Ruxton GD, Wilkinson DM.** Thermoregulation and endurance running in extinct hominins: Wheeler's models revisited. *J Hum Evol*. 2011;61:169–175.
103. **Sharp TA, Bell ML, Grunwald GK, et al.** Differences in resting metabolic rate between white and African-American young adults. *Obes Res*. 2002;10:726–732.
104. **Weyer C, Snitker S, Bogardus C, Ravussin E.** Energy metabolism in African Americans: potential risk factors for obesity. *Am J Clin Nutr*. 1999;70:13–20.
105. **Melby CL, Ho RC, Jeckel K, Beal L, Goran M, Donahoo WT.** Comparison of risk factors for obesity in young, nonobese African-American and Caucasian women. *Int J Obes Relat Metab Disord*. 2000;24:1514–1522.
106. **Foster GD, Wadden TA, Swain RM, Anderson DA, Vogt RA.** Changes in resting energy expenditure after weight loss in obese African American and white women. *Am J Clin Nutr*. 1999;69:13–17.
107. **Kimm SY, Glynn NW, Aston CE, et al.** Racial differences in the relation between uncoupling protein genes and resting energy expenditure. *Am J Clin Nutr*. 2002;75:714–719.
108. **Cicarma E, Mørk C, Porojnicu AC, et al.** Influence of narrowband UVB phototherapy on vitamin D and folate status. *Exp Dermatol*. 2010;19:e67–e72.
109. **Steegmann AT Jr, Platner WS.** Experimental cold modification of cranio-facial morphology. *Am J Phys Anthropol*. 1968;28:17–30.
110. **So JK.** Human biological adaptation to arctic and subarctic zones. *Annu Rev Anthropol*. 1980;9:63–82.
111. **Takasaki Y, Loy SF, Juergens HW.** Ethnic differences in the relationship between bioelectrical impedance and body size. *J Physiol Anthropol Appl Human Sci*. 2003;22:233–235.
112. **Snodgrass JJ, Leonard WR, Sorensen MV, Tarskaia LA, Mosher MJ.** The influence of basal metabolic rate on blood pressure among indigenous Siberians. *Am J Phys Anthropol*. 2008;137:145–155.
113. **Snodgrass JJ, Leonard WR, Tarskaia LA, Alekseev VP, Krivoshapkin VG.** Basal metabolic rate in the Yakut (Sakha) of Siberia. *Am J Hum Biol*. 2005;17:155–172.
114. **Snodgrass JJ, Sorensen MV, Tarskaia LA, Leonard WR.** Adaptive dimensions of health research among indigenous Siberians. *Am J Hum Biol*. 2007;19:165–180.
115. **Leonard WR, Sorensen MV, Galloway VA, et al.** Climatic influences on basal metabolic rates among circumpolar populations. *Am J Hum Biol*. 2002;14:609–620.
116. **Milan FA, Evonuk E.** Oxygen consumption and body temperatures of Eskimos during sleep. *J Appl Physiol*. 1967;22:565–567.
117. **Rode A, Shephard RJ.** Basal metabolic rate of Inuit. *Am J Hum Biol*. 1995;7:723–729.
118. **Wong WW, Butte NF, Ellis KJ, et al.** Pubertal African-American girls expend less energy at rest and during physical activity than Caucasian girls. *J Clin Endocrinol Metab*. 1999;84:906–911.
119. **Júlíusson PB, Roelants M, Eide GE, Hauspie R, Waaler PE, Bjerknes R.** Overweight and obesity in Norwegian children: secular trends in weight-for-height and skinfolds. *Acta Paediatr*. 2007;96:1333–1337.
120. **Midthjell K, Lee CM, Langhammer A, et al.** Trends in overweight and obesity over 22 years in a large adult population: the HUNT Study, Norway. *Clin Obes*. 2013;3:12–20.
121. **Lin M, Chu CC, Lee HL, et al.** Heterogeneity of Taiwan's indigenous population: possible relation to prehistoric Mongoloid dispersals. *Tissue Antigens*. 2000;55:1–9.
122. **Beals KL.** Head form and climatic stress. *Am J Phys Anthropol*. 1972;37:85–92.
123. **Raghavan M, Skoglund P, Graf KE, et al.** Upper Palaeolithic Siberian genome reveals dual ancestry of Native Americans. *Nature*. 2014;505:87–91.
124. **Criado JR, Gilder DA, Kalafut MA, Ehlers CL.** Obesity in American Indian and Mexican American men and women: associations with blood pressure and cardiovascular autonomic control. *Cardiovasc Psychiatry Neurol*. 2013;2013:680687.
125. **Fontvieille AM, Lillioja S, Ferraro RT, Schulz LO, Rising R, Ravussin E.** Twenty-four-hour energy expenditure in Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1992;35:753–759.
126. **Ravussin E, Bogardus C.** Energy balance and weight regulation: genetics versus environment. *Br J Nutr*. 2000;83(suppl 1):S17–S20.
127. **Balaresque PL, Ballereau SJ, Jobling MA.** Challenges in human genetic diversity: demographic history and adaptation. *Hum Mol Genet*. 2007;16(Spec No 2):R134–R139.
128. **Rising R, Keys A, Ravussin E, Bogardus C.** Concomitant interindividual variation in body temperature and metabolic rate. *Am J Physiol*. 1992;263(4 Pt 1):E730–E734.
129. **Spraul M, Ravussin E, Fontvieille AM, Rising R, Larson DE, Anderson EA.** Reduced sympathetic nervous activity. A potential mechanism predisposing to body weight gain. *J Clin Invest*. 1993;92:1730–1735.
130. **Young JH, Chang YP, Kim JD, et al.** Differential susceptibility to hypertension is due to selection during the out-of-Africa expansion. *PLoS Genet*. 2005;1:e82.
131. **Amos W, Hoffman JI.** Evidence that two main bottleneck events shaped modern human genetic diversity. *Proc Biol Sci*. 2010;277:131–137.
132. **Tamm E, Kivisild T, Reidla M, et al.** Beringian standstill and spread of Native American founders. *PLoS One*. 2007;2:e829.
133. **Horai S, Kondo R, Nakagawa-Hattori Y, Hayashi S, Sonoda S, Tajima K.** Peopling of the Americas, founded by four major lineages of mitochondrial DNA. *Mol Biol Evol*. 1993;10:23–47.
134. **Pritchard JK, Pickrell JK, Coop G.** The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation. *Curr Biol*. 2010;20:R208–R215.
135. **Bodner M, Perego UA, Huber G, et al.** Rapid coastal spread of First Americans: novel insights from South America's Southern Cone mitochondrial genomes. *Genome Res*. 2012;22:811–820.
136. **Darwin CR.** *The Voyage of the Beagle*. Vol 29. New York, NY: PF Collier; 1909.
137. **Fisher FR.** *Man Living in the Arctic; Proceedings of a Conference, Quartermaster Research and Engineering Center, Natick, Massachusetts, 1, 2 December 1960*. Washington, DC: The National Academies Press; 1961.
138. **Yesner DR.** Prehistoric maritime adaptations of the subarctic and subantarctic zones: The Aleutian/Fuegian connection reconsidered. *Arctic Anthropol*. 2004;41:76–97.
139. **Cameron TC, O'Sullivan D, Reynolds A, Piertney SB, Benton TG.** Eco-evolutionary dynamics in response to selection on life-history. *Ecol Lett*. 2013;16:754–763.
140. **González Burchard E, Borrell LN, Choudhry S, et al.** Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. *Am J Public Health*. 2005;95:2161–2168.
141. **Wyndham CH, McPherson RK, Munro A.** Reactions to heat of Aborigines and Caucasians. *J Appl Physiol*. 1964;19:1055–1058.
142. **Bakker LEH, Boon MR, van der Linden RAD, et al.** Brown adipose tissue volume in healthy lean south Asian adults compared with white Caucasians: a prospective, case-controlled observational study. *Lancet Diabetes Endocrinol* [published online ahead of print November 12, 2013]. doi:10.1016/S2213-8587(13)70156-6.

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143. **Li M, McCulloch B, McDermott R.** Metabolic syndrome and incident coronary heart disease in Australian indigenous populations. *Obesity (Silver Spring)*. 2012;20:1308–1312.
144. **O'Dea K.** Westernisation, insulin resistance and diabetes in Australian aborigines. *Med J Aust*. 1991;155:258–264.
145. **Davis J, Busch J, Hammatt Z, et al.** The relationship between ethnicity and obesity in Asian and Pacific Islander populations: a literature review. *Ethn Dis*. 2004;14:111–118.
146. **Esperat MC, Inouye J, Gonzalez EW, Owen DC, Feng D.** Health disparities among Asian Americans and Pacific Islanders. *Annu Rev Nurs Res*. 2004;22:135–159.
147. **Friedlaender JS, Friedlaender FR, Reed FA, et al.** The genetic structure of Pacific Islanders. *PLoS Genet*. 2008;4:e19.
148. **Lee JY, Wakabayashi H, Wijayanto T, Hashiguchi N, Saat M, Tochihara Y.** Ethnic differences in thermoregulatory responses during resting, passive and active heating: application of Werner's adaptation model. *Eur J Appl Physiol*. 2011;111:2895–2905.
149. **Saat M, Tochihara Y, Hashiguchi N, Sirisinghe RG, Fujita M, Chou CM.** Effects of exercise in the heat on thermoregulation of Japanese and Malaysian males. *J Physiol Anthropol Appl Human Sci*. 2005;24:267–275.
150. **Wildman RP, Gu D, Muntner P, et al.** Trends in overweight and obesity in Chinese adults: between 1991 and 1999–2000. *Obesity (Silver Spring)*. 2008;16:1448–1453.
151. **Levi JV, Vintner S, Richardson L, St Laurent R, Segal LM.** *F As in Fat: How Obesity Policies Are Failing in America*. Washington, DC: Trust for America's Health; 2008.
152. **Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO.** Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care*. 1994;17:1067–1074.
153. **Hancock AM, Clark VJ, Qian Y, Di Rienzo A.** Population genetic analysis of the uncoupling proteins supports a role for UCP3 in human cold resistance. *Mol Biol Evol*. 2011;28:601–614.
154. **de Souza BM, Brondani LA, Boucas AP, et al.** Associations between *UCP1* −3826A/G, *UCP2* −866G/A, Ala55Val and Ins/Del, and *UCP3* −55C/T polymorphisms and susceptibility to type 2 diabetes mellitus: case-control study and meta-analysis. *PLoS One*. 2013;8:e54259.
155. **Oelkrug R, Goetze N, Exner C, et al.** Brown fat in a protoendothermic mammal fuels eutherian evolution. *Nat Commun*. 2013;4:2140.
156. **Saito S, Saito CT, Shingai R.** Adaptive evolution of the uncoupling protein 1 gene contributed to the acquisition of novel nonshivering thermogenesis in ancestral eutherian mammals. *Gene*. 2008;408:37–44.
157. **Lowell BB, Spiegelman BM.** Towards a molecular understanding of adaptive thermogenesis. *Nature*. 2000;404:652–660.
158. **Au-Yong IT, Thorn N, Ganatra R, Perkins AC, Symonds ME.** Brown adipose tissue and seasonal variation in humans. *Diabetes*. 2009;58:2583–2587.
159. **Stock MJ, Rothwell NJ.** The role of brown fat in diet-induced thermogenesis. *Int J Vitam Nutr Res*. 1986;56:205–210.
160. **Rothwell NJ, Stock MJ.** A role for brown adipose tissue in diet-induced thermogenesis. *Nature*. 1979;281:31–35.
161. **Ouellet V, Labb SM, Blondin DP, et al.** Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. *J Clin Invest*. 2012;122:545–552.
162. **Lowell BB, Bachman ES.** β-Adrenergic receptors, diet-induced thermogenesis, and obesity. *J Biol Chem*. 2003;278:29385–29388.
163. **Nielsen B.** Does diet-induced thermogenesis change the preferred ambient temperature of humans? *Eur J Appl Physiol Occup Physiol*. 1987;56:474–478.
164. **Lanzola E, Tagliabue A, Bozzi G, Meroni G.** Obesity, diet and body temperature. *Ann Nutr Metab*. 1991;35:274–283.
165. **Jia JJ, Tian YB, Cao ZH, et al.** The polymorphisms of UCP1 genes associated with fat metabolism, obesity and diabetes. *Mol Biol Rep*. 2010;37:1513–1522.
166. **Feldmann HM, Golozoubova V, Cannon B, Nedergaard J.** UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. *Cell Metab*. 2009;9:203–209.
167. **Yoneshiro T, Ogawa T, Okamoto N, et al.** Impact of UCP1 and beta3AR gene polymorphisms on age-related changes in brown adipose tissue and adiposity in humans. *Int J Obes (Lond)*. 2013;37:993–998.
168. **Nakayama K, Miyashita H, Yanagisawa Y, Iwamoto S.** Seasonal effects of UCP1 gene polymorphism on visceral fat accumulation in Japanese adults. *PLoS One*. 2013;8:e74720.
169. **Forga L, Corbalán M, Marti A, Fuentes C, Martinez-Gonzalez MA, Martinez A.** Influence of the polymorphism 03826 A→G in the UCP1 gene on the components of metabolic syndrome. *An Sist Sanit Navar*. 2003;26:231–236.
170. **Valve R, Heikkinen S, Rissanen A, Laakso M, Uusitupa M.** Synergistic effect of polymorphisms in uncoupling protein 1 and β_3-adrenergic receptor genes on basal metabolic rate in obese Finns. *Diabetologia*. 1998;41:357–361.
171. **Dhall M, Chaturvedi MM, Rai U, Kapoor S.** Sex-dependent effects of the UCP1 −3826 A/G polymorphism on obesity and blood pressure. *Ethn Dis*. 2012;22:181–184.
172. **Proenza AM, Poissonnet CM, Ozata M, et al.** Association of sets of alleles of genes encoding β_3-adrenoreceptor, uncoupling protein 1 and lipoprotein lipase with increased risk of metabolic complications in obesity. *Int J Obes Relat Metab Disord*. 2000;24:93–100.
173. **Matsushita H, Kurabayashi T, Tomita M, Kato N, Tanaka K.** Effects of uncoupling protein 1 and beta3-adrenergic receptor gene polymorphisms on body size and serum lipid concentrations in Japanese women. *Maturitas*. 2003;45:39–45.
174. **Orava J, Nuutila P, Noponen T, et al.** Blunted metabolic responses to cold and insulin stimulation in brown adipose tissue of obese humans. *Obesity (Silver Spring)* [published online ahead of print April 2, 2013]. doi: 10.1002/oby.20456.
175. **Church C, Moir L, McMurray F, et al.** Overexpression of Fto leads to increased food intake and results in obesity. *Nat Genet*. 2010;42:1086–1092.
176. **Speliotes EK, Willer CJ, Berndt SI, et al.** Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948.
177. **Thorleifsson G, Walters GB, Gudbjartsson DF, et al.** Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. 2009;41:18–24.
178. **Willer CJ, Speliotes EK, Loos RJ, et al.** Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009;41:25–34.
179. **Fesinmeyer MD, North KE, Ritchie MD, et al.** Genetic risk factors for BMI and obesity in an ethnically diverse population: results from the population architecture using genomics and epidemiology (PAGE) study. *Obesity (Silver Spring)*. 2013;21:835–846.
180. **Godfrey KM, Sheppard A, Gluckman PD, et al.** Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes*. 2011;60:1528–1534.
181. **Gurrieri F, Accadia M.** Genetic imprinting: the paradigm of Prader-Willi and Angelman syndromes. *Endocr Dev*. 2009;14:20–28.
182. **Shore A, Karamitri A, Kemp P, Speakman JR, Lomax MA.** Role of Ucp1 enhancer methylation and chromatin remodelling in the control of Ucp1 expression in murine adipose tissue. *Diabetologia*. 2010;53:1164–1173.
183. **Kiskinis E, Hallberg M, Christian M, et al.** RIP140 directs histone and DNA methylation to silence Ucp1 expression in white adipocytes. *EMBO J*. 2007;26:4831–4840.
184. **Wang H, Zhang Y, Yehuda-Shnaidman E, et al.** Liver X receptor

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alpha is a transcriptional repressor of the uncoupling protein 1 gene and the brown fat phenotype. *Mol Cell Biol*. 2008;28:2187–2200.
185. **Tao YX.** The melanocortin-4 receptor: physiology, pharmacology, and pathophysiology. *Endocr Rev*. 2010;31:506–543.
186. **Xi B, Chandak GR, Shen Y, Wang Q, Zhou D.** Association between common polymorphism near the MC4R gene and obesity risk: a systematic review and meta-analysis. *PLoS One*. 2012;7:e45731.
187. **Xi B, Takeuchi F, Chandak GR, et al.** Common polymorphism near the MC4R gene is associated with type 2 diabetes: data from a meta-analysis of 123,373 individuals. *Diabetologia*. 2012;55:2660–2666.
188. **Tataranni PA, Christin L, Snitker S, Paolisso G, Ravussin E.** Pima Indian males have lower beta-adrenergic sensitivity than Caucasian males. *J Clin Endocrinol Metab*. 1998;83:1260–1263.
189. **Virtanen KA, Lidell ME, Orava J, et al.** Functional brown adipose tissue in healthy adults. *N Engl J Med*. 2009;360:1518–1525.
190. **Cypess AM, Lehman S, Williams G, et al.** Identification and importance of brown adipose tissue in adult humans. *N Engl J Med*. 2009;360:1509–1517.
191. **Johnson F, Mavrogianni A, Ucci M, Vidal-Puig A, Wardle J.** Could increased time spent in a thermal comfort zone contribute to population increases in obesity? *Obes Rev*. 2011;12:543–551.
192. **Chechi K, Nedergaard J, Richard D.** Brown adipose tissue as an anti-obesity tissue in humans. *Obes Rev*. 2014;15:92–106.
193. **Whittle A, Relat-Pardo J, Vidal-Puig A.** Pharmacological strategies for targeting BAT thermogenesis. *Trends Pharmacol Sci*. 2013;34:347–355.
194. **Shabalina IG, Petrovic N, de Jong JM, Kalinovich AV, Cannon B, Nedergaard J.** UCP1 in brite/beige adipose tissue mitochondria is functionally thermogenic. *Cell Rep*. 2013;5:1196–1203.
195. **Giralt M, Villarroya F.** White, brown, beige/brite: different adipose cells for different functions? *Endocrinology*. 2013;154:2992–3000.
196. **Carobbio S, Rosen B, Vidal-Puig A.** Adipogenesis: new insights into brown adipose tissue differentiation. *J Mol Endocrinol*. 2013;51:T75–T85.
197. **Villarroya F, Vidal-Puig A.** Beyond the sympathetic tone: the new brown fat activators. *Cell Metab*. 2013;17:638–643.
198. **Berg M, Ejnell H, Kovács A, et al.** Replacement of a tracheal stenosis with a tissue-engineered human trachea using autologous stem cells: a case report. *Tissue Eng Part A*. 2014;20:389–397.
199. **Liu X, Zheng Z, Zhu X, et al.** Brown adipose tissue transplantation improves whole-body energy metabolism. *Cell Res*. 2013;23:851–854.
200. **Stanford KI, Middelbeek RJ, Townsend KL, et al.** Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *J Clin Invest*. 2013;123:215–223.

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