FOCUS: OBESITY

Thinking Evolutionarily About Obesity

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Obesity, diabetes, and metabolic syndrome are growing worldwide health concerns, yet their causes are not fully understood. Research into the etiology of the obesity epidemic is highly influenced by our understanding of the evolutionary roots of metabolic control. For half a century, the thrifty gene hypothesis, which argues that obesity is an evolutionary adaptation for surviving periods of famine, has dominated the thinking on this topic. Obesity researchers are often not aware that there is, in fact, limited evidence to support the thrifty gene hypothesis and that alternative hypotheses have been suggested. This review presents evidence for and against the thrifty gene hypothesis and introduces readers to additional hypotheses for the evolutionary origins of the obesity epidemic. Because these alternate hypotheses imply significantly different strategies for research and clinical management of obesity, their consideration is critical to halting the spread of this epidemic.

INTRODUCTION

The incidence of obesity worldwide has risen dramatically in the past century, enough to be formally declared a global epidemic by the World Health Organization in 1997 [1]. Obesity (defined by a body mass index exceeding 30 kg/m), together with insulin resistance, dyslipidemia, and related conditions, defines "metabolic syndrome," which strongly predisposes suffers to type 2 diabetes, cardiovascular disease, and early mortality [2]. Metabolic syndrome affects 34 percent of Americans, 53 percent of whom are obese [3]. Obesity is a growing concern in developing nations [4,5] and is now one of the leading causes of preventable death worldwide [6].

Logically, a rapid increase in any medical condition should be attributed to envi-

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ronmental changes, yet obesity has been shown in numerous studies to have a strong genetic component [7,8], indicating a potential gene-environment interaction [9]. Curiously, certain populations appear particularly susceptible to obesity and metabolic syndrome [1,10], while others appear resistant [10,11]. The high prevalence of this seemingly detrimental condition, combined with its uneven distribution among both individuals and populations, has led to speculation about potential evolutionary origins of obesity and metabolic syndrome [12-15].

Here I will review several hypotheses (both competing and complementary) for the evolutionary origins of the obesity epidemic and discuss their implications. I argue that a better understanding of the evolutionary forces that have shaped human metabolic control is critical to fighting the modern day obesity epidemic. Understanding the evolutionary origins of obesity can lead to novel approaches for research into the pathophysiology of obesity as well as its clinical management.

WHY CONTROL BODY WEIGHT?

To understand the modern pathophysiology of obesity, it is useful to examine the part that body weight regulation plays in the evolutionary fitness of animals. What forces drive an organism to maintain a minimum or maximum weight limit? It is important to first note that "body weight regulation" is an extremely complex process involving much more than simple metabolic efficiency. It comprises both peripheral and central satiety/hunger signals [16,17] as well as cognitive control [18], all of which are influenced by both genetic and environmental factors.

There are many forces acting to control body weight and adiposity of mammals. The threat of starvation drives the need to maintain a lower limit on body fat. Energy stores are needed to avoid starving to death at any minor disruption in food access. Fertility is also profoundly affected by body fat [19]. Ovarian cycles are very sensitive to energy balance signals [20], and a certain percentage of body fat is needed for female mam-

mals to retain fertility and successfully gestate offspring [19]. Additionally, body fat helps to maintain temperature homeostasis. White adipose tissue acts as an insulator [21], while brown adipose actively contributes to thermogenesis [22].

Several forces maintain the upper boundary of body fat in animals. The time needed to devote to foraging is one. Maintaining high adiposity is energetically costly and requires large caloric input [23]. For most wild animals, far too much time would need to be devoted to foraging at the expense of other important activities such as mating, sleeping, or avoiding predators [23]. Prey animals must remain lean enough to avoid predation. An obese animal cannot move as quickly nor hide as efficiently as a lean animal [24]. It has been demonstrated in laboratory studies that many small prey animals are resistant to diet-induced obesity, even with unlimited access to highly caloric food [25]. In addition, some prey animals have been shown experimentally to reduce body weight when predators are present in their habitat [26,27], presumably to avoid predation.

Modern humans are largely buffered from these factors. Global economies safeguard developed nations from starvation and allow for easy access to highly caloric food. Shelter and clothing protect us from the cold. We are seldom forced to hunt prey, and neither do we worry about becoming prey ourselves [24]. Though modern humans may no longer be subject to these forces, they are still highly relevant to our health. Understanding how these forces contributed to human evolution gives us insight into how human body weight is regulated and what changes need to be made to our societies and health care strategies to better protect against metabolic disease.

ADAPTATIONS FOR THRIFTINESS

The Thrifty Gene Hypothesis

In 1962, geneticist James Neel introduced the first major evolution-based explanation for the modern obesity epidemic [12].

His original hypothesis centered on explaining the unusually high prevalence of diabetes in certain human populations, but has been revised to include both obesity and other components of the metabolic syndrome [28].

Neel argued that the tendency to develop diabetes (or become obese) is an adaptive trait that has become incompatible with modern lifestyles. His "thrifty gene hypothesis (TGH†)" rests on the assumption that during the course of human evolution, humans were constantly subjected to periods of feast and famine. During famines, individuals who had more energy stores were more likely to survive and produce more offspring. Therefore, evolution acted to select for genes that made those who possessed them highly efficient at storing fat during times of plenty. In modern industrialized societies where feasts are common and famines rare, this evolutionary adaptation becomes maladaptive. Thus, there is a mismatch between the environment in which humans live and the environment in which we evolved. Thrifty genes act to efficiently store energy to prepare for a famine that never comes [12].

The TGH provides a simple and elegant explanation for the modern obesity epidemic and was quickly embraced by scientists and lay people alike. Some evidence supports this hypothesis. An important implication of the TGH is that identifiable genetic polymorphisms that confer a "thrifty" phenotype should exist. Both obesity and diabetes are known to have a strong genetic component [7,8,29,30], and several genetic polymorphisms have been found that predispose individuals to obesity [31,32], suggesting potential components of the "thrifty genotype." Many single nucleotide polymorphisms (SNPs) associated with increased risk of obesity have now been identified through genome-wide association (GWA) studies, though each has relatively small effect [13].

One main criticism to the thrifty gene hypothesis is that it is unable to explain the heterogeneity of diabetes and obesity between and within populations [33]. If the cycle of feast and famine was an important driving force throughout all of human evolution, why are not all humans obese? Human populations show great differences in their susceptibility to obesity and diabetes [1,10]. Further, even within populations living in the same environments there are many individuals who appear to be resistant to obesity [34]. To address this shortcoming, Andrew Prentice later proposed that rather than famine being an "ever present" selective pressure throughout human evolution, it is only much more recently, in the approximately 10,000 years since the advent of agriculture, that famine has become a major selective pressure, and as such it's possible that there hasn't been sufficient time for thrifty genes to reach fixation [35]. Hunter-gatherer societies, the main lifestyle of archaic humans, do not often experience famine because their mobility and flexibility allows them to move or utilize alternative food sources when they encounter environmental hardship [36]. In contrast, agriculturalists exploit relatively few staple crops and have less flexibility to handle droughts and other calamities. Thus, the feast/famine cycle may have selected for thrifty genes only in agricultural societies [36]. This could explain why not all humans become obese and why there is variation between populations. Some populations may have experienced more famine or periods of food scarcity throughout their history and thus had more pressure to develop a thrifty genotype.

The TGH provides several testable predictions. One such prediction, if the post-agricultural model is assumed, is that genetic loci associated with obesity and diabetes should show characteristic signs of recent positive selection. However, a study by Southam et al. (2007) testing 13 obesity- and 17 type 2 diabetes-associated genetic variants (comprising a comprehensive list of the most well-established obesity- and diabetes-associated loci at the time of publication) found little evidence for recent positive selection [37]. This study found only one risk loci, a mutation in the obesity-associated FTO gene, showing evidence for recent

positive selection. This would appear to mainly be evidence against the TGH; however, it relied on SNP data, and so these loci may only be associative rather than functional. Refinement of the genetics of obesity and diabetes risk should result in more informative tests for selection.

Another prediction of the post-agricultural TGH is that populations that have historically encountered more famine and food scarcity should be more prone to obesity and diabetes once exposed to an obesogenic environment. So far, there is mixed evidence for this prediction. Some hunter-gatherer populations, for whom famine would have been historically uncommon, seem to show some resistance to diet-induced obesity [35] compared to populations with a history of agriculture, which is consistent with the TGH's predictions. However, this model also predicts that agricultural societies, particularly those from colder climates, would have experienced the strongest selective pressures for genetic thriftiness and thus be particularly prone to obesity and type 2 diabetes. Europe is a prime example of this type of environment: Its peoples have long been practicing agriculture, and the historical record for war and famine in this region is long and extensive [38]. Yet Europeans have a lower rate of obesity than many populations and seem partially resistant to type 2 diabetes [10,11]. Pacific Islanders, in contrast, have some of the highest rates of obesity and type 2 diabetes in the world [10], despite living in a tropical climate with very little history of famine [15,38].

Some researchers explain these discrepancies by taking a flipped view of the TGH, arguing that instead of recent selection for thrifty genes, it is actually genes conferring resistance to obesity and other metabolic disorders that are a modern adaptation. This modified TGH posits that adaptations for thriftiness are ancient, but populations that have switched to richer food sources since the advent of agriculture have gained some adaptations to prevent metabolic disorders. Riccardo Baschetti's genetically unknown foods hypothesis argues that Europeans have become partially

adapted to a diabetogenic diet [38]. Introduction of a European-style diet to populations that are not used to it, such as Native Americans and Pacific Islanders, creates a mismatch between their modern diet and the diet they have evolved with, leading to metabolic dysfunction. This potentially explains the recent dramatic increase in diabetes and obesity in these populations. Others suggest that loss of thriftiness is a recent adaptation, causing differences in the prevalence of metabolic disease between populations [39]. Instead of searching for disease-risk genes conferring susceptibility to metabolic disease, we should instead focus efforts on finding genetic variants conferring resistance to these disorders [39]. The study by Southam et al. found evidence of recent positive selection on one allele that is protective against diabetes [37]. A large-scale study searching for signs of recent positive selection on diabetes and obesity resistance alleles could be fruitful to test these hypotheses.

In terms of clinical management of obesity and other metabolic disorders, the TGH implies that a return to the traditional lifestyle of a population would be beneficial for treating the metabolic syndrome. If obesity is caused by a mismatch between our genes and the environment we currently live in, changing the environment to match how our genomes have adapted should reverse the obesity epidemic. Obviously, returning to the traditional hunter-gather lifestyles of our ancestors is not practical. However, it is possible to restrict calories and increase exercise to more closely mimic various traditional lifestyles [40]. Current medical guidelines for the management of obesity and diabetes are based on this strategy [41,42]. Though this strategy seems to work for some patients, there is much variability in its efficacy, especially in managing obesity and diabetes long-term [43,44].

The Thrifty Phenotype Hypothesis

Not all researchers were convinced that the TGH satisfactorily explained the etiology of obesity and metabolic syndrome. In 1992, Charles Hales and David Barker pro-

posed his "thrifty phenotype hypothesis" (also sometimes called the Barker Hypothesis), partly to address the inadequacies of gene-based obesity hypotheses such as TGH and also to explain an observed phenomenon: that babies with low birth weight seem particularly prone to diabetes, obesity, heart disease, and other metabolic disorders later in life [45].

Barker's hypothesis centers on the concept of "thriftiness," but in a much different way than Neel's hypothesis. In Barker's hypothesis, it is the developing fetus that must be thrifty. An undernourished fetus must allocate resources carefully if it is to survive to birth and adulthood. Barker argues that the developing fetus, when faced with an energy shortage, will allocate energy away from the pancreas in favor of other tissues such as the brain. This is a reasonable tradeoff, since if the same nutritional environment in which the fetus develops persists into its childhood and adult life, there will be little need for well-developed glucose-response systems. However, if nutrition improves later in life, the individual who once had a thrifty fetus will possess a pancreas ill-equipped to deal with the glucose energy it now has access to and will be prone to developing diabetes and other metabolic diseases. This could explain why babies with low birth weight seem particularly prone to adulthood metabolic disorders [45].

Barker's original hypothesis does not specifically address evolutionary history, but it does have evolutionary implications. In this hypothesis, it is genes allowing completion of prenatal development and survival of the fetus that are selected for, rather than adaptive capability in adult life. It is only because in the past prenatal nutrition matched adulthood nutrition that this process was adaptive. Now that this is often not the case, this allocation of resources away from the pancreas becomes maladaptive.

Since its proposal, the thrifty phenotype hypothesis has inspired much further work connecting the hypothesis to evolutionary theory. Jonathan Wells reviewed several competing or complementary models for the evolutionary uses of the thrifty phenotype

hypotheses in 2007 [14]. These models generally fall into two categories: weather forecast models and maternal fitness models.

Weather forecast models argue that the fetus uses signals from the *in utero* environment — particularly nutritional signals — to "predict" what kind of environment it is likely to encounter during childhood and/or adult life. It can be argued that it is evolutionarily advantageous to "prime" metabolic systems for thriftiness if poor nutrition is sensed early in life, in order to better deal with a lifetime of poor nutrition. Metabolic disorders then occur if the adult or childhood environment and fetal environment are mismatched. An individual whose fetal environment "predicted" a lifetime of starvation will readily develop diabetes and obesity when he or she encounters a high caloric diet [14,46,47]. Although this family of models can explain the rapid onset of the obesity epidemic in cultures suddenly introduced to Western diets, it does not adequately explain why obesity and diabetes persist after subsequent generations.

Maternal fitness models argue that the signals a fetus receives about nutrition in the womb allow it to align its energy needs with its mother's ability to supply during childhood. Humans have an unusually long period of childhood growth, during which time children are nearly completely dependent on their mother for resources, even beyond weaning. It is therefore adaptive to both mother and child if the child's metabolic demand is synchronized with the mother's own phenotype, so that the child will not require more (or less) than she can provide. Aligning infant and maternal metabolism eases parent-offspring conflict and is important for the successful rearing of the child [14,48], and thus this adaptation enhances inclusive fitness. This thrifty phenotype model could explain why obesity is possible even when a fetus is not malnourished.

The implications of the thrifty phenotype hypotheses for clinical management of the metabolic syndrome are clear: Proper maternal and gestational nutrition are much more important than interventions in adult life. If the thrifty phenotype hypothesis is

correct, focusing preventive public health resources on pregnant woman will do much more to combat the obesity epidemic than focusing on treating disease in adults or even children.

The Thrifty Epigenome Hypothesis

One of the main criticisms of the TGH is that if famine were such a strong driving force throughout human evolution, why do not all humans become obese? As mentioned earlier, proponents of the TGH often argue that perhaps famine only became a strong selective pressure since the rise of agriculture and, therefore, only certain populations have been subject to this kind of selective pressure [49]. Richard Stöger's "thrifty epigenome" hypothesis takes the opposite view and argues that all humans harbor a thrifty genome. In fact, he argues that food scarcity has likely been one of the key evolutionary forces throughout all the history of life, and metabolic thrift is likely a feature of all organisms. Stöger's hypothesis sets out to reconcile some of the holes in the thrifty genotype hypothesis while integrating it with the thrifty phenotype hypotheses [50].

Stöger's hypothesis relies on the concept of genetic canalization. Genetic canalization is a process through which a polygenic phenotype becomes "buffered" against genetic polymorphism and environmental variation. This process is adaptive because fluctuating environmental pressures can leave subsequent generations unfit for their new environment. Thus, the long-term evolutionary history of the species selects for a multigenetic system in which small mutations make little difference in overall phenotypic expression [51]. One potential way that species are able to maintain this kind of phenotypic robustness is through epigenetic regulation [50].

Stöger argues that metabolic thrift has been subject to genetic canalization and is a phenotypic trait that is able to adjust to differing environmental pressures through epigenetic modification. All humans have a thrifty genome, but phenotypic expression can vary based on environmental input due to epigenetic modifications inherited across generations. Thus, a generation born during a time of famine may have epigenetic genome modifications that allow for more efficient energy storage, and these modifications can be passed down through the germ line. Evidence from the "Dutch Hunger Winter" study supports this. This study tracked the health of a cohort of males born before, after, and during a severe famine that occurred in the Netherlands during World War II [52]. The study found that males whose mothers had experienced famine during the first two trimesters of pregnancy had a much higher rate of obesity and diabetes than males born before or after the famine [53]. Importantly, many of the traits of the Dutch famine cohort have passed down to subsequent generations, leading to the hypothesis that this cohort was subject to some kind of epigenetic modification affecting body weight and can thus be said to have a "thrifty epigenotype" [50]. To test this hypothesis, Tobi et al. (2009) examined methylation patterns in individuals conceived during or shortly before the 1944 famine and compared them to their un-exposed same-sex siblings [54]. They found changes in the pattern of DNA methylation of several growth and metabolism-associated loci in famine-exposed individuals, providing support for the hypothesis that *in utero* nutritional environment can induce epigenetic modifications [54].

Likewise, a generation born during times of great food excess should be programmed for this environmental condition and thus less prone to obesity. Stöger argues that this is exactly what is beginning to happen among the Nauru people of the South Pacific. This population is believed to have encountered repeated bouts of food scarcity throughout history and currently has one of the highest obesity and diabetes rates in the world, indicating that they have a "thrifty genotype." However, in recent years, this trend has begun to reverse, with the rate of type 2 diabetes falling, despite little change in diet or lifestyle. Stöger argues that the Nauruans are beginning to transition to a "feast epigenotype" [50].

An important implication of this hypothesis is that genetic polymorphisms likely have very little effect on the pathophysiology of obesity. This could be an explanation for why, despite decades of research and countless GWA studies of genetic polymorphism, relatively few genetic variants have been found that are associated with development of obesity or type 2 diabetes. Instead, the thrifty epigenome hypothesis implies that GWA studies of epigenetic markers for obesity would be more fruitful.

Additionally, implicit in this hypothesis is the idea that the obesity epidemic will eventually solve itself, if Western diets remain constant. Populations currently experiencing an obesity problem will eventually transition from a thrifty epigenome to a feast epigenome. Recent evidence shows that this transition has already begun. The U.S. obesity rate seems to have leveled off in recent years [34], and worldwide data shows that the rate of childhood obesity has also plateaued [55].

A BEHAVIORAL ADAPTATION

While obesity and metabolic syndrome are often only considered in terms of purely physiological processes and basic survival mechanisms, many others have framed these disorders in a more social context. Mankar (2008) showed that humans associate different adiposity levels with social status [56]. Others argue that during human history, obesity has been a signal for wealth or fertility, allowing those who easily became obese to attract more mates and successfully produce and rear more offspring [57]. Indeed, some of the oldest examples of human art — Paleolithic Venus figurines — depict women with obese bodies and are thought to be fertility symbols [58]. Humans are a highly social species, and thus, social interactions have played a major part in shaping human evolution.

Watve and Yajnik's (2007) "behavioral switch hypothesis" integrates both social and physiological mechanisms into a unified theory for the evolutionary origins of insulin resistance and obesity. It argues that metabolic diseases are byproducts of a socio-ecological adaptation that allows humans to switch between both reproductive and socio-behavioral strategies. The strategies they switch between are r- and K-selected reproduction and "stronger and smarter" lifestyle strategies (which they describe as the "soldier to diplomat" transition). r/K selection theory deals with the concept of parental investment in offspring and the trade-off between quality and quantity. Organisms that practice "r" selection invest more energy into producing many offspring, with less investment into the care of each [59]. It is favored when a species is well below the carrying capacity of their environment [59]. Organisms that practice K-selection invest much time and energy into their offspring, but produce relatively few [59]. It is favored in species close to the carrying capacity of their environment [59]. The authors argue that the environmental and social conditions that favor a "K-selected" reproductive strategy (such as high population density) are the same as those that favor a "diplomat" behavioral strategy (such as food abundance and social competition stress), and insulin has evolved to be a common switch for both these transitions.

In this hypothesis, environmental stimuli such as food abundance, population density, social stressors, and others serve as a single for the body to alter its use of insulin. Their hypothesis hinges on the idea that different tissues have different levels of dependence on insulin for glucose uptake, with skeletal muscle tissue being among the most insulin-dependent and brain and placental tissue being among the most insulin-independent [15]. By decreasing the use of insulin by muscle and other insulin-dependent tissues, insulin resistance frees up energy for use in the brain and/or placenta, facilitating a switch in both behavioral and reproductive strategies. More glucose diverted to the placenta could result in larger infant birth weights and mediate a switch to a K-selected reproductive strategy. Additionally, insulin resistance reduces ovulation, thus resulting in fewer offspring and allowing greater in-

vestment in each. Diverting glucose from muscle tissue to the brain could mediate a switch from a "soldier" to "diplomat" lifestyles. When food is scarce, energy is diverted to the skeletal muscle to enhance foraging ability, so insulin sensitivity would be increased. When food is plentiful, the brain is more important than the muscles to the fitness of a social animal, so insulin sensitivity would decrease in order to allocate more resources to brain development. Insulin signaling in the brain is involved in many cognitive processes. The authors propose that when intense brain activity is needed, plasma levels of insulin increase, allowing for more insulin signaling in the brain. Because high plasma insulin levels can result in hypoglycemia, the body develops peripheral insulin resistance to compensate [15].

The hypothesis suggests an explanation for the association between insulin resistance and morbidity. The authors note that elevated testosterone increases male aggression and is associated with a "soldier" lifestyle, redistributing immune system function to emphasize the sub-cutaneous tissues in anticipation of increased need for wound healing [60]. They posit that the abdominal obesity associated with a transition from a soldier to diplomat lifestyles does the opposite: It redistributes immune function away from the periphery and focuses it on more central tissues. In the exaggerated "diplomat" lifestyles of modern civilization, this redistribution becomes pathological, leading to slowed wound healing and the increased inflammatory response that has been shown to be associated with many disorders of the metabolic syndrome [15]. Importantly, this implies the morbidity of insulin resistance is driven by changes in inflammatory response that are by-products of behavioral transition, not because of insulin itself. If this is true, it has profound implications for the clinical management of insulin resistance and obesity. A focus on controlling the immunological changes that come with the metabolic syndrome could do more to mitigate disease and mortality than attempting to treat obesity or insulin resistance themselves [15].

The behavioral switch hypothesis explains the modern pandemic of metabolic diseases as caused by extreme environmental stimuli: population density, urbanization, social competition, caloric access, and sedentary lifestyles exaggerated to an extent never before seen in human history [15]. As with the "thrifty" family of hypotheses, physiological responses that were adaptive in the past have become maladaptive in modern environments. This implies a clinical and epidemiological management strategy much different from the standard care guidelines. The hypothesis strongly suggests that social reforms will be critical to combatting obesity and metabolic syndrome as a pandemic. The hypothesis predicts that obesity and diabetes should be more prevalent in areas with higher population densities and with greater socioeconomic competition [15]. Reducing overcrowding in urban areas and alleviating social competition by reducing wealth gaps and making societies more egalitarian might affect this out-of-control insulin response.

NON-ADAPTIVE ORIGINS OF OBESITY

While all other explanations so far offered in this review have relied on the assumption that obesity was once an adaptive mechanism of our evolutionary past, biologist John Speakman argues in his "drifty gene hypothesis" just the opposite: that obesity is non-adaptive and has risen to high frequency through neutral (i.e., random, non-selective) evolutionary processes [9,24,33].

Speakman's hypothesis is offered as a direct alternative to Neel's hypothesis. Through statistical models, he argues that if the feast/famine cycle was an "ever-present" driving force of human evolution, as the original TGH argued, even small selective advantages for increased adiposity would have resulted in near fixation in all humans over 2 million years of human evolution [13]. If this version of the TGH is accurate, Speakman argues, all humans would be obese. However, even in the highly obeso-

geneic environments of modern industrialized nations, only a fraction of the population is obese, while others seem resistant to obesity [33]. Indeed, as mentioned previously, the obesity rate in the United States has stalled recently [34]. A possible explanation is that all people who are prone to obesity have already become obese, leaving no room for further growth. Alternatively, Speakman argues that if thriftiness is a post-agricultural adaptation, as Prentice and others argue [49], not enough time has passed to explain the extent of the modern obesity epidemic, given the small contribution to adiposity conferred by the obesity-associated genes identified thus far.

Speakman also argues that the TGH's feast/famine cycle is not historically accurate. He notes that while periods of minor food scarcity are relatively common, these periods do not result in increased mortality. True famines that result in high mortality have been relatively rare throughout human history, and during these periods the greatest mortality is among the very old and very young and thus unlikely to be a strong evolutionary force [9].

Speakman argues that freedom from selective constraint over high adiposity, not adaptation, is a better model to explain the current prevalence of obesity in modern society. To explain what could have allowed this freedom from selective constraint, Speakman offers a "predation-release" hypothesis. It has been shown that predation-threat impacts weight regulation in prey animals. Prey mammals reduce body size and foraging time when predators are present [26,27]. When predators are experimentally excluded from an area, bank and prairie voles increase their body weight compared to controls [27]. In the laboratory, these same animals decrease their body mass when exposed to feces from a predator, but not feces from a non-predator [24,27]. This is thought to protect against predation, since smaller animals are able to move faster, fit into a greater number of hideaways, and make for less appealing prey targets [24].

In the past, archaic humans were also subject to strong predation pressure [61].

However, beginning approximately 2 million years ago with the rise of the Homo genus, archaic humans developed larger body size, increased intelligence, tool use, and were largely no longer subject to predation pressure [24]. Speakman argues that because predation was no longer important, there was no more strong selective pressure to remain lean. Thus, genes controlling the upper limit of body weight in humans were freed from selective constraint and subject to genetic drift. This allowed mutations to occur freely in these genes, resulting in their function being lost or reduced in some individuals and populations [33]. Speakman argues that genetic drift is a better explanation for the variability seen in human body weight than adaptation-based models.

Speakman's hypothesis has been criticized on a few points, most notably in failing to take into account the profound impact that famine has on fertility. In direct rebuttal to Speakman's hypothesis, Prentice et al. (2008) [35] agreed with Speakman that mortality during famine was not great enough to drive evolution of a thrifty genotype, but argued instead that the profound effect that starvation has on female fertility drove selection for metabolic thriftiness. They point out that near-complete suppression of fertility has been observed in historical severe famines and that fertility can be reduced by 30 to 50 percent during normal hungry seasons in modern day Gambia and Bangladesh [35]. Thus, the TGH could still be viable, because metabolic thriftiness increases inclusive fitness. Speakman has countered these arguments by noting that after periods of famine, there is often a "bounce-back" in fertility, with an increase in conceptions occurring to make up for the period of low fertility during the famine [13,33].

Despite the controversy, this hypothesis has intriguing implications for the study of human obesity. If mechanisms once existed in humans who suppressed weight gain in response to predators, finding similar mechanisms in animals may lead to identification of human genes and metabolic mechanisms responsible for the control of body weight and the variation we see in populations. True

Table 1. Summary of evolutionary hypotheses for the metabolic syndrome.

Name		Proposed by	Description	Sources
Thrifty gene hypothesis		James Neel	Repeated exposure to famine led to positive selection for genes promoting efficient energy storage.	[12,28]
Thrifty phenotype hypotheses	Barker hypothesis	Charles Hales and David Barker	An undernourished fetus must be "thrifty" with its resources, and sacrifices pancreas development in favor of other tissues.	[45]
	Weather Forecast model	Patrick Bateson	Fetal environment predicts the quality of the childhood environment. Mismatches between fetal and childhood environments lead to disease.	[14,46]
	Maternal Fitness model	Jonathan Wells	Fetal environment uses nutritional signals to align its metabolism with its mothers.	[14,48]
	Intergenerational phenotypic inertia model	Christopher Kuzawa	Intrauterine nutritional signals provide information about long-term nutritional history of the mother and her recent ancestors through epigenetic mechanisms.	[14,62]
	Predictive adaptive response model	Peter Gluckman and Mark Hanson	Fetal environment predicts adult environment and primes metabolism for adult life.	[14,47]
Thrifty epigenome hypothesis		Reinhard Stöger	All humans have a thrifty genotype. Phenotypic expression of this is altered by epigenetic modifications that respond to environmental conditions.	[50]
Behavioral switch hypothesis		Milind Watve and Chittaranjan Yajnik	Insulin resistance is a mechanism for both a switch between r/K reproductive strategies and a switch between soldier/diplomat behavioral strategies.	[15]
Aggression control hypothesis		Prakakta Belsare et al.	Insulin and satiety mediate aggressive and non-aggressive lifestyle strategies.	[63]
Drifty gene/predation release		John Speakman	Genes controlling the upper limit of body weight have been freed from selective constrain and subject to genetic drift.	[9,24,33]
Maladaptation to brown adipose tissue requirement		John Speakman	Obesity is a byproduct of variation in positive selection for thermogenesis.	[13]
Genetically unknown foods hypothesis		Riccardo Baschetti	Obesity and diabetes occurs when populations are introduced to new foods that they haven't adapted to.	[38]
Fertility first hypothesis		Stephen Corbett et al.	Fertility, rather than starvation, is the main driver of selection for thrifty phenotypes.	[64]

or not, Speakman's hypothesis highlights the need for a better understanding of body weight regulation in other animals with a range of evolutionary histories in order to truly understand the origins of human obesity.

In terms of clinical implications, if obesity is the result of deleterious mutations and genetic drift, rather than an ingrained adaptive mechanism, it can be treated like a heterogenic disease. Insights from studying how lean people (and other animals) regulate their body weight can help identify which genes have been mutated in obese individuals. Speakman's hypothesis would predict that many different systems in weight regulation might have suffered loss-of-function mutations due to genetic drift, and different systems may be affected in different individuals. Modern science is rapidly approaching the era of personal genetics. If the genetics of the control of body weight limit were well understood, weight management interventions could be tailored to an individual based on his or her individual genetic profile. For example, weight management strategies would be very different for someone whose obesity was caused by an underlying genetic problem with control of food intake versus someone who had a genetic defect in metabolic rate.

CONCLUSIONS

In this review, I have discussed several prominent competing hypotheses for the evolutionary origins of the obesity epidemic. They are summarized in Table 1, with additional hypotheses listed for reader interest. These hypotheses appear disparate, but are not necessarily incompatible. The thrifty epigenome hypothesis is a bridge between the thrifty gene and thrifty phenotype hypotheses. It offers a mechanism by which thrifty phenotypes work to shape metabolism *in utero*, while making the same assumptions about evolutionary forces on the genome that the TGH posits. The behavioral switch hypothesis is also not incompatible with the thrifty family of hypotheses. Food scarcity pressures (or lack thereof) are an

important factor in mediating the switch between reproductive and lifestyle strategies. Food scarcity favors a "soldier" lifestyle, while food abundance favors a "diplomat" lifestyle. Metabolic thriftiness is still an important evolutionary force in the behavioral switch hypothesis. Finally, despite the fact that the drifty gene hypothesis was formed to directly challenge the TGH, it is possible for elements of both hypotheses to be accurate. Selection for thrifty genes could have been accelerated in a predation-release/freedom from selective constraint scenario. In the distant past, a balance may have existed between metabolic thriftiness and weight-control to avoid predation, which may have limited selection for thrifty genes. Once predator threat was eliminated and there was no more selection for leanness, it would be possible for selection for thriftiness to take off.

Though there is room for more than one hypothesis to be correct, it is still important to determine the accurate evolutionary origins of obesity. Despite very little rigorous research to back it up, both researchers and the general public have largely accepted the TGH. As a result, many assumptions have been made about the causes of obesity based on the TGH, which have highly influenced research and clinical management of obesity and diabetes. Substantial research funds have been poured into finding the elusive "thrifty" genes that would explain the extent of the obesity epidemic, yet those that have been found either explain obesity in only a very small fraction of the population or increase risk of obesity by extremely small measures. A more rigorous examination of the validity of the TGH could lead to a more directed and efficient approach to the etiology of obesity. Each hypothesis I have discussed suggests very different research strategies.

Finally, the evolutionary mechanisms that allow for obesity are highly relevant to clinical and public health management of the epidemic. The TGH suggests that simple changes in diet and exercise should prevent obesity, and while this intuitively makes sense, we know that this strategy is easier

said than done. Although correction of the "mismatch" between the environment in which humans evolved and our modern environment could conceivably combat the obesity epidemic according to most of the hypotheses discussed, other hypotheses provide much different and more specific strategies into the treatment and prevention of obesity then does the TGH. The drifty gene hypothesis implies that a more disease-based strategy focusing on individual genetic history is needed to treat obesity. Both the thrifty phenotype and thrifty epigenome hypotheses put emphasis on *in utero* nutrition and imply that lifestyle changes made during adulthood are largely futile. These hypotheses have particular importance to fighting the rise of obesity in the developing world. Finally, the behavioral switch hypothesis suggests a radically different treatment strategy for type 2 diabetes and obesity, with emphasis largely on fighting inflammatory response, rather than these disorders themselves. Additionally, the behavioral switch hypothesis suggests that sweeping social and economic reforms will reduce the underlying causes of the obesity epidemic and halt its growth.

While all of these strategies for clinic management are not incompatible and could certainly be applied in parallel, given the limited resources of global health care facilities, it is clear that further research is needed to tailor treatments and find those that will prove most effective. Far from being a simple academic pursuit, the study of human evolution is critically important to the health of modern humans.

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