Thrifty genes for obesity and the metabolic syndrome - time to call off the search?

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Abstract

Over the last 50 years there has been a major epidemic of obesity and associated co-morbidities, the so-called ‘metabolic syndrome’, mostly in the western world but with an increasingly global dimension. The development of such chronic diseases has a strong genetic component, yet the timescale of their increase cannot reflect a population genetic change. Consequently, the most accepted model is that obesity and its sequelae are a result of a gene-environment interaction, an ancient genetic selection to deposit fat efficiently that is maladaptive in modern society. Why we have this genetic predisposition has been a matter of much speculation.

Following the seminal contribution of Neel,1 there has been a broad consensus that over evolutionary time we have been exposed to regular periods of famine, during which fatter individuals would have enjoyed a selective advantage by their greater survival. Consequently, individuals with genes promoting the efficient deposition of fat during periods between famines (‘thrifty genes’) would be favoured. In the modern environment this genetic predisposition prepares us for a famine that never comes, and an epidemic of obesity with all the attendant chronic illnesses follows.

In this review I present details of the evidence supporting the famine hypothesis and then show that this idea has five fundamental flaws. In essence, famines are a relatively modern phenomenon and occur only about once every 100–150 years. Consequently, most human populations have only experienced at most 100 famine events in their evolutionary history. Famines involve increases in total mortality that only rarely exceed 10% of the population. Moreover, most people in famines die of disease rather than starvation and the age distribution of mortality during famine would not result in differential mortality between lean and obese individuals. A simple genetic model shows that famines provide insufficient selective advantage over an insufficient time period for a thrifty gene to have any penetration in the modern human population.

Over the 40 or so years since Neel proposed the thrifty gene hypothesis, no convincing candidates for these genes have been discovered. My analysis suggests that perhaps it is time to call off the search.

Key words: obesity, famine, thrifty genes, mortality.

Introduction

The epidemic of obesity and the metabolic syndrome that is sweeping through western society is characterised by two important factors. First, it has occurred rapidly. The timescale is so short that large-scale changes in the genetic structure of the population cannot be an explanation. Nevertheless, the second point is the seemingly conflicting finding that individual variation in both obesity and its sequelae has a very high genetic component. The inevitable conclusion is that obesity and the chronic conditions that come with it result from a gene/environment interaction.2,3 Individuals appear to have a genetic predisposition to become obese which is particularly expressed in the modern environment, where it is maladaptive.

Several previous researchers have speculated about the evolutionary processes that may generate this genetic predisposition. Probably the first exposition of these ideas was Neel,1 who suggested that diabetes and obesity stemmed from natural selection on our ancient ancestors favouring a ‘thrifty genotype’ that enabled highly efficient storage of fat during periods of food abundance. Neel argued that such a genotype would be extremely advantageous for primitive man, who was exposed to periods of food shortage, because it would allow them to deposit fat stores efficiently and thus survive subsequent periods of food shortage. In modern society, however, where food supply is almost always available, this thrifty genotype proves deleterious because it promotes efficient storage of fat in preparation for a period of shortage that never comes. The development of insulin resistance was seen as part of this adaptive ‘thrifty genotype’, helping early humans with the process of efficient fat deposition.

This original idea has been heavily promoted in many papers as a plausible evolutionary scenario.4-11 In these papers the critical role that has been played by historical periods of famine in the process of selection is strongly reiterated.

My aim in this review is to challenge the orthodox opinion that famine and food shortage have been a significant
force in the process of moulding our genetic predisposition to obesity and the metabolic syndrome. I will first present the evidence that has been suggested to support the famine hypothesis. I will then highlight several fundamental flaws in the famine argument. I do not wish to imply that the metabolic syndrome and obesity have no gene/environment interaction at their base: my contention is that the genetic predisposition must have come about in a manner other than selection favouring efficient fat deposition during periods between famines. Searching for ‘thrifty genes’ favouring this process may then be a rather empty exercise. I am not the first to suggest that thrifty genes may not exist, although the reasons presented here are different.

The famine hypothesis – supportive evidence

Famine has been a common feature of human history for a long time, and during famine individuals face enormous deprivation and increased mortality. Prentice et al. enumerated many records of famine that date back to 5,000 years ago. Moreover, it is clear that famine continues to affect contemporary human populations. It is argued that such an ubiquitous and persistent force of nature must have had profound effects on the process of human evolution for up to 50,000 years, although others claim its effect stretches back only about 6,000 years.

The evolution of an advantageous allele depends on the intensity of selection (differential mortality with respect to the trait it codes for) and the frequency at which such selective events takes place. The frequency of famines depends on an extent on definitions, but periods of starvation due to natural shortages of food supply appear to occur frequently. Keys et al. for example, suggest that historically in Britain periods of severe food deprivation occurred about once every 10 years. Depending on one’s viewpoint of how long famine has been a significant process, this suggests between 600 and 5,000 selection events that have moulded the modern human genome.

That individuals involved in famines undergo extreme deprivation and suffering is also beyond doubt. Prentice et al. and Prentice have documented many instances of individuals resorting to cannibalisation of their own children during famines. Since individuals are unlikely to sacrifice their own children unless they are under extreme risk of mortality themselves, the argument is advanced that not only is famine a common event but that the level of selection during famine must be intense. Some estimates of maximal mortality during famines indicate between 25% and 60% of individuals may have died. For example, in the great famine in Finland in 1696 between 25% and 33% are said to have perished. Perhaps the highest estimate comes for the Italian famine of 1376, where two-thirds of the population are supposed to have died.

We have very little direct evidence that this mortality during famine falls differentially on the lean. Theoretically, however, this should be the case because individuals who are obese store much greater amounts of energy and, despite burning energy at a faster rate, the time period that a fatter person can survive in the total absence of food is in theory longer. Data concerning the time that people of different body weights survive under conditions of total food abstinence are available from measurements made on people engaged in political hunger strikes. These studies confirm that individuals who are fatter at the start of a complete fast live longer.

Given these rough parameters, how realistic is it to expect the evolution of thrifty genes during only 600 to 5,000 famine events? I have recently modelled the penetration of an advantageous recessive allele (a thrifty gene) that occurs as a single mutation in one individual in a population of five million individuals, which is a realistic estimate for the paleolithic world population, assuming that the recessive homozygotic genotype (aa) confers a 3% increase in survival during famine and the heterozygote provides a 1.5% increase in survival. From a single mutation in a population of five million individuals, the thrifty gene would entirely replace the alternative ‘unthrifty’ allele after about 950 famine events. This model shows that even if the selection favouring a thrifty gene that confers efficient fat deposition is small (the homozygotic aa genotype, having only a 3% mortality advantage over the AA genotype), it would still spread through a population after far fewer famine events than are speculated to have happened since the early paleolithic (although not more than have been speculated to have occurred since the start of the neolithic).

Some problems

The simple modelling of speed at which a ‘thrifty gene’ would spread in a population under the repeated famine scenario seems to support the famine hypothesis for the genetic disposition to obesity. In the second part of this review I will outline five fundamental problems with the ‘famine hypothesis’.

The extent of mortality during famine and the frequency of famine are insufficient

Although stories of eating their own children indicate the desperation that famine victims endure, this information is not necessarily related to the key aspect of importance in terms of the evolutionary significance of famine: the effect it has on rates of mortality. Estimates of mortality in ancient famines are generally vague, imprecise and unsupported by documentary evidence. It is only since the 1800s that well supported estimates of numbers of people dying during famines have been generated. However, translating even these more reliable figures into mortality statistics is beset with difficulty. Numbers that die are frequently reported, but the population they stem from are not. As a general trend, as the area involved in the estimates gets smaller, the estimated mortality gets larger. Larger areas are more likely closed to emigration and famines are generally limited in their geographical extent. When sensible bounds are set on the affected area by a famine and comparisons are made between periods involving famine and periods of intervening feast, then the total rates of mortality for most famines are generally under 10% per annum, and more often than not even this figure is inflated by emigration.

The frequency of famines depends to an extent on the inclusion criteria for what constitutes a famine. Keys et al.
identified 190 famines that occurred in Britain over 2,000 years, giving a rough occurrence rate of one famine per 10 years. It is clear, however, that not all of these involved the same duration of food shortage or levels of mortality. In fact, severe mortality crises in Europe (defined as crises leading to significant increases in mortality in a given year relative to the baseline over the previous 10 years) only occurred about once per century. Consequently, when more reliable data are considered, famine is actually quite a rare event, and when it does occur the mortality impact is relatively low.

The historical pattern of famine occurrence is incompatible with other aspects of the hypothesis. Although it has been suggested that famine is a feature of our history stretching back to the earliest part of the paleolithic 50,000 years ago, famine is actually more likely a phenomenon born of the age of agriculture. As pointed out by Prentice, it is widely accepted that pre-neolithic hunter-gathering communities were probably far less prone to famine because they exploited a range of food types and had the mobility to follow food resources. Once agriculture and stable communities developed, however, large populations became dependent on agricultural crop production. Since crop production is sensitive to weather patterns, adverse weather events could cause severe problems. However, there is a broad school of thought which suggests that most famine events have very little to do with natural factors interfering with food production patterns, and much more to do with societal factors leading to inequable distribution of resources – the so-called ‘entitlement hypothesis’.

Such causes for famine can only occur after the emergence of quite sophisticated societies. Prentice therefore considered that famine has basically only been an important evolutionary phenomenon for the last 6,000 years or so. Using this estimate suggests that most human populations have probably only experienced 60 or so famine events in their history.

Relatively few people in famines die of starvation. It may come as a surprise to discover that during most famines relatively few people die from frank starvation – that is, depleting their body reserves to the point where they run out of energy. Perhaps the most comprehensive data available on causes of mortality during famine come from the Irish potato famine (1845–50). During these famine years the potato crop was devastated by an infection of the potato blight fungus. In 1841 the population of Ireland was just over 8.17 million. In 1851, after the famine, the population was about 6.55 million. By factoring in the likely population increase between 1841 and the start of the famine in 1846, and also accounting for the 925,000 people who are estimated to have emigrated away from Ireland during the famine years, the mortality has been estimated at slightly over one million people. This matches closely the records of 985,000 deaths documented in mortality statistics meticulously compiled in the immediate post-famine period.

These data provide a comprehensive picture of the major causes of mortality during one of the most serious famine events ever reported. In fact mortality during the worst famine years averaged 17.3% per annum, compared with only 5.3% in the pre-famine period. During 1847, the recorded deaths numbered 250,000 yet only 6,000 were attributed to starvation. Consequently, although the mortality directly attributable to the famine (excess deaths above background) was 12% of the population per annum, only 5% of these deaths could be attributed directly to starvation. Stavation-induced mortality during the peak famine years was therefore only about 0.6% of the population per annum.

The major factors causing death during famine are infectious diseases and diarrhoea. Of the 985,000 deaths in Ireland, 23% were attributed to fever (probably typhoid) and approximately 35% were caused by diarrhoea and dysentery. During 1849 the major cause of mortality included an epidemic of cholera.

The Irish famine is far from unique. Data on cause of death are available from many other famines and the patterns are all similar. Starvation generally results in less than 25% of the observed mortality. Infectious disease and diarrhoea make up the vast majority of the effect. Infectious diseases, rather than starvation, cause mortality in famines because of radical differences in the situation between people voluntarily starving themselves to death to make a political statement and people who face externally imposed food shortages (natural or man-made) but do not wish to die. In these latter conditions people try to find food; in the former they do not.

Problems arise because people in famines who are facing starvation become relatively unselective in their food choices – eating tree bark, weeds and various other plants that they would not normally select. Moreover, people will readily eat decomposing carrion and even corpses. This shift in food choice has several major consequences. Many people die during famine of direct poisoning from eating poisonous plants. Second, eating decomposing carrion or corpses can lead to intestinal infections and diarrhoea. Third, the decline in food nutritional quality (vitamins and micronutrients) may lead to a decrease in immunocompetence and hence the ability to fight off infectious disease. Individual immunosuppression, however, may be less significant during famine than a general breakdown in sanitary conditions. This is at least partly because people move to search for food and become disconnected from fixed assets that are a necessary part of good hygiene (such as water and sinks).

Although most people in famine do not die because of starvation, it could be argued that lean people would be more likely to succumb to these problems because their need to feed would be greater because of their lower energy reserves. Lean people might therefore be more prone to poison themselves accidentally, or to resort to eating bad food which leads to gut problems. Therefore, while mortality is not caused primarily by frank starvation, there might still be a mortality bias in this additional mortality favouring selection for ‘thrifty genes’. A bias in mortality towards lean people because they are ‘more hungry’ and hence more likely to make poor food choices seems improbable, however. There is no evidence that perceptions of hunger that drive people to feed are greater in the lean than the obese. In fact, absolute energy demands and food intake are greater the
larger a person is. If hunger is driven by a shortfall in intake relative to demands then one would predict that hunger would actually be greater in the obese.

The role of individual immunosuppression in the spread of infectious disease is another area where it might be argued that the immune system would become more rapidly compartmented in a lean compared with an obese person. Yet the association of immune status to body weight is confounded by the co-variation of low body weight and malnutrition (low nutrient intake). If the absence of essential minerals and vitamins underlies the poor immune status of famine victims, rather than low fat mass, then there is no reason to suspect lean subjects would be more disease-prone than the obese.

The burden of mortality in famines affects the wrong individuals for there to be selection for energy efficiency

Although we have no direct information about the variation in mortality during famines with respect to the body mass index, we do have information with respect to other parameters such as age. Demographic studies of mortality in famine almost universally show that the burden of mortality falls disproportionately on the young (< 5 years old) and the old (> 60 years old). A well documented example is the change in mortality in relation to age during the Bangladesh famine in the 1970s (figure 1). For the youngest age group mortality increased by 6-8%, and in the older individuals by 3-5%, but for individuals in their late teens and early twenties mortality was virtually unaffected. This variation in mortality reflects the fact that most people who die during famine conditions die of infectious diseases and it is the very young and the old that are most susceptible to death from these causes.

This pattern of mortality is a fatal blow for the famine hypothesis. Any mortality in the post-reproductive elderly is completely unimportant in terms of its impact on selection. Childhood mortality might be more significant. However, it is very unlikely to be biased with respect to obesity simply because until recently obesity in this age class was virtually unknown. The key group in which differential mortality might have some impact because the individuals involved may exhibit a substantial variation in their phenotype and still have reproductive investments to make are exactly the people who remain virtually unaffected by the impact of famine mortality.

The prevalence of obesity between famines is too low. Even if famines are much more serious and frequent than I have suggested, if the famine argument is correct that in hunter-gatherer and subsistence agriculture communities there is strong selection for ‘thrift genes’, then during periods when these communities are not experiencing famine, individuals should become obese – their thrifty genes will ensure this. Although hunter-gathering has largely died out as a lifestyle there are still many communities in the third world subsisting on agriculture, using practices that have remained effectively unchanged for thousands of years. Yet, despite being in non-famine conditions, the body mass index (BMI) of individuals from these populations always ranges from 17.5 to 21.0 – at the very lean end of normal. Clearly these individuals have not inherited the supposed thrifty genes that predispose them to weight gain and obesity during periods between famines. The empirical data therefore support the modelling, which suggests that famines are an insufficient selective force to result in the evolution of thrifty genes (and incidentally that any other force has generated genes that make individuals fat between famines).

Summary
In summary, I have highlighted five fundamental problems with the suggestion that the modern obesity epidemic has at its core a mismatch between an ancient metabolism finely tuned to cope with an environment characterised by periodic famine, and a modern environment where opportunities to prepare for famine are plenty but the famine never comes.

The problems are that severe famines involving significant mortality are rare events, probably occurring less than once every 100 years, and are a phenomenon of advanced agriculture-based societies.

Most human populations have experienced probably fewer than 60 significant famine events in their history.

Even in the worst famines mortality seldom exceeds 10% per annum, and of that figure probably only 5-20% is due to actual starvation. Consequently, excess mortality attributable to starvation during famines rarely exceeds 2% per annum once per century.

Almost all this mortality is restricted to the very young and very old, which is probably incompatible with a distribution of mortality favouring obese over lean subjects.

Finally, the prevalence of obesity between famines is low. Population genetic models suggest that given these parame-
ters thrifty genes would not have had sufficient advantage or
time to spread in the human population. This is compatible
with empirical observations that hunter-gatherer and subsis-
tence agriculture communities universally have very lean
phenotypes during periods between famines – indicating
they do not have ‘thrifty genes’ helping them to deposit fat
stores in preparation for any forthcoming period of famine.
Prentice has pointed out that although more than 40 years
have elapsed since Neel first advanced the ‘thrifty gene'
hypothesis, no actual thrifty genes have yet been discovered.
My analysis suggests that perhaps it is time to call off the
search.

Conflict of interest
Author to declare.

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