Obesity in Emerging Nations: Evolutionary Origins and the Impact of a Rapid Nutrition Transition

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Abstract
Here we explore whether there is any evidence that the rapid development of the obesity epidemic in emerging nations, and its unusual coexistence with malnutrition, may have evolutionary origins that make such populations especially vulnerable to the obesogenic conditions accompanying the nutrition transition. It is concluded that any selection of so-called ‘thrifty genes’ is likely to have affected most races due to the frequency and ubiquity of famines and seasonal food shortages in ancient populations. Although it remains a useful stimulus for research, the thrifty gene hypothesis remains a theoretical construct that so far lacks any concrete examples. There is currently little evidence that the ancestral genomes of native Asian or African populations carry particular risk alleles for obesity. Interestingly, however, there is evidence that a variant allele of the FTO gene that favors leanness may be less active in Asians or Africans. There is also some evidence that Caucasians may be less prone to developing type 2 diabetes mellitus than other races suggesting that there has been recent selection of protective alleles. In the near future, recently developed statistical methods for comparing genome-wide data across populations are likely to reveal or refute the presence of any thrifty genes and might indicate mechanisms of vulnerability.

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Introduction
There are many obvious and plausible reasons (and some less obvious ones) that may account for the rapid increase in obesity rates in developing and emerging nations. Changes in diet and activity patterns brought about by the economic transition have been previously discussed in this symposium by Popkin [1]. Later papers will explore the possibility that undernutrition
in fetal and early life can reset the metabolic phenotype in ways that make people especially vulnerable to the influences of an obesogenic environment if they escape from the frugality of a subsistence living [2, 3].

Here we seek to answer whether people from developing countries may have a genetic predisposition to obesity and its most common clinical outcome, type 2 diabetes mellitus (T2DM).

**Possibility of Evolutionary Selection of Genes Predisposing Populations to Obesity**

The concept of ‘thrifty genes’, first proposed by Neel [4] in the 1960s, has been prominent amongst the various theories proposed to explain the sudden rise in global obesity levels in the late 20th century. The basic premise of the thrifty gene hypothesis is that an ability to rapidly deposit energy as body fat in times of plenty would have assisted individuals to survive periods of starvation, and hence would have been under positive natural selection. Many of the earlier proponents of the theory used it to explain why certain populations had very high levels of obesity and diabetes. For instance, it was suggested that modern Polynesian Islanders are the product of a small founder group that had survived starvation during the long sea journeys across the Pacific as the islands were first colonized. The survivors of these journeys, it was argued, would either have started off as fatter individuals, or would have had mechanisms for conserving their energy when food supplies ran out. Similar arguments have been used as a possible explanation for the high rates of diabetes in the Pima Indians in Arizona, where there is evidence that their forebears may have suffered a famine that greatly depleted a formerly large population [5]. These simplistic interpretations were not those intended by Neel himself whose original theory focused more on the likely mechanism than on the theory’s evolutionary origins.

Contemporary interpretations of the evolutionary and ecological implications of the thrifty gene story reappear at frequent intervals. Elsewhere [6–8] I have proposed some modifications to the widely accepted interpretations of Neel’s original theory which can be summarized as follows.

First, there is abundant historical evidence to support the view that almost all ancient populations have been frequently subjected to selective pressure by famine. Paradoxically such cataclysmic events have been much more common in the past 10,000–12,000 years because the dawn of agriculture permitted the growth of large populations, but also made them vulnerable to climatic and political instability that would have had little significance for hunter-gatherer groups. Agriculture also led to annual hungry seasons in most traditional populations which can also have a selective effect (see below). These arguments suggest that thriftiness, in whatever biological form it might take, is likely to affect all racial groups. Thriftiness is no more likely
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Second, the evidence suggests that transmission of thrifty traits is unlikely to have been strongly selected by mortality within famines (viability selection) and is much more likely to have been due to fertility selection mediated through the powerful effects of regular annual hungry seasons, or episodic starvation, on female fecundity. We have shown in both Bangladesh and The Gambia that birth frequencies show a smooth sinusoidal variation with a two-fold amplitude between peaks and troughs [6]. The data from these and other populations [9] suggest that the variation is driven by a suppression of the hypothalamic-pituitary-ovarian axis when women lose weight in the hungry season. Women who can remain fertile when their peers have stopped ovulating have a greater chance of transmitting their genes and of passing on this trait, which could be considered a form of thriftiness. Modeling such effects easily demonstrates that fertility selection could have had a powerful impact in the 600 or so generations since agriculture started.

Thirdly, we believe that the concept of thriftiness (which is generally interpreted in relation to the saving of energy) should also encompass an element of the ‘greedy gene’ since disregulated appetite control systems are the most
common cause of the genetically based human obesity syndromes so far identified [10]. In primitive conditions, where post-harvest crop losses are high due to inadequate storage systems, it has been calculated that it can be more efficient to store energy in subcutaneous fat rather than to leave crops vulnerable to attack by vermin, insects or moulds. Such a strategy also avoids pressure to share food with others when supplies dwindle in the hungry season. These responses reveal body fat acting as nature intended (fig. 2), namely as a metabolic buffer when external energy supplies are beneath subsistence levels. This adaptation has now become largely redundant in modern societies since the hungry seasons that used to regularly deplete body fat stores seldom, if ever, occur. Hence the famous title of Neel's [4] original paper: Diabetes mellitus: a ‘thrifty’ genotype rendered detrimental by ‘progress’.

**Absence of Evidence for Obesity Susceptibility Genes in Different Populations Groups**

The fact that certain population groups are highly susceptible to obesity suggests the presence of genetic factors but does not in itself provide any proof of that fact. The most intensively studied group has been the Pima Indians, noted for their very high rates of obesity and T2DM. Extensive genetic analysis of candidate genes known to be involved in susceptibility to obesity at the individual level in various population groups has yielded little evidence in support of a clear genetic susceptibility for Pima Indians as a whole [11–14]. There is similarly a notable absence of publications claiming robust identification of possible ‘thrifty’ alleles in other obesity-prone populations such as in Nauru.

Recent findings in relation to the FTO gene (the first of the multigenic contributors to human obesity to be identified with certainty [15,16]) reveal some interesting new clues. An FTO variant has been shown, across numerous studies to affect BMI. The effect size is small (at about 0.35 BMI units per
copy) but has been confirmed to a very high degree of statistical certainty in several European, Caucasian-American and Hispanic-American populations. The variant allele promotes leanness, not obesity, and hence it is the wild-type that represents the thrifty form. Interestingly our research indicates that the same variant has no effect in native Africans [Fulford, et al., unpublished data] and others have also failed to replicate the findings in non-Caucasians, albeit on small sample sizes. This offers some initial support for the possibility, based on the historical ubiquity of famines and food shortages described above, that most human populations carry genetic mechanisms for thrift.

Although relating to diabetes, rather than obesity per se, there is some evidence that non-Caucasians are more vulnerable to T2DM [17]. It has been controversially suggested by Diamond [17] that susceptible individuals within Caucasian populations must have died out during a previous epidemic of obesity, but no historical evidence supports such a view and it is possible to suggest more cogent mechanisms, based on fertility selection, for their relative protection against T2DM. The likelihood that Caucasians are somewhat protected from T2DM is further suggested by analysis of admixture among the Pima Indians which shows an inverse relationship between the degree of European admixture and susceptibility to T2DM; in other words the greater the proportion of European genes, the lower will be the risk of T2DM [18].

In summary, the concept of the thrifty gene remains nebulous and intangible, and there is very little concrete evidence that even the most obesity-prone populations have any clear-cut genetic susceptibility to obesity, though they may be more prone to diabetes. This has led Joffe and Zimmet [19] to argue that the thrifty phenotype is a more likely explanation. Other possibilities are that susceptibility is driven by cultural ‘memes’. Families that have spent generations working extremely hard and consuming a very frugal diet can hardly be blamed for relishing sedentary lifestyles and rich diets when they become available (fig. 3). Such desires are readily apparent among the newly affluent members of developing country societies, and may be propagated further by the notion that a higher BMI is desirable, particularly for women [20, 21].

**New Methods in Analysis and Interpretation of Data from Genome-Wide Scans**

Exciting times lie ahead with respect to understanding whether or not evolution has endowed any of us with particular susceptibility to obesity and/or diabetes. First the increasing speed and decreasing cost of genome-wide scans have recently opened up the study of multigenic disorders [22]. In 2007, 11 new genes linked to T2DM were added to the 3 that had previously been identified. Second, advances in bioinformatics and the development of new statistical methods using a variety of methods to interrogate haplotype
patterns now permit us to test whether individual gene variants have been the subject of recent selective pressure [23, 24]. Similar advances in methods for comparing genome-wide scans between different ethnic/racial groups are starting to pinpoint those genes that show evidence of geographic diversity, and of recent differential selection within each of the major racial groups [25, 26]. Together these new approaches will soon assist in resolving the issues surrounding putative thrifty genes and other evolutionary influences on the obesity epidemic.

**Is Understanding the Evolutionary Origins of Obesity Important?**

Many readers could be forgiven for asking: So what? Is it really important to understand whether or not different populations have a genetically endowed enhanced risk of becoming fat and contracting the associated chronic diseases? One argument in favor of seeking such knowledge is that it might help to direct interventions. Table 1 lists the primary domains through which thriftiness might operate. Some of them (those listed as metabolic, physiologic and adipogenic) may be non-modifiable except through pharmacologic intervention, but the behavioral domains would be amenable to intervention.
and distinguishing the relative importance of these might therefore be useful. However, the absence of certainty on any of these issues should never inhibit the development and propagation of public health messages and government initiatives to combat obesity. We already have strong evidence that urban populations in developing countries do exhibit high levels of obesity, and this fact alone should drive the public health agenda.

**References**


| Table 1. Examples of the possible manifestations of ‘thriftiness’ |
|-----------------------------|-----------------------------|
| Metabolic | ‘Energy-sparing’ super-efficient metabolism |
| Adipogenic | Propensity to rapidly deposit fat |
| Physiological | Ability to switch off less-essential processes (e.g. adaptive immunity in the short-term) |
| Gluttony | Tendency to gorge when food is available |
| Slothfulness | Tendency to conserve energy through inactivity |
| Behavioral | Hoarding, meanness, theft, etc. |
Discussion

Dr. Raju: One thing about the Western population, the Caucasians, is that the incidence of diabetes is very low. Is there a possibility that over a period of several thousands of years they had their share of obesity epidemics and got rid of all those people who have a tendency to become obese and do you think they are more refined and adapted to the modern environment?

Dr. Prentice: That's a very good question. You are, I think, alluding to a paper by Diamond [1] in 2003 in which he described the double puzzle of diabetes. Diamond argues first that diabetes rates for a given level of obesity tend to be lower in Caucasians. His suggestion is that this must have been caused by a previous epidemic of obesity which allowed selection to occur. Now there I disagree profoundly with Diamond. I really cannot see that having been the case. I think there is no historical evidence. The argument that we have made is that actually it is not postnatal viability selection, it is prenatal selection [2]. A colleague, Stephen Corbett from Sydney, has written a paper, which is under review at the moment, suggesting that this may be tied up with fertility selection and polycystic ovary syndrome is part of this story. It may be that insulin sensitivity and resistance were crucial to determining which women would conceive at which BMI and during which periods in the past, and that diabetes may actually be an accidental sequel of a selection that has selected people differently in European and Asian and African populations and which leads to differential susceptibility to diabetes.

Dr. Haschke: Very interesting information on the famine risk in populations living on agricultural products as opposed to the hunting population. What about populations living in coastal areas because this was the first area where people survived.
There should be minimum famine risk. Did you find anything in the literature about the selectivity of change in these populations?

*Dr. Prentice:* I am not aware of anything.

*Dr. Popkin:* The lactase gene story is interesting. According to research, 6,000 years ago Northern Europeans adjusted to deal with the lactase enzyme in milk. 3,000 years ago they did that in Southern Africa. We don't really know how long it took in each of these populations to create these genetic adjustments. But does this history give us any hope that perhaps a gene will develop in South Asia so that people will survive with diabetes and be healthy and so forth?

*Dr. Prentice:* I think there is hope. It is interesting that, as you suggested, there is evidence for independent selection of lactase persistence in both Europe and Africa [3]. Estimates of the time scale for these genetic changes are difficult because they compare the changes within the lactase persistence gene to background variations. First we don't have a good measure of that background; what the natural mutation rate is. Secondly we would have to know how fast populations reproduced, but most importantly the mathematics is profoundly changed by population size and by population growth. So without being able to figure out how populations have changed, it is going to be very difficult to give this an absolute number. So we don't know how fast these things have occurred but I would argue that they probably can occur very fast and I think now we are getting into populations where the obesity rate is so great that it is starting to impact quite significantly on reproductive fitness, and that ultimately may cause a fairly rapid selection of protective genes.

*Dr. Whitelaw:* I was very interested to see your data about the 9-month lag. As a biologist who often deals with animals and even plants, have you considered the possibility that this is a response to the changes in light/dark cycles and seasonal events that are not necessarily about the availability of food but about other cues that change each year, certainly with mice and certainly with plants, which are known to have long-term effects?

*Dr. Prentice:* We have. The first thing we can say is that if this was driven by light/dark cycles then we would expect to see this phenomenon in almost all populations – we don’t. The phenomenon only occurs in populations where there is seasonal food availability. We tried to look at folate supply and other possibly significant variables such as the frequency and timing of husbands migrating away from the village. It does seem that it is probably very strongly driven by their energy status. We have got data which have also been submitted for publication showing that twinning rates change very radically in these two populations and the increase is in advance of the conception of singletons. This shows us some very clever biology. The woman is able to recognize very quickly when the harvest comes in. Then she is in a good nutritional state and is more likely to conceive twins. This phenomenon may help us to understand why twinning persists in the human genome.

*Dr. Ravussin:* Speakman [4] has challenged the thrifty genotype and has proposed that a genetic drift over many generations is sufficient to explain the variability in BMI. I'm not siding with Speakman, but on the other hand some geneticists have tried to simulate this, not only with one gene as Speakman did but with many genes, and they also explain this variability as just a random genetic drift over thousands of generations. What is your answer to that?

*Dr. Prentice:* First of all I would like to say very clearly that I have no definitive answer. As you know I happen to disagree with Speakman and I don't think it is genetic drift. But perhaps he is right; it is intriguing. The answer, I think, will be out within the next 2 years. As you say there are some very clever geneticists doing a lot of modeling at the moment with a lot of data which is going to give us those answers fairly soon.
Dr. Chittal: With the idea that the thrifty gene was indeed determining the survival of the fittest, maybe it should be survival of the fattest. The same gene in times of abundance, could it be a process of natural selection of disasters for the fattest? Is it in any way trying to restrain the human population from overrunning the earth? Is it possible that it is the same gene which is causing destruction now? Do genes work that way? At one time it will be survival, at another time it will be destruction.

Dr. Prentice: I think that would be very difficult to argue. I am going to be very cautious in my response and probably there is someone in the audience who could respond much better. The general thesis I think is that most genetic selection has to occur at the individual level rather than at the population level, and of course there is an interrelationship between those, but I think it would be difficult to model a scenario where what you suggested was true.

Dr. Ray: What is the genetic relation between leptin deficiency and genes?

Dr. Prentice: Leptin deficiency in humans is extraordinarily rare. Dr. Ravussin will probably give me an update on the numbers but I think there are less than 20 individuals in the whole world who are known to have a monogenic leptin deficiency. They are all the offspring of first-cousin marriages, so it is an extraordinarily rare defect which, under most circumstances, is not fatal, but the offspring of those marriages are non-reproductive.

Dr. Ray: Is there any autosomal recessive inheritance?

Dr. Prentice: There is a little bit of evidence I think that it may be beneficial in the heterozygote form.

Dr. Jaigirdar: Bangladesh is a country of disaster, famine, flood, and it is one of the mostly densely populated countries in the world. Don’t you think that it satisfies your thrifty gene idea?

Dr. Prentice: I have a lecture I give to the students which is called ‘Reproduction against the Odds’. I start off pointing out this paradox that the world’s fastest reproductive growth rates are in the most undernourished populations. It is amazing. How do we do it? We are a very efficient species in terms of our ability to reproduce when the chips are down. So yes, I think in a way it is a measure of our thriftiness, but I caution against moving from that general statement, to a specific statement about thrifty genes.

Dr. Popkin: Related to that, I wanted just to follow up with an issue. In India perhaps a third of adult women in rural areas have BMIs of <17.5 and very high reproductive efficiency, and high low birthweight rates as well. Does that fit into the talk about the fact that in India and even in South Asia there has been a shift over in the BMI–reproduction ratio for biological adaptation? The BMI is at such a low level that it has to play some role when a BMI of 20 is seen in Ranjan, a body fat level that is equal to a BMI of 35 in the US.

Dr. Prentice: Exactly. This is precisely the thesis that Prof. Stephen Corbett has submitted. Data from the Nurses’ Health Study show that there is a U-shaped curve between BMI and fertility in the US, and it’s actually a very sharp optimal fertility at a BMI of around 21–22. If a woman is too thin of course we know she will become anovulatory, etc., but also if a woman is too fat, she will also stop reproducing efficiently. Leptin is probably the key driver here; Indians with abdominal obesity even at very low BMI have higher leptin levels, so that story would fit together exactly as you suggested that this is an adaptation to remain fertile under highly energetically deficient conditions.

Dr. Yajnik: This brings us to comparing BMI across populations. We know this is influenced by adiposity. Recently we compared the whole body MRIs of Indian newborns with those of Caucasian newborns. Although lighter by 800 g, the Indian baby has comparable body fat and higher intra-abdominal fat (submitted for publication).
We have also shown that the cord blood leptin concentrations are higher in Indian babies compared with white babies, even after correction for birthweight [5], and adiponectin concentrations are lower. This means the adipocyte function is also different. This might be related to an epigenetic rather than a structural change.

Dr. Prentice: A very important question for which I don’t know the answer. We look forward to learning about that in the years to come.

Dr. Raju: You said something tantalizing about whether it is normal to be thrifty or unthrifty. You also said something about being very unthrifty and probably you were referring to oxidative phosphorylase decoupling or whatever, and about human migration up to colder altitudes, thermogenesis. Is that what you are referring to?

Dr. Prentice: Partly those. You have picked up on an important point. There are people who suggest that a high level of mitochondrial fatty acid turnover is important in terms of quenching oxidative damage in the mitochondria; there are people who maintain the other view, and we will be hearing some of that no doubt from Dr. Ravussin in terms of caloric restriction. You have also mentioned the issue of northern latitudes and we can see some evidence of variations in mitochondrial DNA which would support that story. Another important one is the ability to concentrate nutrients, so if you are on a nutrient-poor diet you may need to eat a lot of that food in order to get enough micronutrients, so the trick of being able to burn off calories but hang on to the micronutrients would also be an important adaptation.

References
