Evidence increasingly suggests that ethnic differences in cardiovascular risk are partly mediated by adipose tissue biology, which refers to the regional distribution of adipose tissue and its differential metabolic activity. This paper proposes a novel evolutionary hypothesis for ethnic genetic variability in adipose tissue biology. Whereas medical interest focuses on the harmful effect of excess fat, the value of adipose tissue is greatest during chronic energy insufficiency. Following Neel’s influential paper on the thrifty genotype, proposed to have been favoured by exposure to cycles of feast and famine, much effort has been devoted to searching for genetic markers of ‘thrifty metabolism’. However, whether famine-induced starvation was the primary selective pressure on adipose tissue biology has been questioned, while the notion that fat primarily represents a buffer against starvation appears inconsistent with historical records of mortality during famines. This paper reviews evidence for the role played by adipose tissue in immune function and proposes that adipose tissue biology responds to selective pressures acting through infectious disease. Different diseases activate the immune system in different ways and induce different metabolic costs. It is hypothesized that exposure to different infectious disease burdens has favoured ethnic genetic variability in the anatomical location of, and metabolic profile of, adipose tissue depots.

Keywords Adipose tissue, obesity, cardiovascular disease risk, ethnicity, adaptation, human evolution

Introduction
Cardiovascular risk is increased in South Asians compared with Europeans. Adipose tissue biology, which refers to the amount, regional distribution and metabolic activity of adipose tissue, is increasingly considered to account for some of this risk. For a given body weight, South Asians have more body fat, including visceral fat, compared with Europeans. However, this difference is merely part of a broader range of variability between populations in the relationship between weight and adiposity, in adipose tissue distribution and in the relationship between adipose tissue depots and metabolic risk.

From an evolutionary perspective, adipose tissue comprises a store of energy representing the generic strategy of ‘thrift’, but recent research also emphasizes its role as a regulatory organ. Subtle variability in the regional distribution of adipose tissue, and in its metabolic sensitivity, may be considered as the adaptation of these combined traits to local conditions. However, the dominant paradigm simply considers fat as protection against the negative energy balance induced by starvation, despite little evidence...
supporting this hypothesis, and insufficient attention has been directed to accounting for population genetic variability in adipose tissue biology.

The aims of this article are several. First, different biological models of thrift are briefly reviewed. These are relevant to the different models of adiposity considered below. Second, the fitness value of adipose tissue is described, specifying the different biological functions of energy stores in humans. Third, previously published hypotheses for ethnic differences in adiposity are reviewed. Fourth, adipose tissue is discussed within the framework of trade-offs between competing biological functions. Fifth, the role played by adipose tissue in immune function is discussed in greater detail. Finally, ethnic variability in adipose tissue biology is considered in relation to the hypothesis that natural selection may have favoured the emergence of such variability through the stress of infectious disease.

Biological models of thrift

The influential ‘thrifty genotype’ hypothesis proposed selection favouring metabolic thrift in ancestral populations exposed to regular ‘cycles of feast and famine’. The genetic factors underlying such thrift would then predispose to diseases such as obesity and type 2 diabetes when exposed to the abundant food supplies and sedentism characteristic of the modern Western lifestyle. Contemporary population variability in susceptibility to type 2 diabetes may indeed derive in part from genetic factors. Geneticists have identified a variety of polymorphisms attributed to local selective pressures deriving from particular ecological or agricultural circumstances, which must have emerged since the evolution of Homo sapiens and which are one plausible explanation for ethnic variability in adipose tissue biology.

However, population variability in the prevalence of type 2 diabetes and obesity could also derive from cumulative environmental experience in recent generations, rather than the inheritance of genetic factors. Foetal exposure to maternal type 2 diabetes is strongly predictive of the offspring developing the same disease, along with obesity. More generally, developmental plasticity is increasingly understood to play a key role in the ontogenetic development of body composition and obesity susceptibility. Plausible underlying mechanisms include hormonal programming or epigenetic modifications of DNA expression.

In both models, the profile of adiposity in one generation is considered to be influenced by the experience of previous generations. The key difference comprises the timescale over which the ancestral legacy has accumulated—transgenerational phenotypic plasticity operates over a substantially shorter time-scale than genetic selection and may respond to quite transient pressures. Both models are likely to be relevant in explaining ethnic variability in adipose tissue biology and distinguishing their relative importance is currently an important research priority. This paper addresses the genetic level of adaptation and hence seeks to generate a new hypothesis regarding the selective pressures that might have favoured genetic variation in adipose tissue biology across different ecosystems.

The fitness value of adipose tissue

Adipose tissue is a specialized physical manifestation of pursuing a strategy of storing energy. Such a strategy benefits a number of different biological functions, described in detail previously, which may be briefly summarized as follows. First, adipose tissue clearly represents a store of energy capable of accommodating fluctuations in energy supply, including severe famine. Second, adipose tissue contributes to mechanisms regulating female reproductive function. In particular, the hormone leptin produced by adipose tissue acts on the availability of oxidisable fuels, which are the fundamental components of the mechanism. The contribution of leptin to this mechanism generates associations between reproductive capacity and energy stores, although lipid stores are not themselves the fundamental constraint. Third, adipose tissue provides a store of energy for buffering the obligatory and high requirements of the large human brain. This need, especially in early life, when the brain comprises the majority of body weight, favours large energy stores in the neonate and infant and also in the reproducing female to supply this energy to the offspring. Fourth, adipose tissue contributes to the energy required for infant and child growth. Fifth, adipose tissue provides energy for the immune system, now known to have a significant energy cost. Sixth, adipose tissue is subject to sexual selection, contributing to reproductive fitness by affecting mating opportunities as well as physiological function. Seventh, adipose tissue is more than just an energy store. Traditionally, lean mass has been regarded as the metabolically active tissue and lipid as an inert fuel depot. Recent research has challenged this by demonstrating adipose tissue to be the source of a number of proteins such as leptin and cytokines that impact on a wide range of physiological processes and target tissues.

To the extent that ethnic differences in adipose tissue biology derive from genetic factors, population variability must be related to differential exposure to selective pressures acting on one or more of these functions in the context of local ecological conditions. The alternative model that ethnic variability derives from more transient environmental exposures by non-genetic adaptations will be considered elsewhere.

Previous evolutionary models of ethnic variability in adiposity

Several evolutionary models have been put forward in order to account for ethnic variability in adiposity. First, the greater susceptibility to obesity of populations...
such as Pima Indians and Cook Islanders has been attributed to harsh selective pressures during the migration of their ancestors to their current territory. Proposed migrations of ancestors of the Pima Indians across the Bering Strait and of the Cook Islanders and other South Pacific populations in long canoe voyages have been proposed to have resulted in selection for thrifty genes.\textsuperscript{11} Recent studies have suggested that this hypothesis may apply more broadly, in view of evidence of genetic differences in metabolism,\textsuperscript{13} some of which have been linked with climatic variability.\textsuperscript{19} However, while genetic variability in metabolism undoubtedly impacts on body fat content, it may be less relevant to adipose tissue distribution and biology, which are the primary target of this paper.

Second, Sniderman and colleagues\textsuperscript{20} have suggested that ethnic differences in fat distribution derive from an inability of South Asians to deposit as much fat in subcutaneous depots as can Europeans. According to their model, this leads to the excess energy ‘overflowing’ into the visceral depot, which subsequently proves particularly harmful to health. Such a hypothesis requires an underlying constraint, which these authors suggest might be heat stress.

Third, in a commentary on this hypothesis, I suggested that rather than the subcutaneous fatness of South Asians being constrained, the allocation of energy to the visceral fat depot may rather be \textit{favoured} during undernutrition.\textsuperscript{21} Since South Asians have been subjected to regular famines,\textsuperscript{22} selective pressures might have acted on genetic or epigenetic factors underlying the sensitivity of this allocation mechanism. This hypothesis was only briefly sketched out and is developed in greater detail below.

Such a model departs from the conventional ‘thrifty gene’ approach by incorporating the notion of trade-offs between competing tissues. A similar approach, though not directed at ethnicity per se, was described by Watve and Yajnik.\textsuperscript{23} These authors suggested the relative allocation of energy to fat vs lean tissue to be a function of population density. Below, I discuss how the energy stores maintained in adipose tissue are subject to trade-offs between competing biological functions.

### Adipose tissue and functional trade-offs

Energy allocation strategies have rarely received attention from the biomedical community.\textsuperscript{23} Most work on visceral adipose tissue, for example, has involved quantifying the health risks of those overweight or obese. Whilst clearly relevant to the identification of those at risk, and the development of treatment strategies, this is inappropriate for elucidating the broader functions of adipose tissue.

Before describing trade-offs relating to adipose tissue, it is critical to distinguish the \textit{strategy of allocating energy to storage from the strategy of accumulating large fat depots}. The first strategy only results in the second during sustained positive energy balance. Prior to agriculture, energy expenditure on subsistence effort would have been displaced in time from energy intake. Individuals would regularly have experienced transient fluctuations between positive and negative energy balance and fat and glycogen stores would have fluctuated concomitantly. Since the emergence of agriculture, some individuals have been able to access plentiful food with minimal physical effort and accumulate substantial fat stores, most notably in the contemporary obesity epidemic.

Trade-offs in energy allocation are addressed by life history theory, focusing on the hypothesis that limited resources are subject to competing needs, with natural selection favouring the optimal allocation strategy.\textsuperscript{24} In this case, organisms must initially either use or store incoming energy (Figure 1). If energy is stored, the organism must further allocate it between competing targets: for example, structural protein in organs or muscles, or fuel depots. These targets may be considered to contribute in different ways to survival or reproduction, for example vital organs represent infrastructure, muscle mass represents work capacity and glycogen and adipose tissue represent

![Figure 1 Competing targets for dietary energy intake.](https://academic.oup.com/ije/article-abstract/38/1/63/694434)
short- and long-term fuel depots. The optimum allocation between these ends trades off short-term survival against longer term investment in reproduction. The notion of trade-offs is equally applicable to negative as well as positive energy balance, with weight loss favouring selective preservation of specific tissues or fuel depots. The organism can therefore prioritize different strategic energy allocation or tissue maintenance according to circumstances.

Factors influencing the optimum allocation strategy may include age, gender, body size, growth rate, current energy stores and reproductive status. First, differences in energy allocation are clearly illustrated in the growth process. Once normal growth has ceased, the majority of storage energy is allocated to fat or reproduction, unless vigorous exercise is performed. Second, the sexes pursue different allocation strategies, evident from foetal life onwards but becoming substantially stronger during puberty. The sexes also contrast in their allocation between competing adipose tissue depots, with younger females allocating substantially more energy to peripheral subcutaneous depots. In later life, female strategy alters and energy shifts from peripheral to central depots. Physical exercise is an important mediator of allocation strategy, targeting muscle mass, basal metabolism and glycogen stores at the expense of abdominal fat.

Allocation strategies are further influenced by nutritional status. Growth-retarded neonates show depleted subcutaneous fat stores but similar intra-abdominal fat to normal-weight neonates. Likewise, women suffering from anorexia nervosa deplete their subcutaneous stores substantially more than their visceral fat but reduce this difference on refeeding. These findings are strongly indicative of a prioritization of the deep-lying adipose depots during malnutrition. Thus the trade-off selected in any given situation reflects the differential benefits of competing functions in promoting survival and reproduction.

During chronic negative energy balance, some functions are ‘put on hold’, whilst other more fundamental functions are prioritized. Evidence from studies of chronic weight loss allows us to differentiate these priorities. Anorexia nervosa results in loss of peripheral fat stores, resulting in the conversion of ‘hourglass’ shape to a tubular form that negates the function of fat in sexual selection. At the same time, negative energy balance interacts with the regulatory mechanism controlling female reproductive biology, reducing the likelihood of conception. Biopsy measurements indicate that the energy cost of lactation are met disproportionately from peripheral fat depots such as the thigh, hence prolonged weight loss reduces breast milk output as well. Sustained negative energy balance therefore either curtails female reproductive function or substantially reduces investment in this end. Childhood growth is also temporarily slowed or halted when energy intake is reduced, until sufficient supply is restored.

Closing down these functions reduces the more fundamental priorities of adipose tissue to two functions: meeting obligatory energy needs and funding the immune system. Support for these functions being prioritized also derives from the fact that both sexes are vulnerable to starvation and disease, whereas the contribution of adipose tissue to reproduction is primarily a female trait. Previously, most evolutionary perspectives have focused on the role of fat in meeting obligatory maintenance needs, on the assumption that the primary risk of mortality occurs through starvation. The role of fat in immune function has only recently attracted attention.

Adipose tissue and immune function

The contribution of energy stores to immune function became clear from early studies noting reduced survival in those of low relative weight. As discussed previously, infection imposes a metabolic burden on account of the need to synthesize immunoglobins and acute phase proteins and other processes such as inflammation and fever. To meet these costs of infection, lipolytic factors such as cortisol, glucagon and various hormones release energy from adipose tissue. The use of energy from fat during infections in infants is demonstrated by ketosis, while cytokines also alter lipid metabolism during infection, increasing triglyceride concentrations as a component of innate immunity. Kuzawa addressed age-specific stresses including disease load in order to account for age-associated variability in human fat patterning. This article uses a similar approach in the context of possible ethnic genetic variability.

More recently, animal studies have clarified the contribution of adipose tissue to immune function. Whereas immune function was once considered to be protected from environmental conditions and to act as a ‘closed circuit’, studies of rodents occupying seasonal environments have elegantly demonstrated its sensitivity to energy availability. Experimental manipulation of body fatness in rodents decreases immune function, while artificial induction of the immune response under conditions of starvation impairs survival in insects. Such work clearly demonstrates the energy costs of responding to infection and expresses them in the primary ‘currency’ of evolution—survival and hence inclusive fitness.

The underlying regulatory mechanisms linking fat and immune function have likewise become clearer following the discovery of the hormone leptin. The immune system is suppressed in leptin-deficient mice, while experimental work on hamsters has shown that exogenous leptin administration counteracts this suppression by providing a false signal of energy availability. The rare condition of genetic leptin deficiency in humans is also associated with
increased vulnerability in infections. Leptin is now understood to control lipoprotein function, acute phase reactants, glucocorticoid metabolism, inflammation and immune function as well as reproduction and hence is key to integrating adipose tissue with competing biological functions.

Finally, the profound impact that HIV/AIDS has on lipid metabolism further highlights the importance of adipose tissue biology in immune function. Both the disease itself and the induction of lipodystrophy by antiretroviral treatment demonstrate the sensitivity of adipose tissue biology to immune system dynamics. The novelty of HIV/AIDS as an ecological stress precludes the possibility of selective pressures having optimized the body’s response in previous generations and offers a useful lens through which to assess the adaptive value of adipose tissue.

Whilst energy is thus critical for immune function, the energetics of immunity is complex. Although some components of the immune system lose efficacy when energy supply is reduced, other aspects are maintained or paradoxically increased and this in turn indicates trade-offs within the immune system. For example, malnourished prisoners experienced substantially lower mortality from diseases such as typhus compared with their guards during the Second World War. Consistent with such findings, there is increasing evidence that immune function tends to be of greater importance for survival during famine than energy stores per se.

**Starvation vs disease as selective pressures**

Accurate interpretation of the effects of famine on human biology requires detailed information about the proportion of individuals dying and the cause of death. Even where records have been compiled, they often suffer from methodological problems. However, recent re-evaluation of the Irish famine during the 19th century has highlighted the contribution of disease, as opposed to starvation, as the principal cause of death. Famines increase the risk of disease through several mechanisms, including reducing quality and quantity of nutritional intake, decreasing the energy available for immune function, increasing exposure to novel pathogens, reducing the facilities available for hygiene and creating favourable conditions for the spread of infectious diseases such as cholera and influenza. Clearly, each famine is different and starvation has sometimes been a more important primary cause of death (see below); however, there is no doubt that the immune system represents a priority function of adipose tissue during malnutrition.

In addition to providing the energy required to mount an immune response, adipose tissue, especially the visceral depot, is increasingly being recognized as the source of cytokines that contribute to inflammation. This is widely interpreted as adipose tissue representing a toxic substance but it may be more appropriate to consider an innate link between allocating energy to the visceral depot and activating immune function to increase protection against infectious diseases. Likewise, at the molecular level it is now recognized that nutrient-sensing and pathogen-sensing pathways have much in common, such that the connection between metabolic and inflammatory responses is fundamental to the ‘mechanistic core of chronic and common metabolic diseases’.

Such a strategy would be beneficial during chronic negative energy balance, allocating energy to maintain the deep-lying adipose tissue depots primarily responsible for supporting immune function and increasing resistance to infection. This perspective is consistent with findings of greater expression of complement genes in the visceral adipose depot than in subcutaneous fat, while animal studies also demonstrate that artificial viral infection increases adiposity.

If we accept that adipose tissue biology is directed primarily towards coordinating trade-offs between survival and reproductive function at the lower end of the range of nutritional status and has undergone millennia of selection within this context, there is no reason to assume that the inherent connection between deep-lying fat depots and inflammation will be altered as body weight accumulates. When individuals minimize the energy demand for exercise or pregnancy/lactation, weight gain will manifest disproportionately as central abdominal fat. In contemporary populations, high levels of central fat generate a state of chronic inflammation, now understood to increase atherosclerotic risk. Importantly, this chronic inflammation can be at least partially reversed through massive weight loss by surgical intervention. Equally, the raised levels of markers of inflammation in South Asians compared with Europeans appear attributable to their increased levels of visceral fat.

**The variable disease selection hypothesis**

If we transpose the notion of a costly immune response into different ecological environments, immune function emerges as a plausible target of local selective pressures, which could generate ethnic genetic variability in adipose tissue biology. This argument is based on the knowledge, as discussed below, that different diseases activate different components of the immune system and these in turn impose different energetic costs.

The obligatory energy needs of essential organs are common to all humans, whereas populations inhabiting different conditions have been exposed to different disease loads. Although visceral fat has
The immune response is composed of several components, which differ in their energetic costs according to the particular disease invoking them. Such costs include immune defence of tissues, repair of damaged tissues, metabolic costs of fever and the production and maintenance of lymphocytes, antibodies and other immune agents. These costs also include the growth and metabolism of the pathogens themselves. Several components of the immune response are adaptive and yet commonly considered indices of disease. Hypertriglyceridaemia is one of the earliest metabolic responses to infection and may contribute not only to the mobilization of energy stores but also to host defence. Fever is considered to provide a number of benefits, but imposes a high cost as each degree centigrade rise in temperature increases metabolic rate by ∼15%. Importantly, this effect is induced not directly by the external pathogen but by the cytokines produced in response to the pathogen’s appearance. Other diseases may induce prioritized defence of the mucosal lining. Thus, the overall energy costs of infectious diseases depend on the sum of these different components.

Diseases vary in their site and level of infection, and hence in their relative demands on specific components of immunity, and therefore are predicted to impose different energetic burdens on the organism. Infections of the gut such as giardia or amoebic dysentery induce a different set of responses compared with plasmodium infections of erythrocytes. The immune response is also understood to be characterized by internal trade-offs, such that only some components are promoted in any given scenario.

The burden of disease is strongly associated with local ecosystems and climatic factors. For example, malaria has long been one of the harshest pressures in Africa but is geographically specific in Asia, whereas cholera, a long-term stress in Asian populations, only reached Africa relatively recently. More generally, the prevalence of gastrointestinal diseases, particularly in children, reflects regional and seasonal climatic factors such as rainfall and temperature.

I hypothesize that the tendencies of African and Asian populations to prioritize the intramuscular and visceral depots of adipose tissue, respectively, may therefore derive from contrasting exposures to fevers vs gastrointestinal infectious diseases as the primary selective pressure. Such adaptations may then predispose to ethnic differences in cytokine biology in contemporary populations.

To illustrate why different diseases might impact on regional adipose tissue distribution and biology, consider the evidence on metabolic differences induced by malaria and gastrointestinal disease. Malaria is associated with increased rates of glucose turnover, which in turn induces hypoglycaemia, increasing the risk of mortality. Malarial toxins contribute directly to this hypoglycaemia by altering insulin signalling, increasing lipogenesis whilst also inhibiting lipolysis. Appreciation of the effects of malarial toxins on insulin metabolism inspired successful attempts to reverse type 2 diabetes in mice. Deep intramuscular adipose tissue might plausibly reflect either the direct allocation of energy stores within muscle tissues in order to ‘fund’ fever or the allocation of energy stores away from other organs that are adversely affected by malaria. In adults with malaria, plasma hypoglycaemia is attributable to increased peripheral glucose uptake, i.e. in muscle tissue.

In malnourished children with diarrhoea, which is often the proximate cause of death, organ-specific malnutrition of the intestinal epithelium occurs. The major respiratory fuel in the small intestine is glutamine; however, during fasting this is supplemented by ketone bodies. The sensitivity of this tissue to energy availability is demonstrated by the fact that refeeding often worsens the diarrhoea due to impaired intestinal ability to control absorption efficiently. The deposition of adipose tissue within the viscera might therefore protect intestinal function and hence represent a plausible adaptation to the selective pressure of gastrointestinal disease.

Clearly diarrhoeal diseases and fevers have a complex global distribution and the optimum allocation of energy to different adipose tissue depots is likely to derive from the relative importance of particular diseases as selective pressures in any given ecosystem. The above examples simply serve to illustrate my hypothesis that where fat is stored in the body may be related to the pattern of infectious disease.

Re-evaluating thrifty genes and thrifty phenotypes

The hypothesis that population genetic variability in adipose tissue biology might relate more to the
epidemiology of disease than that of starvation is consistent with Speakman’s argument that famine-induced starvation was not the primary selective pressure favouring ‘thrift genes’. Disease represents an ever present stress on human populations, merely acting more powerfully during chronic energy insufficiency and particularly strongly on infants and children, whose deaths play a key role in shaping population genetic adaptations. Both malaria and diarrhoeal disease for example are leading causes of mortality in young age groups.

Nevertheless, the possibility that recurring starvation may have shaped adiposity in specific populations should not be discarded entirely. Previously, I suggested that prioritized allocation of energy to visceral fat by South Asians may have been favoured during regular famines. Detailed Victorian censuses indicate that the level of mortality frequently reached 30–40% in the Indian subcontinent and in some cases was recorded at >60%, although imperial economic policies appear greatly to have exacerbated climatic stresses. Regular famines, imposing drastic mortality from starvation rather than disease, may therefore have selected for a more thrifty allocation strategy (i.e. increased prioritization of energy allocation to adipose rather than lean tissue) as well as a more central fat distribution. This might then have contributed to contemporary differences in fat content and distribution for a given level of weight. However, such differences need not necessarily be genetically determined and might instead derive from transgenerational developmental plasticity. For example, females exposed to famine in utero may have managed to survive and reproduce more successfully on exposure to subsequent famines during adulthood. The high body fat content for a given BMI value in South Asians relative to Europeans may reflect their lower birth weight, since low birth weight programmes reduced adult lean mass and hence a higher proportion of fat in weight. Furthermore, both parents may transmit their phenotype to subsequent generations through plasticity.

Both the biological models of thrift described above may apply to this population; hence, ethnic variability in adipose tissue biology should not be assumed to comprise a wholly genetic trait. The aim of this paper has been simply to hypothesize how any genetic component of ethnic variability in adipose tissue biology might have evolved.

Conclusions

This article has presented a novel hypothesis regarding ethnic genetic variability in adipose tissue biology. Population variability in adiposity may therefore be due to (i) genetic factors underlying metabolism, (ii) genetic factors underlying adipose tissue biology and (iii) more recent environmental exposures impacting via non-genetic mechanisms. I suggest that exposure to varying burdens of infectious disease may have been a particularly important selective pressure accounting for gene-based ethnic variability in adipose tissue distribution and hence in the production of cytokines secreted by adipose tissue depots. This hypothesis may be tested by (i) probing in greater detail the extent to which more locally defined populations demonstrate variability in their adipose tissue biology and in their ancestral and recent disease loads and (ii) evolutionary game theory.

References

3. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev 2002;3:141–46.


