Could mitochondrial efficiency explain the susceptibility to adiposity, metabolic syndrome, diabetes and cardiovascular diseases in South Asian populations?

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Background South Asians are susceptible to cardiovascular disease (CVD), especially after migration to affluent countries. Contributing factors include high prevalence of diabetes, and possibly insulin resistance. Excess adiposity centrally may underlie such metabolic disturbances. The thrifty genotype, thrifty phenotype, adipose tissue compartment and variable disease selection hypotheses are among the explanations posed.

Methods Data from individual studies and review articles known to the authors were examined. A Medline bibliographic database search was also performed. Reference lists were reviewed to identify additional relevant data sources. Key references were examined by both authors.

Results We propose, and evaluate, the evidence for a ‘mitochondrial efficiency hypothesis’ i.e. that ancestral changes in mitochondrial coupling efficiency enhanced the successful adaptation of South Asians to environmental stressors by maximizing the conversion of energy to adenosine triphosphate (ATP) rather than heat. This adaptation may be disadvantageous when South Asians are physically inactive and consume high-caloric diets. There is evidence that common mitochondrial mutations vary geographically. Mutations, including those affecting the function of mitochondrial uncoupling proteins (UCPs), may influence the balance of energy and heat production. These may influence basal metabolic rate (BMR), energy efficiency, the tendency to gain weight and hence metabolic disease. UCP gene polymorphisms are related to differences in BMR between African-Americans and Europeans. Similar data for South Asians are lacking but the few studies comparing BMR indicate that South Asians have a lower BMR, which is explained by a lower lean body mass, and higher fat mass. Once adjusted for body composition, BMR is similar. A high fat mass, per se, is a strategy for reducing energy use while conserving body size. Indians in the USA had higher oxidative phosphorylation capacity than Northern European Americans.

Conclusion The evidence justifies full exploration of this mitochondrial efficiency hypothesis in South Asians, which may also be relevant to other warm-climate adapted populations.

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Introduction: the burden of cardiovascular diseases in South Asian populations

About one quarter of the world’s population lives in South Asia (1.5 billion), with an estimate of 25 million outside South Asia. Coronary heart disease (CHD) and stroke are major causes of morbidity and mortality in South Asians (people originating from the Indian subcontinent), particularly after migration to affluent countries. Over recent decades, higher mortality rates from CVD in South Asians compared with European populations have been reported from many countries. In the UK, people born in India, Pakistan and Bangladesh experience ~50% greater mortality from ischaemic heart disease, and about ≥100% mortality from stroke. Similarly, in parts of the Indian subcontinent, CVD has established itself as a major cause of premature death in urban and rural areas following periods of rapid socio-economic development. The Indian subcontinent is presently one of the regions with the highest burden of CVD. In addition to high mortality rates, CHD is diagnosed 5–10 years earlier in South Asians compared with other populations, resulting in comparatively more deaths among those <70 years of age. This earlier onset reflects the average younger age of South Asians, but may also indicate an early onset of atheroma.

Causes of CVDs in South Asians–role of metabolic risk factors and diabetes

The standard causes of CVD, e.g. smoking, hypertension and hypercholesterolaemia, are also important in South Asians. However, the causes of the excess CHD risk in South Asians, especially compared with populations in the countries where South Asians migrate to, are currently not completely understood and remain under intensive study. Specifically, the comparatively higher rates in South Asians have been hard to explain solely on the basis of elevated levels of conventional CHD risk factors including serum cholesterol, smoking and hypertension. For example, a systematic review of the literature reported lower blood pressure levels in South Asians, especially in Bangladeshis who have the highest rate of CHD and stroke. Smoking prevalence is generally lower in most South Asian subgroups (one exception being Bangladeshi men) than in the UK general population, and particularly so in South Asian women. Whereas total cholesterol levels tend to be either lower or similar in South Asians in comparison with the UK Whites, some heterogeneity exists between subgroups. In contrast, the prevalence of impaired glucose tolerance, impaired fasting glucose, metabolic syndrome and diabetes type 2 is increased 3–5-fold in South Asians compared with the UK population. Clustering of other risk factors representative of the metabolic syndrome, including low plasma high-density lipoprotein cholesterol and high plasma triglycerides is also commonly observed in South Asians.

The high prevalence of diabetes, insulin resistance and the related metabolic syndrome in South Asians may predispose to atherosclerosis and CVD, but has not explained the excess compared with White populations in Southall. Important underlying reasons for such metabolic disturbances include excess centrally distributed body fat in South Asians, even with a normal body mass index (BMI). South Asians have, compared with White populations, high body fat in relation to BMI and there is evidence for a stepwise increase in the body fat percentage from rural to urban and migrant populations. This tendency to central adiposity is seen at birth, and in later life. Excess abdominal fat increases the risk of insulin resistance, metabolic syndrome, diabetes and CVD. In mice, in addition to increased adipose tissue mass per se, altered tissue physiology, including impaired adipocyte function or adipose tissue composition or secretory function, is required to induce obesity-related metabolic changes. Despite increasing the fat mass, intra-abdominal transplantation of adipose tissue (from lean littermates to lean recipients) did not produce the metabolic effects of greater visceral fat in obesity. If this applies to humans, it emphasizes the subtleties involved. Why adiposity, and especially central adiposity, and metabolic consequences are so common in South Asians has led to several hypotheses that are discussed below.

Why are South Asians susceptible to central obesity? The thrifty genotype and phenotype, adipose tissue overflow and variable disease selection hypotheses

The storage of energy as body fat is important to survival and critical during periods of food shortage; whether this is cyclical (as in the seasons) or occasional e.g. crop failure or even famine. These general considerations have given rise to the concepts of the thrifty genotype and thrifty phenotype. The thrifty
genotype potentially explains why some populations may be more prone to obesity and central obesity, i.e. their ancestors were subjected to food shortage and hence selected by evolution to store energy as fat, and especially central fat, that can be mobilized quickly to release nutrients. The thrifty phenotype, in contrast, especially central fat, that can be mobilized quickly to hence selected by evolution to store energy as fat, and their ancestors were subjected to food shortage and may be more prone to obesity and central obesity, i.e. genotype potentially explains why some populations hypothesises.26 Sniderman and colleagues developed the ‘adipose tissue compartment overflow hypothesis’ to help focus on why central rather than generalized obesity occurred in South Asians and was metabolically harmful in ways that peripheral obesity was not. The ‘adipose tissue overflow hypothesis’ builds on the premise that South Asians may have a reduced capacity to store fat in the relatively inactive, superficial subcutaneous, adipose tissue (primary adipose tissue compartment), which would result in earlier utilization of more metabolically active, deep subcutaneous, and intra-abdominal, adipose tissue compartments (secondary adipose tissue compartments). This hypothesis would explain why, for example, South Asians had a greater waist to hip ratio or more pronounced atherogenic lipoprotein profile than White people at a similar level of BMI. Moreover, it might also help clarify why the White population seems to be relatively protected from metabolic abnormalities and diabetes compared with non-White populations, including those of South Asian and African origin.

Although the ‘adipose tissue overflow hypothesis’ awaits the challenge of empirical test, its authors proposed an evolutionary basis for the proposed reduced fat storage capacity of the primary adipose tissue compartment in South Asians based on climatic influences impacting on adipose tissue physiology. Wells’s alternative view of the above hypothesis was that South Asians allocate fat disproportionately to the secondary adipose tissue compartments (especially the visceral adipose tissue compartment) because, in the absence of excess weight gain, chronic energy deficiency over evolutionary periods favours a relatively greater allocation to these metabolic compartments. As a result, the ‘El Nino hypothesis’ of Wells suggests that fat metabolism of South Asians has evolved to become more sensitive to fluctuations in energy supply relative to other populations inhabiting more stable environments. This is, therefore, essentially the same concept as Neel’s ‘thrifty gene hypothesis’.26

Well’s more recent ‘variable disease selection hypothesis’ suggests that exposures to different population burdens of infectious diseases (rather than climatic or nutritional exposures per se) cause genetic ethnic variability in the anatomical location of adipose tissue compartments. Two fundamental priorities of adipose tissue include meeting obligatory energy needs of essential organs and immune system maintenance. Adipose-derived hormones such as leptin are highly involved in the regulation of lipoprotein functions and diverse immune system and inflammatory processes. Immune function may be of greater importance for survival during starvation than energy stores alone. The burden of disease (and hence exposure to different disease loads) is likely to vary according to different geographical and climatic factors. As deep adipose tissue depots are more appropriate for meeting the immediate energy demands of the immune system, the tendency of South Asians to prioritize deep visceral adipose tissue depots may therefore have resulted from chronic exposures to geographically specific, endemic diseases, including cholera (e.g. it is possible that following the selective pressure of long-standing gastrointestinal diseases, adipose tissue became to be deposited within the internal viscera for the protection of the intestinal system).

Along with the ‘adipose tissue compartment overflow hypothesis’, this hypothesis offers a novel account of why South Asians are particularly susceptible to central obesity. Although both hypotheses rest on the premise that ethnic differences in adipose tissue distribution result from specific adaptive genetic mutations, they do not pinpoint them. As we suggest below, it is possible that ethnic differences in energy production, allocation and storage and utilization may partly be explained by differences in mitochondrial gene structure and function. If the above hypotheses are correct, then selective evolutionary pressures (whether climatic, nutritional or infectious separately or in combination) acted on a geographically defined population to favour individuals capable of conserving energy in deep visceral adipose tissue depots. How did they conserve the energy? Our ‘mitochondrial efficiency hypothesis’ (which focuses on adaptive mitochondrial changes in energy vs heat production) underpins and extends these observations.

The mitochondrial efficiency hypothesis

Our hypothesis is summarized in Figure 1. Specifically, genetic alterations leading to increased energy vs heat production (i.e. mitochondrial coupling efficiency) would conserve energy. As Mishmar and others have pointed out, this would foster adaptation to different climates.
Mitochondria are found in most human cells (one exception being erythrocytes). On average there are 300–400 per cell, totalling ~10 million billion in the average person. Metabolically active cells, such as those of the liver, kidneys, muscles and brain, have hundreds or thousands of mitochondria, making up some 40% of the cell’s cytoplasm.

Mitochondria provide much of the cell’s energy needs by oxidative phosphorylation (OXPHOS) where hydrogen from dietary carbohydrates and fats is oxidized to give water. The two primary physiological functions of OXPHOS are: (i) production of the high energy phosphate molecule ATP from adenosine diphosphate (ADP) and phosphate (Pi), which is used to store and release energy for work within the body; and (ii) heat generation. During OXPHOS, electrons are transferred from electron donors (hydrogen) to electron receivers (e.g. O2) in successive ‘coupled’ redox reactions (one agent is reduced and the other simultaneously oxidized) by molecular complexes (the respiratory chain) in the inner mitochondrial membrane. Energy is released as electrons flow through the respiratory chain, and is used to transport protons across the membrane. This generates potential energy in the form of a pH gradient and an electrical potential across the inner membrane. This energy store is tapped by allowing protons to flow back across the membrane and down this gradient through an enzyme called ATP synthase, which uses the energy to generate ATP from ADP.

The efficiency with which dietary calories are converted to ATP is determined by the coupling efficiency of OXPHOS. If the respiratory chain is highly efficient at pumping protons out of the mitochondrial inner membrane, and the ATP synthesis is highly efficient at converting the proton flow through its proton channel into ATP (from ADP), then the mitochondria will generate maximum ATP and minimum heat per calorie. These mitochondria are said to be ‘tightly coupled’. In contrast, if the efficiency of proton pumping is reduced and/or more protons are required to make each ATP molecule, then each calorie will yield less ATP but more heat. Such mitochondria are said to be ‘loosely coupled’. Therefore, the coupling efficiency determines the balance of calories used to perform work (ATP) or to maintain body temperature (heat generation).
Mitochondrial DNA mutations, environmental adaptation and disease outcomes

Mitochondria are predominantly inherited down the female line (from mother to daughter) because the sperm cell has few or none, so the mitochondria of the fertilized cell are those of the ovum. Mitochondria have their own DNA (mtDNA); in humans, of the 80 proteins or so in OXPHOS, 13 are encoded by mtDNA (the rest by nuclear DNA). Hence, mtDNA is central to the generation of ATP and heat. Mutations of the mtDNA, whether of the structural genes or the components for mitochondrial protein synthesis, may affect OXPHOS. Such mutations may have been critical for human adaptation to different global climates.

Evidence that climatic adaptation, rather than random or neutral drift (i.e. when genetic material is transmitted randomly from one generation to the next), has influenced mtDNA diversity is demonstrated because the mutations of particular mitochondrial genes show strong geographical specificity. For example, striking differences in common mtDNA polymorphisms (haplogroups) between Africa and Eurasia, and between southern Asia and Siberia, seem to correlate with latitude. Climate may have been an important selective pressure for such mtDNA diversity. For example, the cytochrome oxidase I (COI) gene, which encodes for an oxidizing enzyme that aids electron transfer from cytochrome molecules to oxygen molecules during OXPHOS, is variable in the tropics whereas invariant in both temperate and arctic regions. The opposite is found for other genes (e.g. ATP6 and cyt b). In contrast, others have not supported the idea that climate was important for mtDNA variability.

Mitochondrial uncoupling proteins, basal metabolic rate and energy metabolism

Uncoupling proteins are known or strongly suspected to participate in basal and regulatory thermogenesis although their exact biochemical and physiological roles have yet to be confirmed. Uncoupling protein-1 (UCP1) is expressed exclusively in brown adipose tissue found in small mammals and newborn humans. In these adipocytes, UCP1 activation results in dissipation of the inner mitochondrial membrane potential through transportation of protons back into the matrix surrounded by the inner mitochondrial membrane. This reduces ATP generation and respiration proceeds in the uncoupled mitochondrion, releasing energy solely as heat. The capacity of brown adipose tissue to produce heat is largely determined by the UCP1 content in the mitochondria. Since brown adipose tissue in humans is mostly shed after infancy, UCP1 expression is limited or non-existent in adults. However, in 1997, two further UCPs (UCP2 and UCP3) were discovered, both of which were homologous to UCP1 and expressed in adults. Specifically, UCP2 is expressed in many tissues (including adipose tissue, muscle, heart, kidney, digestive tract and brain) whereas the expression of UCP3 is mostly limited to skeletal muscle. The wide tissue distribution of UCP2 and UCP3 indicates that their biological role differs from that of UCP1 which influences heat generation through adaptive, non-shivering thermogenesis. UCP2 and UCP3 have been implicated in determining the BMR. Basal proton leak in the mitochondrial inner membrane is associated with BMR in most tissues. In one study of Pima Indians, for example, certain UCP2 and UCP3 polymorphisms were associated with the metabolic rate during sleep as well as 24 h energy expenditure. This implies that UCP2 and UCP3 gene variation may be related to differences in metabolic rate.
in mitochondrial uncoupling and energy utilization efficiency.

Studies of differences in BMR between populations with ancestry from different climate zones are equivocal; those comparing White controls with Asian Indians, Pima Indians, African American children, Malaysians, UK Asians, Gambian and Thai women and Gurka soldiers have not observed differences in BMR after taking body composition differences into account. There are substantial differences in BMR as the proportion of body fat and lean mass differs greatly. In contrast, even after adjusting for fat-free mass, fat mass, visceral fat and age, African Americans enrolled in the CARDIA study had ~5% lower BMR than White Americans. Similar findings have been reported in other studies of African Americans and in an investigation comparing BMR in Polynesian women with that of White women. Furthermore, in African Americans compared with White controls, there is evidence that fat oxidation rates may also be lower.

One study has so far reported ethnic differences in the relationship between UCP genotype and BMR. After genotyping two polymorphic sites on the UCP1, UCP2 and UCP3 genes in 141 African American and White women, Kimm and colleagues showed an association between an UCP3 exon 5 polymorphism and lower BMR in the African Americans. The study also found an association between fat mass and this polymorphism only for the African Americans, suggesting it might increase their susceptibility to the development of obesity. To our knowledge there are no publications on whether UCP polymorphisms are commoner in South Asians than other populations, and whether they are associated with BMR or might help explain South Asia’s propensity to central obesity. Nair et al., however, explored mitochondrial function in Asian Indians in the USA and their work is discussed below.

The association between tightly coupled OXPHOS, metabolic disturbances and CVD in South Asians

Important insights were provided by Nair and colleagues, who set out to examine variation in skeletal muscle mitochondrial activity by comparing both diabetic and non-diabetic Asian Indians (13 in each group) with 13 non-diabetic Northern European Americans in an age, sex and BMI-matched analysis.

Detailed testing involved determining mitochondrial coupling efficiency through the measurement of mtDNA copy number, OXPHOS gene transcripts, citrate synthase activity and maximal mitochondrial ATP production rate. Interestingly, the study showed that, although the diabetic and non-diabetic Indians had similar OXPHOS levels to each other, both groups had higher OXPHOS activity levels than the Northern European Americans. Moreover, the results revealed a cluster of mitochondrial genes involved in OXPHOS, including NADH hydrogenase, cytochrome c oxidase and ATP synthase, were up-regulated in the non-diabetic Indians compared with the Northern European Americans. In contrast, the study found no differences in OXPHOS gene regulation between the two Indian groups.

The study by Nair and colleagues, although limited with respect to both size and sample selection procedures, provides evidence suggesting relatively high OXPHOS activity levels in South Asians. This evidence supports our prior hypothesis written in January 2006. Tightly coupled mitochondria in South Asian populations, combined with low physical activity levels and a caloric intake beyond their needs, may underlie current metabolic disorders. Although we were unable to find published information specifically on whether tightly coupled OXPHOS confer an increased risk of obesity, metabolic disturbances and CVD in South Asians, given Nair et al.’s data, this is likely unless exercise levels are higher. Recent data suggest that physical exercise levels are substantially lower in UK-resident South Asians compared with the general population. The Health Survey for England, in particular, showed that all major South Asian ethnic groups and both sexes were less engaged in physical activity than the general population.

While dietary practices of UK South Asians are variable, high-fat food intakes, particularly from vegetable ghee and cooking oils, are commonly found in South Asians. In the UK, Bangladeshi men and women, in particular, consume less fruits and vegetables than any other ethnic minority group. Moreover, they have high consumption of red meat and dietary fat. In the UK, consumption of British high-fat diet (e.g. chips, cakes, etc.) is also common in South Asians. Still further, across tropical and sub-tropical regions, including South Asia, large increases in the consumption of fat and added sugars in the diet have occurred.

Conclusions

We hypothesized that energy producing efficiency of mitochondria enhanced the successful adaptation of South Asians to climatic (heat) and other nutritional exposures (especially low-calorie diets) on the Indian subcontinent. Subsequent to Wells’ hypotheses, this
may also help combat infection by reserving fat energy for immune function. Mitochondrial efficiency might be maladaptive when South Asians adopt new lifestyles following migration to Western countries, e.g. low physical activity levels and high consumption of fat and sugars.

If our hypothesis is correct then it offers a biological mechanism in common (i.e. mitochondrial gene mutations) for the ‘thrifty genotype and/or phenotype hypotheses’\(^26,27\), which themselves would result from the El Nino-type weather effect.\(^29\) A hot climate was postulated as a possible underlying evolutionary driver of central obesity. The ‘variable disease selection hypothesis’\(^30\) also offers an evolutionary driver for prioritizing deep visceral adipose tissue compartments. The new ‘mitochondrial efficiency hypothesis’, in combination with the above hypotheses, helps explain the tendency of South Asians to obesity \(\textit{per se}\), central obesity and adverse metabolic outcomes. The research now required to explore the hypothesis is considered below.

We found no studies of South Asians on the prevalence of polymorphisms associated with variable mitochondrial coupling. Studies proposing the hypothesis that climatic pressures account for geographical mtDNA diversity have been criticized for not examining mtDNA from all relevant climatic regions, including South Asia.\(^42\) This hypothesis could be investigated relatively easily using existing databases and genetic material where information on South Asian mitochondrial haplogroups is available. We found one study\(^70\) that suggests OXPHOS is relatively efficient in South Asians. Larger, follow-up studies of healthy South Asian and European-origin groups should now be carried out in order to confirm these findings. South Asians have lower BMR than comparable European origin populations. This is usually explained by their lower lean body mass and correspondingly higher fat mass. This, seemingly, goes against the mitochondrial efficiency hypothesis. The studies done, however, are small in scale, and given the importance of the hypothesis, larger studies are warranted. The line of reasoning that hot climate combined with availability of a small number of calories favour high mitochondrial efficiency to reduce heat production and conserve energy is, nonetheless, supported. A body with a high fat content, especially truncal fat, will have a low overall BMR, hence lower heat production, than one with a high lean mass. We could not find any studies of the association between mitochondrial coupling efficiency and intermediate or actual disease outcomes in South Asians.

We conclude that mitochondrial efficiency offers potentially important mechanisms explaining the propensity for reduced physical activity and overnutrition, leading to insulin resistance, diabetes and CVD in populations with a South Asian ancestry. So far, there are insufficient data to evaluate this hypothesis rigorously. The evidence is sufficient to justify its exploration. If there is evidence in its favour, it could help integrate and underpin the thrifty genotype and phenotype, the adipose tissue compartment and the variable disease selection hypotheses. The hypothesis is likely to have relevance to other warm climate-adapted populations with evolutionary histories similar to South Asians.

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**KEY MESSAGES**

- South Asians’ susceptibility to metabolic disorders and CVD is under debate.
- The thrifty genotype, thrifty phenotype, adipose tissue compartment and the variable disease selection hypotheses are among the contenders as explanations.
- We propose a mitochondrial mechanism that underlies these and related hypotheses.
- Selection pressures such as hot climate, food scarcity or gastrointestinal infections may have favoured mitochondrial function that favours energy conservation over heat production.
- A literature search found some evidence in favour of the hypothesis, which now merits rigorous examination.
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