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Review

Energy metabolism in relation to diet and physical activity: a South Asian perspective

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Short Title: energy metabolism in South Asians

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Abstract

The prevalence of overweight and obesity is increasing worldwide not only in Western countries but also in Asian countries. Among Asian countries, South Asian countries experience the rapid increase of overweight and obesity that co-exist with the rapid increase of obesity-related non communicable diseases such as diabetes, dyslipidemia and cardiovascular. The phenomena in South Asian countries are triggered by growth in population size, population aging, urbanization and changes in lifestyle including increases in energy intake and reductions in physical activity.

The imbalance between energy intake and energy expenditure leads to the development of positive energy balance, which over the time acumulate in a higher body fat. South Asians were reported to have a more unfavorable body composition with a higher body fat percentage as compared to BMI-matched Caucasians. The differences in body composition between South Asians and Caucasians contribute to differences in resting energy expenditure, in which South Asians have a lower resting energy expenditure as compared to BMI-matched Caucasians. Resting energy expenditure is the largest component of daily total energy expenditure, and therefore play an important role in determining the energy balance between energy intake and expenditure.

Keywords: energy metabolism, South Asian, diet, physical activity

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Introduction

The prevalence of overweight and obesity is increasing globally, not only in western countries but also in developing countries that are progressing towards a more industrial way of living such as in Asia. In 1995, WHO found a greater problem with overweight than underweight in developing countries (1). The world incidence of overweight and obesity was projected to be 1.3 billion and 573 million individuals respectively by 2030, with 43% and 21% of that number respectively living in Asia (2). In addition, the world prevalence of diabetes among adults (20-79 years old) was estimated to increase from 6.4% in 2010 to 7.7% in 2030 affecting more than 400 million people (3). Considering the current trends, the increase was expected to be around 69% in developing countries and 20% in developed countries (3). By 2030, around 80% of people with diabetes live in developing countries of which India and China share the largest contribution (4). Unlike in western countries, diabetes in Asia has developed in a shorter time (3-5 fold increase within 30 years), in a younger age group (20-64 years old) and in people with a lower BMI (5). The much larger increase of overweight and obesity as well as obesity-related non-communicable diseases in developing regions are triggered by growth in population size, population aging, urbanization and changes in lifestyle including increases in energy intake and reductions in physical activity (2,6).

Obesity and metabolic syndrome: a South Asian perspective

Among Asians, people of South Asian descent (Indian sub-continent) were reported to have the highest prevalence of obesity and obesity-associated diseases (5,7). The increasing number of adults with type 2 diabetes is extremely high reaching 1.8 million annually (3) and continues to rise both in native and migrant South Asians (8,9). In their home countries, recent data showed the prevalence was increasing in urban, semi urban and rural areas and included especially people belonging to middle and low socio-economic strata (10). About one-third of the urban population in large cities in India was reported to have metabolic syndrome (11). Diabetes is not the only non-communicable disease that South Asians are prone to, they also have earlier onset, more severe and more prevalent cardiovascular disease (CVD) than other ethnicities (12). Several studies have revealed the higher risk of CVD in South Asians is associated with an unfavorable lipid profile or dyslipidemia (9) such as an elevated fasting plasma triglyceride and LDL (13,14), a lower HDL cholesterol (14,15) and a lower HDL to total cholesterol ratio (16).

While India already has the highest number of patients with type 2 diabetes globally, rapid increase in childhood obesity is the prime reason for increasing insulin resistance, dyslipidemia and metabolic syndrome (17). Children from South Asian ancestry manifest adiposity, insulin resistance and metabolic perturbations earlier in life compared to other ethnic groups (17-19). South Asian adolescents were found to be more insulin resistant with more body fat and exhibited a high risk of cardiovascular disease with a higher blood pressure and fasting triglycerides (20) compared to white British adolescents. A strong gene-environment interaction was suggested to be the cause of the rapid increase of diabetes and metabolic syndrome in South Asians (4). This condition is worsened by lower disease awareness and health-seeking behavior, delayed diagnosis due to uncommon presentation and language barrier, and socio-cultural as well as religious factors (21).

The features of body composition, body fat distribution, ectopic fat accumulation and lipodistrophy in South Asians

The high prevalence of metabolic syndrome in South Asians may be partly explained by the unfavorable body composition, where Asians are reported to have a higher body fat percentage for the same BMI as compared to white Caucasians (22-28). The difference in body composition was observed in men as well as in women. For the same BMI as Caucasians, South Asian men have a 4-7% higher body fat percentage (22-26) while women have an 8% higher body fat percentage (27,28). Additionally, it has been reported consistently that Asians have a lower fat-free mass (lean body mass) and/or appendicular skeletal muscle mass compared to other ethnicities (26,27,29), also after adjusting for height. The fat-free mass index (FFMI) was the lowest for Asians compared to other ethnicities such as Caucasians, African-Americans and Hispanics (30). In South Asian men, lean body mass was 3.4 kg lower than in Aboriginals, 3.0 kg lower than in Chinese and 3.6 kg lower than in Caucasians (31). In South Asian women, the lean body mass was 2.0 kg lower than in Aboriginals, 2.2 kg lower than Chinese and 3.0 kg lower than Caucasians (31).

Interestingly, the unfavorable body composition is already present at young age. South Asian adolescents of 14-17 y old (32), 11-12 y old (33) and children of 5-7 y old (34) had a higher body fat percentage compared to their European counterparts in the UK. Percentage body fat was significantly higher in middle school South Asian children compared to children of Caucasian, East Asian, African-American and Hispanic backgrounds living in the US (35). A recent study (36) showed that in early infancy (6-12 weeks), South Asian infants had 0.34 kg less FFM, and an indication towards a higher FM than white European infants. This difference persisted after adjustment for the smaller body size of South Asians. The most interesting findings of the study were; that for a given infant weight, the balance of body composition of South Asians was shifted by 0.16 kg from FFM to FM. These differences in the amount of FFM were almost completely accounted for by ethnic differences in the rate of growth in utero and length of gestation (36). This finding confirmed the results of previous studies on neonatal anthropometry, comparing Indian babies born in India and white babies born in the UK, observing a lower weight, smaller waist and mid circumference but a higher subscapular skinfold thickness in Indian babies (37,38). Truncal adiposity was larger at 4 y of age (38), suggesting a thin-fat phenotype from young age onwards. A longitudinal study performed in a New Delhi cohort, India (39) showed that birth weight and BMI gain during infancy and early childhood predicted adult lean mass more strongly than adult adiposity, whereas larger BMI gain in late childhood and adolescence predicted adult adiposity. This suggests that postnatal environment may modify the development of an unfavorable body composition in South Asians.

Estimation of body fat using BMI may not adequately reflect the amount of atherogenic adipose tissue i.e. visceral and ectopic fat (40). Fat distribution might be a more informative parameter. The sum of truncal skinfolds in South Asian men were found to be higher and was associated with lower glucose disposal rate (41) and increased incidence of diabetes in women but not in men (42). Simple anthropometric indices such as waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR) and skinfold thickness are useful measures to assess obesity related metabolic disease risk in large population studies focusing on South Asians, however those measures are a proxy of abdominal fat content (total abdominal fat: TAT, subcutaneous fat: SAT, visceral fat: VAT) and may differ in the accuracy when comparing ethnicities. Depending on the age and gender of the populations studied, some studies found differences in indices of abdominal adiposity (TAT, SAT and VAT) when South Asian and BMI matched Caucasians were compared, while others did not. Studies that compared a group of South Asian men and women matched for age, BMI and WC with Caucasian men and women found a higher abdominal adiposity in South Asians (22,43). Despite similar WC, part of that study (22) also showed South Asians displayed an unfavorable lipid profile (44). Visceral fat was found to mediate the effect of ethnicity on the risk factors of developing dyslipidemia and CVD, suggesting that the high risk for CVD in South Asians may be attributed to higher visceral fat (45), whereas another study found a

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stronger correlation between CVD risk and subcutaneous fat (46). One study in relatively older aged and BMI matched South Asian and Caucasian men did not find any difference in WHR and visceral fat area, despite a higher body fat percentage of the South Asians (23). Comparing young South Asian and BMI matched Caucasian men, body fat percentage, subcutaneous fat and adipocyte size were higher in South Asians, with no difference in intra-peritoneal fat (24). When the subcutaneous abdominal compartment was further divided into superficial and deep subcutaneous, South Asians had a higher deep subcutaneous fat than BMI-matched Europeans (47,48). Interestingly, a recent study in young South Asian and white women, showed no difference in any of the abdominal obesity measures and no metabolic disease observed (49). Besides subject characteristics, the way the compared ethnicity groups were matched and the number of subjects seemed to affect the differences in the findings of many studies. However, in large population studies (22,45,47,48), differences were observed in the body fat distribution between South Asians and white Caucasians towards a more centrally fat depot in South Asians. A gene-environment interaction of obesity-related traits was confirmed by a longitudinal genome-wide association study in a large cohort in South India, as indicated by an association between the rs9939609 variant in the FTO locus with measures of adiposity (BMI, WC, HC, WHR, skinfold thickness) and metabolic consequences (50).

The unfavorable body fat distribution towards a more centrally fat depot may not be the only feature responsible for the development of metabolic complications in South Asians. Adipose tissue does not function as energy stores only, but also as an endocrine organ producing adipokines for energy balance regulation. It was suggested that South Asians and Caucasians differ in adipokine production, where a lowered adiponectin and an elevated leptin in South Asians contributed to higher diabetes prevalence (51,52). In addition, a higher ApoB/ApoA-I ratio in South Asians with central adiposity was suggested as a risk factor for developing CVD (53).

Last but not least, the susceptibility of South Asians to central adiposity and atherogenic dyslipidemia at a lower range of body fat than white Caucasians raised the hypothesis of adipose tissue expandability and lipid overflow (54). It was suggested that South Asians may have a smaller superficial subcutaneous adipose tissue compartment (present throughout the body) than Caucasians. When obesity develops, South Asians exceed the storage capacity of that compartment before Caucasians do, leading to lipid overflow to the deep subcutaneous adipose tissue compartment (present at upper body) and visceral adipose tissue, subsequently triggering dyslipidemia (54). The limited storage capacity of the superficial subcutaneous adipose tissue may be characterized by a larger adipocyte size in South Asians than Caucasians, accounting for ethnic differences in insulin, HDL-cholesterol, adiponectin and ectopic fat accumulation in the liver (55).

Are South Asians more susceptible to the negative effect of high energy density foods?

Developing countries are undergoing a rapid nutritional transition concurrent with an increase incidence of obesity and metabolic syndrome (56,57). Dietary factors are likely to exaggerate the incidence of metabolic syndrome in South Asians, already predisposed to obesity. The South Asian dietary pattern is characterized by a high intake of carbohydrate (60-67%), SFA (from animal fat, coconut oil, palm oil and *ghee* butter), TFA, n-6 PUFA (sunflower, safflower, corn, soybean, sesame oil) and a low intake of n-3 PUFA (thus a lower ratio of n-3/n-6 PUFA) and a low intake of dietary fiber (56,58). Increased dietary n-6 PUFA and SFA intakes in South Asians were found to be associated with fasting hyperinsulinemia and sub-clinical inflammation, respectively (59).

Immigration to developed countries was shown to increase the risk for atherosclerosis in South Asians, the longer the time since immigrated the higher the development of atherosclerosis risk (60). Body composition of South Asians was altered towards a higher body fat with increasing residence time in the UK (61). It was suggested that dietary acculturation after migration to western countries may be involved in the development of metabolic syndrome in South Asians (61). The main dietary trend of South Asians after migration to Norway was a substantial increase in energy and fat intake, a reduction in carbohydrate intake in particular a switch from complex to refined carbohydrate, an increased consumption of meat and dairy products and a reduced vegetable intake (62). In the UK (63) and Canada (13), South Asians had a significantly higher carbohydrate intake (50% or more), associated with a lower HDL and HDL/total cholesterol ratio. In a 12 country study, the prevalence of low HDL was the highest in South Asians (63% in non-diabetic and 67% in diabetic) (15). With increasing length of residence in Canada, South Asians adopted a more positive dietary practice (higher consumption of fruits and vegetables and reduced consumption of frying foods), however there was also an increased consumption of convenience foods, sugar-sweetened beverage, meat and dining out (64), whereas no difference in the dietary pattern in multi-ethnic adolescents (including South Asians) suggesting an acculturation (65).

Nutrient imbalances in the indigenous dietary pattern of native South Asians as well as the dietary acculturation of migrant South Asians in western countries may deteriorate metabolic complications in the long term. For Caucasians, it has been shown that high carbohydrate intake (mono- and polysaccharides) is associated with an elevated TAG, as result of increased TAG production (via increased de novo lipogenesis and VLDL secretion) or reduced TAG clearance (66). In South Asians consuming a large amount of carbohydrates in their diet, HDL cholesterol was reduced as well (13). Additionally SFA and TFA intake, cholesterol-increasing dietary fatty acids, was associated with increased LDL-cholesterol (67). Thus, a combination of imbalanced nutrients in South Asian diet may contribute to the excessive risk of CVD in this population.

Does sedentarism have a more adverse effect on South Asians?

Numerous epidemiological studies have been performed to assess the physical activity level of South Asians prone to obesity. Indeed, migrant South Asians in western countries were reported to have a lower physical activity level than Caucasians (68-71), this was also observed in adolescents (65). In South Asians, lower physical activity was associated with higher adiposity, whereas higher physical activity levels were associated with lower waist circumference (68). South Asians with a higher visceral fat had a lower to moderate physical activity, and moderate-to-vigorous activity as compared to Caucasians; however after adjustment for physical activity levels, the visceral fat remained significantly higher (69). In addition, vigorous activity was a predictor for liver fat accumulation, but moderate or moderate-to-vigorous activity may not be enough to prevent liver fat accumulation (72). Since South Asians exhibit an increased cardio-metabolic disease risk, it is intriguing whether the recommendation of a moderate intensity physical activity (MPA) of 150 min/week for Caucasians is appropriate for South Asians (73). It was shown that South Asians should undertake more moderate physical activity (MPA= 266 min/week) to elicit a similar cardio-metabolic risk profile as Caucasians (73).

Compared to Caucasians, South Asians were also shown to have a lower cardiorespiratory fitness and VO_2max (71,74). Those studies however did not correct for a difference in fat-free mass between ethnicities. Lower cardiorespiratory fitness, lower physical activity and greater total adiposity together explained 83% of the ethnic difference in HOMA(IR), whereas 63% ethnic difference in fasting glucose was explained by cardiorespiratory fitness and total adiposity (71). Cardiorespiratory fitness is closely related to skeletal muscle lipid oxidative capacity; it was shown that South Asians oxidized less fat during sub-maximal exercise but no difference in fat oxidation during rest than Caucasians (74). Interestingly, the lower oxidative capacity during sub-maximal exercise was not explained by a higher expression of oxidative and lipid metabolism genes in the skeletal muscle, but it did relate to a lower expression of insulin-signaling proteins in the skeletal muscle (74). Mitochondria, as a primary organelle involved in fuel metabolism, had a higher capacity for oxidative phosphorylation (OXPHOS) in diabetic and non-diabetic South Asian Indians compared with BMI matched Caucasians, (25). Thus, mitochondrial dysfunction and oxidative genes expression in the skeletal muscle may not be the explanation for the lower oxidative capacity during sub-maximal exercise, as previously thought to be the reason for the development of obesity and insulin resistance. It could be that increased gene expression may not be followed by an increase in proteins responsible for lipid metabolism. In addition, fatty acids oxidation may provide only one part of the story, fatty acids mobilization and handling as well as their storage may also be important.

Body composition and energy expenditure in Asian populations

Comparative studies have shown that Asians differ from Caucasians in their body composition when matched for BMI. Asians have a higher body fat percentage whereas

Caucasians have a higher fat-free mass (FFM) as reported by us (75) and others (76-87). Among three major ethnic groups in Asia, South Asian Indians had the most pronounced difference in body fat percentage compared with those of Caucasians, followed by Malay and Chinese subjects (88). As there is an ethnic-specific BMI-body fat relationship (89), differences in body fat percentage can be a confounding factor when Asians and Caucasians matched for BMI are compared in an intervention study. By matching the two ethnicities for body fat percentage instead of BMI (90) one could avoid misinterpretation of the response to a diet or physical activity intervention.

The relationship between body composition and energy expenditure has been studied in health and diseases. Studies have established FFM as the major determinant of resting energy expenditure (REE) or resting metabolic rate (RMR) (91), which is the largest component (60-70% in moderately active adults) of total energy expenditure (TEE). Although RMR and also sleeping metabolic rate (SMR) correlate best with FFM, RMR is also independently influenced by fat mass; the greater the FM, the higher the RMR (92). Asians were reported to have a lower RMR (93) and a lower SMR in the study by Wulan et.al (75) than Caucasians because of having a lower FFM. The difference in RMR and SMR disappeared when adjusted for body composition (75,93).

Body composition and fat oxidation in Asians and Caucasians

A low RMR, after adjustment of fat-free mass, fat mass, age and gender have been associated with an increased risk of body weight gain in a follow-up study of 3-4 y (94,95). An unfavorable body composition, shown by a higher body fat accumulation, may be a consequence of a lower rate of energy expenditure and a higher respiratory quotient (RQ), indicating a lower proportion of fat to carbohydrate oxidation. Alternatively, a low rate of energy expenditure may be due to an unfavorable body composition. In a longitudinal study, a higher RQ was associated with susceptibility to weight gain in Pima Indians (96). However, Weyer et al. (97) reported no evidence for a lower metabolic rate or impairment in 24-h fat oxidation in obesity prone-Pima Indians as compared to whites. Similarly, Bergouignan et al. (98) showed no difference in 24-h fat oxidation in obese, reduced obese and lean subjects under similar eucaloric and negative energy balance. Despite differences in body composition, 24-h fat oxidation was similar between Asians and Caucasians, when they were fed in energy balance with the same diet (75).

The 24-h fat oxidation reflected both endogenous fat oxidation, mostly during the post absorptive period, and exogenous fat oxidation from dietary fat during the postprandial period. Most exogenous fat is stored during the postprandial period, whereas a limited fraction (~ 10%) is directly oxidized (99). In the study by Wulan et al., despite differences in body composition, dietary fat oxidation was similar in Asians and Caucasians being on average 11.7% and 10.4% from dietary fat consumed respectively (75). Previous tracer studies showed that dietary fat oxidation was negatively correlated with body fat percentage in men and women (100), whereas others found increased dietary fat oxidation with increasing body fat percentage in men (101). Interestingly, a recent study showed no difference in dietary fat oxidation between obese, reduced-obese and lean subjects (men and women) (99). The discrepancy of the results may be due to the differences in the metabolic fate of dietary fatty acid tracers (palmitic acid or oleic acid) used in different studies, the labelling (^{2}H or ^{14}C) and the duration of the observation (99).

When comparing lean subjects and post-obese subjects (predisposed to obesity) instead of obese subjects and providing them with both isocaloric low- and high fat diets, Astrup et al. (102) and Buemann et al. (103) found that formerly obese women failed to increase fat oxidation in response to increased dietary fat compared to lean women. This was expressed as the ratio of fat to carbohydrate oxidation (102) and measured as postprandial fat oxidation after supper (103) and was independent of energy balance.

Substrates partitioning: the role of energy balance, substrates balance and macronutrients composition when overfeeding South Asian and Caucasian men with a high fat diet

Energy balance in the respiration chamber predicted 24 h fat oxidation in Asians and Caucasians (75) and predicted 24 h RQ (96). The more negative energy balance the higher the fat oxidation (the lower the RQ), the more positive energy balance the lower the fat oxidation (the higher the RQ). When South Asian and Caucasian men were overfed with a high fat diet under sedentary conditions, the association between 24 h fat oxidation and energy balance was weak because all subjects were in a massively positive energy balance of 8-8.5 MJ/d as a result of the combination of overfeeding and the sedentary conditions (104).

Energy balance status indicates whether there is a gap between energy intake and energy expenditure. Total substrate oxidation in the body is determined by the need to regenerate ATP (30) thus equals TEE. In this regard, nitrogen (protein) balance is readily maintained on high or low (but adequate) protein intakes (105). Similarly, the capacity of the body to store glycogen is limited to a few hundred grams and is usually maintained within a relatively stable range (105). Therefore, protein and carbohydrate oxidation are adjusted to protein and carbohydrate intakes respectively; consequently protein and carbohydrate balance are achieved.

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In contrast to the other two macronutrients, numerous studies on dietary fat supplementation or isoenergetic diets with high-or low- fat content have shown that fat intake does not stimulate its own oxidation; on the other hand, body fat stores are large (106). Adaptation of fat oxidation to increased fat intake in lean subjects consuming an isocaloric diet occurred within 7 days (107) and the adjustment of fat oxidation to match fat intake can be accelerated when glycogen stores are lowered through exhausting exercise in both lean (108) and obese subjects (109). This suggests that fat oxidation is regulated primarily by events pertaining to the use and storage of carbohydrate in the body, or in other occasions, is determined by the gap between total energy expenditure and the energy ingested in the form of carbohydrate and protein, rather than by the amount of fat consumed in a given day (106).

Isocaloric diets differing in macronutrients composition (protein/carbohydrate/fat, in a mixed diet: 15/55/30, a high fat diet: 15/25/60 and a high carbohydrate diet: 15/70/15) showed a relative contribution of each macronutrient oxidation to TEE (substrate partitioning), close to the macronutrient composition (110). Likewise, reduced oxidation of dietary fat was also observed after a high carbohydrate diet (111).

When South Asian and Caucasian men were overfed with a high fat diet under sedentary conditions, a massively positive energy balance of 8-8.5 MJ/d was created and glycogen stores were relatively maintained (not depleted) since physical activity was low (104). Therefore, although the diet was high in dietary fat (60% energy intake), substrate partitioning showed a greater reliance on carbohydrate oxidation in both South Asians and Caucasians being on average 53% and 47% of TEE respectively; whereas average fat oxidation was 31% and 39% of TEE in South Asians and Caucasians respectively (104). As the need for replenishment of the body's glycogen stores was low, most of the glucose was oxidized to match carbohydrate intake; whereas fat was oxidized to a lesser extent to meet energy requirements, resulting in a positive fat balance of 7-7.5 MJ/d (104). Thus, most of the dietary fat was stored.

Molecular adaptations in the adipose tissue in relation to fat metabolism in South Asian and Caucasian Men overfed with a high fat diet

The most striking finding in the molecular adaptation to overfeeding with a high fat diet (under sedentary conditions) in South Asian and Caucasian men was the significant decrease in the HADH level (111), a crucial enzyme for mitochondrial β-oxidation involved in the rate-limiting acyl CoA dehydrogenase step (112) in both South Asians and Caucasians. The decrease of HADH was as expected, along with some metabolic alterations such as elevated insulin concentrations, decreased fasting plasma NEFA (104) indicating a suppression of lipolysis, and decreased fasting TAG concentration indicating fatty acid uptake in adipose tissue, all together pointing towards fatty acids storage rather than oxidation. Opposite results have been reported in caloric restriction studies, where HADH level increased (113,114). Caucasians had a relatively higher HADH level at baseline and while decreasing, the HADH level after overfeeding remained higher as compared to South Asians. This characteristic may be important in the long term energy (fat) metabolism in this population.

The entry of the acyl group into the matrix space of the mitochondria is catalyzed by the Carnitine palmitoiltransferases (CPT1a), converting cytoplasmic long-chain fatty acyl-CoA to acylcarnitine (112,113). Here, the study (111) showed CPT1a significantly changed with diet; decreasing in South Asians, but increasing in Caucasians. This may suggest a higher capacity of mitochondrial fatty acids uptake in Caucasians.

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Perilipin (PLINA) that plays a role in the turn-over of stored TAG and localized in the lipid droplets (115) did not significantly change with diet, but the changes differed between ethnicities (111). PLINA decreased more in Caucasians, whereas, the baseline and after intervention PLINA levels were relatively higher in South Asians, which may influence the long-term energy utilization in this population as well (111).

Conclusion

Despite differences in body composition, fat oxidation and other substrates partitioning did not differ between Asians and Caucasians in response to a normal fat diet in energy balance or overfeeding with a high-fat diet in South Asian and Caucasian men. A crucial enzyme in mitochondrial β-oxidation, HADH, significantly decreased in response to overfeeding with a high fat diet in both South Asian and Caucasian men. The differences in HADH and PLINA levels as well as in the response of CPT1a between ethnicities may be important for the long-term regulation of energy (fat) metabolism in these populations.

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Guy Plasqui: Conceptualization, Supervision, writing-reviewing and editing.
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