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ARTICLE

Physiology

Substrate utilization and metabolic profile in response to overfeeding with a high-fat diet in South Asian and white men: a sedentary lifestyle study

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Abstract

Background For the same BMI, South Asians have a higher body fat percentage, a higher liver fat content and a more adverse metabolic profile than whites. South Asians may have a lower fat oxidation than whites, which could result in an unfavorable metabolic profile when exposed to increased high-fat foods consumption and decreased physical activity as in current modern lifestyle.

Objective To determine substrate partitioning, liver fat accumulation and metabolic profile in South Asian and white men in response to overfeeding with high-fat diet under sedentary conditions in a respiration chamber.

Design Ten South Asian men (BMI, 18–29 kg/m^2) and 10 white men (BMI, 22–33 kg/m^2), matched for body fat percentage, aged 20–40 year were included. A weight maintenance diet (30% fat, 55% carbohydrate, and 15% protein) was given for 3 days. Thereafter, a baseline measurement of liver fat content (1H-MRS) and blood parameters was performed. Subsequently, subjects were overfed (150% energy requirement) with a high-fat diet (60% fat, 25% carbohydrate, and 15% protein) over 3 consecutive days while staying in a respiration chamber mimicking a sedentary lifestyle. Energy expenditure and substrate use were measured for 3 × 24-h. Liver fat and blood parameters were measured again after the subjects left the chamber.

Results The 24-h fat oxidation as a percentage of total energy expenditure did not differ between ethnicities ($P = 0.30$). Overfeeding increased liver fat content ($P = 0.02$), but the increase did not differ between ethnicities ($P = 0.64$). In South Asians, overfeeding tended to increase LDL-cholesterol ($P = 0.08$), tended to decrease glucose clearance ($P = 0.06$) and tended to elevate insulin response ($P = 0.07$) slightly more than whites.

Conclusions Despite a similar substrate partitioning and similar accretion of liver fat, overfeeding with high-fat under sedentary conditions tended to have more adverse effects on the lipid profile and insulin sensitivity in South Asians.

Introduction

Globally, the number of overweight and obese people was projected to be 1.35 billion and 573 million respectively in 2030 [1]. It is also estimated that by 2020, two-thirds of the global burden of diseases will be attributable to chronic noncommunicable diseases; most of them are strongly associated with diet, i.e., an increased consumption of refined foods or fats [2] and decreased physical activity [1].

Interestingly, in South Asian countries the development of diabetes and cardiovascular disease (CVD) was observed in people with a younger age and at a lower body mass index (BMI) compared to that in western countries [3] and may be explained by a higher body fat % in South Asians for the same BMI as whites [4–7]. It is suggested that differences in fat oxidation may be underlying the differences

Supplementary information The online version of this article (https://doi.org/10.1038/s41366-019-0368-2) contains supplementary material, which is available to authorized users.

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in body fat between ethnicities. However, we previously showed that despite differences in body composition, Asians and BMI-matched whites had a comparable dietary and 24-h fat oxidation when they were fed a normal fat diet in energy balance [8]. Whether South Asians oxidize as much fat as whites when they are exposed to a high fat diet and reduced physical activity is unknown.

Sedentarism is known to be able to aggravate the effect of obesogenic factors. Low-physical activity accentuated the effect of the FTO-gene on body fat accumulation [9], whereas a high level of occupational activity was associated with a decreased likelihood of being obese [10]. Moderate intensity [11] or a single bout of exercise [12] and a high-intensity exercise that lowered glycogen stores [13] were shown to increase fat oxidation. Training a group of sedentary men increased palmitate and oleate oxidation, whereas detraining a group of trained men by reducing structured and spontaneous activity reduced the oxidation of those fatty acids [14].

In the present study, we introduced a 3-day stay under sedentary conditions in a respiration chamber while overfed South Asians and whites with a high-fat diet, to create obesogenic environment to mimic the current lifestyle. To avoid potential confounders, South Asians and whites were matched for body fat percentage. Thus, the objectives of the present study were to compare: (1) substrate partitioning; (2) the change in liver fat content; and (3) the changes in metabolic profile between South Asians and whites in response to a massively positive-energy balance.

Subjects and methods

Subjects

Subjects were ten healthy adult nondiabetic South Asian men and ten body fat-matched white men. The number of subjects was determined based on previous studies showing an increase in liver fat content [15, 16] and changes in metabolic profile [17] in response to short-term high-fat feeding. Asian subjects had four grandparents from South Asia, while white subjects were European Caucasians. Subjects were selected based on the following inclusion criteria: healthy, not having diabetes or CVD, not using medication, aged between 20 and 40 year with BMI (in kg/m^2) between 18–29 for South Asians and 22–33 for whites, having a stable body weight for the last 3 months, not being on a diet and not being an athlete. Written informed consent was obtained from all subjects. The study was approved by the Medical Ethics Committee of Maastricht University Medical Centre, MEC No. 10-3-013 and registered in the public trial registry (www.ccmo.nl No. NL31217.068.10).

Experimental design

The study was a diet-intervention study under sedentary conditions in a respiration chamber. Body composition was measured before the start of the intervention to match body fat percentage between two ethnicities. Energy requirement of a weight maintenance diet for 3 days preceding the intervention were calculated based on fat-free mass (FFM) and daily physical activity level (PAL) of each subject. On the third day of the weight maintenance period, subjects came to the university in the morning to have a baseline measurement of the liver fat content and metabolic profile. On the same day, after having dinner, subjects entered the respiration chamber and stayed for the next 3 days. During this period, subjects were overfed with a high-fat diet, while no exercise or strenuous physical activity was allowed. Liver fat content and metabolic profile were measured again after the subjects left the chamber in the morning. The study protocol is presented in Fig. 1. All measurements were carried out at the Metabolic Research Unit Maastricht and MRI unit, Maastricht University Medical Center, Maastricht, The Netherlands.

Body composition

Body composition was determined according to a three-compartment model based on body weight, body volume, and total body water. Body weight and body volume were determined in the morning, in a fasted state. Body volume was determined by hydro-densitometry with simultaneous measurement of residual lung volume using the helium

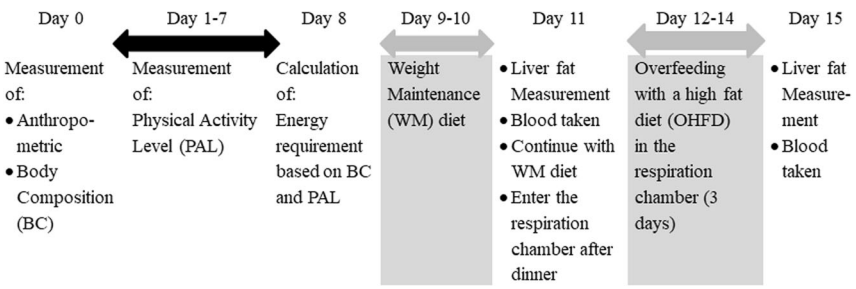

Fig. 1 Study protocol

dilution technique. Total body water was determined with deuterium dilution according to the Maastricht protocol [18]. Body composition was calculated from body density and total body water using the equation of Siri [19].

Daily physical activity level

The daily PAL was measured for 7 consecutive days (during waking hours except water activities) using a tri-axial accelerometer for movement registration (Tracmor-D, Philips New Wellness Solutions; http://www.directlife.philips.com). A detail description about the device has been provided elsewhere [20]. Accelerometer output was expressed as activity counts/minute and were summed over the entire monitoring period, then divided by the number of monitoring days to determine the average counts per day (counts/d).

Daily PAL was calculated based on the activity counts/d with the formula, $\mathrm{PAL} = 1.354 + 256 \times 10^{-9} \times \mathrm{counts/d}$ [20]. Total energy expenditure (TEE) was calculated with the formula of Bonomi et al., TEE accelerometer (MJ/d) = $0.04 + 0.17\ \mathrm{FFM\ (kg)} + 1.67 \times 10^{-6} \times \mathrm{counts/d}$ [20].

Energy intake

The energy intake was predicted based on energy requirement of each subject. The energy requirement was calculated as TEE, based on the FFM and daily PAL of each subject. The TEE was used to arrange the weight maintenance diet, whereas for overfeeding with a high-fat diet TEE was multiplied by 1.5. The weight maintenance diet to be consumed at home for 3 days before the intervention was calculated based on TEE as shown above, containing 30% energy as fat, 55% carbohydrate, and 15% protein. The overfeeding with a high-fat diet was given with 50% excess energy above the TEE of the weight maintenance diet [21], containing 60% fat, 25% carbohydrate, and 15% protein [22, 23].

A written instruction was given to prepare the weight maintenance diet at home. Subjects were provided with the diet in an excess amount, than the amount needed to match calculated TEE and were allowed to eat ad libitum. Any additional intake from those prescribed foods was recorded. All unfinished foods were collected and returned to the university, to calculate actual energy intake [17].

During overfeeding, subjects stayed in the respiration chamber. They were asked to eat all the foods prepared, but on failing to do so, the left overs were weighed. The diet consisted of normal ready-to-eat foods combining a typical Western and Asian diet. Foods and drinks were selected by reviewing the ingredients content to ensure there was no (or only a minimal) effect of certain ingredients on fat oxidation (such as spices, caffeine). Alcohol was not allowed to be consumed in the respiration chamber.

Energy expenditure

Subjects stayed in the respiration chamber from 20:00 in the evening of the third day of their weight maintenance diet (day 3) until 07:00 in the morning of day 7 (83 h). The respiration chamber is a 14-m^3 room furnished with a bed, table, chair, freeze-toilet, washing bowl, television, and computer [24].

During the 83-h stay, oxygen consumption and carbon dioxide production were measured continuously. Subjects were allowed to move freely, sit, lie down, study, use the telephone, watch television, and use the computer from 07:00 to 23:00, but were not allowed to do strenuous physical activity (exercise) or sleeping during the day. TEE over 3 × 24-h and 3 × 24-h-RQ were calculated from 07:00 on the first morning until 07:00 on the fourth morning in the chamber. TEE was calculated by using the equation of Carpenter, as published by Brouwer [25]

$$\mathrm{TEE(kJ/d)} = 16 \times \mathrm{O_2(L/d)} + 5\mathrm{CO_2(L/d)} - 0.95 \times P,$$

where P is oxidized protein in g/d.

Sleeping metabolic rate (SMR) was calculated by assessing the lowest mean activity of the subjects during 3 consecutive hours between 00:00 and 07:00 of the second, third, and fourth night of their stay in the chamber. SMR was the mean energy expenditure in which the activity was the lowest [26]. SMR was also corrected for FFM [27]. Resting metabolic rate (RMR), including diet-induced thermogenesis (DIT) was calculated by plotting energy expenditure (y-axis) against radar output (x-axis), both being averaged over 30 min intervals every 24-h of the stay. The RMR (including DIT) was calculated by entering the earlier mentioned lowest mean activity into the formula of the linear regression line of the plot. DIT was calculated by subtracting SMR from RMR that includes DIT as mentioned above. Activity energy expenditure (AEE) [28] was calculated by subtracting RMR from TEE [26].

Substrate oxidation

Substrate oxidation was calculated from 24-h urinary nitrogen, O_2 consumption, and CO_2 production. Urine samples (3 × 24-h) were collected from the second voiding on day 4 until the first voiding on day 7. To prevent nitrogen loss through evaporation, 24-h urine was collected in containers with 10 mL HCl, whereas total volume was measured afterwards. Nitrogen concentrations were measured with a nitrogen analyzer (CHN-O-Rapid; Heraeus, Hanau, Germany). Protein oxidation (g/d) was calculated by multiplying 24-h urinary nitrogen (g/d) by 6.25. Carbohydrate (g/d) and fat oxidation (g/d) were calculated with the following equations of

Carpenter, as published by Brouwer [25]

$$\text{Carbohydrate oxidation} = -2.97 \times O_2(\text{L/d}) + 4.17 \times CO_2(\text{L/d}) - 0.39 \times P,$$

$$\text{Fat oxidation} = 1.72 \times O_2(\text{L/d}) - 1.72 \times CO_2(\text{L/d}) - 0.32 \times P,$$

where P is protein oxidation (g/d).

Hepatic lipid content

Liver fat content was measured before and after overfeeding with a high-fat diet, on a 3.0 T scanner (Achieva, Philips Healthcare, Best, The Netherlands) using a SENSE-cardiac coil [29]. A single voxel of $20 \times 20 \times 20\,mm^3$ was positioned in the right liver lobe, avoiding large biliary or vascular structures [29]. Spectra were acquired using a point-resolved spectroscopy sequence [29] with repetition time of 4000 ms, echo time of 33 ms, and number of averages of 64. To minimize the motion artifacts, subjects were asked to breathe in the rhythm of the measurement and to be at end-expiration during acquisition of spectra [30]. To determine the intensity of the lipid peak, the water signal was suppressed using frequency-selective prepulses. The unsuppressed water resonance was used as internal reference (number of averages = 16). The spectra were fitted with AMARES [31] in the jMRUI software [32]. Values are given as T2-corrected ratios of the CH_2 peak, relative to the unsuppressed water resonance (as percentage) according to Hamilton et al. [33].

Oral glucose tolerance test

Subjects underwent an oral glucose tolerance test (OGTT) before and after overfeeding with a high-fat diet under sedentary conditions. A fasting blood sample was taken ($t = 0$), after which subjects drank a glucose solution (82.5 g glucose monohydrate dissolved in 600 mL water) within 5 min [34], a modification of the American Diabetes Association (ADA) guidelines [35]. Venous blood samples were collected every 15 min for the first hour ($t = 15$, $t = 30$, $t = 45$, and $t = 60$) and every 30 min for the second hour ($t = 90$ and $t = 120$). Plasma glucose and insulin concentrations were measured to determine glucose tolerance according to ADA criteria [36], the homeostasis model assessment (HOMA)-index [37] and the oral glucose insulin sensitivity (OGIS)-index [38].

Blood analysis

Blood was collected in tubes containing 30 µl of 0.2 mol/L EDTA. Plasma was immediately centrifuged at 3000 rpm for 10 min, frozen in liquid nitrogen and stored at −80 °C until analysis. Glucose (Roche, Basel, Switzerland) concentrations were determined enzymatically. Insulin levels were determined using a RIA (Linco Research, St. Charles, MO). Free-fatty acids using the Wako Nefa C test kit (Neuss, Germany), triglyceride with correction for free-glycerol (Sigma Diagnostics, St. Louis, MO), total cholesterol [39] by using the oxidase phenol 4-aminoantipyrine peroxidase method. High density lipoprotein-cholesterol was measured using the precipitation method, while low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald equation [40].

Statistical analysis

Data were first tested for normal distribution by using normality test Kolmogorov–Smirnov and Shapiro–Wilk. When normality was met, statistical comparison was performed using independent sample t test. Nonnormally distributed data were compared using the nonparametric Mann–Whitney U test. Repeated-measures ANOVA were performed to compare within- and between-groups difference in changes in liver fat accumulation and metabolic profile before and after overfeeding with a high-fat diet. Regression analysis was applied to assess the main effect of ethnicity on parameters of interest by including potential independent variables. The IBM SPSS Statistic program version 21 (SPSS, Chicago, IL) was used for statistical analysis, and statistical significance was set as $P < 0.05$.

Results

Subject characteristics

South Asian subjects were Indian ($n = 7$), Pakistani ($n = 1$), and Nepali ($n = 2$). White subjects were Dutch ($n = 2$), German ($n = 1$), Irish ($n = 1$), British ($n = 1$), Polish ($n = 2$), Italian ($n = 2$), and Portuguese ($n = 1$). South Asians were measured within 3 year ($n = 2$) and within 1 year ($n = 8$) of their stay in The Netherlands. Subjects' characteristics are presented in Table 1. South Asians had a slightly lower BMI than whites but not statistically significant (23.5 ± 2.8 versus 24.8 ± 3.3; $P = 0.36$). Groups were matched for body fat percentage ($22.0 \pm 5.1\%$ and $22.8 \pm 7.2\%$ for South Asians and whites respectively; $P = 0.78$). The FFM was lower in South Asians ($P = 0.005$), after corrected for height, the difference in FFM disappeared ($P = 0.29$). Both ethnicities had similar activity counts ($P = 0.91$).

Table 1 Subjects' characteristics

Characteristics	South Asian	White	*P*
N	10	10	–
Age (year)	26 ± 4	23 ± 2	0.05
Body weight (kg)	69.2 ± 7.3	81.9 ± 13.6	0.04
Body height (m)	1.72 ± 7.9	1.81 ± 6.2	0.02
BMI (kg/m^2)	23.5 ± 2.8	24.8 ± 3.3	0.36
Fat mass (%)	22.0 ± 5.1	22.8 ± 7.2	0.78
Fat-free mass (kg)	53.7 ± 4.3	61.9 ± 6.4	0.005
Fat mass index (kg/m^2)	5.3 ± 1.7	5.8 ± 2.6	0.59
Fat-free mass index (kg/m^2)	18.2 ± 1.5	18.9 ± 1.6	0.29
Fat mass/fat-free mass ratio	0.29 ± 0.1	0.31 ± 0.1	0.71
Waist circumference (cm)	85.1 ± 6.5	88.2 ± 8.6	0.37
Hip circumference (cm)	97.7 ± 5.8	102.0 ± 9.9	0.25
Waist to hip ratio	0.87 ± 0.03	0.87 ± 0.03	0.68
Physical activity accelerometer (10^3 counts/d)	1254 ± 395	1271 ± 243	0.91
PAL	1.67 ± 0.10	1.68 ± 0.06	0.89

Values are mean ± SDs. *PAL* physical activity level.

Differences between the groups in normally distributed data were assessed using Independent *t* test, nonnormally distributed data were assessed using nonparametric test Mann–Whitney *U* test

Energy intake and macronutrients composition during the dietary intervention

Whites had a higher energy need due to a higher FFM. Whites had a slightly higher energy intake during the weight maintenance period, although not statistically significant ($P = 0.39$). The actual energy intake was 11.5 ± 1.0 and 12.2 ± 2.1 MJ/d, containing fat, 29.3 ± 0.8% and 28.8 ± 1.1% ($P = 0.13$); carbohydrate, 55.2 ± 1.1% and 56.0 ± 1.5% ($P = 0.21$); protein, 15.5 ± 0.5% and 15.4 ± 0.6% ($P = 0.70$) for South Asians and whites, respectively.

During the overfeeding period, South Asians and whites consumed 150 ± 13% and 161 ± 27% ($P = 0.28$) of weight maintenance requirements, respectively. The macronutrient composition was 59.4 ± 0.6% and 59.0 ± 0.6% fat ($P = 0.21$), 26.3 ± 0.8% and 26.4 ± 0.7% carbohydrate ($P = 0.77$) and 14.3 ± 0.3% and 14.5 ± 0.4% protein ($P = 0.14$) for South Asians and whites, respectively.

Energy expenditure and substrate oxidation

The compliance to the overfeeding intervention along with the energy and substrate use is presented in Table 2. Whites had a higher energy intake ($P = 0.03$) and a higher TEE ($P = 0.004$), but energy balance was similar between groups ($P = 0.32$). Substrate balances (Fig. 2) were also similar between groups (protein balance, $P = 0.25$; carbohydrate balance, $P = 0.48$; fat balance, $P = 0.99$). Whites had a higher SMR due to their higher FFM than South Asians, after corrected for FFM, SMR did not differ between groups ($P = 0.12$). The contribution of SMR, AEE and DIT to TEE did not differ between groups and was on average 75–76%

Table 2 Energy expenditure and substrate oxidation during short-term overfeeding

	South Asian	White	*P*
N	10	10	
Energy intake (MJ/d)	17.4 ± 1.4	19.3 ± 1.7	0.03
Total energy expenditure, TEE (MJ/d)	9.4 ± 0.8	10.8 ± 0.9	0.004
Sleeping metabolic rate, SMR corrected for FFM (MJ/d)	7.4 ± 0.3	8.2 ± 0.3	0.12
SMR contribution (% of TEE)	76.6 ± 4.3	75.1 ± 6.4	0.82
Resting energy expenditure (MJ/d)	8.2 ± 0.7	9.2 ± 0.7	0.009
Diet-induce thermogenesis, DIT (MJ/d)	1.0 ± 0.3	1.1 ± 0.3	0.52
DIT contribution (%TEE)	10.6 ± 2.8	10.2 ± 2.8	0.76
Activity energy expenditure, AEE (MJ/d)	1.2 ± 0.3	1.6 ± 0.6	0.04
AEE contribution (%TEE)	12.8 ± 3.0	14.7 ± 3.9	0.17
Energy balance (MJ/d)	8.0 ± 1.2	8.5 ± 1.7	0.32
Average RQ	0.88 ± 0.05	0.86 ± 0.03	0.29
24-h Fat oxidation (MJ/d)	2.8 ± 2.0	3.9 ± 1.3	0.16
Fat oxidation (%TEE)	30.9 ± 19.4	38.6 ± 12.0	0.30
24-h Carbohydrate oxidation (MJ/d)	4.6 ± 1.5	4.7 ± 1.0	0.91
Carbohydrate oxidation (%TEE)	53.6 ± 18.3	46.6 ± 9.6	0.30
24-h Protein oxidation (MJ/d)	1.4 ± 0.3	1.5 ± 0.4	0.44
Protein oxidation (%TEE)	15.5 ± 3.1	14.8 ± 4.0	0.68

Values were means ± SDs. Values were averaged of a 3 day measurement. Differences between groups in normally distributed data were assessed using Independent *t* test, nonnormally distributed data were assessed using nonparametric test Mann–Whitney *U* test.

FFM fat-free mass, *RQ* respiratory quotient

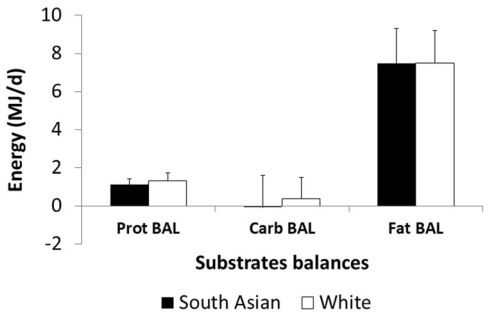

Fig. 2 Substrate balances during overfeeding period. South Asians (black bars), whites (white bars). Values were means ± SDs ($N = 10$ South Asians and 10 whites), differences was assessed using independent sample *t* test, protein balances ($P = 0.25$), carbohydrate balances ($P = 0.48$) and fat balances ($P = 0.99$)

($P = 0.82$), 13–15% ($P = 0.17$) and 10% ($P = 0.76$), respectively.

Substrate oxidation as a percentage of TEE was comparable between groups, with a large inter-individual variation in the fat and carbohydrate oxidation in each group. For South Asians and whites respectively, fat oxidation was 30.9 ± 19.4% and 38.6 ± 12.0% of TEE ($P = 0.30$), carbohydrate oxidation was 53.6 ± 18.3% and 46.6 ± 9.6% of TEE ($P = 0.30$) and protein oxidation was 15.5 ± 3.1% and 14.8 ± 4.0% of TEE ($P = 0.68$). Average RQ did not differ between two ethnicities ($P = 0.29$), neither did delta sleep-day RQ during 3 days of overfeeding ($P = 0.37$, $P = 0.79$, $P = 0.89$) for day 1, 2 and 3 respectively. Detailed information about day-RQ and night-RQ are provided in a supplemental file.

Liver fat content

Liver fat content at baseline did not differ between ethnicities (1.7 ± 1.4% and 2.6 ± 3.5%, $P = 0.45$) in South Asians and whites respectively. In Fig. 3, high-fat overfeeding increased liver fat ($P = 0.02$), being 2.7 ± 1.9% and 3.1 ± 4.9% in South Asians and whites respectively, but the increase was similar between ethnicities ($P = 0.64$). There was no association between the change in liver fat content and 24-h fat oxidation ($r = -0.17$, $P = 0.47$) and fat balance ($r = -0.03$, $P = 0.90$).

Fasting plasma parameters

Plasma parameters are presented in Table 3. High-fat overfeeding decreased fasting non-esterified fatty acids (NEFA) ($P = 0.03$) and TAG ($P = 0.001$) similarly ($P = 0.44$ and $P = 0.83$, respectively) in both ethnicities. LDL-cholesterol tended to increase more in South Asians than in whites ($P = 0.08$).

Overfeeding increased fasting insulin ($P = 0.04$) and the HOMA-index ($P = 0.04$) similarly between ethnicities ($P = 0.56$ and $P = 0.55$, respectively).

Glucose clearance (insulin sensitivity)

High-fat overfeeding under sedentary conditions decreased glucose clearance ($P = 0.001$) expressed as the OGIS-index (Table 3) and the decrease tended to be larger in South Asians than whites ($P = 0.06$). Figure 4 shows that overfeeding increased glucose ($P = 0.002$) and insulin ($P = 0.002$) response during the 2-h OGTT, with a tendency toward a higher increase in South Asians than whites ($P = 0.06$ and $P = 0.07$) for glucose and insulin response, respectively.

The change in liver fat content was positively correlated with the change in fasting insulin ($r = 0.55$, $P = 0.01$), HOMA-index ($r = 0.57$, $P < 0.01$), glucose response over 2-h ($r = 0.48$, $P = 0.03$), insulin response over 2-h OGTT ($r = 0.39$, $P = 0.09$) and was negatively correlated with the change in OGIS-index/glucose clearance ($r = -0.40$, $P = 0.09$).

In a multiple regression analysis, the increase in liver fat content predicted ($P = 0.04$) and a higher body fat tended to predict ($P = 0.08$) the increased fasting insulin, together explained 42% of the variation. The increased liver fat content predicted ($P = 0.03$) and a higher body fat tended to predict ($P = 0.08$) the increased HOMA-index, explained

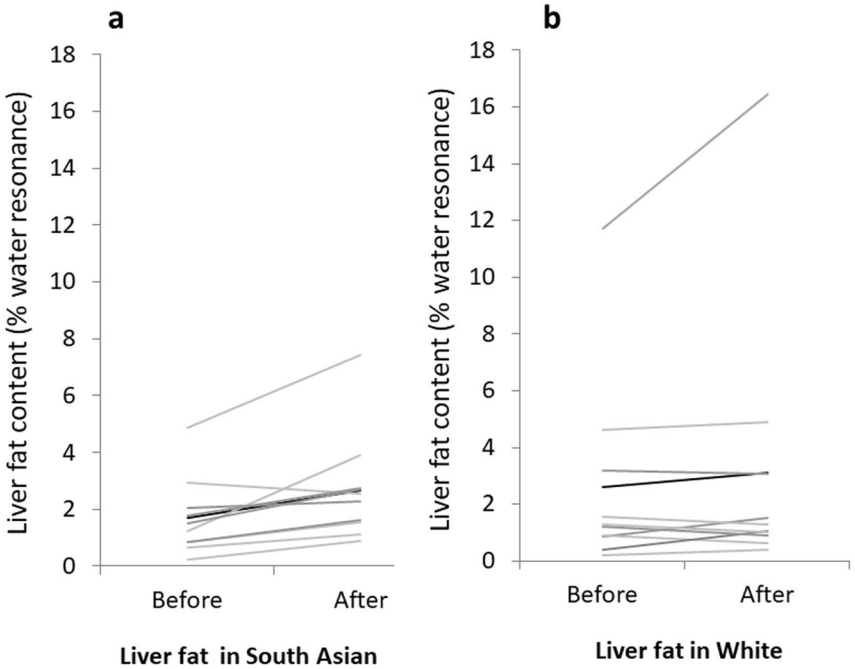

Fig. 3 Individual (gray line) and the mean (black line) response of liver fat content to overfeeding with a high-fat diet in South Asians (**a**) and whites (**b**). Liver fat content before and after overfeeding with a high-fat diet were assessed using ANOVA repeated measure ($N = 10$ South Asians and 10 whites). Overfeeding with a high-fat diet increased liver fat content ($P = 0.02$) but the increase did not differ between ethnicities ($P = 0.64$) and no interaction between diet and ethnicity ($P = 0.43$)

Table 3 Metabolic profile in response to overfeeding with a high-fat diet in a sedentary lifestyle[a]

Parameters	South Asian ($N = 10$)		White ($N = 10$)		Changes		P[b]		
	Before OHFD	After OHFD	Before OHFD	After OHFD	South Asian	White	Diet	Ethnicity	Diet × ethnicity
NEFA (μmol/L)	350.5 ± 138.4	308.5 ± 116.8	466.9 ± 247.4	289.1 ± 151.4	−42 ± 163.0	−177.8 ± 241.3	0.03	0.44	0.16
TAG (mmol/L)	1.0 ± 0.3	0.7 ± 0.3	0.9 ± 0.5	0.8 ± 0.3	−0.3 ± 0.2	−0.1 ± 0.3	0.001	0.83	0.13
Total chol (mmol/L)	5.0 ± 1.0	5.3 ± 1.0	4.4 ± 1.0	4.5 ± 1.2	0.3 ± 0.6	0.1 ± 0.5	0.17	0.15	0.50
HDL-chol (mmol/L)	1.1 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	0.2 ± 0.1	0.2 ± 0.1	0.001	0.72	0.55
LDL- chol (mmol/L)	3.4 ± 0.8	3.6 ± 1.0	2.8 ± 0.8	2.7 ± 1.1	0.2 ± 0.5	−0.04 ± 0.45	0.59	0.08	0.36
Ratio of HDL-chol/total chol	0.23 ± 0.04	0.26 ± 0.04	0.28 ± 0.1	0.33 ± 0.1	0.03 ± 0.02	0.04 ± 0.03	0.001	0.07	0.29
Ratio of LDL-chol/total chol	0.68 ± 0.04	0.676 ± 0.04	0.62 ± 0.07	0.59 ± 0.09	−0.003 ± 0.03	−0.03 ± 0.05	0.05	0.01	0.10
Glucose (mmol/L)	4.9 ± 0.3	5.0 ± 0.2	4.9 ± 0.3	4.88 ± 0.3	0.1 ± 0.3	−0.02 ± 0.15	0.21	0.73	0.11
Insulin (μU/ml)	11.8 ± 5.0	14.3 ± 7.7	10.5 ± 3.4	12.7 ± 6.6	2.6 ± 4.3	2.2 ± 5.5	0.04	0.56	0.89
HOMA-index	2.6 ± 1.1	3.2 ± 1.9	2.3 ± 0.8	2.8 ± 1.5	0.7 ± 1.1	0.5 ± 1.2	0.04	0.55	0.77
Glucose clearance, OGIS-index[c] (ml/min/m^2)	433.2 ± 74.1	330.1 ± 89.1	473.7 ± 53.8	416.8 ± 95.9	−103.2 ± 76.9	−57.0 ± 66.7	0.001	0.06	0.17

[a]Values were means ± SDs. Plasma parameters are in fasting condition except for the OGIS-index, which was based on the 2 h-oral glucose tolerance test (OGTT).

[b]Differences in the changes in parameters within groups (P_{diet}), between groups ($P_{ethnicity}$) and the interaction between diet and ethnicity were assessed using ANOVA repeated measures.

[c]For the OGIS-index (glucose clearance, ml/min per m^2 body surface)

OHFD overfeeding a high-fat diet, NEFA nonesterified fatty acids, TAG tri acyl glycerol, HOMA homeostasis model assessment, OGIS oral glucose insulin sensitivity

44% of the variation. Ethnicity was not a significant predictor for those parameters. The increased glucose response over 2-h OGTT was predicted by ethnicity ($P = 0.05$), South Asians more than whites and by a higher body fat ($P = 0.04$) which explained 35% of the variation.

Discussion

Our study demonstrated that South Asian and white men matched for body fat percentage, oxidized fat (as percentage of TEE), similarly in response to overfeeding with a high-fat diet under sedentary conditions. However, there was a large inter-individual variation in the contribution of fat oxidation to TEE in each ethnic group. Liver fat content increased similarly in both groups. Despite an equal contribution of fat oxidation to TEE and a comparable increase in liver fat content, South Asians tended to have an adverse lipoprotein profile and a larger decrease in glucose clearance and insulin sensitivity.

The sedentary conditions were confirmed by the large contribution of SMR to TEE, reaching on average 75–76% of TEE in both groups, resulting in a mean PAL of 1.32. AEE was only 13–15% of TEE, whereas at the same time overfeeding resulted in a similar DIT of around 10% for both ethnicities. AEE is a major determinant of dietary fat oxidation [41], it lowers glycogen storage [13] and stimulates fat oxidation [42].

Although the diet was high in dietary fat (60%), substrate partitioning showed a greater reliance on carbohydrate oxidation in both groups (on average 47–53% of TEE). Under sedentary conditions, glycogen stores were maintained (not depleted) therefore the degree of replenishment of the body's glycogen stores was low. This condition influences the contribution made by glucose and fatty acids to the fuel mix oxidized [43]. Most of the glucose was oxidized to match carbohydrate intake, as the body glycogen stores are small [42]. The contribution of carbohydrate oxidation to TEE was higher and fat was oxidized to a lesser extent to meet total energy requirement. Thus, most of the dietary fat was stored, resulting in a positive fat balance of 7–7.5 MJ/d. In addition, overfeeding prolonged the postprandial period and high insulin levels, thus promoting fat storage rather than oxidation. To meet energy requirements, the body oxidized more carbohydrate during the prolonged postprandial period. Consequently, the contribution of fat oxidation was lower during the postabsorptive period.

Indeed, we observed a large interindividual variation in the contribution of carbohydrate and fat oxidation to TEE, whereas protein oxidation was comparable and did not vary between ethnicities. Most individuals maintain relatively stable body weights and body composition during long periods of their lives [44, 45]. This steady state of

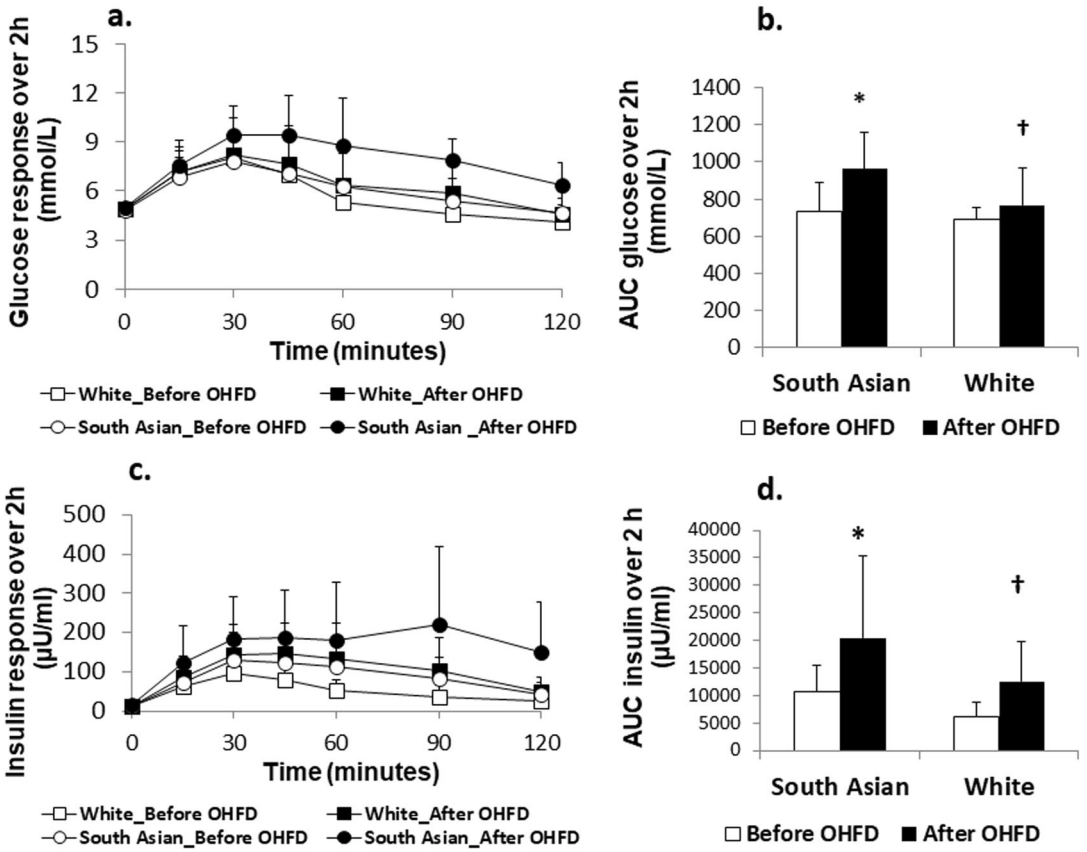

Fig. 4 Glucose **a** and insulin **c** responses in South Asians (before,○; after, ●) and whites (before,□; after,■) an overfeeding with a high-fat diet (OHFD) and the corresponding area under the curve (AUC) of glucose (**b**) and insulin (**d**) over 2-h OGTT (white bars, before OHFD; black bars, after OHFD). Values were means and SDs ($N = 10$ South Asians and 10 whites). Differences within and between groups after diet intervention as well as the interaction between diet and ethnicity were assessed with ANOVA repeated measures. AUC glucose ($P_{diet} = 0.002$; $P_{ethnicity} = 0.06$; $P_{diet \times ethnicity} = 0.09$), AUC insulin ($P_{diet} = 0.002$; $P_{ethnicity} = 0.07$; $P_{diet \times ethnicity} = 0.42$). Thus, *(significantly different before and after overfeeding with a high-fat diet for South Asians) and † (significantly different before and after overfeeding with a high-fat diet for White)

approximate weight maintenance, implies that their average energy intake matches their average energy expenditure (also the composition of the fuel mix that the body oxidizes is equivalent to the nutrient mix consumed) [45]. We assumed that before overfeeding, our subjects were in a steady state condition, in which glycogen level was maintained at the habitual level. Overfeeding disturbed this steady state. Fat oxidation is restrained until the expansion of the body fat mass is sufficient to promote fat oxidation to a rate proportional to dietary fat intake [45]. For many individuals the new steady state is reached only after an excessive amount of body fat has been accumulated, which may explain the observed large variation.

There was lack of association between the changes in liver fat content with 24-h fat oxidation, suggesting that liver fat accumulation may be affected by hepatic fat oxidation [46] rather than whole-body fat oxidation. A significant fraction of fatty acids are taken up by the liver during the postprandial period [15, 47, 48]. Depending on the amount of fat given, liver fat increased within 3 days [46] up to 2-3 weeks [15, 16]. South Asians were reported to have a higher liver fat content as compared to BMI-matched Caucasians [49], which may be expected as Asians have a higher body fat for the same BMI than whites [4, 8, 50]. Matching the two ethnicities for body fat percentage instead of BMI showed that baseline liver fat content and the increase in response to overfeeding did not differ between ethnicities.

Under sedentary conditions, LDL-cholesterol increased slightly more in South Asians in response to overfeeding, thus consistent with the study performed in free-living condition [17]. This may indicate differences in the rate of LDL clearance and production between ethnicities [51]. Fasting NEFA decreased similarly in both ethnicities and may be due to the suppression of lipolysis by relatively higher insulin levels [52]. TAG decreased after high-fat overfeeding but similar between ethnicities, and may be attributed to a lower proportion of carbohydrate in the high-fat diet [53–55]. High-carbohydrate intakes are hypothesized to increase TAG by inhibiting LPL action through

increased apo-C III production [56], high-fat intakes do not affect LPL and TAG clearance from the circulation [57].

Previously, we observed a similar decrease in insulin sensitivity in South Asians and whites in response to overfeeding with a high-fat diet under free-living conditions [17]. In the present study, subjects were sedentary and South Asians tended to have a larger decrease in insulin sensitivity than whites. South Asians may be more susceptible to the negative effect of being sedentary. The increase in fasting insulin and HOMA-index was strongly associated with the increased liver fat content. Insulin is well-known to hamper fat oxidation and to stimulate triglyceride storage in the liver, thereby favoring accretion of liver fat [46]. On the other hand, increased liver fat may be underlying insulin resistance, which in turn leads to elevated plasma insulin levels [52].

The low number of subjects was a limitation of our study, which is a direct consequence of the use of these state-of-the-art and labor-intensive techniques. However, the experimental set-up used is highly relevant, creating sedentary conditions for 3 days and simultaneously overfeeding with a high-fat diet, is a more physiological approach than lipid infusions and/or a very high-fat drink, as we are commonly exposed to short-term overfeeding with a high-fat during feast period. Another Dutch study [58] comparing these two ethnicities also found similar results whereby no difference in hepatic lipid content but impaired insulin sensitivity in South Asian men after a 5 day of high-fat diet. This study, however, matched South Asian and Caucasian men for Body Mass Index, whereas our study matched the two ethnicities for body fat percentage.

In conclusions, in South Asians and whites with similar body fat percentage, substrate partitioning was similar in response to overfeeding with a high-fat diet. Despite similar response of the two ethnicities in terms of substrate oxidation and liver fat accumulation, insulin sensitivity seems to be affected more severely in the South Asian population. The practical implication of the findings are; as South Asians were shown to be more susceptible to the negative effect of obesogenic environment, this population may need different dietary and physical activity guidelines as compared to Caucasian population.

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Author contributions SNW: conducted the research, performed the data analysis, and wrote the paper; KRW, VBS-H, and GP: designed the study, interpreted the data, and reviewed the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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