Dietary fat and total energy intake modifies the effect of genetic profile risk score on obesity: evidence from 48,170 UK Biobank participants

Running title - Macronutrients, Genetic Risk and Obesity

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Abbreviations: Body mass index (BMI), percentage of total energy intake (% TE), genetic profile risk score for obesity (GPRS-obesity), waist circumference (WC), standard deviation (SD), 95% confidence intervals (95% CI).

ABSTRACT

Background - Obesity is a multifactorial condition influenced by both genetics and lifestyle. The aim of this study was to investigate whether the association between a validated genetic profile risk score for obesity (GPRS-obesity) and body mass index (BMI) or waist circumference (WC) was modified by macronutrient intake in a large general population study.

Methods - This study included cross-sectional data from 48 170 white European adults, aged 37-73 years, participating on the UK Biobank. Interactions between GPRS-obesity, and macronutrient intake (including total energy, protein, fat, carbohydrate and dietary fibre intake) and its effects on BMI and WC were investigated.

Results - The 93-SNPs genetic profile risk score was associated with a higher BMI (β:0.57 $kg.m^{-2}$ per standard deviation (SD) increase in GPRS, [95%CI:0.53-0.60]; $P=1.9x10^{-183}$) independent of major confounding factors. There was a significant interaction between GPRS and total fat intake ($P_{[interaction]}=0.007$). Among high fat intake individuals, BMI was higher by 0.60 [0.52, 0.67] $kg.m^{-2}$ per SD increase in GPRS-obesity; the change in BMI with GPRS was lower among low fat intake individuals (β:0.50 [0.44, 0.57] $kg.m^{-2}$). Significant interactions with similar patterns were observed for saturated fat intake (High β:0.66 [0.59, 0.73] versus Low β:0.49 [0.42, 0.55] $kg.m^{-2}$, P-interaction=$2x10^{-4}$), and total energy intake (High β:0.58 [0.51, 0.64] versus Low β:0.49 [0.42, 0.56] $kg.m^{-2}$, P-interaction=0.019), but not for protein intake, carbohydrate intake and fiber intake (P-interaction >0.05). The findings were broadly similar using WC as the outcome.

Conclusions - These data suggest that the benefits of reducing the intake of fats and total energy intake, may be more important in individuals with high genetic risk for obesity.

Keywords – Obesity, adiposity, genetic risk score, diet, macronutrients

INTRODUCTION

The environment in many societies is today considered 'obesogenic' suggesting that the dramatic increase in obesity prevalence over the past three decades has been driven by changes in lifestyle, including increases in energy intake and reductions in energy expenditure.[1, 2] The fact that international obesity prevalence worldwide is not uniform, implies that there might be gene-environment interactions and that the overall genetic risk is modulated by lifestyle/environment.[3, 4] Some genetic factors may operate independently of environment, but others may confer greater predisposition to weight gain in an obesogenic environment,[5] a hypothesis supported by the results of twin studies of changes in adiposity in response to environmental influences.[6, 7]

Thus far, limited evidence of genotype-diet interaction effects on adiposity outcomes has been generated, and most of these studies have been at the single locus level,[8-11] despite the genetic influences on BMI being polygenic.[12] Furthermore, the only one study considering GPRS-obesity have used macronutrients to investigate the interaction between diet and GPRS-obesity,[13] whereas other 2 studies have used food groups instead of macronutrients.[14, 15] To date, no study has investigated the interaction effect between a GPRS and macronutrient intake on adiposity outcomes. In the current study, therefore, we investigated whether the associations between GPRS-obesity and adiposity outcomes were modulated by macronutrient intake (including total energy, protein, fats, carbohydrate, and dietary fibre) in the UK Biobank cohort, a large population sample.

METHODS

Study design

This study included cross-sectional baseline data from UK Biobank. Between April 2007 and December 2010, UK Biobank recruited 502 628 participants (5.5% response rate), aged 37-69 years from the general population.[16] Participants attended one of 22 assessment centres across UK[17] where they completed a screening questionnaire (including self-reported dietary intake), had physical measurements taken and provided biological samples, as described in detail elsewhere.[17] Aiming to maximize homogeneity and GPRS-obesity applicability, we restricted the sample to those who reported being of white UK ancestry and for whom BMI data were available. Of these participants, 119 859 had genotype data available for the GPRS-obesity SNPs used in this study and 48 170 participants had both dietary intake and genotype data available (Supplemental Figure 1).

The main outcome measures considered were BMI and waist circumference (WC). The independent predictor variable of interest was a genetic profile risk score for BMI; macronutrients intake (including total energy, protein, fats, carbohydrate, and dietary fibre) were treated as effect modifiers. Macronutrient intakes were expressed as age- and sex specific-thirds of total energy, protein, fat, carbohydrate, and dietary fibre intakes.

Ethics

UK Biobank received ethical approval from the North West Multicenter Research Ethics Committee (reference: 11/NW/03820). All participants gave written, informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Procedures

Dietary information was collected via the Oxford WebQ; a web-based 24-hour recall questionnaire which was developed specifically for use in large population studies.[18] The Oxford WebQ derives energy intake (total and from specific macronutrients) from the information recorded in McCance and Widdowson's "The composition of food. 5th edition".[19] Data for total energy intake is presented as kilocalories per day (kcal.day^{-1}) and protein, carbohydrate and fat intake are presented as a percentage of total energy (% TE), with dietary fibre presented as grams per day (g.day^{-1}). Subsequently for analysis purpose these dietary intake variables were converted into tertiles of intakes using the following cut-off points: Total energy intake (Lower <1845; Middle 1846 to 2319; Higher >2319 kcal.day^{-1}), protein intake (Lower <13.8; Middle 13.8 to 16.5; Higher >16.5 % of TE per day), fat intake (Lower <29.3; Middle 29.3 to 34.8; Higher >34.8 % of TE per day), saturated fat intake (Lower <10.8; Middle 10.8 to 13.6; Higher >13.6 % of TE per day), carbohydrates (Lower <44.1; Middle 44.1 to 50.6; Higher >50.6 % of TE per day), and dietary fibre intake (Lower <13.2; Middle 13.2 to 18.3; Higher >18.3 g.day^{-1}).

Physical activity self-reported PA was recorded using a self-completed questionnaire based on the International Physical Activity Questionnaire (IPAQ), as described elsewhere.[20, 21] Participants were asked "In a typical day, how many hours do you spend watching TV, doing PC screening or driving?", and this combined figure was used as a proxy for sedentary measure.[20, 21] Height and body weight were measured by trained nurses and body mass index (BMI) was calculated as (weight/height^2) and the WHO criteria[22] used to classify BMI into categories: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m^{-2}. Central obesity was defined as WC >88 cm for women and >102 cm for men.[22]

Area-based socioeconomic status was defined from postcode of residence using the Townsend score.[23] Medical history (physician diagnosis of depression, longstanding illness, diabetes, CVD, and cancer) was collected from baseline assessment questionnaire. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Genetic data analysis

For the present study, we used the first genetic data release (June 2015) based on approximately one-third of UK Biobank participants. Approximately 67% of this sample was genotyped using the Affymetrix UK Biobank Axiom array (Santa Clara, CA, USA) and the remaining 33% were genotyped using the Affymetrix UK BiLEVE Axiom array. The two arrays share over 95% marker content. Further information on the genotyping process is available on the UK Biobank website (http://www.ukbiobank.ac.uk/scientists-3/genetic-data), which includes detailed technical documentation (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf).

We deployed a standard set of sample quality control procedures and excluded participants of a non-white ethnic background, those with a relatedness coefficient >0.0442, those with a mismatch between self-reported and genetically determined gender, we also excluded participants who failed quality control for samples and genotype.

GPRS-obesity was derived from a set of 93 SNPs which were in turn derived from the 97 genome-wide significant BMI-associated SNPs reported by Locke et al.[12] 95 of these 97 SNPs were genotyped in the UK Biobank cohort (the two missing SNPs were rs2033529 and rs12016871), while two further SNPs (rs9925964 and rs17001654) were excluded on the basis of deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$) as assessed with PLINK v1.90;[24] there were no proxy SNPs

(r>0.8) within the UK Biobank dataset (Supplementary Supplemental Table 1). We constructed an externally-weighted GPRS-obesity for each participant, weighted by the per allele effect size estimates reported in the GIANT consortium study (*beta* per one-SD unit of BMI)[12] and calculated according to the procedure given in the PLINK manual (http://pngu.mgh.harvard.edu/~purcell/plink/profile.shtml), using the -no-mean-imputation flag. All SNPS included in the GPRS-obesity were significantly associated with BMI.

Statistical analysis

Baseline phenotypic and morbidity data were used for the present analyses. Linear robust regression analysis were used to test for associations between the main outcomes (BMI and WC) and GPRS-obesity. The GPRS was transformed to a z-score before use in models, so data are presented as BMI or WC changes per SD increase in GPRS. Associations between GPRS and BMI/WC categories (overweight: BMI ≥25 – 29.9 $kg.m^{-2}$; obese: BMI ≥30 $kg.m^{-2}$; centrally-obese: WC ≥88 cm for women and ≥102 cm for men) were investigated using logistic regression, with the 'normal' category as the referent.

Interactions between macronutrient intake (including total energy, protein, fat, carbohydrate, and dietary fibre) and GPRS-obesity in their effects on the continuous outcome measures (BMI and WC) were investigated using robust regression analysis. Whereas the interaction between macronutrient intake and GPRS-obesity for categorical outcomes (obesity and central obesity) were investigated using logistic regression. For these the interaction terms each macronutrient intake and GPRS-obesity were fitted treating all factors as continuous variables [BMI=GPRS x Diet + GPRS + Diet + covariates]. Continuous measures of macronutrients were used to limit spurious results from gene x environment interactions. Where interactions were statistically significant, stratified analyses were undertaken for each exposure.

For each of the approaches described above, we ran two incremental models that included an increasing number of covariates: "model 0" included age, sex, deprivation index score, month of recruitment, recruitment centre location, medical history (diabetes, long-standing illness, CVD, cancer, and depression), assessment centre, genetic-related measurement variables (batch, array number, genetic platform, and 10 principal components axes); "model 1" included all variables in Model 0, but also adjusted for smoking status, alcohol intake, total physical activity, sedentary behaviours, and total energy intake (this last one was only included as covariates when not being included in an interaction term).

All analyses were performed using STATA 14 statistical software (StataCorp LP). The P-value threshold for significance was set at <0.05.

RESULTS

The main characteristics of the participants by GPRS-obesity quartile, macronutrients intake (including total energy, protein, fat, carbohydrate and dietary fibre) are summarised in Tables 1 and Supplemental Table 2-7, respectively. In summary, 53.9% of the cohort was female, mean age was 56.5 years, 8.8% were current smokers, 63.0% were overweight or obese based on their BMI, and 30.0% were centrally obese based on their waist circumference (WC). Based on self-report total PA, 56.2% of the participants were physically active (>600 $MET\text{-}min.week^{-1}$). Correlations within dietary variables are presented in Supplemental Table 8; Correlations between obesity markers (BMI and WC) and GPRS-obesity and macronutrient are presented in Supplemental Table 9. In summary, no significant correlations were found between

macronutrients and GPRS-obesity, however, BMI and WC were significantly correlated with all macronutrients, these correlations varied from -0.087 for carbohydrates to 0.127 for total energy intake (Supplemental Table 9).

Association of genetic profile risk score with obesity measures

GPRS-obesity explained 1.9% and 1.1% of the variance in BMI and WC, respectively, with greater genetic risk being associated, as expected, with a higher BMI [β: 0.60 $kg.m^{-2}$ increase per SD change in GPRS (95%CI: 0.55, 0.64), $p=8x10^{-189}$] and greater waist circumference [β: 1.25 cm per SD change in GPRS (95%CI: 1.15, 1.36), $p=1.3x10^{-129}$]. After adjustment for socio-demographics, medical history, total sedentary behaviour and dietary factors these associations were marginally attenuated but remained highly significant for both BMI [β: 0.57 $kg.m^{-2}$ (95%CI: 0.53, 0.60), $p=1.9x10^{-183}$] and waist circumference [β: 1.17 cm (95%CI: 1.07, 1.27), $p=6.0x10^{-125}$] (Supplemental Table 10 and 11). The odds of having a BMI ≥25, BMI ≥30, or being centrally obese are presented in supplementary Supplemental Table 10 and 11, and are broadly consistent: those with increased genetic risk were at increased risk of being overweight or obese in every model.

Interactions between genetic profile risk score and macronutrient intake

The effect of the GPRS-obesity on adiposity was modified by these macronutrients (Figures 1, 2, and Tables 2, 3). The strongest interaction effect between diet and GPRS was observed for saturated fat intake (P-interaction=$2.2x10^{-4}$) independent of main confounder factors (Tables 2 and 3). For the fully adjusted model, the strength of the GPRS association with the outcomes increased with increasing saturated fat intake: from 0.45 [95% CI: 0.38, 0.51] $kg.m^{-2}$ per 1 SD increase in the GPRS in participants with the lowest third of intake to 0.65 [0.59, 0.72] $kg.m^{-2}$ in participants with the highest third of saturated fat intake (Table 2 and Figure 1). Those in the lowest saturated fat intake third and who were in the highest quarter of the GPRS-obesity had 1.1 units higher BMI than the lowest quarter of the GPRS-obesity individuals. However, the individuals with the highest saturated fat intake and in the highest GPRS quarter had 1.8 units higher BMI compared to the lowest quarter of the GPRS-obesity individuals with the same levels of saturated fat intake (Figure 1). Similarly, a strong interaction was found for total energy (P-interaction=0.007) and total fat (P-interaction=0.007) but not carbohydrate, protein and dietary fiber intake (P-interaction >0.05), which significantly modified the effect of the GPRS-obesity on BMI independent of main confounder factors (Table 2 and Figure 1). Comparable findings were found for waist circumference (Table 3 and Figure 2), although the interaction between GPRS-obesity and total energy intake on WC was borderline significant (P-interaction =0.016).

Sensitivity analyses were conducted to elucidate whether the interaction between total fat or saturated fat intake and the GPRS-obesity was independent of total energy intake, and vice versa. These sensitivity analyses did not alter the interaction and magnitude of the association of our findings (Data not shown).

In addition, we investigated whether the association between GPRS-obesity and overall obesity (BMI >30.0) or waist circumference cut-offs (WC ≥88 and ≥102 cm for women and men) were modified by nutrient intake. These results revealed no significant interactions for any outcomes (Supplemental Table 12 and 13).

DISCUSSION

Main findings

This study provides novel evidence that the associations between a 93 SNP genetic profile risk score for obesity and phenotypic measures of adiposity (BMI and WC) may be substantially modulated by total fat, total energy intake, and in particular saturated fat. These results extend the limited evidence available to date on the interaction between GPRS-obesity and diet. Moreover, our data indicate that these interactions are likely independent of a range of confounders including socio-demographic factors, diet, and co-morbidities. These findings emphasise that, although obesity is partly genetically determined, diet plays an important role in mediating this relationship. Participants with the highest genetic predisposition to obesity (Quartile 4) who have a high level of saturated fat intake had 1.8 $kg.m^{-2}$ higher BMI and 3.7 cm higher WC compare to those with the lowest saturated fat intake but same genetic predisposition; Thus individuals who are unfortunate enough to be genetically predisposed to obesity can potentially reduce their adiposity by maintaining a lower level of saturated fat, total fat and therefore total energy intake. Thus, identifying this sub-group of genetically prone (and thus susceptible) individuals, offering personalised dietary advice and supporting their adoption of a healthier lifestyle, perhaps particular in following a low fat diet, may be of potential value for personalised health advice.

It has previously been shown that diet can modulate the effect of genes on obesity traits; however, most of this evidence has been generated from single genes studies,[8, 10, 11] with only a few studies investigating the effect of macronutrients[13] or foods[14, 15] on GPRS-obesity. Rukh et al., is the only study to date that have investigated the interaction effect between a 13-SNP genetic risk score and macronutrients on BMI among 26 107 nondiabetic participants.[13] This study did not found any significant interaction between GPRS and dietary intakes of fat, carbohydrates, protein, fibre and total energy intake on BMI or risk of obesity. These findings are in disagreement with results from the current study, as we provided novel evidence on the interaction of fats and energy intake with GPRS-obesity on BMI and WC, in a large cohort of white European adults, and strengthened the limited evidence that genetic predisposition to obesity can be modulated by lifestyle factors, such as diet[8, 10, 14, 15] and physical activity.[25] Differences within Rukh et al., and our study could be explained by difference in the number of SNP used to construct the genetic risk score. Additionally, our study included a larger sample and used a weighted GPRS-obesity whereas Rukh et al, reported their finding based on an unweighted genetic risk score, which may not capture difference on the magnitude of association within each SNP and the outcome.

An interesting observation from our study was that the magnitude of the interaction with GPRS-obesity and adiposity was stronger for saturated fat intake compared to other macronutrients (1.8 $kg.m^{-2}$ difference in BMI between low and high GPRS-obesity for a high intake of saturated fat vs 1.1 $kg.m^{-2}$ difference for a low saturated fat intake). Moreover, this association was apparently independent of total energy intake. This greater magnitude of the association is in line with recent finding from the UK Biobank, that suggest that fat makes a greater contribution to overall energy intake than other macronutrients in all BMI categories, but especially in the obese group.[26] Fat intake, especially saturated fat is consider a surrogate of unhealthy food intake, including processed and other high energy density foods.[27, 28] There is ample research from animal and clinical studies, from controlled trials, and from epidemiologic and ecologic analyses that provides strong evidence that dietary fat plays a role in the development and treatment of obesity.[27, 28] A reduction in fat and total energy intake will help to maintain energy balance and thus is an effective strategy for reducing the present epidemic of obesity worldwide.[27, 28] A review of the results from 33 randomized controlled trials that studied the effects of a reduction in the amount of energy from fat in the diet provided high quality and consistent evidence that lower total fat intake leads to statistically significant and clinically meaningful, sustained reductions in body weight in adults.[28] Our results suggest that individuals with high genetic risk for obesity could moderate the effect of their "bad genes or obesity genes" by reducing

their total energy intake. This goal can be facilitated by reducing the amount of fats in the diet. Indeed, our results predict that such individuals would do better on low fat versus low carbohydrate diets, a testable hypothesis in future trials.

Strengths and limitations of the study

UK Biobank provided an opportunity to test our research question in a very large general population cohort and the main outcomes used in this study were collected using validated and standardised methods. Additionally, dietary intake was assessed using validated methods, trained staff and standard operating procedures.[17] Although those who reported unfeasible energy intake values were removed from the analysis we cannot discard the potential dilution bias due to the self-reported nature of the dietary data, which could distort the true underlying relationships between diet and our genetic profile and its effect on adiposity. Another limitation of the study is that the GPRS only captures a small proportion of the genetic variance in BMI. A polygenic risk score (PRS) analysis may provide greater accuracy in the measurement of the interaction effects reported here, although it is likely that this will have to await even larger GWAS studies to ensure that only genuine BMI loci are included in the PRS. Nevertheless, significant interaction effects were detected in our analysis and power was clearly adequate. A further important limitation is the cross-sectional nature of the study. Future prospective studies on a massive scale will be needed to estimate the effects of dietary interventions in groups with different genetic liabilities based on GPRS or PRS variables, and such an analysis was beyond the scope of our study.

Implications of findings

Data from 900 000 adults reported that 5-kg.m^{-2} increase in BMI was associated with 40% higher risk for CVD mortality.[29] Given the high current prevalence of overweight and obesity worldwide,[30] it is important to develop strategies to reduce adiposity in pursuit of improved public health. The present data – with the most comprehensive genetic profile risk score for obesity available to date – clearly demonstrate that the association of total energy intake, total fat and saturated fat on adiposity outcomes are strongest in those with a high genetic predisposition to obesity. Our finding suggest that fat and total energy intake are other factors which need to be consider, alongside socio-demographic,[31] sleep,[32] physical activity[31, 33] and other dietary intake patterns.[11, 13-15, 31] Evidence of such gene–lifestyle interactions may empower and motivate individuals with high genetic risk for obesity to adopt healthier lifestyle behaviours through knowledge that such behaviour change can be effective in preventing obesity and, therefore, risk of obesity-related non-communicable diseases.[34-36]

In conclusion, despite the fact that this 93-SNP genetic profile risk score was robustly associated with BMI and WC, our results show that lower levels of total fat and saturated fat intake attenuates the strength of the association between genetic predisposition to obesity with BMI and waist circumference. These findings are potentially relevant for public health and suggest that promotion of reducing saturated fat intake particularly in those who are genetically susceptible to higher BMI, could be an important strategy for addressing the current obesity epidemic and disease burden. Future trials would usefully test such a hypothesis.

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AUTHOR CONTRIBUTIONS

CCM, JPP, JMRG and NS contributed to the conception and design of the study, advised on all statistical aspects and interpreted the data. CCM, DL, YG and FP perform the statistical analysis. CCM, JPP, JMRG and NS drafted the manuscript. CCM, DLM, PW, JA, SI, SG, YG, LS, FP, DM, MESB, JPP, JMRG and NS reviewed the manuscript and approved the final version to be published. CCM, DML, JPP, JMRG and NS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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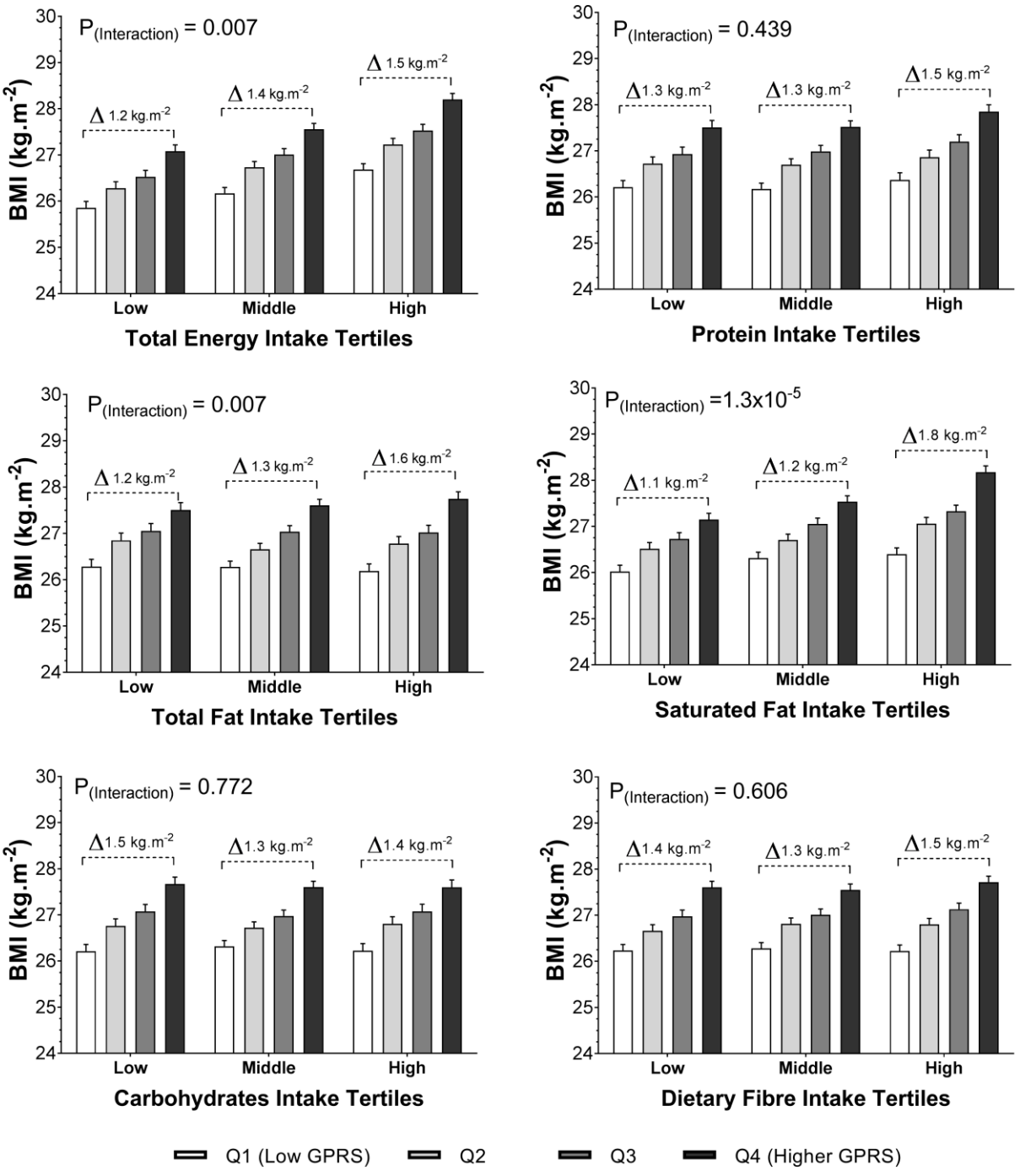
414 **Figures legends**



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416 **Figure 1. Association between BMI and genetic profile risk score by macronutrients strata**

417 Data presented as adjusted means by dietary intake tertile. Models were adjusted for age, sex, CVD, cancer, diabetes,
418 depression, long standing illness, genetic-related measurement variables (batch, array number, genetic platform, and 10
419 principal components axes), smoking, deprivation, month of recruitment, alcohol intake, total PA, sedentary behaviour and
420 total energy intake (only when this last one was not used as an interaction term).

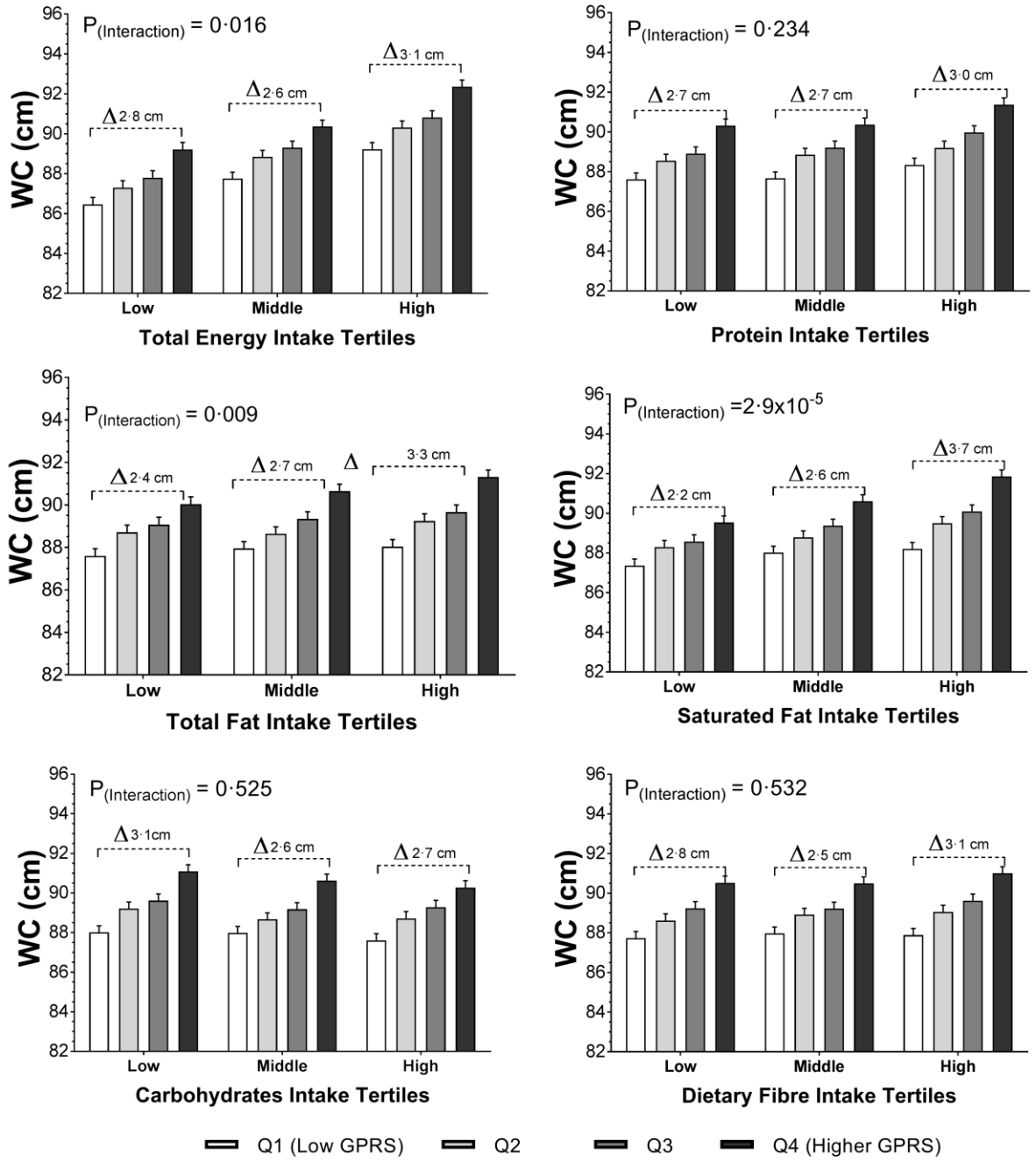

Figure 2. Association between WC and genetic profile risk score by macronutrients strata

Data presented as adjusted means by dietary intake tertile. Models were adjusted for age, sex, CVD, cancer, diabetes, depression, long standing illness, genetic-related measurement variables (batch, array number, genetic platform, and 10 principal components axes), smoking, deprivation, month of recruitment, alcohol intake, total PA, sedentary behaviour and total energy intake (only when this last one was not used as an interaction term).

428 **Table 1. Cohort characteristic by genetic profile risk score quartiles**

	Overall	Q1 (Lowest GPRS)	Q2	Q3	Q4 (Highest GPRS)
Socio-demographics					
Total, n	48 170	12 229	12 037	11 863	12 041
Women, n (%)	25 982 (53.9)	6 615 (54.1)	6 438 (53.5)	6 425 (54.2)	6 504 (54.0)
Age (years), mean (SD)	56.5 (7.8)	56.5 (7.8)	56.5 (7.8)	56.5 (7.8)	56.6 (7.8)
Deprivation index, mean (SD)	-1.75 (2.8)	-1.74 (2.8)	-1.76 (2.7)	-1.77 (2.7)	-1.75 (2.8)
Deprivation index Tertile, n (%)					
Lower (Less deprived)	17 964 (37.3)	4 542 (37.2)	4 468 (37.2)	4 454 (37.6)	4 500 (37.4)
Middle	16 853 (35.0)	4 310 (35.3)	4 225 (35.2)	4 147 (35.0)	4 171 (34.7)
Higher (Most deprived)	13 290 (27.6)	3 358 (27.5)	3 327 (27.7)	3 251 (27.4)	3 354 (27.9)
Smoking status, n (%)					
Never	27 109 (56.4)	6 968 (57.1)	6 843 (56.9)	6 672 (56.3)	6 626 (55.1)
Previous	16 728 (34.8)	4 132 (33.9)	4 177 (34.8)	4 160 (35.1)	4 259 (35.4)
Current	4 250 (8.8)	1 106 (9.1)	1 000 (8.3)	1 010 (8.5)	1 134 (9.4)
Obesity-related markers					
BMI ($kg.m^{-2}$), mean (SD)	26.9 (4.5)	26.2 (4.1)	26.7 (4.4)	27.1 (4.5)	27.7 (4.9)
BMI Categories, n (%)					
Underweight (<18.5 $kg.m^{-2}$)	259 (0.5)	92 (0.8)	67 (0.6)	44 (0.4)	56 (0.5)
Normal weight (18.5-24.9 $kg.m^{-2}$)	17 586 (36.5)	5 184 (42.4)	4 588 (38.1)	4 128 (34.8)	3 686 (30.6)
Overweight (25.0-29.9 $kg.m^{-2}$)	20 353 (42.3) 9	5 047 (41.3)	5 035 (41.8)2 347	5 170 (43.6)	5 101 (42.4)
Obese (≥30.0 $kg.m^{-2}$)	972 (20.7)	1 906 (15.6)	(19.5)	2 521 (21.3)	3 198 (26.6)
Body fat (%), mean (SD)	30.8 (8.5)	30.0 (8.2)	30.5 (8.4)	30.9 (8.5)	31.7 (8.6)
Waist Circumference (cm), mean (SD)	89.2 (13.0)	87.6 (12.5)	88.9 (12.8)	89.4 (13.0)	91.0 (13.6)
Central Obesity, n (%)	14 443 (30.0)	3 060 (25.0)	3 487 (29.0)	3 636 (30.7)	4 260 (35.4)
Physical activity					
Total PA ($METs.hr^{-1}.week^{-1}$), mean (SD)	41.9 (53.7)	41.9 (53.4)	41.5 (53.2)	41.9 (53.4)	42.1 (54.6)
Physically active individuals, n (%)	27 046 (56.2)	6 844 (56.0)	6 811 (56.6)	6 641 (56.0)	6 750 (56.1)
TV viewing ($h.day^{-1}$), mean (SD)	2.58 (1.5)	2.54 (1.5)	2.57 (1.5)	2.59 (1.5)	2.63 (1.6)
Total Sedentary Behaviour ($h.day^{-1}$), mean (SD)	5.08 (2.2)	5.02 (2.2)	5.07 (2.2)	5.10 (2.2)	5.14 (2.2)
Dietary intake, mean (SD)					
Total energy intake ($Kcal.day^{-1}$)	2 171 (563)	2 175 (566)	2 174 (564)	2 172 (561)	2 164.3 (563)
Protein intake (% of TE)	15.5 (3.4)	15.4 (3.5)	15.3 (3.4)	15.5 (3.4)	15.6 (3.5)
Carbohydrates intake (% of TE)	46.9 (7.9)	47.0 (7.8)	47.0 (7.9)	47.0 (7.9)	46.8 (8.1)
Total Fat intake (% of TE)	32.2 (6.6)	32.2 (6.5)	32.2 (6.6)	32.2 (6.5)	32.2 (6.7)
Saturated intake (% of TE)	12.4 (3.3)	12.4 (3.3)	12.4 (3.3)	12.4 (3.3)	12.4 (3.3)

Dietary fibre intake (g.day^{-1})	16.4 (6.2)	16.3 (6.1)	16.4 (6.2)	16.4 (6.2)	16.5 (6.3)
Health status, n (%)					
Diabetes history	1 959 (4.1)	453 (3.7)	447 (3.7)	468 (4.0)	591 (4.9)
Cancer history	3 651 (7.6)	942 (7.7)	941 (7.8)	858 (7.3)	910 (7.6)
CVDs	12 956 (26.9)	3 064 (25.1)	3 225 (26.8)	3 236 (27.3)	3 431 (28.5)
Depression	16 143 (33.7)	4 109 (33.8)	3 938 (32.9)	3 955 (33.5)	4 141 (34.5)
Long standing illness	14 310 (30.2)	3 499 (29.1)	3 540 (29.9)	3 538 (30.4)	3 733 (31.6)

Data presented as mean and SD for continuous variables and as n and % for categorical variables. TE: total energy intake. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Deprivation was derived using the Townsend score (a greater Townsend index score implies a greater degree of deprivation). Range for the GPRS-obesity are as follow Q1: -4.06 to -0.67 SD; Q2: -0.68 to -0.001 SD; -0.002 to 0.67 SD; Q4: 0.67 to 4.03 SD.

Table 2. Association between Genetic Profile Risk Score (GPRS) and BMI by tertile of each macronutrient

		Lower intake		Middle intake		Higher intake		Interaction
	n	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	p-value
Total energy intake (Kcal.day^{-1})								
Model 0	48 170	0.49 (0.42; 0.56)	$3.4x10^{-46}$	0.58 (0.51; 0.64)	$3.9x10^{-68}$	0.58 (0.51; 0.64)	$1.9x10^{-62}$	0.019
Model 1	47 608	0.47 (0.41; 0.54)	$7.4x10^{-45}$	0.54 (0.48; 0.60)	$2.7x10^{-63}$	0.56 (0.50; 0.63)	$2.1x10^{-64}$	0.007
Protein intake (% of TE)								
Model 0	48 170	0.51 (0.44; 0.58)	$8.4x10^{-52}$	0.54 (0.47; 0.60)	$7.6x10^{-59}$	0.58 (0.52; 0.65)	$1.1x10^{-61}$	0.173
Model 1	47 609	0.50 (0.44; 0.56)	$5.7x10^{-53}$	0.52 (0.46; 0.58)	$2.9x10^{-58}$	0.55 (0.48; 0.62)	$8.6x10^{-58}$	0.439
;tal fat intake (% of TE)								
Model 0	48 170	0.50 (0.44; 0.57)	$3.6x10^{-52}$	0.55 (0.49; 0.61)	$1.1x10^{-62}$	0.60 (0.52; 0.67)	$2.4x10^{-61}$	0.024
Model 1	47 609	0.48 (0.41; 0.54)	$1.6x10^{-49}$	0.52 (0.46; 0.58)	$4.1x10^{-60}$	0.58 (0.51; 0.64)	$3.8x10^{-61}$	0.007
Saturated fat intake (% of TE)								
Model 0	48 170	0.49 (0.42; 0.55)	$8.0x10^{-50}$	0.50 (0.43; 0.56)	$4.5x10^{-52}$	0.66 (0.59; 0.73)	$4.7x10^{-75}$	$2.2x10^{-4}$
Model 1	47 609	0.45 (0.38; 0.51)	$3.5x10^{-44}$	0.48 (0.41; 0.54)	$1.8x10^{-50}$	0.65 (0.59; 0.72)	$1.2x10^{-77}$	$1.3x10^{-5}$
Carbohydrates intake (% of TE)								
Model 0	48 170	0.58 (0.52; 0.65)	$6.0x10^{-68}$	0.49 (0.42; 0.56)	$5.1x10^{-47}$	0.57 (0.50; 0.63)	$7.9x10^{-60}$	0.575
Model 1	47 609	0.56 (0.50; 0.63)	$2.7x10^{-67}$	0.47 (0.40; 0.53)	$1.2x10^{-45}$	0.54 (0.47; 0.60)	$4.8x10^{-57}$	0.772
Dietary fibre intake (g.day^{-1})								
Model 0	48 170	0.56 (0.49; 0.62)	$3.6x10^{-59}$	0.49 (0.43; 0.56)	$4.0x10^{-48}$	0.61 (0.54; 0.67)	$6.5x10^{-70}$	0.505
Model 1	47 609	0.54 (0.47; 0.60)	$6.9x10^{-58}$	0.47 (0.41; 0.53)	$3.5x10^{-47}$	0.57 (0.50; 0.63)	$5.8x10^{-66}$	0.606

Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI by 1-tertile increase in the genetic profile risk score by the exposure.

Model 0 was adjusted for age, sex, deprivation, CVD, cancer, diabetes, depression, month of recruitment, and genetic-related measurement variables (assessment centre, batch, array number, etc.).

Model 1 was adjusted for model 0 plus smoking, alcohol intake, total PA and sedentary behaviour. In addition, model 1 was also adjusted for total energy intake when this was not used as a main interaction factor in the model.

Table 3. Association between Genetic Profile Risk Score (GPRS) and waist circumference by tertile of each macronutrient

		Lower intake		Middle intake		Higher intake		Interaction
Tertile	**n**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**p-value**
Total energy intake (Kcal.day^{-1})								
Model 0	47 783	1.09 (0.92; 1.26)	$7.4x10^{-36}$	1.12 (0.95; 1.27)	$2.0x10^{-40}$	1.20 (1.02; 1.37)	$5.7x10^{-42}$	0.042
Model 1	47 596	1.04 (0.88; 1.21)	$1.2x10^{-34}$	1.02 (0.86; 1.18)	$9.7x10^{-37}$	1.17 (1.00; 1.34)	$2.9x10^{-43}$	0.016
Protein intake (% of TE)								
Model 0	47 784	1.04 (0.87; 1.21)	$2.3x10^{-33}$	1.10 (0.93; 1.26)	$1.0x10^{-38}$	1.23 (1.05; 1.40)	$1.2x10^{-43}$	0.095
Model 1	47 597	1.03 (0.86; 1.19)	$2.0x10^{-34}$	1.05 (0.89; 1.21)	$1.8x10^{-37}$	1.14 (0.98; 1.31)	$1.8x10^{-40}$	0.234
Total fat intake (% of TE)								
Model 0	47 784	1.02 (0.85; 1.19)	$1.7x10^{-32}$	1.12 (0.96; 1.29)	$1.6x10^{-41}$	1.24 (1.07; 1.42)	$2.2x10^{-43}$	0.031
Model 1	47 597	0.96 (0.80; 1.12)	$6.9x10^{-31}$	1.06 (0.90; 1.22)	$3.7x10^{-39}$	1.20 (1.03; 1.37)	$3.8x10^{-43}$	0.009
Saturated fat intake (% of TE)								
Model 0	47 784	0.96 (0.79; 1.13)	$2.1x10^{-29}$	1.06 (0.89; 1.22)	$1.0x10^{-36}$	1.37 (1.19; 1.55)	$1.6x10^{-52}$	0.0003
Model 1	47 597	0.86 (0.70; 1.03)	$1.4x10^{-25}$	1.01 (0.85; 1.17)	$1.7x10^{-35}$	1.35 (1.18; 1.52)	$5.8x10^{-54}$	$2.6x10^{-5}$
Carbohydrates intake (% of TE)								
Model 0	47 784	1.22 (1.05; 1.38)	$8.3x10^{-47}$	1.04 (0.87; 1.20)	$1.6x10^{-33}$	1.10 (0.93; 1.27)	$2.1x10^{-35}$	0.879
Model 1	47 597	1.19 (1.03; 1.35)	$2.8x10^{-47}$	0.98 (0.82; 1.15)	$2.6x10^{-32}$	1.03 (0.86; 1.20)	$4.6x10^{-33}$	0.525
Dietary fibre intake (g.day^{-1})								
Model 0	47 784	1.14 (0.97; 1.30)	$1.1x10^{-39}$	0.99 (0.82; 1.16)	$2.6x10^{-31}$	1.27 (1.10; 1.45)	$2.1x10^{-47}$	0.414
Model 1	47 597	1.10 (0.93; 1.26)	$6.5x10^{-39}$	0.94 (0.78; 1.10)	$3.7x10^{-30}$	1.18 (1.02; 1.35)	$2.4x10^{-44}$	0.532

Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in waist circumference by 1-tertile increase in the genetic profile risk score by the exposure.

Model 0 was adjusted for age, sex, deprivation, month of recruitment, CVD, cancer, diabetes, depression and genetic-related measurement variables (assessment centre, batch, array number, etc.).

Model 1 was adjusted for model 0 plus smoking, alcohol intake, total PA and sedentary behaviour. In addition, model 1 was also adjusted for total energy intake when this was not used as a main interaction factor in the model.