The combination of physical activity and sedentary behaviours modifies the genetic predisposition to obesity

Carlos A Celis-Morales[1], Donald M Lyall[2], Mark ES Bailey[3], Fanny Petermann[1,2], Jana Anderson[2], Joey Ward[2], Daniel F Mackay[2], Paul Welsh[1], Jill Pell[2]*, Naveed Sattar[1]*, Jason MR Gill[1]* and Stuart R Gray[1]*

Author affiliations

[1] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.

[2] Institute of Health and Wellbeing, University of Glasgow, Glasgow, U.K.

[3] School of Life Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, U.K.

*These authors also contributed equally to this work and are joint senior authors.

CORRESPONDING AUTHOR

Dr Stuart Gray

BHF Glasgow Cardiovascular Research Centre,

Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8TA, UK.

Tel: 044 (0) 141 3302569

Fax: 044 (0) 141 3305481

E-mail address: stuart.gray@glasgow.ac.uk

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

Keywords – Obesity, adiposity, genetics, physical activity.

What is already known about this subject? Previous work has indicated that both physical activity (PA) and sedentary behaviour may moderate the association between genes and obesity.

What does your study add? This study provides novel evidence that the combination of lower levels of PA and higher levels of sedentary behaviours results in stronger associations between our genetic risk score for BMI.

Abstract

Objective - To investigate whether the association between a validated genetic profile risk score for body mass index (BMI) (GPRS-BMI) (based on 93 SNPs) and phenotypic obesity (BMI) was modified by the combined categories of PA and sedentary behaviours in a large population-based study.

Methods - This study included cross-sectional baseline data from 338,216 white European adult men and women aged 37-73 years. Interaction effects of GPRS-BMI with the combined categories of PA and sedentary behaviour on BMI were investigated.

Results - There was a significant interaction between GPRS-BMI and the combined categories of objectively-measured PA and total sedentary behaviour ($P_{[interaction]}=3.5x10^{-6}$): among physically inactive and highly sedentary individuals, BMI was higher by 0.60 $kg.m^{-2}$ per SD increase in GPRS-obesity ($p=8.9x10^{-50}$); whereas the relevant BMI difference was 38% lower among physically active and low sedentary individuals (β:0.37 $kg.m^{-2}$, $p=2.3x10^{-51}$). A similar pattern was observed for the combined categories of objective PA and TV-viewing (inactive/high TV-viewing β:0.60 versus active/low TV-viewing β:0.40 $kg.m^{-2}$, $P_{[interaction]}=2.9x10^{-6}$).

Conclusions - This study provides evidence that combined categories of PA and sedentary behaviours modify the extent to which genetic predisposition to obesity results in higher BMI.

Introduction

The environment in many societies is today considered 'obesogenic' and it has been suggested that the dramatic increase in obesity prevalence in recent years has been driven by changes in lifestyle, including increases in energy intake and reductions in physical activity (PA) (1, 2, 3). However, there is also robust evidence from twin studies suggesting that obesity is a "multifactorial" condition and that 40-70% of the variability in obesity can be attributed to genetic factors (1, 4). Whilst the obesogenic environment and genes can individually account for a large proportion of the prevalent obesity recent research has also indicated that these two factors interact to further increase obesity (5). Some genetic factors may operate independently of environment, but others may confer greater predisposition to weight gain in an obesogenic environment (6), a hypothesis supported by the results of twin studies of changes in adiposity in response to environmental influences (4).

Thus far, limited evidence of genotype-lifestyle interaction effects on BMI has been generated, and most of these studies have been at single locus level, despite the genetic influences on BMI being polygenic. Most studies to date investigating potential gene-PA or gene-sedentary behaviour interactions for adiposity, have been focused on the effect of individual genes (7, 8, 9, 10, 11, 12). Only a few studies have investigated whether polygenic risk scores or genetic profile risk scores for BMI (GPRS-BMI), which provide great BMI prediction than a single gene, interact with PA (13, 14, 15, 16, 17, 18, 19) or sedentary behaviour (16, 20, 21). To date, only one study has investigated the modifying effect of combined PA and TV-viewing on the genetic predisposition related to adiposity outcomes (15). However, this study had a relatively small sample size (n~12,000), the genetic risk score was derived from a relatively small number of BMI loci (32-SNPs) and TV-viewing was used as main exposure, which only represents part of the sedentary behaviour spectrum (15). Recent evidence suggests that the joint effect of physical activity and sedentary behaviours

may be more informative (22) than considering the effect of physical activity or sedentary behaviour independently. Recent prospective studies have demonstrated that being highly sedentary and physically inactive is associated with a larger adverse effect on mortality than those who are active but highly sedentary, or vice versa (22). This joint detrimental effect of physical activity and sedentary behaviours may also modify the genetic predisposition to obesity; however, there is limited evidence on this regard (15). In the current study, we therefore investigated whether the associations of a comprehensive and validated GPRS-BMI (23) with BMI was modulated by the combined categories of PA (both objectively-measured and self-reported) and sedentary behaviours (total sedentary behaviour and TV-viewing) in the UK Biobank cohort, a large population sample.

Methods

Study design

Between April 2006 and December 2010, UK Biobank recruited more than 500,000 participants (5.5% response rate), aged 40-69 years from the general population (24). Participants attended one of 22 assessment centres across England, Wales and Scotland (25), where they completed a touch-screen questionnaire (including self-reported PA), had physical measurements taken and provided biological samples, as described in detail elsewhere (25). Imputed genotypes were available for 488 369 participants, of these participants, 338,216 had full data available for genotype data available for the GPRS-BMI SNPs, self-reported physical activity and sedentary-related behaviours used in this study after exclusions (detailed below, due to quality control, relatedness, mismatching of reported gender and genetically estimated sex, and non-white ethnicity). 103,712 participants (including 62,881 with genotyping data) had objectively-measured PA data available.

The main outcome measure considered was BMI. The independent predictor variable of interest was a genetic profile risk score for BMI; combined categories of PA and sedentary behaviours or TV-viewing were treated as moderators. The combined categories were a) High PA / Low sedentary time "busy bees"; b) High PA / High Sedentary time; c) Low PA / Low Sedentary time; and d) Low PA / high sedentary time "couch potato". Socio-demographic factors, major illness, smoking status, dietary intake and genetic principal components analysis were included in the statistical models as potential confounders.

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants have given written informed consent in accord with the principles of the Declaration of Helsinki.

Procedures

At baseline assessment, self-reported PA was recorded using a self-completed questionnaire based on the International Physical Activity Questionnaire (IPAQ) short form (26), with participants reporting frequency and duration of walking, and of moderate and vigorous activity undertaken in a typical week (26). Data were analysed in accordance with the IPAQ scoring protocol (weighting applied: walking: 3.3 metabolic equivalents [METS]; moderate physical activity 4 METS and vigorous physical activity: 8 METS), and total PA was calculated as the sum of times spent walking and engaged in moderate and vigorous activity, expressed in METs-min.week^{-1}. Physically active individuals were identified if they meet the PA recommendation of ≥600 MET-min.week^{-1} of moderate-to-vigorous PA (26).

A proxy measure of total time spent in sedentary activities was calculated by asking "how many hours do you spend during your leisure time watching TV, doing PC screening or driving in a typical day?", and this combined figure was used as a proxy for sedentary behaviours (expressed as hours.day^{-1}). High sedentary individuals were identified using the

median (the cut-off point for low and high total sedentary time was >4.5 hours.day^{-1}) and the identification of high TV-viewing was >3 hours.day^{-1}.

An objective, accelerometer-based measure of PA was obtained in a subset of participants using a tri-axial wrist-worn accelerometer (AX3, Logging Accelerometer), collected from May 2013 until December 2015. Devices were dispatched to 106,053 participants and were returned by 103,720. Of the participants who provided accelerometry data 7,001 participants were excluded due to poor accelerometer wear time - defined as not having at least three days (72 hours) of data and or lacking data in each one-hour period of the 24-hour cycle scattered over multiple days. A further 11 were excluded due to poor device calibration, leaving a total of 96,706 participants. Of these only 62,881 had genetic data available. Mean daily accelerations (cumulative acceleration during each day; expressed in milli-gravity.day^{-1}) calculated using Open Movement AX3 open-source software (Open Lab, Newcastle University, UK) (27), were used as the objectively-measured total PA. The grouping of active and inactive individuals was estimated using the median value for the UK Biobank cohort equivalent to >24.0 milli-gravity.day^{-1}.

Dietary information was collected via a self-reported dietary frequency questionnaire (Oxford WebQ), with questions about usual consumption of a range of foods (28). Participants were invited to complete the online questionnaire on five occasions between April 2009 and June 2012. For participants who completed more than one questionnaire, we used an average estimate of the 5 questionnaires completed. Total energy intake and total energy derived from macronutrients were calculated from the information recorded in the 5th edition of McCance and Widdowson's "The composition of food" (29).

Area-based socioeconomic status was defined from postcode of residence using the Townsend score, which is derived from census data on housing, employment, social class and car availability (30). Smoking status was self-reported at baseline and included 3 categories

(smoker, ex-smokers, non-smokers). Medical history (physician diagnosis of diabetes, hypertension, CVD, cancer and other major illness) was collected from the self-completed, baseline questionnaire. Height and body weight were measured by trained nurses during the initial assessment visit. BMI was calculated as (weight/height^2) and the WHO criteria (2) used to classify BMI into: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 kg.m^{-2}. Waist circumference was used to classify participants as central obese (women ≥88cm and men ≥102 cm) (2).

Genetic data analysis

Imputed genotypes were available for 488 369 participants in the UK Biobank cohort. Genotyping was performed using the Affymetrix UK BiLEVE Axiom array (Santa Clara, CA, USA) on an initial 50,000 participants; the remaining 450,000 participants were genotyped using the Affymetrix UK Biobank Axiom® array. The two arrays are extremely similar (with over 95% common content). Aiming to maximize homogeneity and GPRS-BMI applicability, we excluded those who self-reported ancestry other than white British, related people (second degree or greater: kinship coefficient ⩾0.884), people with high levels of heterozygosity and missingness (>5%), and people whose reported sex was inconsistent with sex inferred from the genetic data. The UK Biobank core team centrally performed a check for excessive heterozygosity. Extreme heterozygosity or high rates of missingness, or both, can be indicators of poor sample quality due to, for example, DNA contamination. UK Biobank provided a list of samples with unusually high heterozygosity and we excluded those samples according to their recommendations. Further information on the genotyping process is available on the UK Biobank website (http://www.ukbiobank.ac.uk/scientists-3/genetic-data).

GPRS-BMI was derived from a set of 93 SNPs that was in turn derived from the 97 genome-wide significant BMI-associated SNPs reported by Locke et al. (23) (Supplementary Table

S1). 95 of these 97 SNPs were genotyped in the UK Biobank cohort, the two missing SNPs were rs2033529 (chr6, position 40,456,631, gene TDRG1) and rs12016871 (chr13; 26,915,782; MTIF3), 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 (31); there were no proxy SNPs (r>0.8) within the UK Biobank dataset. We constructed an externally-weighted GPRS-BMI for each participant, weighted by the per allele effect size estimates reported in the GIANT consortium study (*beta* per one-SD unit of BMI) (23) 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. GPRS-BMI values were normally distributed across the UK Biobank cohort.

Statistical analysis

Baseline data were used for present analyses. Robust regression analysis was used to test for associations between BMI and GPRS-BMI. Robust regression analyses were conducted instead of standard regression, as the latter can produce biased standard errors if heteroscedasticity is present (a statistical term that describes unequal variance in data), as shown previously (16). We tested for heteroscedasticity using the Breusch-Pagan test as implemented with the estat hettest in STATA (32). Robust regression analysis produces robust standard errors, using the vce(robust) option in STATA, which relaxes the assumption that errors are both independent and identically distributed and are therefore more robust.

The weighted GPRS was transformed to a z-score before use in models, so data are presented as BMI changes per SD increase in GPRS. Associations between GPRS and BMI were investigated using robust regression analyses for continuous variables and robust logistic regression for BMI categories (BMI $\geq$25.0 $kg.m^{-2}$; BMI $\geq$30.0 $kg.m^{-2}$), with the lower BMI category treated as the referent. These analyses were conducted using a fully adjusted model

(as specified below) but also using a sensitivity analyses where all participants with comorbidities (diabetes, hypertension, CVD, cancer and all major illness were excluded from analyses (n=108,345).

Interactions between the combined categories of PA (derived from total PA expressed as MET.min.week) and sedentary behaviours (derived from discretionary TV-viewing and PC-screen time expressed in hours.day^{-1}) and GPRS-BMI in their effects on BMI were investigated using robust regression analysis. For this a multiplicative interaction term of GPRS-BMI x categories of PA/SED were fitted in the model.

For each of the approaches described above, we adjusted our models for age, sex, deprivation, education qualifications, recruitment center, month of recruitment, the first 10 principal components of ancestry and genotyping batch, smoking status, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases, cancer, major illness). Analyses performed for objectively measured PA were additionally adjusted for season and wear time. All analyses were performed using STATA 14 statistical software (StataCorp LP).

Results

The main characteristics of the participants by GPRS-BMI quartile, the combined categories of PA (self-reported and objectively-measured total PA) and sedentary-related behaviours (total sedentary behaviour and TV-viewing) are summarised in Table 1, S2-S5, respectively. In summary, 53.7% of the cohort was female, mean age was 56.9 years, 10.1% were current smokers, 66.8% were overweight or obese based on their BMI. Based on self-report total PA, 54.4% of the participants were physically active (>600 MET-min.week^{-1}). The correlation between objective and self-reported PA was r=0.180, whereas the correlation between overall

discretionary sedentary time and TV-viewing was r=0.640. There was non-significant association between the GPRS-BMI and the exposures of interest (Supplementary Table S6).

Association of genetic profile risk score with BMI

GPRS-BMI explained 1.5% of the variance in BMI, with greater genetic risk being associated, as expected, with a higher BMI (Supplementary Table S7).

Interactions between GPRS-BMI and the combined categories of PA and sedentary behaviours

Before we investigated the combined effects of PA and sedentary behaviours on the genetic risk for BMI, we performed analyses for each exposure, separately (Figure 1 and Supplementary Table S8). These results show that the association between the GPRS-BMI and BMI were of similar magnitude for those with low levels of PA (objective and self-reported) and those with high levels of sedentary behaviour and TV-viewing.

The combined categories of objectively-measured PA and total sedentary behaviour significantly modified the association of GPRS-BMI with BMI (P-interaction=$3.5x10^{-6}$) (Figure 2 and 3, and Supplementary Table S9). The genetic effect of the GPRS on BMI increased across the combined categories of objective PA and sedentary behaviour: an increase of 1 SD in the weighed GPRS was associated with an increment of 0.37 $kg.m^{-2}$ in participants who were physically active and had low sedentary behaviour "busy bees", but the magnitude of the association was significantly higher in those participants who were physically inactive and had high sedentary behaviour "couch potato" (Beta: 0.60 $kg.m^{-2}$ per 1 SD change in the GPRS) (Figure 2 and 3, and Supplementary Table S9). Those in the lowest quartile (Q1) of the GPRS-BMI and who were in the "couch potato" category had 2.6 units higher BMI than those who were physically active and had reported lower sedentary behaviour (Figure 3). However, those in the highest quartile of GPRS and who were in the

"couch potato" category had a 3.2 $kg.m^{-2}$ higher BMI compared to those who were physically active and had low sedentary behaviour (Figure 3). These findings were replicated for self-reported PA with an even higher magnitude of association between self-reported PA and sedentary behaviour combined categories (Figure 2 and 3 and Supplementary Table S9).

Similar results were found when TV-viewing was used as a proxy for sedentary behaviour (P-interaction=$2.9x10^{-6}$) (Table 3 and Figure 2 and 3, and Supplementary Table S10). The strength of the GPRS-BMI association with BMI was higher for those in the "couch potato" category (lower accelerometer PA and high TV-viewing) (Beta: 0.60 $kg.m^{-2}$ per 1 SD increment in the GPRS) compared to those who were physically active and reported low TV-viewing time (Beta: 0.40 $kg.m^{-2}$ per 1 SD increment in the GPRS) (Figure 2). Those with the lowest GPRS-BMI (Q1) but who were in the "couch potato" category were 2.5 $kg.m^{-2}$ heavier than those with high PA and low TV-viewing individuals. However, this difference increased to 3.1 $kg.m^{-2}$ in the highest quartile (Q4) for GPRS-BMI) (Figure 2 and 3). Similar interaction effects were found for self-reported PA (Figure 2 and 3, and Supplementary Table S10).

Discussion

Main findings

This study provides novel evidence that the associations between a 93-SNP GPRS-BMI and BMI are substantially moderated by the combination of PA (self-reported and objectively-measured PA) and sedentary behaviour (total sedentary behaviour and TV-viewing). These results substantially and meaningfully extend the limited evidence available to date on interaction between GPRS-BMI and the combination of PA and TV-viewing (15). Moreover, our data indicate that these interactions were independent of a range of confounders including socio-demographic factors, diet, and co-morbidities. In this study, we provide novel evidence that the genetic predisposition to obesity was higher in those with low PA (<600 MET-

min.week^{-1}) and higher discretionary sedentary behaviour (>4.5 h.day^{-1}), based on the weighed 93-SNP GPRS-BMI. These findings emphasise that, although obesity is partly genetically determined, lifestyle could play an important moderating role. Indeed, our findings suggest that being physically active may, in part, overcome a genetic predisposition to obesity and it is also possible that the potential benefits of favourable lifestyle factors may act more strongly in individuals with higher genetic propensity to obesity. In individuals with highest GPRS-BMI (Q4), having a low level of objectively-measured PA combined with higher sedentary time was associated with a 2.9 kg.m^{-2} higher BMI (over 8.5 kg bodyweight for someone 1.75 m tall) compared to those having a high level of PA and low sedentary time. Thus, individuals who have high genetic predisposition to obesity may be able to reduce their adiposity by maintaining both a high level of PA and lower levels of sedentary behaviour. While the causality of this association cannot be ascertained from the present data, the present findings make a case for intervention studies to determine the effects of adopting healthier physical activity behaviours, particularly in individuals genetically susceptible to obesity.

All previous studies have investigated the interaction between genetic risk of obesity and PA (13, 14, 15, 16, 17, 18, 19) or sedentary behaviour (16, 20, 21), as separate exposures. However, there is new evidence suggesting that both PA and sedentary behaviour are independently associated with detrimental health outcomes and that they act in an additive manner on health outcomes (22). Examining the joint effects of these two behaviours is important as participation in both occurs to varying degrees throughout the day and are both considered separately in public health guidelines. To date, only one small scale study has investigated the effect of TV-viewing and PA joint classification on the genetic predisposition to obesity in 7,740 women and 4,564 men using a 32-SNPs genetic risk score (15). Although, Qi et al., failed to report a significant interaction between the GPRS and the

joint classification for TV and PA, they did find that among individuals with the lowest tertile of physical activity and >21 hour per week of TV watching, an increment of 10 points in the weighted GRS was associated with an increase of 2.5 [95% CI: 1.5; 3.5] $kg.m^{-2}$ in BMI (P<0.001), while the genetic effect was largely attenuated (β=0.5 [0.1, 1.0] kg/m2, P=0.03) among individuals with the highest tertile of physical activity and 0-5 hour per week of TV watching (15). Our study, therefore, provides novel evidence and the limited evidence available to date. Our study has reported that the joint classification of PA and sedentary behaviour significantly modify the genetic predisposition to obesity in a large cohort, this was true for both self-reported and objectively measured PA. Moreover, we used total sedentary behaviour in addition to TV viewing as the main exposure, which provide a more accurate quantification of sedentary activities that occur on a daily basis, other than just TV-viewing.

On the question of self-reported PA, previous studies have found that self-reporting of PA can attenuate the apparent association between PA-related variables and health outcomes, due to regression-dilution bias (33). All previous studies considering GPRS-BMI have used self-reported data on PA (10, 11, 34, 35, 36, 37, 38), which is prone to substantial measurement error (33) and can result in biased estimates of the interaction (39). Thus, both objectively-measured and self-reported PA were adopted in this study to provide a more robust estimate of the magnitude of the genetic susceptibility and, interestingly, the present data show similar patterns of interactions with both measures: difference in BMI between the inactive/high sedentary and active/low sedentary groups was 2.6 $kg.m^{-2}$ and 3.2 $kg.m^{-2}$ for the lowest (Q1) and highest (Q4) quartiles of GPRS- BMI, respectively, when PA was objectively measured; however, this BMI difference between these two groups was 1.9 $kg.m^{-2}$ and 2.8 $kg.m^{-2}$ for Q1 and Q4 when PA was self-reported. This effect is similar for the combined categories of PA and TV-viewing.

Strengths and limitations of the study

Previously, most studies have been conducted in relatively small cohorts, using a restricted number of genes to derive their genetic risk scores. Thus, the present data with more than 330,000 participants and a comprehensive 93-SNP genetic risk score, substantially extends the current evidence base. The UK Biobank cohort is representative of a large general population cohort with respect to age, sex, ethnicity and deprivation, although it is not representative in other regards (24, 40). The wider generalizability of the findings are limited to White Europeans and similar work is needed in different ethnic populations. PA was measured by self-report using a validated questionnaire, and also objectively assessed using validated methods, trained staff and standard operating procedures. This enables direct comparison to previous reports and quantification of the extent to which errors in self-reported PA could distort the true underlying relationships between PA and adiposity (33). Sedentary behaviour and TV-viewing were self-reported, thus mis-reporting biases (33) may have led to an underestimation or overestimation of the magnitude of the association between GPRS and BMI. However, based on the present data with accelerometer PA, this may not substantially influence their interaction with GPRS- BMI on adiposity.

A limitation of the study is that the GPRS only captures a small proportion of the genetic variance in BMI. The variance explained here is 1.5%, compared with the 2.7% of variance explained by the 97 SNPs identified in the GIANT consortium's mega-GWAS (13). This difference likely reflects the differences in cohort structure (single cohort vs multiple cohorts) and small biases unaccounted for in the meta-analysis methodology. As shown recently by Tyrell et al., residual confounding is another limitation likely to happen in gene x environment interactions studies, including UK Biobank (16). Moreover, collider bias is also another limitation in the UK Biobank, as participants were biased towards being from more affluent backgrounds. Finally, we performed robust regression analyses to account for potential statistical artefacts that can bias gene x environment interaction studies. This is

relevant when groups of overweight individuals have a wider variance in BMI than groups of thinner individuals and these differences in BMI can create false positive evidence of interaction.

Implications of findings

Data from 900,000 adults from the collaborative analyses of 57 prospective studies reported that a 5 $kg.m^{-2}$ increase in BMI was associated with 30% higher risk of all-cause mortality and 40% higher risk for CVD mortality, over 13 years of follow up – with events in first 5 years excluded (41). Given the high current prevalence of overweight and obesity worldwide (42), it is important to develop strategies to reduce adiposity to public health. The present data – the largest study to date, with the most comprehensive GPRS for BMI available – clearly demonstrate that the association between the combined indices of PA and sedentary behaviour on adiposity outcomes are evident in those with a high genetic predisposition to obesity. Evidence of such gene–lifestyle interactions may empower and motivate individuals to adopt healthier lifestyle and sleep-related behaviours through knowledge that such behaviour change can be effective in preventing obesity and, therefore, risk of obesity-related non-communicable diseases (43). Our findings are relevant to the health and employment sectors and suggest that promoting higher physical activity and less time spent in sedentary behaviours should be promoted, alongside with other key lifestyle behaviours including healthy sleep (44) and diet (16), as a means of combating the obesity epidemic. As described previously (16), PA and sedentary behaviours are only two factors from an extensive list of obesogenic risk factors, which together are best captured by an individual's socioeconomic status. Therefore, public health messages targeting only PA or sedentary behaviours would have limited effect on attenuating the genetic predisposition to obesity if other lifestyle key risk factors are not considered.

In conclusion, despite the fact that this 93-SNP GPRS was associated with BMI, our results show that the combined lower levels of PA and higher levels of sedentary behaviours results in stronger associations between our genetic profile and obesity. These findings are relevant for public health and suggest that promoting PA and reducing sedentary behaviours, alongside with other healthy lifestyle behaviours, particularly in those who are genetically susceptible, could be an important strategy for addressing the current obesity epidemic and disease burden.

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Table 1. Cohort characteristic by genetic risk score quartiles

	Overall	Lower	Low/Middle	Middle/High	Higher
Socio-demographics					
Total n	388,616	84,738	84,656	84,625	84,597
Women, n (%)	181,752 (53.7)	45,528 (53.7)	45,574 (53.8)	45,457 (53.7)	45,193 (53.4)
Age (years), mean (SD)	56.9 (8.0)	56.9 (8.0)	56.9 (8.0)	56.9 (8.0)	56.8 (8.0)
Deprivation index tertile					
Lower	121,571 (36.0)	30,771 (36.4)	30,468 (36.0)	30,189 (35.7)	30,143 (35.6)
Middle	116,090 (34.3)	29,089 (34.4)	29,046 (34.4)	29,157 (34.5)	28,798 (34.1)
Higher	100,547 (29.7)	24,767 (29.3)	25,034 (29.6)	25,170 (29.8)	25,576 (30.3)
Smoking status, n (%)					
Never	184,448 (54.7)	46,937 (55.6)	46,372 (55.0)	46,021 (54.6)	45,118 (53.5)
Previous	118,951 (35.2)	29,261 (34.7)	29,514 (35.0)	29,874 (35.4)	30,302 (36.0)
Current	34,023 (10.1)	8,227 (9.7)	8,501 (10.0)	8,422 (10.0)	8,873 (10.5)
Obesity-related markers					
BMI, $kg.m^{-2}$	27.4 (4.8)	26.6 (4.4)	27.2 (4.6)	27.6 (4.8)	28.2 (5.1)
BMI Categories, n (%)					
Underweight (<18.5)	1,700 (0.5)	597 (0.7)	448 (0.5)	368 (0.4)	287 (0.3)
Normal weight (18.5-24.9)	110,757 (32.7)	32,239 (38.0)	28,833 (34.1)	26,485 (31.3)	23,200 (27.4)
Overweight (25.0 to 29.9)	144,553 (42.7)	35,925 (42.5)	36,251(42.8)	36,183 (42.8)	36,194 (42.8)
Obese (≥30.0)	81,606 (24.1)	15,977 (18.8)	19,124 (22.6)	21,589 (25.5)	24,916 (29.5)
Body fat (%)	31.3 (8.5)	30.6 (8.4)	31.1 (8.5)	31.6 (8.5)	32.1 (8.6)
Waist Circumference (cm)	90.3 (13.4)	88.8 (12.8)	89.8 (13.2)	90.7 (13.5)	92.0 (14.0)
Central Obesity, n(%)	113,182 (33.4)	23,990 (28.3)	27,199 (32.1)	29,399 (34.8)	32,594 (38.5)
Physical activity					
Total PA ($METs\text{-}hour.week^{-1}$), mean (SD)	44.6 (62.4)	44.4 (62.0)	44.6 (62.6)	44.8 (63.1)	44.6 (61.8)
Objective total PA ($milli\text{-}gravity.day^{-1}$), mean (SD)	27.9 (8.2)	28.1 (8.2)	27.9 (8.2)	27.9 (8.3)	27.8 (8.2)
Physical active individuals, n (%)	184,083 (54.4)	45,921 (54.2)	46,194 (54.6)	45,935 (54.3)	46,033 (54.4)
TV viewing ($h.day^{-1}$)	2.8 (1.6)	2.8 (1.6)	2.8 (1.6)	2.8 (1.6)	2.8 (1.6)
Total Sedentary Behaviour ($h.day^{-1}$)	5.0 (2.3)	5.0 (2.2)	5.0 (2.3)	5.1 (2.3)	5.1 (2.3)

Dietary intake					
Total energy intake (Kcal.day^{-1})	2,174 (650)	2,180 (642)	2,177 (652)	2,171 (646)	2,168 (660)
Protein intake (% of TE)	15.5 (3.5)	15.4 (3.4)	15.4 (3.5)	15.5 (3.5)	15.6 (3.6)
Carbohydrates intake (% of TE)	47.1 (8.0)	47.1 (7.9)	47.2 (8.0)	47.1 (8.0)	47.1 (8.1)
Total Fat intake (% of TE)	32.1 (6.6)	32.2 (6.5)	32.0 (6.6)	32.1 (6.6)	32.1 (6.7)
Saturated intake (% of TE)	12.4 (3.3)	12.4 (3.3)	12.3 (3.3)	12.4 (3.3)	12.4 (3.3)
Polyunsaturated fat intake (% of TE)	14.4 (7.2)	14.5 (7.2)	14.4 (7.3)	14.4 (7.2)	14.4 (7.3)
Processed meat intake, n(%)					
Never	27,775 (8.2)	6,857 (8.1)	6,968 (8.2)	6,954 (8.2)	6,996 (8.3)
<1 a week	101,290 (30.0)	25,165 (29.7)	25,212 (29.8)	25,587 (30.3)	25,326 (30.0)
2-4 a week	195,809 (58.0)	49,331 (58.3)	48,982 (57.9)	48,632 (57.5)	48,864 (57.8)
>5 times a week	13,259 (3.8)	3,262 (3.9)	3,379 (4.0)	3,334 (4.0)	3,284 (3.9)
Sugar intake (% of TE)	22.4 (6.8)	22.4 (6.8)	22.5 (6.8)	22.5 (6.9)	22.4 (6.9)
Starch intake (g.day^{-1})	122.9 (46.1)	123.1 (45.4)	123.3 (46.2)	122.4 (46.0)	122.6 (46.7)
Alcohol intake (% of TE)	5.3 (6.5)	5.4 (6.5)	5.4 (6.6)	5.3 (6.6)	5.2 (6.5)
Health status, n (%)					
Diabetes history	16,199 (4.8)	3,586 (4.2)	3,838 (4.5)	4,080 (4.8)	4,695 (5.6)
Cancer history	26,490 (7.8)	6,744 (8.0)	6,672 (7.9)	6,571 (7.8)	6,503 (7.7)
CVDs	101,039 (29.8)	23,871 (28.2)	25,036 (29.6)	25,585 (30.2)	26,547 (31.4)
Hypertension	77,662 (22.9)	18,273 (21.6)	19,254 (22.7)	19,691 (23.3)	20,444 (24.2)

[1]Data presented as mean and standard deviation (SD) for continuous variables, and as n and % for categorical variables. BMI: body mass index; PA: physical activity; MET: metabolic equivalent task; TE: total energy intake; CVD: cardiovascular disease; GPRS: genetic profile risk score. Physically inactive individuals were defined as achievement <600 MET.min.week^{-1}.

Figures legends

Figure 1. Association between genetic profile risk score and BMI by physical activity (self-reported and objective) and discretionary sedentary-related behaviours.

Data presented as beta coefficients and their 95%CI. The beta coefficient indicates the change in BMI per SD increase in the genetic profile risk score by the high and low levels of PA (self-reported or objectively-measured PA) and high or low levels of total sedentary behaviours. High sedentary individuals were identified using the population median equivalent to >4.5 hours.day^{-1}, high TV-viewing was defined as >3 hours.day^{-1}, physically inactive individuals was defined as <600 MET-min.week^{-1} and the population median was used to define inactive individuals based on accelerometer PA (<24.0 milli-gravity.day^{-1}). The p-value for the interaction between GPRS and the categories of PA or sedentary behaviour indicate that the association between the GPRS-BMI and BMI differ by levels of PA or sedentary-related behaviours. Analyses were adjusted for age, sex, deprivation, education qualifications, recruitment centre, month of recruitment, the first 10 principal components of ancestry and genotyping batch, smoking status, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases, cancer and major illness). Analyses performed for objectively measured PA were additionally adjusted for season and wearing time whereas analyses performed for sedentary behaviours and TV-viewing were additionally adjusted for total self-reported PA and those for PA (self-reported and objectively) were additionally adjusted for overall sedentary behaviours.

PA: physical activity; BMI: body mass index. *objectively measured physical activity.

Figure 2. Association between genetic profile risk score and BMI by combined categories of physical activity and discretionary sedentary-related behaviours.

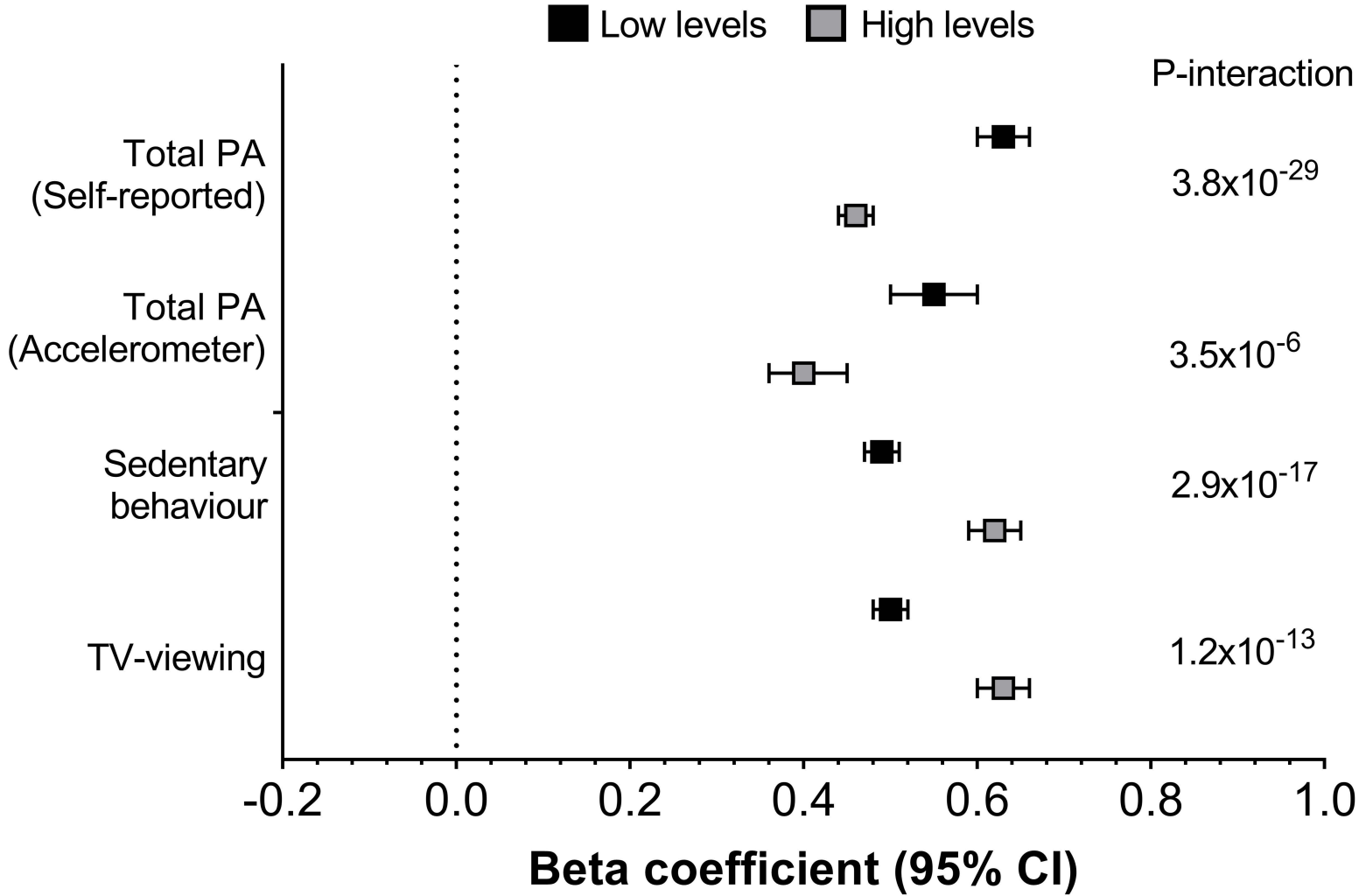
Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI per SD increase in the genetic profile risk score by the combined categories of PA (self-reported or objectively-measured PA) with total sedentary behaviours (top panel figure) and TV-viewing (bottom panel). The p-value for the interaction between GPRS and combined categories of PA and sedentary behaviour indicate that the association between the GPRS-BMI and BMI differ by these categories. Analyses were adjusted for age, sex, deprivation, education qualifications, recruitment centre, month of recruitment, the first 10 principal components of ancestry and genotyping batch, smoking status, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases, cancer and major illness). Analyses performed for objectively measured PA were additionally adjusted for season and wearing time.

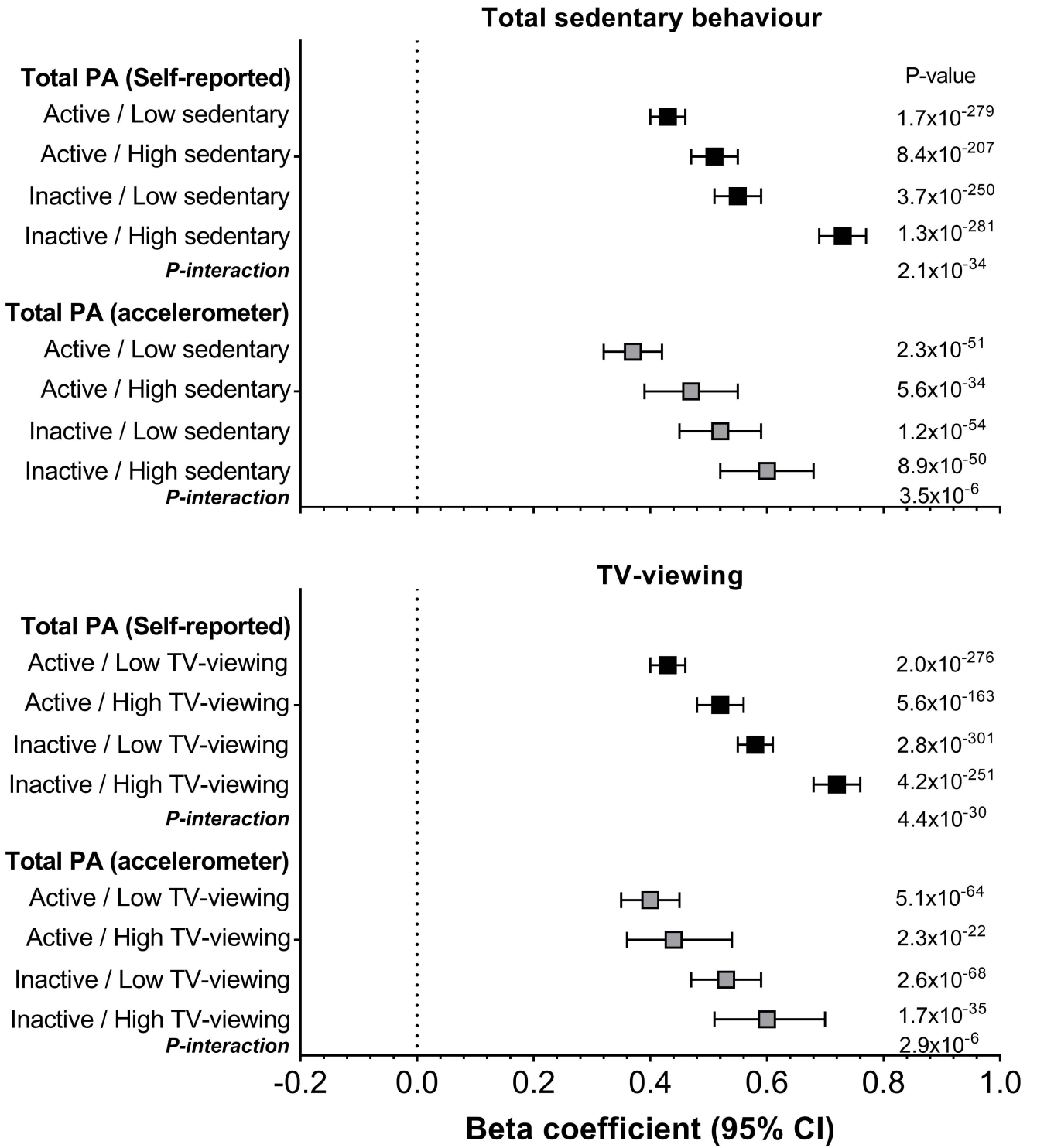
PA: physical activity; BMI: body mass index.* objectively measured physical activity.

Figure 3. Association between genetic profile risk score and BMI by the combined categories of physical activity and sedentary-related behaviours.

Data presented as adjusted BMI means by combined categories of PA, total sedentary behaviour and quartiles of GPRS. Figure (A) is self-reported PA and total discretionary sedentary behaviour, (B) is objective PA and total discretionary sedentary behaviour, C is self-reported PA and TV-viewing, and D is objective PA and TV-viewing. Analyses were adjusted for age, sex, deprivation, education qualifications, recruitment centre, month of recruitment, the first 10 principal components of ancestry and genotyping batch, smoking status, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases and

cancer). Analyses performed for objectively measured PA were additionally adjusted for season and wearing time.


Low levels
High levels
P-interaction
Total PA (Self-reported)
3.8x10-29
Total PA (Accelerometer)
3.5x10-6
Sedentary behaviour
2.9x10-17
TV-viewing
1.2x10-13
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Beta coefficient (95% CI)


Total sedentary behaviour
Total PA (Self-reported)
Active / Low sedentary
Active / High sedentary
Inactive / Low sedentary
Inactive / High sedentary
P-interaction
Total PA (accelerometer)
Active / Low sedentary
Active / High sedentary
Inactive / Low sedentary
Inactive / High sedentary
P-interaction
P-value
1.7x10-279
8.4x10-207
3.7x10-250
1.3x10-281
2.1x10-34
2.3x10-51
5.6x10-34
1.2x10-54
8.9x10-50
3.5x10-6
TV-viewing
Total PA (Self-reported)
Active / Low TV-viewing
Active / High TV-viewing
Inactive / Low TV-viewing
Inactive / High TV-viewing
P-interaction
Total PA (accelerometer)
Active / Low TV-viewing
Active / High TV-viewing
Inactive / Low TV-viewing
Inactive / High TV-viewing
P-interaction
2.0x10-276
5.6x10-163
2.8x10-301
4.2x10-251
4.4x10-30
5.1x10-64
2.3x10-22
2.6x10-68
1.7x10-35
2.9x10-6
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
Beta coefficient (95% CI)