Do physical activity, commuting mode, cardiorespiratory fitness and sedentary behaviours modify the genetic predisposition to higher BMI? Findings from a UK Biobank study

AUTHORS

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ABSTRACT

Objective - Investigate associations between a genetic profile risk score for obesity (GPRS-obesity) (based on 93 SNPs) and body mass index (BMI) was modified by physical activity (PA), cardiorespiratory fitness, commuting mode, walking pace and sedentary behaviours.

Methods – For the analyses we used cross-sectional baseline data from 310,652 participants in the UK Biobank study. We investigated interaction effects of GPRS-obesity with objectively-measured and self-reported PA, cardiorespiratory fitness, commuting mode, walking pace, TV-viewing, playing computer games, PC-screen time and total sedentary behaviour on BMI were explored. Body mass index (BMI) was the main outcome measure.

Results - GPRS-obesity was associated with BMI (β:0.54 $kg.m^{-2}$ per standard deviation (SD) increase in GPRS, [95%CI: 0.53; 0.56]; $P=2.1x10^{-241}$). There was a significant interaction between GPRS-obesity and objectively-measured PA ($P_{[interaction]}= 3.3x10-^{11}$): among inactive individuals, BMI was higher by 0.58 $kg.m^{-2}$ per SD increase in GPRS-obesity ($p=1.3x10^{-70}$) whereas among active individuals the relevant BMI difference was less (β:0.33 $kg.m^{-2}$, $p=6.4x10^{-41}$). We observed similar patterns for fitness (Unfit β:0.72 versus Fit β:0.36 $kg.m^{-2}$, $P_{[interaction]}= 1.4x10^{-11}$), walking pace (Slow β:0.91 versus Brisk β:0.38 $kg.m^{-2}$, $P_{[interaction]}= 8.1x10^{-27}$), discretionary sedentary behaviour (High β:0.64 versus Low β:0.48 $kg.m^{-2}$, $P_{[interaction]}= 9.1x10^{-12}$), TV-viewing (High β:0.62 versus Low β:0.47 $kg.m^{-2}$, $P_{[interaction]}=1.7x10^{-11}$), PC-screen time (High β:0.82 versus Low β:0.54 $kg.m^{-2}$, $P_{[interaction]}=0.0004$) and playing computer games (Often β:0.69 versus Low β:0.52 $kg.m^{-2}$, $P_{[interaction]}= 8.9x10^{-10}$). No significant interactions were found for commuting mode (car, public transport, active commuters).

Conclusions – Physical activity, sedentary behaviours and fitness modify the extent to which a set of the most important known adiposity variants affect BMI. This suggests that the adiposity benefits of high PA and low sedentary behaviour may be particularly important in individuals with high genetic risk for obesity.

INTRODUCTION

Obesity is a multifactorial condition which is influenced by genes, lifestyle and the environment, with ~40-70% of its variation attributable to genetic factors.[1-5] Obesity is highly prevalent worldwide and has deleterious effects on morbidity and mortality which are responsible for large burdens at both an individual and population level.[6-8] Many societies today live in what is considered an 'obesogenic' environment, indicating that the rise in obesity prevalence over the past three decades has been driven by changes in lifestyle, including increases in energy intake and reductions of physical activity (PA), although the relative contribution of these two factors is debated.[1, 9-11] However, within these obesogenic environments obesity is not ubiquitous and this suggests that there may be gene-environment interactions and that the overall genetic risk is modulated by lifestyle/environment and *vice versa*. Indeed it is possible, therefore that part of the heritability of obesity (and its counterpart quantitative trait, body mass index; BMI) may be accounted by such unappreciated gene/environment interactions.[4, 5] It is postulated that whilst some genetic factors may operate independently of the environment, others may confer greater predisposition to weight gain in an obesogenic environment;[12] a hypothesis supported by the results of twin studies of changes in adiposity in response to environmental influences.[3, 13, 14]

A recent genome-wide association study meta-analysis (Mega-GWAS) conducted on 339,224 participants identified 97 BMI-associated single nucleotide polymorphism (SNP) loci at genome-wide significance.[15] These SNPs explains a small, but significant, proportion (2.7%) of the variance in BMI in adult individuals of White European descent and can be used in prediction of an individual's genetic predisposition to obesity.[15]

Thus far, only a few studies have investigated the effect of genotype-lifestyle interactions on adiposity outcomes, and many of these studies have been at the single locus level. [2, 16-19] Only a few studies have investigated whether overall genetic predisposition, as measured using polygenic risk scores or genetic profile risk scores for obesity (GPRS-obesity), interacts with PA.[20-22] One study[23] has investigated interactions between a GPRS-obesity and 12 measures of an obesogenic environment (including binary exposures of physical activity and TV viewing) using 120,000 participants from the UK Biobank data set, with gene-environment interactions found for both physical activity and TV viewing.

Twin studies of cardiorespiratory fitness – the ability of the cardiovascular and respiratory systems to supply oxygen to working muscles during sustained physical activity – suggest ~25-65% heritability in this trait, indicating important contributions of both environment and genes.[24] There is evidence that fitness is associated with prospective changes in adiposity,[25-27] and this may be independent of self-reported physical activity. [27] However, to date, no studies have investigated whether cardiorespiratory fitness could modulate the association between GPRS-obesity and BMI. In the current study, we therefore investigated whether the associations between GPRS-obesity and BMI outcomes were

modulated by objectively-measured and self-reported physical activity, cardiorespiratory fitness, commuting mode, walking pace and sedentary behaviours in the UK Biobank cohort, a large population sample.

METHODS

Study design

We used cross-sectional baseline data from UK Biobank. UK Biobank recruited 502,549 participants (5.5% response rate), aged 37-69 years from the general population between April 2007 and December 2010.[28] Participants attended one of 22 assessment centres across England, Wales and Scotland[29, 30] and completed a touch-screen questionnaire, had physical measurements made and provided biological samples, as described in detail elsewhere.[29, 30] Imputed genotype data were available for 488,369 participants, and of these participants 338,216 had full data available for the GPRS-obesity SNPs, self-reported physical activity and sedentary-related behaviours used in this study after exclusions (detailed below). Objectively measured PA data was available for 103,712 participants (including 62,881 with genotyping data).

The main outcome measure considered was BMI. A genetic profile risk score for BMI was the independent predictor variable and self-reported total PA, objectively-measured PA, fitness, commuting mode (car, public transport, walking and cycling), self-reported walking pace and self-reported discretionary sedentary behaviours (TV-viewing, PC-screen time and playing computers games) were treated as moderators. Socio-demographic factors, month and center of recruitment, major illness, smoking status, sleep duration, dietary intake and genetic principal components analysis for ethnicity and genotyping batch 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 gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

Procedures

During the baseline assessment, self-reported PA was recorded using a self-completed questionnaire based on the International Physical Activity Questionnaire (IPAQ) short form.[31] Participants reported the frequency and duration of walking, and of moderate and vigorous activity undertaken in a typical week.[31] These data were analysed in accordance

with the IPAQ scoring protocol (http://www.ipaq.ki.se/scoring.pdf). Total PA was calculated as the sum of time spent walking and participating in moderate and vigorous activity and was expressed as metabolic equivalents (MET-hours.week^{-1} or MET-mins.week^{-1}) (weighting applied: walking: 3.3 metabolic equivalents [METS]; moderate physical activity 4 METS and vigorous physical activity: 8 METS). Moderate-to-vigorous PA was estimated as the sum of moderate and vigorous PA expressed in their MET-equivalent. Participants were excluded from analyses if they recorded implausible total daily PA values which was defined as the sum of their total physical activity, sleeping time and TV viewing exceeding 24 hours. Physically active individuals were classified as those meeting the PA recommendations of at least 600 MET-min.week^{-1} of moderate-to-vigorous PA.[32] Self-reported walking pace was recorded using the question "How would you describe your usual walking pace?": slow pace was defined as less than 3 miles per hour, steady average pace was defined as between 3-4 miles per hour, and brisk pace was defined as more than 4 miles per hour. We calculated a proxy measure of total time spent in sedentary activities based on the question "In a typical day, how many hours do you spend watching TV, doing PC screening or driving?", with the combined figure used (expressed as hours per week). Participants were also asked how often they played computer games in a week, their response were categorised as never/rarely, sometimes and often.

The mode of transportation was recorded. Participants were asked "In a typical day, what types of transport do you use to get to and from work?" and could select one or more of the following options: car/motor vehicle, walk, public transport, and cycle. From this we derived five commuting categories: non-active (car/motor vehicle), public transport only (train and bus); walking only; cycling only and active commuting (cycling and/or walking)[33].

An objective, accelerometer-based measure of PA was obtained in a subset of participants using a tri-axial wrist-worn accelerometer (AX3, Logging Accelerometer) in a second wave of data collection between May 2013 and December 2015. Invitations to use accelerometers were sent to 240,000 participants, with an overall response rate of 44%. Devices were dispatched to 106,053 participants; of these, devices 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 62,756 had genetic data available. Mean daily accelerations (expressed in milli-gravity.day^{-1}) calculated using Open Movement AX3 open-source software (Open Lab, Newcastle University, UK),[34, 35] (which provides outputs equivalent to those generated by the GENEActiv accelerometer used in other large-scale population cohorts)[34, 35] were used as the objective measure of total PA.

Cardiorespiratory fitness was only assessed in a subset of participants (n=67,702), using a 6-minute incremental ramp cycle ergometer test, with workload calculated according to age, sex, height, weight and resting heart rate, as described previously.[36, 37]

A self-reported dietary frequency questionnaire (Oxford WebQ), with participants asked about usual consumption of a range of foods, was used to collect dietary information.[38] The Townsend score was calculated and used as a measure of area-based socioeconomic status.[39] Age was calculated from dates of birth and baseline assessment. Medical history (physician diagnosis of depression, longstanding illness, diabetes, CVD, and cancer) was collected using a self-completed, baseline assessment questionnaire. Height and body weight were measured by trained nurses , BMI was calculated and the WHO criteria[40] used to classify participants into the following 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 a waist circumference >88 and >102 cm for women and men, respectively. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk) and in the supplementary material.

Genetic data analysis

Imputed genotype data were available for 488,369 participants. Genotyping was performed using the Affymetrix UK BiLEVE Axiom array (Santa Clara, CA, USA) on an initial 50,000 participants and the Affymetrix UK Biobank Axiom® array used for the remainder of the participants. These arrays are extremely similar (with over 95% common content). 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 were excluded. Samples with unusually high heterozygosity were excluded. Further information on the genotyping process is available on the UK Biobank website (http://www.ukbiobank.ac.uk/scientists-3/genetic-data).

A GPRS-obesity was derived from a set of 93 SNPs based on the 97 genome-wide significant BMI-associated SNPs reported by Locke et al.[15] (See Table S1). Of these 97 SNPs 95 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). 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 [41]; there were no proxy SNPs (r>0.8) within the UK Biobank dataset. 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) [15] 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-obesity values were normally distributed across the UK Biobank cohort.

Statistical analysis

Baseline phenotypic and morbidity data were used for the present analyses. Robust regression analysis was used to test for associations between BMI and GPRS-obesity. 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 [23]. We tested for heteroscedasticity using the Breusch-Pagan test as implemented with the estat hettest in STATA [42]. 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 categories (overweight: BMI ≥25 $kg.m^{-2}$; obese: BMI ≥30 $kg.m^{-2}$) were investigated using robust logistic regression, with the 'normal BMI' category as the referent (underweight individuals were excluded from the logistic regression analyses). 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). Interaction effect of GPRS-obesity with age and sex were investigated, however, as no significant interactions were found analyses were not stratified.

Interactions between the exposures (PA, commuting mode, fitness, and sedentary behaviours) and GPRS-obesity in their effects on BMI were investigated using robust regression analysis. For this a multiplicative interaction term of 'GPRS-obesity' x 'exposure' was fitted in the model. For this the interaction terms, all exposures of interest, were fitted into the model as an ordinal variable (coded as 1=Low, 2=Middle and 3=High). Cut-off points used to define categories or tertiles of each exposure are presented in Table S2. Except for those related to commuting which were coded as a binary variable (0 "car commuters" vs 1 "active commuters"). GPRS-obesity was fitted into the models as a continuous variable.

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, sleep duration, 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. Analyses for sedentary-related behaviours were additionally adjusted for total PA and vice versa. All analyses were performed using STATA 14 statistical software (StataCorp LP).

RESULTS

The main characteristics of the participants by GPRS-obesity quartile, PA (self-reported and objectively measured), fitness, walking pace, commuting mode and sedentary-related behaviours are summarised in Tables 1 and Supplementary Tables S3-S11, respectively. In summary, 53.3% of the cohort was female, mean age was 56.8 years, 9.7% were current smokers, 66.8% were overweight or obese based on their BMI, and 33.0% were centrally obese based on their WC. Based on self-report total PA, 55.2% of the participants were physically active (>600 MET-min.week^{-1}). Correlations between BMI and PA-related variables were significant but of moderate magnitude (Table S12).

Association of genetic profile risk score with obesity measures

GPRS-obesity explained 1.5% of the variance in BMI, with greater genetic risk being associated, as expected, with a higher BMI [β: 0.54 kg.m^{-2} increase per SD change in GPRS (95%CI: 0.53; 0.56), p=2.1x10^{-241}]. After the exclusion of participants with comorbidities these associations were marginally attenuated but remained highly significant (Table S13). The odds of having a BMI $\geqslant$25, BMI $\geqslant$30, are presented in Table S13, and are broadly consistent: those with increased genetic risk were at increased risk of being overweight or obese.

Interactions between genetic profile risk score and physical activity and sedentary behaviours

The GPRS-obesity was not associated with any of the exposures of interest (PA, cardiorespiratory fitness or sedentary behaviour variables: Supplementary Table S12). However, the effect of the GPRS-obesity on adiposity was modified by PA-related variables, sedentary behaviours and fitness but not by commuting mode. Objectively-measured PA significantly modified the association of GPRS-obesity with BMI (P-interaction=3.3x10^{-11}) (Fig 1 and Table S14). The strength of the GPRS association with BMI decreased with increasing PA: from 0.58 kg.m^{-2} per 1 SD increase in the GPRS in participants in the lowest tertile of objectively-measured PA to 0.33 kg.m^{-2} in participants in the highest tertile of PA. Those in the lowest quartile of the GPRS-obesity and who were in the most physically inactive (bottom tertile) had 1.8 units higher BMI than the most active individuals (top tertile). However, inactive individuals in the highest GPRS quartile had 2.5 kg.m^{-2}

higher BMI compared to active individuals with the same genetic risk (Fig 2 and Table S14). Similar findings were also observed for total and different intensities of self-reported PA (walking, moderate, vigorous and moderate-to-vigorous), fitness and walking pace (Fig 1, Fig 2 and Table S14). The biggest interaction effects were observed for fitness and walking pace as illustrated in Figure 1 and 2. Those in the highest quartile of the GPRS-obesity and who were unfit had 4.0 units higher BMI than the most fit individuals. Similarly, those in the highest quartile of the GPRS-obesity who reported a slow walking pace had 5.3 units higher BMI than brisk walkers (Figure 2).

Similarly, discretionary sedentary behaviours (sedentary behaviour, TV-viewing, PC-screen time and playing computer games) modified the effect of the GPRS-obesity on BMI independent of main confounder factors (Fig 1, Fig 3 and Table S15). The strength of the GPRS-obesity association with BMI increased with increasing time spent in sedentary-related behaviours. The highest modifier effect was observed for discretionary PC-screen time, with the strength of the GPRS association with BMI higher with increasing PC-screen time: from 0.54 $kg.m^{-2}$, per 1 SD increase in the GPRS, in participants in the lowest tertile of PC-screen time to 0.82 $kg.m^{-2}$ in participants in the highest tertile of PC-screen time (P-interaction=0.0004). For overall discretionary sedentary behaviour: individuals with a low GPRS-obesity (quartile 1) but in the highest tertile for sedentary behaviour had 2.1 units higher BMI than those in the lowest sedentary behaviour tertile. However, those in the highest quartile for GPRS-obesity and with high sedentary behaviours had 2.6 units higher BMI than those in the lower tertile for sedentary behaviours (P-interaction=$9.1x10^{-12}$). Similar interaction effects were found for TV-viewing, PC-screen time and playing computer games (Fig 1, Fig 3 and Table S15). No significant interactions were found for commuting mode (car, public transport, active commuters) (Fig 1, Fig 4 and Table S16).

DISCUSSION

Main findings

This study provides novel evidence that the associations between a 93 SNP genetic profile risk score for obesity and BMI are modulated by objectively-measured PA, cardiorespiratory fitness, as well as self-reported PA, walking pace, and discretionary sedentary-related behaviours (TV-viewing, playing computer games, PC-screen time and total sedentary behaviour) but not commuting modes (car, public transport and active commuting). These results substantially and meaningfully extend the limited evidence available to date on interactions between GPRS-obesity and *self-reported* PA.[20-22] Our findings are in agreement with the previous findings of Tyrell et al[23] but we have extended these findings to investigate measures such as cardiorespiratory fitness, walking pace, commuting mode and other measures of sedentary behaviour in a larger sample size. Moreover, our data indicate that these interactions were independent of a range of confounders

253 including socio-demographic factors, diet, and co-morbidities. These findings emphasise that, although obesity is partly
254 genetically determined, lifestyle plays a major role. Indeed, our findings suggest that the potential benefits of favourable
255 lifestyle factors may act more strongly in individuals with higher genetic propensity to obesity. In individuals with a high
256 GPRS-obesity, having a high level of objectively-measured PA was associated with a 2.5 $kg.m^{-2}$ lower BMI (7 kg weight
257 for someone 1.7 m tall). Thus, individuals who are unfortunate enough to be genetically predisposed to obesity can
258 nonetheless substantially attenuate their adiposity by maintaining a high level of PA. Indeed, BMI in active individuals
259 with high GPRS-obesity scores were substantially lower than in those with low GPRS-obesity scores who were inactive.
260 Thus, identifying this sub-group of genetically prone (and thus susceptible) individuals and supporting their adoption of a
261 healthier lifestyle may help to stem the increasing prevalence of obesity.
262
263 It is well-known that self-reporting of PA can attenuate the apparent association between PA and health outcomes, due to
264 regression-dilution bias.[43] This was evident in the present data: difference in BMI between the high and low PA groups was
265 1.8 $kg.m^{-2}$ and 2.5 $kg.m^{-2}$ for the lowest and highest quartiles of GPRS-obesity, respectively, when PA was objectively
266 measured, but this BMI difference between high and low PA groups was attenuated by ~30-40% to 0.9 $kg.m^{-2}$ and 1.6
267 $kg.m^{-2}$ for the lowest and highest quartiles of GPRS-obesity when PA was self-reported. However, despite the overall
268 association between PA and adiposity being substantially attenuated by self-report, the extent of the GPRS-obesity
269 interaction was broadly similar whether PA was objectively-measured or self-reported: the 'benefit' of a high compared to
270 low level of PA was 0.7 $kg.m^{-2}$ greater in those with a high compared to low GPRS-obesity score in both cases. The
271 findings are in agreement with the Tyrell study[23], although the cohort was smaller (120,000 people), the exposures was only
272 presented as binary variable restricting the possibility to investigate a dose-response interaction effect and the GPRS using
273 a smaller number of SNPs (69 variants).Thus the present data with almost 310,652 participants and a comprehensive 93
274 SNP genetic profile risk score substantially extend the current evidence base. Nevertheless, previously reported findings
275 have been broadly similar to the more extensive data reported here. Li and colleagues reported the interaction between a
276 12-SNP unweighted genetic profile risk score and self-reported categories of PA on BMI in 20,430 individuals from the
277 EPIC-Norfolk cohort.[44] This study reported that on average each additional susceptibility allele was associated with an
278 increase in body weight of 445g. They also reported a significant interaction (p=0.005) between genetic risk and PA levels,
279 with a more pronounced effect of the genetic score for inactive individuals (β: 0.20±0.02 $kg.m^{-2}$, $p=3.6x10^{-18}$) than active
280 people (β: 0.13±0.01 $kg.m^{-2}$, $p=7.9x10^{-21}$).[44] Another study conducted by Qi and colleagues,[22] in 7740 women and 4564
281 men from the Nurses' Health Study and Health Professionals Follow-up Study, found that the genetic association with BMI
282 weakened with increased levels of physical activity. An increment of 10 points in the weighted genetic score was

associated with 1.5, 1.3, 1.2, 1.2 and 0.8 kg.m^{-2} higher BMI across the quintiles from lowest to highest PA, respectively. A further study in 17,423 participants from a multi-ethnic longitudinal study did not find any significant interaction between a 14-SNP genetic score and self-reported PA,[21] however this could potentially be explained by issues related to deriving a genetic risk score in multi-ethnic populations.

A novel result of our study was the inclusion of commuting mode (car, public transport and active commuting) as a measure of transport physical activity. Previous studies using UK Biobank data had reported important health benefits associated with active commuting in comparison to those who reported driving their car to and from work.[33, 45, 46] Furthermore, Flint et al, reported that those who commute by car to and from work, compared to those who commute by public transport or active commuting (walk or cycle to work), had higher adiposity levels [45]. However, prior to the current study there was no evidence on whether commuting modes could modify the genetic predisposition to BMI. Although our study found no difference between car, public transport or active commuters, those who reported active commuting (walking or cycling to and from work) had on average 0.9 to 1.1 lower BMI than those who reported car commuting only. This effect was similar across all genetic risk categories, suggesting that regardless of genetic predisposition to obesity active commuters have lower levels of BMI. However, no difference was observed between public transport and car commuters. Unfortunately, we were unable to account for distance of commuting, therefore, it was not possible to investigate whether there was a dose-response relationship between commuting and adiposity.

Another interesting observation is that the association of cardiorespiratory fitness and walking pace with phenotypic adiposity was stronger than for either self-reported or objective PA. Furthermore, the magnitude of the interaction with GPRS-obesity and adiposity was stronger for cardiorespiratory fitness (4.1 kg.m^{-2} difference in BMI between low and high fitness for a high GPRS-obesity vs 2.8 kg.m^{-2} difference for a low GPRS-obesity: a 1.3 kg.m^{-2} difference in the 'benefit' of high fitness in those with high compared with low GPRS-obesity) and walking pace (1.5 kg.m^{-2} difference in 'benefit' of brisk vs slow walking pace in those with high compared with low GPRS-obesity), than for PA (0.7-0.8 kg.m^{-2} difference in benefit). Although fitness is often considered a surrogate of PA, animal and human studies show that fitness is more than just a marker of PA[47] and has a substantial heritable component;[48] walking pace is likely to reflect both PA and fitness level. Both low fitness[47, 49] and slow walking pace[50] are more strongly associated with adverse health outcomes than low levels of PA: this stronger association for fitness does not appear to be related solely due to greater measurement precision compared to typical subjective PA assessments.[47, 49] Fitness is associated with increased capacity for skeletal muscle fat oxidation[51] and there is evidence that a high ratio of fat to carbohydrate oxidation is associated with protection from future weight gain, independent of metabolic rate,[52, 53] thus an association between fitness *per se* and adiposity is mechanistically

plausible. However, irrespective of the possibility that having a high level of 'natural' fitness may help attenuate the adverse effects of genetic risk of obesity on adiposity, the general advice to be more active still holds, as this is the only way for an individual to increase their own fitness level.

We found an association between TV viewing and total sedentary behaviour with BMI and WC, consistent with other reports in the literature.[23, 54] However, we have extended previous evidence by investigating the interaction between GPRS-obesity and PC-screen time as well as novel sedentary behaviours such as how often do you play computer games. In common with the findings for PA and fitness, the association of TV viewing, PC-screen time, playing computer games and sedentary behaviour with BMI was greatest amongst those with high GPRS-obesity. The 'benefits' of a low level of total sedentary behaviour on BMI were 0.4 $kg.m^{-2}$ greater, in those with a high compared to low GPRS-obesity score – which is broadly equivalent to the associations observed for PA. As observed for PA, those with high GPRS-obesity, with low levels of TV viewing or sedentary behaviour had lower BMIs than those with low GPRS-obesity but high TV viewing or sedentary behaviour. Importantly, these relationships were observed after adjustment for PA, suggesting that it may be important for those with a high GPRS-obesity to limit sedentary behaviour as well as maintain a high level of PA activity to maximally offset their increased genetic predisposition to obesity. This work extends earlier observations from Qi and colleagues, who in a study of 12,304 individuals reported that the association between a 32-SNP obesity genetic risk score and BMI was accentuated with increasing hours per week of TV viewing.[22]

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. The UK Biobank cohort is representative of the general population with respect to age, sex, ethnicity and deprivation within the age range recruited, although it is not representative in other regards.[28] The wider generalizability of the findings are limited to White Europeans and similar work is needed in different ethnic populations. All methods of dietary assessment can incur extensive errors, and biases which are diminished, but not eliminated, by studying large numbers.[55, 56] Dietary intake was self-reported outside the clinic, which may encourage more truthful reporting, and was collected using a 24-h recall questionnaire which has been shown to produce more accurate results than a food frequency questionnaire (the usual approach adopted in large-scale studies).[57] Accuracy was further improved by administering the questionnaire on four occasions over the course of a year and deriving mean values. Additionally, whilst PA was objectively assessed using validated methods, trained staff and standard operating procedures, PA data collection took place at a different time point

than BMI data collection, which may influence some of the estimates. However, self-reported PA, which was collected at the same time as the BMI data, shows a similar trend to objectively-measured PA. Another limitation was the lack of objective PA-specific intensity domains (sedentary, light and other intensity PA), which has not yet been derived yet or made available yet by the UK Biobank, limiting our ability to compare different PA domains between objective and self-reported PA. Physical activity was also measured by self-report using a validated questionnaire, which enabled direct comparison to previous reports in the literature and quantification of the extent to which errors in self-reported PA measures could distort the true underlying relationships between PA and adiposity. Sedentary behaviour, TV-viewing and walking pace were self-reported, and thus mis-reporting biases may have led to an underestimation of the strength of the true relationship between these behaviours and adiposity measures.[43] However, based on the present data comparing self-reported and objectively-measured PA, this may not have substantially influenced the interaction of these behaviours with GPRS-obesity on BMI. However, PA was recorded over a 7-day period and how this reflects life-long PA is not known, but this remains the best way currently to quantify physical activity objectively.

A limitation of the study is that the GPRS only captures a small proportion of the genetic variance in BMI. Nevertheless, highly significant interaction effects were detected in our analysis and power was clearly not limited. As shown recently by Tyrell et al., residual confounding is another limitation likely to happen in gene x environment interactions studies, including UK Biobank[23]. 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 5 $kg.m^{-2}$ increase in BMI was associated with 30% higher risk of all-cause mortality and 40% higher risk for CVD mortality.[58] Given the high current prevalence of overweight and obesity worldwide,[6, 59] it is important to develop strategies to reduce adiposity in pursuit of improved public health. The present data clearly demonstrate that the association between indices of PA and sedentary behaviour on BMI outcomes are strongest in those with a high genetic predisposition to obesity. As described previously [23], 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 genetic profile risk score was robustly associated with BMI and waist circumference, our results show that higher levels of PA and fitness attenuates, while high levels of sedentary behaviours accentuate, the strength of the association between genetic predisposition to obesity with BMI. These findings are relevant for public health and suggest that promotion of increased PA and reduced sedentary behaviours, alongside with other healthy lifestyle behaviours, particularly in those who are genetically susceptible to higher BMI, could be an important strategy for addressing the current obesity epidemic and disease burden.

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COMPETING INTERESTS

The authors have no competing interests to disclose.

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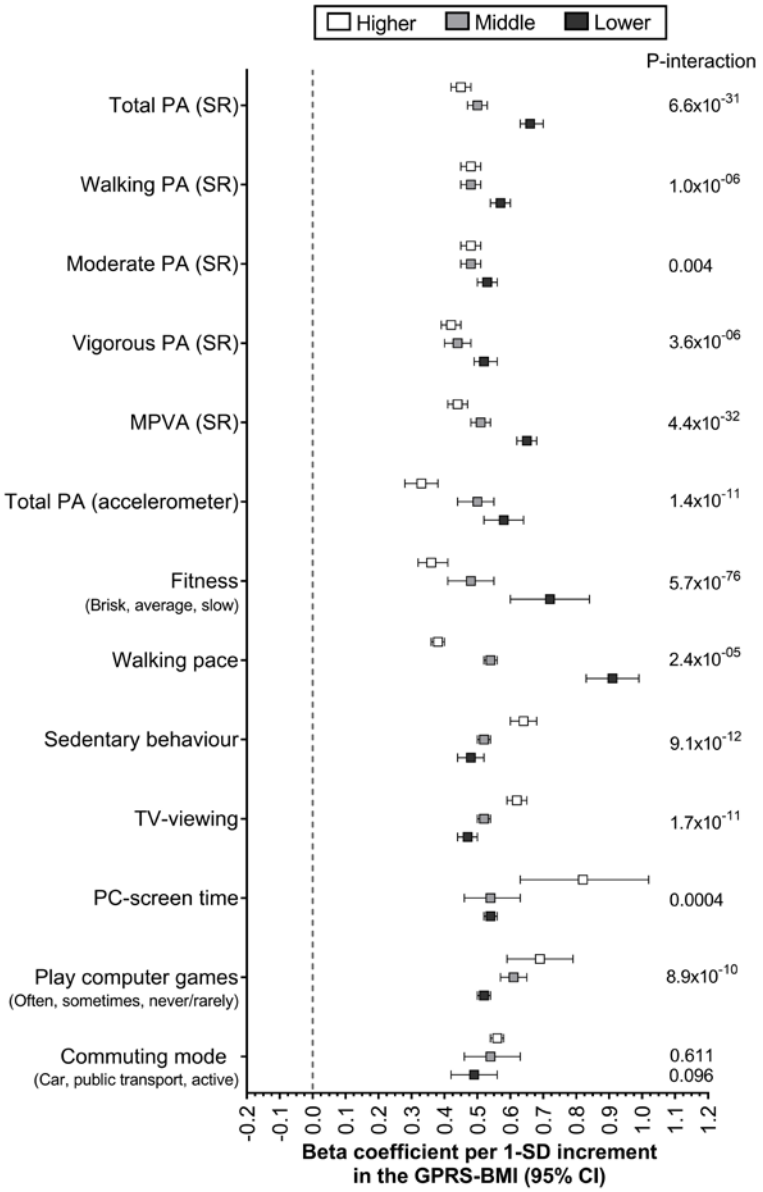
595 **FIGURE LEGENDS**

Figure 1



596

597 **Fig 1. Association between genetic profile risk score and BMI by physical activity (self-reported and objective),**
598 **fitness, commuting modes and discretionary sedentary-related behaviours.**

599 Data presented as beta coefficients and their 95%CI. The beta coefficient indicates the change in BMI per SD increase in the
600 genetic profile risk score by tertiles or categories of (self-reported or objectively-measured PA), fitness, commuting mode
601 and sedentary-related behaviours. The p-value for the interaction between GPRS and the exposure of interest (PA or sedentary
602 behaviour) indicates that the association between the GPRS-obesity and BMI differ by levels of PA or sedentary-related
603 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, sleep duration, 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 were additionally adjusted for total self-reported PA and those for PA were additionally adjusted for overall sedentary behaviours. Cut-off points for categories or tertiles of PA, fitness and sedentary behaviours exposures are presented in Table S2.

PA: physical activity; BMI: body mass index. SR: self-reported.

Figure 2

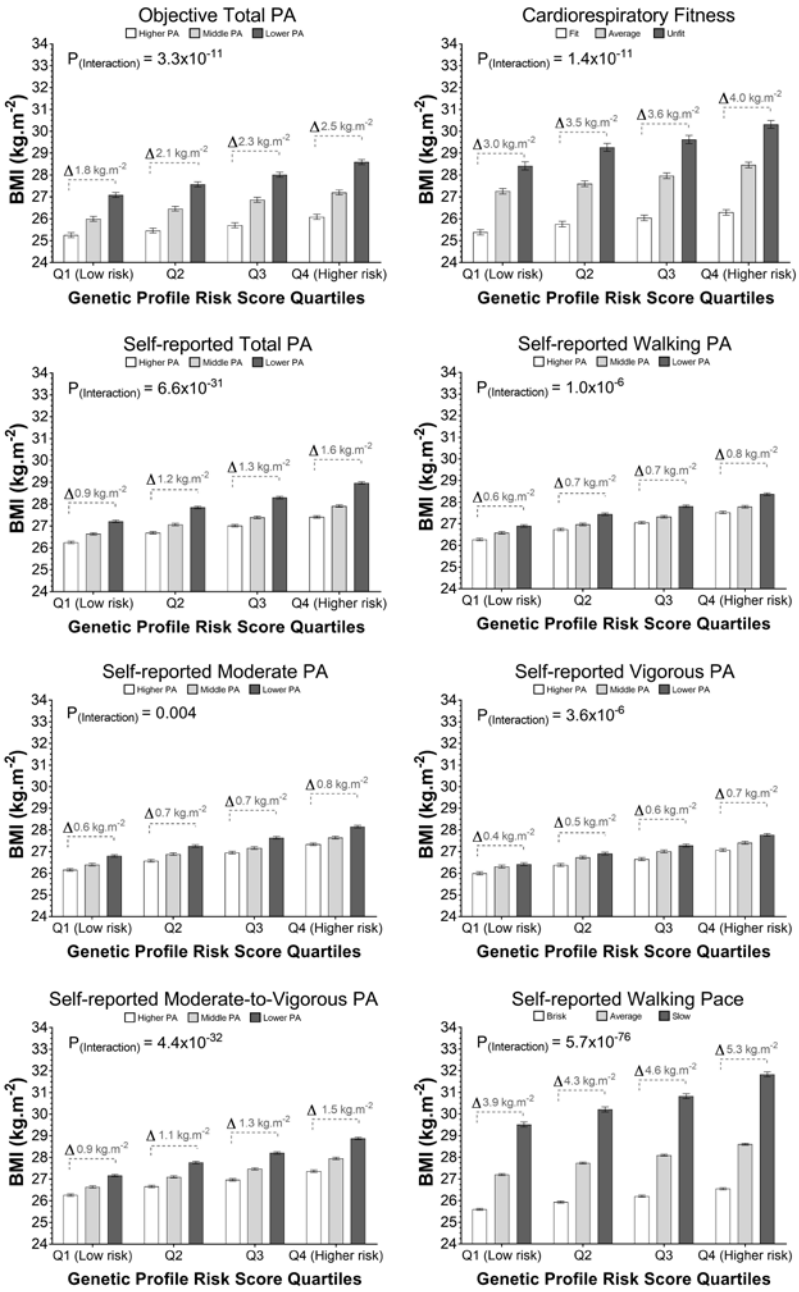


Fig 2. Association between BMI and genetic profile risk score by levels of physical activity and fitness.

Data presented as adjusted BMI means by categories or tertiles of PA, fitness and quartiles of GPRS. 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, sleep duration, total sedentary behaviour, 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. Cut-off points for categories or tertiles of PA, fitness and sedentary behaviours exposures are presented in Table S2.

Figure 3

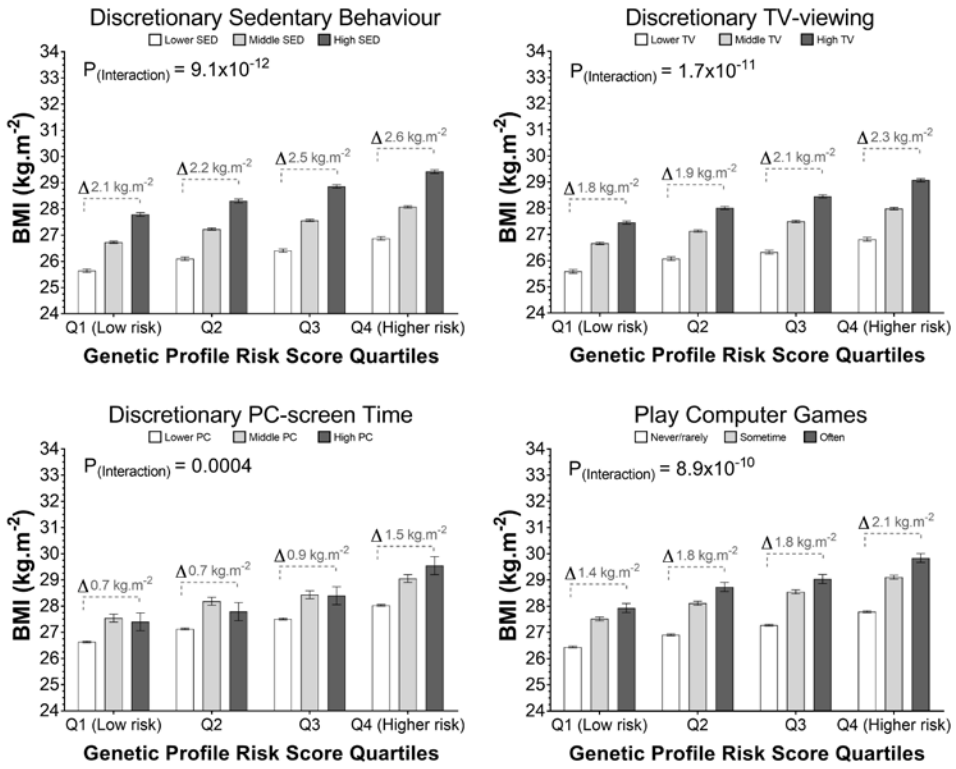


Fig 3. Association between BMI and genetic profile risk score by levels of sedentary-related behaviours.

Data presented as adjusted BMI means by categories or tertiles of overall discretionary sedentary behaviour, TV-viewing, PC-screen time, play computer game and quartiles of GPRS. 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, sleep duration, total PA, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases and cancer).

Figure 4

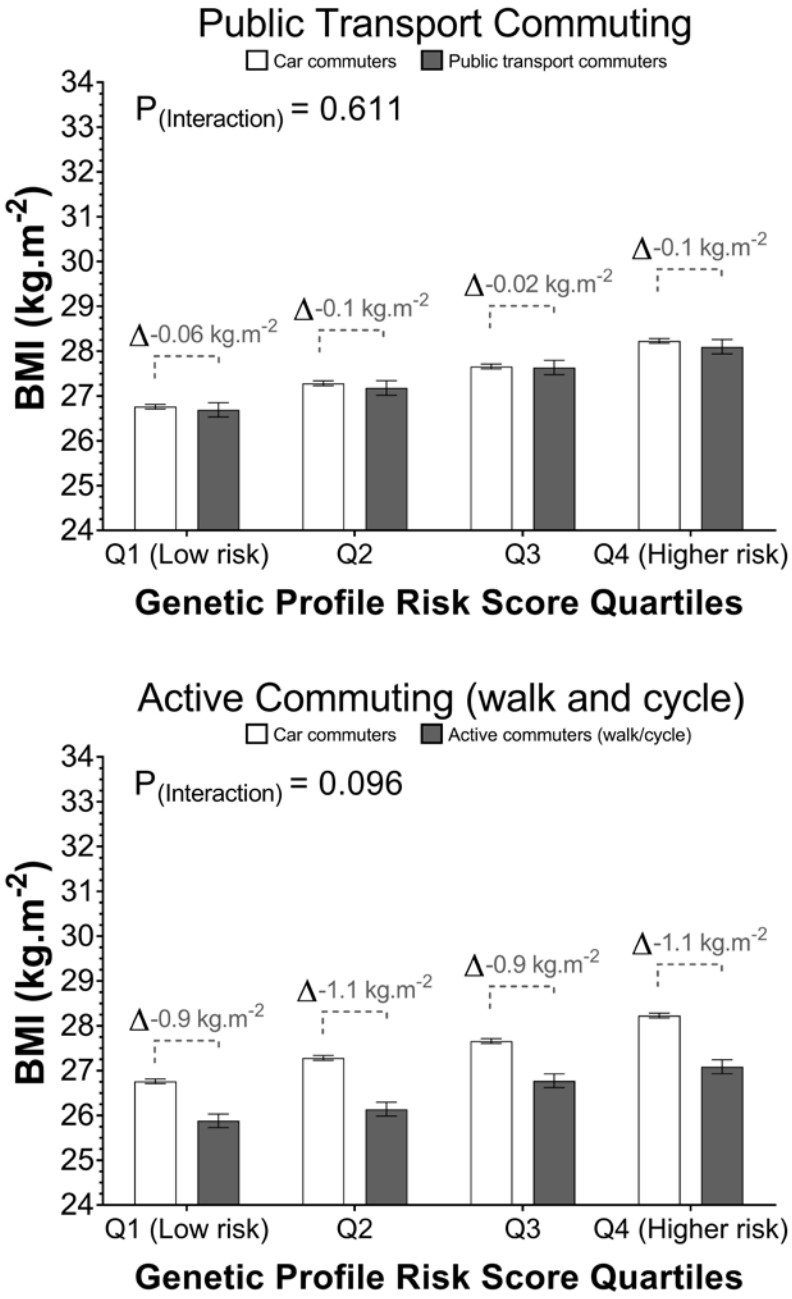


Fig 4. Association between BMI and genetic profile risk score by commuting modes.

Data presented as adjusted BMI means by commuting modes (car, public transport and active commuting including walking and/or cycling) and quartiles of GPRS. 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, sleep duration, total sedentary behaviours, dietary intake (alcohol, fruit & vegetable, red meat, processed meat, cereals, bread and cheese) and comorbidities (diabetes, hypertension, cardiovascular diseases and cancer).

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

		Quartiles of Genetic Profile Risk Score			
	Overall	**Q1 (Lowest risk)**	**Q2**	**Q3**	**Q4 (Highest risk)**
Socio-demographics					
Total n	307,765	77, 164	76, 937	76, 911	76,753
Women, n (%)	163,897 (53.3)	41,150 (53.3)	41,038 (53.3)	41,038 (53.4)	40,671 (53.0)
Age (years)	56.8 (8.0)	56.8 (8.0)	56.9 (8.0)	56.8 (8.0)	56.8 (8.0)
Deprivation index					
Lower (least deprived)	112, 238 (36.5)	28,451 (36.8)	28, 167 (36.6)	27,847 (36.2)	27, 773 (36.2)
Middle	106,299 (34.5)	26,675 (34.6)	26,591 (34.6)	26,720 (34.7)	26, 313 (34.3)
Higher (most deprived)	89,228 (29.0)	22, 038 (28.6)	22, 179 (28.8)	22, 344 (29.1)	22, 667 (29.5)
Education					
CSEs	16,608 (6.2)	4, 054 (6.0)	4, 126 (6.1)	4, 204 (6.2)	4, 224 (6.3)
O-levels	68,383 (25.4)	17, 010 (25.1)	16, 970 (25.2)	17, 255 (25.7)	17, 148 (25.6)
A-levels	35,233 (13.1)	8, 940 (13.2)	8, 904 (13.2)	8, 616 (12.8)	8, 773 (13.1)
College/University Degree	98,455 (36.5)	25, 449 (37.5)	24, 808 (36.8)	24, 322 (36.2)	23, 876 (35.6)
None of the above	50,732 (18.8)	12, 339 (18.2)	12, 573 (18.7)	12, 809 (19.1)	13, 011 (19.4)
Smoking status, n (%)					
Never	169,550 (55.1)	43, 229 (56.0)	42, 579 (55.3)	42, 296 (55.0)	41, 446 (54.0)
Previous	108,452 (35.2)	26, 746 (34.7)	26, 918 (35.0)	27, 226 (35.4)	27, 562 (35.9)
Current	29, 763 (9.7)	7, 189 (9.3)	7, 440 (9.7)	7,389 (9.6)	7,745 (10.1)
Obesity-related markers					
Height (cm)	169.0 (9.2)	169.0 (9.2)	168.9 (9.2)	168.9 (9.2)	169.1 (9.3)
Weight (kg)	78.3 (15.8)	76.3 (14.9)	77.7 (15.5)	78.8 (15.9)	80.5 (16.5)
BMI ($kg.m^{-2}$)	27.4 (4.7)	26.6 (4.3)	27.2 (4.6)	27.5 (4.7)	28.1 (5.0)
BMI Categories, n (%)					
Underweight (<18.5)	1,470 (0.4)	524 (0.7)	395 (0.5)	310 (0.4)	241 (0.3)
Normal weight (18.5-24.9)	100,929 (32.8)	29, 391 (38.1)	26, 242 (34.1)	24, 195 (31.5)	21, 101 (27.5)

Overweight (25.0 to 29.9)	132,239 (43.0)	32, 919 (42.6)	33, 118 (43.1)	33, 085 (43.0)	33, 085 (43.1)
Obese (≥ 30.0)	73,127 (23.8)	14, 330 (18.6)	17, 182 (22.3)	19, 321 (25.1)	19, 321 (25.1)
Waist Circumference (cm)	90.3 (13.3)	88.7 (12.7)	89.8 (13.2)	90.6 (13.4)	91.9 (13.8)
Central Obesity, n (%)	101, 625 (33.0)	21, 588 (28.0)	24, 433 (31.8)	26, 408 (34.3)	29, 196 (38.0)
Physical activity					
Walking PA (min.day^{-1})*	54.0 (74.9)	53.5 (74.4)	54.1 (75.5)	54.1 (75.3)	54.3 (74.6)
Moderate PA (min.day^{-1})*	46.2 (68.3)	46.0 (68.3)	46.4 (68.7)	46.4 (68.9)	46.0 (67.1)
Vigorous PA (min.day^{-1})*	21.0 (33.0)	20.6 (32.3)	21.0 (33.1)	21.3 (34.3)	21.2 (32.1)
Total PA (MET-hour.week^{-1})*	45.2 (62.5)	44.9 (62.1)	45.4 (63.0)	45.4 (63.3)	45.2 (61.7)
Physically active individuals, n (%)*	169, 962 (55.2)	42, 363 (54.9)	42, 740 (55.6)	42, 422 (55.2)	42, 437 (55.3)
Objective total PA (milli-gravity.day^{-1})	28.0 (8.2)	28.1 (8.2)	28.0 (8.2)	28.0 (8.3)	27.9 (8.1)
Fitness (METs)	8.9 (3.5)	9.0 (3.5)	8.9 (3.5)	8.9 (3.4)	8.8 (3.5)
Walking pace, n (%)					
Slow	21, 675 (7.0)	4, 907 (6.3)	5, 277 (6.9)	5, 476 (7.1)	6, 015 (7.8)
Middle	161, 691 (52.5)	39, 775 (51.6)	40, 049 (52.0)	40, 831 (53.1)	41, 036 (53.5)
Brisk	124, 399 (40.5)	32, 482 (42.1)	31, 611 (41.1)	30, 604 (39.8)	29, 702 (38.7)
Car commuters, n (%)	12, 719 (10.7)	3, 284 (11.1)	3, 186 (10.8)	3, 184 (10.7)	3, 065 (10.3)
Public Transport commuters, n (%)	12, 045 (10.2)	3, 107 (19.6)	3, 006 (10.2)	3,030 (10.2)	2, 902 (9.8)
Walking commuters, n (%)	8, 522 (7.4)	2, 191 (7.7)	2, 086 (7.3)	2, 178 (7.6)	2, 067 (7.2)
Cycling commuters, n (%)	3, 663 (3.3)	944 (3.5)	958 (3.5)	875 (3.2)	886 (3.2)
Total Sedentary Behaviour (h.day^{-1})	5.1 (2.2)	5.0 (2.2)	5.1 (2.2)	5.1 (2.2)	5.1 (2.3)
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)
PC-screen time (h.day^{-1})	1.2 (1.3)	1.2 (1.3)	1.2 (1.3)	1.2 (1.3)	1.2 (1.3)
Plays Computer Games					
Never/Rarely	243, 048(79.0)	61, 060 (79.2)	60, 843 (79.1)	60, 814 (79.1)	60, 331 (78.6)
Sometimes	54, 443 (17.7)	13, 617 (17.7)	13, 541 (17.6)	13, 537 (17.6)	13, 748 (17.9)
Often	10, 174 (3.3)	2, 461 (3.1)	2, 529 (3.3)	2, 538 (3.3)	2, 646 (3.5)

Dietary intake					
Total energy intake (Kcal.day^{-1})	2,181 (646)	2,187 (638)	2,183 (648)	2,178 (642)	2, 177 (656)
Protein intake (% of TE)	15.5 (3.5)	15.4 (3.4)	15.4 (3.5)	15.5 (3.5)	15.6 (3.6)
Carbohydrate intake (% of TE)	47.2 (7.9)	47.2 (7.8)	47.2 (7.9)	47.2 (7.9)	47.2 (8.0)
Total Fat intake (% of TE)	32.0 (6.6)	32.1 (6.5)	32.0 (6.6)	32.0 (6.6)	32.0 (6.6)
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)	5.9 (2.2)	5.9 (2.2)	5.9 (2.2)	5.9 (2.2)	5.9 (2.2)
Sugar intake (% of TE)	22.5 (6.8)	22.5 (6.7)	22.5 (6.8)	22.5 (6.8)	22.4 (6.8)
Starch intake (g.day^{-1})	22.8 (6.0)	22.8 (5.9)	22.9 (6.0)	22.8 (6.1)	22.8 (6.1)
Alcohol intake (% of TE)	5.3 (6.5)	5.3 (6.4)	5.3 (6.5)	5.3 (6.5)	5.2 (6.4)
Red meat (portion.day^{-1})	1.9 (2.3)	2.0 (1.4)	2.0 (1.4)	1.9 (1.4)	1.9 (1.4)
Processed meat (portion.day^{-1})	1.9 (1.0)	1.9 (1.0)	1.9 (1.0)	1.9 (1.0)	1.9 (1.0)
Fruit and vegetable (portion.day^{-1})	4.0 (2.3)	4.0 (2.2)	4.0 (2.3)	4.0 (2.3)	4.1 (2.3)
Health status, n (%)					
Diabetes	14, 329 (4.7)	3, 193 (4.1)	3, 400 (4.4)	3, 601 (4.7)	4, 135 (5.4)
Hypertension	70, 053 (22.8)	16, 539 (21.4)	17,406 (22.6)	17, 752 (23.1)	18, 356 (23.9)
Cancer	23, 776 (7.7)	6, 065 (7.9)	6, 003 (7.8)	5, 895 (7.7)	5, 813 (7.6)
CVDs	90, 627 (29.5)	21, 475 (27.8)	22, 518 (29.3)	22, 893 (29.8)	23, 741 (30.9)

Data presented as mean and SD for continuous variables and as n and % for categorical variables. CVD: cardiovascular diseases; TE: total energy intake; MET: metabolic equivalent task.