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Sleep characteristics modify the association between genetic predisposition to obesity and anthropometric measurements in 119,679 UK Biobank participants

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Short running head: Sleep characteristic, genetic risk and obesity

Abbreviations: Body mass index (BMI), 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 genetics, lifestyle and environment.

Objective - To investigate whether the association between a validated genetic profile risk score for obesity (GPRS-obesity) with body mass index (BMI) and waist circumference (WC) was modified by sleep characteristics.

Design - This study included cross-sectional data from 119,859 white European adults, aged 37-73 years, participating on the UK Biobank. Interactions between GPRS-obesity, and sleep characteristics (sleep duration, chronotype, day napping, and shift work) in their effects on BMI and WC were investigated.

Results - The GPRS-obesity was associated with BMI (β:0.57 $kg.m^{-2}$ per standard deviation (SD) increase in GPRS, [95%CI:0.55, 0.60]; $P=6.3x10^{-207}$) and WC (β:1.21 cm, [1.15, 1.28]; $P=4.2x10^{-289}$). There were significant interactions between GPRS-obesity and a variety of sleep characteristics in their relationship with BMI (P-interaction <0.05). In participants who slept <7 hrs or >9 hrs daily, the effect of GPRS-obesity on BMI was stronger (β:0.60 [0.54, 0.65] and 0.73 [0.49, 0.97] $kg.m^{-2}$ per SD increase in GPRS, respectively) than in normal length sleepers (7-9 hours; β:0.52 [0.49, 0.55] $kg.m^{-2}$ per SD). A similar pattern was observed for shiftworkers (β:0.68 [0.59, 0.77] versus 0.54 [0.51, 0.58] $kg.m^{-2}$ for non-shiftworkers) and for night-shiftworkers (β:0.69 [0.56, 0.82] versus 0.55 [0.51, 0.58] $kg.m^{-2}$ for non-night-shiftworkers), for those taking naps during the day (β:0.65 [0.52, 0.78] versus 0.51 [0.48, 0.55] $kg.m^{-2}$ for those who never/rarely had naps) and for those with a self-reported evening chronotype (β:0.72 [0.61, 0.82] versus β:0.52 [0.47, 0.57] $kg.m^{-2}$ for morning chronotype). Similar findings were obtained using WC as the outcome.

Conclusions – This study shows that the association between genetic risk for obesity and phenotypic adiposity measures is exacerbated by adverse sleeping characteristics.

Key Words: Obesity, sleep, chronotype, nap, shiftwork, night-shiftworkers, genetic risk score, genes

INTRODUCTION

Sleep is a fundamental behaviour, with growing evidence suggesting that certain sleep behaviours are a strong risk factor for obesity (1). Previous studies suggest a U-shaped relationship between sleep duration and obesity, whereby both short and long sleep duration are associated with higher risk of obesity (1, 2). Although less well studied, other sleep characteristics including chronotype (i.e. being an evening versus morning person)), daytime napping, and shift work (including night shift work) may also be associated with obesity (3-5).

The worldwide obesity epidemics, and its consequent effects on morbidity and mortality, are responsible for a large public health burden (6, 7). The dramatic increase in obesity prevalence over the past three decades has been attributed to changes in lifestyle in response to an "obesogenic" environment (8). However, obesity is a multifactorial condition influenced by lifestyle and environment, as well as by genetics (8). It has a largely polygenic genetic architecture and its heritability is approximately 40-70% (8). However, the fact that obesity prevalence varies throughout the world and is changing over timescales too short to be influenced by changing risk allele frequencies, suggests that there may be gene-environment interactions and that genetic risk is moderated by lifestyle/environment. The remaining unexplained heritability may be accounted for in part by such unappreciated gene/environment interactions (9). Some genetic factors may operate independently of environment, but others may confer greater predisposition to weight gain in an obesogenic environment (10), a hypothesis supported by the results of twin studies of changes in adiposity in response to environmental influences (11).

Thus far, there is growing evidence regarding the contribution of genetic factors on different sleep-related characteristics (12). However, there is limited evidence on genotype-lifestyle interactions in the area of obesity and circadian biology. No studies have yet investigated whether overall genetic predisposition to obesity, as measured using genetic profile risk scores for obesity (GPRS-obesity), interacts with sleep characteristics, such as sleep duration, chronotype, day napping, and shift work, to influence adiposity. In the current study, we therefore investigated whether the associations between of a comprehensive and validated GPRS-obesity (13) with adiposity outcomes were modulated by sleep-related characteristics in the UK Biobank cohort, a large population sample.

SUBJECTS AND METHODS

Study design

Between April 2007 and December 2010, UK Biobank recruited 502,549 participants (5.5% response rate), aged 37-73 years from the general population (14). Participants attended one of 22 assessment centres across England, Wales and Scotland (15) where they completed a touch-screen questionnaire (including self-reported sleep duration, chronotype, day napping, shiftwork and nightshift work), had physical measurements taken and provided biological samples, as described in detail elsewhere (15). Of these participants, 119,859 had genotype data available for the GPRS-obesity SNPs 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. The number of participants with data on sleep characteristics (and genotype data) was as follows: sleep duration - 498,463 (115,139); chronotype - 444,331 (37,016); day napping - 500,784 (115,646); shiftwork - 286,522 (65,491).

The outcome measures considered were BMI and waist circumference (WC). The independent predictor variable of interest was a genetic profile risk score for BMI (GPRS-obesity). Sleep duration, chronotype, day napping, shift work, and nightshift work were treated as potential moderators.

Ethics

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

At baseline assessment, sleep, socio-demographic and lifestyle variables were collected from all participants using a self-completed, touch-screen questionnaire. Self-reported sleep duration was obtained using the following question "About how many hours sleep do you get in every 24 hours?”. Sleep duration was used to derived sleep categories including short sleeper (<7 $h.day^{-1}$), normal sleepers (between 7 and 9 $h.day^{-1}$) and long sleepers (>9 $h.day^{-1}$). Chronotype was self-reported and collected using the following question "Do you consider yourself to be?" a) Definitely a 'morning' person; b) more morning than evening; c) more evening than morning; and d) Definitely an 'evening' person. We restricted our analyses to individuals in categories a) and d) to robust phenotyping for chronotype, in line with previous analyses on the UK Biobank cohort (16). Daytime napping was self-reported and participants were asked “Do you have a nap during the day?” with the responses being a) Never/rarely; b) Sometimes; or c) Usually. Shift work and night shift work variables were also self-reported and collected using the questions "Does your work involve shift work?” and "Does your work involve night shifts?" with responses of a) Never/rarely; b) Sometimes; c) Usually; or d) Always; for this study we recoded answers into two categories for both shift-related variables “Never/rarely” and “Yes” which include “sometimes”; “usually” and “always”.

Self-reported physical activity was recorded using a self-completed questionnaire based on the International Physical Activity Questionnaire (IPAQ) short form (17). Physically active individuals were defined as those who met the recommendation of at least 600 METs.min^{-1}.week^{-1} of moderate or vigorous PA (17). Total time spent in sedentary behaviour (h.week^{-1}) was estimated as the sum of self-reported time spent driving, using a computer and watching television (TV).

Dietary information was collected via a self-reported dietary frequency questionnaire (Oxford WebQ) (18). Area-based socioeconomic status was defined from postcode of residence using the Townsend score (19). Age was calculated from dates of birth and baseline assessment. Medical history (physician diagnosis of depression, longstanding illness, diabetes, CVD, and cancer) was collected from the self-completed, baseline questionnaire. Height and body weight were measured by trained nurses during the initial assessment centre visit. BMI was calculated from weight/height^2 and the WHO criteria (20) used to classify BMI into categories: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese $\geq$30.0 kg.m^{-2}. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Genetic data analysis

For this study, we used the first genetic data release (June 2015), which included approximately one-third of the UK Biobank participants (n=152,770). 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 phenotype data were available. 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 on the basis of sample failure (Biobank Data Dictionary item #22010: UK Biobank genomic analysis exclusions), relatedness (#22012: genetic relatedness factor; a random member of each pair of individuals with KING-estimated kinship coefficient >0.0442 was removed), gender mismatch (#22001 derived from genotype analysis and self-reported sex), ethnicity (non-white Europeans were removed from the analysis based on self-reported ethnicity) and quality control failure in the UK BiLEVE study (#22050: UK BiLEVE Affymetrix quality control for samples and #22051: UK BiLEVE genotype quality control for samples). This left 119,859 of whom 119,679 had BMI data available.

GPRS-obesity 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 and colleagues (13). (See Supplemental Table 1). 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 (21); 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) (13) 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 analyses

Baseline phenotypic and morbidity data were used in the analyses. General linear models (GLM) were used to test for associations between GPRS-obesity and the outcomes (BMI and WC). 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 (BMI $\geq$25.0 kg.m^{-2}; BMI $\geq$30.0 kg.m^{-2}; centrally-obese: WC $\geq$88 cm for women and $\geq$102 cm for men) were investigated using binary logistic regression, with the lower adiposity category treated as the referent.

Interactions between sleep characteristics and the GPRS-obesity in the association with the outcome measures (BMI and WC) were investigated using GLM. For this the interaction terms for sleep characteristics (sleep duration categories, chronotype, day napping, shift work, and nightshift work), were fitted treating all sleep factors as categorical variables and GPRS-obesity as a continuous variable. Where interactions were statistically significant, stratified analyses were undertaken for each sleep variable.

For each of the approaches described above, we ran two incremental models that included an increasing number of covariates: “model 0” included age, sex, month of recruitment, deprivation score, medical history (diabetes, long-standing illness, CVD, cancer, and depression), and genetic principal components variables; “model 1” included all variables in model 0, but also adjusted for smoking status, portions of food categories eaten per day (alcohol, fruit, coffee, vegetables, meats, processed meat, cereals, bread, and cheese), and total physical activity, as well as sedentary behaviours and sleep characteristic (sleep duration, chronotype, and day napping) when these were not being tested as potential effect modifiers. All analyses were performed using STATA 14 statistical software (StataCorp LP).

RESULTS

The main characteristics of the participants by GPRS-obesity quartile, and sleep characteristics are summarised in Tables 1 and 2 and Supplemental Tables 2-5, respectively. In summary, 52.6% of the cohort was female, mean age was 56.9 years, 12.3% were current smokers, 67.6% were overweight or obese, and 34.5% were centrally obese. Based on self-report, 54% of the participants were physically active (>600 $MET.min^{-1}.week^{-1}$), 24.3% had short sleep duration (<7 $h.day^{-1}$) and 1.8% had long sleep duration (>9 $h.day^{-1}$), 25.4% had evening chronotype, 5.5% usually napped during the day, 16.9% did shift work and 9.4% nightshift work. All sleep characteristics were significantly associated with BMI and WC (Table 3).

Genetic profile risk score and obesity measures

GPRS-obesity explained 1.9% and 1.1% of the variance in BMI and WC, respectively, with greater genetic risk being associated with a higher BMI (β:0.57 $kg.m^{-2}$ increase per SD change in GPRS-obesity [95%CI:0.55, 0.60], $p=6.3x10^{-207}$) and greater WC (β:1.21 cm per GPRS-obesity SD [95%CI:1.15, 1.28], $p=4.2x10^{-289}$). After adjustment for socio-demographic factors, medical history, total sedentary behaviour, dietary intake, and sleep characteristics, these associations were marginally attenuated but remained highly significant for both BMI (β:0.55 $kg.m^{-2}$ [0.52, 0.57]; $p=5.9x10^{-201}$) and WC (β:1.16 cm [1.09, 1.22], $p=2.0x10^{-254}$) (Supplemental Figure 1 and Supplemental Table 6). Odds ratios for having a BMI ≥25, BMI ≥30, or being centrally obese are presented in Supplemental Table 6 and Supplemental Figure 1, 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 sleep characteristic

The GPRS-obesity was not associated with sleep duration or any other sleep characteristics (data not shown; all P-values > 0.05). However, the association between GPRS-obesity and adiposity was modified by several of these sleep characteristics (Figures 1 and 2). Sleep duration significantly modified the association of GPRS-obesity with both BMI (P-interaction=3.5×10^{-4}) and WC (P-interaction=0.037) (Table 4). The association between GPRS and BMI was stronger for participants with both short and long sleep duration compared with those who reported normal sleep duration: 0.62 [0.56, 0.68] kg.m^{-2} and 0.84 [0.61, 1.07] kg.m^{-2} per GPRS-obesity SD compared to 0.55 [0.52, 0.58] kg.m^{-2}. Among participants in the lowest quartile of the GPRS-obesity, the BMI of short and long sleepers was ~0.2 kg.m^{-2} higher than that of normal sleepers, but this was not statistically significant. Among those in the highest quartile for GPRS-obesity the difference was greater: BMI was 0.6 and 1.1 kg.m^{-2} higher for short and long sleepers respectively (Figure 1). Comparable results were found for WC (Figure 2 and Table 4). Similar findings were observed for day napping, shift work, nightshift work and chronotype (Figure 1 and 2 and Supplemental Tables 7-10). The association between GPRS-obesity and BMI was stronger among participants who worked shifts (β:0.70 [0.61, 0.78] kg.m^{-2} per GPRS-obesity SD versus 0.57 [0.54, 0.61] kg.m^{-2} in non-shift workers), worked night shifts (β:0.70 [0.58, 0.82] kg.m^{-2} versus 0.58 [0.54, 0.61] kg.m^{-2} in non-nightshift workers), had day naps (β:0.69 [0.56, 0.82] kg.m^{-2} versus 0.53 [0.50, 0.56] kg.m^{-2} in those who did not has day naps), and were of evening chronotype (β:0.76 [0.66, 0.86] kg.m^{-2} versus 0.55 [0.50, 0.60] kg.m^{-2} in morning chronotype). Further adjustment for potential confounders, including smoking, physical activity, sedentary behaviour, dietary factor, and sleep characteristics (when these were not used as a factor in the interaction term) did not alter any of these associations (Supplemental Tables 7-10).

DISCUSSION

Main findings

This study provides novel evidence that the association between genetic predisposition to obesity and actual measures of adiposity (BMI and WC) is moderated by sleep characteristics including sleep duration, chronotype, day napping, shift work, and nightshift work. Moreover, our results show that, in the UK Biobank cohort, the interaction between GPRS-obesity and sleep characteristics in their effects on adiposity were independent of a range of confounders including socio-demographic factors, diet, and co-morbidities. These findings emphasise that, although obesity is partly genetically determined, lifestyle plays a major role. The effects of the genetic predisposition to obesity appear to be augmented by sleeping behaviours including short and long duration, evening chronotype, day napping, shift work, and nightshift work. In those with a high GPRS-obesity, being a short sleeper was associated with a 0.6 $kg.m^{-2}$ higher BMI and, being long sleeper was associated with a 1.1 $kg.m^{-2}$ BMI, compared with those with similar genetic risk but normal sleep duration. In contrast, short and long sleep duration was only associated with ~0.2 $kg.m^{-2}$ higher BMI in those in the lowest quartile for GPRS-obesity. This means that the adverse associations of short or long sleep durations is more pronounced in those who have increased genetic predisposition to obesity, and, conversely, less pronounced in those with lower genetic predisposition. 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 sleep behaviours, particularly in individuals genetically susceptible to obesity.

Although no previous studies have investigated possible interaction between GPRS-obesity and sleep characteristics, there is evidence that other lifestyle behaviours including diet and physical activity modify the relationship between the genetic risk score and adiposity outcomes (22, 23). Our results therefore extend previous evidence of gene-environment interactions by reporting the effect of several sleep-related characteristics on genetic predisposition to obesity in a large cohort, using a more extensive genetic risk profile derived from 93-SNPs previously associated with BMI. We also need to consider that there is evidence that some sleep characteristics are partially genetically determined. It has been estimated that the heritability of sleep duration is between 31% and 55%, suggesting a substantial amount of sleep need is genetically determined (24). Similarly, chronotype is also heritable as estimated by twin and family studies (12–42%), and its genetic basis has been recently defined (12, 16). Nonetheless, some of the sleep characteristics studied such as shift work and nightshift work are potentially amenable to modification, particularly at an organisation level.

Furthermore, this study corroborates previous findings regarding the association between sleep characteristics and obesity. Modal sleep duration in UK Biobank was 7 hours, consistent with previous reports (25). Our observations that sleep duration (1) and other sleep characteristics including chronotype (3), day napping (26), and shift work (27) were associated with increased risk of obesity are consistent with previous reports.

Strengths and limitations of the study

UK Biobank provided an opportunity to test our research question in a very large cohort and the outcomes used in this study were collected using validated and standardised measurements, rather than self-report. Although misreporting of self-reported sleep characteristics is possible, it is likely to be random in nature rather than varying systematically by the exposure or outcome of interest (28). Also our results were consistent across all sleep-characteristics. Additionally, in order to reduce misreporting we excluded outliers and extreme cases (although this did not materially affect the results). Another limitation of this study was the lack of data on the duration of some exposures such as day napping and shiftwork. Despite this, the results observed for these exposures were consistent with those seen for other sleep characteristics for which full data was available. Chronotype was assessed using a single question, rather than a more comprehensive instrument such as the Morningness-Eveningness Questionnaire (29). The Townsend score used to estimate socio-economic deprivation is an area-based proxy rather than an individual-level metric of deprivation.

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 1.9%, compared with the 2.7% of variance explained by the 97 SNPs identified in the GIANT consortium's mega-GWAS (13). This difference is not huge and probably just reflects the differences in cohort structure (single cohort vs multiple cohorts) and small biases unaccounted for in the meta-analysis methodology. In an underpowered study, the small effect size of the genetic predictor could result in type 2 error or an inflated type 1 error rate, but the effect sizes reported here suggest that the GPRS is not underpowered. A polygenic risk score (PRS) analysis explaining more of the variance in BMI 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. A further limitation is the cross-sectional nature of the study. The size and nature of the main and interaction effects found, however, are encouraging and in the case of genetic predictors, reverse causality is unlikely to be factor influencing our interpretation of the results. Future studies of the effectiveness of sleep interventions on obesity should be sufficiently powered to study the effectiveness among sub-groups defined by genetic predisposition to obesity, as well as overall effectiveness.

Implications of findings

In light of the public health threat being posed by obesity and increased adiposity worldwide, (30) our findings are highly relevant for improving global health. They highlight the fact that modifiable risk factors associated with lifestyle, including sleeping behaviours, can moderate or exacerbate the effects of genetic influences on body weight, just as physical activity and diet are known to do (22, 23). Although this study was cross-sectional, the likelihood is that identification of individuals that are genetically predisposed to increased adiposity may allow targeted interventions aimed at modifying their lifestyle risk factors for obesity and its associated diseases, with increased benefits relative to less genetically predisposed individuals. The magnitude of the associations demonstrated in our study (for example, the difference in body mass between long versus normal duration sleeper in those with high GPRS-obesity was ~4.5 kg) is sufficiently large to be clinically relevant. Previous evidence on 900,000 adults from the collaborative analyses of 57 prospective studies reported that a 5 $kg.m^{-2}$ increase in BMI is associated with 30% higher all-cause mortality and 40% higher risk for CVD mortality (7). 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 (31, 32). Our findings are relevant to the health and employment sectors and suggest that promoting healthy sleep should be promoted, alongside a healthy diet and physical activity, as a means of combating the obesity epidemic.

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The sponsor had no role in any aspect of the study's (design, data collection, analysis and writing up). The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Table 1. Cohort characteristics by quartile of genetic profile risk score for obesity (GPRS-obesity)[1]

		GPRS-obesity Quartiles			
	Overall	**Q1 (Lowest risk)**	**Q2**	**Q3**	**Q4 (Highest risk)**
Socio-demographics					
Total, n	119,859	30,047	29,958	29,894	29,960
Women, n (%)	63,043 (52.6)	15,950 (53.1)	15,686 (52.4)	15,726 (52.6)	15,681 (52.3)
Age (years), mean (SD)	56.9 (7.93)	56.9 (7.93)	56.9 (7.93)	56.8 (7.95)	56.9 (7.91)
Townsend deprivation index score, mean (SD)	-1.47 (3.00)	-1.49 (3.00)	-1.47 (2.98)	-1.46 (3.00)	-1.44 (3.01)
Townsend deprivation index Tertile, n (%)					
Lower (Less deprived)	41,704 (34.8)	10,612 (35.4)	10,344 (34.6)	10,429 (34.9)	10,319 (34.5)
Middle	40,777 (34.1)	10,165 (33.9)	10,296 (34.4)	10,122 (33.9)	10,194 (34.1)
Higher (Most deprived)	37,224 (31.1)	9,224 (30.7)	9,277 (31.0)	9,310 (31.2)	9,413 (31.5)
Smoking status, n (%)					
Never	63,840 (53.4)	16,304 (54.4)	16,058 (53.7)	15,904 (53.4)	15,574 (52.1)

Previous	41,026 (34.3)	10,049 (33.5)	10,211 (34.2)	10,272 (34.5)	10,494 (35.1)
Current	14,673 (12.3)	3,623 (12.1)	3,618 (12.1)	3,631 (12.2)	3,801 (12.7)
Obesity-related markers					
BMI (kg.m^{-2}), mean (SD)	27.5 (4.83)	26.7 (4.47)	27.2 (4.65)	27.7 (4.84)	28.3 (5.18)
BMI Categories, n (%)					
Underweight (<18.5)	622 (0.5)	242 (0.8)	168 (0.6)	108 (0.4)	104 (0.4)
Normal weight (18.5-24.9)	38,080 (31.9)	11,230 (37.5)	9,974 (33.4)	9,005 (30.2)	7,871 (26.3)
Overweight (25.0 to 29.9)	50,896 (42.6)	12,653 (42.2)	12,702 (42.5)	13,005 (43.6)	12,539 (42.0)
Obese (≥30.0)	29,932 (25.0)	5,834 (19.5)	7,040 (23.6)	7,691 (25.8)	9,367 (31.4)
Body fat (%), mean (SD)	31.4 (8.5)	30.6 (8.4)	31.1 (8.5)	31.6 (8.5)	32.2 (8.6)
Waist Circumference (cm), mean (SD)	90.8 (13.6)	89.0 (13.1)	90.3 (13.3)	91.2 (13.6)	92.7 (14.2)
Central Obesity, n (%)	41,243 (34.5)	8,710 (29.0)	9,940 (33.2)	10,572 (35.4)	12,021 (40.2)
Sleep-related characteristics					
Sleep duration, n (%)					
Normal 7-9h	88,030 (73.8)	22,169 (74.1)	22,088 (74.1)	21,880 (73.6)	21,893 (73.5)
Short sleepers <7h	29,005 (24.3)	7,193 (24.1)	7,185 (24.1)	7,282 (24.5)	7,345 (24.7)

Long sleepers >9h	2,190 (1.8)	538 (1.8)	534 (1.8)	563 (1.9)	555 (1.9)
Chronotype, n (%)					
Morning	28,605 (74.6)	7,083 (74.4)	7,017 (74.6)	7,175 (75.0)	7,330 (74.5)
Evening	9,728 (25.4)	2,441 (25.6)	2,388 (25.4)	2,394 (25.0)	2,505 (25.5)
Nap during the day, n (%)					
Never/rarely	67,020 (55.9)	16,975 (56.5)	16,709 (55.8)	16,799 (56.2)	16,537 (55.2)
Sometimes	46,254 (38.6)	11,488 (38.3)	11,609 (38.8)	11,409 (38.2)	11,748 (39.2)
Usually	6,544 (5.5)	1,574 (5.2)	1,635 (5.5)	1,672 (5.6)	1,663 (5.6)
Shift work, n (%)	11,429 (16.9)	2,726 (16.0)	2,872 (17.0)	2,935 (17.4)	2,896 (17.2)
Night shift work, n (%)	5,855 (9.4)	1,390 (8.9)	1,436 (9.3)	1,526 (9.9)	1,503 (9.7)
Physical activity					
Total PA (MET.hr.week^{-1}), mean (SD)	44.9 (62.9)	44.8 (62.9)	44.6 (62.0)	45.2 (64.1)	45.2 (62.7)
Accelerometer total PA, (milli-gravity.day^{-1}), mean (SD)	27.8 (8.2)	27.9 (8.3)	27.8 (8.3)	27.7 (8.2)	27.6 (8.07)
Physically active individuals, n (%)	64,679 (54.0)	16,122 (53.7)	16,279 (54.3)	16,098 (53.9)	16,180 (54.0)
Fitness (METs), mean (SD)	8.86 (3.5)	8.88 (3.54)	8.93 (3.4)	8.88 (3.5)	8.73 (3.5)

Sleep time (h.day^{-1}), mean (SD)	7.17 (1.0)	7.17 (1.0)	7.17 (1.0)	7.16 (1.0)	7.17 (1.1)
TV viewing (h.day^{-1}), mean (SD)	2.86 (1.6)	2.82 (1.6)	2.85 (1.6)	2.87 (1.6)	2.90 (1.6)
Total Sedentary Behaviour (h.day^{-1}), mean (SD)	5.13 (2.3)	5.08 (2.2)	5.12 (2.3)	5.14 (2.3)	5.17 (2.3)
Dietary intake					
Total energy intake (Kcal.day^{-1}), mean (SD)	2170.6 (653.9)	2184.9 (662.8)	2169.3 (642.2)	2170.3 (649.4)	2158.0 (660.7)
Alcohol intake (% of energy intake), mean (SD)	5.36 (6.6)	5.42 (6.7)	5.40 (6.7)	5.29 (6.6)	5.33 (6.6)
Vegetable intake (portions.day^{-1}), mean (SD)	2.68 (1.7)	2.65 (1.7)	2.68 (1.7)	2.68 (1.7)	2.70 (1.8)
Fruit intake (portions.day^{-1}), mean (SD)	2.22 (1.5)	2.19 (1.5)	2.21 (1.5)	2.23 (1.5)	2.24 (1.6)
Processed meat intake (portions.day^{-1}), mean (SD)	1.91 (1.0)	1.92 (1.0)	1.91 (1.0)	1.91 (1.0)	1.91 (1.0)
Health status					
Diabetes history, n (%)	6,290 (5.3)	1,341 (4.5)	1,456 (4.9)	1,604 (5.4)	1,889 (6.3)

Cancer history, n (%)	9,394 (7.9)	2,423 (8.1)	2,388 (8.0)	2,273 (7.6)	2,310 (7.7)
Cardiovascular diseases, n (%)	36,481 (30.4)	8,645 (28.8)	8,995 (30.0)	9,204 (30.8)	9,637 (32.2)
Depression, n (%)	41,377 (34.7)	10,429 (34.9)	10,211 (34.3)	10,267 (34.5)	10,470 (35.2)
Long-standing illness, n (%)	39,214 (33.5)	9,461 (32.2)	9,669 (33.0)	9,842 (33.7)	10,242 (35.0)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 METs.hr.week^{-1}. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

Table 2. Cohort characteristics by sleep duration categories[1]

Quintiles of	Normal sleeper	Short sleeper	Long sleeper
Socio-demographics			
Total, n	88,030	29,005	2,190
Women, n (%)	46,440 (52.8)	15,045 (51.9)	1,158 (52.9)
Age (years), mean (SD)	56.9 (8.0)	56.7 (7.6)	58.4 (7.8)
Townsend deprivation index score, mean (SD)	-1.63 (2.9)	-1.09 (3.1)	-0.53 (3.4)
Townsend deprivation index Tertile, n (%)			
Lower (Less deprived)	31,888 (36·3)	9,099 (31·4)	593 (27·1)
Middle	30,560 (34·8)	9,403 (32·5)	636 (29·1)
Higher (Most deprived)	25,462 (29·0)	10,472 (36·1)	959 (43·8)
Smoking status, n (%)			
Never	48,184 (54.9)	14,400 (49.8)	946 (43.3)
Previous	29,876 (34.0)	10,118 (35.0)	838 (38.4)
Current	9,776 (11.1)	4,388 (15.2)	399 (18.3)
Obesity-related markers			

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BMI (kg.m^{-2}), mean (SD)	27.3 (4.65)	28.0 (5.15)	29.3 (5.83)
BMI Categories, n (%)			
Underweight (<18.5)	440 (0.5)	155 (0.5)	21 (1.0)
Normal weight (18.5-24.9)	29,112 (33.2)	8,363 (28.9)	467 (21.5)
Overweight (25.0 to 29.9)	37,769 (43.0)	12,030 (41.6)	846 (38.9)
Obese (≥30.0)	20,495 (23.3)	8,365 (28.9)	840 (38.6)
Body fat (%), mean (SD)	31.2 (8.4)	31.7 (8.8)	34.2 (8.8)
Waist Circumference (cm) , mean (SD)	90.2 (13.3)	92.0 (14.1)	96.0 (15.3)
Central Obesity, n (%)	28,802 (32.8)	11,008 (38.0)	1,117 (51.1)
Sleep-related characteristic			
Chronotype, n (%)			
Morning	20,061 (75.1)	7,975 (74.5)	455 (60.5)
Evening	6,638 (24.9)	2,737 (25.6)	297 (39.5)
Nap during the day, n (%)			
Never/rarely	49,468 (56.2)	16,848 (58.1)	483 (22.1)
Sometimes	34,029 (38.7)	10,863 (37.5)	1,043 (47.7)

Usually	4,522 (5.1)	1,283 (4.4)	660 (30.2)
Shift work, n (%)	7,514 (15.1)	3,712 (21.7)	143 (27.4)
Nigh shift work, n (%)	3,669 (8.0)	2,075 (13.4)	79 (17.3)
Physical activity			
Total PA (MET.hr.week^{-1}), mean (SD)	44.5 (60.1)	47.7 (71.5)	33.5 (54.1)
Accelerometer total PA, (milli-gravity.day^{-1}), mean (SD)	27.9 (8.2)	27.6 (8.3)	23.7 (7.35)
Physically active individuals, n (%)	48,663 (55.3)	15,019 (51.)	849 (38.8)
Fitness (METs), mean (SD)	8.99 (3.4)	8.62 (3.5)	6.98 (3.6)
Sleep time (h.day^{-1}), mean (SD)	7.56 (0.6)	5.74 (0.5)	10.4 (0.8)
TV viewing (h.day^{-1}), mean (SD)	2.79 (1.6)	2.98 (1.7)	3.83 (2.2)
Total Sedentary Behaviour (h.day^{-1}), mean (SD)	5.06 (2.2)	5.33 (2.5)	5.61 (2.5)
Dietary intake			
Total energy intake (Kcal.day^{-1}), mean (SD)	2171.3 (638.2)	2170.2 (701.8)	2142.2 (691.2)
Alcohol intake (% of energy intake), mean	5.38 (6.6)	5.34 (6.9)	4.60 (7.3)

(SD)			
Vegetable intake (portions.day^{-1}), mean (SD)	2.69 (1.7)	2.65 (1.9)	2.70 (2.1)
Fruit intake (portions.day^{-1}), mean (SD)	2.22 (1.5)	2.23 (1.7)	2.12 (2.1)
Processed meat intake (portions.day^{-1}), mean (SD)	1.90 (1.0)	1.93 (1.0)	1.99 (1.1)
Health status			
Diabetes history, n (%)	4,255 (4.8)	1,679 (5.8)	280 (12.9)
Cancer history, n (%)	6,858 (7.8)	2,237 (7.7)	244 (11.2)
Cardiovascular diseases, n (%)	25,581 (29.1)	9,624 (33.2)	989 (45.2)
Depression, n (%)	28,775 (32.9)	11,158 (38.7)	1,145 (52.9)
Long-standing illness, n (%)	26,637 (30.1)	10,913 (38.7)	1,335 (62.6)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 METs.hr.week^{-1}. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

Table 3. Association between sleep characteristics and obesity-related outcomes

	BMI ≥25.0 kg.m^{-2}		BMI ≥30.0 kg.m^{-2}		Central Obesity*	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Sleep duration						
Normal	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Short Sleeper (<7 h.day^{-1})	1.13 (1.09, 1.16)	<0.0001	1.24 (1.18, 1.29)	<0.0001	1.14 (1.11, 1.18)	<0.0001
Long Sleeper (>9 h.day^{-1})	1.17 (1.04, 1.32)	0.012	1.23 (1.06, 1.42)	0.007	1.22 (1.10, 1.35)	<0.0001
Chronotype						
Morning	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Evening	1.12 (1.04, 1.21)	0.003	1.15 (1.04, 1.27)	0.005	1.08 (1.01, 1.16)	0.027
Day napping						
Never/rarely	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Sometimes	1.21 (1.18, 1.25)	<0.0001	1.33 (1.28, 1.38)	<0.0001	1.26 (1.22, 1.30)	<0.0001
Usually	1.21 (1.13, 1.30)	<0.0001	1.40 (1.28, 1.53)	<0.0001	1.39 (1.31, 1.48)	<0.0001
Shift work						
Never/rarely	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	

Sometimes/Usually	1.27 (1.20, 1.33)	<0.0001	1.40 (1.30, 1.50)	<0.0001	1.22 (1.16, 1.28)	<0.0001
Nightshift work						
Never/rarely	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
Sometimes/Usually	1.28 (1.19, 1.38)	<0.0001	1.44 (1.31, 1.58)	<0.0001	1.18 (1.10, 1.26)	<0.0001

Data presented as Odd ratio and their 95% CI. *Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Models were adjusted for socio-demographics (age, sex, month of recruitment, deprivation), diabetes, depression, long-standing illness, cardiovascular disease, cancer, lifestyles factors (smoking, physical activity, sedentary behaviour, dietary intakes related variables including alcohol, fruits, coffee, vegetables, meats, processed meats, cereals, bread and cheese, and sleep characteristics (sleep duration, day napping, chronotype), when these ones were not used as main exposure in the models). Logistic regression performed to investigate the association between variables of interest.

Table 4. Association between genetic profile risk score for obesity (GPRS-obesity) and BMI by sleep duration

		Normal sleeper		Short sleeper		Long sleeper		
BMI	**n**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**	**P***
Model 0	114,983	0.55 (0.52, 0.58)	$1.1x10^{-292}$	0.62 (0.56, 0.68)	$8.2x10^{-101}$	0.84 (0.61, 1.07)	$5.6x10^{-13}$	$1.4x10^{-4}$
Model 1	101,451	0.52 (0.49, 0.55)	$2.0x10^{-256}$	0.60 (0.54, 0.65)	$1.8x10^{-90}$	0.73 (0.49, 0.97)	$2.5x10^{-9}$	$3.5x10^{-4}$
WC								
Model 0	115,139	1.18 (1.11, 1.25)	$3.5x10^{-212}$	1.28 (1.14, 1.42)	$1.7x10^{-71}$	1.60 (1.06, 2.15)	$9.9x10^{-9}$	0.015
Model 1	101,578	1.13 (1.05, 1.21)	$1.4x10^{-188}$	1.21 (1.07, 1.35)	$1.8x10^{-61}$	1.40 (0.83, 1.97)	$1.8x10^{-6}$	0.037

Data presented as beta coefficients (95%CI). The beta coefficient (β) indicates the change in BMI ($kg.m^{-2}$) and WC (cm) per 1 SD increase in GPRS-obesity by sleep duration. The p-value for the interaction between genetic risk score and sleep duration is presented as P*. The interaction between sleep characteristic and GPRS-obesity were tested using GLM analysis.

Model 0 was adjusted for age, sex, month of recruitment, deprivation, disease history (diabetes, depression, long-standing illness, cardiovascular diseases, and cancer) and genetic-quality measurement.

Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristics (chronotype, day napping, and getting up in the morning), and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).

Figure legends

Figure 1. Interaction between GPRS-obesity and sleep characteristics in their effects on BMI

Data are presented as adjusted mean and 95% CI. Models were adjusted as described in the Methods. In addition, each model was adjusted for the sleep characteristics (sleep duration, chronotype, and day napping) not being included in the interaction term for that model. The interaction between sleep characteristic and GPRS-obesity were tested using GLM analysis. *Shows significant differences between categories ($P < 0.05$). Number of individuals by quartile of GPRS-obesity and sleep characteristics are as follow: Sleep duration (Q1: 19,141/6,063/440; Q2: 19,073/5,990/439; Q3: 18,967/6,150/447; Q4: 18,894/6,175/451 for 'Short', 'Normal' and 'Long' sleepers, respectively); Day napping (Q1: 14,658/9,746/1,307; Q2: 14,355/9,859/1,374; Q3: 14,522/9,758/1,383; Q4: 14,301/9,955/1,374 for 'Never/rarely', 'Sometime' and 'Usually' categories, respectively); Shift work (Q1: 12,363/2,305; Q2: 12,188/2,410; Q3: 12,045/2,497; Q4:12,045/2,468 for 'Never/rarely' and 'Yes' categories, respectively); Nightshift work (Q1: 12,363/1,178; Q2: 12,188/1,197; Q3: 12,045/1,307; Q4:12,045/1,259 for 'Never/rarely' and 'Yes' categories, respectively); Chronotype (Q1: 6,094/2,003; Q2: 6,046/1,977; Q3: 6,221/1,973; Q4:6,318/2,083 for 'Morning' and 'Evening' categories, respectively).

Figure 2. Association between waist circumference and genetic profile risk score by sleep characteristics.

Data presented as adjusted mean and their 95% CI. Models were adjusted as described in the Methods. In addition, each model was adjusted for the sleep characteristics (sleep duration, chronotype, and day napping) not being included in the interaction term for that model. The interaction between sleep characteristic and GPRS-obesity were tested using GLM analysis. *Shows significant differences between categories ($P < 0.05$). Number of individuals by quartile of GPRS-obesity and sleep characteristics are as follow: Sleep duration (Q1: 19,158/6,072/445; Q2: 19,094/5,999/440; Q3: 18,984/6,161/449; Q4: 18,914/6,185/454 for 'Short', 'Normal' and 'Long' sleepers, respectively); Day napping (Q1: 14,671/9,762/1,309; Q2: 14,366/9,873/1,380; Q3: 14,535/9,772/1,386; Q4: 14,310/9,974/1,379 for 'Never/rarely', 'Sometime' and 'Usually' categories, respectively); Shift work (Q1: 12,369/2,307; Q2: 12,198/2,412; Q3: 12,058/2,499; Q4:12,052/2,470 for 'Never/rarely' and 'Yes' categories, respectively); Nightshift work (Q1: 12,369/1,181; Q2: 12,198/1,198; Q3: 12,058/1,307; Q4:12,052/1,261 for 'Never/rarely' and 'Yes' categories, respectively); Chronotype (Q1: 6,109/2,005; Q2: 6,051/1,979; Q3: 6,227/1,977; Q4: 6,332/2,092 for 'Morning' and 'Evening' categories, respectively).

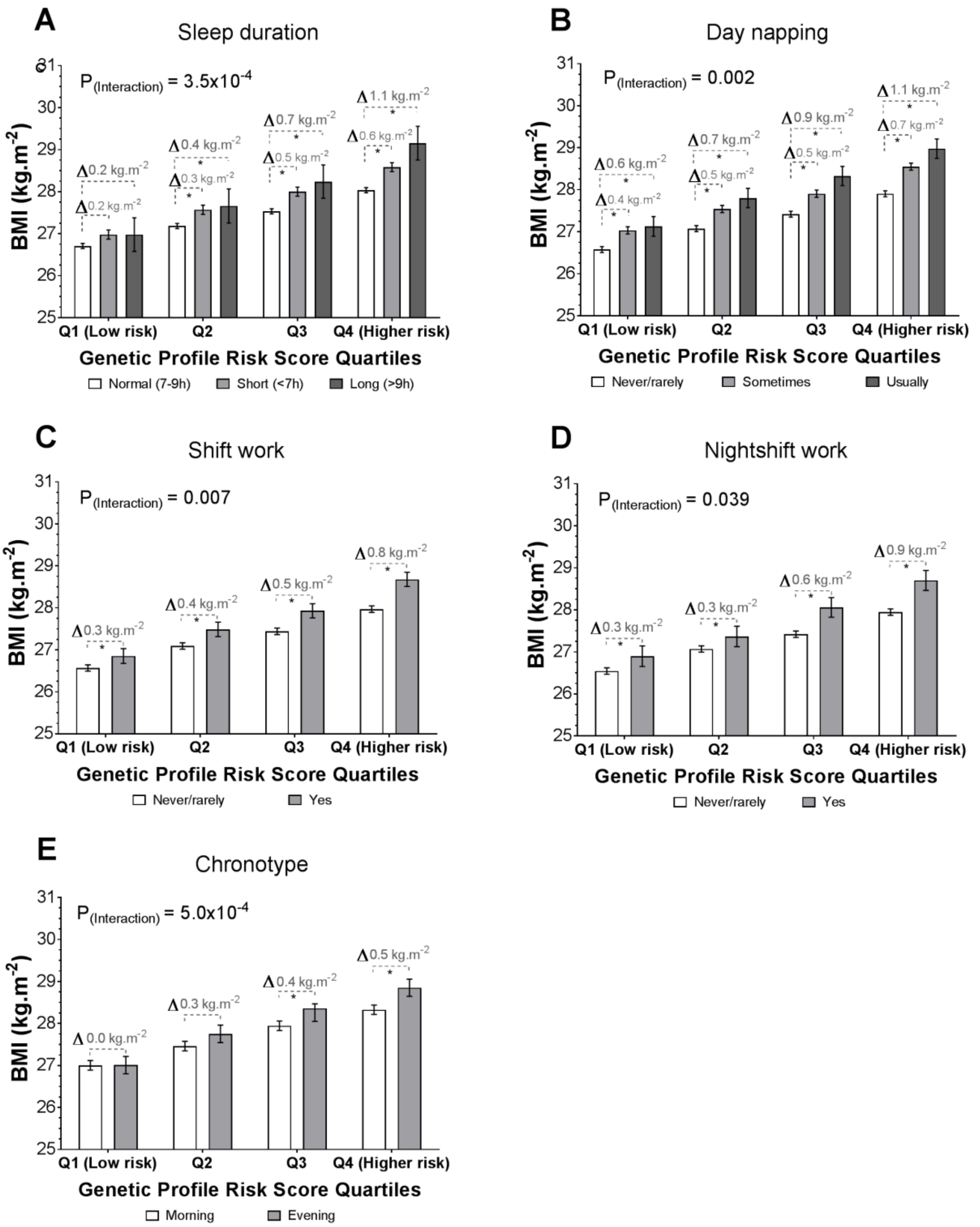
A
Sleep duration
P(Interaction) = 3.5x10-4
Δ0.2 kg.m-2
Δ0.4 kg.m-2
Δ0.7 kg.m-2
Δ1.1 kg.m-2
Δ0.2 kg.m-2
Δ0.3 kg.m-2
Δ0.5 kg.m-2
Δ0.6 kg.m-2
BMI (kg.m-2)
Q1 (Low risk)
Q2
Q3
Q4 (Higher risk)
Genetic Profile Risk Score Quartiles
Normal (7-9h)
Short (<7h)
Long (>9h)
B
Day napping
P(Interaction) = 0.002
Δ0.6 kg.m-2
Δ0.7 kg.m-2
Δ0.9 kg.m-2
Δ1.1 kg.m-2
Δ0.4 kg.m-2
Δ0.5 kg.m-2
Δ0.5 kg.m-2
Δ0.7 kg.m-2
Never/rarely
Sometimes
Usually
C
Shift work
P(Interaction) = 0.007
Δ0.3 kg.m-2
Δ0.4 kg.m-2
Δ0.5 kg.m-2
Δ0.8 kg.m-2
Never/rarely
Yes
D
Nightshift work
P(Interaction) = 0.039
Δ0.3 kg.m-2
Δ0.3 kg.m-2
Δ0.6 kg.m-2
Δ0.9 kg.m-2
Never/rarely
Yes
E
Chronotype
P(Interaction) = 5.0x10-4
Δ0.0 kg.m-2
Δ0.3 kg.m-2
Δ0.4 kg.m-2
Δ0.5 kg.m-2
Morning
Evening

Figure 1

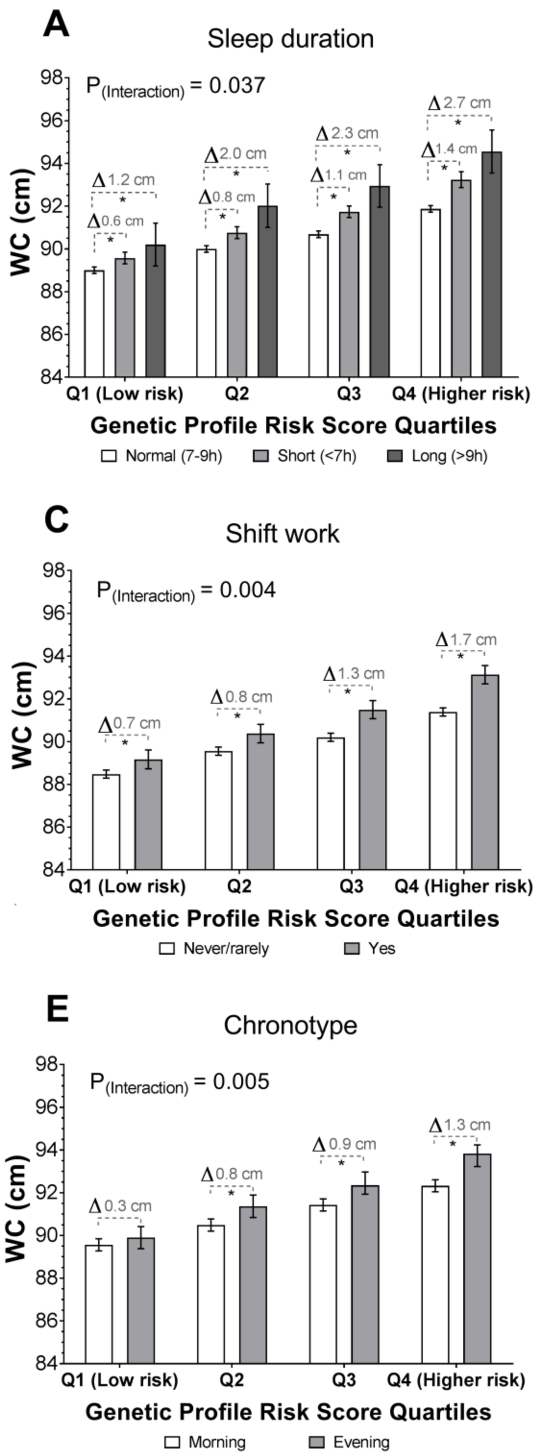
A
Sleep duration
P(Interaction) = 0.037
Δ 1.2 cm
Δ 0.6 cm
Δ 2.0 cm
Δ 0.8 cm
Δ 2.3 cm
Δ 1.1 cm
Δ 2.7 cm
Δ 1.4 cm
WC (cm)
Q1 (Low risk)
Q2
Q3
Q4 (Higher risk)
Genetic Profile Risk Score Quartiles
Normal (7-9h)
Short (<7h)
Long (>9h)
B
Day napping
P(Interaction) = 0.011
Δ 2.1 cm
Δ 1.4 cm
Δ 2.2 cm
Δ 1.4 cm
Δ 2.6 cm
Δ 1.5 cm
Δ 2.9 cm
Δ 1.7 cm
Never/rarely
Sometimes
Usually
C
Shift work
P(Interaction) = 0.004
Δ 0.7 cm
Δ 0.8 cm
Δ 1.3 cm
Δ 1.7 cm
Never/rarely
Yes
D
Nightshift work
P(Interaction) = 0.018
Δ 0.8 cm
Δ 0.9 cm
Δ 1.5 cm
Δ 1.8 cm
Never/rarely
Yes
E
Chronotype
P(Interaction) = 0.005
Δ 0.3 cm
Δ 0.8 cm
Δ 0.9 cm
Δ 1.3 cm
Morning
Evening

Figure 2

Online Supplemental Material

Supplemental Table 1. List of the 93 SNPs used for GPRS-obesity

SNP	Chr	Position	Gene	BMI-increasing allele	Other allele	BMI β per 4 kg.m^{-2}
rs1558902	16	52,361,075	*FTO*	A	T	0.0818
rs6567160	18	55,980,115	*MC4R*	C	T	0.0556
rs13021737	2	622,348	*TMEM18*	G	A	0.0601
rs10938397	4	44,877,284	*GNPDA2*	G	A	0.0402
rs543874	1	176,156,103	*SEC16B*	G	A	0.0482
rs2207139	6	50,953,449	*TFAP2B*	G	A	0.0447
rs11030104	11	27,641,093	*BDNF*	A	G	0.0414
rs3101336	1	72,523,773	*NEGR1*	C	T	0.0334
rs7138803	12	48,533,735	*BCDIN3D*	A	G	0.0315
rs10182181	2	25,003,800	*ADCY3*	G	A	0.0307
rs3888190	16	28,796,987	*ATP2A1*	A	C	0.0309
rs1516725	3	187,306,698	*ETV5*	C	T	0.0451
rs12446632	16	19,842,890	*GPRC5B*	G	A	0.0403
rs2287019	19	50,894,012	*QPCTL*	C	T	0.0360
rs16951275	15	65,864,222	*MAP2K5*	T	C	0.0311
rs3817334	11	47,607,569	*MTCH2*	T	C	0.0262
rs2112347	5	75,050,998	*POC5*	T	G	0.0261
rs12566985	1	74,774,781	*FPGT*	G	A	0.0242
rs3810291	19	52,260,843	*ZC3H4*	A	G	0.0283
rs7141420	14	78,969,207	*NRXN3*	T	C	0.0235
rs13078960	3	85,890,280	*CADM2*	G	T	0.0297
rs10968576	9	28,404,339	*LINGO2*	G	A	0.0249
rs17024393	1	109,956,211	*GNAT2*	C	T	0.0658
rs12429545	13	53,000,207	*OLFM4*	A	G	0.0334
rs13107325	4	103,407,732	*SLC39A8*	T	C	0.0477
rs11165643	1	96,696,685	*PTBP2*	T	C	0.0218
rs17405819	8	76,969,139	*HNF4G*	T	C	0.0224
rs1016287	2	59,159,129	*LINC01122*	T	C	0.0229

rs4256980	11	8,630,515	*TRIM66*	G	C	0.0209
rs12401738	1	78,219,349	*FUBP1*	A	G	0.0211
rs205262	6	34,671,142	*C6orf106*	G	A	0.0221
rs12016871	13	26,915,782	*MTIF3*	T	C	0.0298
rs12940622	17	76,230,166	*RPTOR*	G	A	0.0182
rs11847697	14	29,584,863	*PRKD1*	T	C	0.0492
rs2075650	19	50,087,459	*TOMM40*	A	G	0.0258
rs2121279	2	142,759,755	*LRP1B*	T	C	0.0245
rs29941	19	39,001,372	*KCTD15*	G	A	0.0182
rs6091540	20	50,521,269	*ZFP64*	C	T	0.0188
rs7715256	5	153,518,086	*GALNT10*	G	T	0.0163
rs2176040	2	226,801,046	*LOC646736*	A	G	0.0141
rs657452	1	49,362,434	*AGBL4*	A	G	0.0227
rs12286929	11	114,527,614	*CADM1*	G	A	0.0217
rs7903146	10	114,748,339	*TCF7L2*	C	T	0.0234
rs10132280	14	24,998,019	*STXBP6*	C	A	0.0230
rs17094222	10	102,385,430	*HIF1AN*	C	T	0.0249
rs7599312	2	213,121,476	*ERBB4*	G	A	0.0220
rs2365389	3	61,211,502	*FHIT*	C	T	0.0200
rs2820292	1	200,050,910	*NAV1*	C	A	0.0195
rs12885454	14	28,806,589	*PRKD1*	C	A	0.0207
rs16851483	3	142,758,126	*RASA2*	T	G	0.0483
rs1167827	7	75,001,105	*HIP1*	G	A	0.0202
rs758747	16	3,567,359	*NLRC3*	T	C	0.0225
rs1928295	9	119,418,304	*TLR4*	T	C	0.0188
rs9925964[1]	16	31,037,396	*KAT8*	A	G	0.0192
rs11126666	2	26,782,315	*KCNK3*	A	G	0.0207
rs2650492	16	28,240,912	*SBK1*	A	G	0.0207
rs6804842	3	25,081,441	*RARB*	G	A	0.0185
rs4740619	9	15,624,326	*C9orf93*	T	C	0.0179
rs13191362	6	162,953,340	*PARK2*	A	G	0.0277

rs3736485	15	49,535,902	*DMXL2*	A	G	0.0176
rs17001654[2]	4	77,348,592	*SCARB2*	G	C	0.0306
rs11191560	10	104,859,028	*NT5C2*	C	T	0.0308
rs1528435	2	181,259,207	*UBE2E3*	T	C	0.0178
rs1000940	17	5,223,976	*RABEP1*	G	A	0.0192
rs2033529[1]	6	40,456,631	*TDRG1*	G	A	0.0190
rs11583200	1	50,332,407	*ELAVL4*	C	T	0.0177
rs9400239	6	109,084,356	*FOXO3*	C	T	0.0188
rs10733682	9	128,500,735	*LMX1B*	A	G	0.0174
rs11688816	2	62,906,552	*EHBP1*	G	A	0.0172
rs11057405	12	121,347,850	*CLIP1*	G	A	0.0307
rs11727676	4	145,878,514	*HHIP*	T	C	0.0358
rs3849570	3	81,874,802	*GBE1*	A	C	0.0188
rs6477694	9	110,972,163	*EPB41L4B*	C	T	0.0174
rs7899106	10	87,400,884	*GRID1*	G	A	0.0395
rs2176598	11	43,820,854	*HSD17B12*	T	C	0.0198
rs2245368	7	76,446,079	*DTX2P1*	C	T	0.0317
rs17724992	19	18,315,825	*PGPEP1*	A	G	0.0194
rs7243357	18	55,034,299	*GRP*	T	G	0.0217
rs1808579	18	19,358,886	*C18orf8*	C	T	0.0167
rs2033732	8	85,242,264	*RALYL*	C	T	0.0192
rs1441264	13	78,478,920	*MIR548A2*	A	G	0.0175
rs2080454	16	47,620,091	*CBLN1*	C	A	0.0168
rs7164727	15	70,881,044	*LOC100287559*	T	C	0.0180
rs17203016	2	207,963,763	*CREB1*	G	A	0.0210
rs977747	1	47,457,264	*TAL1*	T	G	0.0167
rs9914578	17	1,951,886	*SMG6*	G	C	0.0201
rs9374842	6	120,227,364	*LOC285762*	T	C	0.0187
rs16907751	8	81,538,012	*ZBTB10*	C	T	0.0350
rs9540493	13	65,103,705	*MIR548X2*	A	G	0.0172
rs7239883	18	38,401,669	*LOC284260*	G	A	0.0164

rs13201877	6	137,717,234	*IFNGR1*	G	A	0.0233
rs2836754	21	39,213,610	*ETS2*	C	T	0.0164
rs492400	2	219,057,996	*USP37*	C	T	0.0158
rs9641123	7	93,035,668	*CALCR*	C	G	0.0191
rs1460676	2	164,275,935	*FIGN*	C	T	0.0197
rs4787491	16	29,922,838	*INO80E*	G	A	0.0159
rs6465468	7	95,007,450	*ASB4*	T	G	0.0166

[1] Not genotyped in UK Biobank cohort and therefore not analysed in the current report.
[2] Excluded from the SNP set for GPRS-obesity calculation on the basis of Hardy-Weinberg equilibrium $p < 10^{-6}$.

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Supplemental Table 2. Cohort characteristics by chronotype[1]

Quintiles of	Morning	Evening
Socio-demographics		
Total, n	28,605	9,728
Women, n (%)	13,016 (45.5)	4,670 (48.0)
Age (years), mean (SD)	57.7 (7.6)	55.4 (8.1)
Townsend index score, mean (SD)	-1.42 (3.0)	-1.02 (3.1)
Townsend index score Tertile, n (%)		
Lower (Less deprived)	9,804 (34.3)	2,913 (30.0)
Middle	9,750 (34.1)	3,180 (32.7)
Higher (Most deprived)	9,014 (31.6)	3,624 (37.3)
Smoking status, n (%)		
Never	15,975 (56.0)	4,081 (42.1)
Previous	9,609 (33.7)	3,502 (36.1)
Current	2,922 (10.3)	2,123 (21.9)
Obesity-related markers		
BMI ($kg.m^{-2}$), mean (SD)	27.7 (4.86)	28.1 (5.31)
BMI Categories, n (%)		
Underweight (<18.5)	157 (0.6)	61 (0.63)
Normal weight (18.5-24.9)	8,786 (30.8)	2,778 (28.7)
Overweight (25.0 to 29.9)	12,088 (42.4)	3,937 (40.7)
Obese (≥30.0)	7,485 (26.3)	2,910 (30.0)
Body fat (%), mean (SD)	31.7 (8.4)	31.9 (9.0)
Waist Circumference (cm), mean (SD)	90.8 (13.8)	92.7 (14.3)
Central Obesity, n (%)	10,232 (35.8)	3,909 (40.3)
Sleep-related characteristic		
Sleep duration, n (%)		
Normal 7-9h	20,061 (70.4)	6,638 (68.6)
Short sleepers <7h	7,975 (28.0)	2,737 (28.3)
Long sleepers >9h	455 (1.6)	297 (3.1)
Nap during the day, n (%)		
Never/rarely	15,058 (52.7)	5,290 (54.4)
Sometimes	11,587 (40.5)	3,770 (38.8)
Usually	1,952 (6.8)	664 (6.8)
Shift work, n(%)	2,643 (16.9)	1,183 (20.7)
Nigh shift work, n(%)	1,260 (8.8)	717 (13.6)
Physical activity		
Total PA ($MET.hr.week^{-1}$), mean (SD)	51.3 (69.0)	37.3 (55.9)
Accelerometer total PA, ($milli\text{-}gravity.day^{-1}$), mean (SD)	28.6 (8.4)	26.1 (8.0)
Physically active individuals, n (%)	16,456 (57.5)	4,634 (47.6)
Fitness (METs), mean (SD)	8.82 (3.5)	8.48 (3.5)
Sleep time ($h.day^{-1}$), mean (SD)	7.09 (1.1)	7.12 (1.2)
TV viewing ($h.day^{-1}$), mean (SD)	2.87 (1.6)	2.97 (1.9)
Total Sedentary Behaviour ($h.day^{-1}$), mean (SD)	5.09 (2.3)	5.49 (2.5)
Dietary intake		
Total energy intake ($Kcal.day^{-1}$), mean (SD)	2137.2 (661.3)	2219.2 (691.0)
Alcohol intake (% of TE), mean (SD)	5.06 (6.5)	5.93 (7.5)
Vegetable intake ($portions.day^{-1}$), mean (SD)	2.78 (1.8)	2.62 (1.8)
Fruit intake ($portions.day^{-1}$), mean (SD)	2.39 (1.6)	2.00 (1.6)
Processed meat intake ($portions.day^{-1}$), mean (SD)	1.82 (1.0)	2.00 (1.1)
Health status		
Diabetes history, n (%)	1,560 (5.5)	682 (7.0)
Cancer history, n (%)	2,303 (8.1)	722 (7.4)
Cardiovascular diseases, n (%)	9,248 (32.3)	2,938 (30.2)
Depression, n (%)	9,540 (33.6)	4,046 (41.9)

Long-standing illness, n (%)	9,306 (33.2)	3,873 (40.8)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; TE: total energy; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 METs.hr.week^{-1}. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

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Supplemental Table 3. Cohort characteristic by day napping[1]

Quintiles of	Never/rarely	Sometimes	Usually
Socio-demographics			
Total, n	67,020	46,254	6,544
Women, n (%)	38,488 (57.4)	22,355 (48.3)	2,179 (33.3)
Age (years), mean (SD)	55.8 (7.9)	58.1 (7.6)	59.7 (7.3)
Townsend index score, mean (SD)	-1.64 (2.9)	-1.30 (3.0)	-0.90 (3.2)
Townsend index score Tertile, n (%)			
Lower (Less deprived)	24,461 (36.5)	15,330 (33.2)	1,905 (29.1)
Middle	23,154 (34.6)	15,499 (33.6)	2,114 (32.3)
Higher (Most deprived)	19,326 (28.9)	15,354 (33.3)	2,521 (38.6)
Smoking status, n (%)			
Never	38,001 (56.8)	22,995 (49.9)	2,821 (43.3)
Previous	21,512 (32.2)	16,896 (36.6)	2,614 (40.1)
Current	7,352 (11.0)	6,234 (13.5)	1,082 (16.6)
Obesity-related markers			
BMI ($kg.m^{-2}$), mean (SD)	27.0 (4.5)	28.1 (5.0)	28.9 (5.5)
BMI Categories, n (%)			
Underweight (<18.5)	377 (0.6)	209 (0.5)	36 (0.6)
Normal weight (18.5-24.9)	24,007 (35.9)	12,557 (27.2)	1,508 (23.2)
Overweight (25.0 to 29.9)	28,119 (42.0)	20,043 (43.5)	2,718 (41.8)
Obese (≥30.0)	14,376 (21.5)	13,304 (28.9)	2,238 (34.4)
Body fat (%), mean (SD)	31.2 (8.49)	31.7 (8.60)	30.9 (8.53)
Waist Circumference (cm), mean (SD)	88.7 (13.0)	92.9 (13.7)	97.2 (14.4)
Central Obesity, n (%)	20,107 (30.0)	18,156 (39.3)	2,960 (45.4)
Sleep-related characteristic			
Sleep duration, n (%)			
Normal 7-9h	49,468 (74.1)	34,029 (74.1)	4,522 (70.0)
Short sleepers <7h	16,848 (25.2)	10,863 (23.7)	1,283 (19.9)
Long sleepers >9h	483 (0.7)	1,043 (2.3)	660 (10.2)
Chronotype, n (%)			
Morning	15,058 (74.0)	11,587 (75.5)	1,952 (74.6)
Evening	5,290 (26.0)	3,770 (24.6)	664 (25.4)
Shift work, n(%)	5,776 (13.8)	5,030 (21.5)	619 (25.3)
Nigh shift work, n(%)	2,794 (7.2)	2,721 (12.9)	337 (15.5)
Physical activity			
Total PA ($MET.hr.week^{-1}$), mean (SD)	45.4 (63.0)	44.4 (62.6)	44.6 (64.3)
Accelerometer total PA, ($milli\text{-}gravity.day^{-1}$), mean (SD)	28.6 (8.2)	26.7 (8.0)	25.4 (8.0)
Physically active individuals, n (%)	37,289 (55.6)	24,146 (52.2)	3,233 (49.4)
Fitness (METs), mean (SD)	9.07 (3.4)	8.64 (3.5)	8.13 (3.8)
Sleep time ($h.day^{-1}$), mean (SD)	7.07 (0.9)	7.23 (1.1)	7.70 (1.5)
TV viewing ($h.day^{-1}$), mean (SD)	2.63 (1.5)	3.11 (1.7)	3.53 (2.1)
Total Sedentary Behaviour ($h.day^{-1}$), mean (SD)	4.92 (2.2)	5.35 (2.3)	5.76 (2.6)
Dietary intake			
Total energy intake ($Kcal.day^{-1}$), mean (SD)	2133.6 (634.9)	2211.3 (670.0)	2322.1 (719.5)
Alcohol intake (% of TE), mean (SD)	5.55 (6.8)	5.09 (6.5)	5.18 (6.8)
Vegetable intake ($portions.day^{-1}$), mean (SD)	2.67 (1.7)	2.68 (1.8)	2.70 (1.9)
Fruit intake ($portions.day^{-1}$), mean (SD)	2.24 (1.5)	2.19 (1.6)	2.14 (1.7)
Processed meat intake ($portions.day^{-1}$), mean (SD)	1.83 (1.0)	1.99 (1.0)	2.15 (1.1)
Health status			
Diabetes history, n (%)	2,337 (3.5)	3,213 (7.0)	735 (11.3)
Cancer history, n (%)	4,914 (7.4)	3,863 (8.4)	615 (9.4)
Cardiovascular diseases, n (%)	17,266 (25.8)	16,243 (35.1)	2,957 (45.2)
Depression, n (%)	21,466 (32.2)	17,234 (37.5)	2,666 (41.0)
Long-standing illness, n (%)	18,257 (27.8)	17,514 (38.8)	3,427 (53.7)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; TE: total energy; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 $METs.hr.week^{-1}$. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

Supplemental Table 4. Cohort characteristic by shift work[1]

Quintiles of	Never/rarely	Sometimes/Usually
Socio-demographics		
Total, n	56,247	11,429
Women, n (%)	29,053 (51.7)	5,035 (44.1)
Age (years), mean (SD)	53.2 (7.0)	52.1 (6.9)
Townsend index score, mean (SD)	-1.65 (2.8)	-0.86 (3.1)
Townsend index score Tertile, n (%)		
Lower (Less deprived)	20,301 (36.1)	3,151 (27.6)
Middle	19,590 (34.9)	3,721 (32.6)
Higher (Most deprived)	16,281 (29.0)	4,537 (40.0)
Smoking status, n (%)		
Never	32,206 (57.4)	5,580 (48.9)
Previous	17,538 (31.3)	3,695 (32.4)
Current	6,386 (11.4)	2,133 (18.7)
Obesity-related markers		
BMI (kg.m^{-2}), mean (SD)	27.2 (4.69)	28.2 (5.00)
BMI Categories, n (%)		
Underweight (<18.5)	260 (0.5)	43 (0.4)
Normal weight (18.5-24.9)	19,299 (34.4)	3,076 (27.0)
Overweight (25.0 to 29.9)	23,691 (42.2)	4,886 (42.8)
Obese (≥30.0)	12,887 (23.0)	3,407 (29.9)
Body fat (%), mean (SD)	30.4 (8.5)	30.4 (8.5)
Waist Circumference (cm), mean (SD)	89.7 (13.4)	92.7 (13.9)
Central Obesity, n(%)	17,177 (30.1)	4,212 (36.9)
Sleep-related characteristic		
Sleep duration, n (%)		
Normal 7-9h	42,337 (75.4)	7,514 (66.1)
Short sleepers <7h	13,413 (23.9)	3,712 (32.7)
Long sleepers >9h	379 (0.7)	143 (1.3)
Chronotype, n (%)		
Morning	13,036 (74.1)	2,643 (69.1)
Evening	4,547 (25.9)	1,183 (31.0)
Nap during the day, n (%)		
Never/rarely	36,023 (64.1)	5,776 (50.6)
Sometimes	18,387 (32.7)	5,030 (44.0)
Usually	1,832 (3.3)	619 (5.42)
Physical activity		
Total PA (MET.hr.week^{-1}), mean (SD)	42.7 (62.1)	69.0 (95.1)
Accelerometer total PA, (milli-gravity.day^{-1}), mean (SD)	28.9 (8.3)	29.2 (8.7)
Physically active individuals, n (%)	29,537 (52.5)	6,718 (58.8)
Fitness (METs), mean (SD)	9.63 (3.3)	9.52 (3.2)
Sleep time (h.day^{-1}), mean (SD)	7.08 (0.9)	6.94 (1.0)
TV viewing (h.day^{-1}), mean (SD)	2.42 (1.3)	2.70 (1.5)
Total Sedentary Behaviour (h.day^{-1}), mean (SD)	4.94 (2.3)	5.49 (2.7)
Dietary intake		
Total energy intake (Kcal.day^{-1}), mean (SD)	2167.4 (644.5)	2234.8 (724.4)
Alcohol intake (% of TE), mean (SD)	5.59 (6.7)	5.34 (7.2)
Vegetable intake (portions.day^{-1}), mean (SD)	2.59 (1.7)	2.55 (1.7)
Fruit intake (portions.day^{-1}), mean (SD)	2.22 (1.5)	2.10 (1.7)
Processed meat intake (portions.day^{-1}), mean (SD)	1.89 (1.1)	2.04 (1.1)
Health status		
Diabetes history, n (%)	1,958 (3.5)	492 (4.3)
Cancer history, n (%)	3,271 (5.8)	567 (5.0)
Cardiovascular diseases, n (%)	12,870 (22.9)	2,847 (24.9)
Depression, n (%)	18,292 (32.7)	3,898 (34.3)
Long-standing illness, n (%)	13,969 (25.3)	3,221 (28.9)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; TE: total energy; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 METs.hr.week^{-1}. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

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Supplemental Table 5. Cohort characteristic by nightshift work[1]

Quintiles of	Never/rarely	Sometimes/Usually
Socio-demographics		
Total n	56,247	5,855
Women, n (%)	29,053 (51.7)	2,142 (36.6)
Age (years), mean (SD)	53.2 (7.0)	51.5 (6.7)
Townsend index score, mean (SD)	-1.65 (2.8)	-0.86 (3.1)
Townsend index score Tertile, n (%)		
Lower (Less deprived)	20,301 (36.1)	1,623 (27.8)
Middle	19,590 (34.9)	1,906 (32.6)
Higher (Most deprived)	16,281 (29.0)	2,318 (39.6)
Smoking status, n (%)		
Never	32,206 (57.4)	2,792 (47.8)
Previous	17,538 (31.3)	1,839 (31.5)
Current	6,386 (11.4)	1,212 (20.7)
Obesity-related markers		
BMI ($kg.m^{-2}$), mean (SD)	27.2 (4.69)	28.4 (4.95)
BMI Categories, n (%)		
Underweight (<18.5)	260 (0.5)	16 (0.3)
Normal weight (18.5-24.9)	19,299 (34.4)	1,467 (25.1)
Overweight (25.0 to 29.9)	23,691 (42.2)	2,522 (43.2)
Obese (≥30.0)	12,887 (23.0)	1,839 (31.5)
Body fat (%), mean (SD)	30.4 (8.5)	29.7 (8.38)
Waist Circumference (cm), mean (SD)	89.7 (13.4)	93.7 (13.8)
Central Obesity, n(%)	17,177 (30.6)	2,136 (36.5)
Sleep-related characteristic		
Sleep duration, n (%)		
Normal 7-9h	42,337 (75.4)	3,669 (63.0)
Short sleepers <7h	13,413 (23.9)	2,075 (35.6)
Long sleepers >9h	379 (0.7)	79 (1.4)
Chronotype, n (%)		
Morning	13,036 (74.1)	1,260 (63.7)
Evening	4,547 (25.9)	717 (36.3)
Nap during the day, n (%)		
Never/rarely	36,023 (64.1)	2,794 (47.7)
Sometimes	18,387 (32.7)	2,721 (46.5)
Usually	1,832 (3.3)	337 (5.8)
Physical activity		
Total PA ($MET.hr.week^{-1}$), mean (SD)	42.7 (62.1)	74.2 (99.3)
Accelerometer total PA, ($milli\text{-}gravity.day^{-1}$), mean (SD)	28.9 (8.3)	29.3 (8.9)
Physically active individuals, n (%)	29,537 (52.5)	3,601 (61.5)
Fitness (METs), mean (SD)	9.63 (3.3)	9.66 (3.1)
Sleep time ($h.day^{-1}$), mean (SD)	7.08 (0.9)	6.88 (1.1)
TV viewing ($h.day^{-1}$), mean (SD)	2.42 (1.3)	2.75 (1.5)
Total Sedentary Behaviour ($h.day^{-1}$), mean (SD)	4.94 (2.3)	5.69 (2.8)
Dietary intake		
Total energy intake ($Kcal.day^{-1}$), mean (SD)	2167.4 (644.5)	2274.7 (739.4)
Alcohol intake (% of TE), mean (SD)	5.59 (6.7)	5.40 (7.3)
Vegetable intake ($portions.day^{-1}$), mean (SD)	2.59 (1.7)	2.51 (1.7)
Fruit intake ($portions.day^{-1}$), mean (SD)	2.22 (1.5)	2.08 (1.7)
Processed meat intake ($portions.day^{-1}$), mean (SD)	1.89 (1.1)	2.11 (1.0)
Health status		
Diabetes history, n (%)	1,958 (3.5)	248 (4.3)
Cancer history, n (%)	3,271 (5.8)	264 (4.5)
Cardiovascular diseases, n (%)	12,870 (22.9)	1,450 (24.8)
Depression, n (%)	18,292 (32.7)	1,899 (32.7)
Long-standing illness, n (%)	13,969 (25.3)	1,638 (28.7)

[1]Data presented as mean and SD for continuous variables and as n and % for categorical variables. MET: Metabolic equivalent; PA: physical activity; TE: total energy; SD: standard deviation. Central obesity was defined as a waist circumference >88 cm for women and >102 cm for men. Physically active individuals were defined as those who achieve >600 $METs.hr.week^{-1}$. Deprivation was derived using the Townsend score. A greater Townsend index score implies a greater degree of deprivation.

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Supplemental Table 6. Association of genetic profile risk score with BMI and waist circumference[1]

		Model 0			Model 1	
	n	**Beta (95% CI)**	**p-value**	**n**	**Beta (95% CI)**	**p-value**
BMI (kg.m^{-2})	115,517	0.57 (0.55, 0.60)	$6.3x10^{-207}$	101,859	0.55 (0.52, 0.57)	$5.9x10^{-201}$
WC (cm)	115,675	1.21 (1.15, 1.28)	$4.2x10^{-289}$	101,986	1.16 (1.09, 1.22)	$2.0x10^{-254}$
	n	**Odds ratio (95% CI)**	**p-value**	**n**	**Odds ratio (95% CI)**	**p-value**
BMI ≥25.0	115,517	1.22 (1.21, 1.24)	$3.5x10^{-197}$	101,859	1.22 (1.21, 1.24)	$3.2x10^{-193}$
BMI ≥30.0	65,655	1.38 (1.35, 1.40)	$9.4x10^{-321}$	58,121	1.39 (1.36, 1.42)	$8.5x10^{-317}$
Central obesity	115,675	1.20 (1.18, 1.21)	$4.4x10^{-401}$	101,986	1.20 (1.18, 1.22)	$4.0x10^{-397}$

[1]Data presented as beta coefficients or odd ratio and the corresponding 95%CI. The beta coefficient indicates the change in BMI in kg.m^{-2} per or in WC in cm per 1 SD increase in the genetic risk score. The OR indicates the odds ratio for extra risk of having BMI ≥25.0 kg.m^{-2} or BMI ≥30.0 kg.m^{-2} or central obese (WC ≥88 for females and ≥102 for males) per SD increase in GPRS.

Model 0 was adjusted for age, sex, month of recruitment, disease history (deprivation, diabetes, depression, long-standing illness, CVDs, and cancer) and genetic-quality measurement.

Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristic (sleep duration, chronotype, day napping, and getting up in the morning), and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).

Supplemental Table 7. Association between genetic profile risk score and BMI by Chronotype[1]

		Morning		Evening		
BMI	**n**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**P***
Model 0	36,943	0.55 (0.50, 0.60)	$1.2x10^{-88}$	0.76 (0.66, 0.86)	$6.6x10^{-49}$	$7.0x10^{-5}$
Model 1	32,540	0.52 (0.47, 0.57)	$5.1x10^{-77}$	0.72 (0.61, 0.82)	$1.9x10^{-41}$	$5.0x10^{-4}$
WC						
Model 0	37,016	1.13 (1.00, 1.27)	$9.6x10^{-61}$	1.53 (1.28, 1.78)	$1.0x10^{-33}$	0.002
Model 1	32,598	1.08 (0.94, 1.22)	$4.1x10^{-53}$	1.45 (1.20, 1.71)	$1.1x10^{-28}$	0.005

[1]Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI/WC by 1 SD increase in the genetic risk score by chronotype. The p-value for the interaction between genetic risk score and chronotype is presented as P*.
Model 0 was adjusted for age, sex, month of recruitment, smoking, deprivation, disease history (diabetes, depression, long-standing illness, CVDs, and cancer), and genetic-quality measurement.
Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristic (sleep duration, day napping, and getting up in the morning), and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).

Supplemental Table 8. Association between genetic profile risk score and BMI by day napping[1]

		Never/rarely		Sometimes		Usually		
BMI	**n**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**P***
Model 0	115,489	0.53 (0.50, 0.56)	$2.7x10^{-211}$	0.62 (0.58, 0.66)	$6.9x10^{-171}$	0.69 (0.56, 0.82)	$1.7x10^{-26}$	$5.5x10^{-5}$
Model 1	101,842	0.51 (0.48, 0.55)	$8.0x10^{-193}$	0.58 (0.54, 0.63)	$1.4x10^{-145}$	0.65 (0.52, 0.78)	$1.0x10^{-22}$	0.002
WC								
Model 0	115,646	1.13 (1.04, 1.21)	$5.4x10^{-151}$	1.29 (1.18, 1.39)	$2.1x10^{-121}$	1.49 (1.17, 1.80)	$1.9x10^{-20}$	$9.4x10^{-4}$
Model 1	101,969	1.10 (1.01, 1.18)	$1.1x10^{-137}$	1.22 (1.11, 1.33)	$5.7x10^{-104}$	1.40 (1.08, 1.72)	$1.2x10^{-17}$	0.011

[1]Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI/WC by 1 SD increase in the genetic risk score by day napping. The p-value for the interaction between genetic risk score and day napping is presented as P*.
Model 0 was adjusted for age, sex, month of recruitment, smoking, disease history (deprivation, diabetes, depression, long-standing illness, CVDs, and cancer), and genetic-quality measurement.
Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristic (sleep duration, chronotype, and getting up in the morning) and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).

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Supplemental Table 9. Association between genetic profile risk score and BMI by shift work[1]

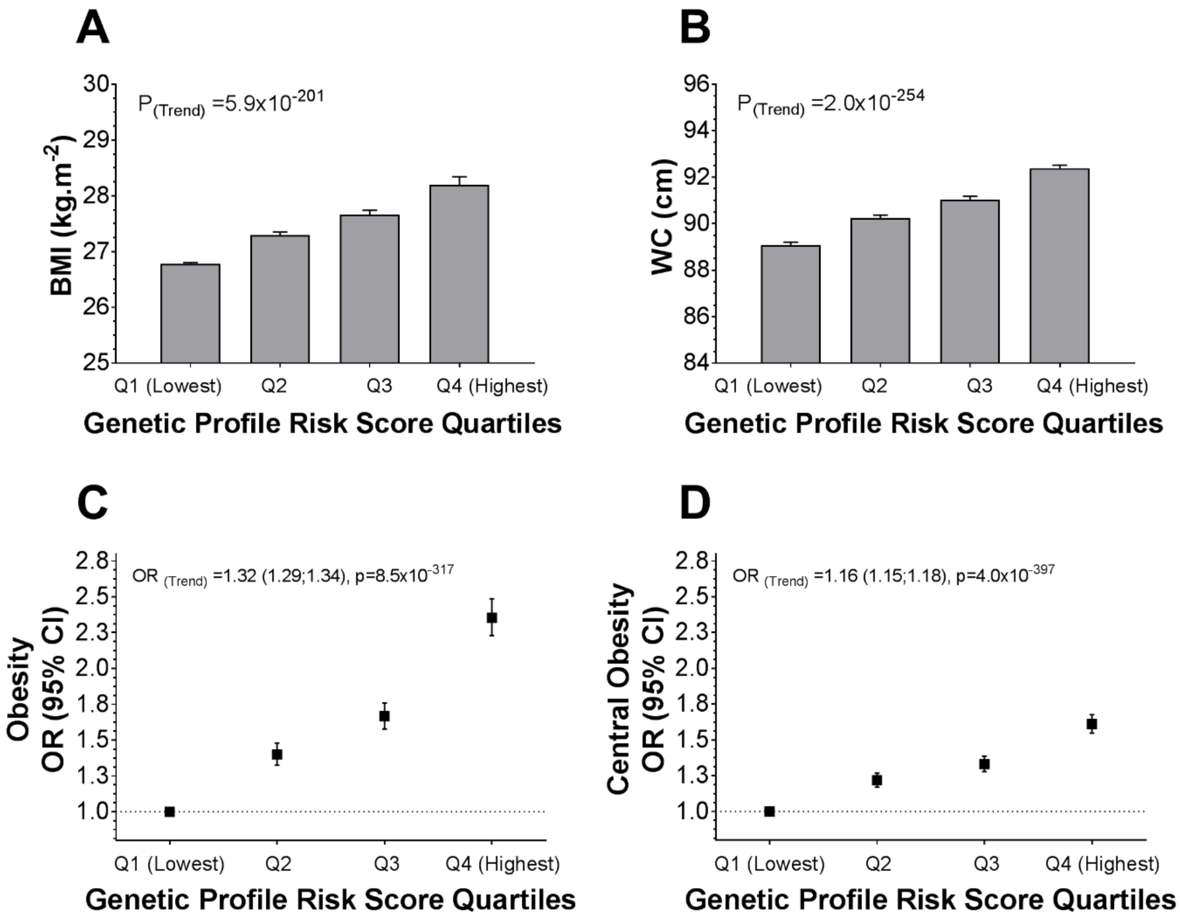
		Never/ Rarely		Yes		P*
BMI	**n**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**p-interaction**
Model 0	65,491	0.57 (0.54, 0.61)	$1.5x10^{-199}$	0.70 (0.61, 0.78)	$1.1x10^{-53}$	0.006
Model 1	57,647	0.54 (0.51, 0.58)	$1.7x10^{-175}$	0.68 (0.59, 0.77)	$1.1x10^{-49}$	0.007
WC						
Model 0	65,550	1.18 (1.09, 1.28)	$2.1x10^{-137}$	1.57 (1.35, 1.79)	$5.3x10^{-44}$	$9.4x10^{-4}$
Model 1	57,694	1.13 (1.03, 1.22)	$1.6x10^{-119}$	1.49 (1.27, 1.72)	$2.0x10^{-38}$	0.004

[1]Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI by 1 SD increase in the genetic risk score by shift work. The p-value for the interaction between genetic risk score and shift work is presented as P*.
Model 0 was adjusted for age, sex, month of recruitment, smoking, disease history (deprivation, diabetes, depression, long-standing illness, CVDs, and cancer), and genetic-quality measurement.
Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristic (sleep duration, chronotype, getting up in the morning, and day napping), and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).

Supplemental Table 10. Association between genetic profile risk score and BMI by nightshift work[1]

		Never/rarely		Yes		
BMI	**n**	**B (95% CI)**	**p-value**	**B (95% CI)**	**p-value**	**P***
Model 0	60,138	0.58 (0.54, 0.61)	$1.5x10^{-199}$	0.70 (0.58, 0.82)	$1.9x10^{-28}$	0.054
Model 1	52,976	0.55 (0.51, 0.58)	$1.7x10^{-175}$	0.69 (0.56, 0.82)	$8.4x10^{-27}$	0.039
WC						
Model 0	60,194	1.18 (1.09, 1.28)	$2.1x10^{-137}$	1.61 (1.30, 1.91)	$3.5x10^{-24}$	0.009
Model 1	53,020	1.13 (1.03, 1.22)	$1.6x10^{-119}$	1.54 (1.22, 1.86)	$1.8x10^{-21}$	0.018

[1]Data presented as beta coefficients (95%CI). The beta coefficient indicates the change in BMI/WC by 1 SD increase in the genetic risk score by nightshift work. The p-value for the interaction between genetic risk score and nightshift work is presented as P*.
Model 0 was adjusted for age, sex, month of recruitment, smoking, disease history (deprivation, diabetes, depression, long-standing illness, CVDs, and cancer), and genetic-quality measurement.
Model 1 was adjusted for model 0 plus smoking, physical activity, sedentary behaviour, sleep characteristic (sleep duration, chronotype, getting up in the morning, and day napping), and dietary intake variables (alcohol, fruits, coffee, vegetables, meats, processed meat, cereals, bread, and cheese).



Supplemental Figure 1. BMI, waist circumference and obesity prevalence by quartile of Genetic Profile Risk Score

Data are presented as adjusted mean for Figure A and B or Odds ratio and 95%CI for Figure C and D. Models were adjusted as described in the Methods. OR (Trend) indicates the linear estimate of the odds ratio increase per quartile of the genetic profile risk score. This trend test was performed using GLM analysis for continuous variables (Figure A and B) and with logistic regression for outcomes on Figure C and D, the Q1 (lowest genetic risk score) was used as the referent group for the OR analysis. Obesity (Figure C) was defined as a BMI ≥30.0 and central obesity (Figure D) was defined as a WC >88 cm for women and >102 cm for men.