EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health

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Please cite this article as: Strausz S, Ruotsalainen S, Ollila HM, *et al*. Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.03091-2020).

Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health

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Five OSA associated loci were found highlighting the causal link between obesity and OSA but also providing evidence for non-BMI dependent effects. OSA comorbidities were correlated genetically for OSA showing these diseases may have shared genetic basis.

Abstract

There is currently limited understanding of the genetic aetiology of obstructive sleep apnoea (OSA). We aimed at identifying genetic loci associated with OSA risk and to test if OSA and its comorbidities share a common genetic background.

We conducted the first large-scale genome-wide association study of OSA using FinnGen Study (217,955 individuals) with 16,761 OSA patients identified using nationwide health registries.

We estimated 8.3% [0.06-0.11] heritability and identified five loci associated with OSA ($P < 5.0 \times 10^{-8}$): rs4837016 near GTPase activating protein and VPS9 domains 1 (*GAPVD1*), rs10928560 near C-X-C motif

chemokine receptor 4 (*CXCR4*), rs185932673 near Calcium/calmodulin-dependent protein kinase ID (*CAMK1D*) and rs9937053 near Fat mass and obesity-associated protein (*FTO*) - a variant previously associated with body mass index (BMI). In a BMI-adjusted analysis, an association was observed for rs10507084 near Rhabdomyosarcoma 2 associated transcript *(RMST*)/NEDD1 gamma-tubulin ring complex targeting factor (*NEDD1*). We found high genetic correlations between OSA and BMI (rg=0.72 [0.62-0.83]) and with comorbidities including hypertension, type 2 diabetes (T2D), coronary heart disease (CHD), stroke, depression, hypothyroidism, asthma and inflammatory rheumatic diseases (IRD) (rg > 0.30). Polygenic risk score (PRS) for BMI showed 1.98-fold increased OSA risk between the highest and the lowest quintile and Mendelian randomization supported a causal relationship between BMI and OSA.

Our findings support the causal link between obesity and OSA and joint genetic basis between OSA and comorbidities.

Introduction

Obstructive sleep apnoea (OSA) is a severe sleep disorder affecting at least 9% of the population. Prevalence increases with higher age reaching over 35% in individuals over 60 years of age[1]. Despite a recognized health impact and available diagnostic tools and treatments the condition remains underdiagnosed[2,3]. OSA is characterized by repetitive episodes of nocturnal breathing cessation due to upper airway collapse resulting in mild to severe sleep deprivation and dysregulation of sleep, breathing and blood pressure. These conditions may lead to serious comorbidities through intermittent

hypoxia, systemic inflammation and sympathetic activation[4]. Furthermore, OSA is influenced by multiple risk factors such as obesity, male sex, family history of OSA, high age and problems of upper airway flow or jaw anatomy[5].

Consequently, OSA is a serious public health problem due to its many cardiometabolic comorbidities including an increased risk to coronary heart disease (CHD), type 2 diabetes (T2D) and its complications[6] and ultimately, increased mortality[7]. In addition, comorbidities such as depression[8], hypothyroidism[9], asthma[10] and inflammatory rheumatic diseases (IRD)[11] are linked with OSA. IRD might manifest as a comorbidity of OSA through the affection of the temporomandibular joint, which rotates the lower jaw backward causing narrowing of the upper airway[12].

Genetic studies provide a tool to identify independent genetic risk factors that modulate disease risk, and to examine causal pathways between comorbidity traits.

Genome-wide association studies (GWAS) in OSA patients have previously identified associations with OSA severity measured with apnoea-hypopnea index (AHI, number of apnoeas and hypopneas per hour of sleep) or respiratory event duration[13-15]. The genome-wide significant findings from these studies and the corresponding associations our study are found in **Supplementary Table 1**. Larger-scale GWAS studies have been performed on OSA-related phenotypes such as snoring[16]. However, knowledge about OSA predisposing genetic loci is thus far limited[17] .

To test genetic associations with OSA we utilized FinnGen study with genetic profiling for 217,955 individuals and OSA diagnosis based on International Statistical Classification of Diseases (ICD) codes obtained from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. The registries have excellent validity and coverage[18]. Combining the OSA diagnosis (ICD-10: G47.3, ICD-9: 3472A) and related risk factors and comorbidities with the genotyping data allows identification of risk variants, helps elucidating biological disease mechanisms and enables evaluation of OSA-related disease burden on a population level.

The aim of the study is to identify genetic loci associated with OSA risk and to test if OSA and its comorbidities share a common genetic background. While there are previous small scale GWAS studies on OSA severity, to our knowledge this is the first large-scale GWAS study on the risk of OSA.

Materials and Methods

General information

We selected into further analyses comorbidities which have previously been shown to associate with OSA in epidemiological studies, including obesity[19], hypertension[20] , T2D[21] , CHD, stroke[22], depression[8], hypothyroidism[9], asthma[10] and IRD[11,12].

Variant positions are reported in Genome Reference Consortium Human genome build 38 co-ordinates (GRChb38). All effect sizes and allele frequencies are reported in terms of alternate allele.

Study sample in FinnGen

FinnGen (https://www.finngen.fi/en) is a large biobank study that aims to genotype 500,000 Finns including prospective and retrospective epidemiological and disease-based cohorts as well as hospital biobank samples (**Supplementary Table 2**). FinnGen combines this data with longitudinal registry data that record health care events over the entire lifespan including The National Hospital Discharge Registry (available from 1968), Causes of Death Registry (available from 1969), Cancer Registries (available from 1953) and medication reimbursement registries (available from 1995), all these using unique national personal identification codes. Registry data was available from the beginning of the registry until 31.12.2018 **(Supplementary Figure 1)**. The data consists of censored 218,792 individuals until the spring of 2020. FinnGen's genotyping and imputation protocols are described in **Supplementary Information**.

To examine OSA patients more specifically 837 individuals who had ICD-code G47 (Sleep disorders) were excluded from the controls and thus the remaining sample size was 217,955 participants. Of them, 16,761 (7.7%) had OSA diagnosis and 10,557 (63.0%) of OSA patients were male. Baseline characteristics

and OSA comorbidities of the participants are presented in **Table 1.** Differences in baseline demographics and clinical characteristics were tested using logistic regression model. The model was adjusted for sex, age and 10 first principal components (PC), except the model for age was adjusted for sex and 10 first PCs and the model for sex was adjusted for age and 10 first PCs.

The diagnosis of OSA was based on ICD-codes (ICD-10: G47.3, ICD-9: 3472A), which were obtained from the Finnish National Hospital Discharge Registry and the Causes of Death Registry. This diagnosis is based on subjective symptoms, clinical examination and sleep registration applying AHI≥5/hour or respiratory event index (REI)≥5/hour. By combining ICD-codes from different registries, we generated disease endpoints. **Supplementary Table 3** describes how endpoints were constructed for each phenotype.

All prescription medicine purchases were retrieved from the Social Insurance Institution of Finland (KELA) registry for prescription drug purchases, since 1995 (excluding over-the-counter medicines and medication administered at hospitals). The drugs are coded by the Anatomical Therapeutic Chemical (ATC) Classification System (Supplementary Figure 1).

Study samples in other cohorts

UK Biobank (UKBB, https://www.ukbiobank.ac.uk/) is a major national and international health resource, with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses. UKBB recruited 500,000 people in 2006-2010 from across the United Kingdom. OSA diagnosis was based on ICD-10: G47.3. The study sample in the UKBB included 4,471 OSA cases and 403,723 controls.

The Estonian Biobank is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT, www.biobank.ee). The cohort size is currently close to 150,000 participants. Patients were selected by ICD-10: G47.3. For additional conformation of the diagnosis treatment service codes from the Health Insurance Fund were also used. The study sample in the EGCUT included 4,930 OSA patients and 61,056 controls.

The All New Diabetics in Scania (ANDIS, http://andis.ludc.med.lu.se/) aims to recruit all incident cases of diabetes within Scania County in Southern Sweden. All health care providers in the region were invited; the current registration covered 14,625 patients. OSA was defined by ICD-10: G47.3. The study sample included 947 OSA patients and 9,829 controls.

The validation of OSA diagnoses

For the validation of OSA diagnoses, we collected 1,000 OSA patients treated in Hospital District of Helsinki and Uusimaa (HUS) during the years 2008-2011 and 2016-2019 using the diagnoses derived from HUS's Hospital Discharge Registry and the individual level medical records.

The diagnosis for OSA was confirmed using the International Classification criteria for Sleep Disorders which requires either signs/symptoms (eg. associated sleepiness, fatigue, insomnia, snoring, subjective nocturnal respiratory disturbance, or observed apnoea) or associated medical or psychiatric disorder (ie. hypertension, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction, or mood disorder) coupled with five or more predominantly obstructive respiratory events per hour. Alternatively, a frequency of obstructive respiratory events 15/h satisfies the criteria, even in the absence of associated symptoms or disorders[23].

Genome-wide association testing

A total of 218,792 samples from FinnGen Data Freeze 5 with 2,925 disease endpoints were analyzed using Scalable and Accurate Implementation of Generalized mixed model (SAIGE), which uses saddle point approximation (SPA) to calibrate unbalanced case-control ratios[24]. Analyses were adjusted for current age or the age at death, sex, genotyping chip, genetic relationship and first 10 PCs. For OSA, we performed GWAS in a similar manner (n=217,955, including 16,761 OSA patients and 201,194 controls), but adjusting also for body mass index (BMI) (n=159,731, including 12,759 OSA patients and 146,972 controls).

For the replication of the FinnGen OSA GWAS results we merged the evidence from the UKBB, EGCUT and ANDIS cohorts. The results were combined using inverse-variance weighted fixed-effect meta-analysis using beta estimates and beta standard errors in the Metagen R package as implemented in R version V.4.0.2 (www.r-project.org). The merged data consisted 10,348 OSA cases and 474,608 controls.

The GWAS using UKBB data was calculated using SAIGE[24] . This subset included 4,471 OSA cases and 403,723 controls and was adjusted for birth year, sex, genetic relatedness and the first 4 PCs. In the EGCUT the data were analyzed using SAIGE and the model was adjusted for current age or the age at death, sex, genetic relatedness and the first 10 PCs and included 4,930 OSA patients and 61,056 controls. In ANDIS, the GWAS was calculated using logistic regression model, which was adjusted for current age or the age at death, sex and first 10 PCs. The analysis included 947 cases and 9,829 controls.

Linkage disequilibrium score regression (LDSC)

To estimate single nucleotide polymorphism (SNP) -based heritability, genetic correlation and tissue specific SNP-heritability we used LDSC-software[25]. LDSC uses linkage disequilibrium (LD) score regression method, which quantifies the contribution of each variant by examining the relationship between test statistics and LD. In calculation we used LD scores calculated from the 1000 Genomes Project[26]. To restrict to a set of common, well-imputed variants, we retained only those SNPs in the HapMap 3 reference panel[27].

To study genetic correlations between OSA, BMI, hypertension, T2D, CHD, stroke, depression, hypothyroidism, asthma and IRD we used summary statistics from the FinnGen data. For sleep traits we used summary statistics derived from the UKBB data. Study subjects self-reported snoring[16], sleep duration, sleepiness[28] and chronotype[29]. Sleep efficiency (sleep duration divided by the time between the start and end of the first and last nocturnal inactivity period, respectively) was based on accelerometer-derived measures[30]. For tissue specific SNP-heritability we used a method, which combined data from Encyclopedia of DNA Elements (ENCODE, https://www.encodeproject.org/) and the Genotype-Tissue Expression (GTEx, https://gtexportal.org/home/) resources[31,32].

Polygenic risk score (PRS) and Mendelian randomization (MR)

PRS for BMI was calculated using summary statistics for 996,250 variants[33]. The posterior effect sizes were calculated with PRS-CS utilising method[34] and the score was calculated using Plink2 (https://www.cog-genomics.org/plink/2.0/) for the FinnGen data.

We performed MR analysis to investigate the causality between BMI and OSA using independent BMI SNPs[33]. A genetic variant associated with the exposure of interest (genetic instrument) is used to test the causal relationship with the exposure (BMI) and outcome (OSA)[35].

Gene based analysis

Gene-based tests were performed using Multi-marker Analysis of GenoMic Annotation (MAGMA) as implemented on the Functional Mapping and Annotation (FUMA) platform, which provides aggregate association p-values based on all variants located within a gene and its regulatory region using information from 18 biological data repositories and tools[36]. This analysis includes a gene-based test to detect significant SNPs associated with OSA using FinnGen OSA summary statistics.

Results

OSA diagnosis shows excellent validity

We validated the OSA diagnosis using HUS's Hospital Discharge Registry collecting information of 1,000 patients and compared the registry data to the patient medical records. OSA diagnosis has a validity showing over 98% positive predictive value (PPV) **Supplementary Figure 2**.

OSA correlates strongly with cardiovascular and metabolic traits

To estimate strengths of associations between OSA and comorbidities we utilised data from 217,955 individuals who have participated in the FinnGen project. 16,761 (7.7%) had OSA diagnosis and 10,557 (63%) of cases were male. The diagnoses were derived from ICD-codes in the Finnish National Hospital Discharge Registry and from the Causes of Death Registry. Baseline characteristics of the FinnGen participants and odds for OSA associated comorbidities are presented in Table 1. Also, two thirds of the patients had BMI 25 or over (66.2%) as suggested by previous epidemiological reports [37].

GWAS of OSA reveals BMI dependent and independent associations

We estimated the heritability for OSA in FinnGen to be 8.3% [0.06-0.11] before and 6.0% [0.04-0.08] after BMI adjustment. In a genome-wide association test, five distinct genetic loci were associated with OSA ($P < 5.0 \times 10^{-8}$) outlined in **Table 2** and **Figure 1a, Supplementary Figure 3a** and regional associations in **Supplementary Figure 4**. The lead variant in a locus on chromosome 16 was rs9937053, an intronic variant near Fat mass and obesity-associated protein (*FTO)*, $P = 4.3 \times 10^{-16}$. In chromosome 12, the lead variant was rs10507084, near Rhabdomyosarcoma 2 associated transcript *(RMST)/* NEDD1 gamma-tubulin ring complex targeting factor *(NEDD1)*, $P = 2.8 \times 10^{-11}$, where *RMST*, a long non-coding RNA, was the nearest gene and *NEDD1* the nearest protein coding gene. On chromosome 10, the lead variant was rs185932673, an intronic variant near Calcium/calmodulin-dependent protein kinase ID *(CAMK1D),* $P = 2.4 \times 10^{-8}$. In chromosome 9, the lead variant was rs4837016 near GTPase activating protein and VPS9 Domains 1 (*GAPVD1)*, $P = 1.5 \times 10^{-8}$ and in chromosome 2, the lead variant rs10928560 was near C-X-C motif chemokine receptor 4 (*CXCR4)*, $P = 2.8 \times 10^{-8}$. Four out of five of these OSA associated lead variants have also been previously associated with BMI ($p<0.01$)[38-40], with the exception of rs10507084 at the *RMST/NEDD1* locus. Conditional analyses of the associated loci did not suggest any additional associations. Adjusting for BMI did not affect the association for variant rs10507084 (Table 2, **Figure 1b, Supplementary Figure 3b** and 4), ($OR_{unadjusted} = 1.11[1.08\text{-}1.15]$, $P=2.8 \times 10^{-11}$ vs. $OR_{BMI\ adjusted} = 1.12[1.08\text{-}1.17]$, $P=9.7 \times 10^{-10}$) suggesting BMI-independent mechanisms for rs10507084 in OSA predisposition. As a sensitivity analysis we conducted a GWAS where individuals with snoring (ICD-10: R06.5) were removed after which 197,797 individuals remained in the control group. This did not reveal any new associations nor did it affect notably to our estimates (**Supplementary Figure 5, 6** and **Supplementary Table 4**).

As an exploratory analysis we used MAGMA. This tool annotates FinnGen OSA summary statistics based on 18 biological data repositories and tools[36]. Using MAGMA, we detected 25 significant associations ($P < 2.54 \times 10-6$) with various biological processes, which were driven by the same loci as the significant GWAS variants in FTO and GAPVD1 (**Supplementary Figure 7a**). These may be potential target genes at these loci for the variants that associate with OSA, and overall indicate that the genes at this region may be relevant for OSA. Similarly, the gene-based test for BMI-adjusted OSA revealed three further associated genes (**Supplementary Figure 7b**).

We performed a phenome-wide association analysis (PheWAS) using Finngen data and examined the associations between the lead SNPs and 2,925 disease endpoints. Rs10507084 was specific for OSA also after BMI adjustment suggesting an independent role from cardiometabolic traits for the association between rs10507084 and OSA (**Figure 2a**). While the FTO was detected to be associated with OSA, it was also associated with a wide spectrum of cardiometabolic diagnoses as shown earlier [33,41] and also to coffee consumption [42]. The strongest PheWAS associations were observed with OSA-related comorbidities including obesity ($P=4.14 \times 10^{-41}$), T2D ($P=5.67 \times 10^{-28}$) and hypertension ($P=1.40 \times 10^{-10}$), **Supplementary Table 5**. In addition, there was a strong correlation between rs10507084 and the use of antidepressants (OR=1.013, [1.007-1.019], $P=4.4 \times 10^{-6}$) (**Figure 2b**). This result remained significant further adjusting for OSA (OR=1.011, [1.005-1.017], $P=1.9 \times 10^{-4}$.

Genetic correlations and MR connect OSA with cardiovascular outcomes and dysregulation of metabolism

To study the potential common genetic background of OSA and its known epidemiological correlates, we computed genetic correlations between OSA and its comorbidities using FinnGen summary statistics. The results showed strong genetic correlations between OSA and BMI (rg = 0.72, [0.62-0.83], $P=3.49 \times 10^{-40}$) and between OSA and comorbidities: hypertension (rg=0.35, [0.23-0.48], $P=4.06 \times 10^{-8}$), T2D (rg=0.52, [0.37-0.66], $P=6.40 \times 10^{-12}$), CHD (rg=0.38, [0.17-0.58], $P=3.84 \times 10^{-4}$), stroke (rg=0.33, [0.03-0.63], $P=2.93 \times 10^{-2}$), depression (rg=0.43, [0.27-0.60], $P=2.79 \times 10^{-7}$), hypothyroidism (rg=0.40, [0.27-0.54], $P=7.07 \times 10^{-9}$), asthma (rg=0.50, [0.33-0.68], $P=1.53 \times 10^{-8}$) and IRD (rg=0.34, [0.09-0.58], $P=6.97 \times 10^{-3}$). Furthermore, we observed high genetic correlations between OSA comorbidities. Since many of OSA comorbidities are

correlated with BMI, we calculated the genetic correlations after BMI adjustment. This analysis showed somewhat lower estimates for genetic correlations between OSA and CHD (rg=0.24 [0.012-0.47], P=0.04) , depression (rg=0.33, [0.17-0.50], $P=1.1 \times 10^{-3}$), asthma (rg=0.33 [0.11-0.54], $P=2.6 \times 10^{-3}$) and hypothyroidism, (rg=0.28 [0.11-0.44], $P=8.0 \times 10^{-4}$). Genetic correlations between OSA and BMI (rg=0.08, [-0.05-0.22], P=0.22), hypertension (rg=0.05, [-0.10-0.20], P=0.51), T2D (rg=0.15, [-0.03-0.33], P=0.11), stroke (rg=0.32, [-0.05-0.69], P=0.09) and IRD (rg=0.27, [-0.01-0.54], $P=5.7 \times 10^{-2}$) attenuated after BMI adjustment (**Figure 3)**. We also estimated a strong genetic correlation between males and females (rg=1, [1.15-0.85], $p=1.85 \times 10^{-12}$).

To estimate genetic correlations between FinnGen OSA summary statistics and other sleep traits we used UKBB derived summary statistics for sleep variables. We observed genetic correlation with snoring[16] rg = 0.81 [0.93-0.69], $P=1.24 \times 10^{-38}$, sleep efficiency [30] rg = -0.31, [-0.44 - -0.17], $P=9.80 \times 10^{-6}$) and this was reflected with higher genetic correlation with daytime sleepiness [28] (rg = 0.44, [0.33-0.54], $P=1.27 \times 10^{-15}$). These associations remained significant also after BMI adjustment (rg=0.68 [0.55-0.81), $P=2.93 \times 10^{-26}$, rg=-0.19, [-0.36 - -0.03], P= 0.02, rg=0.42, [0.29-0.55], $P=1.06 \times 10^{-10}$, respectively). We did not find significant genetic correlations between OSA and sleep duration or chronotype[29] (**Table 3).**

To investigate the biological mechanisms behind OSA, we also examined tissue enrichment of association signals using partitioned heritability analysis using LDSC: an approach which combines data from ENCODE and the GTEx resources[31,32] to FinnGen OSA summary statistics. Concordantly with the association of BMI and cardiometabolic traits, we observed strongest association with cardiovascular tissues and connective and bone tissues ($P < 0.05$). Furthermore, enrichments with BMI adjusted OSA implicated central nervous system (CNS) as the strongest associating single tissue ($P < 0.05$) when nominal alpha level 0.05 is shown (**Supplementary Figure 8)**.

To test if there is a causal relationship between OSA and its comorbidities, we performed analysis of PRS followed by formal MR analysis using FinnGen OSA summary statistics and independent BMI SNPs[33]. The BMI PRS showed a strong association with OSA risk (**Table 4)** and the individuals in the highest BMI PRS quintile had 1.98-fold increased ([1.88-2.09], $P=3.38 \times 10^{-140}$) OSA risk after adjustment for age, sex

and 10 first PCs. Similarly, this association was further accentuated in formal MR. We used 64 independent BMI SNPs[33] as instrumental variables to predict OSA. In line with epidemiological observations and genetic correlation, we discovered a strong causal predictive effect from BMI to OSA (IVW: beta=0.67, $P=8.32 \times 10^{-16}$) (**Figure 4, Supplementary Table 6)**.

Replication

For each lead variants associated with OSA, we examined the estimates from the additional, comparable cohorts: UKBB, ANDIS and EGCUT. The results were combined using inverse-variance weighted fixed effect meta-analysis. These additional independent datasets support the role of FTO and GAPVD1 loci in OSA ($P < 0.05$) (**Supplementary Table 7a)**.

In addition, we calculated PRS using the lead variants from our study and UKBB's individual level data to predict OSA. The OSA PRS showed an association with OSA risk and the individuals in the highest OSA PRS quintile had a modest 1.24-fold increased ([1.15-1.33], $P=6.89 \times 10^{-9}$) OSA risk compared to the lowest quintile after adjustment for birth year, sex and 10 first PCs. Furthermore, the association remained significant after BMI-adjustment (OR=1.11, [1.03-1.20], $P=4.70 \times 10^{-3}$) (**Supplementary Table 8**).

Discussion

In this study, using biobank data of over 217,000 individuals we show that OSA risk has a strong genetic component and identify five genetic loci that are associated with the risk for OSA. Our results show high genetic correlations between OSA and cardiometabolic diseases and risk factors, with strongest connections between OSA and BMI, hypertension, T2D and CHD, which are in line with previous epidemiological and clinical observations. These genetic correlations tracked with phenotypic correlations and comorbidities for OSA. In addition, both our association findings and the MR results support the causal role of obesity in OSA.

These results allow us to draw several conclusions. First, genetic variation plays an important role in development of OSA. This is supported by both the SNP heritability estimates and the associated loci.

Second, our results show that obesity plays a central causal role in the OSA risk. This is supported by high genetic correlations between OSA and BMI. We found that four out of five associated loci were

mediated through their associations with BMI. These findings are in line with the finding that weight loss is an important contributor of lowering AHI and the severity of OSA[43,44].

Third, we also identified an association near RMST/NEDD1, which was specific for OSA independent of BMI. The lead SNP associated with antidepressant purchases, which connects this locus with regulation of sleep and mood. The finding may also reflect the earlier observation that depression is prevalent among patients with OSA[8].

Fourth, a strong genetic correlation was observed between OSA and sleep traits, especially with sleepiness and sleep efficiency. These findings highlight the pathological effects of OSA on sleep. As OSA is manageable with Continuous Positive Airway Pressure (CPAP) or oral appliance, these genetic correlations implicate the importance of OSA treatment.

Our study does have some limitations. First, registry-based ascertainment through hospitalisation may miss non-hospitalised cases (false negatives) and treatment information such as CPAP compliance or oral sleep apnoea appliance usage. However, to our knowledge this is the largest number of cases combined for a GWAS. Second, due to a relatively small number of cases in the replication datasets, our statistical power was limited in the replication analysis. The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population and the association was not replicated in the other study samples.

Here we present associations between five genetic loci and OSA. Two of these were replicated in independent cohorts. Our findings highlight the causal links between obesity and OSA but also provide evidence for non-BMI dependent genetic effects. In addition to BMI, we show that genetic effects that modify risk of cardiometabolic diseases, depression, hypothyroidism, asthma and IRD are also correlated with genetic effects for OSA showing that the observed comorbidities between OSA and these diseases may have a joint genetic basis. Our results support that OSA is a heterogenic disease with several distinct comorbidities, which would be beneficial to consider when treating patients with OSA.

Acknowledgements

We would like to thank all participants of the FinnGen study for their generous participation. We would also like to thank Sari Kivikko for management assistance. Patients and controls in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, older research

cohorts, collected prior to the start of FinnGen (in August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Valvira, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Valvira. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol Nr HUS/990/2017.

The FinnGen study is approved by the Finnish Institute for Health and Welfare (THL), approval numberTHL/2031/6.02.00/2017,amendmentsTHL/1101/5.05.00/2017,THL/341/6.02.00/2018,THL/2222/6.02.00/2018,THL/283/6.02.00/2019,THL/1721/5.05.00/2019, Digital and population data service agency VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3 the Social Insurance Institution (KELA) KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, and Statistics Finland TK-53-1041-17.

The Biobank Access Decisions for FinnGen samples and data utilised in FinnGen Data Freeze 5 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154, Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018, Finnish Clinical Biobank Tampere MH0004, Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

This research has been conducted using the UK Biobank Resource under Application Number 22627.

The validation study is approved by Hospital District of Helsinki and Uusimaa under approval number HUS/466/2019.

This work was supported by the Academy of Finland Center of Excellence in Complex Disease Genetics [Grant No 312062 to S.R., 312074 to A.P.]; Academy of Finland [Grant No 285380 to S.R, 128650 to A.P, 309643 to H.M.O]; the Finnish Foundation for Cardiovascular Research [to S.R., V.S., and A.P.]; the Sigrid Jusélius Foundation [to S.R. and A.P.]; University of Helsinki HiLIFE Fellow grants 2017-2020 [to S.R.] and Foundation and the Horizon 2020 Research and Innovation Programme [grant number 667301 (COSYN) to A.P.]; Oskar Öfflund foundation and Yrjö Jahnsson foundation [to H.M.O]; The Finnish Dental Society Apollonia [to S.S].

The FinnGen project is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and eleven industry partners (AbbVie Inc, AstraZeneca UK Ltd, Biogen MA Inc, Celgene

Corporation, Celgene International II Sàrl, Genentech Inc, Merck Sharp & Dohme Corp, Pfizer Inc., GlaxoSmithKline, Sanofi, Maze Therapeutics Inc., Janssen Biotech Inc). Following biobanks are acknowledged for collecting the FinnGen project samples: Auria Biobank (https://www.auria.fi/biopankki), THL Biobank (https://thl.fi/fi/web/thl-biopankki), Helsinki Biobank (https://www.terveyskyla.fi/helsinginbiopankki), Biobank Borealis of Northern Finland (https://www.oulu.fi/university/node/38474), Finnish Clinical Biobank Tampere (https://www.tays.fi/en-US/Research_and_development/Finnish_Clinical_Biobank_Tampere), Biobank of Eastern Finland (https://ita-suomenbiopankki.fi), Central Finland Biobank (https://www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (https://www.veripalvelu.fi/verenluovutus/biopankkitoiminta) and Terveystalo Biobank (https://www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/). All Finnish Biobanks are members of BBMRI.fi infrastructure (www.bbmri.fi).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest

V.S. has received honoraria from Novo Nordisk and Sanofi for consultations and has ongoing research collaboration with Bayer AG (all unrelated to this study).

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S.R. and T. P. supervised the study. S.E.R, S.S, H.M.O, M. K. and J.K. performed the statistical and bioinformatics analyses. A.S.H. and T.K. phenotyped study samples. S.S and E.L collected the data for the chart review. S.S, H.M.O. and S.E.R. wrote the paper with the feedback from all co-authors.

Data availability

The FinnGen data may be accessed through Finnish Biobanks' FinnBB portal (www.finbb.fi).

Code availability

The full genotyping and imputation protocol for FinnGen is described at https://doi-org.libproxy.helsinki.fi/10.17504/protocols.io.nmndc5e.

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References

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017; 34: 70-81.

2. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep* 1997; 20: 705-706.

3. Finkel KJ, Searleman AC, Tymkew H, Tanaka CY, Saager L, Safer-Zadeh E, Bottros M, Selvidge JA, Jacobsohn E, Pulley D, Duntley S, Becker C, Avidan MS. Prevalence of undiagnosed obstructive sleep apnea among adult surgical patients in an academic medical center. *Sleep Med* 2009; 10: 753-758.

4. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol* 2010; 7: 677-685.

5. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. *JAMA* 2004; 291: 2013-2016.

6. Strausz S, Havulinna AS, Tuomi T, Bachour A, Groop L, Makitie A, Koskinen S, Salomaa V, Palotie A, Ripatti S, Palotie T. Obstructive sleep apnoea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland. *BMJ Open* 2018; 8: e022752-2018.

7. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. *Sleep Breath* 2017; 21: 181-189.

8. BaHammam AS, Kendzerska T, Gupta R, Ramasubramanian C, Neubauer DN, Narasimhan M, Pandi-Perumal SR, Moscovitch A. Comorbid depression in obstructive sleep apnea: an under-recognized association. *Sleep Breath* 2016; 20: 447-456.

9. Bahammam SA, Sharif MM, Jammah AA, Bahammam AS. Prevalence of thyroid disease in patients with obstructive sleep apnea. *Respir Med* 2011; 105: 1755-1760.

10. Kong DL, Qin Z, Shen H, Jin HY, Wang W, Wang ZF. Association of Obstructive Sleep Apnea with Asthma: A Meta-Analysis. *Sci Rep* 2017; 7: 4088-017.

11. Taylor-Gjevre RM, Nair BV, Gjevre JA. Obstructive sleep apnoea in relation to rheumatic disease. *Rheumatology (Oxford)* 2013; 52: 15-21.

12. Redlund-Johnell I. Upper airway obstruction in patients with rheumatoid arthritis and temporomandibular joint destruction. *Scand J Rheumatol* 1988; 17: 273-279.

13. Farias Tempaku P, Leite Santoro M, Bittencourt L, D'Almeida V, Iole Belangero S, Tufik S. Genome-wide association study reveals two novel risk alleles for incident obstructive sleep apnea in the EPISONO cohort. *Sleep Med* 2019; 66: 24-32.

14. Cade BE, Chen H, Stilp AM, Gleason KJ, Sofer T, Ancoli-Israel S, Arens R, Bell GI, Below JE, Bjonnes AC, Chun S, Conomos MP, Evans DS, Johnson WC, Frazier-Wood AC, Lane JM, Larkin EK, Loredo JS, Post WS, Ramos AR, Rice K, Rotter JI, Shah NA, Stone KL, Taylor KD, Thornton TA, Tranah GJ, Wang C, Zee PC, Hanis CL, Sunyaev SR, Patel SR, Laurie CC, Zhu X, Saxena R, Lin X, Redline S. Genetic Associations with Obstructive Sleep Apnea Traits in Hispanic/Latino Americans. *Am J Respir Crit Care Med* 2016; 194: 886-897.

15. Chen H, Cade BE, Gleason KJ, Bjonnes AC, Stilp AM, Sofer T, Conomos MP, Ancoli-Israel S, Arens R, Azarbarzin A, Bell GI, Below JE, Chun S, Evans DS, Ewert R, Frazier-Wood AC, Gharib SA,

Haba-Rubio J, Hagen EW, Heinzer R, Hillman DR, Johnson WC, Kutalik Z, Lane JM, Larkin EK, Lee SK, Liang J, Loredo JS, Mukherjee S, Palmer LJ, Papanicolaou GJ, Penzel T, Peppard PE, Post WS, Ramos AR, Rice K, Rotter JI, Sands SA, Shah NA, Shin C, Stone KL, Stubbe B, Sul JH, Tafti M, Taylor KD, Teumer A, Thornton TA, Tranah GJ, Wang C, Wang H, Warby SC, Wellman DA, Zee PC, Hanis CL, Laurie CC, Gottlieb DJ, Patel SR, Zhu X, Sunyaev SR, Saxena R, Lin X, Redline S. Multiethnic Meta-Analysis Identifies RAI1 as a Possible Obstructive Sleep Apnea-related Quantitative Trait Locus in Men. *Am J Respir Cell Mol Biol* 2018; 58: 391-401.

16. Campos AI, García-Marín LM, Byrne EM, Martin NG, Cuéllar-Partida G, Rentería ME. Insights into the aetiology of snoring from observational and genetic investigations in the UK Biobank. *Nat Commun* 2020; 11: 817-020.

17. Veatch OJ, Bauer CR, Keenan BT, Josyula NS, Mazzotti DR, Bagai K, Malow BA, Robishaw JD, Pack AI, Pendergrass SA. Characterization of genetic and phenotypic heterogeneity of obstructive sleep apnea using electronic health records. *BMC Med Genomics* 2020; 13: 105-020.

18. Tolonen H, Salomaa V, Torppa J, Sivenius J, Immonen-Raiha P, Lehtonen A, FINSTROKE register. The validation of the Finnish Hospital Discharge Register and Causes of Death Register data on stroke diagnoses. *Eur J Cardiovasc Prev Rehabil* 2007; 14: 380-385.

19. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest* 2010; 137: 711-719.

20. Konecny T, Kara T, Somers VK. Obstructive sleep apnea and hypertension: an update. *Hypertension* 2014; 63: 203-209.

21. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *Respirology* 2013; 18: 140-146.

22. Dong JY, Zhang YH, Qin LQ. Obstructive sleep apnea and cardiovascular risk: meta-analysis of prospective cohort studies. *Atherosclerosis* 2013; 229: 489-495.

23. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014; 146: 1387-1394.

24. Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, LeFaive J, VandeHaar P, Gagliano SA, Gifford A, Bastarache LA, Wei WQ, Denny JC, Lin M, Hveem K, Kang HM, Abecasis GR, Willer CJ, Lee S. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet* 2018; 50: 1335-1341.

25. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson N, Daly MJ, Price AL, Neale BM. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015; 47: 291-295.

26. 1000 Genomes Project Consortium, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, Kang HM, Marth GT, McVean GA. An integrated map of genetic variation from 1,092 human genomes. *Nature* 2012; 491: 56-65.

27. International HapMap 3 Consortium, Altshuler DM, Gibbs RA, Peltonen L, Altshuler DM, Gibbs RA, Peltonen L, Dermitzakis E, Schaffner SF, Yu F, Peltonen L, Dermitzakis E, Bonnen PE,

Altshuler DM, Gibbs RA, de Bakker PI, Deloukas P, Gabriel SB, Gwilliam R, Hunt S, Inouye M, Jia X, Palotie A, Parkin M, Whittaker P, Yu F, Chang K, Hawes A, Lewis LR, Ren Y, Wheeler D, Gibbs RA, Muzny DM, Barnes C, Darvishi K, Hurles M, Korn JM, Kristiansson K, Lee C, McCarrol SA, Nemesh J, Dermitzakis E, Keinan A, Montgomery SB, Pollack S, Price AL, Soranzo N, Bonnen PE, Gibbs RA, Gonzaga-Jauregui C, Keinan A, Price AL, Yu F, Anttila V, Brodeur W, Daly MJ, Leslie S, McVean G, Moutsianas L, Nguyen H, Schaffner SF, Zhang Q, Ghori MJ, McGinnis R, McLaren W, Pollack S, Price AL, Schaffner SF, Takeuchi F, Grossman SR, Shlyakhter I, Hostetter EB, Sabeti PC, Adebamowo CA, Foster MW, Gordon DR, Licinio J, Manca MC, Marshall PA, Matsuda I, Ngare D, Wang VO, Reddy D, Rotimi CN, Royal CD, Sharp RR, Zeng C, Brooks LD, McEwen JE. Integrating common and rare genetic variation in diverse human populations. *Nature* 2010; 467: 52-58.

28. Lane JM, Liang J, Vlasac I, Anderson SG, Bechtold DA, Bowden J, Emsley R, Gill S, Little MA, Luik AI, Loudon A, Scheer FA, Purcell SM, Kyle SD, Lawlor DA, Zhu X, Redline S, Ray DW, Rutter MK, Saxena R. Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits. *Nat Genet* 2017; 49: 274-281.

29. Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Hu Y, Teder-Laving M, Hayward C, Roenneberg T, Wilson JF, Del Greco F, Hicks AA, Shin C, Yun CH, Lee SK, Metspalu A, Byrne EM, Gehrman PR, Tiemeier H, Allebrandt KV, Freathy RM, Murray A, Hinds DA, Frayling TM, Weedon MN. Genome-Wide Association Analyses in 128,266 Individuals Identifies New Morningness and Sleep Duration Loci. *PLoS Genet* 2016; 12: e1006125.

30. Jones SE, van Hees VT, Mazzotti DR, Marques-Vidal P, Sabia S, van der Spek A, Dashti HS, Engmann J, Kocevska D, Tyrrell J, Beaumont RN, Hillsdon M, Ruth KS, Tuke MA, Yaghootkar H, Sharp SA, Ji Y, Harrison JW, Freathy RM, Murray A, Luik AI, Amin N, Lane JM, Saxena R, Rutter MK, Tiemeier H, Kutalik Z, Kumari M, Frayling TM, Weedon MN, Gehrman PR, Wood AR. Genetic studies of accelerometer-based sleep measures yield new insights into human sleep behaviour. *Nat Commun* 2019; 10: 1585-019.

31. Finucane HK, Bulik-Sullivan B, Gusev A, Trynka G, Reshef Y, Loh PR, Anttila V, Xu H, Zang C, Farh K, Ripke S, Day FR, ReproGen Consortium, Schizophrenia Working Group of the Psychiatric Genomics Consortium, RACI Consortium, Purcell S, Stahl E, Lindstrom S, Perry JR, Okada Y, Raychaudhuri S, Daly MJ, Patterson N, Neale BM, Price AL. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet* 2015; 47: 1228-1235.

32. Finucane HK, Reshef YA, Anttila V, Slowikowski K, Gusev A, Byrnes A, Gazal S, Loh PR, Lareau C, Shoresh N, Genovese G, Saunders A, Macosko E, Pollack S, Brainstorm Consortium, Perry JRB, Buenrostro JD, Bernstein BE, Raychaudhuri S, McCarroll S, Neale BM, Price AL. Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat Genet* 2018; 50: 621-629.

33. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, MÃ¤gi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Zhao JH, Zhao W, Chen J, Fehrmann R, Hedman Ã, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa

MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Leach IM, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, StanÄ□Ã¡kovÃ¡ A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan, S W, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Ã„rnlÃ¶v J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, BlÃ¼her M, BÃ¶hringer S, Bonnycastle LL, BÃ¶ttcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Chen YI, Clarke R, Daw EW, de Craen, A J M, Delgado G, Dimitriou M, Doney ASF, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, GrÃ¤ÃŸler J, GrÃ¶nberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson Ã, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, LindstrÃ¶m J, Lo KS, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PKE, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, MÃ¼ller G, MÃ¼ller-Nurasyid M, Musk AW, Nagaraja R, NÃ¶then MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Smith AV, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, SundstrÃ¶m J, Swertz MA, Swift AJ, SyvÃ¤nen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A,

Wright AF, Zhang Q, LifeLines Cohort Study, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, GÃ¥din JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JRB, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, van 't Hooft, F M, Vinkhuyzen AAE, Westra HJ, Zheng W, Zondervan KT, ADIPOGen Consortium, AGEN-BMI Working Group, CARDIOGRAMplusC4D Consortium, CKDGen Consortium, GLGC, ICBP, MAGIC Investigators, MuTHER Consortium, MIGen Consortium, PAGE Consortium, ReproGen Consortium, GENIE Consortium, International Endogene Consortium, Heath AC, Arveiler D, Bakker SJL, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, FerriÃ¨res J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorff LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, HyppÃ¶nen E, Illig T, Jacobs KB, Jarvelin MR, JÃ¶ckel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJP, Keinanen-Kiukaanniemi SM, Kiemeney LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Marchand LL, LehtimÃ¤ki T, Lyssenko V, MÃ¤nnistÃ¶ S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PAF, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD,

Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PEH, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, TÃ¶njes A, TrÃ©gouÃ«t DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, VÃ¶lker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker, P I W, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, MÃ¤rz W, Melbye M, Metspalu A, Moebus S, Munroe PB, NjÃ¸lstad I, Oostra BA, Palmer CNA, Pedersen NL, Perola M, PÃ©russe L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJF, Speliotes EK. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; 518: 197-206.

34. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun* 2019; 10: 1776-019.

35. Paternoster L, Tilling K, Davey Smith G. Genetic epidemiology and Mendelian randomization for informing disease therapeutics: Conceptual and methodological challenges. *PLoS Genet* 2017; 13: e1006944.

36. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* 2017; 8: 1826-017.

37. Malhotra A, White DP. Obstructive sleep apnoea. *Lancet* 2002; 360: 237-245.

38. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, Yengo L, Ferreira T, Marouli E, Ji Y, Yang J, Jones S, Beaumont R, Croteau-Chonka DC, Winkler TW, GIANT Consortium, Hattersley AT, Loos RJF, Hirschhorn JN, Visscher PM, Frayling TM, Yaghootkar H, Lindgren CM. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet* 2019; 28: 166-174.

39. Hoffmann TJ, Choquet H, Yin J, Banda Y, Kvale MN, Glymour M, Schaefer C, Risch N, Jorgenson E. A Large Multiethnic Genome-Wide Association Study of Adult Body Mass Index Identifies Novel Loci. *Genetics* 2018; 210: 499-515.

40. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A

common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; 316: 889-894.

41. Pulit SL, Stoneman C, Morris AP, Wood AR, Glastonbury CA, Tyrrell J, Yengo L, Ferreira T, Marouli E, Ji Y, Yang J, Jones S, Beaumont R, Croteau-Chonka DC, Winkler TW, GIANT Consortium, Hattersley AT, Loos RJF, Hirschhorn JN, Visscher PM, Frayling TM, Yaghootkar H, Lindgren CM. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Hum Mol Genet* 2019; 28: 166-174.

42. Zhong VW, Kuang A, Danning RD, Kraft P, van Dam RM, Chasman DI, Cornelis MC. A genome-wide association study of bitter and sweet beverage consumption. *Hum Mol Genet* 2019; 28: 2449-2457.

43. Joosten SA, Khoo JK, Edwards BA, Landry SA, Naughton MT, Dixon JB, Hamilton GS. Improvement in Obstructive Sleep Apnea With Weight Loss is Dependent on Body Position During Sleep. *Sleep* 2017; 40: 10.1093/sleep/zsx047.

44. Myllymaa K, Myllymaa S, LeppÃ¤nen T, Kulkas A, Kupari S, Tiihonen P, Mervaala E, SeppÃ¤ J, Tuomilehto H, TÃ¶yrÃ¤s J. Effect of oxygen desaturation threshold on determination of OSA severity during weight loss. *Sleep Breath* 2016; 20: 33-42.

Table 1. Baseline characteristics and previously known OSA comorbidities between OSA and non-OSA individuals in the FinnGen cohort

	All	Non-OSA	OSA	OR [95% CI]	P-value
	n=217955	n=201194	n=16761		
Male (n, %)	94799 (43.5)	84242 (41.9)	10557 (63.0)	2.26[2.19-2.34]	$< 2.00 \times 10^{-16}$
Female (n, %)	123156 (56.5)	116952 (58.1)	6204 (37.0)		
Age (mean, sd)	52.4 (17.5)	51.8 (17.7)	58.9 (13.3)	1.02[1.02-1.03]	$< 2.00 \times 10^{-16}$
Age at OSA diagnosis (mean, sd)			55.3 (11.9)		
BMI (mean, sd)	27.25 (5.34)	26.87 (5.02)	31.72 (6.74)	1.15[1.15-1.16]	$< 2.00 \times 10^{-16}$
Hypertension (number of cases, %)	55678 (25.5)	47549 (23.6)	8129 (48.5)	2.44[2.36-2.53]	$< 2.00 \times 10^{-16}$
T2D (number of cases, %)	29054 (13.3)	23932 (11.9)	5122 (30.6)	2.60[2.50-2.70]	$< 2.00 \times 10^{-16}$
CHD (number of cases, %)	20925 (9.6)	18495 (9.2)	2430 (14.5)	1.11[1.06-1.17]	1.04×10^{-5}
Stroke (number of cases, %)	11671 (5.4)	10414 (5.2)	1257 (7.5)	1.10[1.03-1.17]	3.29×10^{-3}
Depression (number of cases, %)	23160 (10.6)	20094 (10.0)	3066 (18.3)	2.56[2.45-2.67]	$< 2.00 \times 10^{-16}$
Hypothyroidism (number of cases, %)	26228 (12.0)	23384 (11.6)	2844 (17.0)	1.85[1.77-1.94]	$< 2.00 \times 10^{-16}$
Asthma (number of cases, %)	20520 (9.4)	17358 (8.6)	3162 (18.9)	2.58[2.47-2.69]	$< 2.00 \times 10^{-16}$
IRD (number of cases, %)	12961 (5.9)	11555 (5.7)	1406 (8.4)	1.48[1.39-1.57]	$< 2.00 \times 10^{-16}$

Age and body mass index (BMI) were measured at the time when the biobank sample was given. BMI was measured of 159731 individuals including 12759 OSA cases and 146972 controls. OSA=obstructive sleep apnoea, T2D = type 2 diabetes, CHD = coronary heart disease, IRD = inflammatory rheumatic diseases, OR = odds ratio, CI=confidence interval

Table 2. Characterization of five genome-wide significant OSA loci in GRChb38

CHR	Position	RSID	REF	ALT	Nearest gene	Consequence	Fin.enr.	AF	AF cases	AF controls	INFO	OR [95% CI]	p-value	p-value BMIadj
16	53765595	rs9937053	G	A	FTO	intron	0.97	0.43	0.45	0.43	0.999	1.11[1.08-1.13]	4.3×10^{-16}	0.04

12	97359374	rs10507084	C	T	RMST/ NEDD1	intergenic	3.03	0.18	0.19	0.18	0.993	1.11[1.08-1.15]	2.8×10^{-11}	9.7×10^{-10}
10	12656440	rs185932673	C	T	CAMK1D	intron	0.55	0.0033	0.0051	0.0032	0.972	1.87[1.50-2.33]	2.4×10^{-8}	9.3×10^{-6}
9	125379530	rs4837016	G	A	GAPVD1	intergenic	1.12	0.47	0.45	0.47	0.995	0.93[0.91-0.95]	1.5×10^{-8}	2.2×10^{-4}
2	136234237	rs10928560	C	T	CXCR4	downstream	1.04	0.20	0.18	0.20	0.993	0.92[0.89-0.94]	2.8×10^{-8}	8.5×10^{-5}

All effect sizes and allele frequencies are reported in terms of alternate (ALT) allele.

The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population.

OSA=obstructive sleep apnoea, GRChb38=Genome Reference Consortium Human genome build 38 co-ordinates, CHR=chromosome, Fin.enr=Finnish enrichment is computed using The Genome Aggregation Database (Gnomad) data comparing Finnish to other European populations in the Gnomad data. AF=allele frequency, OR=odds ratio, CI=confidence interval, p-value BMIadj=p-value after body mass index (BMI) adjustment. FTO=Fat mass and obesity-associated protein, RMST=Rhabdomyosarcoma 2 associated transcript / NEDD1=NEDD1 gamma-tubulin ring complex targeting factor, CAMK1D=Calcium/calmodulin-dependent protein kinase ID, GAPVD1= GTPase activating protein and VPS9 Domains 1, CXCR4=C-X-C motif chemokine receptor 4.

Table 3. **Genetic correlations between OSA and other sleep traits**

	Snoring	**Sleepiness**	**Sleep duration**	**Chronotype**	**Sleep efficiency**
OSA	rg = 0.81 [0.93-0.69] p=1.24×10^{-38}	rg = 0.44 [0.33-0.54] p = 1.27×10^{-15}	rg = 0.0096 [-0.085-0.10] p = 0.84	rg = -5.0×10^{-4} [-0.079-0.078] p = 0.99	rg = -0.31 [-0.44 - -0.17] p = 9.80×10^{-6}
OSA BMI-adjusted	*rg=0.68 [0.55-0.81) p=2.93×10^{-26}	rg = 0.42 [0.29-0.55] p = 1.06×10^{-10}	rg = 0.078 [-0.031-0.19] p = 0.14	rg = -0.063 [-0.154-0.028] p = 0.18	rg = -0.19 [-0.36 - -0.03] p = 0.02

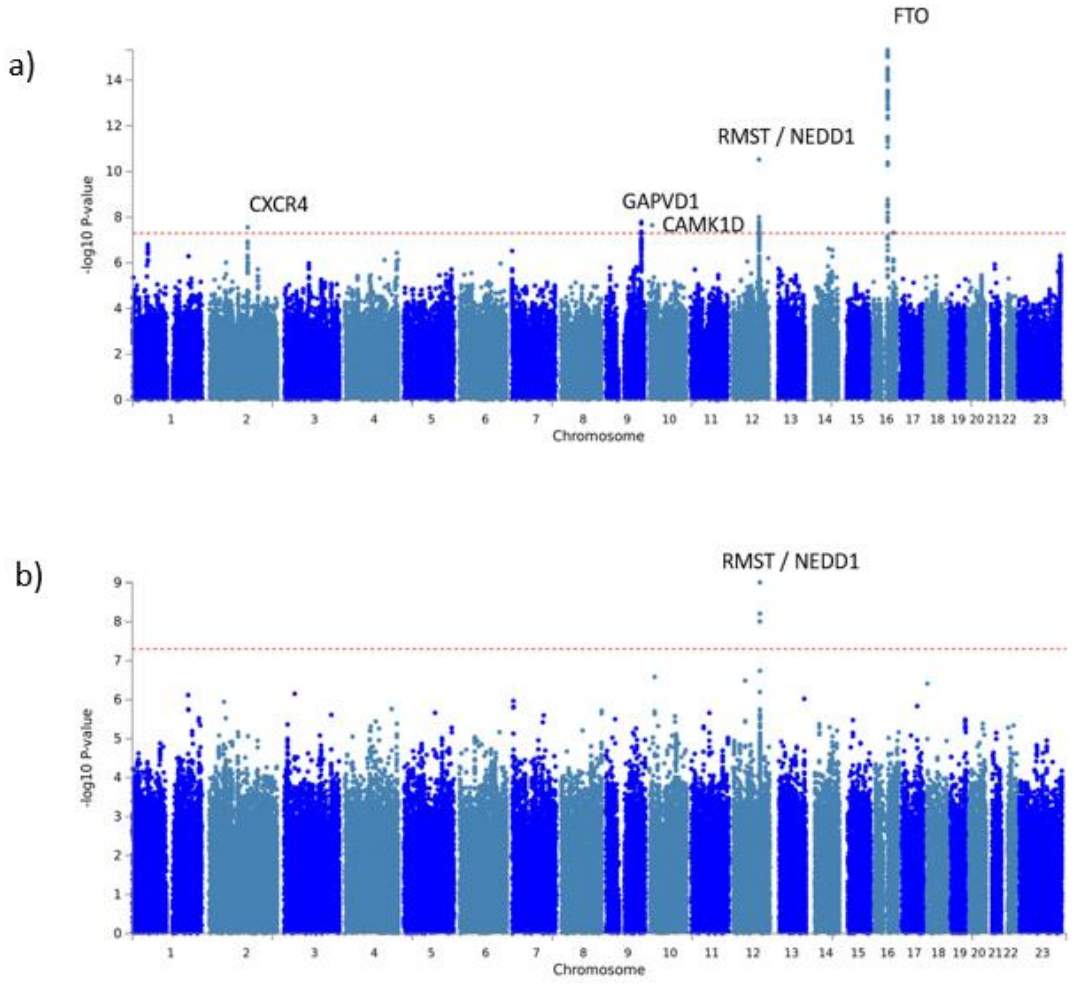
Summary statistics for sleep traits that were used to calculate the genetic correlations were obtained in previous genome-wide association studies (GWAS) from the UK Biobank (UKBB). *GWAS for snoring was also BMI-adjusted. OSA=obstructive sleep apnoea, BMI=body mass index, [95% confidence interval].

Table 4. BMI's polygenic risk score predicts OSA

BMI's PRS			
	OR	CI	p-value
BMI_Q1	-		-
BMI_Q2	1.29	1.22-1.36	3.49×10^{-19}
BMI_Q3	1.45	1.37-1.53	5.61×10^{-40}
BMI_Q4	1.61	1.53-1.70	7.93×10^{-67}
BMI_Q5	1.98	1.88-2.09	3.38×10^{-140}

Estimated effect coefficients for the body mass index (BMI)'s polygenic risk score (PRS) as a predictor of obstructive sleep apnoea (OSA). The BMI's PRS was stratified into quintiles and BMI_Q5 is the highest quintile. OR=odds ratio, CI = 95% confidence interval.

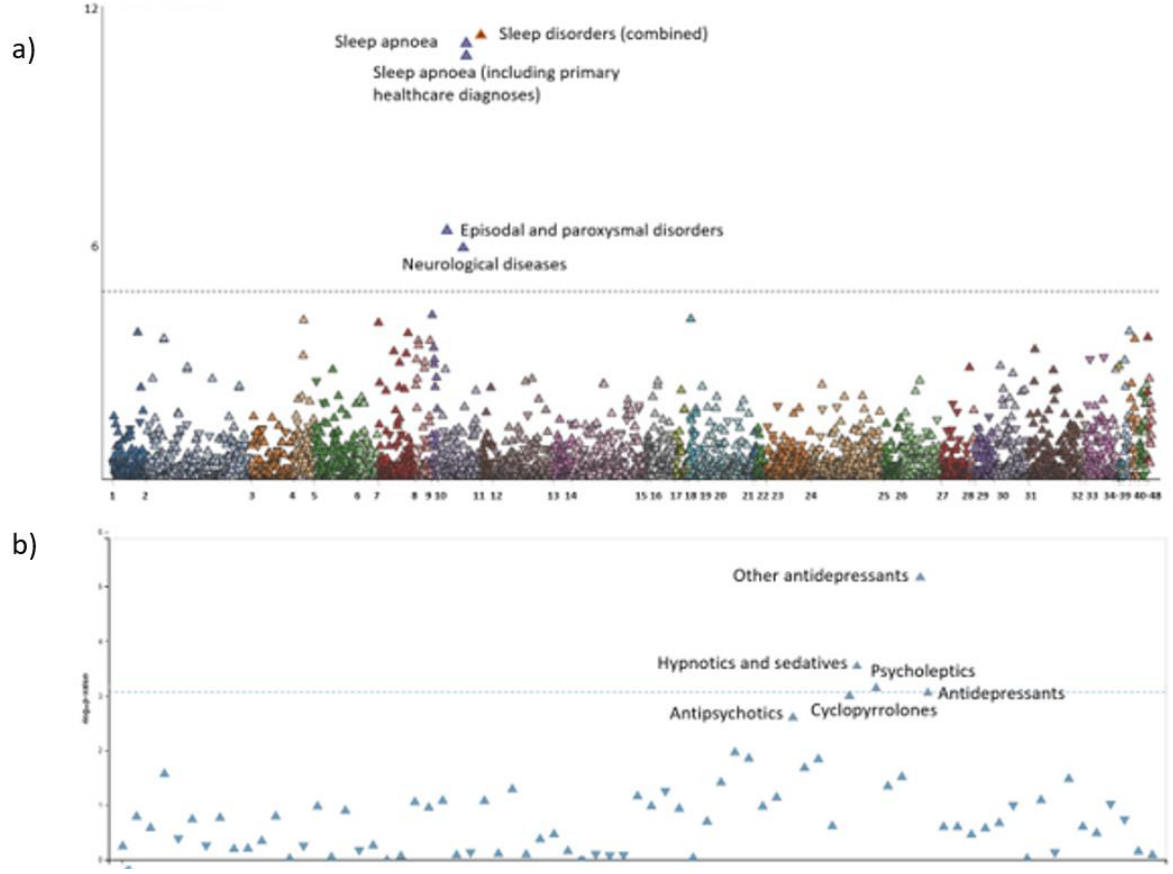
Figure 1



a) Manhattan plot for obstructive sleep apnoea (OSA) including 16 761 OSA cases and 201 194 controls. For each genetic variant, the x-axis shows chromosomal position, while y-axis shows the $-\log_{10}$(P) value.
The horizontal line indicates the genome-wide significance threshold of $P = 5 \times 10^{-8}$. Five genetic loci were identified at the genome-wide significance level. *CXCR4*=C-X-C motif chemokine receptor 4, *GAPVD1*= GTPase activating protein and VPS9 Domains 1, *CAMK1D*=Calcium/calmodulin-dependent protein kinase ID, *RMST*=Rhabdomyosarcoma 2 associated transcript / *NEDD1*=NEDD1 gamma-tubulin ring complex targeting factor, *FTO*=Fat mass and obesity-associated protein

b) Manhattan plot for obstructive sleep apnoea (OSA) after body mass index (BMI) adjustment including 12 759 OSA cases and 146 972 controls. For each genetic variant, the x-axis shows chromosomal position, while y-axis shows the $-\log_{10}$(P) value.
The horizontal line indicates the genome-wide significance threshold of $P = 5 \times 10^{-8}$. One genetic locus was identified at the genome-wide significance level. *RMST*=Rhabdomyosarcoma 2 associated transcript / *NEDD1*=NEDD1 gamma-tubulin ring complex targeting factor.

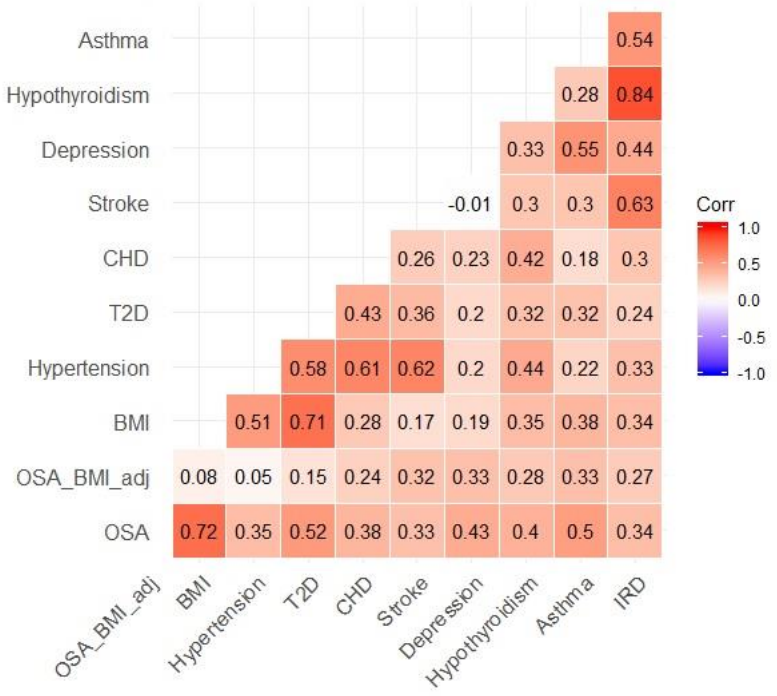
Figure 2



a) Phenome-wide association analysis (PheWAS) associations after body mass index (BMI) adjustment between rs10507084 and 2,925 disease endpoints. Significance Bonferroni corrected threshold was defined at $P = 0.05/2925 = 1.71 \times 10^{-5}$. Associated P-values on the $-\log_{10}$ scale on the vertical axis. Sleep apnoea represents a validated disease. Primary health care diagnoses have not been validated. Sleep disorders, Episodal and paroyxsmal disorders and Neurological diseases include Sleep apnoea. The disease definition along the horizontal axis: 1. I Certain infectious and parasitic diseases, 2. II Neoplasms from hospital discharges , 3. II Neoplasms, from cancer registry , 4. III Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, 5. IV Endocrine, nutritional and metabolic diseases, 6. Diabetes endpoints, 7. V Mental and behavioural disorders, 8. Psychiatric endpoints, 9. Alcohol related diseases, 10. VI Diseases of the nervous system, 11. Neurological endpoints, 12. VII Diseases of the eye and adnexa, 13. VIII Diseases of the ear and mastoid process, 14. IX Diseases of the circulatory system, 15. Cardiometabolic endpoints, 16. X Diseases of the respiratory system, 17. Asthma and related endpoints, 18. Chronic obstructive pulmonary disease and related endpoints, 19. Interstitial lung disease endpoints, 20. XI Diseases of the digestive system, 21. Dental endpoints, 22. Gastrointestinal endpoints, 23. XII Diseases of the skin and subcutaneous tissue, 24. XIII Diseases of the musculoskeletal system and connective tissue, 25. Rheumatoid arthritis endpoints, 26. XIV Diseases of the genitourinary system, 27. XV Pregnancy, childbirth and the puerperium , 28. XVI Certain conditions originating in the perinatal period, 29. XVII Congenital malformations, deformations and chromosomal abnormalities, 30. XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified, 31. XIX Injury, poisoning and certain other consequences of external causes, 32. XX External causes of morbidity and mortality, 33. XXI Factors influencing health status and contact with health services, 34. Drug purchase endpoints, 35. Diseases marked as autoimmune origin, 36. Common endpoint, 37. Demonstration endpoints, 38. ICD-10 main chapters, 39. Operation endpoints, 40. Other, not yet classified endpoints, 41. Miscellaneous, not yet classified endpoints, 42. Comorbidities of Asthma, 43. Comorbidities of Chronic obstructive pulmonary disease, 44. Comorbidities of Diabetes, 45. Comorbidities of Gastrointestinal endpoints, 46. Comorbidities of Interstitial lung disease endpoints, 47. Comorbidities of Neurological endpoints, 48. Comorbidities of Rheumatoid arthritis endpoints

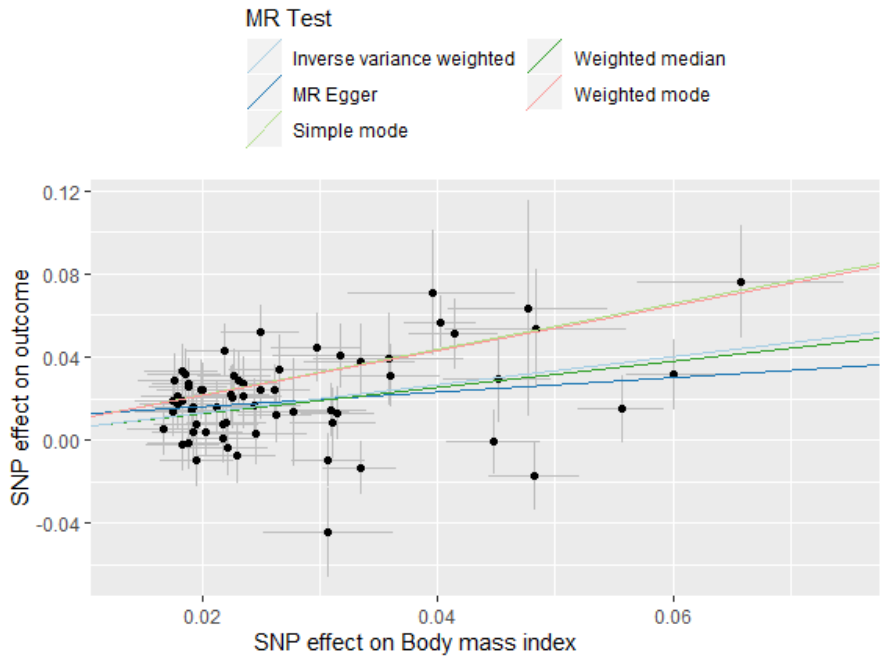
b) Phenome-wide association analysis (PheWAS) analysis concerning drug purchases. The x-axis shows phenotypes based on Anatomical Therapeutic Chemical – drug codes (ATC), while y-axis shows the significance Bonferroni corrected threshold $-\log_{10}(P)$ value which was defined as $0.05/69 = 7.25 \times 10^{-4}$. Drugs were coded as continuous variables and inverse normalized to ensure normal distribution for analysis. Other antidepressant=ATC N06AX, Hypnotics and sedatives=ATC N05C, Psycholeptics=ATC N05, Antidepressants=ATC N06A, Cycclopyrrolones=ATC N05CF, Antipsychotics=ATC N05A.

Figure 3.



Genetic correlations between obstructive sleep apnoea (OSA), body mass index (BMI) and previously known comorbidities using LD-score regression. Colour-scale represents the strength of the correlation. Correlations between OSA and other traits have been calculated with and without BMI-adjustment. CHD=coronary heart disease, T2D=type 2 diabetes, IRD=inflammatory rheumatic diseases.

Figure 4.



Formal Mendelian randomization (MR) suggesting a strong causal relationship between body mass index (BMI) and obstructive sleep apnoea (OSA) where BMI predicts OSA as an outcome.

Supplementary information

FinnGen samples were genotyped with Illumina and Affymetrix arrays (Thermo Fisher Scientific, Santa Clara, CA, USA). Genotype calls were made with GenCall and zCall algorithms for Illumina and AxiomGT1 algorithm for Affymetrix chip genotyping data. Genotyping data produced with previous chip platforms were lifted over to build version 38 (GRCh38/hg38) following the protocol described here: dx.doi.org/10.17504/protocols.io.nqtddwn. Samples with sex discrepancies, missingness (> 5%), excess heterozygosity (+-4SD) and non-Finnish ancestry were removed. Variants with high missingness (> 2%), deviation from Hardy–Weinberg equilibrium (P < 1e-6) and low minor allele count (MAC < 3) were removed. Pre-phasing of genotyped data was performed with Eagle 2.3.5 (https://data.broadinstitute.org/alkesgroup/Eagle/) with the default parameters, except the number of conditioning haplotypes was set to 20,000. Imputation was carried out by using the population-specific Sequencing Initiative Suomi (SISu) v3 imputation reference panel with Beagle 4.1 (version 08Jun17.d8b, https://faculty.washington.edu/browning/beagle/b4_1.html) as described in the following protocol: [dx.doi.org/10.17504/protocols.io.nmndc5e]. SISu v3 imputation reference panel was developed using the high-coverage (25–30x) whole-genome sequencing data generated at the Broad Institute of MIT and Harvard and at the McDonnell Genome Institute at Washington University, USA; and jointly processed at the Broad Institute. Variant callset was produced with Genomic Analysis Toolkit (GATK) HaplotypeCaller algorithm by following GATK best-practices for variant calling. Genotype-, sample- and variant-wise quality control was applied in an iterative manner by using the Hail framework v0.1 (https://Github.com/hail-is/hail/releases/tag/0.2.13, http://Doi.org/10.5281/zenodo.2646680). The resulting high-quality whole genome sequencing data for 3775 individuals were phased with Eagle 2.3.5 as described above. Post-imputation quality control involved excluding variants with INFO score < 0.7.

Supplementary Table 1. The main findings of the previous GWAS studies

1st author	Trait	Sample size	Original GWAS finding		Corresponding finding in FinnGen	Corresponding finding in FinnGen (BMI adjusted)
Tempaku F[13]	Obstructive sleep apnoea trait (AHI, change over time)	706	rs12415421	beta=0.28 p=3.4 x 10^{-8}	beta=0.032 p=0.38	beta=0.048 p=0.26
			rs4731117	beta=0.28 p=4.4 x 10^{-8}	beta=0.014 p=0.37	beta= 0.019 p=0.29
Chen H[14]	Obstructive sleep apnoea trait (AHI) NREM AHI in men	Total: 19,744 Men: 6,737	rs12936587	beta=0.12 p=1.7 × 10^{-8}	beta=0.0023 p=0.86	beta=0.0097 p=0.53
Cade B[15]	Obstructive sleep apnoea trait (apnoea hypopnea index, average respiratory event duration)	12,558	rs116791765	beta=-0.32 p=1. 9 x 10^{-8}	Not defined in the FinnGen data	Not defined in the FinnGen data
			rs35424364	beta=0.03 p=4.9 x 10^{-8}	beta=-0.014 p=0.51	beta=-0.0034 p=0.89

The main results of the previous genome-wide association studies (GWAS) and comparison to the FinnGen data findings. BMI=body mass index, AHI=apnoea-hypopnea index, NREM= non-rapid eye movement sleep.

Supplementary Table 2. The prospective epidemiological and disease-based cohorts, and hospital biobank samples in FinnGen Data Freeze 5

Cohort	N
Auria Biobank	22729
Biobank of Central Finland	1470
Biobank of Eastern Finland	6495
Blood Service Biobank	29047
Borealis Biobank	5441
Biobank Botnia	6691
Biobank Corogene	4753
Biobank FinHealth	5770
Helsinki Biobank	45481
Tampere Biobank	7430
Terveystalo Biobank	102
THL Biobank FinIPF	203
THL Biobank FINRISK 1992	4982
THL Biobank FINRISK 1997	7060
THL Biobank FINRISK 2002	7013
THL Biobank FINRISK 2007	5185
THL Biobank FINRISK 2012	5302
THL Biobank GENERISK	6955
THL Biobank Health 2000	6574
THL Biobank Health 2011	708
THL Biobank HHS	1981
THL Biobank Kuusamo	128
THL Biobank Migraine	7764
THL Biobank SUPER	8543
THL Biobank Diabetes	9405
THL Biobank Twins	11578
Total:	218792

THL= Finnish Institute for Health and Welfare Helsinki, Finland

Supplementary Table 3. ICD-codes for OSA and comorbidities

Phenotype endpoint	ICD-10	ICD-9	ICD-8
OSA	G47.3	3472A	
HYPERTENSION	I10-I13, I15, I67.4	4019X, 4029A, 4029B, 4039A, 4040A, 4059A, 4059B, 4372A, 4059X	400, 401, 402, 403, 404
T2D*	E11	250A	
CHD	I20.0, I21, I22	410, 4110	410, 411,0
STROKE	I61, I63, I64	431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436	431, 433, 434, 436
DEPRESSION	F32, F33	2961, 2968	790,20, 298,0
HYPOTHYROIDISM	E00, E01, E02, E03.0-E03.5, E03.8, E03.9	243, 2443, 2448, 2449, 2448A, 2448B	243, 244
ASTHMA	J45, J46	493	493
IRD	M05, J99.0, M06.0, M30-M35, M45, M08.0, L40.5	7140A, 7140B, 7141, 7100, 7431, 7101, 7340, 7200, 7143A, 6960A	712,10, 712,4, 712,0, 696,00
SNORING	R06.5		

By combining codes from different registries, we generate phenotype endpoints. Finnish national version for each International Statistical Classification of Diseases (ICD)-codes were used. These ICD-code criteria are all regular expressions for a hierarchical search. T2D* includes also medication purchases for Anatomical Therapeutic Chemical (ATC) code A10B, Blood glucose lowering drugs, excluding insulins. At least three separate purchases were required to ensure the correct diagnosis if diabetic medication was the only evidence. OSA=obstructive sleep apnoea, T2D=type 2 diabetes, CHD=coronary heart disease, IRD= inflammatory rheumatic diseases.

Supplementary Table 4. Characterization of five genome-wide significant OSA loci when snorers were excluded from controls

CHR	Position	RSID	REF	ALT	Nearest gene	Consequence	Fin.enr.	AF	AF cases	AF controls	INFO	OR [95% CI]	p-value	p-value BMIadj
16	53765595	rs9937053	G	A	FTO	intron	0.97	0.43	0.45	0.43	0.999	1.11[1.08-1.13]	1.8×10^{-16}	0.03
12	97359374	rs10507084	C	T	RMST/ NEDD1	intergenic	3.03	0.18	0.19	0.18	0.993	1.12[1.08-1.15]	2.4×10^{-11}	9.5×10^{-10}
10	12656440	rs185932673	C	T	CAMK1D	intron	0.55	0.0033	0.0051	0.0032	0.972	1.85[1.49-2.30]	3.6×10^{-8}	9.4×10^{-6}
9	125379530	rs4837016	G	A	GAPVD1	intergenic	1.12	0.47	0.45	0.47	0.995	0.93[0.91-0.95]	1.5×10^{-8}	2.0×10^{-4}
2	136234237	rs10928560	C	T	CXCR4	downstream	1.04	0.20	0.18	0.20	0.993	0.92[0.89-0.95]	4.7×10^{-8}	1.2×10^{-4}

All effect sizes and allele frequencies are reported in terms of alternate (ALT) allele.
The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population.
OSA=obstructive sleep apnoea, Genome Reference Consortium Human genome build 38 co-ordinates (GRCh38), CHR=chromosome, Fin.enr=Finnish enrichment is computed using The Genome Aggregation Database (Gnomad) data comparing Finnish to other European populations in the Gnomad data. AF=allele frequency, OR=odds ratio, CI=confidence interval, p-value BMIadj=p-value after body mass index (BMI) adjustment. FTO=Fat mass and obesity-associated protein, RMST=Rhabdomyosarcoma 2 associated transcript / NEDD1=NEDD1 gamma-tubulin ring complex targeting factor, CAMK1D=Calcium/calmodulin-dependent protein kinase ID, GAPVD1= GTPase activating protein and VPS9 Domains 1, CXCR4=C-X-C motif chemokine receptor 4.

Supplementary Table 5. Bonferroni corrected significant PheWAS findings of the five associated loci

Rs10928560		
Phenotype	**OR**	**pval**
Lactose intolerance	1.87[1.82-1.93]	2.74×10^{-12}
Lactose intolerance, other/unspecified	1.89[1.84-1.95]	3.20×10^{-11}
Sleep disorders (combined)	0.92[0.89-0.94]	6.53×10^{-9}
Internal derangement of knee	0.93[0.91-0.96]	4.97×10^{-6}
Episodal and paroxysmal disorders	0.95[0.93-0.98]	7.18×10^{-6}
Arthropathies	0.96[0.93-0.99]	1.32×10^{-5}
Neurological diseases	0.96[0.93-0.99]	1.68×10^{-5}
Rs4837016		
Phenotype	**OR**	**pval**
Sleep disorders (combined)	0.94[0.92-0.97]	8.51×10^{-7}
Rs185932673		
Phenotype	**OR**	**pval**
Sleep disorders (combined)	1.69[1.64-1.74]	3.81×10^{-7}
Rs10507084		
Phenotype	**OR**	**pval**
Sleep disorders (combined)	1.11[1.08-1.14]	1.56×10^{-11}
Episodal and paroxysmal disorders	1.05[1.02-1.08]	8.69×10^{-7}
Neurological diseases	1.04[1.01-1.08)	2.98×10^{-6}
Rs9937053		
Phenotype	**OR**	**pval**
Arthrosis related co-morbidities	1.28[1.24-1.32]	2.47×10^{-44}
Obesity	1.25[1.22-1.29]	4.14×10^{-41}
Obesity and other hyperalimentation	1.25[1.21-1.29]	9.05×10^{-41}
Other nutritional deficiencies	1.23[1.19-1.27]	1.69×10^{-36}
Obesity, other/unspecified	1.30[1.27-1.34]	7.12×10^{-33}
Other (not insulin) diabetes medications	1.14[1.10-1.17]	6.23×10^{-32}
Type 2 diabetes with other specified/multiple/unspecified complications	1.14[1.11-1.17]	1.84×10^{-28}
Type 2 diabetes	1.12[1.09-1.15]	5.67×10^{-28}
Type 2 diabetes, definitions combined, including primary healthcare diagnoses	1.13[1.10-1.16]	9.09×10^{-28}
Type 2 diabetes, strict (exclude DM1)	1.12[1.09-1.16]	6.65×10^{-27}
Obesity due to excess calories	1.24[1.20-1.27]	7.79×10^{-27}

Type 2 diabetes, definitions combined	1.12[1.09-1.16]	7.93×10^{-27}
Diabetes medication	1.11[1.08-1.15]	5.62×10^{-26}
Diabetes mellitus	1.11[1.07-1.14]	1.98×10^{-24}
Diabetes, insuline treatment (Kela reimbursement) (more controls excluded)	1.11[1.08-1.15]	4.48×10^{-24}
Diabetes, insuline treatment (Kela reimbursement)	1.11[1.08-1.15]	5.17×10^{-24}
Type 2 diabetes without complications	1.15[1.12-1.19]	2.36×10^{-23}
Other diabetes, wide definition	1.11[1.08-1.14]	5.29×10^{-23}
Diabetes, varying definitions	1.1[1.07-1.13]	6.46×10^{-23}
Type 2 diabetes, wide definition	1.14[1.10-1.17]	4.59×10^{-22}
Diabetes 1 & 2, IBD comorbidity	1.11[1.08-1.14]	8.54×10^{-18}
Gout-related comorbidities	1.08[1.05-1.12]	2.77×10^{-17}
Sleep disorders (combined)	1.1[1.07-1.13]	3.31×10^{-15}
Rheumatological diseases related comorbidities	1.06[1.03-1.09]	4.55×10^{-15}
Endocrine, nutritional and metabolic diseases	1.06[1.03-1.09]	7.25×10^{-14}
ILD Comorbidities, CVD and metabolic diseases	1.06[1.03-1.09]	3.23×10^{-12}
Comorbidities, CVD and metabolic diseases	1.07[1.04-1.1]	5.13×10^{-12}
Multimorbidity, for COPD	1.05[1.02-1.08]	2.01×10^{-11}
COPD comorbidities, CVD and metabolic diseases	1.06[1.03-1.09]	2.06×10^{-11}
Hypertensive diseases	1.06[1.03-1.09]	1.36×10^{-10}
Hypertensive diseases (excluding secondary)	1.06[1.03-1.09]	1.36×10^{-10}
Hypertension	1.06[1.03-1.09]	1.40×10^{-10}
Hypertension (no controls excluded)	1.06[1.03-1.09]	1.42×10^{-10}
ILD-related co-morbidities	1.05[1.02-1.08]	1.85×10^{-10}
Gonarthrosis	1.08[1.05-1.11]	3.34×10^{-10}
Artrhrosis, including primary healthcare diagnoses	1.06[1.03-1.09]	6.59×10^{-10}
Cardiovascular diseases (excluding rheumatic etc)	1.05[1.02-1.08]	6.81×10^{-10}
Arthrosis	1.06[1.03-1.09]	6.90×10^{-10}
Gonarthrosis [arthrosis of knee]	1.07[1.04-1.10]	3.75×10^{-9}
Gonarthrosis,primary	1.07[1.04-1.10]	4.25×10^{-9}
Hypertension, essential	1.06[1.03-1.09]	6.76×10^{-9}
COPD-associated comorbidities	1.04[1.01-1.07]	8.70×10^{-9}
Insulin medication	1.09[1.06-1.12]	3.84×10^{-8}

Asthma associated comorbidities	1.04[1.01-1.07]	7.11×10^{-8}
Primary gonarthrosis, bilateral	1.1[1.07-1.13]	1.29×10^{-7}
Obesity related asthma	1.13[1.10-1.16]	1.56×10^{-7}
Hypertension, essential (no controls excluded)	1.05[1.02-1.08]	1.87×10^{-7}
Gonarthrosis, primary, with knee surgery	1.09[1.06-1.13]	1.88×10^{-7}
Cardiovascular diseases	1.04[1.01-1.07]	3.50×10^{-7}
Antihypertensive medication - note that there are other indications	1.04[1.01-1.07]	4.04×10^{-7}
Neurological diseases	1.05[1.02-1.08]	7.20×10^{-7}
Arthropathies	1.04[1.01-1.07]	8.59×10^{-7}
Heart failure and antihypertensive medication	1.07[1.04-1.1]	1.30×10^{-6}
Carpal tunnel syndrome	1.07[1.04-1.11]	1.77×10^{-6}
Psoriatic arthropathies related comorbidities	1.05[1.02-1.08]	3.64×10^{-6}
Diabetes, several complications	1.1[1.06-1.13]	4.27×10^{-6}
Type 2 diabetes with coma	1.16[1.12-1.19]	5.56×10^{-6}
Extreme obesity with alveolar hypoventilation	1.36[1.32-1.4]	5.58×10^{-6}
Coxarthrosis,	1.07[1.04-1.11]	5.95×10^{-6}
All-cause Heart Failure	1.05[1.02-1.08]	6.56×10^{-6}
Hypertensive Heart Disease	1.12[1.09-1.15]	6.62×10^{-6}
Heart failure, not strict	1.05[1.02-1.08]	7.10×10^{-6}
Heart failure and BMI 25plus	1.05[1.02-1.08]	7.10×10^{-6}
Erysipelas	1.07[1.04-1.10]	8.41×10^{-6}
Type 2 diabetes with ophthalmic complications	1.15[1.12-1.19]	1.63×10^{-5}

Significance Bonferroni corrected threshold was defined at P = 0.05/2925 = 1.71. × 10^{-5}. OR=odds ratio [95% confidence interval]. KELA= Social Insurance Institution of Finland. DM1 = type 1 diabetes, IBD = inflammatory bowel disease, ILD = interstitial lung disease, COPD = chronic obstructive pulmonary disease.

Supplementary Table 6. Mendelian randomization suggesting a strong causal relationship between BMI and OSA.

Method	number of SNPs	beta	se	p-value
MR Egger	64	0.35	0.24	0.15
Weighted median	64	0.64	0.11	1.53×10^{-8}
Inverse variance weighted	64	0.67	0.08	8.32×10^{-16}
Simple mode	64	1.09	0.30	6.42×10^{-4}
Weighted mode	64	1.08	0.26	1.25×10^{-4}

Mendelian randomization (MR) analysis uses 64 independent body mass index (BMI) associated SNPs[33] as an instrumental variable to predict obstructive sleep apnoea (OSA).

Supplementary Table 7. Replication of the lead variants

RSID	G47.3 OSA UKBB	G47.3 OSA ANDIS	G47.3 OSA EGCUT	G47.3 OSA Combined
case/control	4471/403723	947/9829	4930/61056	10348/474608
rs9937053	OR=1.12 [1.07-1.17] $P=5.5 \times 10^{-7}$	OR=1.13 [1.03-1.24] P=0.01	OR=1.06 [1.02-1.11] $P=6.55 \times 10^{-3}$	OR=1.09 [1.06-1.12] $P=2.68 \times 10^{-9}$
rs10507084	OR=1.07 [0.98-1.17] P=0.15	OR=0.89 [0.73-1.06] P=0.18	OR=1.01 [0.94-1.09] P=0.80	OR=1.02 [0.96-1.08] P=0.51
rs185932673	OR=0.96 [0.73-1.26] P=0.74	Not defined in ANDIS	OR=1.09[0.84-1.43] P=0.52	OR=1.02[0.84-1.23] P=0.82
rs4837016	OR=0.97 [0.93-1.01] P=0.16	OR=0.87 [0.79-0.95] $P=4.6 \times 10^{-3}$	OR=0.98 [0.94-1.02] P=0.32	OR=0.96 [0.94-0.99] P=0.01
rs10928560	OR=1.00 [0.94-1.06] P=0.94	OR=1.01[0.90-1.15] P=0.38	OR=1.01 [0.96-1.07] P=0.60	OR=1.01 [0.97-1.05] P= 0.57

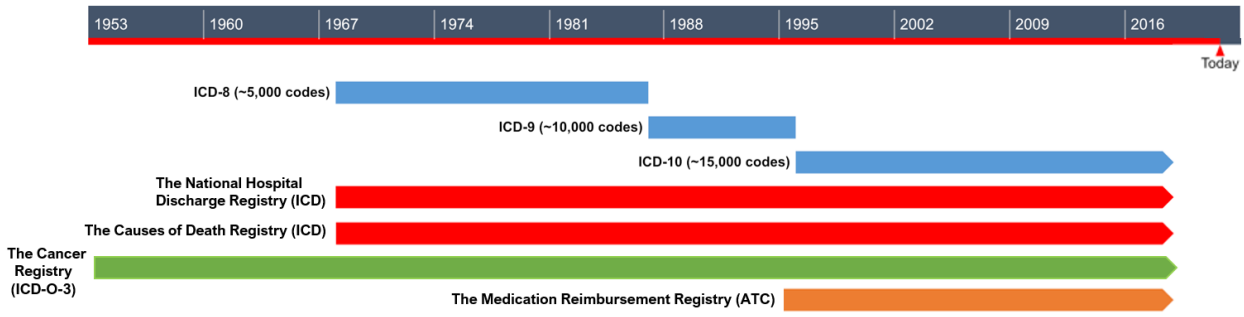
Inverse-variance weighted meta-analysis combining the results of the replication cohorts of the main FinnGen findings considering obstructive sleep apnoea (OSA). OR=odds ratio, [95% confidence interval], UKBB = UK Biobank, ANDIS = All New Diabetics in Scania, EGCUT = Estonian Genome Center - University of Tartu.

Supplementary Table 8.

	OSA's PRS			OSA's PRS BMI-adjusted		
	OR	CI	p-value	OR	CI	p-value
OSA_Q1	-	-	-	-	-	-
OSA_Q2	1.07	0.92-1.15	0.080	1.02	0.95-1.10	0.585
OSA_Q3	1.09	1.01-1.18	0.029	1.03	0.95-1.11	0.464
OSA_Q4	1.10	1.02-1.19	0.013	1.00	0.92-1.08	0.966
OSA_Q5	1.24	1.15-1.33	6.89×10^{-9}	1.11	1.03-1.20	4.70×10^{-3}

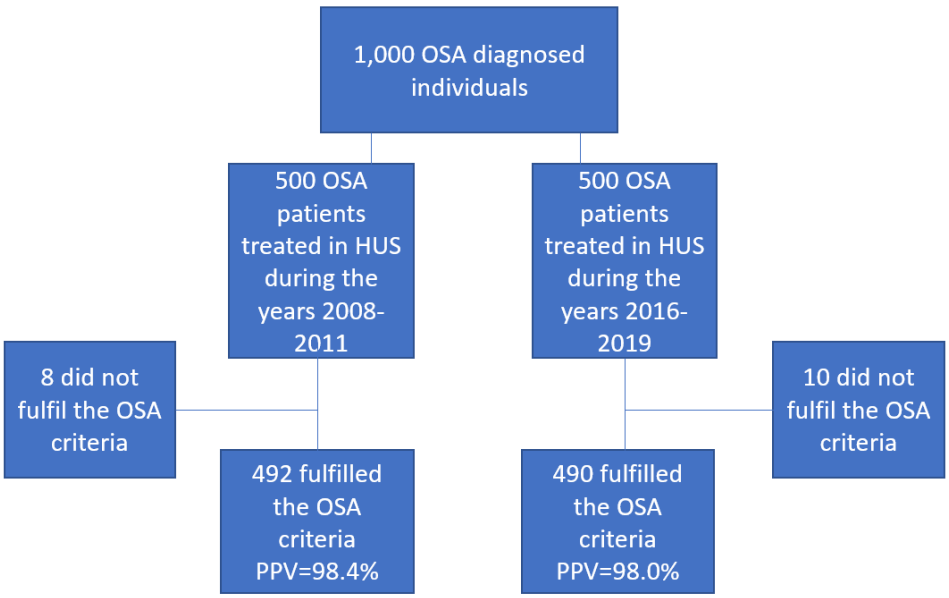
OSA's polygenic risk score (PRS) predicts obstructive sleep apnoea (OSA) in the UKBB data with and without BMI-adjustment. The OSA's PRS was stratified into quintiles and OSA_Q5 is the highest quintile. OR=odds ratio, CI = 95% confidence interval.

Supplementary Figure 1.



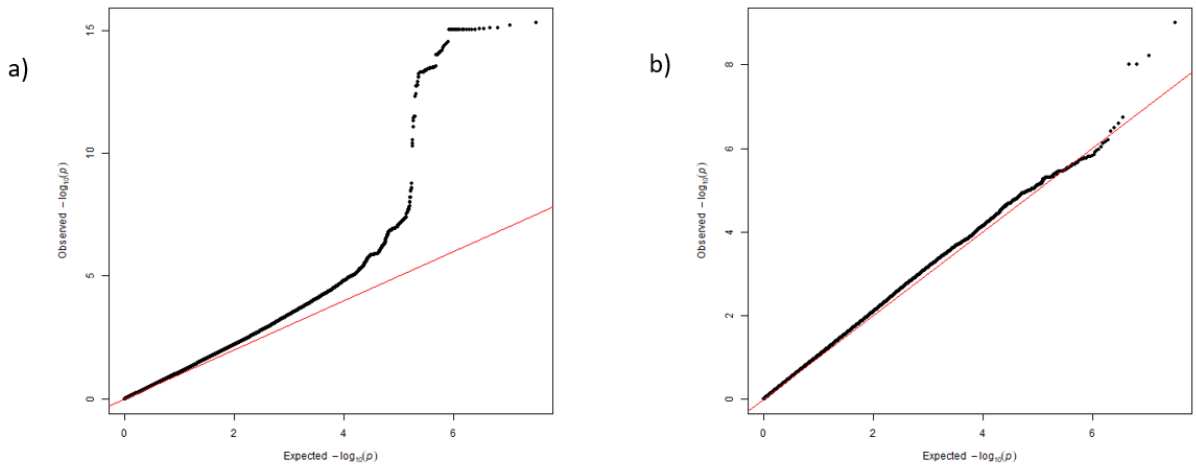
Nationwide registries combined by FinnGen. X-axel represents when a certain registry collection has started. Each arrow on Y-axis shows the origin of the ICD or ATC-code. ICD=International Statistical Classification of Diseases, ICD-O-3=International Classification of Diseases for Oncology, 3rd Edition, ATC=Anatomical Therapeutic Chemical Classification System.

Supplementary Figure 2.



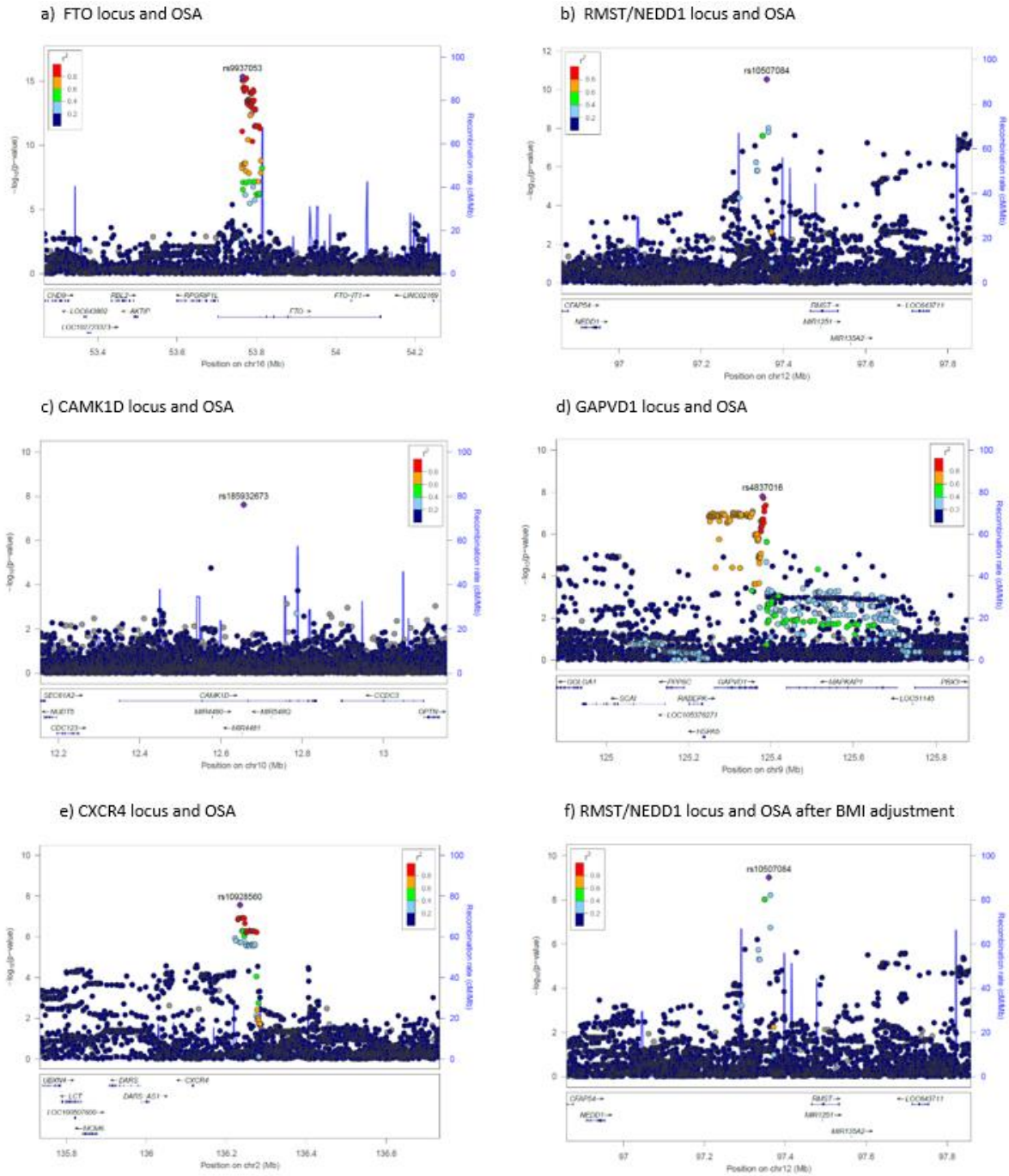
OSA diagnosis was validated using HUS's Hospital Discharge Registry collecting information of 1,000 patients and compared the registry data to the patient medical records. OSA diagnosis has a validity showing over 98% positive predictive value (PPV) when using International International Classification criteria for Sleep Disorders for OSA [23]. OSA=obstructive sleep apnoea, AHI=apnoea-hypopnea-index, PPV=positive predictive value.

Supplementary Figure 3.



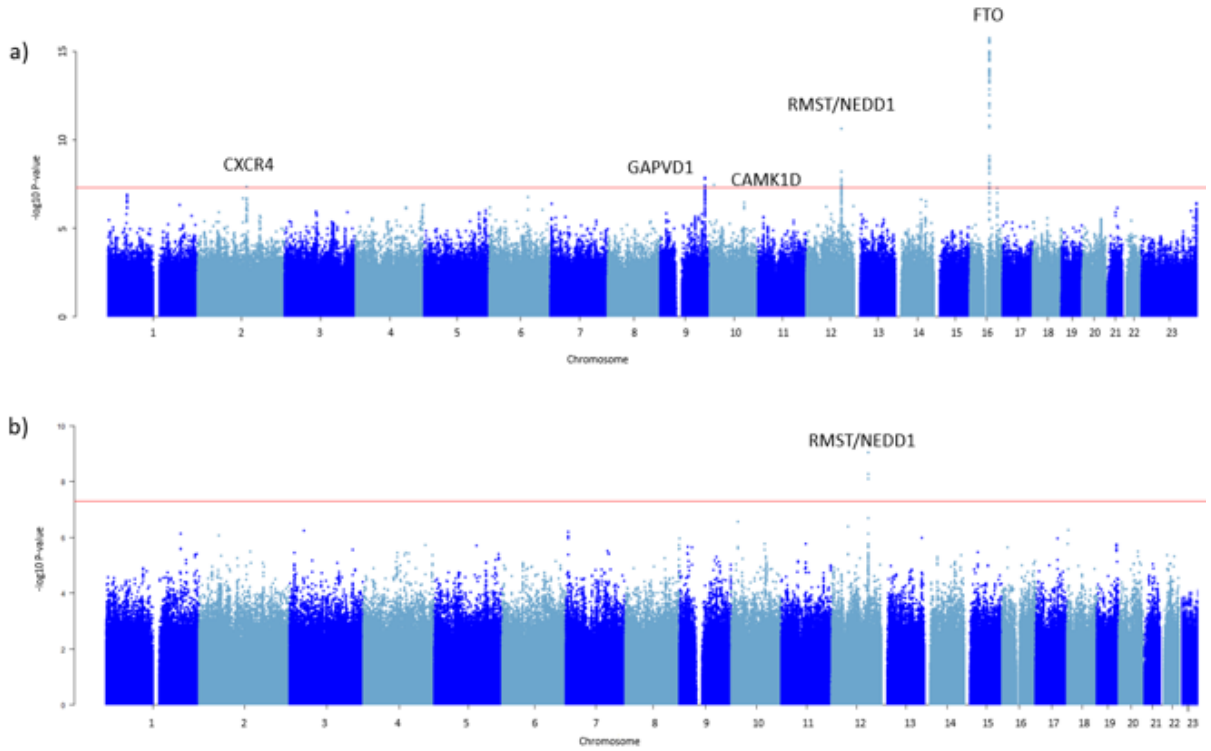
Quantile-Quantile (QQ) plot from the association analysis concerning a) obstructive sleep apnoea (OSA), λ = 1.12, b) body mass index (BMI) adjusted OSA, λ = 1.07. The observed *P* values for each single nucleotide polymorphism (SNP) are sorted from largest to smallest and plotted against expected values from a theoretical χ^2-distribution.

Supplementary Figure 4.



Regional plots of 5 associations. Locus Zoom plots a-f show associated P-values on the $-\log_{10}$ scale on the vertical axis, and the chromosomal position along the horizontal axis. Purple diamonds indicate SNP at each locus with the strongest associated evidence. LD (r^2 values) between the lead SNP and the other SNPs are indicated by colour. *FTO*=Fat mass and obesity-associated protein, *RMST*=Rhabdomyosarcoma 2 associated transcript / *NEDD1*=NEDD1 gamma-tubulin ring complex targeting factor, *CAMK1D*=Calcium/calmodulin-dependent protein kinase ID, *GAPVD1*= GTPase activating protein and VPS9 domains 1, *CXCR4*=C-X-C Motif chemokine receptor 4.

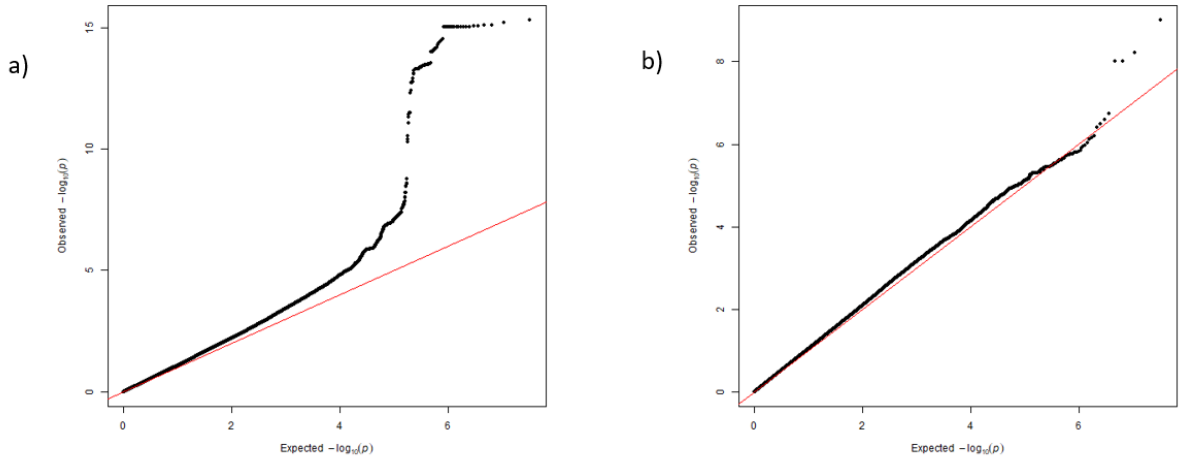
Supplementary Figure 5.



a) Manhattan plot for obstructive sleep apnoea (OSA) after excluding snorers from the control group with 16 761 OSA cases and 197 797 controls. For each genetic variant, the x-axis shows chromosomal position, while y-axis shows the $-\log_{10}$(P) value. The horizontal line indicates the genome-wide significance threshold of $P = 5 \times 10^{-8}$. Five genetic loci were identified at the genome-wide significance level. *CXCR4*=C-X-C motif chemokine receptor 4, *GAPVD1*= GTPase activating protein and VPS9 Domains 1, *CAMK1D*=Calcium/calmodulin-dependent protein kinase ID, *RMST*=Rhabdomyosarcoma 2 associated transcript / *NEDD1*=NEDD1 gamma-tubulin ring complex targeting factor, *FTO*=Fat mass and obesity-associated protein

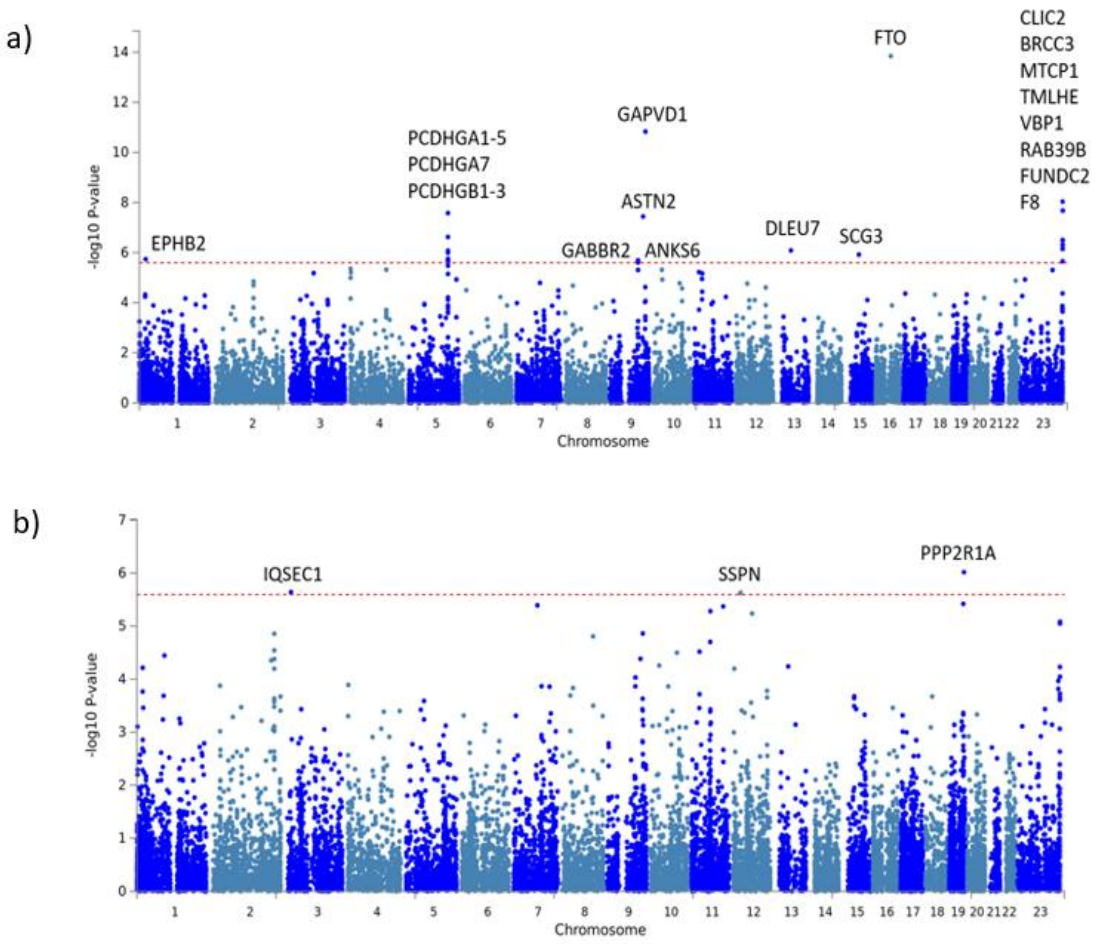
b) Manhattan plot for obstructive OSA after body mass index (BMI) adjustment, snorers excluded with 12 759 OSA cases and 144 583 controls. For each genetic variant, the x-axis shows chromosomal position, while y-axis shows the $-\log_{10}$(P) value. The horizontal line indicates the genome-wide significance threshold of $P = 5 \times 10^{-8}$. One genetic locus was identified at the genome-wide significance level. *RMST*=Rhabdomyosarcoma 2 associated transcript / *NEDD1*=NEDD1 gamma-tubulin ring complex targeting factor

Supplementary Figure 6.



Quantile-Quantile (QQ) plot from the association analysis concerning a) obstructive sleep apnoea (OSA) after excluding snorers from the control group, λ = 1.12, b) body mass index (BMI) adjusted OSA after excluding snorers from the control group, λ = 1.07. The observed *P* values for each single nucleotide polymorphism (SNP) are sorted from largest to smallest and plotted against expected values from a theoretical χ^2-distribution.

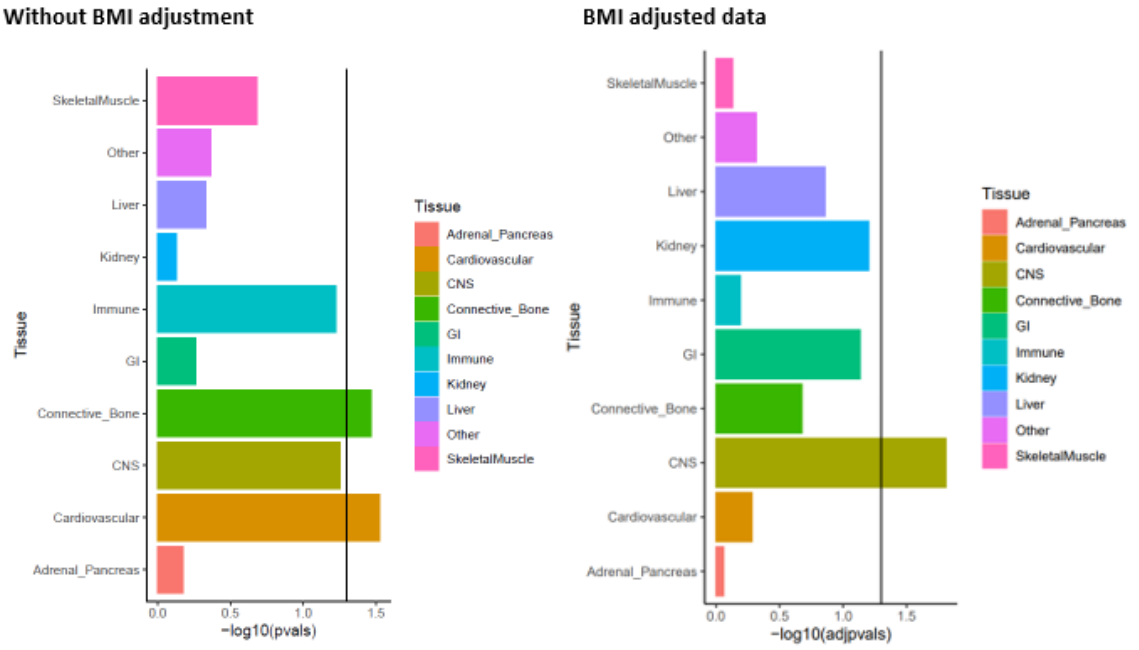
Supplementary Figure 7.



a) Manhattan plot of the gene-based test as computed by MAGMA. Single nucleotide polymorphisms (SNP)s were mapped to 19,651 protein coding genes. Significance Bonferroni corrected threshold was defined at P = 0.05/19,651 = 2.54 $\times 10^{-6}$. Primarily the same genes were identified as in single variant associations. For each annotated gene x-axis shows the chromosomal position while y-axis shows the −log10(P) value. *EPHB2*=Ephrin type-B receptor 2, *PCDHGA*=Protocadherin gamma subfamily A, *PCDHGB*=Protocadherin gamma subfamily B, *GAPVD1*=GTPase activating protein and VPS9 domains 1, *ASTN2*= Astrotactin 2, *GABBR2*=Gamma-aminobutyric acid type A receptor subunit rho2, *ANKS6*=Ankyrin repeat and sterile alpha motif domain containing 6, *DLEU7*=Deleted in lymphocytic leukemia 7, *SCG3*=Secretogranin III, *FTO*=Fat mass and obesity-associated protein, *CLIC2*=Chloride intracellular channel 2, *BRCC3*=BRCA1/BRCA2-containing complex subunit 3, *MTCP1*=Mature T cell proliferation 1, *TMLHE*=Trimethyllysine hydroxylase, epsilon, *VBP1*= VHL binding protein 1, *RAB39B*=RAB39B, member RAS oncogene family, *FUNDC2*=FUN14 domain containing 2 and *F8*= Coagulation factor VIII.

b) Manhattan plot of the gene-based test as computed by MAGMA using body mass index (BMI) adjusted GWAS data. Single nucleotide polymorphisms (SNP)s were mapped to 19,651 protein coding genes. Significance Bonferroni corrected threshold was defined at P = 0.05/19,651 = 2.54 × 10^{-6}. For each annotated gene x-axis shows the chromosomal position while y-axis shows the −log10(P) value. *IQSEC1*= IQ motif and sec7 domain arfGEF 1, *SSPN*=Sarcospan, *PPP2R1A*= Protein phosphatase 2 scaffold subunit aalpha.

Supplementary Figure 8.



Tissue specific enrichment analysis. Stratified LD score regression based on 1000 Genomes Project phase 1. LD was calculated by each tissue types. Each bar represents -log10 p-value for enrichment and computed for obstructive sleep apnoea (OSA) and body mass index (BMI) adjusted OSA. CNS=central nervous system, GI=gastrointestinal.