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

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Abstract

There is currently only limited understanding of the genetic aetiology of obstructive sleep apnoea (OSA). The aim of our study is to identify 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 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 utilised 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: 3472) 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. To our knowledge, this is the first population-level longitudinal GWAS study regarding OSA.

Materials and Methods

General information

First, using the FinnGen data, a GWAS was calculated for 2,925 ICD-code based phenotype definitions including OSA. Second, 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].

Study sample in FinnGen

FinnGen (https://www.finngen.fi/en) is a large biobank study that aims to genotype 500,000 Finns and combine this data with longitudinal registry data including The National Hospital Discharge Registry, Causes of Death Registry and medication reimbursement registries, all these using unique national personal identification codes. FinnGen includes prospective and retrospective epidemiological and disease-based cohorts as well as hospital biobank samples. The data consists of 218,792 individuals until the spring of 2020. FinnGen's genotyping and imputation protocol is 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 disturbance index (RDI)≥5/hour. By combining ICD-codes from different registries, we generated disease endpoints. **Supplementary Table 2** 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.

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.

GWAS

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[23]. Analyses were adjusted for age, 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. The merged data consisted 10,348 OSA cases and 474,608 controls.

The GWAS using UKBB data was calculated using SAIGE[23] . 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 age, 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 age, 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[24]. 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[25]. To restrict to a set of common, well-imputed variants, we retained only those SNPs in the HapMap 3 reference panel[26].

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 sleep duration, sleepiness[27] and chronotype[28]. 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[29]. 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[30, 31].

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

PRS for BMI was calculated using summary statistics for 996,250 variants[32]. The posterior effect sizes were calculated with PRS-CS utilising method[33] 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[32]. 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)[34].

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[35]. This analysis includes a gene-based test to detect significant SNPs associated with OSA using FinnGen OSA summary statistics.

Results

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.

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** and regional associations in **Supplementary Figure 1**. 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 = 2.8×10^{-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 = 2.4×10^{-8}. In chromosome 9, the lead variant was rs4837016 near GTPase activating protein and VPS9 Domains 1 (*GAPVD1)*, P = 1.5×10^{-8} and in chromosome 2, the lead variant rs10928560 was near C-X-C motif chemokine receptor 4 (*CXCR4)*, P = 2.8 x 10^{-8}. Four out of five of these OSA associated lead variants have also been previously associated with BMI ($p<0.01$)[36-38], 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 (**Figure 1b** and Table 2), ($OR_{unadjusted}$ = 1.11[1.08-1.15], P=2.8×10^{-11} vs. $OR_{BMI\ adjusted}$ = 1.12[1.08-1.17], P=9.7×10^{-10}) suggesting BMI-independent mechanisms for rs10507084 in OSA predisposition.

As an exploratory analysis we used MAGMA. This tool annotates FinnGen OSA summary statistics based on 18 biological data repositories and tools[35]. 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 2a)**. Similarly, the gene-based test for BMI-adjusted OSA revealed three further associated genes (**Supplementary Figure 2b)**.

We performed a phenome-wide association analysis (PheWAS) using the 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**). In addition, there was a strong correlation between rs10507084 and the use of antidepressants (OR=1.013[1.007-1.019], P=4.4×10^{-6}) (**Figure 2b**).

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)**.

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 sleep efficiency[13] rg = -0.31, [-0.44 - -0.17], $P=9.80 \times 10^{-6}$) and this was reflected with higher genetic correlation with daytime sleepiness[29] (rg = 0.44, [0.33-0.54], $P=1.27 \times 10^{-15}$). These associations remained significant also after BMI adjustment (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[30, 31] 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 ($P < 0.05$) (**Supplementary Figure 3)**.

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[32]. 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[32] 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 3)**.

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 4)**.

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[39, 40].

Third, we also identified a strong association near *RMST/NEDD1*, which was specific for OSA independent of BMI. The lead SNP associated with antidepressant purchases which may imply that daytime sleepiness caused by OSA together with sleep disturbances may lead to depression and increased antidepressant usage. This is in line with the 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 novel genetic loci and OSA. 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 confirm that OSA is a heterogenic disease with several phenotypes and that implies different approach to OSA management.

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.

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).

Author contributions

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, 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) and THL Biobank data may be accessed through THL Biobank (https://thl.fi/en/web/thl-biobank).

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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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]	$< 2.00 \times 10^{-16}$

Body mass index (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

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

CHR	Position	RSID	Nearest gene	Consequence	Fin.enr.	AF	AF cases	AF controls	OR	p-value	p-value BMIadj
16	53765595	rs9937053	FTO	intron	0.97	0.43	0.45	0.43	1.11[1.08-1.13]	4.3×10^{-16}	0.04
12	97359374	rs10507084	RMST/NEDD1	intergenic	3.03	0.18	0.19	0.18	1.11[1.08-1.15]	2.8×10^{-11}	9.7×10^{-10}
10	12656440	rs185932673	CAMK1D	intron	0.55	0.0033	0.0051	0.0032	1.87[1.50-2.33]	2.4×10^{-8}	9.3×10^{-6}
9	125379530	rs4837016	GAPVD1	intergenic	1.12	0.47	0.45	0.47	0.93[0.91-0.95]	1.5×10^{-8}	2.2×10^{-4}
2	136234237	rs10928560	CXCR4	downstream	1.04	0.20	0.18	0.20	0.92[0.89-0.94]	2.8×10^{-8}	8.5×10^{-5}

The finding of rs185932673 should be interpreted cautiously as the variant is rare in the Finnish population. CHR=chromosome, Fin.enr=Finnish enrichment compared to other European ancestry, AF=allele frequency, OR=odds ratio, [95% confidence interval], p-value BMIadj=p-value after BMI adjustment

Table 3. Genetic correlations between OSA and other sleep traits

	Sleepiness	Sleep duration	Chronotype	Sleep efficiency
OSA	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 = 0.42 [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

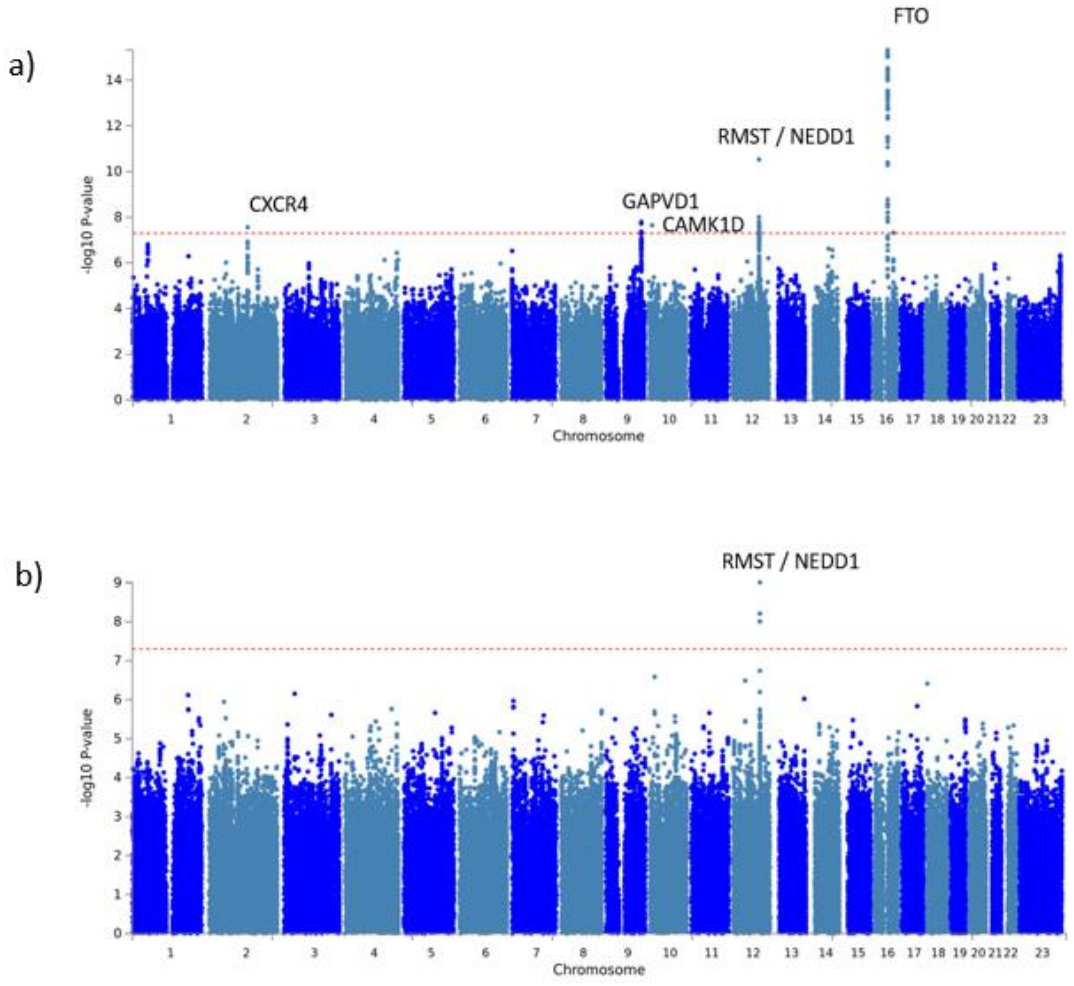
Summary statistics for sleep traits that were used to calculate the genetic correlations were obtained in previous genome-wide association study (GWAS) from the UK Biobank (UKBB). OSA=obstructive sleep apnoea, BMI=body mass index.

Table 4. BMI's polygenic risk score predicts OSA

BMI_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 as a predictor of OSA. The BMI's polygenic risk score was stratified into quintiles and BMI_Q5 is the highest quintile. OSA=obstructive sleep apnoea, OR=odds ratio, CI = 95% confidence interval.

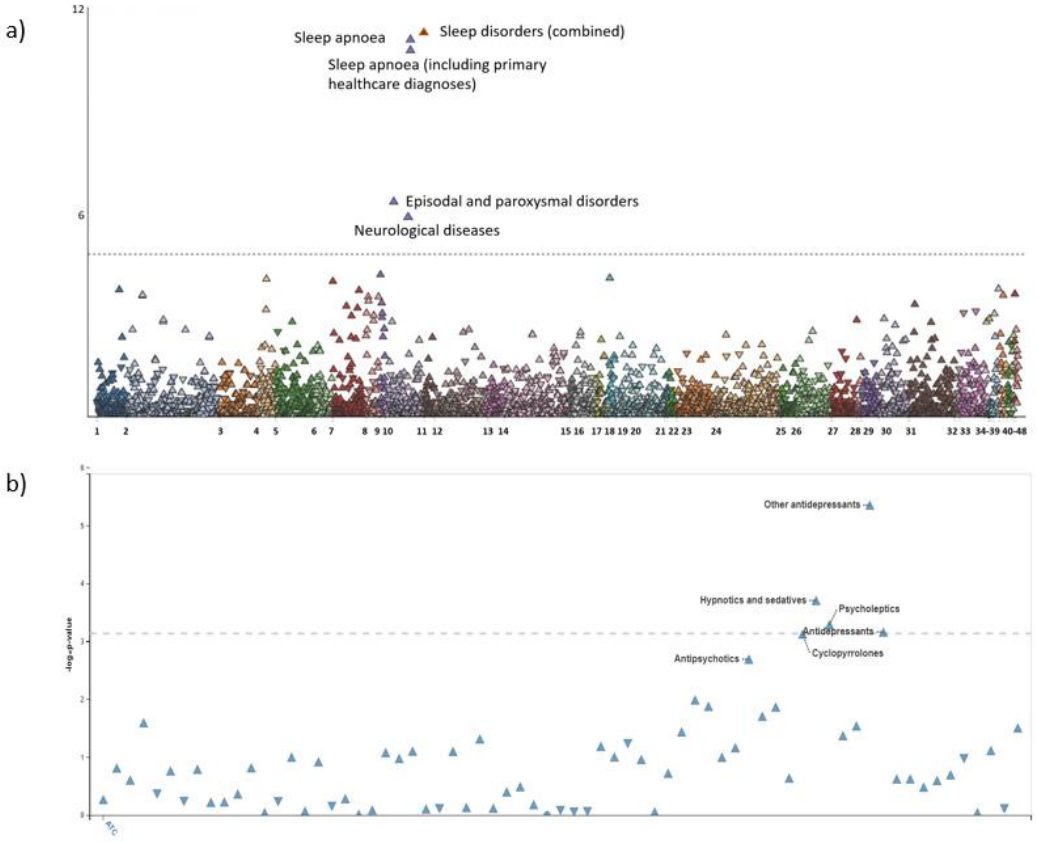
Figure 1



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

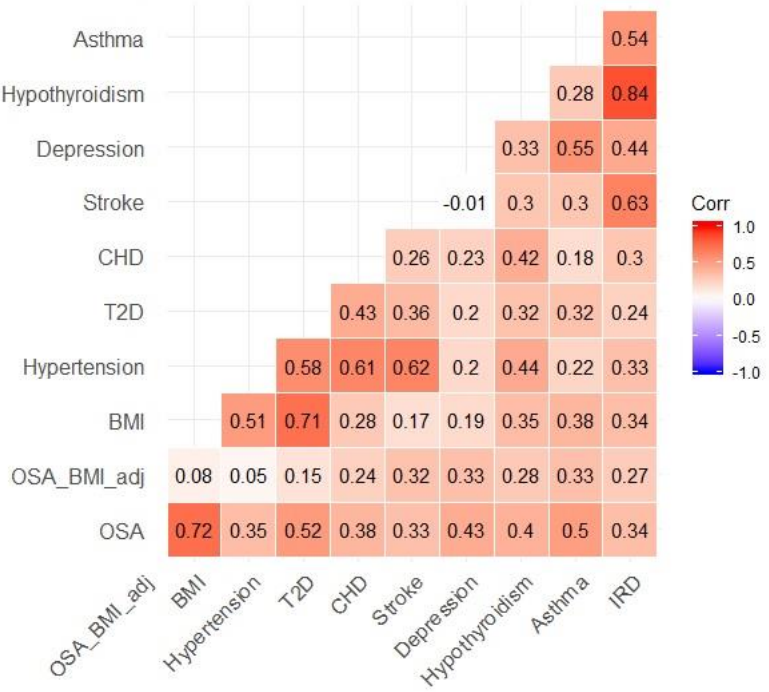
b) Manhattan plot for obstructive sleep apnoea (OSA) after body mass index (BMI) adjustment including 12 759 OSA cases and 146 972 controls. For each genetic variant, the x-axis shows chromosomal position, while y-axis shows the $-\log_{10}$(P) value.
The horizontal line indicates the genome-wide significance 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.



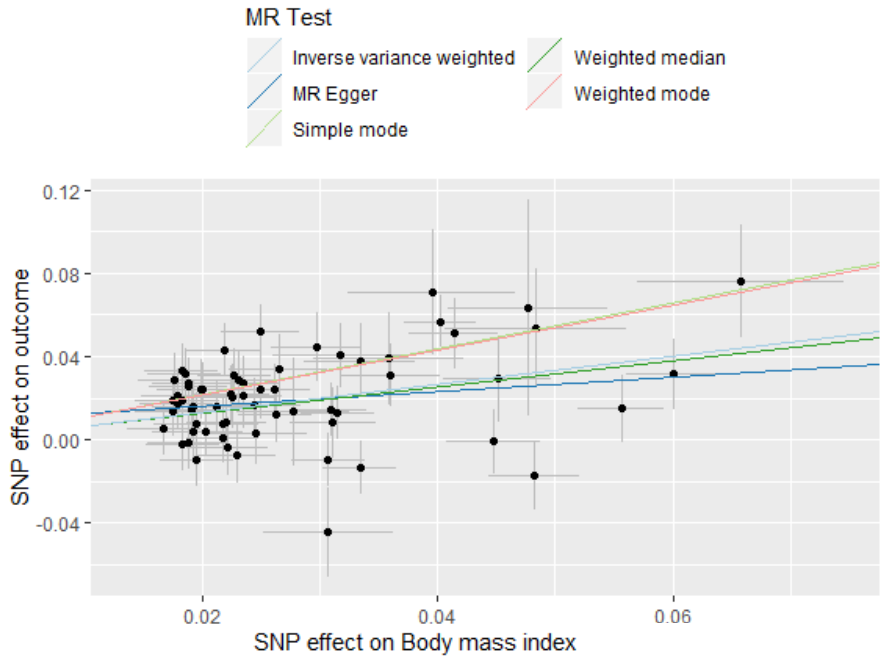
a) Phenome-wide association analysis (PheWAS) associations after body mass index (BMI) adjustment between rs10507084 and 2,925 disease endpoints. Significance Bonferroni corrected threshold was defined at $P = 0.05/2925 = 1.71 \times 10^{-5}$. Associated P-values on the $-\log_{10}$ scale on the vertical axis and 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 $0.05/69 = 7.25 \times 10^{-4}$.

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.