

Sleep apnoea is a risk factor for severe COVID-19

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ABSTRACT

Background Obstructive sleep apnoea (OSA) is associated with higher body mass index (BMI), diabetes, older age and male gender, which are all risk factors for severe COVID-19.

We aimed to study if OSA is an independent risk factor for COVID-19 infection or for severe COVID-19.

Methods OSA diagnosis and COVID-19 infection were extracted from the hospital discharge, causes of death and infectious diseases registries in individuals who participated in the FinnGen study (n=260 405). Severe COVID-19 was defined as COVID-19 requiring hospitalisation. Multivariate logistic regression model was used to examine association. Comorbidities for either COVID-19 or OSA were selected as covariates. We performed a meta-analysis with previous studies.

Results We identified 445 individuals with COVID-19, and 38 (8.5%) of them with OSA of whom 19 out of 91 (20.9%) were hospitalised. OSA associated with COVID-19 hospitalisation independent from age, sex, BMI and comorbidities (p-unadjusted=5.13×10⁻⁵, OR-adjusted=2.93 (95% CI 1.02 to 8.39), p-adjusted=0.045). OSA was not associated with the risk of contracting COVID-19 (p=0.25). A meta-analysis of OSA and severe COVID-19 showed association across 15 835 COVID-19 positive controls, and n=1294 patients with OSA with severe COVID-19 (OR=2.37 (95% 1.14 to 4.95), p=0.021).

Conclusion Risk for contracting COVID-19 was the same for patients with OSA and those without OSA. In contrast, among COVID-19 positive patients, OSA was associated with higher risk for hospitalisation. Our findings are in line with earlier works and suggest OSA as an independent risk factor for severe COVID-19.

INTRODUCTION

COVID-19 is a severe respiratory disease caused by SARS-CoV-2 virus infection. A subset of patients face hospitalisation, respiratory failure or even death. The severity of COVID-19 is highly age dependent but also evidenced by the number of individuals that receive hospital and intensive care treatment.^{1 2} Finland has had a relatively small number of COVID-19 cases in the spring of 2020. However, approximately 1%–6% of those tested positive for the virus in Finland received hospital or intensive care

Key messages

- Is obstructive sleep apnoea (OSA) an independent risk factor for severe COVID-19?
- Patients with OSA have a higher risk to be hospitalised when affected by COVID-19 than non-OSA individuals.
- In assessment of patients with suspected or confirmed COVID-19 infection, OSA should be recognised as one of the comorbidity risk factors for developing a severe form of the disease and patients with OSA with suspected or confirmed COVID-19 infection should be monitored closely.

treatment.³ These percentages are similar to those reported globally.^{1 2} Severe COVID-19 outcome is mediated primarily through respiratory distress.^{4 5} Risk factors for severe COVID-19 have been identified as older age, male sex, obesity, diabetes, cardiovascular disease and poor lung function.⁶ In addition, other respiratory diseases have been listed as potential contributors for COVID-19 severity. Indeed, there are studies suggesting that obstructive sleep apnoea (OSA) may be a risk factor for severe COVID-19.^{7–12} Such risk would have substantial effect as OSA is a common disease affecting at least 8% of the population with higher prevalence in older age groups reaching to over 20% in individuals over 60 years of age.¹³ The disease aetiology of OSA is characterised by repetitive apnoea-hypopnea cycles during sleep causing shortness of breath which can be associated with sometime severe oxygen desaturation, sleep disruption and increase in systolic and diastolic blood pressure.¹⁴ The known risk factors for OSA include obesity, high age, male sex and craniofacial and upper airway structure variations and anomalies.¹⁵ Similarly, OSA is associated with increased risk for cardiovascular mortality, especially if not treated. Finally, it is essential to note that treatment exists for the majority of patients with OSA so that night-time breathing can be



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supported by continuous positive airway pressure (CPAP) or mandibular advancement device (MAD). This treatment substantially decreases the risk for cardiovascular events and death.^{16 17} Recently, questions have been raised about whether OSA constitutes a high risk for COVID-19 infection or COVID-19 hospitalisation.

We specifically aimed at evaluating if OSA associates with the risk for severe COVID-19 infection independently of other potential risk factors including age, sex, body mass index (BMI), hypertension, diabetes (including type 1 and type 2 diabetes), coronary heart disease (CHD) asthma and chronic obstructive pulmonary disease (COPD), and also whether the risk for contracting COVID-19 is elevated among patients with OSA.

METHODS

Study sample set

FinnGen (<https://www.finnngen.fi/en>) is a large biobank study that aims to genotype 500 000 Finns including two types of biobank collections: (1) population-based epidemiological cohorts and (2) mostly disease-based collections in all University Hospitals in Finland (online supplemental table 1). FinnGen combines these data with longitudinal registry data that record healthcare events over the entire lifespan including the National Hospital Discharge Registry (available from 1968), the Causes of Death Registry (available from 1969), the National Infectious Diseases Registry (available from 1995) and the Medication Reimbursement Registry (available from 1995), all these using unique national personal identification codes, for the whole population of Finland for lifetime information since the start of each registry. FinnGen has harmonised data from these registries of 260 405 Finnish individuals. Registry data were available from the beginning of the registry until 31 December 2018 and Infectious Registry data until 30 October 2020. In

addition, demographic and anthropometric data of BMI and smoking status are included.

The information of COVID-19 positive individuals was collected from The National Infectious Diseases Registry and the infection was verified by laboratory test using PCR testing. Data for risk factors, comorbidities and OSA diagnosis were obtained from the National Hospital Discharge Registry, the Causes of Death Registry and the Medication Reimbursement Registry, where the clinical endpoints had been generated using International Classification of Diseases codes for OSA, hypertension, diabetes (including type 1 and type 2 diabetes), CHD, asthma and COPD (online supplemental table 2).

Treatment information concerning OSA was collected from the patient records of Heart and Lung Center or Department of Oral and Maxillofacial Diseases, Helsinki University Hospital (HUU), Finland.

The diagnosis in this special healthcare derived data for OSA is typically based on the following criteria: subjective symptoms, clinical examination and sleep registration applying Apnoea-Hypopnea Index (AHI) ≥ 5 per hour for polysomnography or respiratory event index ≥ 5 per hour for out-of-centre sleep study.

For the meta-analysis, estimates were collected from the previous studies^{7–9} concerning the role of OSA on COVID-19 hospitalisation.

Statistical methods

Differences in baseline demographics and clinical characteristics were tested using on χ^2 tests. Fisher's exact test was used if the expected cell size was ≤ 5 . For continuous variables, Student's t-test was used. We considered $p < 0.05$ as statistically significant, and all tests were two sided (tables 1 and 2). All p values based on forementioned tests are Bonferroni corrected. Logistic regression was used to calculate OR between hospitalised and non-hospitalised groups. Model 1 was adjusted for age and

Table 1 Comparison of the baseline characteristics among COVID-19 positive individuals

	All n=445	Non-hospitalised n=354	Hospitalised n=91	P _{unadjusted}
Age (mean in years, SD)	52.7 (17.4)	49.3 (16.3)	65.9 (14.8)	1.06×10^{-15} *
Sex (male) (N, %)	166 (37.3)	133 (37.6)	33 (36.3)	1
OSA (N, %)	38 (8.5)	19 (5.4)	19 (20.9)	5.13×10^{-5} *
BMI (mean kg/m ² , SD)	27.13 (5.44)	26.54 (5.20)	29.25 (5.78)	0.014*
Hypertension (N, %)	79 (17.8)	40 (11.3)	39 (42.9)	5.03×10^{-11} *
Diabetes (N, %)	46 (10.3)	23 (6.5)	23 (25.3)	3.45×10^{-6} *
CHD (N, %)	21 (4.7)	9 (2.5)	12 (13.2)	5.20×10^{-4} *
Asthma/COPD	54 (12.1)	40 (11.3)	14 (15.4)	1

Differences and associations between non-hospitalised and hospitalised COVID-19 positive individuals. Baseline demographics and clinical characteristics P_{unadjusted} values were based on χ^2 test. For continuous variables, we used Student's t-test. BMI was measured of 264 participants including 206 non-hospitalised and 58 hospitalised individuals.

*Statistically significant.

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnoea.

Table 2 Description of patients with COVID-19 with or without obstructive sleep apnoea (OSA) and a comparison between non-hospitalised and hospitalised patients with OSA

	Non-OSA n=407	OSA n=38	P value	OSA Non-hospitalised n=19	OSA hospitalised n=19	P value
Age (mean in years, SD)	51.9 (17.5)	61.3 (12.9)	$5.60 \times 10^{-4*}$	56.3 (11.0)	66.3 (12.9)	0.057
Sex (male) (N, %)	147 (36.1)	19 (50.0)	0.645	12 (63.2)	7 (36.8)	0.776
BMI (mean kg/m ² , SD)	26.71 (5.27)	31.15 (5.56)	$3.38 \times 10^{-3*}$	30.91 (5.58)	31.37 (5.77)	1
Comorbidities or outcomes (N, %)	118 (29.0)	24 (63.2)	$1.74 \times 10^{-4*}$	12 (63.2)	12 (63.2)	1
Hospitalised (N, %)	72 (17.7)	19 (50.0)	$3.21 \times 10^{-5*}$			

Differences between non-OSA versus OSA individuals and non-hospitalised patients with OSA versus hospitalised patients with OSA among COVID-19-positive individuals. 7/19 patients with hospitalisation had OSA diagnosis but did not have any other disease comorbidities P values were based on χ^2 test. Fisher's exact test was used if the sample size was ≤ 5 . For continuous variables, we used Student's t-test. BMI was measured of 264 participants including 239 non-OSA and 25 OSA individuals. Comorbidities and outcomes=hypertension, diabetes, coronary heart disease, asthma, chronic obstructive pulmonary disease.

*Statistically significant.

BMI, body mass index.

sex. Model 2 was adjusted for BMI in addition to covariates of Model 1. Model 3 was adjusted for BMI, hypertension, diabetes, CHD, asthma and COPD in addition to covariates of Model 1 (table 3) and similarly between COVID-19-positive and non-COVID-19 groups.

Our results and previous findings from the corresponding studies⁷⁻⁹ were pooled together forming a meta-analysis using restricted maximum likelihood estimation of the random effect model in the Metagen R. The merged data consisted of 15 835 COVID-19 positive individuals including 1294 patients with OSA.

The R statistical package (V.4.0.2) was used for all analyses (www.r-project.org)

Patient and public involvement

Patients and public were not involved in the designing process of this study. The patients will not be informed individually of the study results otherwise than through possible media coverage.

RESULTS

The data included 260 405 Finnish individuals from FinnGen Data Freeze 6 with 445 patients with COVID-19.

Table 3 ORs associating obstructive sleep apnoea with severe COVID-19

	OR	95% CI	P value
Model 1	3.85	1.82 to 8.13	$4.13 \times 10^{-4*}$
Model 2	3.45	1.27 to 9.35	0.016*
Model 3	2.93	1.02 to 8.39	0.045*

Model 1 is adjusted for age and sex. Model 2 is adjusted for body mass index (BMI) in addition to covariates of Model 1. Model 3 is adjusted for BMI, hypertension, diabetes, coronary heart disease, asthma and chronic obstructive pulmonary disease in addition to covariates of model 1.

*Statistically significant.

Of them, 38 (8.5%) had OSA. Severe COVID-19 cases (n=91) included 19 (20.9%) patients with OSA. Severe COVID-19 was defined as an infection requiring hospitalisation.

Of all patients with COVID-19 diagnosis (n=445, 37.3% male, mean age 52.7 years) 38 patients also had OSA diagnosis (8.5%, 50.0% male, mean age 61.3 years), (tables 1 and 2). This reflects a similar prevalence of OSA diagnoses in COVID-19 infected as in the normal population in FinnGen, where prevalence is 8%.¹⁸ Ninety-one (20.4%) patients required hospitalisation (36.3% male, mean age 65.9 years) including 19 patients with OSA (table 1).

Prevalence of OSA ($p=5.13 \times 10^{-5}$), hypertension ($p=5.03 \times 10^{-11}$), diabetes ($p=3.45 \times 10^{-6}$) and CHD ($p=5.20 \times 10^{-4}$) were statistically significantly higher in the hospitalised group. Similarly, age and BMI were higher among hospitalised individuals ($p=1.06 \times 10^{-15}$, $p=0.014$, respectively; table 1).

To evaluate the performance of the diagnostic events, we compared the main risk factors among patients with COVID-19 between individuals with OSA (n=38) and those who did not have OSA diagnosis (n=407). Patients with OSA were statistically significantly older and their BMI was higher (mean age 61.3 years, BMI 31.15 kg/m², $p=5.60 \times 10^{-4}$, $p=3.38 \times 10^{-3}$, respectively) than non-OSA individuals (mean age 51.9 years, BMI 26.71 kg/m²). Also, comorbidities were more prevalent among OSA individuals ($p=1.74 \times 10^{-4}$) and they faced hospitalisation more often ($p=3.21 \times 10^{-5}$). We did not observe differences in risk factors when comparing non-hospitalised (n=19, male 63.2%, mean age 56.3 years) and hospitalised patients with OSA (n=19, male 36.8%, mean age 66.3 years; table 2). Furthermore, 7/19 patients with OSA were hospitalised due to COVID-19 did not have any other disease comorbidities. We did not observe significant differences concerning age or BMI between individuals who had only OSA as a comorbidity or also

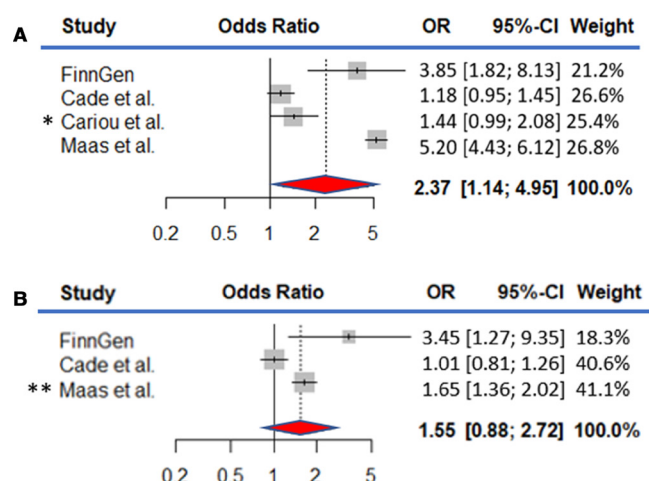


Figure 1 Forest plots of obstructive sleep apnoea (OSA) and the risk of hospitalisation due to COVID-19. The evidence is combined using random-effect meta-analysis. The data consisted of 15 835 COVID-19 positive individuals including 1294 patients with OSA. (A) The model is adjusted for age and sex, and ethnic background if available. *Cariou *et al* study's primary outcome was defined as tracheal intubation and/or death within 7 days of admission. (B) The model is adjusted for age, sex and BMI. **Maas *et al* study is adjusted for diabetes and hypertension in addition to forementioned covariates.

other comorbidities in addition to OSA (62.8 years, 68.9 years, $p=0.72$, 30.26 kg/m², 32.67 kg/m², $p=1.00$, respectively). Time since the first diagnosis of OSA to COVID-19 infection was not significantly different between non-hospitalised and hospitalised groups (6.6 years, 8.6 years, $p=0.37$, respectively).

We tested if OSA is associated with the risk of severe COVID-19 infection, determined as being hospitalised ($n=91$), or COVID-19 infection in general ($n=445$). While OSA did not affect the risk of contracting COVID-19 ($p=0.25$), patients with OSA had a considerably elevated risk for being hospitalised due to severe COVID-19 (OR=2.93 (95% CI 1.02 to 8.39), $p=0.045$, adjusted for age, sex, BMI, hypertension, diabetes, CHD, asthma and COPD; table 3).

We performed a meta-analysis by pooling the comparable endpoints between the published studies^{7–9} and examined the association with severe COVID-19 with and without adjusting for BMI. The studies, including our study, consisted of 15 835 COVID-19 positive individuals including 1294 patients with OSA. Overall, we observed over twofold increase in the pooled estimate prior to adjusting for BMI (OR=2.37 (1.14 to 4.95), $p=0.021$). Adjusted estimates were available in the study of Cade *et al*⁸ (BMI) and Maas *et al*⁹ (BMI, hypertension and diabetes) but not in the study of Cariou *et al*.⁷ The pooled estimate somewhat attenuated after adjustment for BMI (OR=1.55 (0.88 to 2.72), $p=0.13$; figure 1).

To investigate patients with OSA contracted with COVID-19 in more detail, we accessed the healthcare data of 305 COVID-19 positive individuals including 11

Table 4 Healthcare data characteristics of individuals with obstructive sleep apnoea contracted with COVID-19

n=11

Age (mean in years)	55.1 (8.0)
Sex (male) (N, %)	9 (81.8)
BMI (mean kg/m ² , SD)	35.08 (5.96)
Diabetes (N, %)	3 (27.3)
Hypertension (N, %)	7 (63.6)
CHD (N, %)	3 (27.3)
CPAP (N, %)	7 (63.6)
MAD (N, %)	1 (9.1)
AHI (mean, events per hour)	43.3 (20.6)
ODI (mean, events per hour)	39.6 (15.7)
SpO ₂ mean (mean%, SD)	91.0 (3.3)
SpO ₂ min (mean%, SD)	79.4 (8.3)
AHI with CPAP (mean, events per hour)	1.86 (2.07)
ICU (N, %)	3 (27.3)
NIV (N, %)	11 (100)
Intubation (N, %)	2 (18.2)
Treatment time in hospital (mean in days, SD)	15 (8.6)

AHI, Apnoea-Hypopnea Index; BMI, body mass index; CHD, coronary heart disease; CPAP, continuous positive airway pressure; ICU, intensive care unit; MAD, mandibular advancement device; NIV, non-invasive ventilation; ODI, oxygen desaturation index; SpO₂, oxygen saturation.

patients with OSA treated in Heart and Lung Center or Department of Oral and Maxillofacial Diseases, HUH, Finland by the end of October 2020. The mean age of the COVID-19 positive patients with OSA was 55.1 years, mean BMI was 35.08 kg/m² and 9 (81.8%) patients were male. Mean AHI was 43.3 events per hour (table 4) and all 11 patients had either moderate (AHI≥15 but<30 events per hour) or severe (AHI≥30 events per hour) OSA; 9 out of 11 had severe OSA and 2 out of 11 had moderate OSA. 8/11 had treated OSA; 7 patients had CPAP therapy and 1 patient had MAD. CPAP-treated patients used their appliances 98% of the nights with 6.3 hours mean time used. Mean AHI during treatment was 1.86 events/hour prior to the COVID-19 infection. Despite of the OSA treatment, all 11 patients required hospital treatment caused by pneumonia or other COVID-19 caused symptoms, such as high fever. All patients needed non-invasive ventilation and two required intubation. Treatment time in hospital was 15 days (mean, table 4).

DISCUSSION

Here, we examined the role of OSA as a risk factor for COVID-19 leading to hospitalisation. Our analyses revealed 2.93-times higher risk for COVID-19 hospitalisation in patients with OSA, independently of BMI and other known risk factors for OSA, or those for severe

COVID-19 suggesting that OSA is an independent risk factor for COVID-19.

Indeed, our findings are well in line with earlier works on COVID-19 comorbidities and OSA. Three studies have examined the association between COVID-19 and OSA before. Despite different endpoint definitions (contracting COVID-19, severity of the disease, mechanical ventilation, and death), these studies share similar findings with ours. All studies showed a significant association with COVID-19 severity and OSA.^{7–9} However, only one study showed a statistically significant association between OSA and severe COVID-19 after adjusting for BMI.⁹ These findings suggest that while OSA is likely a risk factor for COVID-19, evaluating the magnitude of this association would benefit from harmonised analyses across different cohorts where comorbidities are similarly assessed.

Building on these studies, we set to test the role of OSA on COVID-19 hospitalisation. In our study, patients with OSA had 2.93 times higher risk of being hospitalised and the estimate was comparable and independent of the risk in diabetes patients, where elevated risk has been reported earlier for severe COVID-19.¹⁹ There are at least two potential pathological mechanisms how OSA may relate to severe COVID-19. First, individuals with OSA often have one or more comorbidities that are known risk factors for severe COVID-19. For example, high BMI increases the risk for severe COVID-19. Furthermore, OSA exacerbates the effects of many underlying risk factors increasing blood pressure. Second, OSA may worsen the core symptoms of severe COVID-19, especially during the night, when decreased oxygen saturation levels occur in OSA.¹⁴ Our findings together with earlier reports suggest that OSA should be taken into account when assessing who will develop life-threatening complications of COVID-19 infection.

In addition, we collected treatment information concerning OSA of 11 patients who had contracted COVID-19. Despite of the OSA treatment, patients developed a severe form of COVID-19 and all patients required hospital care suggesting OSA as a risk factor even if treated.

Finally, based on our results and previous studies,^{7–9} we set a meta-analysis to strengthen the role of OSA on COVID-19 hospitalisation. We were able to establish OSA as a risk factor and show that the effect is related to COVID-19 severity indicating over 2-fold risk.

Our findings should be interpreted in the context that registry-based ascertainment through hospitalisation may miss non-hospitalised OSA cases (false negatives). In addition, the population prevalence of OSA is larger than the observed prevalence as OSA is still underdiagnosed in Finland. This may affect to our findings. The high percentage of individuals in hospitals likely reflect the age distribution of the first wave patients in Finland, where infections took place in individuals approximately 50 years of age, and selective testing in those that had clear or severe symptoms. Similarly, early on the testing

was targeted towards older individuals and to those with comorbidities, as not enough testing capacity was available early in the spring 2020. Although sufficient capacity and different strategies are in place now, the number of patients with mild COVID-19 infection may have not been recorded in the registries from the early spring 2020. Finally, compared with other countries there have been relatively small numbers of COVID-19 infections in Finland till the end of October 2020 when these data were curated. Therefore, while the effect estimates are comparable to other studies on OSA and COVID-19, the confidence intervals are relatively large due to the smaller total number of COVID-19 positive individuals in Finland and in the study sample: less than 500 patients compared with several hundred in other studies. Also, FinnGen represents older population (mean 58.6 years) than the average age (mean 42.9 years) in Finland.²⁰

In conclusion, patients with OSA have the same risk of contracting COVID-19 than non-OSA individuals. Meanwhile, in this study, patients with OSA had 2.93 times higher risk to be hospitalised when affected by COVID-19 than non-OSA individuals. Our findings may suggest that, in assessment of patients with suspected or confirmed COVID-19 infection, OSA should be recognised as one of the comorbidity risk factors for developing a severe form of the disease. We believe that our finding may help in identifying high-risk individuals for severe forms of COVID-19 infection and therefore screening for previous indications of OSA could be beneficial among individuals testing positive for the virus.

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Contributors HO is the guarantor of the manuscript. TK, HO, SR and SS conceived the study and designed the study protocol. TK, HO and SS conducted the literature review, statistical analysis and drafted the manuscript. MB and SRu contributed statistical analysis and TK phenotyped study samples. AB, MB, JK, SR, SRu, AP, TP

and SR reviewed the manuscript for intellectual content, made revisions as needed and approved the final version for publication. HO, TP and SR supervised the study.

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Competing interests None declared.

Patient consent for publication Obtained.

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Jukka Partanen	Blood Service Biobank, Helsinki, Finland
Kimmo Pitkänen	Helsinki Biobank, Helsinki, Finland
Seppo Vainio	Northern Finland Biobank Borealis, Oulu, Finland
Kimmo Savinainen	Tampere Biobank, Tampere, Finland
Veli-Matti Kosma	Biobank of Eastern Finland, Kuopio, Finland
Teijo Kuopio	Central Finland Biobank, Jyväskylä, Finland

Supplementary Table 1. The prospective epidemiological and disease-based cohorts, and hospital biobank samples in FinnGen Data Freeze 6

Cohort	N
Auria Biobank	29201
Biobank of Central Finland	7743
Biobank of Eastern Finland	7765
Blood Service Biobank	28901
Borealis Biobank	7390
Biobank Botnia	8681
Biobank Corogene	4689
Biobank FinHealth	5928
Helsinki Biobank	58693
Tampere Biobank	12394
Terveystalo Biobank	1709
THL Biobank ATBC	3836
THL Biobank FinIPF	201
THL Biobank FINRISK 1992	4931
THL Biobank FINRISK 1997	6997
THL Biobank FINRISK 2002	6869
THL Biobank FINRISK 2007	5143
THL Biobank FINRISK 2012	5233
THL Biobank GENERISK	6898
THL Biobank Health 2000	6529
THL Biobank Health 2011	708
THL Biobank HHS	2113
THL Biobank Kuusamo	123
THL Biobank Migraine	7717
THL Biobank SUPER	8466
THL Biobank Diabetes	10145
THL Biobank Twins	11402
Total:	260405

THL= Finnish Institute for Health and Welfare Helsinki, Finland

Supplementary Table 2. ICD-codes for OSA and comorbidities

	ICD-10	ICD-9	ICD-8
OSA	G47.3	3472	
HYPERTENSION	I10-I13, I15, I67.4	4019X, 4029A, 4029B, 4039A, 4040A, 4059A, 4059B, 4372A, 4059X	400, 401, 402, 403, 404
DIABETES	E10-E14	250	250
CHD	I20.0, I21, I22	410, 4110	410, 411,0
ASTHMA	J45, J46	493	493
COPD	J43, J44	492, 4912	492, 491,04

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. OSA=obstructive sleep apnoea, CHD=coronary heart disease.