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Marja Palomäki, Tarja Saaresranta, Ulla Anttalainen, Markku Partinen, Jaana Keto, Miika Linna

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Multimorbidity and overall comorbidity of sleep apnoea. A Finnish nationwide study

Marja Palomäki, MD[1,2], Tarja Saaresranta, MD, PhD[2,3], Ulla Anttalainen, MD, PhD[2,3], Markku Partinen, MD, PhD[4,5], Jaana Keto, PhD[6] Miika Linna, PhD[7,8]

[1]*Central Hospital for Central Ostrobothnia, Department of Pulmonary Diseases, Kokkola, Finland*

[2]*Sleep Research Centre, University of Turku, Turku, Finland*

[3]*Sleep and Breathing Centre and Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital, Turku, Finland*

[4]*Helsinki Sleep Clinic, Terveystalo Healthcare, Helsinki, Finland*

[5]*Department of Clinical Neurosciences, Clinicum, University of Helsinki, Helsinki, Finland*.

[6]*Jazz Pharmaceuticals, Helsinki, Finland*

[7]*Aalto University, Helsinki, Finland*

[8]*University of Eastern Finland, Kuopio, Finland*

Corresponding author

Marja Palomäki, Central Hospital for Central Ostrobothnia, Department of Pulmonary diseases, Mariankatu 16-20, 67200 Kokkola, Finland. E-mail: makrip@utu.fi

Running head: Multimorbidity in sleep apnoea

ABSTRACT

The prevalence of sleep apnoea is increasing globally; however, population-based studies have reported a wide variation of prevalence estimates, and data on incidence of clinically diagnosed sleep apnoea are scant. Data on the overall burden of comorbidities or multimorbidity in individuals with incident sleep apnoea are scarce, and the pathways to multimorbidity have only marginally been studied.

To study the current epidemiology of sleep apnoea in Finland, overall burden of comorbidities, and multimorbidity profiles in individuals with incident sleep apnoea, we conducted a register-based, nationwide, retrospective study of data from January 2016–December 2019.

The prevalence of clinically diagnosed sleep apnoea was 3.7% in the Finnish adult population; 1-year incidence was 0.6%. Multimorbidity was present in 63% of individuals at the time of sleep apnoea diagnosis. Of those with incident sleep apnoea, 34% were heavily multimorbid (presenting with ≥4 comorbidities). The three most common chronic morbidities before sleep apnoea diagnosis were musculoskeletal disease, hypertension, and cardiovascular disease. In multimorbid sleep apnoea patients, hypertension, and metabolic diseases, including obesity and diabetes, cardiovascular diseases, musculoskeletal diseases and dorsopathies, in different combinations, encompassed the most frequent disease pairs preceding a sleep apnoea diagnosis.

Our study adds to the few population-based studies by introducing overall and detailed figures on the burden of comorbidities in sleep apnoea in a nationwide sample and provides up-to-date information on the occurrence of sleep apnoea as well as novel insights in multimorbidity in individuals with incident sleep apnoea.

Keywords: sleep apnoea, comorbidity, multimorbidity, register study, epidemiology

Trial registration number: NA

TAKE-HOME MESSAGE

Two-thirds of individuals with sleep apnoea are multimorbid at diagnosis and one-third are heavily multimorbid. Dorsopathies, musculoskeletal diseases, hypertension, and metabolic diseases are the most common comorbidities preceding sleep apnoea diagnosis.

INTRODUCTION

The global burden of sleep apnoea (SA) has reached epidemic proportions, attributed partly to the obesity pandemic, more sensitive recording techniques, and changes in scoring criteria [1]. In population-based studies, SA is often defined solely by an apnoea-hypopnoea index (AHI) or respiratory disturbance index (RDI) of at least 5 per hour without considering symptoms. Heterogeneity in sampling and methodology has resulted in a wide variation of reported prevalence estimates of SA [2]. A recent European study based on polysomnographic findings in the general population reported an estimated prevalence of 59% in men and 33% in women for any severity of SA. However, the estimated prevalence for symptomatic SA was 9.7% for men and 3.0% for women [3].

Comorbidity is more the rule than the exception in individuals with SA [4], but published studies on the overall or comprehensive burden of comorbidities at population level are scarce. The term “comorbidity” refers to the combined effects of additional conditions in reference to an index chronic condition, whereas the term “multimorbidity”, often defined as two or more chronic diseases or conditions, indicates that no single condition holds priority over any of the co-occurring conditions from the perspective of the patient and the healthcare system [5]. In the era of personalized medicine, we need to better understand the overall burden of comorbidities and multimorbidity profiles in individuals with SA and their role in therapeutic approaches [6].

To investigate the prevalence and incidence of SA, the overall burden of comorbidities in Finnish individuals with SA, and multimorbidity profiles in those with incident SA, we conducted a nationwide study utilizing data from two comprehensive, individual-level, healthcare registers.

MATERIALS AND METHODS

This retrospective, observational study was based on secondary use of healthcare data with a complete coverage of the total population in Finland. As this was a retrospective study including anonymized register data, no ethics committee approval was required according to the Finnish legislation, nor was an approval requested.

Data

We used two comprehensive, individual-level healthcare data repositories of The Finnish Institute for Health and Welfare in this study: 1) The Finnish Secondary Care Register (HILMO), which includes both inpatient (hospitalizations and procedures/interventions with codes) and hospital outpatient contacts (scheduled and emergency care specialist visits), and 2) The Finnish Primary Care Register (AVOHILMO), which includes all primary healthcare contacts at healthcare centres.

Study population

Adults aged ≥18 years with the International Classification of Diseases, Tenth Revision (ICD-10) code G47.3 marked as the primary or secondary diagnosis in either primary or secondary healthcare were defined as individuals with SA. G47.3 includes both obstructive and central SA. The validity of the G47.3 coding in the Finnish Care Registers has been found to be 98% [7]. As our data are based on clinical health care registers with information limited to diagnoses, care level (primary vs secondary), and dates of care, we do not have detailed information on the type of sleep test performed on each individual diagnosed with SA. According to the Finnish national Current care Guidelines for obstructive sleep apnoea (OSA), a sleep test is a prerequisite for SA diagnosis [8]. In some cases, SA may be diagnosed with AHI 5/h or lower e.g., in case that home sleep apnea test has been technically insufficient, patient has typical symptoms and findings suggesting for SA, and trial with automatic positive airways pressure device increases therapeutic pressure with subsequent relief of SA symptoms. The vast majority has been diagnosed with home sleep testing and maybe 1-2% with polysomnography (PSG), as the availability of in-laboratory PSG in Finland is low. For each individual with incident SA from 2017, a matched control case was randomly assigned from the Finnish Care Registers in a 1:1 ratio. Matching was based on age, sex, hospital district, and binary multimorbidity status. Body mass index (BMI) could not be used for matching, as the Finnish Care Registers do not include BMI. For multimorbid individuals, the year of onset of multimorbidity was also used in matching. Hospital district was used in matching because of potential regional differences in lifestyle and genetic risk of cardiovascular disease, and in how chronic conditions are diagnosed and treated [9]. The general population used in the analyses comprised all

≥18-year-old adults who had used primary or secondary healthcare services in Finland during 2017.

Prevalence and incidence of SA

Prevalence of diagnosed SA in 2019 is reported as percentage of the live adult (≥18 years) population who had used primary or secondary healthcare services with the G47.3 diagnosis between January 2015 and December 2019. If an individual had received an SA diagnosis prior to January 2015 but had not used health care services for SA during the study period, he or she was not identified as a SA patient. Individuals with SA who had died between January 2015 and December 2019 were removed from the nominator. The size of the adult population in Finland in December 2019 (n=4,476,235) was used as the denominator for prevalence. This figure was acquired from Statistics Finland (*www.stat.fi/*).

Incidence of diagnosed SA in 2017 was defined similarly, but with a mean washout period of 2.5 years (i.e., no previous SA diagnosis from Jan 2015–date of 2017 diagnosis). The size of the adult population on December 31, 2017 (n=4,446,869) was used as the denominator.

Multimorbidity and comorbidities in incident SA

Multimorbidity was defined as two or more chronic diseases for which the patient had

used healthcare services between January 2015 and time of SA diagnosis in 2017, i.e., on average in the past 2.5 years. We used the chronic disease classification by the Finnish Institute for Health and Welfare (available on request). Any chronic disease or condition in this classification contributed to the multimorbidity status of the study subjects. Individuals with at least four chronic diseases were considered heavily multimorbid

For individuals with SA, multimorbidity status was assessed prior to receiving the SA diagnosis (i.e., the individual was multimorbid if two or more chronic diseases were present prior to the SA diagnosis). We report the most common disease pathways to multimorbidity before SA diagnosis based on the sequence of the first two chronic diseases preceding SA diagnosis. We also present the distribution in the number of chronic diseases in each patient group.

For individuals with incident SA, we report the prevalence of 26 diagnosed major common chronic disease groups, which are listed in the Appendix. We also compare the diagnosed prevalence of these major chronic diseases in the incident SA cohort with a) the matched control population and b) the general population. We present a similar comparison for male vs female individuals with SA. Comparisons are reported by odds ratios (OR) and 95% confidence intervals (CI) for each chronic disease group.

Statistical methods

The 95% confidence intervals (CIs) for odds ratios (OR) were calculated using the normal approximation method. The two-sided z test was used to assess the statistical

significance for a sex difference in chronic morbidity. A p-value of <0.05 was considered statistically significant. Stata version 17.0 was used for all analyses (StataCorp. 2017).

RESULTS

Study demographics, prevalence, and incidence of diagnosed sleep apnoea

In December 2019, 3.7% (166,435) of the national adult population had used primary or secondary health care services with the G47.3 diagnosis (SA) during the past five years. In 2017, 0.6% (25,324) of Finnish adults had incident SA, translating to an annual incidence of 600 per 100,000. Of the incident SA patients, 64.2% were men. Mean age at the time of SA diagnosis was 57.2 years (56.3 for men and 58.8 for women). Demographics for the incident patient cohort, matched controls, and the general population are presented in Table 1. Compared to the general population, incident SA patients were on average 5 years older, more often male, and more often multimorbid.

Multimorbidity prior to SA diagnosis

At the time of SA diagnosis, 63% of individuals were multimorbid compared with 38% in the general population (Table 1). The most common pathways to multimorbidity before SA diagnosis, defined as the sequence of first two chronic diseases before SA diagnosis, are presented in Figure 1. Hypertension and metabolic diseases, including obesity and diabetes, cardiovascular diseases, musculoskeletal diseases and dorsopathies, in different combinations, encompassed the most frequent disease pairs

preceding a SA diagnosis. The most common pathway (true for n = 2 843 out of 15 954 multimorbid SA patients) to multimorbidity was first being diagnosed with arterial hypertension, and then with a metabolic disease or obesity.

The number of diagnosed chronic diseases at the time of SA diagnosis is presented in Figure 2 for individuals with incident SA, for matched controls, and for the general population. Of incident SA patients, 34% were heavily multimorbid, i.e., presented with ≥4 comorbidities, compared to 24% of matched controls and 14% of the general population (Fig 2).

Chronic diseases at the time of SA diagnosis

The diagnosed prevalence (n and %) of 26 major chronic disease (elaborated list in the Appendix) at time of SA diagnosis is presented in Table 2. The most common chronic disease was musculoskeletal disease, which had been diagnosed in 52% of females and 36% of males prior to SA diagnosis. The second and third most common chronic morbidities were hypertension and cardiovascular disease, respectively. Of 26 morbidities analysed, we found statistically significant sex differences in 19.

The ORs for 26 major chronic diseases (elaborated list in the Appendix) are presented in Table 3 for individuals with incident SA vs matched controls, and in Table 4 for those with incident SA vs the general population. In incident SA patients, we found the highest

OR for obesity, and the lowest OR for dementia and related diseases compared to matched controls. Compared to general population, ORs for major chronic diseases were higher in incident SA patients in all disease groups, with the exception of dementia and related diseases.

DISCUSSION

Our results add to the few population-based studies by introducing overall and detailed figures on the burden of comorbidities in SA in a nationwide sample. To our knowledge, this is the first study depicting different pathways of multimorbidity in SA. It is also the largest one giving occurrences of multimorbidity in individuals with SA. Of individuals with incident SA, 34% were heavily multimorbid (i.e., with ≥4 chronic diseases). Multimorbidity was more prevalent in women than in men. We also provide up-to-date information of SA prevalence and incidence in Finland.

In 2002, an expert group estimated that SA prevalence was 3.7% in Finland [10]. In a recent Finnish study combining data from three population-based cohorts with 36,963 participants and follow-up ending, at the latest, at the end of 2015, SA prevalence was 4.2% [11]. Our prevalence estimate of 3.7% is identical with the 2002 figure, but lower than expected based on the increased demand for SA diagnostics and treatment in Finland since 2015 [12]. Our figure may be an underestimation, as we might have missed those individuals who had received the SA diagnosis more than five years

earlier and had not used healthcare services during January 2015–December 2019. Further, the 2002 estimate also included undiagnosed individuals with SA. The current figure of this study is based on diagnosed individuals with SA, and therefore underestimates the true prevalence of SA in the Finnish population, which is likely to be considerably higher. Compared to the earlier Finnish study, the 0.5% difference in prevalence is likely due to sampling bias in the previous study cohorts. Our prevalence figure is based on diagnosed SA patients, not a random population sample, therefore explaining the difference between our modest figure and the figures from epidemiological studies where AHI has been recorded for a random population sample [13]. As the patients in our study have sought medical attention for their disturbed sleep, our figure can also be seen as an estimator for the prevalence of Obstructive Sleep Apnoea Syndrome (OSAS), where the patient is symptomatic, and their quality of life is impacted by excessive daytime sleepiness caused by OSA.

Data on SA incidence are scarce. The 5-year incidence for moderate or severe SA in the Sleep Heart Health Study was 11.1% for men and 4.9% for women and in the Cleveland Family Study 10% [14, 15]. These figures represent polysomnographic data from random population samples, not clinically diagnosed SA. In a Danish register-based study with 15 years of clinical data, annual incidence rate of SA was significantly lower than in our study, 6.5 per 10,000 vs 600 per 100,000, respectively [16]. The higher incidence rate in our study reflects the increased demand for SA diagnostics and treatment in Finland during recent years.

In our study, individuals with incident SA were 5 years older at the time of diagnosis compared to those of the European Sleep Apnoea Database (ESADA) cohort , but in line with the Swedish SA register figures. [4, 17]. In our study, almost one-third of incident SA cases were ≥65 years of age. Delay in the diagnosis, and hence treatment, of SA might add to the comorbidity risk. However, when considering whether diagnostic procedures are timely, we must keep in mind that benefit from positive airway pressure therapy is not limited to younger individuals [18].

In our study, two-thirds of individuals with incident SA were men. This is similar to the Swedish register data from 2018–2019, but lower than in the ESADA cohort, with data from year 2007–2009 [4, 17]. The change in the male:female ratio from 3:1 to 2:1 in 10 years pending might reflect the enhanced awareness of sex differences in SA and better recognition of women with SA, or the geographical differences in SA awareness among healthcare professionals and lay people [19, 20]. Even as women are increasingly diagnosed with SA, underdiagnosing women with SA probably remains a relevant problem [21].

The clinical presentation and symptomatology of women with SA is different from men, and gender modifies SA [19, 22]. There is paucity of large studies analysing comprehensively sex differences in diseases preceding SA diagnosis. In a Danish registry-based study, data of morbidities three years prior to SA diagnosis were presented for the whole SA cohort, but not separately for sexes, and only one-fifth of

patients were women [23]. The large study by Mokhlesi et al found that hypertension and depression were more prevalent in women and diabetes and ischaemic heart disease in men with incident SA [24]. In our study, sex differences in comorbidity profiles in incident SA patients probably comply with disease distribution in the general population. At the time of SA diagnosis, women were more often multimorbid than men (72% vs. 58%, respectively). The increased prevalence of asthma, thyroid disease, obesity, gastro-oesophageal reflux disease and mood disorders in women with incident SA compared to men could be expected. Somewhat surprisingly, there was no sex difference in the prevalence of chronic obstructive pulmonary disease (COPD). Contrary to the study by Mokhlesi et al, we did not find sex difference in the prevalence of cardiovascular disease. Also, dyslipidaemia, cancer, schizophrenia and related disorders, cerebrovascular disease and organic sleep disorders were equally prevalent in both sexes with incident SA. To our knowledge, ours is so far the largest study presenting comprehensive data on sex differences in SA comorbidities. Our findings even suggest that women with incident SA may present with heavier multimorbidity than men.

Our study is the largest to evaluate detailed multimorbidity in individuals with SA. Multimorbidity in SA was considerably more common than in the general population using healthcare services. One-third of individuals with incident SA and one-fourth of matched controls presented with heavy multimorbidity. Previously, correlation between SA and multimorbidity has been reported only in severe SA [25]. However, in a more

recent and larger study, SA was associated with an increased risk of multimorbidity, and in multimorbid men, undiagnosed SA was highly prevalent [26].

In our study, hypertension and metabolic diseases including obesity and diabetes in different combinations encompassed the most frequent disease pairs preceding SA diagnosis and suggest multidirectional mechanisms. Cardiovascular diseases and diseases of the musculoskeletal system and connective tissue also turned out to have a significant role in the development of multimorbidity. Of the major chronic diseases or disease groups, musculoskeletal disease proved to be the most common chronic disorder in both men (36%) and women (52%) among patients with incident SA (Table 2). Despite the fact that back pain has been reported to be the second most common reason for visits in primary care, musculoskeletal disorders have seldom been assessed in the context of SA comorbidities [27]. In an earlier Danish study, OR for musculoskeletal and connective tissue diseases was 1.36 (95% CI 1.29-1.42) in incident SA population compared to matched controls, and the overall prevalence was 13% [23]. In our study, despite the high prevalence of musculoskeletal diseases among both sexes, the OR for these disorders compared to matched controls was slightly increased in women with incident SA, but not in men. However, as SA has been associated with chronic pain, our findings emphasize considering the possibility of SA in individuals with musculoskeletal and connective tissue disorders [28].

As expected, we found increased ORs for cardiovascular disease, mood and neurotic disorders, thyroid disease, dyslipidaemia, diabetes, hypertension, atrial fibrillation, asthma, COPD, heart failure, and obesity in both men and women with incident SA compared to matched controls. Our results are in line with a Canadian study, despite a considerably larger proportion of women and higher age at the time of diagnosis in our study [29].

The largest study to date to report preceding comorbidities before SA diagnosis consisted of 1.7 million individuals with SA (50% women) and their matched controls [24]. That study used data from a US database comprising health insurance claims for working adults and retirees with employer-sponsored health insurance. After adjusting for age and sex, increased ORs with very narrow CIs were found for all studied comorbidities. Compared to matched controls, type 2 diabetes, hypertension, and depression were more prevalent in individuals with SA in all age groups, whereas congestive heart failure, ischaemic heart disease, cardiac arrythmias, and stroke were more prevalent only in older individuals with SA.

In our study, the OR for cerebrovascular disease prior to a diagnosis of SA was increased in women but not in men. Previously, the risk of stroke in SA has been studied both in population-based and clinic-based cohorts with partly inconsistent results and sex differences [30]. In the Wisconsin Sleep Cohort Study, the prevalence of stroke in individuals with SA was increased in a cross-sectional analysis, but in the

prospective analysis and after adjustment for confounding factors, the risk of incident stroke was not significantly increased [31]. In the prospective Sleep Heart Health Study, untreated SA was shown to increase the risk of stroke in men, but only in women with severe SA [32]. In the recent Finnish cohort study, SA did not associate with stroke risk [11]. In a meta-analysis of 10 prospective cohort studies, the risk for stroke was increased in individuals with SA [30].

We found lower risk for dementia and schizophrenia/delusional disorders in both males and females with incident SA compared to matched controls. We surmise sampling bias to be the explanation. SA has been suggested as a risk factor for cognitive decline in the elderly and can increase the risk for dementia or even cause early-onset dementia [33, 34]. The lower OR for dementia or schizophrenia/delusional disorders in individuals with incident SA might be due to under-recognition of SA symptoms and reduced access to healthcare together with other factors in those already diagnosed with these diseases [35].

The Danish nationwide study with ICD10-based morbidities three years prior to SA diagnosis at any age was analysed using data from the Danish National Patient Registry [23]. Due to differences in grouping of comorbidities, direct comparisons with our results can be made only in some diseases or disease groups. Our study confirmed the connection between SA and respiratory diseases (particularly asthma and COPD),

diabetes, atrial fibrillation, and hypertension, but we could not confirm that individuals with incident SA are more prone to neurological diseases than matched controls.

Gastro-oesophageal reflux disease (GERD) has been strongly associated with SA [36]. In sleep-clinic patients, GERD has a female predominance [37]. A recent large study failed to find any differences in GERD symptoms between non-SA and SA individuals, but again women were more often symptomatic [38]. In our study, only women had increased risk for GERD compared to matched controls, supporting previous findings. Further, we could not confirm an association between glaucoma and SA, which has been reported in previous cross-sectional and case-control studies [39, 40].

The lower risk for cancer in both males and females with incident SA compared to matched controls in our study lacks an explanation. Studies addressing incidence and mortality of cancer in individuals with SA have shown conflicting results [41, 42]. In the previous studies addressing comorbidities prior to SA diagnosis, only Jennum et al. reported neoplasms and found no difference between individuals with SA and controls [23]. We were not able to analyze the effect of smoking on the risk for cancer, as our data did not contain information on individual lifestyle habits such as smoking. In a previous Finnish study with baseline data from 2002-2005, 22% of patients compliant with continuous positive airway pressure (CPAP) therapy and 29% of CPAP-noncompliant SA patients were smokers [43]. In the general Finnish population, smoking prevalence was 23% in 2004 [44]. Thus, the overall prevalence of smoking

does not appear to be significantly lower in SA patients compared to general Finnish population and does not explain the difference in cancer prevalence.

We found increased prevalence of nonorganic and organic sleep disorders in individuals with incident SA compared to matched controls. This could reflect diagnostic challenges, which can result in delayed SA diagnosis. Excessive daytime sleepiness is one of the key symptoms of SA, and on the other hand 39%-58% of individuals with SA report insomnia symptoms [45]. It is possible that these symptoms have not been correctly attributed to the underlying SA.

Compared to the general population, incident SA patients were more likely to have been diagnosed with a condition belonging to any major chronic disease group, except for dementia and related diseases. We assume this exception be due to similar factors as the reduced likelihood for dementia in incident SA patients compared to matched controls. We attribute the high ORs for major chronic diseases among incident SA patients vs. the general population partly to demographic differences: incident SA patients were more often male, more often multimorbid, and, on average, 5 years older than general population.

Our study has several strengths. The data with excellent validity from The Finnish Primary Care Register and The Finnish Secondary Care Register cover the majority of both inpatient and outpatient healthcare in Finland. We considered the possible regional

differences in healthcare resources when matching the patients. Compared to studies based on self-reported comorbidities, our study avoids recall bias. Also, we minimized the risk of reporting bias by analysing comorbidity data only prior to SA diagnosis.

Our study has some limitations. First, the above-mentioned registers do not cover private healthcare. However, most of the care for SA in Finland is provided in public facilities due to the excellent coverage of public health insurance in Finland. Second, the Finnish population is quite homogeneous with only small minorities of people of non-Caucasian origin. Regarding differences in healthcare systems, ethnicities, and demographics in other countries, different results could be expected even with the same methodology [46]. Third, as we did not extract any data from neither patient files, nor income and education registers, we were not able to evaluate associations between comorbidities and SA severity, symptomatology, socioeconomic circumstances, or individual lifestyle habits. Also, BMI could not be used in matching, as our data did not include BMI. Fourth, the diagnosis of SA in most cases was based on home sleep testing, as the availability of in-laboratory polysomnography in Finland is low.

To conclude, our study adds to the scarce information on prevalence of clinically meaningful obstructive sleep apnoea and on the overall burden of comorbidities. It also provides novel insights in multimorbidity in individuals with incident SA in a large, nationwide sample. While supporting most of the previous evidence on the association between SA and cardiovascular diseases, hypertension, diabetes and other metabolic

diseases, atrial fibrillation, mood disorders, and respiratory diseases, our findings highlight areas of uncertainty or controversy, especially the relationship between SA and cancer, glaucoma, and stroke/cerebrovascular diseases. Our results signal under-recognition of SA in those with dementia or psychotic disorder, and possible diagnostic delay due to not attributing the patient's sleep disorders to SA. Most of the research on comorbidities in SA uses the time of diagnosis of SA as a starting point. Studying which diseases precede the diagnosis of SA helps broaden the big picture of this worldwide and increasing health problem. Our large database provides an excellent opportunity to further analyse patients' disease history and use of health services in different levels of healthcare and medical specialties before SA diagnosis.

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Author Contributions

All authors were involved in the conception and design of the study. Statistical analysis was performed by Miika Linna and Jaana Keto. All authors were involved in the interpretation of data. The draft was written by Marja Palomäki. All authors reviewed and revised manuscript drafts and approved the version submitted for publication. All authors had full access to the data and take responsibility for the accuracy and integrity of the work.

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Conflict of Interest

Marja Palomäki has received lecture fees from GlaxoSmithCline ltd, Chiesi ltd and Orion ltd, and research grants form Foundation of the Finnish Anti-Tuberculosis Association**,** Väinö and Laina Kivi Foundation, and Ida Montin Foundation.

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Jaana Keto is an employee in Jazz Pharmaceuticals.

Miika Linna has received consulting fee from Jazz Pharmaceuticals.

DATA SHARING STATEMENT

Data sharing is allowed in aggregated form due to Finnish legislation.

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TABLE 1

Demographics for the incident SA cohort at the time of SA diagnosis, matched control population, and total adult population using healthcare services in 2017 (i.e., the general population)

	Sex	N	Male (%)	Age (mean)	Age 18–65 (%)	Age 65–74 (%)	Age ≥75 (%)	Multimorbidity (≥2 chronic diseases) (%)
Incident SA	all	25,324	64.2	57.2	68.8	22.7	8.6	63.3
	male	16,263		56.3	70.6	21.6	7.8	58.3
	female	9061		58.8	65.5	24.7	9.9	72.4
Matched controls	all	25,324	64.2	57.2	68.8	22.7	8.6	61.6
	male	16,263		56.3	70.6	21.6	7.8	56.5
	female	9061		58.8	65.5	24.7	9.9	70.5
General population	all	3,223,399	42.9	52.1	67.7	17.1	15.25	38.1

SA, sleep apnoea.

TABLE 2

Number and % of chronic comorbidities (as elaborated in Appendix) at time of SA diagnosis for all those diagnosed with SA in Finland in 2017

Morbidity	Men (n=16,263)		Women (n=9061)		
	Cases (n)	Prevalence (%)	Cases (n)	Prevalence (%)	p-value
Cancer	871	5.36	536	5.92	0.070
Kidney and urinary tract disease	555	3.41	232	2.56	<0.001
Thyroid disease	337	2.07	891	9.83	<0.001
Other metabolic disease	563	3.46	552	6.09	<0.001
Diabetes	3324	20.44	1705	18.82	0.006
Obesity	1053	6.47	1053	11.62	<0.001
Gastro-oesophageal reflux disease	311	1.91	335	3.70	<0.001
Dementia and other cerebral disorders	703	4.32	291	3.21	<0.001
Schizophrenia and delusional disorders	215	1.32	141	1.56	0.133
Mood and neurotic disorders	1606	9.88	1746	19.27	<0.001
Nonorganic sleep disorders	355	2.18	335	3.70	<0.001
Neurological disorders	1221	7.51	1232	13.60	<0.001
Glaucoma	234	1.44	193	2.13	<0.001
Hypertension	4217	25.93	2752	30.37	<0.001
Cardiovascular disease	3757	23.10	2202	24.30	0.059
Atrial fibrillation	1496	9.20	634	7.00	<0.001
Other respiratory disease	1653	10.16	1311	14.47	<0.001
Gastrointestinal disease	2671	16.42	2065	22.79	<0.001
Musculoskeletal disease	5797	35.65	4717	52.06	<0.001
Urogenital disease	1440	8.85	206	2.27	<0.001
Heart failure	624	3.84	319	3.52	<0.001
Cerebrovascular disease	532	3.27	296	3.27	0.211
Organic sleep disorders	197	1.21	175	1.93	0.985
Asthma	967	5.94	1137	12.55	<0.001
COPD	572	3.52	293	3.23	0.744
Dyslipidaemia	1745	10.73	985	10.87	0.242

SA, sleep apnoea; COPD, chronic obstructive pulmonary disease.

TABLE 3

Odds ratios with 95% CI for prevalence of major chronic disease (as elaborated in Appendix) among individuals with incident sleep apnoea vs matched controls

	ALL, SA vs matched controls			MEN, SA vs matched controls			WOMEN, SA vs matched controls		
	OR	lower CI	upper CI	OR	lower CI	upper CI	OR	lower CI	upper CI
Obesity	4.12	3.74	4.53	4.64	4.03	5.35	3.75	3.29	4.27
Organic sleep disorders	3.13	2.60	3.77	4.14	3.02	5.68	4.8	3.36	6.86
Heart failure	1.98	1.77	2.22	1.9	1.66	2.18	2.15	1.77	2.62
Other respiratory disease	1.80	1.69	1.92	1.90	1.74	2.07	1.79	1.63	1.96
Asthma	1.74	1.62	1.87	1.57	1.41	1.74	1.98	1.79	2.20
Other metabolic disease	1.71	1.55	1.88	1.66	1.45	1.91	1.78	1.55	2.05
COPD	1.57	1.41	1.75	1.43	1.26	1.63	1.96	1.61	2.39
Diabetes	1.51	1.44	1.59	1.44	1.36	1.52	1.68	1.55	1.82
Atrial fibrillation	1.50	1.40	1.61	1.48	1.36	1.6	1.56	1.37	1.77

Hypertension	1.48	1.42	1.55	1.45	1.37	1.52	1.55	1.45	1.66
Nonorganic sleep disorders	1.47	1.30	1.65	1.37	1.16	1.61	1.59	1.34	1.9
Gastro-oesophageal reflux disease	1.32	1.17	1.49	1.09	0.93	1.28	1.65	1.38	1.97
Mood & neurotic disorders	1.29	1.22	1.36	1.18	1.09	1.27	1.44	1.33	1.55
Thyroid disease	1.29	1.18	1.40	1.21	1.03	1.42	1.33	1.2	1.48
Dyslipidaemia	1.27	1.20	1.35	1.31	1.22	1.42	1.24	1.13	1.37
Kidney & urinary tract disease	1.23	1.10	1.37	1.17	1.03	1.32	1.4	1.14	1.71
Cardiovascular disease	1.20	1.15	1.26	1.17	1.11	1.23	1.27	1.18	1.36
Cerebrovascular disease	1.07	0.97	1.18	0.98	0.86	1.1	1.29	1.08	1.54
Urogenital disease	1.06	0.99	1.14	1.1	1.02	1.19	0.86	0.71	1.04
Musculoskeletal disorders	1.02	0.99	1.06	0.99	0.94	1.03	1.08	1.02	1.15
Neurological disorders	1.02	0.96	1.08	0.99	0.91	1.07	1.05	0.96	1.14
Gastrointestinal disease	0.92	0.88	0.97	0.86	0.81	0.91	1.02	0.96	1.1
Glaucoma	0.91	0.80	1.04	0.88	0.74	1.06	0.94	0.77	1.15
Cancer	0.69	0.64	0.74	0.72	0.66	0.79	0.64	0.57	0.72
Schizophrenia & delusional disorders	0.69	0.60	0.79	0.63	0.53	0.75	0.79	0.63	0.99

Dementia & other cerebral disorders	0.62	0.57	0.67	0.58	0.53	0.64	0.71	0.61	0.82

OR, odds ratio; CI, confidence interval; SA, sleep apnoea; COPD, chronic obstructive pulmonary disease.

TABLE 4

Odds ratios with 95% CI for prevalence of major chronic disease (as elaborated in Appendix) among individuals with incident SA vs general population (i.e., the total adult population in Finland who used public healthcare services in 2017)

	ALL, SA vs general population			MEN, SA vs general population			WOMEN, SA vs general population		
	OR	lower CI	upper CI	OR	lower CI	upper CI	OR	lower CI	upper CI
Organic sleep disorders	8.94	8.14	9.83	6.98	6.03	8.07	8.27	7.10	9.63
Obesity	7.19	6.87	7.53	7.70	7.22	8.22	8.57	8.03	9.15
COPD	3.17	2.96	3.39	2.35	2.16	2.55	4.23	3.76	4.76
Other respiratory disease	2.73	2.63	2.84	2.78	2.64	2.93	3.11	2.93	3.30
Diabetes	2.72	2.64	2.81	2.37	2.28	2.46	2.96	2.80	3.12
Other metabolic disease	2.67	2.51	2.84	2.43	2.32	2.54	3.16	2.90	3.44
Hypertension	2.65	2.57	2.72	2.58	2.49	2.68	2.92	2.79	3.05
Asthma	2.62	2.51	2.74	2.43	2.28	2.60	3.49	3.28	3.72
Gastro-oesophageal reflux disease	2.53	2.34	2.74	2.22	1.98	2.49	3.34	2.99	3.73
Nonorganic sleep disorders	2.45	2.27	2.64	2.42	2.17	2.69	2.93	2.63	3.27

Heart failure	2.42	2.26	2.58	2.56	2.36	2.78	2.23	2.00	2.50
Dyslipidaemia	2.39	2.30	2.49	2.31	2.20	2.43	2.47	2.31	2.64
Kidney & urinary tract disease	2.25	2.09	2.42	1.89	1.74	2.06	2.39	2.10	2.73
Cardiovascular disease	2.09	2.03	2.15	1.45	1.33	1.58	1.93	1.71	2.16
Atrial fibrillation	2.04	1.95	2.13	1.91	1.81	2.02	1.91	1.76	2.07
Urogenital disease	2.03	1.93	2.13	1.57	1.49	1.66	1.59	1.39	1.83
Musculoskeletal disorders	1.98	1.93	2.03	1.94	1.88	2.00	2.59	2.48	2.70
Mood and neurotic disorders	1.79	1.73	1.86	1.74	1.65	1.84	2.33	2.21	2.45
Neurological disorders	1.69	1.62	1.76	1.65	1.56	1.75	2.12	1.99	2.25
Cerebrovascular disease	1.69	1.58	1.81	1.45	1.33	1.58	1.93	1.71	2.16
Thyroid disease	1.64	1.54	1.73	1.89	1.70	2.11	2.34	2.18	2.51
Gastrointestinal disease	1.58	1.53	1.63	1.51	1.44	1.57	1.87	1.78	1.97
Cancer	1.14	1.08	1.21	1.02	0.96	1.10	1.29	1.19	1.41
Glaucoma	1.12	1.02	1.24	1.11	0.98	1.27	1.29	1.12	1.48
Schizophrenia & delusional disorders	1.10	0.99	1.22	0.90	0.79	1.04	1.36	1.15	1.60
Dementia & other cerebral disorders	0.92	0.87	0.98	0.87	0.80	0.93	0.86	0.77	0.97

OR, odds ratio; CI, confidence interval; SA, sleep apnoea; COPD, chronic obstructive pulmonary disease.

Appendix.

Major common chronic disease groups in Sleep Apnea

As a basis for the disease grouping, we used the classification of chronic comorbidities used by the Finnish Institute for Health and Welfare, which relies on the proposal made by Calderón-Larrañaga et al. in Gerontol A Biol Sci Med Sci, 2017, Vol. 72, No. 10, 1417–1423.

To make the classification more relevant for sleep apnea, we chose 26 diseases or disease groups of interest for analysis, based on expert opinion. The rationale for inclusion of each disease or disease group in the analyses can be found in the table below.

To better capture the chronic disease diagnoses made in the primary healthcare sector, we included also ICPC-2 coding, which is a primary healthcare coding system proposed by the WHO. It is used by some, but not all primary healthcare providers in Finland. The ICPC-2 coding book includes a ICD-10 to ICPC-2 conversion code list, which was used to select the ICPC-2 codes for our analyses

(https://www.who.int/standards/classifications/other-classifications/international-classification-of-primary-care).

Disease group	ICD-10	ICPC-2	Rationale for including disease group in analyses
Asthma	J45-J46	R81	Possible birectional association with SA
Atrial fibrillation	I48	K78	Associated with SA
Cancer	C00-C97	A79, B72-74, D75-77, L71, N74, R84-85, S77, S79, T71, U75-77, W72, X75-77, Y77-78	Association with SA controversial
Cardiovascular disease	I10-I99 excl. I10, I15, I48, I50, I60-69	B71, K74- K76, K70, K79-80, K82-84, K88, K92-93, K94, K96	Associated with SA
Cerebrovascular disease	I60-I69	K99	Associated with SA
COPD	J44	R95	Co-occurrence of COPD and SA associated with high risk
Dementia & other cerebral disorders	F00-F19, G30-G32	P16, P18-19, P40	Some evidence of association with SA, possible under-recognition of SA symptoms
Diabetes	E10-E14	T89-90	Metabolic syndrome associated with SA
Dyslipidaemia	E78	T93	Associated with SA as part of metabolic syndrome
Gastrointestinal disease	K05-K87	D07, D12, D84-87, D93-99	Some gastrointestinal diseases (e.g., gastro-oesophageal reflux) have been associated with SA
Glaucoma	H40, H42	F93	Some evidence of association with SA
Heart failure	I50	K77	Associated with SA

Hypertension	I10, I15	K86-87	Associated with SA
Kidney & urinary tract disease	N00-N23	U06, U14, U88, U95, U99	Uraemia associated with SA
Other metabolic disease	E15-E90 excl. E65-E66, E78	T80-81, T87, T93, T99	Metabolic syndrome associated with SA
Mood & neurotic disorders	F30-F69	P02, P07, P09, P74-78, P86, P99	Mood and anxiety disorders associated with SA
Musculoskeletal disorders	M05-M94	L01-03, L83-99	SA possibly modifies chronic pain
Neurological disorders	G10-G13, G20-26, G35-37 excl. G47, G25.8	N08, N86-94, N99	Stroke associated with SA; neuromuscular diseases associated with sleep-disordered-breathing
Nonorganic sleep disorders	F51		Insomnia and SA frequently co-occur.
Obesity	E65-66	T82-83	Strong association with SA
Organic sleep disorders	G47, G25.8		Hypersomnia main feature in SA. Periodic limb movement disorder associated with SA
Reflux	K21	D84	Associated with SA
Other respiratory disease	J30-J99 excl. J44-45	R75-79, R90, R95-99	Asthma and COPD associated with SA - limited evidence for other respiratory disease
Schizophrenia & delusional disorders	F20-29	P71-73, P98	Under-recognition of SA in severe psychiatric disorders
Thyroid disease	E00-07	T85-86	Hypothyroidism associated with SA
Urogenital disease	N40-51, N80, N81, N88	Y73, Y85-87, Y99	Prostatic enlargement and nocturia may be associated with SA

SA, sleep apnoea. COPD, chronic obstructive pulmonary disease.

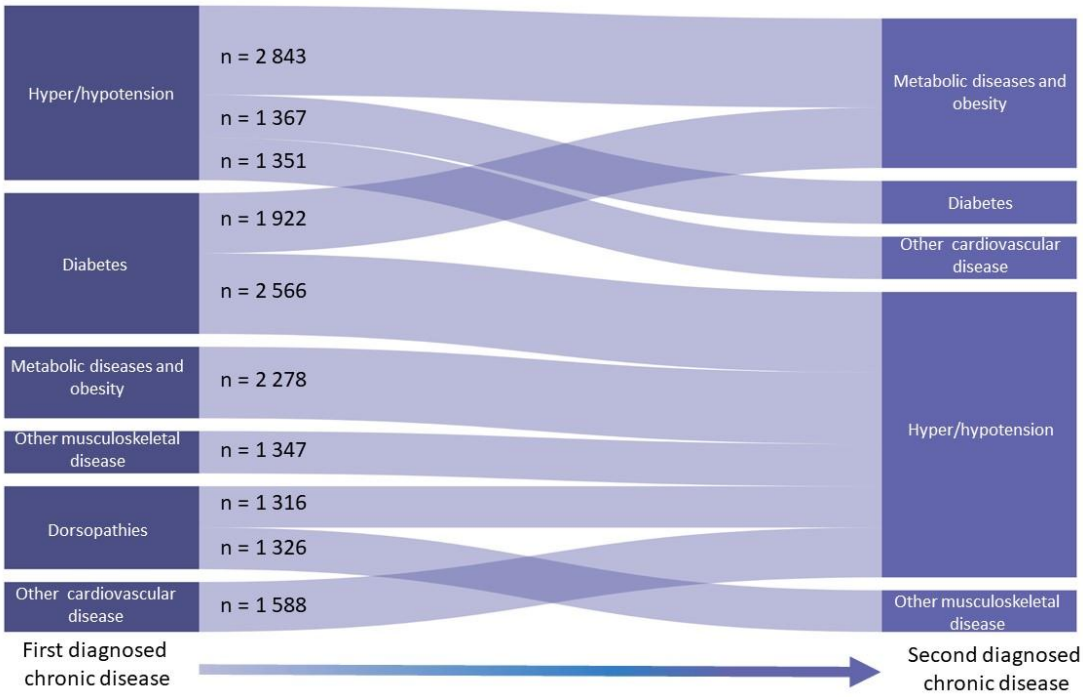

Fig 1. Ten most common disease pathways to multimorbidity before SA diagnosis based on the sequence of the first two chronic diseases. The group "other cardiovascular disease" does not include ischaemic heart disease.

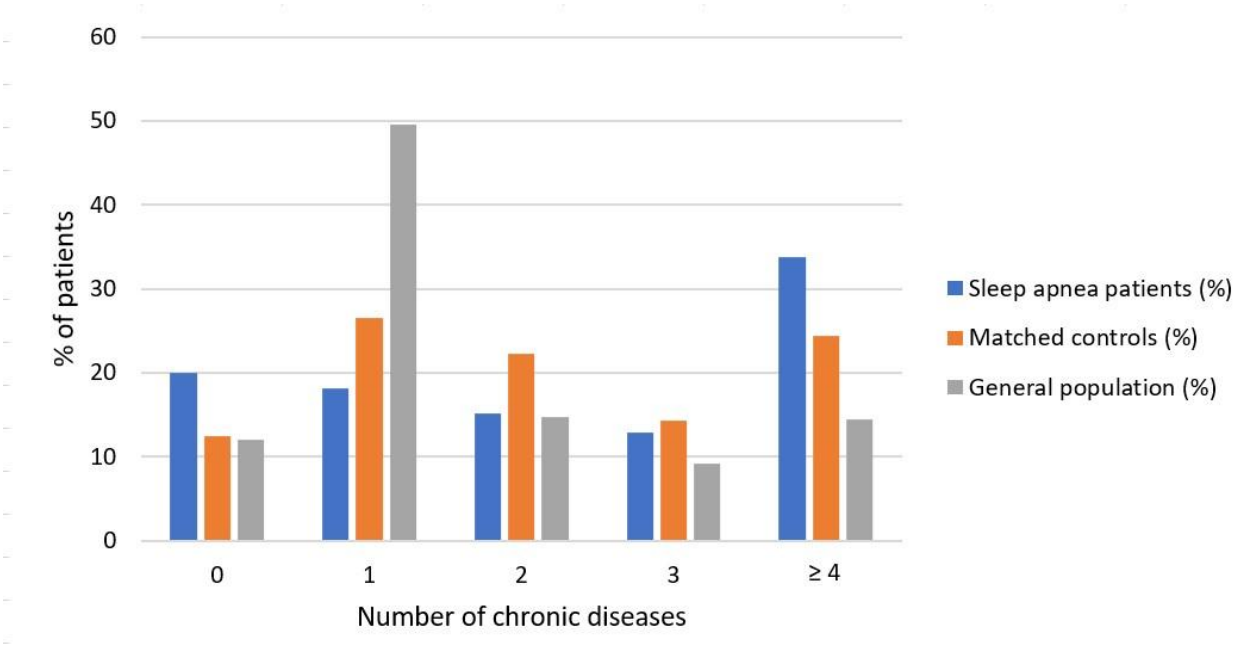

Fig 2. Number of chronic diseases at the time of SA diagnosis for individuals with incident SA (n=25,324), matched controls (n=25,324), and the general population (n=3,223, 399).