Multimorbidity and overall comorbidity of sleep apnoea: a Finnish nationwide study

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

[1]Central Hospital for Central Ostrobothnia, Dept of Pulmonary Diseases, Kokkola, Finland. [2]Sleep Research Centre, University of Turku, Turku, Finland. [3]Sleep and Breathing Centre and Division of Medicine, Dept of Pulmonary Diseases, Turku University Hospital, Turku, Finland. [4]Helsinki Sleep Clinic, Terveystalo Healthcare, Helsinki, Finland. [5]Dept 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 (makrip@utu.fi)

Shareable abstract (@ERSpublications)
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. https://bit.ly/36WMlX1

Cite this article as: Palomäki M, Saaresranta T, Anttalainen U, *et al*. Multimorbidity and overall comorbidity of sleep apnoea: a Finnish nationwide study. *ERJ Open Res* 2022; 8: 00646-2021 [DOI: 10.1183/23120541.00646-2021].

Received: 17 Nov 2021
Accepted: 25 March 2022

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 to 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 four or more 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 into multimorbidity in individuals with incident sleep apnoea.

Introduction

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

Comorbidity is more the rule than the exception in individuals with sleep apnoea [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 personalised medicine, we need to better understand the overall burden of comorbidities and multimorbidity profiles in individuals with sleep apnoea and their role in therapeutic approaches [6].

To investigate the prevalence and incidence of sleep apnoea, the overall burden of comorbidities in Finnish individuals with sleep apnoea, and multimorbidity profiles in those with incident sleep apnoea, we conducted a nationwide study utilising 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 anonymised register data, no ethics committee approval was required according to 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 (hospitalisations 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 sleep apnoea. G47.3 includes both obstructive and central sleep apnoea. 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 healthcare registers with information limited to diagnoses, care level (primary *versus* secondary) and dates of care, we do not have detailed information on the type of sleep test performed on each individual diagnosed with sleep apnoea. According to the current Finnish national care guidelines for obstructive sleep apnoea (OSA), a sleep test is a prerequisite for sleep apnoea diagnosis [8]. In some cases, sleep apnoea may be diagnosed with AHI ⩽5 events·h^{-1}, *e.g.* in cases where a home sleep apnoea test has been technically insufficient, the patient has typical symptoms and findings suggestive of sleep apnoea, and a trial with an automatic positive airway pressure device increases therapeutic pressure with subsequent relief of sleep apnoea symptoms. The vast majority have been diagnosed with home sleep testing, and perhaps 1–2% with PSG, as the availability of in-laboratory PSG in Finland is low. For each individual with incident sleep apnoea 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 adults aged ⩾18 years who had used primary or secondary healthcare services in Finland during 2017.

Prevalence and incidence of sleep apnoea

Prevalence of diagnosed sleep apnoea in 2019 is reported as percentage of the live adult population (age ⩾18 years) who had used primary or secondary healthcare services with the G47.3 diagnosis between January 2015 and December 2019. If an individual had received a sleep apnoea diagnosis prior to January 2015, but had not used healthcare services for sleep apnoea during the study period, he or she was not identified as a sleep apnoea patient. Individuals with sleep apnoea 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 sleep apnoea in 2017 was defined similarly, but with a mean washout period of 2.5 years (*i.e.* no previous sleep apnoea diagnosis from January 2015 to the date of 2017 diagnosis). The size of the adult population on 31 December 2017 (n=4 446 869) was used as the denominator.

Multimorbidity and comorbidities in incident sleep apnoea

Multimorbidity was defined as two or more chronic diseases for which the patient had used healthcare services between January 2015 and time of sleep apnoea 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 sleep apnoea, multimorbidity status was assessed prior to receiving the sleep apnoea diagnosis (*i.e.* the individual was multimorbid if two or more chronic diseases were present prior to the sleep apnoea diagnosis). We report the most common disease pathways to multimorbidity before sleep apnoea diagnosis based on the sequence of the first two chronic diseases preceding sleep apnoea diagnosis. We also present the distribution of the number of chronic diseases in each patient group.

For individuals with incident sleep apnoea, we report the prevalence of 26 diagnosed major common chronic disease groups, which are listed in the supplementary material. In addition, we compare the diagnosed prevalence of these major chronic diseases in the incident sleep apnoea cohort with 1) the matched control population and 2) the general population. We present a similar comparison for male *versus* female individuals with sleep apnoea. Comparisons are reported by odds ratios and 95% confidence intervals for each chronic disease group.

Statistical methods

The 95% confidence intervals for odds ratios 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 (StataCorp, 2017) was used for all analyses.

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 healthcare services with the G47.3 diagnosis (sleep apnoea) during the past 5 years. In 2017, 0.6% (25 324) of Finnish adults had incident sleep apnoea, translating to an annual incidence of 600 per 100 000. Of the incident sleep apnoea patients, 64.2% were men. Mean age at the time of sleep apnoea diagnosis was 57.2 years (56.3 years for men and 58.8 years 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 sleep apnoea patients were on average 5 years older, more often male and more often multimorbid.

Multimorbidity prior to sleep apnoea diagnosis

At the time of sleep apnoea diagnosis, 63% of individuals were multimorbid, compared with 38% in the general population (table 1). The most common pathways to multimorbidity before sleep apnoea diagnosis, defined as the sequence of first two chronic diseases before sleep apnoea 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

TABLE 1 Demographics for the incident sleep apnoea cohort at the time of sleep apnoea diagnosis, matched control population and total adult population using healthcare services in 2017 (*i.e.* the general population)

	Population	Male	Age, years (mean)	Age 18–65 years	Age 65–74 years	Age ⩾75 years	Multimorbidity (⩾2 chronic diseases)
Incident sleep apnoea							
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	3 223 399	42.9	52.1	67.7	17.1	15.25	38.1

Data are presented as n or %.

disease pairs preceding a sleep apnoea diagnosis. The most common pathway (true for n=2843 out of 15 954 multimorbid sleep apnoea 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 sleep apnoea diagnosis is presented in figure 2 for individuals with incident sleep apnoea, matched controls and the general population. Of incident sleep apnoea patients, 34% were heavily multimorbid, *i.e.* presented with four or more comorbidities, compared to 24% of matched controls and 14% of the general population (figure 2).

Chronic diseases at the time of sleep apnoea diagnosis

The diagnosed prevalence (number and percentage) of 26 major chronic diseases (an elaborated list is included in the supplementary material) at time of sleep apnoea 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 sleep apnoea diagnosis. The second and third most common chronic morbidities were hypertension and cardiovascular disease, respectively. Out of 26 morbidities analysed, we found statistically significant sex differences in 19.

The odds ratios for 26 major chronic diseases (supplementary material) are presented in table 3 for individuals with incident sleep apnoea *versus* matched controls, and in table 4 for those with incident sleep apnoea *versus* the general population. In incident sleep apnoea patients, we found the highest odds ratio for obesity, and the lowest odds ratio for dementia and related diseases compared to matched controls. Compared to the general population, odds ratios for major chronic diseases were higher in incident sleep apnoea 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 sleep apnoea in a nationwide sample. To our knowledge, this is the first study depicting different pathways of multimorbidity in sleep apnoea. It is the largest giving occurrences of multimorbidity in individuals with sleep apnoea. Of individuals with incident sleep apnoea, 34% were heavily multimorbid (*i.e.* with four or more chronic diseases). Multimorbidity was more prevalent in women than in men. In addition, we provide up-to-date information on sleep apnoea prevalence and incidence in Finland.

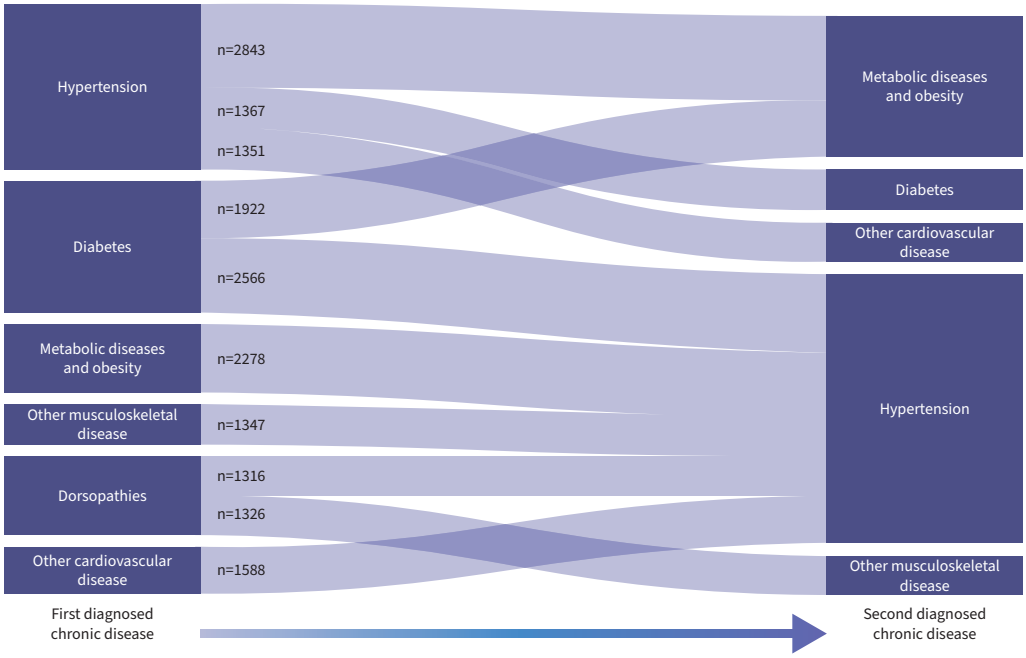

FIGURE 1 The 10 most common disease pathways to multimorbidity before sleep apnoea diagnosis based on the sequence of the first two chronic diseases. The group "other cardiovascular disease" does not include ischaemic heart disease.

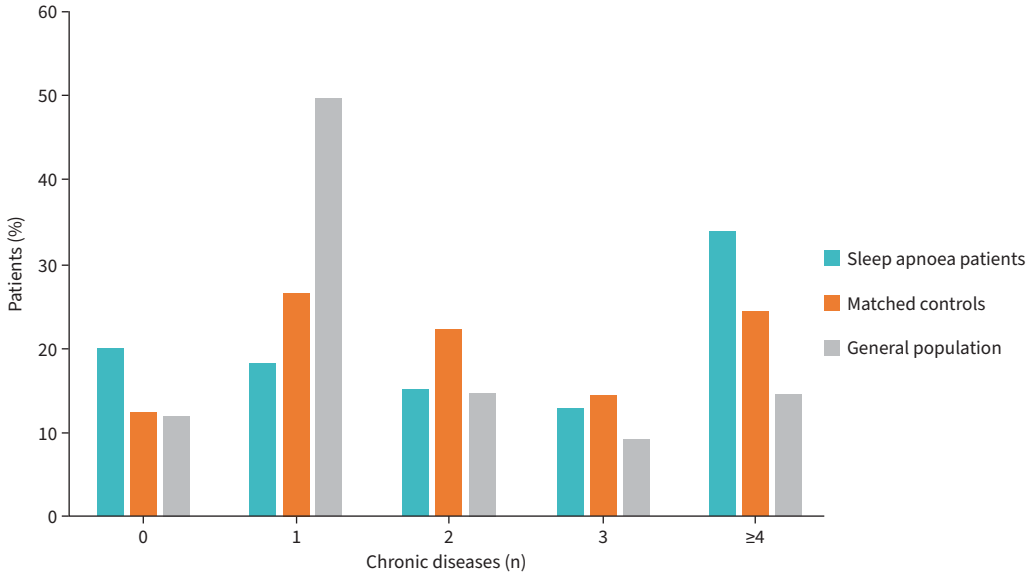

FIGURE 2 Number of chronic diseases at the time of sleep apnoea diagnosis for individuals with incident sleep apnoea (n=25 324), matched controls (n=25 324) and the general population (n=3 223 399).

In 2002, an expert group estimated that sleep apnoea prevalence was 3.7% in Finland [10]. In a 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, sleep apnoea 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 sleep apnoea diagnostics and treatment in Finland since 2015 [12]. Our figure may be an underestimate, as we might have missed those individuals who had received the sleep apnoea diagnosis >5 years earlier and had not used healthcare services during the period January 2015 to December 2019. Furthermore, the 2002 estimate also included undiagnosed individuals with sleep apnoea. The current figure of this study is based on diagnosed individuals with sleep apnoea, and therefore underestimates the true prevalence of sleep apnoea 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 sleep apnoea 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 OSA syndrome, where the patient is symptomatic, and their quality of life is impacted by excessive daytime sleepiness caused by OSA.

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

In our study, individuals with incident sleep apnoea were 5 years older at the time of diagnosis compared to those of the European Sleep Apnea Database (ESADA) cohort, but in line with the Swedish sleep apnoea register figures [4, 17]. In our study, almost one-third of incident sleep apnoea cases were aged ⩾65 years. Delay in the diagnosis, and hence treatment, of sleep apnoea 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 sleep apnoea were men. This is similar to the Swedish register data from 2018–2019, but lower than in the ESADA cohort, with data from the years 2007–2009 [4, 17]. The change in the male:female ratio from 3:1 to 2:1 in 10 years might reflect the enhanced

TABLE 2 Number and percentage of chronic comorbidities (as elaborated in the supplementary material) at the time of sleep apnoea diagnosis for all those diagnosed with sleep apnoea in Finland in 2017

	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

awareness of sex differences in sleep apnoea and better recognition of women with sleep apnoea, or the geographical differences in sleep apnoea awareness among healthcare professionals and lay people [19, 20]. Even as women are increasingly diagnosed with sleep apnoea, underdiagnosing women with sleep apnoea probably remains a relevant problem [21].

The clinical presentation and symptomatology of women with sleep apnoea is different from men, and gender modifies sleep apnoea [19, 22]. There is paucity of large studies analysing comprehensively sex differences in diseases preceding sleep apnoea diagnosis. In a Danish registry-based study, data of morbidities 3 years prior to sleep apnoea diagnosis were presented for the whole sleep apnoea cohort, but not separately for sexes, and only one-fifth of patients were women [23]. The large study by Mokhlesi *et al.* [24] found that hypertension and depression were more prevalent in women with incident sleep apnoea, and diabetes and ischaemic heart disease were more prevalent in men with incident sleep apnoea. In our study, sex differences in comorbidity profiles in incident sleep apnoea patients probably comply with disease distribution in the general population. At the time of sleep apnoea diagnosis, women were more often multimorbid than men (72% *versus* 58%). The increased prevalence of asthma, thyroid disease, obesity, gastro-oesophageal reflux disease (GORD) and mood disorders in women with incident sleep apnoea compared to men could be expected. Somewhat surprisingly, there was no sex difference in the prevalence of COPD. Contrary to the study by Mokhlesi *et al.*, we did not find a sex difference in the prevalence of cardiovascular disease. Furthermore, dyslipidaemia, cancer, schizophrenia and related disorders, cerebrovascular disease and organic sleep disorders were equally prevalent in both sexes with incident sleep apnoea. To our knowledge, ours is so far the largest study presenting comprehensive data on sex differences in sleep apnoea comorbidities. Our findings even suggest that women with incident sleep apnoea may present with heavier multimorbidity than men.

Our study is the largest to evaluate detailed multimorbidity in individuals with sleep apnoea. Multimorbidity in sleep apnoea was considerably more common than in the general population using healthcare services. One-third of individuals with incident sleep apnoea and one-fourth of matched controls presented with heavy multimorbidity. Previously, correlation between sleep apnoea and multimorbidity has

TABLE 3 Odds ratios with 95% confidence intervals for prevalence of major chronic disease (as elaborated in the supplementary material) among individuals with incident sleep apnoea *versus* matched controls

	All, sleep apnoea *versus* matched controls	Men, sleep apnoea *versus* matched controls	Women, sleep apnoea *versus* matched controls
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)	4.80 (3.36–6.86)
Heart failure	1.98 (1.77–2.22)	1.90 (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 and 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 (1.20–1.48)
Dyslipidaemia	1.27 (1.20–1.35)	1.31 (1.22–1.42)	1.24 (1.13–1.37)
Kidney and urinary tract disease	1.23 (1.10–1.37)	1.17 (1.03–1.32)	1.40 (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 (0.86–1.10)	1.29 (1.08–1.54)
Urogenital disease	1.06 (0.99–1.14)	1.10 (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 (0.96–1.10)
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 and delusional disorders	0.69 (0.60–0.79)	0.63 (0.53–0.75)	0.79 (0.63–0.99)
Dementia and other cerebral disorders	0.62 (0.57–0.67)	0.58 (0.53–0.64)	0.71 (0.61–0.82)

been reported only in severe sleep apnoea [25]. However, in a more recent and larger study, sleep apnoea was associated with an increased risk of multimorbidity, and in multimorbid men, undiagnosed sleep apnoea 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 sleep apnoea 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 sleep apnoea (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 sleep apnoea comorbidities [27]. In an earlier Danish study, odds ratio for musculoskeletal and connective tissue diseases was 1.36 (95% CI 1.29–1.42) in the incident sleep apnoea 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 odds ratio for these disorders compared to matched controls was slightly increased in women with incident sleep apnoea, but not in men. However, as sleep apnoea has been associated with chronic pain, our findings emphasise considering the possibility of sleep apnoea in individuals with musculoskeletal and connective tissue disorders [28].

As expected, we found increased odds ratios 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 sleep apnoea 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 sleep apnoea diagnosis consisted of 1.7 million individuals with sleep apnoea (50% women) and their matched controls [24]. That study used

TABLE 4 Odds ratios with 95% confidence intervals for prevalence of major chronic disease (as elaborated in the supplementary material) among individuals with incident sleep apnoea *versus* general population (*i.e.* the total adult population in Finland who used public healthcare services in 2017)

	All, sleep apnoea *versus* general population	Men, sleep apnoea *versus* general population	Women, sleep apnoea *versus* general population
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 and 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 and delusional disorders	1.10 (0.99–1.22)	0.90 (0.79–1.04)	1.36 (1.15–1.60)
Dementia and other cerebral disorders	0.92 (0.87–0.98)	0.87 (0.80–0.93)	0.86 (0.77–0.97)

data from a United States database comprising health insurance claims for working adults and retirees with employer-sponsored health insurance. After adjusting for age and sex, increased odds ratios with very narrow confidence intervals were found for all studied comorbidities. Compared to matched controls, type 2 diabetes, hypertension and depression were more prevalent in individuals with sleep apnoea in all age groups, whereas congestive heart failure, ischaemic heart disease, cardiac arrythmias and stroke were more prevalent only in older individuals with sleep apnoea.

In our study, the odds ratio for cerebrovascular disease prior to a diagnosis of sleep apnoea was increased in women, but not in men. Previously, the risk of stroke in sleep apnoea 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 sleep apnoea 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 sleep apnoea was shown to increase the risk of stroke in men, but only in women with severe sleep apnoea [32]. In the recent Finnish cohort study, sleep apnoea 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 sleep apnoea [30].

We found lower risk for dementia and schizophrenia/delusional disorders in both males and females with incident sleep apnoea compared to matched controls. We surmise sampling bias to be the explanation. Sleep apnoea 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 odds ratio for dementia or schizophrenia/delusional disorders in individuals with incident sleep apnoea might be due to under-recognition of sleep apnoea symptoms and reduced access to healthcare together with other factors in those already diagnosed with these diseases [35].

The Danish nationwide study with ICD-10-based morbidities 3 years prior to sleep apnoea 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 sleep apnoea and respiratory diseases (particularly asthma and COPD), diabetes, atrial fibrillation and hypertension, but we could not confirm that individuals with incident sleep apnoea are more prone to neurological diseases than matched controls.

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

The lower risk of cancer in both males and females with incident sleep apnoea compared to matched controls in our study lacks an explanation. Studies addressing incidence and mortality of cancer in individuals with sleep apnoea have shown conflicting results [41, 42]. In prior studies addressing comorbidities prior to sleep apnoea diagnosis, only Jennum *et al*. [23] reported neoplasms and found no difference between individuals with sleep apnoea and controls. We were not able to analyse the effect of smoking on the risk of 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 sleep apnoea 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 sleep apnoea 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 sleep apnoea compared to matched controls. This could reflect diagnostic challenges, which can result in delayed sleep apnoea diagnosis. Excessive daytime sleepiness is one of the key symptoms of sleep apnoea, and on the other hand 39–58% of individuals with sleep apnoea report insomnia symptoms [45]. It is possible that these symptoms have not been correctly attributed to the underlying sleep apnoea.

Compared to the general population, incident sleep apnoea 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 sleep apnoea patients compared to matched controls. We attribute the high odds ratios for major chronic diseases among incident sleep apnoea patients *versus* the general population partly to demographic differences: incident sleep apnoea 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 minimised the risk of reporting bias by analysing comorbidity data only prior to sleep apnoea diagnosis.

Our study has some limitations. First, the aforementioned registers do not cover private healthcare. However, most of the care for sleep apnoea 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 patient files or income and education registers, we were not able to evaluate associations between comorbidities and sleep apnoea severity, symptomatology, socioeconomic circumstances or individual lifestyle habits. Additionally, BMI could not be used in matching, as our data did not include BMI. Fourth, the diagnosis of sleep apnoea in most cases was based on home sleep testing, as the availability of in-laboratory PSG 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 sleep apnoea in a large, nationwide sample. While supporting most of the previous evidence on the association between sleep apnoea 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 sleep apnoea and cancer, glaucoma and stroke/cerebrovascular diseases. Our results signal under-recognition of sleep apnoea

in those with dementia or psychotic disorder, and possible diagnostic delay due to not attributing the patient's sleep disorders to sleep apnoea. Most of the research on comorbidities in sleep apnoea uses the time of diagnosis of sleep apnoea as a starting point. Studying which diseases precede the diagnosis of sleep apnoea 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 sleep apnoea diagnosis.

Provenance: Submitted article, peer reviewed.

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

Author contributions: All authors were involved in the conception and design of the study. Statistical analysis was performed by M. Linna and J. Keto. All authors were involved in the interpretation of data. The draft was written by M. 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.

Conflict of interest: M. Palomäki has received lecture fees from GlaxoSmithCline Ltd, Chiesi Ltd and Orion Ltd, and research grants from the Foundation of the Finnish Anti-Tuberculosis Association, Väinö and Laina Kivi Foundation, and Ida Montin Foundation. T. Saaresranta is the chairperson of the Finnish Task Force for Current Care Guidelines of Adult Sleep Apnoea. She has received lecture fees from Jazz Pharmaceuticals and financial support for educational events from ResMed Finland and Philips Healthcare Finland. U. Anttalainen has received research grants from the Finnish Government/Turku University Hospital the, Foundation of the Finnish Anti-Tuberculosis Association, the Tampere Tuberculosis Foundation and the Research Foundation for Respiratory Diseases. M. Partinen has received a study grant from the Parkinson Foundation, consulting fees from Jazz Pharmaceuticals and Bioprojet, and lecturing fees from MSD, Takeda and GSK, and has participated in the medical advisory board of Jazz Pharmaceuticals and Bioprojet. J. Keto is an employee of Jazz Pharmaceuticals. M. Linna has received consulting fees from Jazz Pharmaceuticals.

Support statement: This study is based on the IMPRO research dataset funded by the Academy of Finland. Under the direction of the authors, Peloton Advantage, LLC, an Open Health company, provided editorial support for this article, which was funded by Jazz Pharmaceuticals. This study was supported by the Foundation of the Finnish Anti-Tuberculosis Association. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Heinzer R, Vat S, Marques-Vidal P, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015; 3: 310–318.
2 Senaratna CV, Lodge CJ, Lowe AJ, *et al.* Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev* 2017; 34: 70–81.
3 Fietze I, Laharnar N, Obst A, *et al.* Prevalence and association analysis of obstructive sleep apnea with gender and age differences – results of SHIP-Trend. *J Sleep Res* 2019; 28: e12770.
4 Hedner J, Grote L, Bonsignore M, *et al.* The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; 38: 635–642.
5 Nicholson K, Makovski TT, Griffith LE, *et al.* Multimorbidity and comorbidity revisited: refining the concepts for international health research. *J Clin Epidemiol* 2019; 105: 142–146.
6 Bonsignore MR, Baiamonte P, Mazzuca E, *et al.* Obstructive sleep apnea and comorbidities: a dangerous liaison. *Multidiscip Respir Med* 2019; 14: 8.
7 Strausz S, Ruotsalainen S, Ollila HM, *et al.* Genetic analysis of obstructive sleep apnoea discovers a strong association with cardiometabolic health. *Eur Respir J* 2021; 57: 2003091.
8 The Finnish Medical Society Duodecim. Uniapnea (Obstruktiivinen Uniapnea Aikuisilla). [Sleep Apnoea (Obstructive Sleep Apnoea in Adults) Current Care Guidelines]. 2021. www.kaypahoito.fi/hoi50088/ Date last accessed: 30 January 2022.
9 Saarela J, Finnäs F. Geographic ancestry and cause-specific mortality in a national population. *Popul Res Policy Rev* 2009; 28: 169–194.
10 Laitinen L, Anttalainen U, Pietinalho A, *et al.* Sleep apnoea: Finnish National guidelines for prevention and treatment 2002–2012. *Respir Med* 2003; 97: 337–365.
11 Strausz S, Havulinna AS, Tuomi T, *et al.* Obstructive sleep apnoea and the risk for coronary heart disease and type 2 diabetes: a longitudinal population-based study in Finland. *BMJ Open* 2018; 8: e022752.

12 Keränen T. Uniapnea ruuhkautti keuhkopoliklinikat. [Respiratory outpatient clinics are crowded for new sleep apnoea patients]. *Suom Laakaril* 2020; 75: 24.
13 Benjafield AV, Ayas NT, Eastwood PR, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019; 7: 687–698.
14 Newman AB, Foster G, Givelber R, *et al.* Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med* 2005; 165: 2408–2413.
15 Tishler PV, Larkin EK, Schluchter MD, *et al.* Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA* 2003; 289: 2230–2237.
16 Egeberg A, Khalid U, Gislason GH, *et al.* Psoriasis and sleep apnea: a Danish nationwide cohort study. *J Clin Sleep Med* 2016; 12: 663–671.
17 Hedner J, Hellstrand M. SESAR – Svenska Sömnapnéregistret. Årsrapport 2019. [Swedish Sleep Apnoea Registry. Annual Report 2019]. https://registercentrum.blob.core.windows.net/sesar/r/SESAR-arsrapport-2019-HJeaXmsXNv.pdf 2019.
18 Martínez-García MÁ, Chiner E, Hernández L, *et al.* Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. *Eur Respir J* 2015; 46: 142–151.
19 Bonsignore MR, Saaresranta T, Riha RL. Sex differences in obstructive sleep apnoea. *Eur Respir Rev* 2019; 28: 190030.
20 Wimms A, Woehrle H, Ketheeswaran S, *et al.* Obstructive sleep apnea in women: specific issues and interventions. *Biomed Res Int* 2016; 2016: 1764837.
21 Franklin KA, Sahlin C, Stenlund H, *et al.* Sleep apnoea is a common occurrence in females. *Eur Respir J* 2013; 41: 610–615.
22 Saaresranta T, Hedner J, Bonsignore MR, *et al.* Clinical phenotypes and comorbidity in European sleep apnoea patients. *PLoS One* 2016; 11: e0163439.
23 Jennum P, Ibsen R, Kjellberg J. Morbidity prior to a diagnosis of sleep-disordered breathing: a controlled national study. *J Clin Sleep Med* 2013; 9: 103–108.
24 Mokhlesi B, Ham SA, Gozal D. The effect of sex and age on the comorbidity burden of OSA: an observational analysis from a large nationwide US health claims database. *Eur Respir J* 2016; 47: 1162–1169.
25 Robichaud-Hallé L, Beaudry M, Fortin M. Obstructive sleep apnea and multimorbidity. *BMC Pulm Med* 2012; 12: 60.
26 Ruel G, Martin SA, Lévesque JF, *et al.* Association between multimorbidity and undiagnosed obstructive sleep apnea severity and their impact on quality of life in men over 40 years old. *Glob Heal Epidemiol Genom* 2018; 3: e10.
27 Finley CR, Chan DS, Garrison S, *et al.* What are the most common conditions in primary care? Systematic review. *Can Fam Physician* 2018; 64: 832–840.
28 Charokopos A, Card ME, Gunderson C, *et al.* The association of obstructive sleep apnea and pain outcomes in adults: a systematic review. *Pain Med* 2018; 19: S69–S75.
29 Smith R, Ronald J, Delaive K, *et al.* What are obstructive sleep apnea patients being treated for prior to this diagnosis? *Chest* 2002; 121: 164–172.
30 Li M, Hou WS, Zhang XW, *et al.* Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. *Int J Cardiol* 2014; 172: 466–469.
31 Arzt M, Young T, Finn L, *et al.* Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005; 172: 1447–1451.
32 Redline S, Yenokyan G, Gottlieb DJ, *et al.* Obstructive sleep apnea-hypopnea and incident stroke: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2010; 182: 269–277.
33 Kerner NA, Roose SP. Obstructive sleep apnea is linked to depression and cognitive impairment: evidence and potential mechanisms. *Am J Geriatr Psychiatry* 2016; 24: 496–508.
34 Kuruppu DK, Matthews BR. Young-onset dementia. *Semin Neurol* 2013; 33: 365–385.
35 Myles H, Myles N, Antic NA, *et al.* Obstructive sleep apnea and schizophrenia: a systematic review to inform clinical practice. *Schizophr Res* 2016; 170: 222–225.
36 Wu ZH, Yang XP, Niu X, *et al.* The relationship between obstructive sleep apnea hypopnea syndrome and gastroesophageal reflux disease: a meta-analysis. *Sleep Breath* 2019; 23: 389–397.
37 Ju G, Yoon I-YY, Lee SD, *et al.* Relationships between sleep disturbances and gastroesophageal reflux disease in Asian sleep clinic referrals. *J Psychosom Res* 2013; 75: 551–555.
38 Basoglu OK, Vardar R, Tasbakan MS, *et al.* Obstructive sleep apnea syndrome and gastroesophageal reflux disease: the importance of obesity and gender. *Sleep Breath* 2015; 19: 585–592.
39 Huon LK, Liu SYC, Camacho M, *et al.* The association between ophthalmologic diseases and obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath* 2016; 20: 1145–1154.
40 Shi Y, Liu P, Guan J, *et al.* Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review. *PLoS One* 2015; 10: e0115625.

41 Palamaner Subash Shantha G, Kumar AA, Cheskin LJ, *et al.* Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis. *Sleep Med* 2015; 16: 1289–1294.
42 Zhang X-B, Peng L-H, Lyu Z, *et al.* Obstructive sleep apnoea and the incidence and mortality of cancer: a meta-analysis. *Eur J Cancer Care* 2017; 26: e12427.
43 Myllylä M, Hammais A, Stepanov M, *et al.* Nonfatal and fatal cardiovascular disease events in CPAP compliant obstructive sleep apnea patients. *Sleep Breath* 2019; 23: 1209–1217.
44 Official Statistics of Finland. Tobacco Statistics. 2004. www.stat.fi/til/tup/2004/tup_2004_2005-11-25_tie_001.html/ Date last accessed: 24 January 2022.
45 Luyster FS, Buysse DJ, Strollo PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J Clin Sleep Med* 2010; 6: 196–204.
46 Lyons MM, Bhatt NY, Pack AI, *et al.* Global burden of sleep-disordered breathing and its implications. *Respirology* 2020; 25: 690–702.