





A study on the epidemiology of tinnitus in the United Kingdom

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Purpose: Subjective tinnitus is a common symptom with potentially negative impact on quality of life. More research is required to gain a deeper understanding of the disease and its clinical presentation. To estimate the incidence of tinnitus and to describe patient-related characteristics such as lifestyle factors and comorbidities.

Patients and methods: Using the Clinical Practice Research Datalink, we calculated incidence rates of first-time diagnosed tinnitus in an adult population between 2000 and 2016. We stratified incidence rates by sex, age, and year of diagnosis. Additionally, we performed a 1:1 matched case-control study comparing body mass index, lifestyle factors and selected comorbidities between patients with incident tinnitus and tinnitus-free controls.

Results: We identified 109 783 adults with a first-time diagnosis of tinnitus between 2000 and 2016, yielding an overall age-standardized incidence rate of 25.0 new tinnitus cases per 10,000 person-years (95% CI: 24.6–25.5). There was a steady increase in tinnitus incidence throughout the study period. Approximately 80% of tinnitus cases were diagnosed at age 40 years or older. We observed the highest incidence rate in individuals aged 60–69 years (41.2 per 10,000 person-years, 95% CI: 40.7–41.7). Smokers and alcohol drinkers were at lower risk of being diagnosed with tinnitus compared with non-smokers and non-drinkers, respectively. The occurrence of tinnitus was strongly associated with a recent diagnosis of several otological and vestibular disorders as well as head and neck disorders.

Conclusion: The present observational study found an increasing incidence of tinnitus over time, emphasizing the continuously growing health burden. The findings on patient characteristics, lifestyle factors, and selected comorbidities contribute to a better understanding of risk factors for tinnitus.

Keywords: case-control study, clinical practice research datalink, lifestyle factors, incidence rates, tinnitus

Introduction

Patients suffering from subjective tinnitus experience a perception of sound in the absence of an external source. It is a symptom audible only to the patient, and not to the examiner.¹⁻³ The nature of tinnitus varies and is described as ringing, buzzing, clicking, hissing, roaring, humming, or pulsations. The manifestation differs considerably in severity, ranging from mild to very bothersome.^{4,5} A severe, persistent form commonly introduces comorbidities such as sleep disturbance, anxiety or depression, and as a consequence substantially affect the patients' quality of life.⁶⁻⁹

Tinnitus is a frequent symptom in the developed world. Nevertheless, there is no universal definition, and as a result epidemiological studies report a wide range of prevalences extending from 5.1% to 42.7%.¹⁰ In the United Kingdom (UK), a large

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observational study reported an incidence rate of 5.4 cases of clinically significant tinnitus per 10,000 person-years,¹¹ and another study estimated the annual healthcare burden of tinnitus-related costs to be £750 million in the National Health Service (NHS).¹² A similar study in the Netherlands attributed €1.9 billion of direct health care costs to tinnitus, whereas the total cost of illness (health care costs, productivity losses, and out-of-pocket costs) was considerably higher amounting to €6.8 billion.¹³

The pathophysiology of tinnitus is not fully understood,¹⁴ however, there has been remarkable progress in recent years. Results from animal studies, mainly in rodents, complemented by imaging studies in humans suggest various underlying mechanisms affecting auditory and non-auditory brain areas, as well as the interaction between the auditory and the somatosensory structures.^{15,16} Based on these pathophysiological concepts, various therapeutic compounds (mostly approved for other indications) were tested in tinnitus patients. Despite this substantial effort, clear evidence for an effective pharmacological treatment is still lacking.^{16–18} The difficulty to demonstrate replicable significant clinical benefit may be explained by the heterogeneity of tinnitus (in terms of perception, distress, concomitant comorbidities and risk factors, as well as the underlying etiology).^{19–21} Thus, to date guidelines do not recommend any specific drug therapy.^{2,15}

More research is required to gain a deeper understanding of the disease and a better characterization of affected patients, including lifestyle factors and common comorbidities

In this population-based study, we estimate the incidence of tinnitus recorded by general practitioners (GPs) in the UK from January 2000 to December 2016, and describe patient-related characteristics with respect to demography, lifestyle factors and comorbidities compared with persons without tinnitus.

Materials and methods

Data source

We used primary care data derived from the Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The CPRD is an anonymized database created in 1987 that contains ongoing medical records from over 11 million patients provided by approximately 700 GP practices throughout the UK.²² Recorded data include patients' demographics, lifestyle

factors, diagnoses, signs and symptoms, treatments, test results, and referrals to secondary care.^{22–24} CPRD patients represent the general UK population with respect to sex, age and ethnicity.²² Several studies have reported on the high quality and validity of the database.^{23,25,26} The Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency database research (MHRA) approved the study (protocol number: 18_024R) and the study protocol was available to the journal and reviewers.

Study design and study population

We established two separate study populations. First, we conducted a retrospective cohort study to quantify incidence rates (IRs) of first-time diagnosed tinnitus. Therefore, we included all adult patients who were present in the CPRD population between 2000 and 2016 and who had a minimum active history in the CPRD of 3 years prior to cohort entry. We excluded patients if they had a recorded diagnosis for malignant cancer or HIV/AIDS prior to cohort entry.

Second, we conducted a separate case-control study, for which we identified all patients in the CPRD with a first-time Read code for tinnitus at the age of 18 years or older between January 1st, 2000 and December 31st, 2016 (cases). Like in the cohort study, we excluded all patients with less than three years of recorded history in the CPRD prior to the date of the first tinnitus diagnosis (index date) to minimize outcome misclassification by including prevalent tinnitus cases. In addition, we again excluded patients with any record of malignancy or HIV/AIDS prior to the index date, as these patients may receive specialized care and often suffer from various additional comorbidities.

We matched each tinnitus case to a randomly selected control patient who did not have a recorded diagnosis for tinnitus in the CPRD medical record. Cases and controls were matched on sex, age, general practice, years of history in the CPRD, and calendar time and we applied the same exclusion criteria to controls as we did to cases.

Statistical analysis

In the cohort analysis, we calculated crude and age-standardized IRs (ASR) of first-time diagnosed tinnitus in the CPRD population by dividing the total number of incident tinnitus diagnoses by the person-years (PY) at risk overall as well as stratified by age, sex, and year of diagnosis. We assessed PY at risk by summing-up person-time between

cohort entry and the end of follow-up, which was defined as the earliest out of the day of a first-time diagnosis of tinnitus diagnosis, death, leaving the practice, or December 31st, 2016. Age-standardization was performed using the European Standard Population published in 2013 by Eurostat, the Statistical Office of the European Union.²⁷

In the case-control analysis we conducted conditional logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the following exposure groups: BMI (<18.5, 25.0–29.9, ≥30.0, and 30.0–34.9, 35.0–39.9, ≥40 kg m⁻², unknown, compared to normal BMI [18.5–24.9 kg m⁻²]), smoking (ex-smokers, current smokers, unknown smoking status compared to non-smokers) and alcohol consumption (ex-drinkers, current drinkers subdivided in units per week, unknown status, compared to non-drinkers). Furthermore, we investigated the association between tinnitus and selected comorbidities (systemic somatic diseases and neurological/psychological disorders, otological and vestibular disorders, and head and neck disorders) overall as well as stratified by sex. For otological or vestibular disorders as well as for head and neck disorders, we also considered the amount of time between the last record of the respective condition and the index date (≤30, 31–360 days or >360 days prior to (including) the index date). All covariates were assessed prior to the index date.

We adjusted all OR for smoking, alcohol consumption, and BMI. We did not adjust for any other comorbidities due to the descriptive nature of this analysis.

For confidentiality reasons, we do not provide the number of patients in categories containing less than five patients.

We performed all analyses using SAS 9.4 software (SAS Institute, Cary, North Carolina, USA). Statistical significance was set at the alpha level of 0.05.

Results

Characteristics of the study population

We identified 109,783 adults with a first-time recorded Read code for tinnitus between January 2000 and December 2016. There was a similar number of males and females. The mean age was 54.7 years (standard deviation [SD] ±15.9), though women were slightly older than men at the time of diagnosis (55.7 [SD ±16.5] and 53.6 [SD ±15.2] years, respectively). Approximately two thirds of the tinnitus cases were between 40 and 69 years of age at first recording of tinnitus (Table 1).

Incidence rates (IRs)

Age-standardized IR (ASR) of first time GP-recorded tinnitus was 25.0 per 10,000 PY (95% CI: 24.6–25.5), and rates were similar for men (ASR of 25.7, 95% CI: 25.0–26.4) and women (ASR 24.7, 95% CI: 24.0–25.3 per 10,000 PY). The IRs increased with age and were highest in the age group 60–69 years (41.2 per 10,000 PY, 95% CI: 40.7–41.7, Figure 1). During the course of the study period, we found a steady increase in the incidence of tinnitus, which was similar in men and women (Figure 2) as well as in younger and older adults (<30 years and ≥30 years of age; data not shown). IRs stratified by sex, age group, and year of diagnosis (age-standardised and crude incidence rates) are provided in the Table S1.

Lifestyle factors

We observed an adjusted ORs for diagnosed tinnitus of 0.91 (95% CI: 0.89–0.94) in obese patients (BMI ≥30.0 kg/m²), and an adjusted ORs of 0.91 (95% CI: 0.84–0.97) in underweight patients (BMI <18.5 kg/m²), when compared to individuals of normal weight.

Compared with non-smokers, current smokers were at a reduced risk of being diagnosed with tinnitus (adj. OR 0.78, 95% CI: 0.76–0.80). Overall, current alcohol drinkers had a minimally decreased risk compared to non-drinkers. However, the effect became stronger with increasing levels of alcohol consumption (in consumed units of alcohol per week, Table 1).

Comorbidities

Internal diseases and neurological/psychological disorders

We observed an increased risk of being diagnosed with tinnitus in patients with insomnia (adj. OR 1.45, 95% CI: 1.41–1.49), anxiety (adj. OR 1.39, 95% CI: 1.35–1.42), and depression (adj. OR 1.31, 95% CI: 1.28–1.34). We found a decreased risk of being diagnosed with tinnitus in patients with dementia (adj. OR 0.43, 95% CI: 0.37–0.50), Parkinson's disease (adj. OR 0.63, 95% CI: 0.54–0.74), and schizophrenia (adj. OR 0.76, 95% CI: 0.69–0.85). No association was found between tinnitus and seizures/epilepsy or multiple sclerosis.

Cardiovascular comorbidities (arrhythmia, hypertension, myocardial infarction, congestive heart failure, and stroke/transient ischemic attack) did not reveal any meaningfully increased or decreased ORs. Diabetes mellitus revealed a decreased adjusted OR of 0.85 (95% CI: 0.83–0.89), whereas other metabolic diseases (hyperlipidemia, hypothyroidism,

Table 1 Distribution of patient characteristics and lifestyle factors in patients with tinnitus and their matched controls

	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Sex				
Male	53,874 (49.1)	53,874 (49.1)	NA	NA
Female	55,909 (50.9)	55,909 (50.9)	NA	NA
Age (years)				
<20	1097 (1.0)	1100 (1.0)	NA	NA
20–29	7118 (6.5)	7109 (6.5)	NA	NA
30–39	11,757 (10.7)	11,757 (10.7)	NA	NA
40–49	19,454 (17.7)	19,476 (17.7)	NA	NA
50–59	26,247 (23.9)	26,233 (23.9)	NA	NA
60–69	24,097 (22.0)	24,122 (22.0)	NA	NA
70–79	13,860 (12.6)	13,823 (12.6)	NA	NA
≥80	6153 (5.6)	6163 (5.6)	NA	NA
BMI (kg/m²)				
12.0–18.4	1561 (1.4)	1634 (1.5)	0.88 (0.82–0.95)	0.91 (0.84–0.97)
18.5–24.9	36,055 (32.8)	33,901 (30.9)	1.00 (reference)	1.00 (reference)
25.0–29.9	36,138 (32.9)	32,981 (30.0)	1.04 (1.02–1.06)	1.02 (1.00–1.04)
30.0–60.0	21,853 (19.9)	22,157 (20.2)	0.94 (0.91–0.96)	0.91 (0.89–0.94)
30.0–34.9	14,876 (13.6)	14,847 (13.5)	0.95 (0.93–0.96)	0.93 (0.90–0.96)
35.0–39.9	4794 (4.4)	4917 (4.5)	0.93 (0.89–0.97)	0.90 (0.86–0.94)
40.0–60.0	2183 (2.0)	2393 (2.2)	0.87 (0.82–0.92)	0.83 (0.79–0.89)
Unknown	14,176 (12.9)	19,110 (17.4)	0.64 (0.62–0.66)	0.78 (0.75–0.80)
Smoking status				
Non-smoker	53,513 (48.7)	50,517 (46.0)	1.00 (reference)	1.00 (reference)
Ex-smoker	32,952 (30.0)	29,321 (26.7)	1.08 (1.06–1.10)	1.08 (1.06–1.10)
Current smoker	18,334 (16.7)	21,904 (20.0)	0.78 (0.76–0.79)	0.78 (0.76–0.80)
Unknown	4984 (4.5)	8041 (7.3)	0.51 (0.49–0.53)	0.68 (0.65–0.71)
Alcohol consumption				
Non-drinker	17,399 (15.9)	16,062 (14.6)	1.00 (reference)	1.00 (reference)
Ex-drinker	2308 (2.1)	2005 (1.8)	1.07 (1.00–1.14)	1.09 (1.03–1.17)
Current drinker (units/week)				
1–9	29,403 (26.8)	27,743 (25.3)	0.97 (0.95–1.00)	0.96 (0.93–0.98)
10–19	12,159 (11.1)	11,971 (10.9)	0.93 (0.89–0.96)	0.91 (0.88–0.94)
≥20	9132 (8.3)	9462 (8.6)	0.87 (0.84–0.90)	0.88 (0.84–0.91)
unknown	28,443 (25.9)	27,281 (24.9)	0.95 (0.93–0.98)	0.95 (0.92–0.98)
Unknown	10,939 (10.0)	15,259 (13.9)	0.59 (0.57–0.62)	0.74 (0.71–0.77)

Notes: ^aAdjusted for BMI category, smoking status, alcohol consumption.

Abbreviations: BMI, body mass index; CI, confidence interval; NA, not applicable; OR, odds ratio.

and hyperthyroidism) were not associated with the risk of being diagnosed with tinnitus.

Irritable bowel syndrome and fibromyalgia were statistically significantly associated with the risk of being diagnosed with tinnitus (adj. ORs 1.56, 95% CI: 1.51–1.61, and 1.54, 95% CI: 1.42–1.67), whereas ORs for asthma, COPD, and rheumatoid arthritis were not associated (Table 2).

Stratification by sex did not reveal meaningful effect modification for the risk of tinnitus in association with mental health and other comorbidities (Table S2).

Otological and vestibular disorders

Having a medical history of various otological or vestibular disorders was associated with a higher risk of being diagnosed with tinnitus. All inner ear conditions evaluated were found positively associated with tinnitus. This included common conditions such as ear infections (labyrinthitis, otitis media, or otitis externa) and cerumen, as well as rarer conditions such as sensorineural or conductive hearing loss, acute vestibular neuritis or benign positional vertigo. These observed associations were stronger

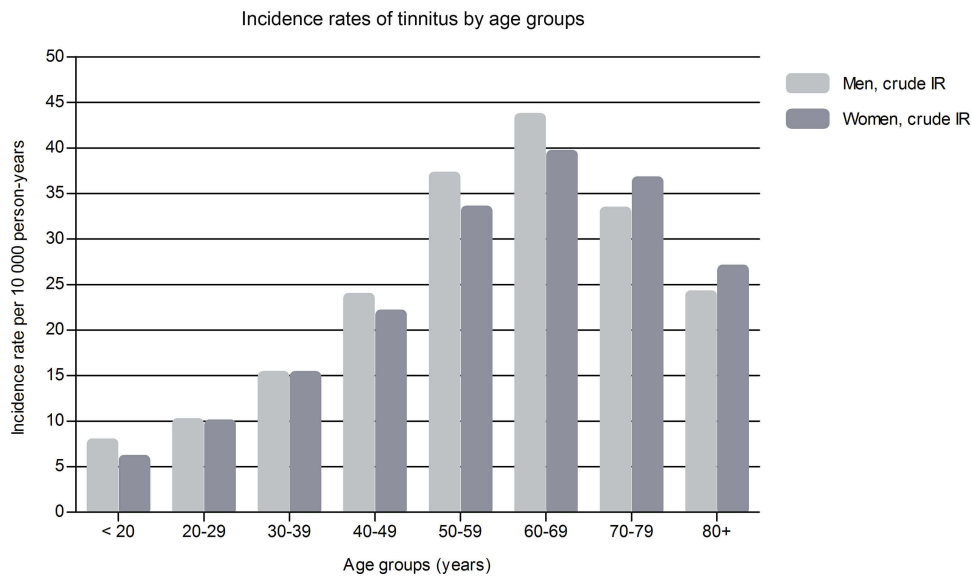


Figure 1 Age- and sex-specific crude incidence rates (IRs) of tinnitus first-time diagnoses in the United Kingdom from 2000 to 2016.

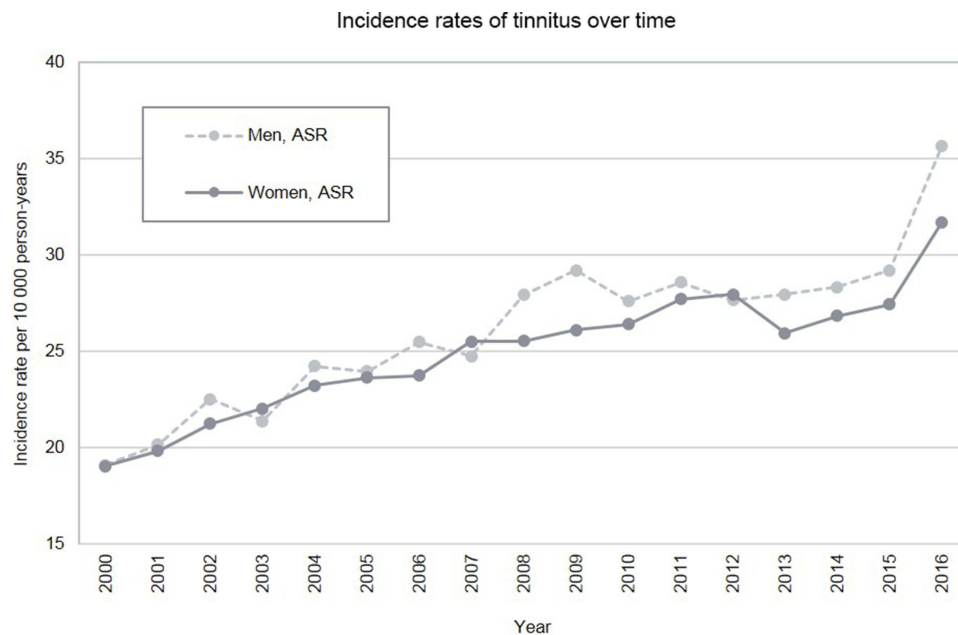


Figure 2 Sex-specific and age-standardised incidence rates (ASRs) of tinnitus first-time diagnoses in the United Kingdom from 2000 to 2016. **Note:** Standard population from Eurostat.²⁷

when the comorbidities were closer in time to the index date (Table 3, stratified by sex in Table S3). The association was strongest with sensorineural hearing loss (adj. OR 161.70, 95% CI: 60.56–431.73) followed by acute vestibular neuritis (adj. OR 34.14, 95% CI: 4.79–243.60), otitis media (adj. OR 22.82, 95% CI: 17.23–30.22), labyrinthitis (adj. OR 20.19, 95% CI: 12.88–31.65), conductive hearing loss (adj. OR 19.51, 95% CI: 6.07–62.74), benign positional vertigo (adj. OR 12.94, 95% CI: 9.24–18.11),

cerumen (adj. OR 11.56, 95% CI: 10.41–13.83), and otitis externa (adj. OR 9.87, 95% CI: 8.52–11.43).

Head and neck disorders

Similarly, tinnitus patients were more likely to have a prior diagnosis of head and neck disorders compared with controls. Risk estimates were particularly increased if these diagnoses were recorded within one month before the ID. We found elevated ORs for tinnitus in patients with

Table 2 Distribution of comorbidities in patients with tinnitus and their matched controls: internal diseases and neurological/psychological disorders

	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Neurological/psychological disorders				
Insomnia	14,944 (13.6)	11,043 (10.1)	1.46 (1.42–1.50)	1.45 (1.41–1.49)
Anxiety	22,872 (20.8)	17,839 (16.3)	1.39 (1.36–1.42)	1.39 (1.35–1.42)
Depression	22,421 (20.4)	18,363 (16.7)	1.30 (1.27–1.33)	1.31 (1.28–1.34)
Seizure/Epilepsy	2393 (2.2)	2366 (2.2)	1.01 (0.96–1.07)	1.01 (0.96–1.08)
Multiple Sclerosis	324 (0.3)	369 (0.3)	0.88 (0.76–1.02)	0.89 (0.76–1.03)
Schizophrenia	623 (0.6)	831 (0.8)	0.75 (0.67–0.83)	0.76 (0.69–0.85)
Parkinson Disease	256 (0.2)	411 (0.4)	0.62 (0.53–0.73)	0.63 (0.54–0.74)
Dementia	282 (0.3)	660 (0.6)	0.42 (0.36–0.48)	0.42 (0.37–0.49)
Cardiovascular disorders				
Arrhythmia	6374 (5.8)	5304 (4.8)	1.23 (1.18–1.28)	1.19 (1.14–1.24)
Hypertension	25,988 (23.7)	25,609 (23.3)	1.02 (1.00–1.05)	0.98 (0.96–1.00)
Myocardial infarction	2935 (2.7)	2974 (2.7)	0.99 (0.94–1.04)	0.95 (0.90–1.00)
Congestive heart failure	1505 (1.4)	1593 (1.5)	0.94 (0.88–1.01)	0.92 (0.85–0.99)
Stroke/TIA	3385 (3.1)	3735 (3.4)	0.90 (0.86–0.94)	0.88 (0.84–0.93)
Metabolic disorders				
Hyperlipidemia	12,081 (11.0)	10,595 (9.7)	1.18 (1.15–1.22)	1.14 (1.11–1.18)
Hypothyroidism	6225 (5.7)	5500 (5.0)	1.15 (1.10–1.19)	1.13 (1.08–1.17)
Hyperthyroidism	1523 (1.4)	1363 (1.2)	1.12 (1.04–1.21)	1.11 (1.03–1.20)
Diabetes mellitus	6915 (6.3)	7626 (7.0)	0.90 (0.87–0.93)	0.85 (0.83–0.89)
Other disorders				
Irritable bowel syndrome	11,008 (10.0)	7288 (6.6)	1.59 (1.54–1.65)	1.56 (1.51–1.61)
Fibromyalgia	1588 (1.5)	1053 (1.0)	1.54 (1.42–1.67)	1.53 (1.41–1.66)
Asthma	16,630 (15.2)	14,842 (13.5)	1.15 (1.12–1.18)	1.11 (1.08–1.14)
Rheumatoid Arthritis	1479 (1.4)	1336 (1.2)	1.11 (1.03–1.20)	1.10 (1.02–1.19)
COPD	2848 (2.6)	3062 (2.8)	0.93 (0.88–0.98)	0.95 (0.90–1.00)

Notes: Comorbidities listed according to their odds ratios in decreasing order. ^aAdjusted for BMI category, smoking status, alcohol consumption.

Abbreviations: CI, confidence interval; COPD, Chronic obstructive pulmonary disease; OR, odds ratio; TIA, transient ischemic attack.

tension-type headache (adj. OR 11.71, 95% CI: 5.92–23.19), concussion (adj. OR 8.45, 95% CI: 2.54–28.05), temporomandibular joint disorders (adj. OR 6.63, 95% CI: 3.98–11.06), whiplash (adj. OR 5.39, 95% CI: 3.11–9.34), cervicgia (adj. OR 5.04, 95% CI: 4.33–5.86), migraine (adj. OR 4.38, 95% CI: 3.43–5.60), or cranial nerve disorders (adj. OR 4.33, 95% CI: 2.69–6.98; Table 4, stratified by sex in Table S4).

Discussion

In this large case-control analysis, we assessed incidence rates of GP-recorded tinnitus in the UK over time, and we characterized life style parameters as well a large range of comorbidities in tinnitus patients. The direct comparison of tinnitus cases with a randomly selected, matched sample of tinnitus-free patients allowed us to characterize which

factors were more and which less frequently observed in tinnitus patients compared to controls, without any claim that such observed association are necessarily causal.

Incidence rates

Between 2000 and 2016, we calculated an overall crude IR of GP-reported tinnitus of 24.3 cases per 10,000 PY. IRs for men and women were comparable, which is consistent with results of previously published studies although there is no general consensus in the field.^{4,11,28–30}

We observed that IRs increased with age, were highest between age 60–69 years, and decreased subsequently thereafter. This pattern has been reported by others.^{4,11,28} It is hypothesized that, with increasing age, the importance of tinnitus in a patient's overall health burden declines, and the ability to cope with symptoms grows.^{28,31} Another theory

Table 3 Distribution of comorbidities in patients with tinnitus and their matched controls: otological and vestibular disorders

	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted^a (95% CI)
Sensorineural Hearing Loss				
≤30 days prior to (including) the ID	618 (0.6)	< 5 ^b (0.0)	156.99 (58.81–419.08)	161.70 (60.56–431.73)
31 to 360 days prior to the ID	179 (0.2)	60 (0.1)	3.18 (2.36–4.28)	3.10 (2.29–4.18)
>360 days prior to the ID	1142 (1.0)	701 (0.6)	1.68 (1.53–1.85)	1.68 (1.53–1.85)
Acute vestibular neuronitis				
≤30 days prior to (including) the ID	37 (0.0)	< 5 ^b (0.0)	36.15 (5.07–257.83)	34.14 (4.79–243.60)
31 to 360 days prior to the ID	68 (0.1)	27 (0.0)	2.58 (1.64–4.05)	2.37 (1.50–3.73)
>360 days prior to the ID	390 (0.4)	236 (0.2)	1.66 (1.41–1.95)	1.63 (1.39–1.92)
Otitis media				
≤30 days prior to (including) the ID	1114 (1.0)	51 (0.1)	22.91 (17.30–30.32)	22.82 (17.23–30.22)
31 to 360 days prior to the ID	1753 (1.6)	489 (0.5)	3.82 (3.45–4.23)	3.81 (3.44–4.22)
>360 days prior to the ID	11,552 (10.5)	9483 (8.6)	1.33 (1.29–1.37)	1.31 (1.27–1.36)
Labyrinthitis				
≤30 days prior to (including) the ID	408 (0.4)	20 (0.0)	20.90 (13.34–32.73)	20.19 (12.88–31.65)
31 to 360 days prior to the ID	867 (0.8)	277 (0.3)	3.26 (2.85–3.74)	3.19 (2.78–3.66)
>360 days prior to the ID	4338 (4.0)	3014 (2.8)	1.49 (1.42–1.57)	1.46 (1.40–1.54)
Conductive Hearing Loss				
≤30 days prior to (including) the ID	52 (0.1)	< 5 ^b (0.0)	17.32 (5.41–55.42)	19.51 (6.07–62.74)
31 to 360 days prior to the ID	29 (0.0)	< 5 ^b (0.0)	7.25 (2.55–20.62)	7.23 (2.53–20.67)
>360 days prior to the ID	290 (0.3)	229 (0.2)	1.27 (1.07–1.51)	1.25 (1.05–1.48)
Benign positional vertigo				
≤30 days prior to (including) the ID	462 (0.4)	37 (0.0)	13.11 (9.37–18.34)	12.94 (9.24–18.11)
31 to 360 days prior to the ID	960 (0.9)	398 (0.4)	2.56 (2.28–2.89)	2.48 (2.20–2.80)
>360 days prior to the ID	3488 (3.2)	2294 (2.1)	1.60 (1.51–1.69)	1.56 (1.48–1.65)
Cerumen				
≤30 days prior to (including) the ID	4249 (3.9)	407 (0.4)	11.74 (10.58–13.04)	11.56 (10.41–12.83)
31 to 360 days prior to the ID	6680 (6.1)	3512 (3.2)	2.17 (2.07–2.26)	2.12 (2.03–2.21)
>360 days prior to the ID	14,702 (13.4)	14,513 (13.2)	1.13 (1.10–1.16)	1.11 (1.08–1.14)
Otitis externa				
≤30 days prior to (including) the ID	1875 (1.7)	203 (0.2)	9.88 (8.54–11.44)	9.87 (8.52–11.43)
31 to 360 days prior to the ID	3575 (3.3)	1506 (1.4)	2.55 (2.40–2.71)	2.54 (2.39–2.70)
>360 days prior to the ID	13,171 (12.0)	11,085 (10.1)	1.28 (1.24–1.31)	1.26 (1.23–1.30)

Notes: ^aAdjusted for BMI category, smoking status, alcohol consumption. ^bFor confidentiality reasons, we do not provide the number of patients in categories containing less than five patients.

Abbreviations: CI, confidence interval; ID, index date; NA, not available; OR, odds ratio.

is that tinnitus may be associated with cardiovascular disease, and that patients with cardiovascular diseases are more likely to die, whereby those who survive are less likely to develop tinnitus.²⁸ However, we did not find a marked increase in tinnitus risk associated with previous cardiovascular diseases, and exploring cardiovascular mortality was not the goal of this study.

We observed a substantial rise in the annual IRs during the study period from 18.3 per 10,000 PY in 2000 to 34.2 per 10,000 PY in 2016. Over the past two decades, other

studies also reported increases in rates of hearing disorders including tinnitus in adolescents and young adults, possibly due to higher exposure to loud music in bars, concerts, discotheques and from personal electronic devices.^{32–34} However, our analysis yielded no difference between young adults below 30 years of age and older adults with respect to the pattern of IRs over time. Other explanations for the rise in tinnitus incidence include more demanding health expectations, and a higher awareness of symptoms over time.^{11,35}

Table 4 Distribution of comorbidities in patients with tinnitus and their matched controls: head and neck disorders

	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Tension-type headache				
≤30 days prior to (including) the ID	104 (0.1)	9 (0.0)	11.72 (5.93–23.17)	11.71 (5.92–23.19)
31 to 360 days prior to the ID	359 (0.3)	145 (0.1)	2.53 (2.09–3.07)	2.52 (2.07–3.06)
>360 days prior to the ID	3331 (3.0)	2176 (2.0)	1.58 (1.49–1.67)	1.54 (1.46–1.63)
Concussion				
≤30 days prior to (including) the ID	25 (0.0)	<5 ^b (0.0)	8.31 (2.51–27.47)	8.45 (2.54–28.05)
31 to 360 days prior to the ID	39 (0.0)	19 (0.0)	2.05 (1.19–3.55)	2.10 (1.21–3.66)
>360 days prior to the ID	539 (0.5)	497 (0.5)	1.09 (0.96–1.23)	1.09 (0.96–1.23)
Temporomandibular joint disorders				
≤30 days prior to (including) the ID	115 (0.1)	17 (0.0)	6.84 (4.11–11.38)	6.63 (3.98–11.06)
31 to 360 days prior to the ID	308 (0.3)	144 (0.1)	2.17 (1.78–2.64)	2.09 (1.71–2.56)
>360 days prior to the ID	2323 (2.1)	1501 (1.4)	1.58 (1.48–1.68)	1.54 (1.44–1.64)
Whiplash				
≤30 days prior to (including) the ID	86 (0.1)	15 (0.0)	5.80 (3.35–10.04)	5.39 (3.11–9.34)
31 to 360 days prior to the ID	345 (0.3)	232 (0.2)	1.51 (1.27–1.78)	1.48 (1.25–1.75)
>360 days prior to the ID	4517 (4.1)	3778 (3.4)	1.21 (1.16–1.27)	1.20 (1.15–1.25)
Cervicalgia				
≤30 days prior to (including) the ID	985 (0.9)	210 (0.2)	5.17 (4.45–6.01)	5.04 (4.33–5.86)
31 to 360 days prior to the ID	3000 (2.7)	1740 (1.6)	1.89 (1.78–2.01)	1.82 (1.72–1.94)
>360 days prior to the ID	18,075 (16.5)	13,399 (12.2)	1.50 (1.46–1.54)	1.47 (1.44–1.51)
Migraine				
≤30 days prior to (including) the ID	346 (0.3)	80 (0.1)	4.54 (3.56–5.79)	4.38 (3.43–5.60)
31 to 360 days prior to the ID	1045 (1.0)	603 (0.6)	1.83 (1.65–2.02)	1.77 (1.59–1.95)
>360 days prior to the ID	9519 (8.7)	7160 (6.5)	1.39 (1.35–1.44)	1.37 (1.32–1.41)
Cranial nerve disorders				
≤30 days prior to (including) the ID	90 (0.1)	21 (0.0)	4.32 (2.69–6.95)	4.33 (2.69–6.98)
31 to 360 days prior to the ID	342 (0.3)	177 (0.2)	1.95 (1.63–2.35)	1.90 (1.58–2.29)
>360 days prior to the ID	2286 (2.1)	1772 (1.6)	1.30 (1.22–1.39)	1.30 (1.22–1.39)

Notes: ^aAdjusted for BMI category, smoking status, alcohol consumption. ^bFor confidentiality reasons, we do not provide the number of patients in categories containing less than five patients.

Abbreviations: CI, confidence interval; ID, index date; NA, not available; OR, odds ratio.

The precise IRs reported in the literature vary due to differences in study periods, regions, and case definitions. We included all patients with GP-reported tinnitus, whereas other authors exclusively focused on i) clinically significant tinnitus defined by Martinez et al,¹¹ ii) self-reported tinnitus symptoms lasting for at least five minutes⁴ or iii) self-reported tinnitus symptoms in the last year of at least moderate severity or leading to sleep disorders.^{28,36} These differences likely explain the higher IRs observed in our study.

Lifestyle factors

We found that obese patients were not at increased risk of developing tinnitus, as did three previous cross-sectional studies^{37–39} and a cohort study.³⁶ On the contrary, our data

suggest a slightly lower risk in obese as well as in underweight patients, though the ORs were very close to the null.

We observed an inverse association between current smoking and tinnitus. The same was found in a cross-sectional study using the UK Biobank resource for persistent tinnitus, but not for transient tinnitus.³⁹ An Italian study published in 2015 reported a comparable trend, but due to the small study population the results did not meet statistical significance.⁴⁰ In contrast, other studies have reported an increased risk of being diagnosed with tinnitus among smokers.^{34,36,41,42} A variety of possible causes of tinnitus as well as differences in the study designs and respective study populations may contribute to these contradictory results.¹⁵

Current alcohol consumption was also inversely related to tinnitus, which is consistent with the findings of several other studies.^{29,36,40} It has been hypothesized that alcohol exerts a favorable effect on microvascular health in the cochlea.²⁹ Another explanation is that tinnitus is underreported in patients with unhealthy lifestyles who may be more likely to suffer from more pressing health-related problems and may not discuss tinnitus with their GP.

Comorbidities

Our analyses yielded a statistically significant association between prevalent anxiety, depression, and insomnia, and the risk of developing tinnitus. It is well known that these disorders have a negative impact on quality of life and on severity of tinnitus,⁷⁻⁹ and they are also often a consequence of bothersome tinnitus.^{5,7,34,43} Some studies have also found that anxiety and depression can precede tinnitus,^{34,44,45} and parallels in pathophysiology have been noted.^{8,9,46} In this study, however, we were careful to establish that the depression-related disorders occurred before the tinnitus diagnosis. It has previously been suggested that tinnitus is associated with greater mental health burden in women than in men.⁴⁷ A prior cross-sectional study further reported a statistically significantly increased risk of suicide attempts in women with severe tinnitus, but not in men.⁴⁸ The absence of any meaningful effect modification by sex for the association of the risk of tinnitus and mental health and other comorbidities may thus reflect that women with mental health diseases are not per se at an increased risk of developing tinnitus compared to men; however, they may suffer more distress from co-existing tinnitus and mental health diseases. Further research is needed to evaluate this potential association.

Our finding of decreased ORs, especially in patients with a diagnosis of dementia, Parkinson's disease or schizophrenia, could be explained by underreporting due to more serious health-related problems or due to difficulties in communication.

Impairment of the auditory system seems to be an important underlying mechanism of tinnitus.^{14,29} It is assumed that hearing impairment may induce tinnitus by initiating changes on a cellular and structural level in the brain. This involves changes within the central auditory system as well as within non-auditory systems.¹⁴ Our results showed that hearing loss, in particular sensorineural hearing loss, and ear infections were highly associated with tinnitus. Previous studies also found this association, and they have also shown that concomitantly occurring

hearing loss may be considered a predictor for tinnitus severity.^{28,49}

Another proposed mechanism of somatosensory system-related tinnitus involves pathological processes of musculoskeletal structures of the head and neck,^{4,28,50-54} such as functional disorders of the cervical spine or neck and the temporomandibular joint.^{37,55-58} Changes in the neuronal activity of the dorsal cochlear nucleus or between somatosensory and auditory systems seem to play an important role in this subtype of tinnitus.⁵⁹ A meta-analysis of eight cross-sectional studies in patients with temporomandibular joint disorders identified tinnitus as a common symptom in over 50% of patients.⁵⁸ The results of our study were similar, with a large proportion of tinnitus occurring in patients suffering from tension headaches, migraine, cervicgia, whiplash, concussion, or cranial nerve disorders.

The highest rate of tinnitus among patients with otological and vestibular disorders as well as head and neck disorders, occurred shortly after the recording of the respective disorder which supports the possibility of a causal association.

Study limitations

When interpreting the results of this study, we took several limitations into account. First, tinnitus is usually a subjective phenomenon, and the diagnosis is based on self-reporting. Case validation is difficult without uniformly followed standardized procedures⁶⁰ and the availability of questionnaires or referral letters. To our knowledge, the tinnitus diagnosis has not been validated in the CPRD, as this is virtually impossible, since tinnitus is a self-diagnosed condition that cannot be confirmed as yet with objective diagnostic procedures; thus, there is likely to be some case misclassification in this study. However, the large sample size of the present clinical data may compensate for such misclassifications. Second, tinnitus severity is mostly mild, and only 10 to 52% of individuals who experience tinnitus discuss this symptom with their GP.^{4,5,50} Therefore, GP-reported tinnitus does not capture all cases, and the true rates are likely to be higher than those presented in our study. Nevertheless, the numbers reflect those cases that present to the GPs in real life in the UK. Third, GPs do not systematically record tinnitus characteristics such as severity, duration, or impact on patients' quality of life. Therefore, it was not possible to carry out detailed analyses to account for these factors or to distinguish between clinically important or less important tinnitus, or between acute or persistent tinnitus. To date, there is no generally accepted definition to

consistently¹⁰ grade tinnitus severity, and the approaches used in the different studies vary.^{4,28,30,36–38,50} Finally, a first-time tinnitus diagnosis does likely not coincide with the actual disease onset in a proportion of cases since patients may not seek medical attention immediately.

Conclusion

We investigated the epidemiology of GP-recorded tinnitus in a large sample of the UK population. IRs increased considerably over time in men and women, emphasizing a growing health burden. Recent diagnosis of several otological and vestibular as well as head and neck disorders was strongly associated with the risk of developing tinnitus. However, we cannot derive causality from these analyses, as we did not intend to run an etiologic study, but rather to descriptively characterize tinnitus patients with regard to life style parameters and comorbidities. These observations may support doctors when diagnosing tinnitus and when putting life style and comorbidity patterns of individual patients into perspective of a large population-based assessment.

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Data sharing statement

Data for this study were derived from CPRD primary care data obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in the study are those of the authors alone.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Incidence rates of tinnitus diagnosed in the UK between 2000 and 2016

	Number of PY at risk	Number of tinnitus patients	crude IR per 10,000 PY (95% CI)	ASR ^a per 10,000 PY (95% CI)
Overall	4,52,48,312	1,09,783	24.3 (24.1–24.4)	25.0 (24.6–25.5)
By sex				
Men	2,18,41,921	53,874	24.7 (24.5–24.9)	25.7 (25.0–26.4)
Women	2,34,06,391	55,909	23.9 (23.7–24.1)	24.7 (24.0–25.3)
By age (years)				
<20	16,50,985	1,097	6.6 (6.3–7.0)	NA
20–29	73,48,559	7,118	9.7 (9.5–9.9)	NA
30–39	78,78,802	11,757	14.9 (14.7–15.2)	NA
40–49	86,20,883	19,454	22.6 (22.3–22.9)	NA
50–59	75,16,334	26,247	34.9 (34.5–35.3)	NA
60–69	58,51,960	24,097	41.2 (40.7–41.7)	NA
70–79	39,82,409	13,860	34.8 (34.2–35.4)	NA
≥80	23,98,378	6,153	25.7 (25.0–26.3)	NA
By year of diagnosis				
2000	25,43,654	4,646	18.3 (17.7–18.8)	19.1 (17.4–20.9)
2001	26,44,954	5,049	19.1 (18.6–19.6)	18.3 (16.7–20.0)
2002	27,28,728	5,671	20.8 (20.2–21.3)	20.0 (18.3–21.6)
2003	28,20,513	5,821	20.6 (20.1–21.2)	19.8 (18.2–21.5)
2004	29,14,236	6,541	22.4 (21.9–23.0)	21.6 (19.9–23.3)
2005	29,73,188	6,713	22.6 (22.0–23.1)	21.9 (20.2–23.5)
2006	30,16,968	7,028	23.3 (22.8–23.8)	22.6 (20.9–24.3)
2007	30,27,173	7,276	24.0 (23.5–24.6)	23.4 (21.6–25.1)
2008	30,47,487	7,775	25.5 (25.0–26.1)	24.7 (23.0–26.5)
2009	30,26,926	8,060	26.6 (26.1–27.2)	26.0 (24.2–27.9)
2010	29,78,185	7,754	26.0 (25.5–26.6)	25.4 (23.6–27.3)
2011	29,04,131	7,903	27.2 (26.6–27.8)	26.4 (24.5–28.2)
2012	28,15,439	7,591	27.0 (26.4–27.6)	26.1 (24.2–28.0)
2013	25,98,517	6,858	26.4 (25.8–27.0)	25.4 (23.5–27.4)
2014	22,81,051	6,190	27.1 (26.5–27.8)	26.0 (23.9–28.1)
2015	18,33,974	5,171	28.2 (27.4–29.0)	26.9 (24.6–29.3)
2016	10,93,189	3,736	34.2 (33.1–35.3)	32.2 (28.8–35.6)

Note: ^aStandard population from Eurostat.²⁷

Abbreviations: ASR, age-standardised incidence rates; CI, confidence interval; IR, incidence rate; PY, person-years.

Table S2 Distribution of patient characteristics and lifestyle factors in patients with tinnitus and their matched controls, stratified by sex

	Men (n=53,874)						Women (n=55,909)					
	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Neurological/psychological disorders												
Insomnia	5942 (11.0)	4175 (7.8)	1.51 (1.45–1.58)	1.49 (1.43–1.56)	9002 (16.1)	6868 (12.3)	1.42 (1.37–1.48)	1.42 (1.37–1.47)				
Anxiety	8806 (16.4)	6880 (12.8)	1.35 (1.31–1.40)	1.35 (1.30–1.40)	14,066 (25.2)	10,959 (19.6)	1.41 (1.37–1.45)	1.41 (1.37–1.46)				
Depression	8143 (15.1)	6390 (11.9)	1.34 (1.29–1.39)	1.33 (1.28–1.38)	14,278 (25.5)	11,973 (21.4)	1.28 (1.24–1.32)	1.30 (1.26–1.34)				
Seizure/Epilepsy	1231 (2.3)	1267 (2.4)	0.97 (0.90–1.05)	0.98 (0.90–1.06)	1162 (2.1)	1099 (2.0)	1.06 (0.97–1.15)	1.06 (0.97–1.15)				
Multiple Sclerosis	98 (0.2)	126 (0.2)	0.78 (0.60–1.01)	0.79 (0.60–1.03)	226 (0.4)	243 (0.4)	0.93 (0.78–1.12)	0.94 (0.78–1.12)				
Schizophrenia	333 (0.6)	402 (0.8)	0.83 (0.71–0.96)	0.84 (0.72–0.98)	290 (0.5)	429 (0.8)	0.67 (0.58–0.78)	0.70 (0.60–0.81)				
Parkinson Disease	124 (0.2)	228 (0.4)	0.54 (0.44–0.68)	0.54 (0.44–0.68)	132 (0.2)	183 (0.3)	0.72 (0.58–0.90)	0.74 (0.59–0.92)				
Dementia	106 (0.2)	207 (0.4)	0.50 (0.40–0.64)	0.51 (0.41–0.65)	176 (0.3)	453 (0.8)	0.38 (0.32–0.45)	0.38 (0.32–0.46)				
Cardiovascular disorders												
Arrhythmia	3111 (5.8)	2632 (4.9)	1.21 (1.14–1.28)	1.16 (1.09–1.22)	3263 (5.8)	2672 (4.8)	1.25 (1.18–1.32)	1.22 (1.16–1.29)				
Hypertension	12,176 (22.6)	11,907 (22.1)	1.04 (1.00–1.07)	0.98 (0.94–1.01)	13,812 (24.7)	13,702 (24.5)	1.01 (0.98–1.05)	0.98 (0.95–1.01)				
Myocardial infarction	2120 (3.9)	2121 (3.9)	1.00 (0.94–1.07)	0.96 (0.90–1.02)	815 (1.5)	853 (1.5)	0.95 (0.86–1.05)	0.92 (0.84–1.02)				
Congestive heart failure	766 (1.4)	828 (1.5)	0.92 (0.83–1.02)	0.89 (0.80–0.98)	739 (1.3)	765 (1.4)	0.96 (0.87–1.07)	0.95 (0.86–1.06)				
Stroke/TIA	1703 (3.2)	1906 (3.5)	0.89 (0.83–0.95)	0.86 (0.81–0.93)	1682 (3.0)	1829 (3.3)	0.91 (0.85–0.98)	0.90 (0.84–0.97)				
Metabolic disorders												
Hyperlipidemia	6238 (11.6)	5445 (10.1)	1.19 (1.14–1.24)	1.13 (1.09–1.18)	5843 (10.5)	5150 (9.2)	1.18 (1.13–1.23)	1.16 (1.11–1.21)				
Hypothyroidism	1074 (2.0)	899 (1.7)	1.20 (1.10–1.31)	1.16 (1.06–1.27)	5151 (9.2)	4601 (8.2)	1.14 (1.09–1.18)	1.12 (1.07–1.17)				
Hyperthyroidism	312 (0.6)	285 (0.5)	1.10 (0.93–1.29)	1.04 (0.89–1.23)	1211 (2.2)	1078 (1.9)	1.13 (1.04–1.22)	1.13 (1.04–1.23)				
Diabetes mellitus	3839 (7.1)	4280 (7.9)	0.88 (0.84–0.93)	0.83 (0.79–0.87)	3076 (5.5)	3346 (6.0)	0.91 (0.87–0.96)	0.88 (0.84–0.93)				
Other disorders												
Irritable bowel syndrome	3405 (6.3)	2028 (3.8)	1.74 (1.64–1.84)	1.66 (1.57–1.76)	7603 (13.6)	5260 (9.4)	1.53 (1.48–1.59)	1.51 (1.46–1.57)				
Fibromyalgia	388 (0.7)	262 (0.5)	1.50 (1.28–1.76)	1.50 (1.27–1.76)	1200 (2.2)	791 (1.4)	1.55 (1.41–1.70)	1.54 (1.40–1.68)				
Asthma	7577 (14.1)	6743 (12.5)	1.15 (1.11–1.19)	1.09 (1.05–1.13)	9053 (16.2)	8099 (14.5)	1.15 (1.11–1.18)	1.12 (1.09–1.16)				
Rheumatoid Arthritis	475 (0.9)	413 (0.8)	1.15 (1.01–1.32)	1.13 (0.99–1.29)	1004 (1.8)	923 (1.7)	1.09 (1.00–1.19)	1.09 (0.99–1.19)				
COPD	1535 (2.9)	1576 (2.9)	0.97 (0.90–1.05)	0.99 (0.91–1.06)	1313 (2.4)	1486 (2.7)	0.88 (0.81–0.95)	0.91 (0.84–0.98)				

Notes: ^aAdjusted for BMI, category, smoking status, alcohol consumption. Comorbidities listed according to their odds ratios in decreasing order

Abbreviations: CI, confidence interval; COPD, Chronic obstructive pulmonary disease; OR, odds ratio; TIA, transient ischemic attack

Table S3 Distribution of comorbidities in patients with tinnitus and their matched controls, stratified by sex: otological and vestibular disorders

	Men (n=53,874)						Women (n=55,909)					
	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Sensorineural Hearing Loss												
≤30 days prior to (including) the ID	330 (0.6)	<5 ^b (0.0)	166.11 (41.47–665.34)	171.24 (42.74–686.06)	288 (0.5)	<5 ^b (0.0)	148.37 (36.97–595.42)	153.01 (38.12–614.15)	288 (0.5)	148.37 (36.97–595.42)	153.01 (38.12–614.15)	
31 to 360 days prior to the ID	85 (0.2)	31 (0.1)	2.94 (1.93–4.49)	2.84 (1.86–4.35)	94 (0.2)	29 (0.1)	3.42 (2.24–5.21)	3.36 (2.20–5.13)	94 (0.2)	3.42 (2.24–5.21)	3.36 (2.20–5.13)	
>360 days prior to the ID	565 (1.1)	380 (0.7)	1.52 (1.33–1.73)	1.52 (1.33–1.74)	577 (1.0)	321 (0.6)	1.88 (1.64–2.16)	1.88 (1.63–2.16)	577 (1.0)	1.88 (1.64–2.16)	1.88 (1.63–2.16)	
Acute vestibular neuritis												
≤30 days prior to (including) the ID	18 (0.0)	<5 ^b (0.0)	17.98 (2.40–134.54)	17.90 (2.38–134.45)	19 (0.0)	0 (0.0)	NA	NA	19 (0.0)	NA	NA	
31 to 360 days prior to the ID	23 (0.0)	5 (0.0)	4.60 (1.75–12.10)	3.95 (1.50–10.46)	45 (0.1)	22 (0.0)	2.10 (1.25–3.52)	1.98 (1.17–3.34)	45 (0.1)	2.10 (1.25–3.52)	1.98 (1.17–3.34)	
>360 days prior to the ID	123 (0.2)	78 (0.1)	1.58 (1.19–2.09)	1.49 (1.12–1.99)	267 (0.5)	158 (0.3)	1.70 (1.39–2.07)	1.69 (1.39–2.07)	267 (0.5)	1.70 (1.39–2.07)	1.69 (1.39–2.07)	
Otitis media												
≤30 days prior to (including) the ID	548 (1.0)	13 (0.0)	44.05 (25.41–76.36)	43.55 (25.11–75.54)	566 (1.0)	38 (0.1)	15.74 (11.33–21.86)	15.76 (11.34–21.91)	566 (1.0)	15.74 (11.33–21.86)	15.76 (11.34–21.91)	
31 to 360 days prior to the ID	784 (1.5)	201 (0.4)	4.12 (3.52–4.82)	4.09 (3.49–4.79)	969 (1.7)	288 (0.5)	3.62 (3.17–4.14)	3.62 (3.17–4.14)	969 (1.7)	3.62 (3.17–4.14)	3.62 (3.17–4.14)	
>360 days prior to the ID	5171 (9.6)	4391 (8.2)	1.27 (1.21–1.33)	1.24 (1.19–1.30)	6381 (11.4)	5092 (9.1)	1.38 (1.32–1.44)	1.37 (1.32–1.43)	6381 (11.4)	1.38 (1.32–1.44)	1.37 (1.32–1.43)	
Labyrinthitis												
≤30 days prior to (including) the ID	155 (0.3)	5 (0.0)	31.29 (12.84–76.23)	29.62 (12.14–72.28)	253 (0.5)	15 (0.0)	17.46 (10.37–29.40)	17.05 (10.11–28.73)	253 (0.5)	17.46 (10.37–29.40)	17.05 (10.11–28.73)	
31 to 360 days prior to the ID	298 (0.6)	89 (0.2)	3.47 (2.73–4.40)	3.43 (2.69–4.36)	569 (1.0)	188 (0.3)	3.16 (2.68–3.74)	3.07 (2.60–3.64)	569 (1.0)	3.16 (2.68–3.74)	3.07 (2.60–3.64)	
>360 days prior to the ID	1453 (2.7)	992 (1.8)	1.51 (1.39–1.64)	1.47 (1.35–1.59)	2885 (5.2)	2022 (3.6)	1.49 (1.40–1.58)	1.46 (1.38–1.55)	2885 (5.2)	1.49 (1.40–1.58)	1.46 (1.38–1.55)	
Conductive Hearing Loss												
≤30 days prior to (including) the ID	19 (0.0)	<5 ^b (0.0)	18.97 (2.54–141.51)	21.20 (2.81–159.97)	33 (0.1)	<5 ^b (0.0)	16.49 (3.96–68.68)	18.60 (4.45–77.82)	33 (0.1)	16.49 (3.96–68.68)	18.60 (4.45–77.82)	
31 to 360 days prior to the ID	13 (0.0)	<5 ^b (0.0)	6.50 (1.47–28.80)	6.95 (1.55–31.13)	16 (0.0)	<5 ^b (0.0)	8.00 (1.84–34.79)	7.62 (1.75–33.25)	16 (0.0)	8.00 (1.84–34.79)	7.62 (1.75–33.25)	
>360 days prior to the ID	127 (0.2)	112 (0.2)	1.13 (0.88–1.46)	1.10 (0.85–1.43)	163 (0.3)	117 (0.2)	1.40 (1.10–1.77)	1.39 (1.09–1.76)	163 (0.3)	1.40 (1.10–1.77)	1.39 (1.09–1.76)	
Benign positional vertigo												
≤30 days prior to (including) the ID	146 (0.3)	12 (0.0)	12.61 (6.99–22.74)	11.95 (6.61–21.60)	316 (0.6)	25 (0.0)	13.32 (8.86–20.03)	13.33 (8.86–20.06)	316 (0.6)	13.32 (8.86–20.03)	13.33 (8.86–20.06)	
31 to 360 days prior to the ID	344 (0.6)	124 (0.2)	2.92 (2.37–3.60)	2.80 (2.27–3.46)	616 (1.1)	274 (0.5)	2.39 (2.07–2.77)	2.33 (2.01–2.69)	616 (1.1)	2.39 (2.07–2.77)	2.33 (2.01–2.69)	
>360 days prior to the ID	1189 (2.2)	725 (1.4)	1.70 (1.55–1.87)	1.65 (1.50–1.82)	2299 (4.1)	1569 (2.8)	1.54 (1.44–1.65)	1.52 (1.42–1.63)	2299 (4.1)	1.54 (1.44–1.65)	1.52 (1.42–1.63)	
Cerumen												
≤30 days prior to (including) the ID	2502 (4.6)	237 (0.4)	11.83 (10.32–13.56)	11.58 (10.10–13.29)	1747 (3.1)	170 (0.3)	11.57 (9.84–13.61)	11.50 (9.77–13.53)	1747 (3.1)	11.57 (9.84–13.61)	11.50 (9.77–13.53)	
31 to 360 days prior to the ID	3737 (6.9)	2037 (3.8)	2.11 (1.99–2.24)	2.06 (1.94–2.18)	2943 (5.3)	1475 (2.6)	2.23 (2.09–2.38)	2.19 (2.05–2.34)	2943 (5.3)	2.23 (2.09–2.38)	2.19 (2.05–2.34)	
>360 days prior to the ID	7841 (14.6)	8009 (14.9)	1.10 (1.06–1.14)	1.07 (1.04–1.11)	6861 (12.3)	6504 (11.6)	1.16 (1.12–1.21)	1.15 (1.11–1.20)	6861 (12.3)	1.16 (1.12–1.21)	1.15 (1.11–1.20)	

(Continued)

Table S3 (Continued).

	Men (n=53,874)			Women (n=55,909)				
	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Otitis externa								
≤30 days prior to (including) the ID	970 (1.8)	96 (0.2)	10.81 (8.74–13.36)	10.71 (8.65–13.25)	905 (1.6)	107 (0.2)	9.03 (7.38–11.06)	9.10 (7.43–11.15)
31 to 360 days prior to the ID	1713 (3.2)	717 (1.3)	2.56 (2.34–2.80)	2.56 (2.34–2.80)	1862 (3.3)	789 (1.4)	2.54 (2.33–2.76)	2.53 (2.32–2.75)
>360 days prior to the ID	6353 (11.8)	5585 (10.4)	1.22 (1.17–1.27)	1.20 (1.15–1.25)	6818 (12.2)	5500 (9.8)	1.34 (1.29–1.39)	1.33 (1.28–1.38)

Notes: ^aAdjusted for BMI category, smoking status, alcohol consumption. ^bFor confidentiality reasons, we do not provide the number of patients in categories containing less than five patients. Abbreviations: CI, confidence interval; ID, index date; NA, not available; OR, odds ratio.

Table S4 Distribution of comorbidities in patients with tinnitus and their matched controls, stratified by sex: head and neck disorders

	Men (n=53,874)			Women (n=55,909)				
	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Tension-type headache								
≤30 days prior to (including) the ID	38 (0.1)	0 (0.0)	NA	NA	66 (0.1)	9 (0.0)	7.47 (3.72–14.99)	7.55 (3.76–15.18)
31 to 360 days prior to the ID	117 (0.2)	48 (0.1)	2.47 (1.77–3.46)	2.38 (1.70–3.35)	242 (0.4)	97 (0.2)	2.56 (2.02–3.24)	2.57 (2.03–3.26)
>360 days prior to the ID	1143 (2.1)	708 (1.3)	1.64 (1.49–1.81)	1.57 (1.43–1.73)	2188 (3.9)	1468 (2.6)	1.54 (1.44–1.65)	1.52 (1.42–1.63)
Concussion								
≤30 days prior to (including) the ID	14 (0.0)	<5 ^b (0.0)	14.00 (1.84–106.41)	13.36 (1.74–102.45)	11 (0.0)	<5 ^b (0.0)	5.50 (1.22–24.80)	5.98 (1.32–27.08)
31 to 360 days prior to the ID	15 (0.0)	7 (0.0)	2.14 (0.87–5.26)	2.31 (0.93–5.75)	24 (0.0)	12 (0.0)	2.00 (1.00–4.00)	2.00 (1.00–4.01)
>360 days prior to the ID	332 (0.6)	324 (0.6)	1.03 (0.88–1.20)	1.02 (0.88–1.20)	207 (0.4)	173 (0.3)	1.20 (0.98–1.47)	1.21 (0.99–1.49)

(Continued)

Table S4 (Continued).

	Men (n=53,874)				Women (n=55,909)			
	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)	Tinnitus cases (%)	Tinnitus-free controls (%)	OR crude (95% CI)	OR adjusted ^a (95% CI)
Temporomandibular joint disorders								
≤30 days prior to (including) the ID	38 (0.1)	7 (0.0)	5.43 (2.42–12.15)	5.27 (2.34–11.85)	77 (0.1)	10 (0.0)	7.81 (4.05–15.10)	7.59 (3.92–14.70)
31 to 360 days prior to the ID	106 (0.2)	38 (0.1)	2.80 (1.93–4.06)	2.73 (1.88–3.97)	202 (0.4)	106 (0.2)	1.93 (1.53–2.45)	1.86 (1.47–2.36)
>360 days prior to the ID	696 (1.3)	413 (0.8)	1.70 (1.51–1.93)	1.64 (1.44–1.85)	1627 (2.9)	1088 (2.0)	1.53 (1.41–1.65)	1.50 (1.39–1.62)
Whiplash								
≤30 days prior to (including) the ID	44 (0.1)	7 (0.0)	6.44 (2.90–14.30)	5.77 (2.59–12.86)	42 (0.1)	8 (0.0)	5.27 (2.47–11.22)	5.12 (2.40–10.92)
31 to 360 days prior to the ID	160 (0.3)	112 (0.2)	1.45 (1.13–1.84)	1.41 (1.10–1.81)	185 (0.3)	120 (0.2)	1.56 (1.24–1.97)	1.54 (1.22–1.94)
>360 days prior to the ID	2144 (4.0)	1724 (3.2)	1.26 (1.18–1.35)	1.25 (1.17–1.33)	2373 (4.2)	2054 (3.7)	1.17 (1.10–1.25)	1.16 (1.09–1.23)
Cervicalgia								
≤30 days prior to (including) the ID	425 (0.8)	81 (0.2)	5.57 (4.39–7.07)	5.41 (4.26–6.88)	560 (1.0)	129 (0.2)	4.90 (4.03–5.95)	4.80 (3.94–5.83)
31 to 360 days prior to the ID	1184 (2.2)	674 (1.3)	1.90 (1.72–2.09)	1.81 (1.64–2.00)	1816 (3.3)	1066 (1.9)	1.88 (1.74–2.03)	1.83 (1.69–1.98)
>360 days prior to the ID	7533 (14.0)	5411 (10.0)	1.53 (1.47–1.59)	1.49 (1.43–1.55)	10,542 (18.9)	7988 (14.3)	1.48 (1.43–1.53)	1.46 (1.41–1.51)
Migraine								
≤30 days prior to (including) the ID	103 (0.2)	17 (0.0)	6.16 (3.69–10.30)	5.73 (3.42–9.60)	243 (0.4)	63 (0.1)	4.09 (3.10–5.39)	3.98 (3.01–5.26)
31 to 360 days prior to the ID	246 (0.5)	134 (0.3)	1.87 (1.51–2.31)	1.77 (1.43–2.19)	799 (1.4)	469 (0.8)	1.81 (1.62–2.04)	1.76 (1.57–1.98)
>360 days prior to the ID	2821 (5.2)	1988 (3.7)	1.45 (1.37–1.54)	1.41 (1.33–1.49)	6698 (12.0)	5172 (9.3)	1.37 (1.32–1.42)	1.35 (1.30–1.40)
Cranial nerve disorders								
≤30 days prior to (including) the ID	33 (0.1)	10 (0.0)	3.30 (1.63–6.70)	3.43 (1.68–6.99)	57 (0.1)	11 (0.0)	5.23 (2.74–9.98)	5.14 (2.69–9.83)
31 to 360 days prior to the ID	122 (0.2)	53 (0.1)	2.36 (1.70–3.28)	2.26 (1.62–3.14)	220 (0.4)	124 (0.2)	1.78 (1.43–2.23)	1.75 (1.40–2.19)
>360 days prior to the ID	874 (1.6)	722 (1.3)	1.22 (1.10–1.35)	1.21 (1.09–1.33)	1412 (2.5)	1050 (1.9)	1.36 (1.26–1.48)	1.37 (1.26–1.48)

Notes: ^aAdjusted for BMI category, smoking status, alcohol consumption. ^bFor confidentiality reasons, we do not provide the number of patients in categories containing less than five patients.

Abbreviations: CI, confidence interval; ID, index date; NA, not available; OR, odds ratio.

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